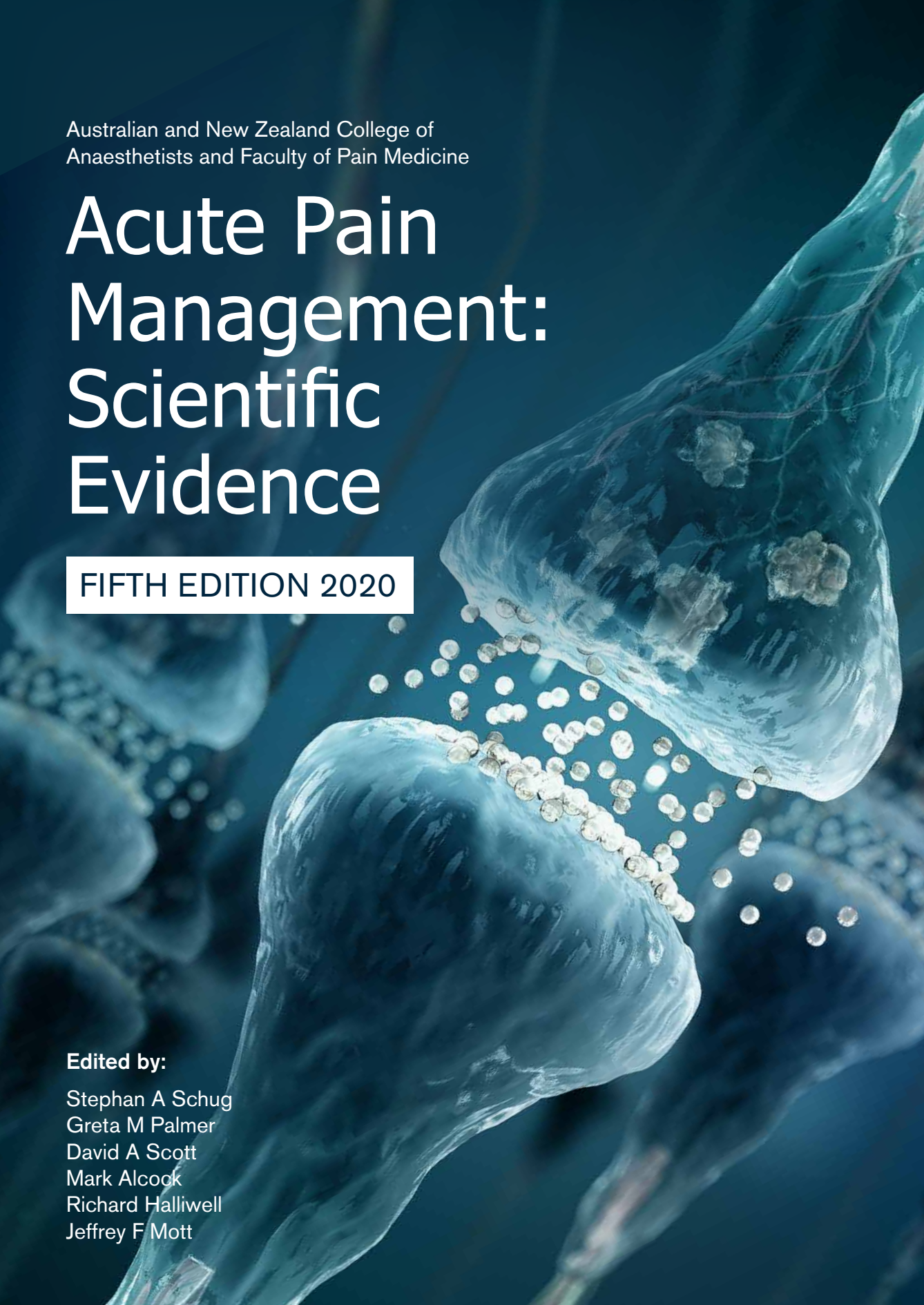
Australian and New Zealand College of
Anaesthetists and Faculty of Pain Medicine

Acute Pain Management: Scientific Evidence

FIFTH EDITION 2020



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Acute Pain Management: Scientific Evidence

Australian and New Zealand College of Anaesthetists
and Faculty of Pain Medicine

Endorsed by:

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Faculty of Pain Medicine of Ireland
Royal Australasian College of Surgeons
Australian Pain Society
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Disclaimer

This document aims to combine a review of the best available evidence for acute pain management with current clinical and expert practice, rather than to formulate specific clinical practice recommendations. It is designed to provide information based on the best evidence available at the time of publication to assist in decision-making. The information provided is not intended to over-ride the clinical expertise of health care professionals and its use is subject to the clinician's judgement and the patient's preference in each individual case. There is no substitute for the skilled assessment of each individual patient's health status, circumstances and perspectives, which health care practitioners will then use to select the treatments that are relevant and appropriate to that person.

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Foreword

The imperative to treat acute pain with innovative evidence-based, patient-centred strategies has never been greater. The lofty goal of personalised, harm-free and adequate relief for every person experiencing acute pain remains just that. The fact that it is not yet reality is more of a testimony to the enormity and complexity of the task rather than for want of trying as can be seen by the exponential increase in publications on this topic.

In 2007, Dr Frank Brennan, Prof Daniel Carr and Prof Michael Cousins, chair of the committee that developed the first edition of *Acute Pain Management: Scientific Evidence,* highlighted the moral imperative to treat pain (Brennan 2007). Indeed, they stated that there is an obligation to treat pain on the basis of restoring patient autonomy and an ethical duty to relieve suffering. This was followed by the "Declaration of Montreal", the outcome of the first International Pain Summit in 2010, which called for "*access to pain management as a fundamental human right*" (Cousins 2011).

The moral imperative to treat all forms of pain remains. Not only does unrelieved pain impair an individual's ability to exercise their fundamental autonomy, it can lead to a wide range of harms even in the short term (Brennan 2007). The well-intentioned promotion that occurred at the turn of this century of the greater use of opioids, in pursuit of the elusive goal of effective pain management for all, has, with the benefit of hindsight, resulted in unexpected injury for many. The number of unintentional drug-induced deaths in Australia continues to rise; prescription opioids and benzodiazepines being the main culprits (Penington Institute 2019). Although many unwanted side-effects are the consequence of long-term use, many opioids are started in the acute pain setting, particularly postoperatively, setting patients on the path to long term use (Bergomi 2018, Brummett 2017, Roughead 2019). Indeed, the use of opioids in acute pain is not without other risks either including opioid-induced ventilatory impairment, cognitive impairment, falls and gastrointestinal adverse effects (Macintyre 2011).

The pendulum seems to be swinging back to a more opioid-phobic position which is unlikely to deliver high-quality care for many individuals either (Kharasch 2020. The pressing need is to better understand what does and does not work from what is already known so that better choices can be made for individuals. The publication of the fifth edition of *Acute Pain Management: Scientific Evidence* is therefore very timely. Recognising the limitations of opioids in the management of acute pain has driven a surge in interest of alternative pain management techniques such as novel non-opioid drugs, new options for regional blockade and non-pharmacological techniques over the last decade (Albrecht 2020, Guay 2017).

For a small percentage of patients however acute pain is still not adequately managed despite the burgeoning range of multimodal pain management techniques, leaving patients at risk of transition to chronicity. Many of the risk factors lie in the psychological, social, cultural and spiritual realms (Sobol-Kwapinska 2016). The need for a broader sociopsychobiomedical approach has been recognised as evidenced by the development of new approaches to preoperative preparation for surgery and extended postoperative care. Transitional pain services and Acute Pain Service outpatient clinics are now being employed to specifically support patients to safely taper medications and identify those who may need early referral to chronic pain services (Huang 2016). Pleasingly, there is now an emerging evidence base addressing the effectiveness of such services from a range of perspectives (Gray 2017). At a time when health system budgets are under huge scrutiny as the costs of new drugs and technologies escalate at unsustainable rates, pain services and even individual pain management techniques are under more pressure than ever to demonstrate cost

benefit especially from reducing complications and facilitating early discharge from hospital (Schofield 2019).

Acute Pain Management: Scientific Evidence: 5th Edition is larger than ever yet comfortingly familiar. In this fifth edition, Professor Schug and the editorial team have compiled the latest high-quality offering of this internationally renowned publication from the Australian and New Zealand College of Anaesthetists and its Faculty of Pain Medicine. It brings together the most recent evidence in acute pain management from the last five years, properly evaluated and collated in the one resource. Its structure has evolved from the solid foundations established in the previous editions, commencing with the first edition published in 1999 by the National Health and Medical Research Council (NHMRC). The foresight of Professor Michael Cousins and the first multidisciplinary committee to develop this first text based on the NHMRC designation of levels of evidence was visionary. Professor Pamela Macintyre and the editorial teams of the subsequent editions in 2005 and 2010 meticulously built on this. In 2015 Professor Stefan Schug and the editorial team enhanced the fourth edition by adding quality scoring using the Jadad Score to the assessment of the evidence. This enabled conflicting evidence to be addressed and enhanced the production of the Key Messages. The fifth edition retains this now standard structure.

Once again, the medical community is indebted to Professor Schug and the editorial team for their diligence and dedication over the last two years. The production of the fifth edition has been an enormous task as the evidence base has more than doubled in some domains and grown even more in others with the addition of some new topic areas to assess. Most sections have more than doubled or trebled in size and, indeed, a second volume has been required for acute pain management in children to contain the growing evidence base in this domain that has tripled. The benefit of the five-yearly cycle of literature review over time is the consolidation of Key Messages with the strengthening of many and only a few being reversed. Many new Key Messages have also been added. Users of this text can feel confident that the information has been expertly assessed and can be relied on to inform their clinical practice which was exactly the original aim of the first edition.

In this edition of *Acute Pain Management: Scientific Evidence,* the chapters on predisposing factors, psychological contributors, hypnosis and alternative strategies to medications contain much new information, reflecting the increasing interest in a "whole-person" approach in addition to more traditional techniques. However, the latter remain of interest as shown by sections on new routes of administration, novel opioids and new uses for old drugs. Cannabis products are just the latest to be addressed. Contemporary cannabis research has been mostly focused on the chronic pain setting where the evidence to date suggests significant limitations in effectiveness and efficacy (Beaulieu 2016, Stockings 2018). However, newer research is addressing a range of acute pain settings with particular interest in the potential for opioid sparing and tapering (Khan 2019).

The use of ultrasound scanning to guide neuraxial and peripheral regional blockade, especially catheter techniques, has become the accepted norm and is being used to explore an increasing number of regional anaesthesia techniques (Anim-Somuah 2018, Smith 2020).

Optimal pain management for every person experiencing acute pain remains elusive; however, the evidence base continues to grow taking us step by step closer to the lofty goal of personalised pain management. The imperative to manage acute pain remains with the caveats that it must be safe and best be personalised. *Acute Pain Management: Scientific Evidence: 5th Edition* provides the latest evidence to support decision-making with that goal in mind for everyone experiencing acute pain.

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Introduction

This is the fifth edition of the book A*cute Pain Management: Scientific Evidence*. The first edition was written by a multidisciplinary committee headed by Professor Michael Cousins and published by the National Health and Medical Research Council (NHMRC) in 1999.

The second and third editions were written by multiple contributors and a working group chaired by Professor Pam Macintyre. The editions were approved by the NHMRC and published by the Australian and New Zealand College of Anaesthetists (ANZCA) and its Faculty of Pain Medicine (FPM) in 2005 and 2010. They were also endorsed by other major organisations worldwide.

As guidelines and key sources of information should be revised as further evidence accumulates (ideally every 5 years), a fourth edition was written by multiple contributors and an editorial working group chaired by Professor Stephan Schug and published by ANZCA and its FPM in 2015. In view of the NHMRC changing its criteria, this edition was not submitted for NHMRC approval, but it was widely endorsed by many significant national and international organisations - the International Association for the Study of Pain (IASP), the Royal College of Anaesthetists and its Faculty of Pain Medicine, the American Academy of Pain Medicine, the Australian Pain Society, Australasian College of Sport and Exercise Physicians, the Australasian Faculty of Rehabilitation Medicine, the College of Anaesthesiologists of the Academies of Medicine of Malaysia and Singapore, the College of Intensive Care Medicine of Australia and New Zealand, the European Society of Regional Anaesthesia and Pain Therapy (ESRA), the Faculty of Pain Medicine of the College of Anaesthetists of Ireland, the Hong Kong College of Anaesthesiologists, the Hong Kong Pain Society, the Malaysian Association for the Study of Pain, the New Zealand Pain Society, the Pain Association of Singapore, PainSA (South Africa), PROSPECT (Procedure Specific Postoperative Pain Management), the Royal Australasian College of Physicians, the Royal Australian and New Zealand College of Psychiatrists, the Royal Australasian College of Surgeons and the South African Society of Anaesthesiologists.

With 5 years' further growth in evidence, it was seen as timely to reassess the available evidence, aiming for a release of the new document in 2020. ANZCA and the FPM therefore again took responsibility for revising and updating this reference to its fifth edition. As for the fourth edition, endorsement is currently being sought from a number of key organisations.

An editorial working group was convened to coordinate and oversee the development process, to edit the reference and also contribute updates to some sections – members were Prof Stephan Schug, A/Prof Greta Palmer, Prof David Scott, Dr Mark Alcock, Dr Richard Halliwell, and Dr Jeff Mott. While all members of the working group contributed to the whole document, A/Prof Greta Palmer and Dr Mark Alcock provided specific input and expertise to the paediatric section. This section will remain as Chapter 10 in the PDF of the book, but In view of the largely increased amount of information in the paediatric section, it will be published as a separate volume II of the hardcopy of the book.

The working group was also assisted by an editorial advisory group comprising Dr Mark Rockett, nominated by the Faculty of Pain Medicine, Royal College of Anaesthetists in the United Kingdom, and Dr Clara Sze Ming Wong, nominated by the Hong Kong College of Anaesthesiologists.

A large panel of contributors was enlisted to draft sections of the document and a multidisciplinary consultative committee was chosen to review the draft of the document and contribute more broadly as required. To ensure general applicability and inclusiveness, there was a very wide range of experts on the contributor and multidisciplinary committees, including medical, nursing, allied health and complementary medicine professionals and consumers.

Acute Pain Management: Scientific Evidence: 5th Edition covers a wide range of clinical areas. The aim of the document is, as with the first four editions, to combine a review of the best available evidence for acute pain management with current clinical and expert practice, rather than to formulate specific clinical practice guidelines. Accordingly, the document aims to summarise the substantial amount of evidence currently available for the management of acute pain in a concise, accessible, and easily readable form to assist the practising health professional. New and updated content has been incorporated with that of the previous version of the book.

A detailed description of the methodology used to generate this document can be found in Appendix B. The following summarises the most important information on the methodology.

Review of the evidence

This document is a revision of the previous edition of *Acute Pain Management: Scientific Evidence* published in 2015. Therefore most of the new evidence included in this fifth edition has been published from August 2014 onwards, which was the cut-off date for literature inclusion in the fourth edition. Literature was considered when published between this date and the cut-off date for this fifth edition (August 2019). However, in rare circumstances, references published after this cut-off were considered but only if they were of high relevance and encountered in the editorial process. In addition, high-quality evidence-based guidelines have been published independently by a number of organisations in the areas of acute back and musculoskeletal pain and the chapters relevant to the management of these conditions refer to these guidelines.

Levels of evidence

Levels of evidence continue to be documented according to the NHMRC designation (NHMRC 1999 **GL**).

Levels of evidence	
I	Evidence obtained from a systematic review of all relevant randomised controlled trials (RCTs)
II	Evidence obtained from at least one properly designed randomised controlled trial
III-1	Evidence obtained from well-designed pseudo-randomised controlled trials (alternate allocation or some other method)
III-2	Evidence obtained from comparative studies with concurrent controls and allocation not randomised (cohort studies), case-controlled studies or interrupted time series with a control group
III-3	Evidence obtained from comparative studies with historical control, two or more single-arm studies, or interrupted time series without a parallel control group
IV	Evidence obtained from case series, either post test or pretest and post-test
Clinical practice points	
☑	Recommended best practice based on clinical experience and expert opinion

Quality scoring

As for the fourth edition, evidence was subjected to quality scoring and other types of references identified to enhance the value of the information provided.

Systematic reviews and meta-analyses

- Reviews performed by the Cochrane Collaboration are identified as [Cochrane] in the text eg (Derry 2013 **Level I** [Cochrane]);
- Reviews that overtly state that the review conformed with an evidence-based minimum set of items for reporting referred to as Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (Liberati 2009 **GL**) are identified as [PRISMA] eg (Moore 2014 **Level I** [PRISMA]);
- Reviews that overtly state that the review conformed with standards previously published as Quality of Reporting of Meta-analyses (QUOROM) (Moher 1999 **GL**), a precursor of PRISMA, are identified as [QUOROM] eg (Macedo 2006 **Level I** [QUOROM]);
- Non-Cochrane meta-analyses (of RCTs) that did not provide evidence of using PRISMA or QUOROM quality and reporting methods are only labelled Level I eg (Thorlund 2014 **Level I**);
- Systematic reviews that included studies other than RCTs are assigned the level of evidence of their lowest level component studies (as outlined in the NHMRC designation of evidence levels [NHMRC 1999 **GL**]) and identified by SR following the level of evidence eg (von Plato 2018 **Level IV SR** [PRISMA], 9 RCTs & 10 studies, n=949);
- Network meta-analyses are identified as [NMA] eg (Martinez 2017 **Level I** (NMA), 135 RCTs, n=13,287).

For all systematic reviews and meta-analyses, the number of RCTs for Level I and the number of studies for all other levels is reported as well as the number of subjects included in these, if reported or immediately obvious eg (Rabbie 2013 **Level I** [Cochrane], 9 RCTs, n=4,473); if this is not the case, the term unspecified is used eg (Hughes 2011 **Level IV SR**, 5 studies, n unspecified).

Randomised-controlled trials

The Jadad scoring instrument was used to score the quality of all RCTs (Level II) (Jadad 1996). The Jadad Score (JS) ranges from 0 (lowest quality) to 5 (highest quality) and is based on randomisation and blinding methods used and accurate accounting of study participants.

In addition to the Jadad score, the number of patients randomised (prior to dropouts) is reported for all Level II references eg (Chan 2010 **Level II**, n=4,484, JS 5).

Other evidence

No quality evaluation was undertaken for lower ranked evidence (Level III and Level IV), when this was the highest available level of evidence. However, the number of patients or events included is provided if reported in the publication and the size of the study relates to the quality of the evidence eg (Morton 2010 **Level IV**, n=5,065).

Identification of other types of references

Narrative reviews containing such evidence are identified by NR following the reference eg (Graham 2013 **NR**). Other study types have been included where relevant and identified by a research identifier following the reference. Thus, readers will find CR (for case report) eg (Madadi 2010 **CR**), GL for clinical practice guidelines eg (Kowalski 2011 **GL**), BS if presenting basic science or animal data eg (LaCrois-Fralish 2011 **BS**), PK if presenting pharmacokinetic study eg (Holford 2012 **PK**) and EH if presenting human experimental data eg (Saxena 2013 **EH**). The latter two were also assigned an evidence level in line with NHMRC hierarchy if applicable eg (Williams 2002 **Level II PK**, n=96, JS 4).

Conflicting evidence

If evidence was consistent, the most recent, highest hierarchy and highest quality references were used. If evidence was conflicting, the same approach was taken (identifying highest level, highest quality evidence); however, examples were given of differences within the literature so that readers could appreciate the ongoing debate. In some instances, particularly in acute pain management in various patient populations, evidence was limited to case reports only, which is made clear in the document as the best available evidence in this instance.

Key messages

Key messages for each topic are given ranked by the highest level of evidence available to support them, or with a tick box symbol indicating that they are based on clinical experience or expert opinion. Levels of evidence were documented according to the NHMRC designation and, as for the previous four editions of this document, clinical practice points have been added.

Key messages are presented in order of level of evidence from the highest to the lowest. Key messages referring to information extracted from Cochrane meta-analyses were marked "Level I [Cochrane Review]", and these were listed first, followed by those marked "Level I [PRISMA]", "Level I [QUOROM]" and "Level I". Level II evidence was included in key messages if supported by a single sufficiently large, or at least two smaller, high quality Level II studies as determined by the editors. Key messages based on lower levels of evidence than Level II are presented with those based upon systematic reviews listed before those based on studies at each level of evidence.

There is no standard approach to updating wording or strength of evidence of existing guideline recommendations (Vernooij 2014 **GL**). An indication of how the key messages in this fifth edition relate to those in the preceding fourth edition is provided. An adapted version of the system used by Johnston et al (Johnston 2003) to reflect the implications of new evidence on clinical recommendations was therefore used as previously. Where the new evidence led to reversal of a conclusion and key message, this was noted in the text.

Review and revision of key messages	
New	New evidence leads to new key message(s).
Unchanged	The new evidence is consistent with the data used to formulate the original key message. The key message in the original report remains unchanged.
Strengthened	The new evidence is consistent with the data used to formulate the original key message. The key message in the original report remains unchanged or expanded. The level of evidence and/or content of the key message in the original report has been strengthened to reflect this additional evidence.
Weakened	The new evidence is inconsistent with the data used to inform the original key message(s). However, the new evidence does not alter the key message but weakens the level of evidence.
Qualified	The new evidence is consistent with the data used to formulate the original key message. The key message in the original report remains unchanged but applicability may be limited to specific patient groups/ circumstances.
Reversed	The new evidence is inconsistent with the data used to inform the original key message(s). The strength of the new evidence alters the conclusions of the original document.

Note *Clinical and scientific judgement informed the choices made by the editorial working group members; there was no mandatory threshold of new evidence (eg number of studies, types of studies, magnitude of statistical findings) that had to be met before classification into categories occurred.*

The first letter of each of the words (New, Unchanged etc) was used to denote the changes (if any) from the last edition of this document.

Acknowledgements

The production of a document such as this requires a considerable amount of time over a long period and the generous input of many. All contributions were honorary and the time contributed freely by the members of the editorial working group and the many contributors need to be acknowledged in particular. The institutional support in terms of time and resources from many hospital departments, including Departments of Anaesthesia throughout Australia and New Zealand, is difficult to quantify but is gratefully acknowledged; these include Queensland Children's Hospital, Redcliffe Hospital, St Vincent's Hospital Melbourne and Westmead Hospital.

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Special thanks are also extended to the staff at ANZCA and the FPM, in particular Ms Liane Reynolds and Ms Frances Rowsell for their ongoing input to the process. The ANZCA library was an extremely effective and valuable resource once more, in particular for provision of difficult to access references.

Stephan Schug
On behalf of the Editorial Working Group of the Australian New Zealand College of Anaesthetists and its Faculty of Pain Medicine

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Summary of key messages

A description of the levels of evidence and associated symbols can be found in the Introduction (see pages vi to x).

1.0 | Physiology and psychology of acute pain

Applied physiology of acute pain

1. High pain-related fear avoidance beliefs in patients with back pain of less than 6 months duration are associated with poor outcomes, which may be improved by treatment approaches aimed at fear avoidance (**U**) (**Level I** [PRISMA]).
2. There is a significant association between high levels of catastrophising in acute and subacute back pain and pain and disability at later points of time (**U**) (**Level III-2 SR**).
3. Psychological factors associated with poor postoperative pain control are in particular anxiety (state and trait) and catastrophising, but also expectation of pain, depression, negative affect and neuroticism/psychological vulnerability (**S**) (**Level IV SR** [PRISMA]).
4. There is significant association between anxiety, pain catastrophising (**U**) (**Level III-2 SR**), depression, psychological vulnerability and stress (**U**) (**Level IV SR**) and the subsequent development of chronic postsurgical pain.
5. Preoperative anxiety and depression are associated with an increased number of PCA demands and dissatisfaction with PCA (**U**) (**Level IV**).

☑ Pain is an individual, multifactorial experience influenced by culture, previous pain events, beliefs, mood and ability to cope (**U**).

Placebo and nocebo effects in acute pain

1. Responses to placebo across all clinical conditions are small but consistently positive. They are more prominent, although highly variable in magnitude, in studies of pain (**U**) (**Level I** [Cochrane Review]).
2. Nocebo effects in studies of pain are of moderate to large size and of high variability (**U**) (**Level I** [PRISMA]).
3. Trials aimed at studying placebo effects demonstrate larger placebo effects than those assessing responses in placebo-control groups (**U**) (**Level I** [QUOROM]).
4. Analgesic placebo effects are based upon multiple neurobiological mechanisms, including involvement of endogenous opioid, cholecystokinin (**U**) (**Level II**), endogenous cannabinoid systems (**U**)(**Level III-1**) and genotype (**N**) (**Level III-2**).
5. Analgesic placebo effects are based upon multiple psychological determinants including expectancy, classical conditioning and social and observational learning (**S**) (**Level II**).
6. Placebo and nocebo effects have significant influence on the efficacy of analgesics (**U**) (**Level II**).

☑ Placebo effects are the consequence of the psychosocial context (or treatment ritual) on the patient's mind, brain and body (**U**).

☑ Placebo effects occur in routine clinical care even when no traditional placebo is given. The outcome of a treatment is attributable to both the treatment itself and the contextual (or placebo) component (**U**).

☑ Nocebo effects occur in routine clinical care and are seen as an increased pain response to a painful stimulus or the development of adverse effects not caused by, or separate from, the intervention (**U**).

☑ Ethical harnessing of placebo and minimisation of nocebo effects will improve response to clinical management interventions (**U**)

Progression of acute to chronic pain

1. Perioperative IV ketamine reduces the incidence of chronic postsurgical pain in selected procedures (**S**) (**Level I** [Cochrane Review]).
2. Following thoracotomy, epidural analgesia reduces the incidence of chronic postsurgical pain (**S**) (**Level I** [Cochrane Review]).
3. Following breast cancer surgery, paravertebral block (**S**), local infiltration (**N**) (**Level I** [Cochrane Review]) and IV lidocaine reduce the incidence of chronic postsurgical pain (**N**) (**Level I** [PRISMA]).
4. For iliac crest bone graft harvest, continuous local anaesthetic infiltration reduces the incidence of chronic postsurgical pain (**N**) (**Level I** [Cochrane Review])
5. Pregabalin reduces the incidence of chronic postsurgical neuropathic pain, but does not affect non-neuropathic chronic postsurgical pain (**N**) (**Level I** [PRISMA]).
6. Sparing of the intercostobrachial nerve during mastectomy does not decrease chest wall hypersensitivity (**U**) (**Level I** [PRISMA]).
7. Cryoanalgesia of the intercostal nerves at the time of thoracotomy results in no improvement in acute pain but an increase in chronic pain (**U**) (**Level I**).
8. There is significant association between anxiety, pain catastrophising (**U**) (**Level III-2 SR**), depression, psychological vulnerability and stress (**U**) (**Level IV SR**) and the subsequent development of chronic postsurgical pain.
9. Other risk factors that predispose to the development of chronic postsurgical pain include the severity of presurgical chronic pain and postsurgical acute pain and intraoperative nerve injury (**U**) (**Level IV SR**).
10. Spinal anaesthesia in comparison to general anaesthesia reduces the risk of chronic postsurgical pain after hysterectomy and Caesarean section (**U**) (**Level III-2**).
11. Chronic postsurgical pain is common and may lead to significant disability (**S**) (**Level IV**).
12. Chronic postsurgical pain often has a neuropathic component (**S**) (**Level IV**).

☑ Gabapentin has no demonstrated effect in preventing chronic postsurgical pain; considerable uncertainty exists regarding efficacy with contradictory meta-analyses of a few, usually small, studies with a large degree of heterogeneity (**Q**).

☑ Implementation of transitional pain services may help manage the complex issues of prolonged postoperative opioid use and chronic postsurgical pain (**N**).

Pre-emptive and preventive analgesia

Pre-emptive analgesia

1. The timing of opioid administration (preincision rather than postincision) may reduce further opioid consumption over 24 h, but has no effect on pain scores **(N)** (**Level I** [Cochrane Review])
2. Pre-emptive use of paracetamol across a range of procedures reduces pain scores up to 2 h, opioid consumption for up to 24 h and postoperative nausea and vomiting (**N**) (**Level I** [PRISMA]).
3. Pre-emptive epidural analgesia has a significant effect on postoperative pain relief (**S**) (**Level I**).

Preventive analgesia

4. Epidural, regional and systemic local anaesthetic administration shows preventive analgesic effects in reducing chronic postsurgical pain (**S**) (**Level I** [Cochrane Review])
5. NMDA-receptor antagonists (ketamine) reduce the incidence of chronic postsurgical pain in selected procedures (**S**) (**Level I** [Cochrane Review]).

☑ In clinical trials assessing acute postoperative pain for many systemic medicines, the range of doses administered, the variable durations of follow-up and variable half-lives following infusion or repeated dosing means that "early" preventive effects, although possible, are difficult to discern from persistence of direct pharmacological effects (**U**).

Adverse physiological effects of acute pain

1. Recognition of the importance of postoperative rehabilitation including pharmacological, physical, psychological and nutritional components has led to enhanced recovery (**U**) (**Level I** [PRISMA]).

☑ Acute pain and injury of various types are inevitably interrelated and, if severe and prolonged, the injury response becomes counterproductive and can have adverse effects on outcome (**U**).

Adverse psychological effects of acute pain

1. Postoperative delirium is exacerbated by unrelieved acute pain and by overuse of sedating analgesics, in particular opioids (**N**) (**Level IV**).

☑ Failure to relieve acute pain can lead to psychological distress (**N**).

Genetics and acute pain

1. CYP2D6 polymorphisms affect plasma concentrations of active metabolites of codeine, oxycodone and tramadol with variable effects on analgesic efficacy (**U**) (**Level II**).
2. The mu opioid receptor OPRM1 polymorphism is unlikely to be clinically relevant as a single gene mutation in Caucasian populations and is more likely to be of clinical relevance in Asian populations (**U**) (**Level III-2 SR**).
3. CYP2D6 ultrarapid metabolisers are at increased risk of codeine and tramadol toxicity (**U**) (**Level IV**).

☑ Genetic polymorphisms contribute to the wide interindividual variability in plasma concentrations of a given dose of methadone (**U**).

2.0 | Assessment and measurement of pain and pain treatment

Assessment

1. There is good correlation between the visual analogue and verbal numerical rating scales (**S**) (**Level I**).
2. Regular assessment of pain leads to improved acute pain management (**U**) (**Level III-3**).
3. Appropriate assessments (including screening tools) are required to determine the presence of neuropathic pain (**N**) (**Level III-2**).

☑ Functional outcomes rather than pain scores alone should be used to guide acute pain management, including non-pharmacological approaches (**N**).

☑ Self-reporting of pain should be used whenever appropriate as pain is by definition a subjective experience (**U**).

☑ The pain measurement tool chosen should be appropriate to the individual patient and the clinical context (eg intensive care, ward, community). Developmental, cognitive, emotional, language and cultural factors should be considered (**U**).

☑ Scoring should incorporate different components of pain including the functional capacity of the patient. In the postoperative patient, this should include static (rest) and dynamic (eg pain on sitting, coughing) pain (**U**).

☑ Uncontrolled or unexpected pain requires a reassessment of the diagnosis and consideration of alternative causes for the pain (eg new surgical/ medical diagnosis, neuropathic pain) (**U**).

Outcome measures in acute pain management

1. Assessment of pain relief (with total pain relief [TOTPAR]) may be more sensitive to treatment effects than assessment of intensity (with summed pain intensity difference [SPID]) (**N**) (**Level I** [PRISMA]).

☑ Multiple outcome measures are required to adequately capture the complexity of the pain experience and how it may be modified by pain management interventions (**U**).

3.0 | Provision of safe and effective acute pain management

Education

1. There is no good evidence in favour of general education for acute neck pain having significant effects on any relevant outcomes (**U**) (**Level I** [Cochrane Review]).
2. Short educational interventions in acute whiplash injury reduce pain and disability and enhance recovery and mobility (**U**) (**Level I** [PRISMA])
3. There is limited evidence that preoperative education may lead to small improvements in postoperative outcomes such as pain, preoperative and postoperative anxiety, but not in analgesic requirements (**Q**) (**Level I** [PRISMA]).

4. General “biomedical” education in patients with acute back pain does not reduce pain or improve other outcomes (**S**) (**Level I**); however, education using a “biopsychosocial/ neuroscience” approach reduces a composite of anxiety, fear, worry, distress and healthcare utilisation (**N**) (**Level I** [PRISMA]).
5. Targeted reassurance in acute back pain by physicians in primary care can result in improved changes in psychological factors such as fear, worry, anxiety, catastrophisation and healthcare utilisation (**U**) (**Level I** [PRISMA].
6. Preoperative education improves patient or carer knowledge of pain and encourages a more positive attitude towards pain relief (**U**) (**Level II**).
7. Specific pain neuroscience education in specific surgical settings may result in less healthcare utilisation (**U**) (**Level II**).
8. Written information given to patients is better than verbal information given at the time of the interview (**S**) (**Level II**).
9. Educational interventions in cancer pain patients improve knowledge, attitudes and pain control (**U**) (**Level III-1 SR**).
10. While evidence for the benefit of patient education in terms of better pain relief is inconsistent, structured preoperative education may be better than routine information (**U**) (**Level III-2**).
11. Staff education and the use of guidelines improve pain assessment, pain relief and prescribing practices (**S**) (**Level III-3**).
12. Pain psychoeducation undertaken before surgery (pre-emptive) or throughout the perioperative period (preventive) is an underutilised component of multimodal analgesia which may reduce pain intensity, analgesic use, length of stay, return to the emergency department, patient anxiety and possibly chronic postsurgical pain (**N**) (**Level IV SR**).
13. Pain score documentation improves with various forms of nursing education, but the impact of this behaviour change has not been adequately assessed (**N**) (**Level IV SR**).
14. Pain medicine education in medical school curricula is restricted in scope and content (**N**) (**Level IV SR**).

☑ Successful management of acute pain requires close liaison between all personnel involved in the care of the patient (**U**).

☑ More effective acute pain management will result from appropriate education and organisational structures for the delivery of pain relief rather than the analgesic techniques themselves (**U**).

Organisational requirements

1. Implementation of an acute pain service may improve pain relief and reduce the incidence of adverse effects (**U**) (**Level III-3**).
2. Even “simple” techniques of pain relief can be more effective if attention is given to education, documentation, patient assessment and provision of appropriate guidelines and policies (**U**) (**Level III-3**).

3. Implementation of root-cause analysis to follow up critical incidents improved the safety of patients under care of an acute pain service (**U**) (**Level III-3**).

☑ Successful management of acute pain requires close liaison between all personnel involved in the care of the patient (**U**).

☑ More effective acute pain management will result from appropriate education and organisational structures for the delivery of pain relief rather than the analgesic techniques themselves (**U**).

☑ Appropriate institutional support and engagement is important for the effective implementation of an acute pain service (**U**).

☑ Procedure-specific analgesic protocols can help optimise analgesia for the individual patient while reducing adverse effects (**U**).

☑ The adoption of individualised care pathways (eg SCAMPS) can improve patient outcomes and reduce clinical variation (**N**).

☑ The benefit of an acute pain service can be enhanced when acute pain management is integrated into the pre, intra and postoperative periods (**N**).

☑ The recruitment of patients 'at-risk' for persistent pain and/or excessive opioid use into a post-discharge treatment service for early review can improve outcomes (**N**).

☑ Appropriately designed, implemented and integrated Electronic Medical Records (EMR) can improve the standards of clinical care (**N**).

Economic considerations in acute pain management

1. Long term economic consequences from the progression of acute to chronic postsurgical and post-traumatic pain can be significant (**S**) (**Level IV**).
2. Strategies to optimise acute and subacute pain management (including involvement of transitional pain services) may reduce the economic burden of chronic pain and inappropriate prescription opioid use (**N**) (**Level IV**).
3. The early pattern of prescription opioid use after surgery may increase the risk of chronic use with significant direct and indirect economic costs (**N**) (**Level IV**).
4. Patients' willingness to pay for good pain relief is high (**S**) (**Level IV**).
5. Costs from PCA errors can be considerable; the most common high cost errors arise from staff communication error and operator error (**S**) (**Level IV**).

☑ There are different measures of economic assessment and analysis used in healthcare; no one method is the most appropriate (**U**).

☑ Prescription drug monitoring may reduce the economic burden through its impact on inappropriate opioid prescribing (**N**).

4.0 | Analgesic medicines

Paracetamol

1. Paracetamol is an effective analgesic for acute pain; the incidence of adverse effects is comparable to placebo (**U**) (**Level I** [Cochrane Review]).
2. Paracetamol given in addition to PCA opioids reduces opioid consumption but does not result in a decrease in opioid-related adverse effects (**U**) (**Level I**).
3. Hepatotoxicity with therapeutic doses of paracetamol is extremely rare (**U**) (**Level IV**) and not associated with alcohol consumption (**U**) (**Level I** [PRISMA]).

☑ Emerging evidence suggests that maternal paracetamol use may influence premature closure of the fetal ductus arteriosus **(N).**

Nonselective NSAIDs and coxibs

Efficacy of systemic NSAIDs

1. Nonselective NSAIDs are effective in the treatment of acute postoperative pain, renal colic, migraine, primary dysmenorrhoea (**S**) (**Level I** [Cochrane Review]), acute muscle injury (**N**) (**Level I** [PRISMA]), chronic low-back pain (**U**) (**Level I** [PRISMA]) and acute ankle sprain (**U**) (**Level I**).
2. Coxibs are as effective as nonselective NSAIDs in the treatment of acute pain (including postoperative pain) (**S**) (**Level I** [Cochrane Review]), chronic low-back pain (**U**) (**Level I** [PRISMA]) and osteoarthritis of the knee (**N**) (**Level I** [PRISMA]).
3. Nonselective NSAIDs given in addition to paracetamol improve analgesia compared with either medicine given alone (**S**) (**Level I**), in particular ibuprofen combined with paracetamol (**U**) (**Level I** [Cochrane Review]).
4. The risk-benefit ratio for coxibs as a discharge medication after orthopaedic surgery is superior to that for nonselective NSAIDs (**U**) (**Level I** [PRISMA]).
5. Nonselective NSAIDs given in addition to PCA opioids reduce opioid consumption and the incidence of nausea and vomiting (**U**) (**Level I**).
6. Coxibs given in addition to PCA opioids reduce opioid consumption but do not result in a decrease in opioid-related adverse effects (**U**) (**Level I**), except after total knee arthroplasty, where they reduce pain scores and adverse effects and improve outcomes (**U**) (**Level I**).
7. Celecoxib given as a single pre-operative dose is effective at reducing opioid usage, pain scores at 24 hours and postoperative nausea and vomiting (**N**) (**Level I**).

Adverse effects of systemic NSAIDs

8. In patients with normal preoperative renal function nonselective NSAIDs slightly increase serum creatinine, but effects on acute kidney injury and need for renal replacement therapy are uncertain due to lack of evidence (**W**) (**Level I** [Cochrane Review]).
9. Nonselective NSAIDs may increase the risk of any bleeding-related outcome after tonsillectomy in adults (**U**) (**Level I**); however, not in paediatric patients (**U**) (**Level I** [Cochrane Review]) except in a large non-inferiority RCT where need for surgical intervention was increased with ibuprofen versus paracetamol (**Q**) (**Level II**). There is an increase in bleeding complications with aspirin in adults and children (**U**) (**Level I**) and with ketorolac in adults only (**U**) (**Level III-2** [PRISMA]).

10. Nonselective NSAIDS, but not coxibs, may cause bronchospasm in individuals known to have NSAID-exacerbated respiratory disease (**U**) (**Level I** [PRISMA]).
11. Coxibs and nonselective NSAIDs exert individual (non-class) adverse effects on the cardiovascular system with rofecoxib appearing to be worse than other coxibs and nonselective NSAIDs (**N**) (**Level I**). Celecoxib is no worse than naproxen or ibuprofen (**N**) (**Level II**) and better than ibuprofen when combined with aspirin (**N**) (**Level II**).
12. Short-term use of parecoxib (**S**) (**Level I**) and other NSAIDs (**U**) (**Level III-2**) compared with placebo does not increase the risk of cardiovascular adverse effects after noncardiac surgery.
13. Use of parecoxib followed by valdecoxib after coronary artery bypass graft surgery increases the incidence of cardiovascular and cerebrovascular effects and is therefore contraindicated (**U**) (**Level I**).
14. Perioperative nonselective NSAIDs may increase the risk of minor and major bleeding after surgery compared with placebo (**W**) (**Level I**).
15. Coxibs do not impair platelet function and are not associated with increased perioperative blood loss (**S**) (**Level I**).
16. In patients with normal renal function, parecoxib perioperatively does not increase renal failure (**N**) (**Level I**).
17. NSAIDs hasten bowel recovery after colorectal surgery (**N**) (**Level I**).
18. With regard to renal function, celecoxib and naproxen are safer than ibuprofen with long-term use (**N**) (**Level II**).
19. Short-term use (5–7 days) of coxibs results in gastric ulceration rates similar to placebo and lower than nonselective NSAIDs (**U**) (**Level II**).
20. The cardiovascular protective effects of low-dose aspirin are reduced by concomitant administration of some NSAIDs, in particular ibuprofen (**S**) (**Level II**).
21. Nonselective NSAIDs, but not coxibs increase the risk of anastomotic leak after colorectal surgery (**N**) (**Level III-2**).
22. Short term use of ketorolac or ibuprofen do not increase bone healing complications in children undergoing posterior spinal fusion, osteotomy, or fractures managed surgically (**S**) (**Level III-3**) or conservatively (**N**) (**Level III-3**).
23. Chronic administration of nsNSAIDs or coxibs is associated with an increased risk of renal impairment (**N**) (**Level III-3 SR**).

☑ The risk of adverse renal effects of nonselective NSAIDs and coxibs may be increased in the presence of factors such as pre-existing renal impairment, hypovolaemia, hypotension and use of other nephrotoxic agents including angiotensin-converting enzyme inhibitors (**W**).

Nonsystemic administration of NSAIDs

1. Topical NSAIDs are effective in treating acute strains, sprains or sports injuries with systemic adverse effects comparable to placebo; gel formulations show superior efficacy over creams (**S**) (**Level I** [Cochrane Review]).

2. Topical NSAIDs are of limited analgesic efficacy for traumatic corneal abrasions, but reduce rescue analgesia requirements (**W**) (**Level I** [Cochrane Review]).
3. Topical NSAIDs reduce anterior chamber inflammation and thereby pain after cataract surgery (**N**) (**Level I** [PRISMA])**.**
4. The efficacy of NSAIDs for peri- or intra-articular injection as a component of local infiltration analgesia compared with systemic administration remains unclear (**U**) (**Level I** [PRISMA]).
5. Intra-articular nonselective NSAIDs may provide more effective analgesia following arthroscopy than intravenous administration (**U**) (**Level I**).
6. Mucosal administration of flurbiprofen provides long-lasting pain relief for sore throat (**N**) (**Level II**).

Opioids

Systemic opioids

1. Dextropropoxyphene has low analgesic efficacy (**U**) (**Level I** [Cochrane Review]).
2. Tramadol is an effective treatment for neuropathic pain (**S**) (**Level I** [Cochrane Review]).
3. Droperidol, metoclopramide, ondansetron, tropisetron, dolasetron, dexamethasone, cyclizine, granisetron (**U**) (**Level I** [Cochrane Review]), supplemental crystalloid infusions (**N**) (**Level I** [Cochrane Review]), palonosetron and mirtazapine (**N**) (**Level I** [PRISMA]) are effective in the prevention of postoperative nausea and vomiting.
4. PC6 acupoint stimulation by multiple techniques reduces postoperative nausea and vomiting (**S**) (**Level I** [Cochrane Review]).
5. Neurokinin-1 receptor antagonists aprepitant (**S**) (**Level I** [PRISMA]) and fosaprepitant (**U**) (**Level II**) are effective in the prevention of postoperative nausea and vomiting.
6. Intraoperative administration of the long acting opioid methadone reduces consumption of shorter acting opioids in the 24 hours after surgery (**N**) (**Level I** [PRISMA]). Safety data suggest an increased risk of opioid induced ventilatory impairment due to the long and unpredictable half-life of methadone (**N**) (**Level IV**).
7. Opioids in high doses, in particular remifentanil, can induce hyperalgesia and/or acute tolerance (**S**) (**Level I** [PRISMA]).
8. Propofol (**U**) (**Level I** [PRISMA]), NMDA-receptor antagonists (**U**) (**Level I** [QUOROM]), pregabalin (**U**) (**Level II**), nitrous oxide (**N**) (**Level II**) and gradual tapering of remifentanil dose (**N**) (**Level II**) attenuate acute tolerance and/or hyperalgesia induced by remifentanil.
9. NSAIDs, gabapentin, pregabalin, systemic lidocaine and ketamine are opioid-sparing medications and reduce opioid-related adverse effects (**S**) (**Level I** [PRISMA]).
10. Paracetamol given preoperatively and intraoperatively reduces postoperative nausea and vomiting; this effect is associated with improved analgesia, not reduced opioid requirements (**S**) (**Level I** [PRISMA]).
11. Opioid antagonists (methylnaltrexone, naloxone, naloxegol, alvimopan, axelopran, or naldemedine) are effective (more so than laxatives) and safe to treat opioid-induced constipation (**S**) (**Level I** [PRISMA]).

12. Alvimopan is an effective treatment for postoperative ileus (**U**) (**Level I** [QUOROM]).
13. Haloperidol, perphenazine and transdermal scopolamine are effective in the prevention of postoperative nausea and vomiting (**U**) (**Level I**).
14. The incidence of clinically meaningful adverse effects (nausea, vomiting) of opioids is dose-related (**U**) (**Level I**).
15. Paired combinations of $5HT_3$ antagonists, droperidol or dexamethasone provide superior prophylaxis of postoperative nausea and vomiting than either compound alone (**U**) (**Level I**).
16. Naloxone, naltrexone, droperidol (**U**), nalbuphine (**S**) (**Level I**) and ondansetron (**N**) (**Level I** [PRISMA]) are effective treatments for opioid-induced pruritus.
17. Opioids administered by PCA, in particular morphine, show higher analgesic efficacy in females than in males (**U**) (**Level I**).
18. Tapentadol has similar efficacy to conventional opioids with a reduced rate of gastrointestinal adverse effects (nausea, vomiting, constipation) (**S**) (**Level I**).
19. Tramadol has a lower risk of respiratory depression and impairs gastrointestinal motor function less than other opioids at equianalgesic doses (**U**) (**Level II**).
20. Pethidine is not superior to morphine or hydromorphone in treatment of pain of renal colic (**U**) (**Level II**).
21. Morphine-6-glucuronide is an effective analgesic (**U**) (**Level II**).
22. In the management of acute pain, one opioid is not superior to others but some opioids are better in some patients (**U**) (**Level II**).
23. High doses of methadone can lead to prolonged QT interval (**U**) (**Level II**).
24. Opioid antagonists are effective treatments for opioid-induced urinary retention (**U**) (**Level III-1**).
25. Pethidine use is associated with an increased risk of delirium in the postoperative period compared to other opioids (**S**) (**Level III-2 SR**).
26. In clinically relevant doses, there is a ceiling effect for respiratory depression with buprenorphine but not for analgesia (**U**) (**Level III-2**).
27. Tapentadol has lower rates of abuse and doctor shopping than oxycodone (**S**) (**Level III-2**).
28. Opioid-related adverse effects in the postoperative period are associated with increased inpatient mortality, length of hospital stay, costs and rates of readmission (**S**) (**Level III-2**).
29. Assessment of sedation is a more reliable way of detecting early opioid-induced ventilatory impairment than a decreased respiratory rate (**S**) (**Level III-3**).
30. The evidence for significant QT prolongation and risk of cardiac arrhythmias following low-dose droperidol, haloperidol and dolasetron is weak (**U**) (**Level III-3**).
31. Opioid-induced ventilatory impairment occurs in particular in the first 24 h after surgery and important risk factors are cardiac and pulmonary disease, obstructive sleep apnoea and use of higher opioid doses (**N**) (**Level IV SR** [PRISMA]).

32. Continuous pulse oximetry in patients receiving opioids postoperatively increases detection rate of desaturation, but continuous capnography is superior in identifying episodes of opioid-induced ventilatory impairment (**N**) (**Level IV SR** [PRISMA]).

33. In adults, patient age rather than weight is a better predictor of opioid requirements, although there is a large interpatient variation (**U**) (**Level IV**).

34. Impaired renal function and the oral route of administration result in higher levels of the morphine metabolite morphine-6-glucuronide with increased risk of sedation and respiratory depression (**U**) (**Level IV**).

34. CYP2D6 ultrarapid metabolisers are at increased risk of codeine toxicity (**N**) (**Level IV**).

☑ Opioid-induced ventilatory impairment is a more appropriate term to describe the effects of opioids on ventilation as it encompasses the central respiratory depression caused by opioids and also the depressed consciousness and the subsequent upper airway obstruction resulting from excessive opioid use (**U**).

☑ The use of pethidine and dextropropoxyphene should be discouraged in favour of other opioids (**S**).

☑ Drug interactions relevant for opioids include pharmacodynamic considerations (eg coadministration of sedative agents) and pharmacokinetic effects (eg CYP 450 enzyme inducers or inhibitors [antidepressants for CYP2D6 and antifungals, antibiotics for CYP3A4 and complementary medicines for both]) (**N**).

Neuraxial opioids

Intrathecal opioids

1. Intrathecal morphine and intrathecal fentanyl prolong spinal local anaesthetic block, with fentanyl being associated with fewer adverse effects (**U**) (**Level I** [PRISMA]).

2. Intrathecal morphine produces better postoperative analgesia than intrathecal fentanyl or sufentanil after Caesarean section (**U**) (**Level I**).

3. Intrathecal morphine doses of 300 mcg or more increase the risk of respiratory depression (**U**) (**Level I**).

Epidural opioids

4. Epidural morphine provides similar analgesia to epidural fentanyl when combined with local anaesthetic, although the incidence of nausea is greater with morphine (**U**) (**Level I** [PRISMA]).

5. Extended-release epidural morphine provides analgesia for up to 48 hours (**U**) (**Level II**), however it is associated with more respiratory depression than intravenous PCA following abdominal surgery (**U**) (**Level I**).

6. Epidural pethidine produces better pain relief and less sedation than intravenous pethidine after Caesarean section (**U**) (**Level II**).

☑ No neurotoxicity has been shown at normal clinical intrathecal doses of morphine, fentanyl and sufentanil (**U**).

☑ Neuraxial administration of bolus doses of hydrophilic opioids carries an increased risk of delayed sedation and respiratory depression compared with lipophilic opioids (**U**).

Peripheral opioids

1. Intra-articular morphine (1 mg) following knee arthroscopy does not improve analgesia compared with placebo (**S**) (**Level I** [Cochrane Review]).
2. Intra-articular morphine/bupivacaine following knee arthroscopy compared to bupivacaine alone improves analgesia without increasing adverse effects (**N**) (**Level I** [PRISMA]).
3. Perineural buprenorphine/local anaesthetic for peripheral nerve blocks compared to local anaesthetic and to systemic buprenorphine/local anaesthetic prolongs duration of analgesia (**N**) (**Level I** [PRISMA]).
4. Perineural tramadol/local anaesthetic for brachial plexus block compared to local anaesthetic alone prolongs duration of analgesia (**N**) (**Level I** [PRISMA]).
5. Peripherally applied opioids (excluding intra-articular, perineural and mucosal administration) show no clinically relevant analgesic effect (**N**) (**Level I** [PRISMA]).
6. Intra-articular tramadol/bupivacaine following knee arthroscopy compared to bupivacaine alone improves analgesia without increasing adverse effects (**N**) (**Level I**).
7. Morphine mouthwash may have analgesic effects in chemotherapy-induced mucositis (**N**) (**Level II**).
8. Evidence for intra-articular analgesic administration is inconclusive for temporomandibular joint arthrocentesis (**N**) (**Level IV SR** [PRISMA]).

Local anaesthetics and other membrane stabilisers

Systemic local anaesthetics and membrane stabilisers

1. Perioperative intravenous lidocaine reduces pain and opioid requirements to a limited extent following a range of surgery types, as well as nausea, but not vomiting, incidence and duration of ileus and length of hospital stay (**W**) (**Level I** [Cochrane Review]).
2. In breast surgery, perioperative lidocaine infusion does not improve pain scores for up to 72 hours, but is associated with lower acute opioid requirements and less chronic postsurgical pain at 3 to 6 months (**N**) (**Level I** [PRISMA])
3. Perioperative intravenous lidocaine has a preventive analgesic effect (extending beyond 5.5 half-lives of lidocaine, ie > 8 hrs after cessation of administration) after a wide range of operations (**U**) (**Level I**).
4. Both intravenous lidocaine and mexiletine are effective in the treatment of chronic neuropathic pain (**U**) (**Level I** [Cochrane Review]); however, guidelines advise against the use of mexiletine for this indication (**N**) (**GL Level I** [PRISMA]).
5. Perioperative IV lidocaine reduces chronic postsurgical pain at 3 months compared to placebo (**N**) (**Level I** [PRISMA]).

☑ The optimal and safe dose and duration of perioperative intravenous lidocaine infusions has yet to be clearly established (**N**).

☑ Based on the experience in chronic neuropathic pain states, it would seem reasonable to use membrane stabilisers including systemic lidocaine in the management of acute neuropathic pain (**U**).

☑ The role and safety of IV lidocaine for analgesia in the emergency department still requires clarification (**N**).

Regional local anaesthetics

1. Lidocaine intrathecal is more likely to cause transient neurologic symptoms than bupivacaine, prilocaine and procaine (**S**) (**Level I** [Cochrane Review NMA]).
2. Local anaesthetics have chondrotoxic effects on articular cartilage, with ropivacaine the least toxic (**N**) (**Level I** [PRISMA]).
3. Wound infiltration with liposomal preparations of bupivacaine is no more effective than ropivacaine or plain bupivacaine for analgesic outcomes up to 48 hours (**N**) (**Level I** [PRISMA]).
4. The quality of epidural analgesia with local anaesthetics is improved with the addition of opioids (**U**) (**Level I**).
5. Ultrasound guidance reduces the risk of vascular puncture during the performance of regional blocks (**S**) (**Level I**).
6. Local anaesthetic systemic toxicity is reduced by the use of ultrasound guidance for regional anaesthesia (**S**) (**Level I**).
7. Continuous perineural infusions of lidocaine result in less effective analgesia and more motor block than long-acting local anaesthetic agents (**U**) (**Level II**).
8. There are no consistent differences between ropivacaine, levobupivacaine and bupivacaine in terms of quality of analgesia or motor block, when given in low doses for regional analgesia (epidural and peripheral nerve block) (**U**) (**Level II**).
9. Cardiovascular and central nervous system toxicity of the stereospecific isomers ropivacaine and levobupivacaine is less severe than with racemic bupivacaine (**U**) (**Level II**).
10. Local anaesthetic systemic toxicity is increased in paravertebral and upper limb blocks, with the use of lidocaine and higher doses of local anaesthetics (**U**) (**Level IV**).
11. Lipid emulsion is effective in resuscitation of circulatory collapse due to local anaesthetic toxicity (**S**) (**Level IV SR**); however, uncertainties relating to dosage, efficacy and adverse effects still remain; therefore, it is appropriate to administer lipid emulsion only once ventilatory support has begun and convulsions are controlled (**S**) (**Level IV**).

☑ Case reports following accidental overdose with ropivacaine, levobupivacaine and bupivacaine suggest that resuscitation is less likely to be successful with bupivacaine (**U**).

Inhalational agents

1. Nitrous oxide has some analgesic efficacy in labour pain (**U**), increases maternal adverse effects (nausea, vomiting, dizziness) (**U**), with no adverse effects on the newborn (**U**) (**Level I** [Cochrane Review]) and increases maternal satisfaction compared to pethidine and epidural analgesia (**U**) (**Level IV SR**).
2. Nitrous oxide has equivalent effectiveness and more rapid recovery compared with intravenous sedation in patients having lower gastrointestinal endoscopy (**U**) (**Level I**).

3. Methoxyflurane, in low doses, is an effective analgesic with rapid onset in the prehospital setting, and a range of procedures in the hospital setting (**U**) (**Level II**) with good safety data (**S**) (**Level IV**); it may have comparable efficacy to nitrous oxide (**N**) (**Level I** [NMA]), but is inferior to IV morphine and IN fentanyl (**N**) (**Level III-2 SR**).
4. Nitrous oxide is an effective analgesic agent in a variety of other acute pain situations (**U**) (**Level II**).
5. Intraoperative use of nitrous oxide reduces the incidence of chronic postsurgical pain in Asian populations (**N**) (**Level II**).
6. Subacute combined degeneration of the spinal cord, myelopathy and generalised demyelinating polyneuropathy are rare but potentially serious complications of nitrous oxide use including in those abusing nitrous oxide (**S**) (**Level IV SR**).
7. Vitamin B_{12} deficiency (identified by vitamin B_{12} level $\leq$74 pmol/L and MCV >100 fL) and age $\geq$40 years are relevant risk factors in nitrous oxide neurotoxicity; total nitrous oxide exposure may not be a risk factor (**N**) (**Level IV SR**).
8. Early supplementation with Vitamin B_{12} in subacute combined degeneration of the spinal cord exacerbated by nitrous oxide use improves neurological recovery (**N**) (**Level IV SR**).

☑ In patients receiving nitrous oxide repeatedly, supplementation with vitamin B_{12}, methionine and folic or folinic acid is a consideration, in particular in those with risk factors (**Q**).

☑ If nitrous oxide is used with other sedative or analgesic agents, appropriate clinical monitoring should be used (**U**).

NMDA-receptor antagonists

Systemic NMDA-receptor antagonists

1. Perioperative IV ketamine reduces opioid consumption, pain intensity and postoperative nausea and vomiting compared to placebo (**S**) (**Level I** [Cochrane Review]); similar outcomes are achieved when ketamine is added to an opioid in a PCA pump (**S**) (**Level I** [PRISMA]).
2. Perioperative IV ketamine reduces the incidence of chronic postsurgical pain in selected procedures (**S**) (**Level I** [Cochrane Review]).
3. NMDA-receptor antagonists reduce the development of acute tolerance/opioid-induced hyperalgesia associated with remifentanil use (**S**) (**Level I** [PRISMA]).
4. IV ketamine reduces ischaemic pain intensity in critical limb ischaemia (**N**) (**Level I** [PRISMA]).
5. IV magnesium as an adjunct to morphine analgesia has an opioid-sparing effect and improves pain scores (**S**) (**Level I** [PRISMA]).
6. IV magnesium is effective in treatment of acute migraine attacks (**N**) (**Level I** [PRISMA]).
7. IV ketamine is effective in the treatment of neuropathic pain following spinal cord injury (**U**) (**Level I**).
8. Morphine/ketamine compared with higher doses of morphine alone improves analgesia and reduces sedation and postoperative nausea and vomiting in postoperative patients (**U**) (**Level I**).

9. IV ketamine does not increase intracranial pressure or reduce cranial perfusion pressure compared to opioids (**U**) (**Level I**).
10. Perioperative dextromethorphan reduces opioid consumption and pain intensity compared to placebo (**N**) (**Level I**)
11. Ketamine is a safe and effective analgesic in the prehospital setting (**U**) (**Level II**).
12. Ketamine reduces postoperative pain and opioid requirements in opioid-tolerant patients (**S**) (**Level II**).
13. IV magnesium extends the duration of sensory block with spinal anaesthesia and reduces subsequent postoperative pain (**N**) (**Level II**).

☑ Increasing rates of ketamine abuse are reported, in particular from South-East Asia and China (**S**).

☑ Ketamine toxicity leads to cognitive impairment and abuse to chronic organ toxicity (bladder, liver) (**U**).

Regional NMDA-receptor antagonists

1. Neuraxial magnesium reduces pain intensity and analgesic requirements after Caesarean section (**N**) (**Level I** [PRISMA].
2. Oral topical magnesium or ketamine (as gargle or lozenge) reduce the incidence of postoperative sore throat (**N**) (**Level I** [PRISMA].
3. Intra-articular magnesium improves analgesia after arthroscopic surgery compared to placebo (**N**) (**Level I** [PRISMA].
4. Magnesium added to local anaesthetics in peripheral nerve blocks prolongs sensory block and analgesic effects (**N**) (**Level I** [PRISMA].
5. Epidural ketamine (without preservative) added to opioid-based epidural analgesia regimens improves pain relief without reducing adverse effects (**U**) (**Level I**).
6. Caudal ketamine in children, in combination with local anaesthetic or as the sole medication, improved and prolonged analgesia with few adverse effects (**U**) (**Level I**).

☑ Variable results for regional and topical administration of ketamine and magnesium may reflect systemic effects (**N**).

Antidepressant medicines

1. In chronic neuropathic pain and fibromyalgia, tricyclic antidepressants and serotonin–noradrenaline-reuptake inhibitor are effective analgesics (**W**) and more effective than selective serotonin-reuptake inhibitors (**U**) (**Level I** [Cochrane Review]).
2. Tricyclic antidepressants are effective in the treatment of chronic headaches (**U**) (**Level I** [PRISMA]).
3. Duloxetine is as effective as other first-line treatments for pain and disability of osteoarthritis (**U**) (**Level I**).
4. Some antidepressants, in particular duloxetine, may be effective in the treatment of chronic low-back pain (**U**) (**Level I**).

5. Perioperative serotonin-noradrenaline reuptake inhibitors reduce acute pain and opioid requirements in a limited number of studies (**U**) (**Level II**).

☑ Based on the experience in chronic neuropathic pain states, it would seem reasonable to use tricyclic antidepressants and serotonin–noradrenaline-reuptake inhibitors in the management of acute neuropathic pain (**U**).

☑ To minimise adverse effects, it is advisable to initiate treatment with tricyclic antidepressants at low doses (**U**).

Anticonvulsant medicines

1. Alpha-2-delta ligands (gabapentinoids) are the only anticonvulsants with proven efficacy in the treatment of chronic neuropathic pain (**S**) (**Level I** [Cochrane Review]).
2. Pregabalin is the only anticonvulsant with proven but limited efficacy in chronic pain due to fibromyalgia (**S**) (**Level I** [Cochrane Review]).
3. Perioperative alpha-2-delta ligands (gabapentinoids) reduce postoperative pain and opioid requirements, in particular after more painful surgery (**Q**) and reduce the incidence of postoperative nausea and vomiting (**S**) as well as pruritus (**S**), but increase the risk of sedation (**S**) and visual disturbances (**N**) (**Level I** [PRISMA]).
4. Overdose toxicity of alpha-2-delta ligands is increased when taken in combination with other agents that cause sedation, particularly opioids (**N**) (**Level III-2**).
5. Alpha-2-delta ligands have the potential for misuse and abuse, in particular in patients with opioid use disorder or psychiatric comorbidity (**N**) (**Level IV SR**).

☑ Based on the experience in chronic neuropathic pain states, it would seem reasonable to use alpha-2-delta ligands in the management of acute neuropathic pain (**U**).

Alpha-2 agonists

Systemic alpha-2 agonists

1. Alpha-2 agonists such as clonidine are more effective than placebo in the management of opioid-withdrawal symptoms (**U**) (**Level I** [Cochrane Review]).
2. The perioperative use of clonidine systemically (excluding transdermal administration) does not reduce pain intensity (at 24 or 48 hours) (**Q**) (**Level I**) but reduces opioid consumption and postoperative nausea and vomiting versus placebo (**Q**) (**Level I** [PRISMA]).
3. The perioperative use of the systemic dexmedetomidine reduces postoperative pain intensity, opioid consumption and requirements for rescue analgesia (**S**) without effect on postoperative nausea and vomiting (**N**) (**Level I** [PRISMA]).
4. The IV administration of dexmedetomidine combined with intrathecal local anaesthetic prolongs time to first analgesic request (**N**) (**Level I** [PRISMA]).

Regional alpha-2 agonists

1. Neuraxial clonidine improves duration and quality of analgesia and is opioid sparing when used as an adjuvant to neuraxial local anaesthetics (in particular after Caesarean section) (**S**) (**Level I** [PRISMA]) or to morphine (**U**) (**Level I** [PRISMA]), but increases the risk of hypotension and sedation (**N**) (**Level I** [PRISMA]).

2. Neuraxial dexmedetomidine improves duration and quality of analgesia when used as an adjuvant to neuraxial local anaesthetics (**S**) (**Level I** [PRISMA]).
3. Intrathecal adrenaline (epinephrine) when combined with local anaesthetic, but not with intrathecal opioids, prolongs analgesia duration (**U**) (**Level I** [PRISMA]).
4. Dexmedetomidine when added to local anaesthetics for peripheral nerve blocks improves duration and quality of analgesia, but is associated with increased hypotension and bradycardia (**S**) (**Level I** [PRISMA]).
5. Intra-articular clonidine reduces pain scores for 4 hours, need for rescue analgesia and incidence of nausea, but increases hypotension (**N**) (**Level I** [PRISMA])
6. Clonidine improves duration of analgesia and anaesthesia when used as an adjuvant to local anaesthetics for peripheral nerve and plexus blocks but is associated with increased hypotension and bradycardia (**U**) (**Level I**).
7. Dexmedetomidine added to intravenous regional anaesthesia improves and prolongs analgesia (**U**) (**Level II**).
8. Epidural adrenaline (epinephrine) in combination with a local anaesthetic improves the quality of postoperative thoracic epidural analgesia (**U**) (**Level II**).

☑ The benefits of perineural adjuvant administration of alpha-2-agonists over systemic administration remains unclear (**N**).

Salmon calcitonin and bisphosphonates

1. Bisphosphonates reduce bone pain associated with metastatic breast cancer (**U**), multiple myeloma (**S**) and Paget's disease (**N**) (**Level I** [Cochrane Review]), but have no beneficial effect for knee arthritis (**N**) (**Level I**).
2. Salmon calcitonin reduces pain and improves mobilisation in the acute phase after osteoporosis-related vertebral compression fractures (**U**) (**Level I** [PRISMA]).
3. Bisphosphonates reduce pain in patients with CRPS Type 1 in the early phase of the disease (**N)** (**Level I**).
4. Salmon calcitonin reduces acute, but not chronic, phantom limb pain (**U**) (**Level II**).
5. Pamidronate reduces pain associated with acute osteoporotic vertebral compression fractures (**U**) (**Level II**).

Cannabis, cannabinoids and cannabimimetics

1. Adverse effects including dizziness, cognitive changes and psychiatric symptoms (eg psychosis) may limit the usefulness of cannabinoids in pain treatment (**S**) (**Level I** [Cochrane Review]).
2. Current evidence does not support the use of cannabinoids in acute pain management (**S**) (**Level I** [PRISMA]).
3. Smoking cannabis has short-term efficacy in neuropathic pain in patients with HIV/AIDS, although potential study bias means that this is not recommended as routine treatment (**Q**) (**Level I** [PRISMA]).

4. Cannabinoids appear to be mildly effective when used in the treatment of pain and spasticity associated with multiple sclerosis and HIV (**W**) (**Level III-2 SR** [PRISMA]).
5. Smoked cannabis increases the risk of acute coronary syndrome and chronic cardiovascular disease (**N**) (**Level IV SR**).

Corticosteroids

Systemic corticosteroids

1. Mild increase in blood glucose concentration follows perioperative administration of dexamethasone (**S**) (**Level I** [Cochrane Review]) and all corticosteroids (**S**) (**Level I** [PRISMA), particularly in patients with diabetes mellitus.
2. Perioperative administration of dexamethasone (**N**) (**Level I** [Cochrane Review]) and all corticosteroids (**N**) (**Level I** [PRISMA]) does not increase the risk of infection.
3. Perioperative administration of dexamethasone reduces postoperative pain and opioid requirements to a limited extent but also reduces nausea and vomiting, fatigue, and improves the quality of recovery compared with placebo (**U**) (**Level I** [PRISMA]).
4. Preoperative dexamethasone appears to be more effective than intraoperative or postoperative administration (**U**) (**Level I** [PRISMA]).
5. Perioperative corticosteroids do not increase the risk of impaired wound healing, anastomotic leakage or postoperative haemorrhage (**N**) (**Level I** [PRISMA]).
6. A single dose of corticosteroids provides more effective and faster relief of pain from sore throat than placebo (**N**) (**Level I**) and decreases incidence and severity of sore throat after extubation when administered at induction (**N**) (**Level I** [PRISMA]).
7. Systemic dexamethasone reduces pain intensity and opioid requirements after spinal anaesthesia (**N**) (**Level I** [PRISMA].

☑ As all adverse event data on corticosteroid use in surgical populations are based to date on efficacy trials (with methodological differences), their long-term safety awaits further evaluation (**N**).

Regional corticosteroids

1. For brachial plexus blocks, addition of dexamethasone to local anaesthetic prolongs the duration of sensory and motor block and improves postoperative analgesia with only very limited benefits over systemic administration (**S**) (**Level I** [Cochrane Review]).
2. For transverse abdominis plane blocks, addition of dexamethasone to local anaesthetics prolongs the duration of sensory block, improves postoperative analgesia and PONV with no comparison to systemic administration (**N**) (**Level I** [PRISMA]).
3. After spinal surgery, epidural steroid application intraoperatively by the surgeon provides analgesic benefit up to 24 hours and reduces length of stay (**N**) (**Level I** [PRISMA]).
4. For acute radicular pain, lumbar epidural corticosteroid administration is effective for short-term relief (**S**) (**Level I** [PRISMA]).
5. Subacromial injections of corticosteroids are superior to oral NSAIDs in treating rotator cuff tendonitis (**U**) (**Level I** [QUOROM]).

6. For peripheral nerve blocks, addition of dexamethasone to local anaesthetics prolongs the duration of sensory block and improves postoperative analgesia with only limited benefits over systemic administration (**N**) (**Level II**).
7. For epidural analgesia, addition of dexamethasone improves postoperative analgesia and reduces opioid requirements (**N**) (**Level II**).
8. Addition of dexamethasone to intravenous regional anaesthesia with lidoocaine improves analgesia for up to 24 hours (**U**) (**Level II**).
9. Addition of corticosteroid to periarticular injection of local anaesthetic does not improve pain relief or range of movement following total knee arthroplasty (**U**) (**Level II**).
10. Following knee joint arthroscopy, intra-articular steroids in combination with either local anaesthetic or opioids reduce pain, analgesic consumption and duration of immobilisation (**U**) (**Level II**).
11. There is a risk of septic arthritis with intra-articular steroids (**U**) (**Level IV**).
12. Repeat epiudural steroid injections are associated with reduced bone mineral density and increased risk of vertebral fractures (**N**) (**Level IV SR).**

☑ Concerns have been raised regarding the safety of epidural steroids (**U**).

☑ There is little data in humans regarding the neurotoxicity of perineural corticosteroids (**N**).

Other regional analgesic medicines

1. Intrathecal midazolam combined with a local anaesthetic improves and prolongs analgesia and reduces postoperative nausea and vomiting (**U**) (**Level I**).
2. Intrathecal neostigmine improves perioperative and peripartum analgesia in combination with other intrathecal medications (**S**) (**Level I**) but is associated with dose-dependent significant adverse effects, in particular nausea and vomiting (**Q**) (**Level I**).
3. Epidural neostigmine combined with local anaesthetics improves postoperative and peripartum analgesia without increasing the incidence of adverse effects (**U**) (**Level I**).
4. Epidural neostigmine combined with an opioid reduces the dose of epidural opioid that is required for analgesia (**U**) (**Level I**).

Complementary and alternative medicine

1. White willow bark (*Salix alba*) and devil's claw (*Harpagophytum procumbens*) are effective in treating acute episodes of low back pain (**U**) (**Level I** [Cochrane Review])
2. A variety of complementary medicines may show efficacy in prevention and treatment of primary dysmenorrhoea based on very limited evidence (**W**) (**Level I** [Cochrane Review]), including aromatherapy (**N**) (**Level III-1 SR**).
3. Curcuminoids and extracts of Zingiberaceae may reduce pain intensity in acute and chronic pain states compared to placebo (**N**) (**Level I** [PRISMA]).
4. Oral administration of honey versus control reduces postoperative pain and analgesic use after tonsillectomy (**N**) (**Level I** [PRISMA]).

5. Vitamin C reduces postoperative opioid requirements (**N**) (**Level I** [PRISMA] and postoperative pain compared to placebo (**N**) (**Level IV SR** [PRISMA]).
6. Aromatherapy (**N**) (**Level I**), homeopathic preparations of arnica (*Arnica montana*) (**U**) (**Level I** [PRISMA]) and St John's wort (*Hypericum perforatum*) are not effective in treating acute postoperative pain (**U**) (**Level I** [QUOROM]).
7. St John's wort (*Hypericum perforatum*) induces metabolism of oxycodone reducing its plasma concentrations and efficacy (**U**) (**Level II**).

☑ There is some evidence that some complementary and alternative medicines may be effective in some acute pain states. Adverse effects and interactions with medications have been described with complementary and alternative medicines and must be considered before their use (**U**).

☑ The evidence on complementary and alternative medicines is characterised by small sample sizes and study designs prone to bias and caution is urged in interpreting results. Additionally, the safety and potential drug interactions of many complementary and alternative medicines have not been adequately assessed **(N).**

5.0 | Administration of analgesic medicines

Oral and sublingual route

1. Oral combinations of paracetamol/ibuprofen provide superior analgesia to paracetamol/codeine; both combinations are more effective than the individual medicines and have a dose-response effect (**S**) (**Level I** [Cochrane Review]).
2. Oral combinations of paracetamol/tramadol are more effective than the individual medications and have a dose-response effect (**U**) (**Level I**).
3. NSAIDs given parenterally or rectally are not more effective and do not result in fewer adverse effects than the same medicines given orally (**U**) (**Level I**).
4. The formulation of oral NSAIDs (eg fast acting [dispersible, solution or gel], sodium versus potassium salt) can greatly affect their efficacy (**N**) (**Level I**).
5. Early postoperative oral administration of paracetamol results in highly variable plasma concentrations that may remain subtherapeutic in some patients (**U**) (**Level II**). However, no difference in clinical efficacy to intravenous administration is seen in hip and knee arthroplasty (**N**) (**Level I**), Caesarean section (**N**) (**Level II**) or laparoscopic cholecystectomy (**N**) (**Level II**).

☑ Other than in the treatment of severe acute pain, and providing there are no contraindications to its use, the oral route is the route of choice for the administration of most analgesic medicines (**U**).

☑ Slow-release opioid preparations (particularly conventional opioids including transdermal fentanyl and methadone) are not recommended in general for the management of acute pain in opioid-naïve patients due to difficulties in short-term dose adjustments needed for titration, an increased risk of opioid-induced ventilatory impairment and risk of initiating long-term use (**S**). In some patients with prolonged postoperative and post-traumatic acute pain states, the use of slow-release opioid preparations may be appropriate on a short-term basis with preference for use of atypical opioids (**N**).

☑ Slow-release oral opioid preparations should only be given at set time intervals (**U**).

Intravenous route

1. Intravenous paracetamol is more effective in reducing pain, opioid consumption and PONV when given prior to versus after surgical incision (**U**) (**Level I** [PRISMA]).
2. The onset of analgesia is faster when NSAIDs are given intravenously for the treatment of renal colic (**U**) (**Level I**).
3. Continuous intravenous infusion of opioids in the general-ward setting is associated with an increased risk of respiratory depression compared with other methods of parenteral opioid administration (**U**) (**Level IV**).

☑ Titration of opioids for severe acute pain is best achieved using intermittent intravenous bolus doses as it allows more rapid titration of effect and avoids the uncertainty of medicine absorption by other routes (**U**).

Intramuscular and subcutaneous route

1. Intermittent subcutaneous morphine injections are as effective as intramuscular injections and have better patient acceptance (**U**) (**Level II**).

Transdermal route

1. Transdermal buprenorphine reduces postoperative pain with a low rate of adverse effects (**N**) (**Level II**).
2. Transdermal fentanyl (except for iontophoretic patient-controlled transdermal devices) should not be used in the management of acute pain because of safety concerns and difficulties in short-term dose adjustments needed for titration (**S**) (**Level IV**).

☑ Transdermal fentanyl preparations should not be used in opioid-naïve patients or in acute pain settings because of safety concerns and, in most countries, the lack of regulatory approval for use in other than chronic pain in opioid-tolerant patients (**S**).

Transmucosal route

1. Intranasal, sublingual and buccal fentanyl preparations are effective treatments for breakthrough pain in cancer patients (**U**) (**Level I** [Cochrane Review]) with similar efficacy to IV administration (**U**) (**Level I** [PRISMA]) and superiority to oral morphine (**U**) (**Level I**).
2. Intranasal fentanyl is an effective treatment for paediatric acute pain management, with an acceptable adverse effect profile and ease of delivery (**N**) (**Level I**).
3. Intranasal fentanyl provides faster and better analgesia for breakthrough pain in cancer patients than oral transmucosal fentanyl and fentanyl buccal tablets (**U**) (**Level I**).
4. Sublingual sufentanil delivered by a PCA device provided analgesia comparable to IV PCA opioids in a number of acute pain settings (**N**) (**Level II**).

☑ Neither transmucosal immediate-release nor transdermal fentanyl preparations should be used in the management of acute pain in opioid-naïve patients because of safety concerns and, in most countries, the lack of regulatory approval for use in other than opioid-tolerant patients (**U**).

Epidural analgesia

1. For all types of surgery, epidural analgesia provides better postoperative pain relief compared with parenteral (including PCA) opioid administration (**S**) (**Level I** [Cochrane Review]); except epidural analgesia using a hydrophilic opioid only (**U**) (**Level I**).
2. Thoracic epidural analgesia for open abdominal aortic surgery reduces pain intensity, time to tracheal extubation, time spent in the intensive care unit, rate of acute respiratory failure, myocardial infarction and gastrointestinal bleeding when compared with intravenous opioids (**S**) (**Level I** [Cochrane Review]).
3. High thoracic epidural analgesia used for coronary artery bypass graft surgery reduces postoperative pain, risk of dysrhythmias, pulmonary complications and time to extubation when compared with intravenous opioid analgesia (**Q**) (**Level I** [Cochrane Review]).
4. Thoracic epidural analgesia for thoracotomy reduces the risk of chronic postsurgical pain (**S**) (**Level I** [Cochrane Review]).
5. Thoracic epidural analgesia improves bowel recovery after abdominal surgery (including colorectal surgery) (**S**) (L**evel I** [Cochrane Review]).
6. Epidural analgesia is not associated with increased risk of anastomotic leakage after bowel surgery (**S**) (**Level I** [Cochrane Review]).
7. Epidural analgesia provided with local anaesthetics for at least 24 hours compared to systemic opioid analgesia reduces perioperative mortality and multiple morbidities (including ileus, pneumonia, respiratory depression and arrhythmias) but increases hypotension (**U**) (**Level I** [PRISMA]).
8. After laparoscopic colectomy, thoracic epidural analgesia compared to intravenous PCA reduces initial pain scores and time to first bowel opening, but length of hospital stay, total rate of complications (**S**) (**Level I** [PRISMA]), urinary tract infection rates and hospital costs are increased (**U**) (**Level III-2**).
9. Combinations of low concentrations of local anaesthetic agents and opioids for epidural analgesia provide consistently superior pain relief compared with either of the medications alone; epidural opioids alone have no advantage over parenteral opioids (**U**) (**Level I**).
10. Epidural local anaesthetic administration improves oxygenation and reduces pulmonary infections and other pulmonary complications compared with parenteral opioids (**U**) (**Level I**).
11. Chlorhexidine-impregnated dressings of epidural catheters in comparison to placebo- or povidone-iodine-impregnated dressings reduce the incidence of catheter colonisation (**U**) (**Level I**).
12. In patients with multiple rib fractures, thoracic epidural analgesia improves pain relief versus parenteral opioids (**N**) (**Level III-2 SR**), but does not reduce incidence of pneumonia and mortality (**U**) (**Level I**) and may not reduce need for ventilation (**Q**) (**Level III-2 SR**).
13. The combination of thoracic epidural analgesia with local anaesthetics and nutritional support leads to preservation of total body protein after upper abdominal surgery (**U**) (**Level II**).

14. The incidence of permanent neurological damage in association with epidural analgesia is extremely low, especially in the obstetric population, but increases with various comorbidities and risk factors; the incidence is higher where there have been delays in diagnosing an epidural haematoma or abscess (**S**) (**Level IV SR**).

15. Immediate decompression of an epidural haematoma (within 8 hours of the onset of neurological signs) increases the likelihood of partial or good neurological recovery (**S**) (**Level IV SR**).

16. Epidural abscesses present mainly with neurological deficits and back pain; they are best diagnosed with early MRI and best treated with empiric antibiotics (until abscess culture) and immediate surgical decompression when neurological deficits are present (**S**) (**Level IV SR).**

☑ The provision of epidural analgesia by continuous infusion, programmed intermittent bolus or patient-controlled administration of local anaesthetic-opioid mixtures is safe on general hospital wards, as long as supervised by an anaesthesia-based pain service with 24-hour medical staff cover and monitored by well-trained nursing staff (**U**).

☑ Prior to insertion of an epidural catheter, thorough handwashing with surgical scrub solution, the use of barrier precautions including the wearing of a cap, mask, sterile gown and gloves and use of chlorhexidine in alcohol for skin preparation are recommended; but meticulous care must be taken to avoid the chlorhexidine solution from reaching epidural space or cerebrospinal fluid (**U**).

Intrathecal analgesia

1. Intrathecal morphine improves analgesia and is opioid-sparing for up to 24 hours after major surgery including abdominal (**S**), orthopaedic (**N**), spinal (**N**) (**Level I** [PRISMA]) and cardiothoracic surgery (**N**) (**Level II**).

2. Adding intrathecal morphine to intrathecal bupivacaine/fentanyl or intrathecal bupivacaine/sufentanil prolongs pain relief after labour (**N**) (**Level I** [PRISMA]).

3. The addition of intrathecal fentanyl (**N**) (**Level I** [PRISMA]) and morphine to spinal anaesthesia prolongs time to first analgesic request after Caesarean section (**N**) (**Level I**).

4. Intrathecal morphine in comparison to peripheral regional analgesia techniques offers similar analgesic benefits, but increases adverse effects (nausea, vomiting, pruritus) after lower limb arthroplasty (**N**) (**Level I**).

5. The incidence of opioid-induced ventilatory impairment, pruritus and postoperative nausea and vomiting is higher with intrathecal morphine compared with intravenous PCA opioids (**S**) (**Level I**).

6. 6Pruritus with intrathecal opioids is dose-dependent (**N**) (**Level I**) and can be effectively prevented and treated with $5HT_3$ antagonists in non-obstetric patients, but only treated but not prevented in obstetric patients (**Q**) (**Level I**)

7. The addition of intrathecal magnesium to opioids and/or local anaesthetics results in slightly longer analgesia in non-obstetric patients (**U**) (**Level I**).

8. The addition of intrathecal clonidine to intrathecal morphine results in slightly longer analgesia and reduced opioid requirements (**U**) (**Level I**).

9. Pruritus with intrathecal opioids cannot be treated with methylnaltrexone (**N**) (**Level II**).

☑ The absence of consistent dose-responsiveness to the efficacy of intrathecal opioids and the increase in adverse effects with higher doses suggests that the lowest effective dose (typically 50-200 mcg morphine) should be used (**Q**).

☑ Patients receiving intrathecal opioids should be monitored for opioid-induced ventilatory impairment for the anticipated duration of opioid effects, eg 18 to 24 hours after intrathecal morphine (**S**).

☑ Clinical experience with morphine, fentanyl and sufentanil has shown no neurotoxicity or behavioural changes at normal clinical intrathecal doses (**U**), however caution is recommended in patients who are at risk of spinal cord ischaemia (**U**).

Other regional and local analgesic techniques

1. Topical EMLA® cream (eutectic mixture of lignocaine [lidocaine] and prilocaine) is effective in reducing the pain associated with venous ulcer debridement (**U**) (**Level I** [Cochrane Review]).
2. Transversus abdominis plane blocks provide pain relief superior to local anaesthetic infiltration for a range of abdominal surgeries (**N**) (**Level I** [PRISMA]).
3. Intraperitoneal local anaesthetic instillation after laparoscopic gastric surgery (**N**) (**Level I** [PRISMA]) and laparoscopic cholecystectomy (**U**) (**Level I**) improves postoperative pain outcomes.
4. Adductor canal block results in similar postoperative pain outcomes following total knee arthroplasty versus femoral nerve block with less quadriceps weakness, earlier mobilisation and better functional recovery (**S**) (**Level I** [PRISMA]).
5. Following thoracotomy, thoracic paravertebral block provides comparable analgesia to thoracic epidural analgesia (**U**) (**Level I**).
6. Continuous peripheral nerve block, compared with single-injection peripheral nerve block, results in improved pain control, decreased need for opioid analgesics, reduced nausea and improved patient satisfaction in some settings, in particular in the first 24 hours postoperatively (**W**) (**Level I**).
7. Femoral nerve block, either single-injection or continuous, provides better analgesia and decreased nausea compared with parenteral opioid-based techniques after total knee arthroplasty (**U**) (**Level I**).
8. Compared with opioid analgesia, continuous peripheral nerve block (regardless of catheter location) provides better postoperative analgesia and leads to reductions in opioid use as well as nausea, vomiting, pruritus and sedation (**U**) (**Level I**).
9. Blocks performed using ultrasound guidance are more likely to be successful, faster to perform, with faster onset and longer duration compared with localisation using a peripheral nerve stimulator (**U**) (**Level I**).
10. Morphine injected into the intra-articular space following knee arthroscopy does not improve analgesia compared with placebo (**U**) (**Level I**).

11. Following total knee arthroplasty, local infiltration analgesia reduces postoperative pain for up to 32 hours when compared to systemic analgesics alone; however, there is limited benefit in comparison to femoral nerve block (**U**) (**Level I**).
12. Following total hip arthroplasty, there is no additional analgesic benefit for local infiltration analgesia over conventional multimodal analgesia (**S**) (**Level I**) and peripheral nerve blocks have limited or no effect on postoperative pain (**Q**) (**Level II**).
13. Following either knee or hip arthroplasty, there is insufficient evidence to support postoperative administration of local infiltration analgesia via catheter (**U**) (**Level I**).
14. Local anaesthetic infusions or intermittent injections through wound catheters provide analgesic benefits following gynaecological and obstetric surgery, but not other abdominal or nonorthopaedic surgery (**Q**) (**Level I**).
15. Intraurethral instillation of lignocaine gel provides analgesia during flexible cystoscopy (**U**) (**Level I**).
16. The benefit of routine sciatic nerve block in addition to femoral nerve block for analgesia following total knee joint arthroplasty remains unclear (**U**) (**Level I**).
17. Continuous interscalene analgesia provides better analgesia, reduced opioid-related adverse effects and improved patient satisfaction compared with intravenous PCA or single-injection interscalene block after open shoulder surgery (**U**) (**Level II**).
18. Erector spinae plane blocks provide postoperative analgesia superior to systemic analgesia after cardiac surgery (**N**) (**Level II**) and to transverse abdominus blocks after laparoscopic cholecystectomy (**N**) (**Level II**).
19. Quadratus lumborum block reduces pain scores and opioid requirements following Caesarean section compared to placebo or control (**N**) (**Level II**).
20. Intra-articular bupivacaine infusions have been associated with chondrolysis and their use has been cautioned against (**U**) (**Level IV**).
21. Postoperative neurologic symptoms or dysfunction is often related to patient and surgical factors and the incidence of neuropathy directly related to peripheral regional anaesthesia is rare (**S**) (**Level III-3**).
22. Ultrasound guidance of regional blocks is associated with a reduced risk of local anaesthetic systemic toxicity in adults (**N**) (**Level IV**).

☑ Continuous peripheral nerve blocks carry a risk of infection; skin preparation with alcohol-based chlorhexidine and full barrier precautions (including face masks) are recommended for insertion of peripheral nerve catheters (**U**).

☑ Ultrasound-guided techniques should be practiced with a high degree of skill and care, including aseptic techniques, as they do not eliminate the risks of injury to tissues and structures, local anaesthetic systemic toxicity or site contamination (**U**).

☑ Caution should be used when considering and performing some peripheral nerve or plexus blocks in patients with impaired coagulation, in particular where the PNB is performed at a deep location that prevents external compression, should bleeding occur (**N**).

Regional analgesia and concurrent anticoagulant medications

1. Anticoagulation and coagulopathy are the two most important risk factors for the development of epidural haematoma after neuraxial block (**U**) (**Level IV**).

☑ Consensus statements of experts guide the timing and choice of regional anaesthesia and analgesia in the context of anticoagulation but do not represent a standard of care and will not substitute the risk/benefit assessment of the individual patient by the individual anaesthetist (**S**).

☑ Caution should be used when considering and performing some peripheral nerve or plexus blocks in patients with impaired coagulation, in particular where the peripheral nerve block is performed at a deep location that prevents external compression, should bleeding occur (**S**).

6.0 | Patient-controlled analgesia

1. Intravenous opioid PCA provides better analgesia than conventional parenteral opioid regimens (**S**) (**Level I** [Cochrane Review]).
2. Opioid administration by IV PCA leads to higher opioid consumption, a higher incidence of pruritus, but no difference in other opioid-related adverse effects, or hospital stay compared with traditional methods of intermittent parenteral opioid administration (**S**) (**Level I** [Cochrane Review]).
3. Patient satisfaction with intravenous PCA is higher when compared with conventional regimens (**S**) (**Level I** [Cochrane Review]).
4. The adjuvant use of ketamine with PCA opioid (in varying ratios) improves pain relief and reduces opioid consumption along with nausea and vomiting, with no increase in neurocognitive effects including hallucinations (**N**) (**Level I** [PRISMA]).
5. Iontophoretic transdermal fentanyl PCA is not as effective as intravenous morphine PCA, with more patients withdrawing from studies because of inadequate pain relief (**U**) (**Level I** [QUOROM]).
6. In settings where there are high nurse to patient ratios, there may be no difference in the effectiveness of PCA and conventional parenteral opioid regimens (**U**) (**Level I**).
7. Tramadol via intravenous PCA provides effective analgesia comparable to morphine by intravenous PCA (**U**) (**Level I**).
8. The addition of a background infusion to intravenous PCA morphine in adults increases the incidence of respiratory depression (**U**) (**Level I**) and does not improve pain relief or sleep, or reduce the number of PCA demands (**U**) (**Level II**).
9. Different opioids by intravenous PCA show different rates of adverse effects; fentanyl PCA has the least rates of sedation, nausea and vomiting while pruritus is most frequent with morphine PCA (**N**) (**Level I** [NMA]). Furthermore, on an individual patient basis, one opioid may be better tolerated than another (**U**) (**Level II**).
10. There is no analgesic benefit in adding naloxone to the PCA morphine solution; however, the incidence of nausea and pruritus may be decreased (**U**) (**Level II**).
11. Subcutaneous PCA opioids can be as effective as intravenous PCA (**U**) (**Level II**).

12. Intranasal PCA opioids can be as effective as intravenous PCA (**U**) (**Level II**).
13. In the emergency department, PCA morphine compared with IV morphine administered by nursing staff, provides more effective analgesia with more rapid onset and with higher patient satisfaction (**U**) (**Level II**).
14. The safety of PCA use can be significantly improved by hospital-wide safety initiatives (equipment, guidelines, education, monitoring) (**U**) (**Level III-3**).
15. The adoption of "smart pump" technologies in PCA design can improve documentation of patient care (**N**) (**Level III-3**), reduce programming errors and improve safety (**N**) (**Level IV SR**).
16. Operator-error, in particular programming error, remains a common safety problem with PCA useoften leading to patient harm (**S**) (**Level IV**).

☑ There is insufficient data to compare the risk of rare but serious adverse events with PCA opioid use to conventionally administered opioid analgesia (**N**).

☑ Adequate analgesia needs to be attained prior to commencement of PCA. Initial orders for bolus doses should consider individual patient factors such as a history of prior opioid use and patient age. Individual PCA prescriptions may need to be adjusted (**U**).

☑ The routine addition of antiemetics to PCA opioids is not encouraged, as it is of no benefit compared with selective administration (**U**).

☑ PCA infusion systems must incorporate anti-siphon valves and, in non-dedicated lines, antireflux valves (**U**).

☑ Drug concentrations, prescription and observation forms should be standardised to improve patient safety (**U**).

☑ The pharmacokinetics of morphine (long equilibration half-time and active metabolites) may make it less suitable for PCA use than other opioids (**U**).

☑ Pethidine, when used in PCA, may cause central nervous system toxicity due to the accumulation of norpethidine (**U**).

☑ Improved methods of patient monitoring (eg continuous pulse oximetry, continuous capnography) may offer opportunities to improve safety in at-risk patient groups (**N**).

7.0 | Nonpharmacological techniques

Psychological interventions

1. Preoperative psychological interventions may be effective at reducing pain, length of stay and negative affect after various procedures (**N**) (**Level I** [Cochrane Review]) but may not be effective after cardiac surgery (**N**) (**Level I** [Cochrane Review]).
2. Distraction (including with video, toys, music or stories) and hypnosis reduces needle related pain (**S**) and distress (**N**) in children and adolescents (**Level I** [Cochrane Review])
3. Hypnosis may reduce procedural pain and anxiety (**N**) (**Level I** [Cochrane Review]), postoperative pain (**R**) (**Level I**), postoperative anxiety (**N**) and analgesia consumption in labour (**R**) (**Level I** [Cochrane Review]).

4. Listening to music produces a small reduction in postoperative or procedural pain, analgesic requirements and emotional distress (**S**) (**Level I**); patient selected music may be more effective than clinician selected music (**N**) (**Level II**).
5. Patient education regarding the procedure or recovery may reduce postoperative pain (**Q**), preoperative anxiety (**N**) and postoperative anxiety (**N**) but does not affect analgesia use (**U**) (**Level I** [PRISMA]).
6. Training in coping methods or behavioural instruction prior to surgery reduces pain, negative affect and analgesic use (**U**) (**Level I**).
7. Relaxation techniques may reduce postoperative pain but do not reduce analgesic consumption (**S**) (**Level I**).
8. Immersive virtual reality distraction is effective in reducing pain (**S**) and anxiety (**N**) in some clinical situations (**Level III-2 SR** [PRISMA]).
9. In work injury-related acute pain, psychologically informed and workplace-oriented interventions may reduce time lost from work (**N**) (**Level III-2 SR**).

☑ Pain catastrophisation and anxiety negatively impact the postoperative experience and are risk factors for the development of chronic postsurgical pain and prolonged opioid use. Interventions aimed at reducing catastrophisation may be useful in improving patient outcomes, but retaining patient engagement with perioperative psychoeducation may also prove challenging (**N**).

☑ Preoperative psychoeducation may be cost effective from the perspective of reducing length of stay (**N**).

☑ The evidence that sensory and combined sensory-procedural information is effective in reducing procedure-related pain is equivocal and not sufficient to make recommendations (**U**).

☑ There is insufficient evidence to make a recommendation about the role of brief mindfulness-based interventions in acute pain (**N**).

Transcutaneous electrical nerve stimulation

1. Transcutaneous electrical nerve stimulation compared to sham reduces acute pain (procedural and nonprocedural) (**U**) (**Level I** [Cochrane Review]), including pain after thoracic surgery (**U**) (**Level I** [PRISMA), after total knee replacement (**N**) and in the prehospital setting (**N**) (**Level I** [PRISMA]).
2. High-frequency transcutaneous electrical nerve stimulation is effective in primary dysmenorrhoea (**U**) (**Level I** [Cochrane Review]).
3. Transcutaneous electrical nerve stimulation has no effect on pain, interventions or outcomes in labour with the exception of a reduction of reports of severe pain when applied to acupuncture points (**U**) (**Level I** [Cochrane Review]).
4. Transcutaneous electrical nerve stimulation used preventatively in migraine reduces attack frequency and medication use (**N**) (**Level I** [PRISMA])

Acupuncture and acupressure

1. Acupuncture and acupressure for labour pain may reduce pain, use of pharmacological pain relief and increase satisfaction with pain management versus standard care or placebo (**Q**) (**Level I** [Cochrane Review]); Caesarean section rates are unchanged (**R**) (**Level I** [Cochrane Review]).
2. For oocyte retrieval, electroacupuncture plus sedation reduced procedural and postoperative pain compared with sedation plus placebo or sedation alone (**U**), but may be inferior to paracervical block plus sedation (**Q**) (**Level I** [Cochrane Review]).
3. Acupuncture or acupressure may be effective in the treatment of primary dysmenorrhoea (**S**) (**Level I** [Cochrane Review]).
4. Acupuncture may reduce the frequency of tension-type headaches and migraine (**U**) (**Level I** [Cochrane Review]); in migraine, it may be better tolerated than pharmacological prophylaxis (**N**) (**Level I** [Cochrane Review]).
5. Acupuncture may be effective in a variety of acute pain conditions in the emergency department setting (**S**) (**Level I** [PRISMA]) including back pain (**N**) (**Level I** [PRISMA])
6. Acupuncture by a variety of techniques may reduce postoperative pain and opioid consumption for a variety of surgical types (**S**) (**Level I**); specifically, the benefit may occur after lumbar spinal surgery (**U**) (**Level I** [PRISMA]), total knee arthroplasty (**U**) (**Level I** [PRISMA]), total hip arthroplasty (**N**) (**Level I**) and craniotomy (**N**) (**Level I** [PRISMA]).
7. There is no difference between distant acupuncture and acupuncture at the incisional site for open abdominal surgery (**S**) (**Level I** [PRISMA]).
8. Acupuncture may reduce post-stroke pain (**N**) (**Level I** [PRISMA]).

Photobiomodulation

1. Photobiomodulation may be effective for both prophylaxis and treatment of mucositis in oncology patients (**S**) (**Level I** [PRISMA]).
2. Photobiomodulation may reduce pain after 3rd molar extraction (**N**) (**Level I** [PRISMA]).
3. Needle related pain after arteriovenous fistula access may be reduced by photobiomodulation (**N**) (**Level I**)
4. After episiotomy, photobiomodulation may not reduce pain (**N**) (**Level II**).

☑ Photobiomodulation may have a role in acute postsurgical pain management, however evidence is currently insufficient to make any furrher recommendations (**N**).

Physical therapies

Exercise therapy

1. Following total knee arthroplasty, an exercise intervention in addition to standard post-operative interventions for 8 weeks after discharge may reduce pain and improve function (**N**) (**Level I**).
2. In primary dysmenorrhoea, exercise may reduce acute pain intensity and pain duration (**N**) (**Level I**).

3. Use of a birth ball may improve labour pain (**N**) (**Level I**).

☑ Clear recommendations on the components of exercise interventions (including time point of application, frequency, mode, dose and duration) for acute postoperative pain management cannot be made; different surgical procedures may require different exercise-based interventions (**N**).

☑ Immediate post-operative weight bearing post anterior cruciate ligament reconstruction may reduce pain and does not appear to result in increased joint laxity (**N**).

Prehabilitation

1. Prior to total hip arthroplasty, prehabilitation may reduce postoperative hip pain at 3 months (**N**) (**Level I** [PRISMA]).

☑ A recommendation for the specific type of prehabilitation and dosing parameters cannot be made at this time (**N**).

Rehabilitation

1. Early comprehensive active physiotherapy in the first 4 weeks post spinal surgery may reduce pain and does not appear to increase adverse events (**N**) (**Level I** [PRISMA]).
2. Movement representation interventions (mirror therapy/motor imagery) may reduce acute pain after trauma and surgery (**N**) (**Level I** [PRISMA]).

☑ Accelerated rehabilitation, started within 24 hours post total knee arthroplasty, may reduce pain at the time of discharge (**N**).

Manual and massage therapies

1. Single and multiple doses of massage in the early postoperative period may reduce pain after surgical procedures, including cardiac surgery (**N**) (**Level I [**PRISMA])
2. Massage may decrease pain in the first stage of labour pain compared to standard care (**N**) (**Level I** [Cochrane Review])

☑ The role of manipulative therapy in primary dysmenorrhea is currently unclear (**N**).

Warming and cooling interventions

1. Heat packs may reduce labour pain during the first and second stages (**N**) (**Level I** [Cochrane Review]).
2. Vapocoolants may reduce the pain of intravenous cannulation in adults but its application is associated with discomfort (**N**) (**Level I** [Cochrane Review]).
3. Cryotherapy may reduce pain after total knee arthroplasty but is not superior to compression (**N**) (**Level I** [PRISMA]).
4. Compression cryotherapy may reduce acute pain and analgesia requirements post anterior cruciate ligament reconstruction and pain on day one to three post knee surgery (**N**) (**Level I** [PRISMA]).
5. Intraoperative cryotherapy may reduce post-tonsillectomy pain (**N**) (**Level I** [PRISMA]).
6. Hilotherapy (the application of cold compression at a regulated temperature through a face mask) may reduce pain and swelling after facial skeletal surgery vs cold compression (**N**) (**Level I** [PRISMA]).

8.0 | Specific clinical situations

Postoperative pain

Multimodal postoperative pain management

1. Multimodal analgesia compared to mainly opioid-based analgesia improves pain control and reduces opioid consumption ("opioid-sparing") and adverse effects (**S**) (**Level I** [NMA]).

☑ The concept of multimodal (or "balanced") analgesia suggests the use of combinations of analgesics with different mode or site of action (**S**).

Procedure-specific postoperative pain management

1. An analgesic may have different efficacy in different surgical settings (**U**) (**Level I**).
2. Different surgical procedures cause different pain states (eg musculoskeletal vs visceral) of different severity in different locations, thereby requiring a procedure-specific approach (**S**) (**Level III-2**).

☑ Pooling of data from different postoperative pain states may ignore the specific effects of a specific analgesic in a specific postoperative pain state (**U**).

Acute rehabilitation after surgery, "fast-track" surgery and enhanced recovery after surgery (ERAS)

1. Adherence to multimodal enhanced recovery protocols after surgery protocols reduces hospital length of stay, complication rates (**S**) (**Level I**), postoperative pain severity and opioid requirements (**N**) (**Level III-2 SR**)**.**

☑ Provision of appropriate analgesia is only one of several elements of enhanced recovery after surgery protocols (**S**).

☑ Analgesic techniques, which permit early mobilisation and early enteral feeding, in particular those that are opioid-sparing, may contribute to early recovery after surgery protocols (**S**).

Risks of acute postoperative neuropathic pain

1. Positive screening for acute postoperative neuropathic pain is a risk factor for positive screening of chronic postsurgical neuropathic pain (**N**) (**Level III-2**).
2. Acute neuropathic pain occurs after trauma and surgery (**S**) (**Level IV**).

☑ Treatment of acute neuropathic pain should follow guidelines for chronic neuropathic pain; ketamine, opioids (including tramadol and tapentadol in particular) and alpha-2-delta ligands may offer faster onset of effect than other treatment options (**U**).

Acute postamputation pain syndromes

1. Morphine, gabapentin, ketamine and dextromethorphan reduce phantom limb pain compared to placebo (**U**) (**Level I** [Cochrane Review]).
2. Calcitonin reduces phantom limb pain in the acute (<7 days post amputation) but not the chronic setting (**U**) (**Level I** [Cochrane Review]).
3. Continuous regional block via nerve sheath catheters provides postoperative analgesia after amputation but has no preventive effect on phantom limb pain (**U**) (**Level I**).

4. Treatments aiming at cortical reorganisation such as mirror therapy (**W**) (**Level IV SR**), sensory discrimination training and motor imagery may reduce chronic phantom limb pain (**W**) (**Level III-2 SR**).
5. Perioperative epidural analgesia reduces the incidence of severe phantom limb pain (**U**) (**Level III-2 SR**).
6. Anxiety may be a predictor of phantom limb pain (**N**) (**Level IV**).

☑ Perioperative ketamine may prevent severe phantom limb pain (**U**).

Other postoperative pain syndromes

1. Following thoracotomy, epidural analgesia reduces the incidence of chronic postsurgical pain (**S**) (**Level I** [Cochrane Review]).
2. Following breast cancer surgery, paravertebral block (**S**) (**Level I** [Cochrane Review]) and lidocaine IV infusions reduce the incidence of chronic postsurgical pain (**N**) (**Level I** PRISMA]).
3. Cryoanalgesia of the intercostal nerves at the time of thoracotomy results in no improvement in acute pain, but an increase in chronic pain (**U**) (**Level I**).
4. Video-assisted thoracoscopic surgery versus open thoracic surgery resulted in a reduced rate of chronic post-thoracotomy pain (**N**) (**Level III-3**).
5. Post-thoracotomy, post-mastectomy, post-herniotomy and post-hysterectomy pain syndromes occur frequently (**S**) (**Level IV**) and psychological factors (eg anxiety, catastrophising), chronic preoperative pain and severe acute postoperative pain are consistently reported risk factors for these pain syndromes (**N**) (**Level IV**).

Ambulatory or short-stay surgery

1. Wound infiltration and intraperitoneal instillation with local anaesthetics for short-stay laparoscopic cholecystectomy has good analgesic efficacy, in particular when combined and administered prior to trocar insertion and at commencement of pneumoperitoneum respectively (**S**) (**Level I** [Cochrane Review]).
2. Intraperitoneal instillation with local anaesthetic provides good analgesia for up to 6 hours after short-stay gynaecological laparoscopy (**U**) (**Level I**) and reduces shoulder tip pain for 24 h (**N**) (**Level I** [Cochrane Review]).
3. Ketamine added to caudal local anaesthetic for paediatric day-stay surgery prolongs analgesia, but not motor block (**U**) (**Level I** [PRISMA]); however, concerns regarding neurotoxicity remain.
4. Continuous peripheral nerve blocks after short-stay surgery provide extended analgesia for at least 24 h, leading to reduced opioid requirements (**S**) (**Level I** [PRISMA]), earlier achievement of discharge criteria, less sleep disturbance and improved early rehabilitation (**S**) (**Level II**).
5. Paravertebral block improves pain-related outcomes after short-stay hernia repair (**S**) (**Level I** [PRISMA]) and major breast surgery (**U**) (**Level II**).
6. After ambulatory anterior cruciate ligament repair, analgesia is superior with local infiltration anaesthesia versus femoral nerve blocks and adductor canal blocks; multimodal systemic analgesia, early mobilisation and cooling/compression are also supported (**N**) (**Level I** [PRISMA]).

7. After ambulatory shoulder arthroscopy, interscalene nerve block is superior to other peripheral nerve blocks; adjuvants to increase block duration and systemic multimodal analgesia are also supported (**N**) (**Level I** [PRISMA]).
8. Gynaecological paracervical block provides superior analgesia to intracervical and transcervical block and topical local anaesthetic administration (the latter both without analgesic effect) for ambulatory hysteroscopy (**N**) (**Level I**).
9. Dexamethasone added to local anaesthetics in peripheral nerve blocks and for caudal analgesia or given systemically prolongs duration of analgesia after short-stay surgery (**S**) (**Level I**).
10. Single injection peripheral nerve blocks with long-acting local anaesthetics provide long-lasting postoperative analgesia after short-stay surgery (**S**) (**Level II**).
11. Infiltration of the wound with local anaesthetic provides effective and long-lasting analgesia after many short-stay procedures (**U**) (**Level II**).
12. In the short-stay surgery setting, anti-inflammatories (nonselective NSAIDs, coxibs and dexamethasone) and paracetamol contribute to reduced pain and improved recovery (**U**) (**Level II**).
13. Buprenorphine or dexmedetomidine added to local anaesthetics for peripheral nerve blocks prolong duration of analgesia after short-stay surgery (**U**) (**Level II**).
14. Anterior cruciate ligament repair performed as a short-stay procedure in comparison to an inpatient setting achieves comparable quality of pain relief and better outcomes (**N**) (**Level III-3 SR**).
15. Pain relief after short-stay surgery remains poor (**U**) (**Level IV**) and is a common cause of unplanned re-presentation (**U**) (**Level III-3**).
16. Continuous peripheral nerve blocks have been shown to be safe at home after short stay surgery, if adequate resources and patient education are provided (**U**) (**Level IV**).
17. Predictive factors of severe pain after short-stay surgery are preoperative pain, high expectation of postoperative pain, younger age and certain types of surgery (in particular orthopaedic surgery) (**N**) (**Level IV**).

☑ Preoperative patient-centered education (verbal and written) and telephone follow-ups may improve anxiety, pain and functional outcomes and patient satisfaction after ambulatory surgery (**N**).

Cranial neurosurgery

1. Local anaesthetic infiltration of the scalp provides early analgesia after craniotomy and reduces opioid requirements (**S**) (**Level I** [PRISMA]).
2. Intraoperative dexmedetomidine provides early analgesia after craniotomy and reduces opioid requirements compared to placebo or remifentanil (**S**) (**Level I** [PRISMA]).
3. Morphine is more effective than codeine and tramadol for pain relief after craniotomy (**U**) (**Level II**).
4. Craniotomy leads to significant pain in the early postoperative period (**U**) (**Level IV**), which is however not as severe as pain from other surgical interventions (**U**) (**Level III-2**).
5. Craniotomy can lead to significant chronic headache (**U**) (**Level IV**).

☑ Acute pain following craniotomy is underestimated and often poorly treated (**U**).

Spinal surgery

1. Epidural analgesia compared to systemic analgesia after spinal surgery in children improves pain up to 72 hours postoperatively (**N**) (**Level I**[Cochrane Review]).
2. Perioperative use of gabapentin or pregabalin improves analgesia and reduces opioid requirements after spinal surgery (**S**) (**Level I** [PRISMA]).
3. NSAIDs provide analgesic benefits as well as opioid-sparing effects after spinal surgery (**S**) (**Level I** [PRISMA]).
4. Intravenous dexmedetomidine improves early postoperative analgesia and reduces analgesic requirement up to 48 hours after spinal surgery (**N**) (**Level I** [PRISMA]).
5. Intravenous corticosteroids improve analgesia and reduce nausea and length of stay after spinal surgery (**N**) (**Level I** [PRISMA]).
6. Epidural steroid application intraoperatively by the surgeon provides analgesic benefit up to 24 hours and reduces length of stay after spinal surgery(**N**) (**Level I** [PRISMA]).
7. Perioperative pregabalin improves functional outcome after laminectomy at 3 months (**U**) (**Level II**).
8. Local infiltration anaesthesia improves analgesia and reduces opioid requirements after spinal surgery; this benefit is enhanced with preincision infiltration compared to infiltration at wound closure (**U**) (**Level II**).
9. Perioperative systemic lidocaine infusion improves analgesia and reduces opioid requirements after spinal surgery (**W**) (**Level II**).
10. NSAID use for less than 14 days does not increase the risk of nonunion after spinal fusion, except with high-dose ketorolac (**U**) (**Level III-3**).

☑ Acute pain management following spinal surgery is often complicated by preoperative chronic pain and long term medication use (**U**).

Acute pain following spinal cord injury

1. Alpha-2-delta ligands (gabapentin/pregabalin) are effective in the treatment of neuropathic pain following spinal cord injury (**S**) (**Level I**).
2. Antidepressants (amitriptyline, duloxetine and venlafaxine) are effective in the treatment of neuropathic pain following spinal cord injury but only in those with co-morbid depression (**N**) (**Level I**).
3. Intravenous opioids, ketamine ((**U**) (**Level I**), lidocaine and tramadol are effective in the treatment of neuropathic pain following spinal cord injury (**U**) (**Level II**).

☑ Treatment of acute spinal cord injury pain is largely based on evidence from studies of other neuropathic and nociceptive pain syndromes (**U**).

☑ There is currently insufficient evidence to support non-pharmacological treatments (TENS, acupuncture, self-hypnosis or cognitive behavioural therapy) for spinal cord injury pain (**N**).

Chest trauma (Rib fractures)

1. Surgical fixation in patients with 3 or more fractured ribs improves outcome with regard to incidence of pneumonia and need for tracheostomy (**N**) (**Level I** [Cochrane Review]), duration of ventilation, ICU and hospital stay (**N**) (**Level I**) and mortality (**N**) (**Level III-2 SR**).
2. Continuous thoracic epidural analgesia and continuous intercostal and paravertebral blocks provide similar analgesia and are superior to intravenous opioids for rib fracture related pain (**N**) (**Level I** [PRISMA]).
3. Systemic NSAIDs and ketamine are efficacious analgesic adjuvants for rib fracture related pain (**N**) (**Level III-3**)

☑ Emerging regional techniques such as serratus anterior and erector spinae plane blocks (single shot and continuous infusion) are supported by case series and could be considered for rib fracture analgesic management (**N**).

☑ Chest trauma with rib fractures carries a high risk of potentially life-threatening complications; excellent analgesia and aggressive physical rehabilitation, ideally provided in a protocolised clinical pathway, can improve outcome (**N**)

Acute pain after hip (neck of femur) fractures

1. Lower limb nerve blocks with local anaesthetics reduce pain, analgesia requirements and lengthen time to rescue analgesia in hip fracture patients compared to systemic analgesia; there is no advantage of a specific nerve block, insertion technique or continuous versus single injection administration (**S**) (**Level I** [Cochrane Review]).
2. Lower limb nerve blocks decrease the risk of pneumonia in hip fracture patients, but do not decrease the risk of delirium, myocardial infarction/ischaemia or mortality (**N**) (**Level I** [Cochrane Review]).
3. Morphine should be avoided due to increased risk of delirium in hip fracture patients, who have a high prevalence of renal impairment (**N**) (**Level III-3 SR**).
4. Arthroplasty techniques in hip fracture patients are associated with less pain and opioid requirements than non-arthroplasty techniques (**N**) (**Level III-2**).

☑ Integrated orthogeriatric care, utilisation of care bundles and adherence to clinical care standards improve outcomes in hip fracture patients (**N**).

Acute burns injury pain

1. The use of biosynthetic dressings is associated with a decrease in time to healing and a reduction in pain during burns dressings changes (**U**) (**Level I** [Cochrane Review]).
2. Virtual reality distraction, augmented reality techniques and multimodal distraction methods reduce pain and unpleasantness during burns dressings (**S**) (**Level I** [PRISMA]).
3. Music interventions are helpful in reducing pain, anxiety and heart rate in burns patients (**N**) (**Level I** [PRISMA])
4. Opioids, particularly via PCA, are effective in burns pain, including procedural pain (**U**) (**Level II**).

5. Pregabalin reduces pain following acute burns injury (**U**) (**Level II**).
6. Sedation and anxiolysis with lorazepam improves procedural pain relief in acute burns injury (**U**) (**Level II**).
7. Regional analgesia reduces donor site pain in selected burns patients (**U**) (**Level II**).
8. Gabapentin reduces pain and opioid consumption following acute burns injury (**U**) (**Level III-3**).
9. PCA with ketamine and midazolam mixture provides effective analgesia and sedation for burns dressings (**U**) (**Level IV**).

☑ Acute pain following burns injury can be nociceptive and/or neuropathic in nature and may be constant (background pain), intermittent or procedure-related (**U**).

☑ Acute pain following burns injury requires aggressive multimodal and multidisciplinary treatment and may benefit from protocolised management approaches (**S**). This is particularly important as severely burn injured patients require repeated procedures and frequently have persistent issues of chronic pain, pruritus, post-traumatic stress and other psychological consequences.

☑ Pruritus is a common symptom following burns injury and alpha-2-delta ligands are useful in its management (**N**).

Acute medical pain

Acute abdominal pain

1. Provision of analgesia does not interfere with the diagnostic process in acute abdominal pain and does not increase the risk of errors in clinical management (**U**) (**Level I** [Cochrane Review]).
2. NSAIDs, opioids and intravenous metamizole (dipyrone) provide effective analgesia for renal colic (**S**) (**Level I** [Cochrane Review]).
3. NSAIDs given for renal colic reduce pain (**N**) (**Level I** [PRISMA]) and rescue analgesia requirements with less vomiting compared with opioids, particularly pethidine (meperidine) (**S**) (**Level I** [Cochrane Review]).
4. Alpha blockers as expulsive therapy for ureteral stones reduce the number of pain episodes and analgesic requirements (**S**) (**Level I** [Cochrane Review]).
5. Antispasmodics and tricyclic antidepressants, but not bulking agents, are effective for the treatment of acute pain in irritable bowel syndrome (**S**) (**Level I** [Cochrane Review]) as well as psychological interventions (**N**) (**Level I**).
6. NSAIDs are effective in primary dysmenorrhoea and superior to paracetamol (**S**) (**Level I** [Cochrane Review]).
7. The smooth muscle relaxant buscopan does not add further analgesic benefit when combined with metamizole (dipyrone) (**U**) (**Level I** [Cochrane Review]), opioids or NSAIDS to treat pain of renal colic (**U**) (**Level II**).
8. High-frequency TENS, possibly some dietary supplements and acupuncture/acupressure are effective in the treatment of primary dysmenorrhoea (**S**) (**Level I** [Cochrane Review]).

9. NSAIDS are superior to placebo and spasmolytics and as effective as opioids in the treatment of biliary colic (**S**) (**Level I** [Cochrane Review])
10. The perioperative use of NSAIDs for endoscopic retrograde cholangiopancreatography (ERCP) reduces the risk of post ERCP pancreatitis (**S**) (**Level I** [PRISMA]).
11. $5HT_3$ antagonists reduce some of the symptoms of irritable bowel syndrome (**S**) (**Level I** [QUOROM).
12. The onset of analgesia is faster when NSAIDs are given intravenously for the treatment of renal colic (**U**) (**Level I**).
13. Intravenous paracetamol is as effective as intravenous morphine and superior to intramuscular piroxicam for analgesia in renal colic (**U**) (**Level II**).
14. There is no difference between pethidine and morphine for analgesia in renal colic (**U**) (**Level II**).
15. Low-dose ketamine is an effective analgesic for renal colic pain (**N**) (**Level II**).
16. IV lidocaine is an effective analgesic for renal colic pain (**N**) (**Level IV SR**).

Herpes zoster-associated pain

1. Antiviral agents started within 72 hours of onset of the herpes zoster rash accelerate the resolution of acute pain (**U**) (**Level I**) but do not reduce the incidence, severity and duration of postherpetic neuralgia (**U**) (**Level I** [Cochrane Review]).
2. Immunisation of persons aged 60 years or older reduces the incidence of herpes zoster and thereby postherpetic neuralgia with Zostavax® (**U**) (**Level I** [Cochrane Review]) and Shingrix® (**N**) (**Level II**).
3. Continuous or repeated paravertebral blocks in the acute phase of herpes zoster reduce the incidence of postherpetic neuralgia at 3, 6 and 12 months (**N**) (**Level I**).
4. Amitriptyline (used in low doses for 90 days from onset of the herpes zoster rash) reduces the incidence of postherpetic neuralgia (**U**) (**Level II**).
5. Topical aspirin, topical lignocaine patch or controlled-release oxycodone provide analgesia in acute pain due to herpes zoster (**U**) (**Level II**).
6. Nerve blocks in the acute phase of herpes zoster reduce the duration of herpes zoster-associated pain (**N**) (**Level III-I SR**).
6. Continuous epidural analgesia in the acute phase of herpes zoster reduces the incidence of postherpetic neuralgia at 3 months (**N**) (**Level III-I SR**).

☑ Provision of early and appropriate analgesia is an important component of the management of herpes zoster and may have benefits in reducing the incidence of postherpetic neuralgia (**U**).

Acute cardiac pain

1. The routine use of oxygen in normoxic patients with acute myocardial infarction does not reduce pain or mortality (**S**) (**Level I** [Cochrane].
2. Morphine is an effective and appropriate analgesic for acute cardiac pain, but may interfere with pharmacokinetics and pharmacodynamics of some platelet inhibitors (**Q**) (**Level II**).

3. Nitroglycerine is an effective and appropriate agent in the treatment of acute ischaemic chest pain (**S**) (**Level IV**).

☑ The mainstay of analgesia in acute coronary syndrome is the restoration of adequate myocardial oxygenation, nitroglycerine, beta blockers and strategies to improve coronary vascular perfusion (**U**).

Acute pain associated with haematological disorders

1. Parenteral corticosteroids reduce the duration of severe pain, analgesia requirements and hospital length of stay, without major adverse effects, during vaso-occlusive crises in sickle cell disease (**U**) (**Level I** [Cochrane Review]).
2. There is no evidence that fluid replacement therapy (**S**) or intravenous or oral magnesium reduces pain associated with vaso-occlusive crises in sickle cell disease (**N**) (**Level I** [Cochrane Review]).
3. Hydroxyurea decreases the frequency of vaso-occlusive crises, life-threatening complications and transfusion requirements in sickle cell disease (**S**) (**Level I** [Cochrane Review]).
4. Zinc reduces the incidence of painful vaso-occlusive crises in sickle cell disease (**U**) (**Level I** [Cochrane Review]).
5. Intravenous opioid loading optimises analgesia in the early stages of a vaso-occlusive crisis in sickle cell disease; effective analgesia may be continued with intravenous opioid therapy, optimally as PCA, or as oral opioids (**S**) (**Level II**).
6. Single-dose ketorolac does not reduce opioid requirements in vaso-occlusive crisis in sickle cell disease (**N**) (**Level II**), but may increase the risk of acute kidney injury (**N**) (**Level III-3**).
7. Oxygen supplementation does not decrease pain during a vaso-occlusive crisis in sickle cell disease (**U**) (**Level II**), but hyperbaric oxygen may be effective (**U**) (**Level III-3**).
8. Intravenous ketamine and intravenous lidocaine reduced pain intensity and opioid requirements in vaso-occlusive crisis in sickle cell disease (**N**) (**Level IV**).

Acute headache

Tension-type headache

1. Acupuncture may be effective in the treatment of tension-type headache (**S**) (**Level I** [Cochrane Review]).
2. Simple analgesics such as paracetamol or NSAIDs, either alone or combined, are effective in the treatment of episodic tension-type headache (**S**) (**Level I** [PRISMA]).
3. Metoclopramide, metamizole and chlorpromazine as parenteral treatments of tension-type headache have high efficacy (**U**) (**Level I** [PRISMA]).
4. The combination of caffeine/aspirin/paracetamol is superior to paracetamol in the treatment of episodic tension-type headache (**U**) (**Level I**).

Migraine

5. Paracetamol is effective in the treatment of migraine, however less than other analgesics; the efficacy is increased when combined with metoclopramide (**U**) (**Level I** [Cochrane Review]).

6. Aspirin, ibuprofen, diclofenac and dipyrone are effective in the treatment of migraine; soluble preparations of ibuprofen provide a faster onset (**U**) (**Level I** [Cochrane Review]).
7. For sumatriptan, subcutaneous administration achieves the fastest onset of effect and highest efficacy (**U**) (**Level I** [Cochrane Review]).
8. The combination naproxen/sumatriptan has increased efficacy and better tolerability than sumatriptan on its own (**N**) (**Level I** [Cochrane Review]).
9. The addition of caffeine to simple analgesics improves their analgesic efficacy and tolerability in acute migraine (**N**) (**Level I** [Cochrane Review]).
10. Hyperbaric oxygen therapy is effective in controlling pain in migraine, but no other symptoms and outcomes (**U**) (**Level I** [Cochrane Review]).
11. A significant placebo effect occurs in migraine treatment (**N**) (**Level I** [QUOROM]), leading to an underestimation of treatment effects of analgesic medications (**N**) (**Level II**).
12. Parenteral antiemetics, metoclopramide (**S**) (**Level I** [PRISMA]) and droperidol (**U**) (**Level I**) are effective in the treatment of migraine.
13. Phenothiazines and butyrophenones (at the expense of more adverse effects) are effective in the treatment of migraine, in particular in the emergency department (**S**) (**Level I**).
14. All triptans are more effective than placebo in the treatment of severe migraine (**S**) (**Level I**), however 30 to 40% of patients may not respond (**N**) (**Level I**).
15. Triptans and mefenamic acid are effective in treatment of menstruation-related migraine (**U**) (**Level I**).
16. Some opioids are more effective than placebo in the treatment of acute migraine (**U**) (**Level I**), but their use in this setting is associated with significant adverse effects and poor outcomes (**S**) (**Level III-2**).
17. Pethidine is less effective than most other migraine treatments and should not be used (**U**) (**Level I**).
18. Intravenous magnesium may have some analgesic effect compared to placebo in migraine (**Q**) (**Level I** [PRISMA]).
19. A "*stratified care strategy*" is effective in treating migraine (**U**) (**Level II**).
20. Ergotamine derivatives, but not triptans, increase the rate of severe myocardial ischaemic events (**U**) (**Level III-2 SR**).
21. Migraine in pregnancy is a risk factor for gestational hypertension, preeclampsia and cardiovascular complications (**U**) (**Level III-2**).

Cluster headache

22. Parenteral triptans (sumatriptan or zolmitriptan) or high-flow oxygen therapy are effective treatments for cluster headache attacks (**S**) (**Level I** [Cochrane Review]).
23. Sphenopalatine ganglion local anaesthetic block has moderate evidence support for the treatment of acute cluster headaches (**N**) (**Level IV SR**).

Postdural puncture headache

24. There is no evidence that bed rest or fluid supplementation are beneficial in the treatment and prevention of postdural puncture headache (**S**) (**Level I** [Cochrane Review]).

25. Epidural blood patch administration is more effective than conservative treatment or a sham procedure in the treatment of postdural puncture headache (**S**) (**Level I** [Cochrane Review]).

26. Risk of postdural puncture headache is reduced with preventive use of morphine, cosyntropin or aminophylline, especially in patients at high risk; preventive dexamethasone use increases risk of postdural puncture headache (**N**) (**Level I** [Cochrane Review]).

27. Caffeine, gabapentin, hydrocortisone or theophylline are effective treatments for postdural puncture headache (**S**) (**Level I** [Cochrane Review]).

28. The incidence of postdural puncture headache is reduced by using smaller-gauge spinal or non-cutting bevel needles or by orientating the cutting bevel parallel to the spinal sagittal plane (**U**) (**Level I**).

Medication overuse headache

29. Frequent use (>8–10 days/month) of paracetamol, NSAIDs and opioids for recurrent acute headache (more so than triptans and ergot derivatives) may lead to medication overuse headache; weaning and use of preventive medication are recommended management approaches (**S**) (**Level IV SR**).

☑ Opioids should be used with extreme caution in the treatment of headache; pethidine should not be used at all (**S**).

Acute pain associated with neurological disorders

1. Various anticonvulsants (**U**) (**Level I** [PRISMA]) and duloxetine (**N**) (**Level II**) have beneficial effects in the treatment of neuropathic pain associated with multiple sclerosis

2. Cannabinoids have a clinically small effect on spasticity caused by multiple sclerosis (**U**) (**Level I**); the effect on neuropathic pain associated with multiple sclerosis is unclear and may depend on the preparation used (**W**) (**Level I** [PRISMA]).

3. With cannabinoid use in multiple sclerosis, there is a high rate of minor adverse effects and serious adverse psychopathological effects occur in nearly 1% of patients (**U**) (**Level I**).

4. Acupuncture (**N**) (**Level I**), non-invasive brain stimulation (**N**) (**Level III-3 SR**) and motor cortex stimulation (**N**) (**Level IV SR**) may reduce post-stroke pain.

5. Local anaesthetics (mainly lidocaine) by local and systemic administration, anticonvulsants (phenytoin or IV fosphenytoin) and sumatriptan reduce pain in acute exacerbations of trigeminal neuralgia (**N**) (**Level IV SR**).

6. Motor cortex stimulation may reduce acute pain in trigeminal neuralgia (**N**) (**Level IV SR**)

7. Deep brain stimulation may improve pain relief in Parkinson's disease (**N**) (**Level IV**).

☑ Treatment of acute pain associated with neurological disorders is based largely on evidence from trials for the treatment of a variety of chronic neuropathic pain states (**S**).

Acute orofacial pain

Acute dental pain

1. NSAIDs and emergency pulpectomy reduce pain in patients with acute apical periodontitis (**U**) (**Level I**) with insufficient evidence to support analgesic benefit from adding antibiotics (**S**) (**Level I** [Cochrane Review]).

Dental extraction

2. Paracetamol, nonselective NSAIDs and coxibs provide safe and effective analgesia with minimal adverse effects after dental extraction (**S**) (**Level I** [Cochrane Review]).
3. Combinations of paracetamol with ibuprofen (**U**) (**Level I** [Cochrane Review]) and other nonselective NSAIDs (**U**) (**Level I**) provide superior analgesia to either drug alone after dental extraction.
4. Tramadol provides equal analgesia to paracetamol/weak opioid and aspirin/weak opioid combinations (**U**) (**Level I** [Cochrane Review]) and tramadol/paracetamol combinations provide superior analgesia to tramadol alone after dental extraction (**U**) (**Level I**).
5. Nonselective NSAIDs and coxibs provide similar analgesia, which is superior to paracetamol, codeine, combinations of paracetamol/codeine (**U**) (**Level I**), tramadol (**S**) (**Level I**) and pethidine (**U**) (**Level II**) after dental extraction.
6. Perioperative corticosteroid administration reduces swelling, but not pain (**U**) (**Level I**), and reduces postoperative nausea (**U**) (**Level II**) after third molar extraction.

Tonsillectomy

7. Nonselective NSAIDs (**U**) (**Level I**), in particular aspirin and ketorolac (**U**) (**Level II**), increase the risk of reoperation for bleeding after tonsillectomy in adults, but not in children (**U**) (**Level I** [Cochrane Review]).
8. Intraoperative dexamethasone administration reduces postoperative pain, nausea and vomiting and time to resumption of oral intake after tonsillectomy (**S**) (**Level I** [Cochrane Review]), with no increase in adverse effects (**U**) (**Level I** [Cochrane Review]).
9. Paracetamol, NSAIDs (**S**) (**Level I** [PRISMA]), dexamethasone, preoperative alpha-2-delta ligands (**S**) and dextromethorphan are effective analgesics after tonsillectomy (**N**) (**Level I** [PRISMA]).
10. Intraoperative cryothgerapy may reduce post-tonsillectomy pain (**N**) (**Level I** [PRISMA]).
11. Oral administration of honey versus control reduces postoperative pain and analgesic use after tonsillectomy (**N**) (**Level I** [PRISMA]).
12. Peritonsillar infiltration or topical application of local anaesthetics are equally effective in producing a modest reduction in acute post-tonsillectomy pain (**U**) (**Level I**).
13. Dexamethasone, magnesium (and with limited support pethidine and tramadol) combined with local anaesthetics for peritonsillar infiltration improve analgesia and other outcomes after tonsillectomy (**N**) (**Level I**).
14. Perioperative antibiotics show no benefit in post-tonsillectomy pain, but increase adverse effects (**S**) (**Level I**).
15. Acupuncture may reduce post-tonsillectomy pain compared to control group or sham acupuncture (**N**) (**Level I**)

16. Peritonsillar infiltration with tramadol or ketamine may reduce post-tonsillectomy pain and analgesia requirements but was no more effective than equivalent doses administered parenterally (**U**) (**Level II**).

Pharyngitis

17. Corticosteroids (**S**) (**Level I** [Cochrane Review]) and antibiotics (**U**) (**Level I** [Cochrane Review]) improve analgesia and reduce duration of pain in pharyngitis.

18. Amylmetacresol/2,4-dichlorobenzylalcohol (AMC/DCBA) lozenges (**N**) (**Level I** [PRISMA]), ketamine gargle (**N**) (**Level I** [PRISMA]), benzydamine spray (**U**) (**Level I**) and other topical analgesics (**U**) (**Level II**) provide analgesia superior to placebo in acute sore throat with minimal adverse effects.

19. Corticosteroids reduce acute pain associated with peritonsillar abscess (following drainage and antibiotics) (**S**) (**Level I** [PRISMA]).

20. Paracetamol, NSAIDs (nonselective NSAIDs or coxibs) and opioids, administered as monotherapy or in combination, are effective analgesics in acute pharyngitis (**U**) (**Level I**).

Sinusitis and otitis media

21. Oral corticosteroids have no analgesic effect in sinusitis (**U**) (**Level I** [Cochrane Review]), but intranasal corticosteroids reduce facial pain and improve recovery (**S**) (**Level I** [Cochrane Review]).

22. Antibiotic treatment of acute otitis media vs placebo or control has no effect on acute pain, only limited effect on later pain, but increases the risk of adverse effects (**N**) (**Level I** [Cochrane Review]).

23. In acute otitis media, topical local anaesthetic drops are effective in children compared to placebo and equivalent to naturopathic drops (**S**) (**Level I** [Cochrane Review]).

☑ Codeine should not be used in children, especially after adenoidectomy or tonsillectomy, due to an increased risk of opioid-induced ventilatory impairment and death (**U**).

☑ Recurrent or persistent orofacial pain requires biopsychosocial assessment and appropriate multidisciplinary approaches (**U**).

☑ Neuropathic orofacial pain, which is often post-traumatic (iatrogenic), may be exacerbated by repeated dental procedures, incorrect drug therapy or psychosocial factors (**U**).

Acute pain in patients with HIV infection

1. High-concentration capsaicin patches have some efficacy in treating neuropathic pain in patients with HIV/AIDS (**S**) (**Level I** [Cochrane Review]).
2. Smoking cannabis has short-term efficacy in treating neuropathic pain in patients with HIV/AIDS, although potential study bias means that this is not recommended as routine treatment (**Q**) (**Level I** [PRISMA])**.**
3. HIV/AIDS patients with a history of problematic drug use report higher opioid analgesic use but also more intense pain (**U**) (**Level III-2**).
4. Pain, and notably neuropathic pain, is common in patients with HIV (**U**) (**Level IV**).

☑ HIV/AIDS has become a chronic, manageable condition; in view of limited specific evidence, the treatment of pain in patients with HIV/AIDS should be based on similar principles to those for the management of acute, cancer and chronic pain in the general population (**S**).

☑ Interactions between antiretroviral medications, antibiotics and analgesics should be considered in this population and reference to a current guide of likely drug interactions is strongly recommended (**S**).

Acute cancer pain

1. Intranasal, sublingual and buccal fentanyl preparations are effective treatments for breakthrough pain in cancer patients (**U**) (**Level I** [Cochrane Review]) with similar efficacy to intravenous administration (**U**) (**Level I** [PRISMA]) and superior to oral morphine (**U**) (**Level I**).
2. Radiotherapy is an effective treatment of acute cancer pain due to bone metastases (**U**) (**Level I** [Cochrane Review]), while bone-targeting agents (bisphosphonates, denosumab) are beneficial in delaying the onset of bone pain rather than providing analgesia (**W**) (**Level I** [PRISMA]).
3. Neurolytic coeliac plexus block in pancreatic cancer lowers pain intensity and opioid analgesic requirements for at least 8 weeks (**U**) (**Level I** [Cochrane Review]).
4. Opioids, via PCA or a continuous infusion, provide effective analgesia in mucositis; PCA is associated with reduced opioid requirements and pain duration (**U**) (**Level I** [Cochrane Review]).
5. Oral cryotherapy (sucking on ice chips or holding ice water in the mouth before, during, and/or after rapid infusions of systemic therapies that result in mucositis) effectively prevents mucositis (**N**) (**Level I** [Cochrane Review]).
6. Music interventions may be effective in reducing pain intensity in patients with cancer (**N**) (**Level I** [Cochrane Review]).
7. Topical treatment with doxepin (**S**), amitriptyline (**N**), diclofenac (**N**), benzydamine (**N**) (**Level I** [PRISMA]), povidone-iodine (**U**) (**Level I**) and morphine (**S**) (**Level II**) compared to placebo improve pain relief due to mucositis.
8. Low-level laser therapy reduces and when used prophylactically prevents pain and severity of mucositis (**S**) (**Level I** [PRISMA]).
9. Patient education about cancer pain is a key factor in optimising pain management (**U**) (**Level I**).
10. Opioid doses for individual patients with cancer pain should be titrated to achieve maximum analgesic benefit with minimal adverse effects (**U**) (**Level II**).
11. Analgesic medications prescribed for cancer pain should be adjusted to alterations of pain intensity (**U**) (**Level III-2**).
12. Neuropathic pain or mixed nociceptive-neuropathic pain has an estimated frequency of 30-40% in patients with cancer (**S**) (**Level IV SR**).

- ☑ Acute pain in patients with cancer often signals disease progression; sudden severe pain in patients with cancer should be recognised as a medical emergency and immediately assessed and treated (**U**).
- ☑ Prompt assessment and fast coordinated management of spinal metastases with suspected spinal cord compression is required to mitigate against neurological deficit (**U**).
- ☑ Cancer patients receiving controlled-release opioids need access to immediate-release opioids for titration of breakthrough pain; ~~s~~election of breakthrough medication should consider the time course and aetiology of the pain flare (**U**).
- ☑ If nausea and vomiting accompany acute cancer pain, parenteral opioids are needed (**U**).
- ☑ Transdermal opioids are inappropriate to control acute unstable pain (**U**).
- ☑ High interindividual variability in opioid conversion rates dictates that all opioid rotations should be individualised and monitored, particularly where higher opioid doses are in use (**U**).

Acute pain management in intensive care

1. Plasma exchange in acute Guillain-Barre syndrome improves outcome including analgesia (**U**) (**Level I** [Cochrane Review]).
2. Carbamazepine and gabapentin may reduce the pain associated with Guillain-Barre syndrome, based on limited and low-quality evidence (**U**) (**Level I** [Cochrane Review]).
3. Non-opioids including NSAIDs and paracetamol improve analgesia in selected intensive care unit patients (**S**) (**Level I** [PRISMA]).
4. Remifentanil provides no advantages over other opioids in ventilated intensive care unit patients (**U**) (**Level I**).
5. Ketamine decreases cumulative opioid doses in mechanically ventilated patients, with positive effects on haemodynamics and reduced requirements for sedation, but with an increased risk of psychomimetic adverse effects (**N**) (**Level II**).
6. The formal assessment and management of pain and agitation in ventilated intensive care unit patients decreases the incidence of pain, the duration of ventilation, the length of ICU stay and mortality (**U**) (**Level III-1**).
7. Prolonged opioid infusions for >6 days and higher cumulative opioid dose increase the risk of acute withdrawal if the opioid infusion is abruptly ceased (**N**) (**Level III-2**).
8. Procedures such as endotracheal tube suctioning are consistently reported as uncomfortable and painful (**U**) (**Level III-2**).

- ☑ The aetiology of acute pain in critically ill patients is complex and encompasses all domains of the sociopsychobiomedical model of pain (**N**).
- ☑ Observation of behavioural and physiological responses permits assessment of pain in unconscious patients (**U**).
- ☑ Routine monitoring for pain in sedated intensive care patients should be performed, using the Behavioural Pain Scale or the Critical-Care Pain Observation Tool (**U**).
- ☑ Analgesia management should be targeted to the potential aetiologies of acute pain (**N**).

☑ Opioids are the recommended first-line analgesic agents in ventilated intensive care patients (**U**).

☑ The risk of NSAIDs in critically ill patients may be overestimated; NSAIDs may provide effective analgesia as a part of multimodal analgesia (**N**).

☑ Regional analgesia techniques should be considered in patients undergoing large intra-abdominal surgical procedures and trauma (**N**).

☑ Intensive care unit patients should be provided with appropriate analgesia prior to and during potentially painful procedures, in particular as recall of discomfort, pain and procedures can be a source of post-traumatic stress (**S**).

Acute pain management in emergency departments

1. Paracetamol, in particular if administered IV, and NSAIDs are effective primary analgesics for use in the emergency department (**N**) (**Level I** [PRISMA]).
2. Sublingual buprenorphine (**N**) (**Level I** [PRISMA]) or intranasal fentanyl (**N**) (**Level I**) are effective alternatives to parenteral opioids in the emergency department.
3. Low dose ketamine is a safe and effective analgesic alone or when combined with opioids in the emergency department, but increases neuro-psychological adverse events (**N**) (**Level I** [PRISMA]).
4. Appropriate doses of intravenous opioids are effective in treating acute severe pain in the emergency department and ideally should be titrated according to nurse-initiated and patient-driven protocols; there is no preference for a specific opioid (**U**) (**Level I**).

Abdominal pain

5. Provision of analgesia does not interfere with the diagnostic process in acute abdominal pain and does not increase the risk of errors in clinical management (**U**) (**Level I** [Cochrane Review]).

Migraine

6. NSAIDs, triptans (**S**) (**Level I** [Cochrane]), phenothiazines (prochlorperazine, chlorpromazine), butyrophenones and metoclopramide are effective to treat migraine in the emergency department (**U**) (**Level I**).

Fractured neck of femur

7. Lower limb nerve blocks with local anaesthetics reduce pain, analgesia requirements and lengthen time to rescue analgesia in hip fracture patients compared to systemic analgesia; there is no advantage of a specific nerve block, insertion technique or continuous versus single injection administration (**S**) (**Level I** [Cochrane Review]).

Shoulder dislocation

8. Intra-articular local anaesthetics provide comparable analgesia for reduction of gleno-humeral dislocation to procedural sedation and analgesia methods with fewer adverse events (**N**) (**Level I** [Cochrane Review]).

Wounds

9. Buffering of lignocaine with bicarbonate reduces the pain of infiltration, particularly when using lignocaine with adrenaline (**U**) (**Level I** [Cochrane Review]).

10. Topical local anaesthetic agents (including those in liposomal formulations) (**S**) (**Level I** [Cochrane Review]) or topical local anaesthetic-adrenaline agents (**U**) (**Level II**) provide effective analgesia for wound care in the emergency department.

Musculoskeletal Pain

11. Centrally acting muscle relaxants do not improve analgesia in the acute treatment of lower back pain (**N**) (**Level II**).

Non-pharmacological management of pain

12. Acupuncture may provide effective analgesia as a single agent or adjunct in the emergency department (**N**) (**Level I** [PRISMA]).

☑ To ensure optimal management of acute pain, emergency departments should adopt systems to ensure adequate assessment of pain, provision of timely, adequate and appropriate analgesia, frequent monitoring and reassessment of pain (**U**).

Prehospital analgesia

1. Transcutaneous electrical nerve stimulation TENS provides pain relief in the prehospital setting (**N**) (**Level I** [PRISMA]).
2. Intravenous morphine, fentanyl and tramadol are equally effective in the prehospital setting (**S**) (**Level II**).
3. Nitrous oxide is an effective analgesic agent in prehospital situations (**U**) (**Level II**).
4. Methoxyflurane, in low concentrations, is an effective analgesic with rapid onset in the prehospital and hospital setting with good safety data (**U**) (**Level II**).
5. Ketamine is a safe and effective analgesic in the prehospital setting (**U**) (**Level II**).
6. Moderate to severe pain is common in both adult and paediatric patients in the prehospital setting (**S**) (**Level IV**) and is often poorly managed (**N**) (**Level III-2**).
7. Fascia iliaca compartment block is an effective analgesic technique for patients with isolated femoral shaft fractures in the prehospital setting (**N**) (**Level IV SR**).
8. The prehospital setting presents challenges beyond those encountered in hospital to the assessment, documentation, treatment and reassessment of pain in both adult and paediatric patients (**N**) (**Level IV**).

☑ Nonpharmacological measures are effective in providing pain relief and should always be considered and used if practical (**U**).

Discharge opioid medication for acute pain management

1. Short-term opioid therapy may lead to long term opioid use and misuse (**S**) (**Level III-2**); risk factors for prolonged postoperative use include preoperative opioid use, type of surgery, slow-release opioids, psychological and social factors and pre-existing alcohol or substance use disorder (N) (**Level III-2**).
2. Recent introduction of opioid therapy may increase the risk of falls (**S**) (**Level III-2**).
3. Recent introduction of opioid therapy or recent dose escalation may impair driving (**S**) (**Level III-2**), thereby leading to increased driving accidents (**N**) (**Level III-3 SR**); this risk is further increased by combined use of opioids and alcohol (**N**) (**Level III-2**).

4. Many patients who retain unused opioid tablets are willing to share them with others (**S**) (**Level III-2**); this contributes to increased risks of abuse and adverse effects in the recipients (**N**) (**Level IV**).
5. The most common source of prescription opioids for nonmedical use is a friend or relative (**N**) (**Level III-3**).

☑ Unused opioids prescribed for postoperative pain are potentially a large reservoir for opioid abuse, misuse and diversion (**S**).

☑ A "universal precautions" approach for opioid prescribing should be used in the setting of prescribing discharge medications (**S**).

☑ Prescribing discharge medications should be done in consideration of opioid requirements on the day before discharge, avoiding slow-release opioids and for a limited duration (**N**).

☑ Patient education about risks of opioids and safe disposal of unused medication by return to a pharmacy and follow-up by GP or pain medicine services in case of ongoing issues improve safety of discharge medications (**N**).

9.0 | Other specific patient groups

The pregnant patient

Use of analgesic medications in pregnancy

1. Short-term use of NSAIDs in late pregnancy is associated with an increase in the risk of premature closure of the ductus arteriosus (**U**) (**Level I** [Cochrane Review]).
2. The chronic use of opioids during pregnancy may be associated with some teratogenic effects, childhood neurocognitive delay and/or negative neurobehavioural outcomes; however, it is difficult to separate the influence of multiple confounders in this patient group (**Q**) (**Level III-2 SR**).
3. Retrospective epidemiological studies linking paracetamol use in pregnancy to later development of childhood asthma are inherently confounded (**U**); when adjusted for respiratory tract infections in the child the association is lost (**Q**) (**Level III-2 SR**).
4. The use of common nsNSAIDS during pregnancy is not associated with increased risk of major congenital malformations, structural heart defects or difference in infant survival (**N**) (**Level III-2**).
5. Exposure to an nsNSAID or coxib is not an independent risk factor for spontaneous abortion (**Q**) (**Level III-2**)
6. The safety of alpha-2-delta ligand use in pregnancy remains unclear; limited data has not raised safety concerns (**N**) (**Level III-2**).

☑ For pain management in pregnancy, nonpharmacological treatment options should be considered where possible before analgesic medications are used (**U**).

☑ Use of medications for pain in pregnancy should be guided by published recommendations; ongoing analgesic use requires close liaison between the patient, the health professional managing the pregnancy and the health professional managing the pain (**U**).

☑ Most of the data reported in this setting are from episodes of prolonged use (eg for chronic conditions) and there is a lack of data on the risk of short-term exposure such as in the treatment of acute pain (**N**).

☑ Studies of analgesic use during pregnancy may be confounded by the indication, recall bias and often the lack of an active comparator; this is exemplified by reported associations between NSAID use in pregnancy and low birth weight and asthma confounded by the maternal indications for their use (ie inflammatory diseases) (**N**).

☑ Nonselective NSAIDs and Coxibs should be used with caution in the last trimester of pregnancy and should be avoided after the 32nd week (**U**).

☑ Emerging evidence suggests that maternal paracetamol use may influence premature closure of the fetal ductus arteriosus (**N**).

☑ Neonates exposed to regular opioid in utero, particularly in the last three months of pregnancy, are at risk of neonatal abstinence syndrome and should be monitored for it after delivery (N).

Pain syndromes in pregnancy

1. Exercise reduces low back and pelvic girdle pain during pregnancy (**S**) (**Level I** [Cochrane Review]).
2. Manual therapy interventions reduce intensity of pregnancy-related back and pelvic pain versus usual care and relaxation, but not to sham interventions (**N**) (**Level I** [PRISMA])

☑ The use of a pelvic support belt may reduce pelvic girdle pain during pregnancy (**N**).

Management of acute pain during labour and after birth

Neuraxial and regional analgesia for pain in labour

1. Epidural and combined spinal-epidural analgesia provides superior pain relief for labour and delivery compared with all other analgesic techniques (**S**) along with improved maternal satisfaction (**R**) (**Level I** [Cochrane Review]).
2. Epidural analgesia compared to systemic opioid reduces maternal nausea and/or vomiting (**N**) and need for maternal oxygen supplementation (**N**), but increases the duration of the first and second stage of labour slightly (**Q**) (**Level I** [Cochrane Review]).
3. Epidural analgesia compared to systemic opioid does not increase the rate of Caesarean section (**S**), long-term backache (**S**), headache (**N**), pruritus (**N**) or postnatal depression (**N**) (**Level I** [Cochrane Review]).
4. Epidural analgesia compared to systemic opioids reduces the risk of fetal acidosis (**S**) and the need for neonatal naloxone administration with no increase in special care/neonatal intensive care unit admissions (**N**) (**Level I** [Cochrane Review]).
5. Epidural analgesia may increase the rate of assisted vaginal delivery (**U**), but not with contemporary techniques of epidural analgesia (use of low-concentrations of local anaesthetics) (**Q**) (**Level I** [Cochrane Review]).
6. Lower concentrations of local anaesthetics for epidural analgesia in labour result in a shorter duration of second stage of labour, fewer assisted vaginal deliveries, greater ambulation and less urinary retention than higher concentrations (**S**) (**Level I** [Cochrane Review]).

7. Early versus late initiation of epidural analgesia leads to no clinically significant differences in outcome (**S**) (**Level I** [Cochrane Review]).
8. In comparison with epidural analgesia, combined spinal-epidural analgesia reduces time to effective analgesia (**U**), does not increase maternal satisfaction (**U**), increases the incidence of mild pruritus (compared to low-dose epidurals) (**U**) (**Level I** [Cochrane Review]) and reduces the risk of unilateral block (**N**) (**Level I** [PRISMA]).
9. Local anaesthetic nerve blocks (in particular paracervical blocks) provide better analgesia than placebo, nonopioids and opioids for labour pain, but at an increased rate of adverse effects (**U**) (**Level I** [Cochrane Review]).
10. Non-reassuring fetal heart rate tracings can be more common with combined spinal-epidural analgesia than epidural analgesia in labour (**N**) (**Level I** [PRISMA]).
11. Ultrasound guidance improves the success of epidural catheter insertion and intrathecal needle placement and reduces traumatic insertions (**N**) (**Level I** [PRISMA]).
12. Patient-controlled epidural analgesia provides effective analgesia for labour (**U**) but optimal settings (**U**) (**Level I**) and the need for a background infusion remain unclear (**U**) (**Level I** [PRISMA]).
13. Programmed intermittent epidural bolus versus continuous epidural infusion reduces the incidence of breakthrough pain without increasing adverse outcome (**S**) (**Level I** [PRISMA]).
14. Dural puncture epidural analgesia does not appear to offer benefit over standard epidural analgesia (N) (**Level I** [PRISMA]).
15. There is no difference between the use of bupivacaine and ropivacaine for epidural analgesia in labour for any outcome (**U**), except ropivacaine may reduce the incidence of motor block (**Q**) (**Level I**).
16. Single-injection intrathecal opioids provide comparable early labour analgesia to epidural local anaesthetics, with increased pruritus but no difference in nausea (**U**) (**Level I**). Adding single injection intrathecal morphine (≤250 mcg) to local anaesthetic combined with shorter acting opioids increases time to first analgesic request, but is associated with increased adverse effects **(N)** (**Level I**).

Systemic analgesia for pain in labour

17. Analgesic concentrations of inhaled volatile anaesthetics provide superior analgesia in labour but more drowsiness, compared to inhaled nitrous oxide (**U**) (**Level I** [Cochrane Review]).
18. Inhaled nitrous oxide has some analgesic efficacy in labour pain (**U**), increases maternal adverse effects (nausea, vomiting, dizziness) (**U**) but has no adverse effects on the newborn (**U**) (**Level I** [Cochrane Review]); pain relief is comparable to pethidine but inferior to epidural analgesia (**U**) (**Level IV SR**).
19. Use of nonopioid analgesics alone for labour analgesia is not supported by current evidence (**U**) (**Level I** [Cochrane Review]).
20. Parenteral opioids other than remifentanil intravenous PCA provide moderate analgesic effects in labour pain (**S**), are inferior to epidural analgesia (**S**) and cause increased adverse maternal effects (sedation, nausea, vomiting) (**S**) and adverse effects on the newborn remain unclear (**Q**) (**Level I** [Cochrane Review]).

21. Remifentanil intravenous PCA is inferior to epidural analgesia (**U**), but provides better analgesia in labour compared to other parenteral opioids (**S**) (**Level I** [Cochrane]).

Complementary and other methods of pain relief in labour

22. Continuous or one-to-one support by a midwife or trained layperson during labour reduces analgesic use, rate of assisted and operative birth and dissatisfaction (**S**) (**Level I** [Cochrane Review]).
23. Immersion in water during labour may reduce the requirements for regional and neuraxial analgesia, with no difference in other maternal outcomes and insufficient evidence for neonatal outcomes compared to no immersion (**W**) (**Level I** [Cochrane Review]).
24. Relaxation by use of yoga, music or audio has limited benefit for pain relief or satisfaction in labour (**Q**) (**Level I** [Cochrane Review]).
25. Acupuncture and acupressure for labour pain may reduce pain, use of pharmacological pain relief and increase satisfaction with pain management vs standard care or placebo (**Q**) (**Level I** [Cochrane Review]); Caesarean section rates are unchanged (**R**) (**Level I** [Cochrane Review]).
26. Acupressure (vs sham) reduces labour pain, but has no effect on the use of pharmacological analgesia (**Q**) (**Level I** [Cochrane Review]).
27. Massage may decrease pain in the first stage of labour pain compared to standard care (**S**) (**Level I** [Cochrane Review]).
28. Transcutaneous electrical nerve stimulation has no effect on pain, interventions or outcomes in labour (**U**) (**Level I** [Cochrane Review]).
29. Biofeedback, sterile water injections intra- or subcutaneously and aromatherapy have no effect on labour pain or other outcomes (**U**) (**Level I** [Cochrane Review]).
30. Use of a birth ball may improve labour pain (**N**) (**Level I**).
31. Heat packs may reduce labour pain during the first and second stages (**N**) (**Level I** [Cochrane Review]).
32. Hypnosis (mostly antenatal interventions) may reduce analgesic requirements for labour pain (**R**) (**Level I** [Cochrane Review]).

Pain relief after Caesarean section

33. Local anaesthetic wound infiltration, in particular abdominal nerve blocks, reduces opioid consumption following Caesarean section (**U**) (**Level I** [Cochrane Review]).
34. Local anaesthetic transversus abdominis plane blocks reduce postoperative opioid requirements and pain scores after Caesarean section but only when intrathecal morphine is not used (**S**) (**Level I** [PRISMA]).
35. In relation to controls only and with no direct comparison between the two approaches, local anaesthetic transversus abdominis plane blocks performed by a posterior approach provide a longer duration of benefit versus the lateral approach after lower abdominal incision surgery including Caesarean section (**U**) (**Level I** [PRISMA]).
36. Intravenous paracetamol given before incision reduces opioid analgesic requirements after Caesarean section (**N**) (**Level I** [PRISMA])

37. Epidural (**U**) (**Level I** [QUOROM]) and intrathecal morphine (**U**) (**Level I**) and patient-controlled epidural analgesia (**U**) (**Level II**) provide effective analgesia after Caesarean section, but neuraxial morphine increases the rate of pruritus and nausea compared with systemic administration (**U**) (**Level I** [QUOROM]).

38. Intrathecal morphine (range of 100 mcg to 250 mcg) increases time to first analgesic request after Caesarean section, but pain scores and opioid consumption are unchanged, and postoperative nausea, vomiting and pruritus increased (**N**) (**Level I**).

☑ Remifentanil IV PCA for relief of labour pain carries a risk of maternal respiratory depression; use is recommended only if there is one-on-one continuous presence of a midwife, continuous oxygen saturation monitoring and continuous cardiotocograph monitoring (as an indirect method of detecting global hypoxaemia) (**U**).

☑ Transversus abdominis plane blocks after Caesarean section may result in high plasma concentrations of local anaesthetic and potential toxicity; minimum effective doses should be used (**U**).

Pain management during lactation

1. Local anaesthetics, paracetamol and several NSAIDs, in particular ibuprofen, are considered to be safe in the lactating patient (**U**) (**Level IV**).

2. Morphine, fentanyl, methadone, and short-term oxycodone immediately after delivery are considered to be safe in the lactating patient and are preferred over pethidine (**U**) (**Level IV**).

3. Repeated dosing of codeine or oxycodone in lactating patients should be avoided if possible and the infant monitored for central nervous system depression (**S**) (**Level IV**).

☑ Prescribing medications during lactation requires consideration of possible transfer into breast milk, uptake by the infant and potential adverse effects for the infant; it should follow available prescribing guidelines (**U**).

☑ Breastfed neonates and infants may become sedated from the transfer of maternal medications; in this case, observation and monitoring of the infant and seeking medical advice is warranted. Maternal sedation may be an early warning sign (**N**).

Pain in the puerperium

1. Routine episiotomy does not reduce perineal pain (**U**) (**Level I** [Cochrane Review]).

2. Continuous suturing of all layers compared with interrupted suturing for repair of episiotomy or second-degree tears reduces perineal pain and analgesic use in the postpartum period (**U**) (**Level I** [Cochrane Review]).

3. Paracetamol and NSAIDs are effective in treating perineal pain after childbirth compared with placebo (**S**) (**Level I** [Cochrane Review]).

4. NSAIDs, but not paracetamol, are effective in treating pain from uterine cramping after vaginal birth (**U**) (**Level I** [Cochrane Review]).

5. There is limited evidence to support the effectiveness of local cooling treatments in treatment of perineal pain after childbirth (**U**) (**Level I** [Cochrane Review]).

6. Topical local anaesthetic preparations are not effective for perineal pain after childbirth (**U**) (**Level I** [Cochrane Review]).
7. There is insufficient evidence to recommend any specific treatments for nipple pain and breast engorgement (**U**) (**Level I** [Cochrane Review]).

☑ Pain after childbirth requires appropriate treatment as it coincides with new emotional, physical and learning demands and may trigger postnatal depression (**U**).

☑ Management of breast and nipple pain should target the cause (U).

The older patient

1. Topical nsNSAIDs for localised pain provide effective analgesia (**U**) (**Level I** [Cochrane Review] with lower plasma concentrations and fewer gastrointestinal adverse effects than oral nsNSAIDs (**U**) (**Level I**); this may improve safety in the elderly.
2. PCA and epidural analgesia are more effective in older people than conventional opioid regimens (**U**) (**Level II**).
3. Experimental pain thresholds to thermal stimuli are modestly increased in older people (**U**) (**Level III-2 SR**).
4. Reported frequency and intensity of acute pain in clinical situations may be reduced in the older person (**U**) (**Level III-2**).
5. Common unidimensional self-report measures of pain can be used in the older patient in the acute pain setting, but need to be appropriate for the individual patient; the verbal descriptor and numerical rating scales are preferred in patients who can self-report (**U**) (**Level III-2**), while in the older patient with cognitive impairment, specific pain assessment tools are more appropriate (**N**) (**Level IV SR**).
6. Undertreatment of acute pain is more likely to occur in cognitively impaired patients (**U**) (**Level III-2**).
7. The use of nsNSAIDs and coxibs in older people requires caution, although use of opioids may result in more complications (**U**) (**Level III-2**); paracetamol is the preferred nonopioid analgesic (**U**) (**Level III-2**).
8. The under-representation of older patients in clinical drug trials limits information about efficacy, safety and pharmacokinetics of many types of medications including analgesic medications **(N) (Level IV SR**}
9. The older patient is at increased risk from adverse effects of medications including many analgesics (**N**) (**Level IV**).
10. Delirium is common in elderly hospitalised patients, including after surgery; risk factors include inadequate pain management and excessive use of opioids and other sedating analgesics (**N**) (**Level IV**).
11. There is an age-related decrease in opioid requirements; significant interpatient variability persists (**U**) (**Level IV**).
12. The age-related decrease in opioid requirements is related more to the changes in pharmacodynamics that accompany ageing than to the changes in pharmacokinetics (**U**) (**Level IV).**

☑ The assessment of pain and evaluation of pain relief therapies in the older patient may present problems, arising from differences in reporting, cognitive impairment and difficulties in measurement (**U**).

☑ Measures of present pain may be more reliable than past pain, especially in patients with some cognitive impairment (**U**).

☑ The physiological changes associated with ageing are progressive; while the rate of change can vary markedly between individuals and is related to frailty, these changes may decrease the dose (maintenance and/or bolus) of drug required for pain relief and may lead to increased accumulation of active metabolites (**U**).

☑ The high prevalence of frailty in the older patient is an independent risk factor for increased adverse drug effects to analgesic medications (**N**).

☑ The use of regional analgesics techniques, as an alternative to systemic analgesics, can confer benefits of improved pain relief, and minimise adverse effects (cognitive, pulmonary) (**N**).

☑ Cognitive impairment in the older patient may limit the appropriate use of PCA (**N**).

Culturally responsive care for Culturally and Linguistically Diverse patients

1. Disparities in assessment, analgesic requirements and effective treatment of pain exist across ethnic groups (**S**) (**Level III-2 SR**).
2. Ethnic and cultural background of both healthcare professional and patient can influence the ability to assess and treat acute pain (**N**) (**Level III-2 SR**).

☑ Cultural competence of health professionals supported by specific training improves health outcomes for culturally and linguistically diverse patients (**U**).

☑ Pain assessment and management should be done on an individual patient basis. Differences between ethnic and cultural groups should not be used to stereotype patients but should only be used to inform of possible cultural preferences (**U**).

☑ Multilingual printed information and pain measurement scales are useful in managing patients from different cultural or ethnic backgrounds (**U**).

☑ If language proficiency poses a communication barrier, then an accredited health care interpreter should be included when conducting a pain assessment, to ensure correct assessment; the use of friends, family or staff member should be avoided (**N**).

☑ The use of health-care specific language translation apps may be only considered as an alternative option in non-clinical situations in the sub-acute setting (eg daily routine communication) when formal healthcare interpreter services are not available (**N**).

Aboriginal and Torres Strait Islander Peoples

1. Verbal descriptor scales may be a better choice of pain measurement tool than verbal numerical rating scales in some Aboriginal and Torres Strait Islander Peoples (**U**) (**Level III-3**).
2. Medical comorbidities such as renal impairment are more common in Aboriginal and Torres Strait Islander Peoples and may influence the choice of analgesic agent (**U**) (**Level IV**).

☑ Heterogeneity between differing populations of Aboriginal Peoples may require tailoring of the service delivered to the population and individual being serviced (**U**).

☑ Pain expression in Aboriginal and Torres Strait Islander Peoples may not reflect that which is expected by the health professional's cultural background. This places the onus on the health professional to understand nuances of pain expression and beliefs within such populations (**U**).

☑ Aboriginal and Torres Strait Islander Peoples are at increased risk of underrecognition and undertreatment of pain (**N**).

Māori peoples

1. Experimental ischaemic pain is tolerated for longer in Māori people than in European New Zealanders (**U**) (**Level III-2**).
2. Māori people report higher levels of pain and/or disability with dental pain, gout and after trauma and joint replacement surgery than European New Zealanders (**U**) (**Level III-2**).

☑ High healthcare inequalities exist regarding access and quality of care (across age ranges, genders and for various medical conditions) between the Māori and Pacific Islander peoples compared with New Zealanders of European origin (**S**).

☑ Māori culture embraces the multidimensional aspects of pain experiences (**S**).

The patient with sleep-disordered breathing including obstructive sleep apnoea

1. Continuous pulse oximetry compared to intermittent nursing spot-checks detects more episodes of hypoxaemia in postoperative patients with obstructive sleep apnoea prescribed opioids (**N**) (**Level I**).
2. The STOP-Bang questionnaire has high sensitivity for the identification of patients at risk of moderate to severe obstructive sleep apnoea (**S**) (**Level III-2 SR**).
3. Patients with sleep-disordered breathing, including obstructive sleep apnoea, having surgery are at increased risk of adverse cardiac and respiratory effects (**S**) (**Level III-2 SR**), in particular cardiac arrest/shock, atrial fibrillation, aspiration pneumonia, acute respiratory distress syndrome and need for intubation, mechanical and noninvasive ventilation (**N**) (**Level III-2**) and increased hospital length of stay (**N**) (**Level III-2 SR**).
4. Patients with obstructive sleep apnoea have an increased risk of exacerbation of obstructive episodes and hypoxaemia during the postoperative period (**U**) (**Level III-2**), in particular in the first 72 hours with peaks on the first and third postoperative night (**N**) (**Level III-2**).
5. Morbidly obese patients may be at increased risk of postoperative hypoxaemia, independent of a diagnosis of obstructive sleep apnoea (**U**) (**Level III-2**).
6. Continuous positive airway pressure does not increase the risk of anastomotic leak after upper gastrointestinal surgery (**S**) (**Level III-2**).
7. Increasing severity of obstructive sleep apnoea is associated with increased risk of postoperative respiratory complications including opioid-induced ventilatory impairment (**Q**) (**Level III-3**).
8. The prevalence of obstructive sleep apnoea in the surgical patient population is high and the majority (80%) of these patients are undiagnosed (**S**) (**Level IV SR**).

9. Higher preoperative apnoea-hypopnoea index and identification of nocturnal hypoxemia are risk factors associated with postoperative complications in patients with sleep-disordered breathing (**N**) (**Level IV SR**).
10. Patients with obstructive sleep apnoea have increased sensitivity to pain that improves with use of continuous positive air way pressure (**N**) (**Level IV SR**).
11. Opioids in patients with obstructive sleep apnoea attenuate arousal to hypoxia and prolong airway obstruction, and thereby lead to more severe hypoxaemia (**S**) (**Level IV SR**).

☑ Preoperative screening for obstructive sleep apnoea combined with treatment (ideally instituted preoperatively) and increased postoperative observation may decrease postoperative morbidity and mortality (**S**).

☑ Management strategies that may increase the efficacy and safety of pain relief in patients with obstructive sleep apnoea include multimodal nonsedating opioid-sparing analgesia such as regional techniques, continuous positive airway pressure, monitoring and supervision (in a high-dependency area if necessary) and supplemental oxygen (**U**).

☑ Perioperative commencement of continuous positive airway pressure may be beneficial in patients with obstructive sleep apnoea but requires high levels of supervision; significant problems are poor patient acceptance and postoperative adherence (**U**).

☑ In patients with obstructive sleep apnoea, monitoring should be extended beyond 24 hours to capture the high-risk period for late postoperative hypoxaemia (**N**).

The obese patient

1. Perioperative dexmedetomidine infusion reduces pain intensity, opioid requirements and PONV after bariatric surgery (**N**) (**Level I** [PRISMA]).
2. Intraoperative peritoneal local anaesthetic administration reduces pain intensity and opioid requirements after bariatric surgery (**N**) (**Level I** [PRISMA]).
3. Paracetamol (multi-dosing) r educes opioid requirements, hospital length of stay and representations for pain after bariatric surgery (**N**) (**Level II**).
4. Intraoperative systemic lidocaine infusions reduce pain intensity, opioid requirements and improve the quality of recovery after bariatric surgery (**N**) (**Level II**).
5. Epidural administration of local anaesthetics in obese patients has been associated with increased risk of cephalad spread (**N**) (**Level III-2**).
6. Obesity increases the failure rate of neuraxial and peripheral nerve blocks (**N**) (**Level IV**); ultrasound guidance improves the success rate (**N**) (**Level IV**).

☑ Obesity has significant detrimental effects on respiratory function and is linked to an increased rate of obstructive sleep apnoea (**N**).

☑ Obesity influences pharmacokinetic and pharmacodynamic parameters of analgesic medications leading to uncertainty about dosing and caution should be used with weight-based dosing (**N**).

☑ Multimodal analgesic techniques including use of regional techniques result in opioid-sparing effects and thereby improve safety of acute pain management after bariatric surgery (N).

The patient with concurrent renal or hepatic disease

☑ Consideration should be given to the choice and dose regimen of analgesic agents in patients with hepatic and particularly renal impairment (**S**).

The opioid-tolerant patient

1. Alpha-2 agonists (clonidine and lofexidine) reduce opioid-withdrawal symptoms (**U**) (**Level I** [Cochrane Review]).
2. Remifentanil use leads to opioid-induced hyperalgesia (**U**), which is attenuated by propofol (**U**) (**Level I** [PRISMA]), NMDA-receptor antagonists (**U**) (**Level I** [QUOROM]), pregabalin (**U**) (**Level II**), nitrous oxide (**N**) (**Level II**) and gradual tapering of remifentanil dose (**N**) (**Level II**).
3. Gabapentin and pregabalin attenuate opioid-induced hyperalgesia/tolerance and reduce opioid-withdrawal symptoms (**U**) (**Level II**).
4. In opioid-tolerant patients, ketamine improves pain relief after surgery and reduces opioid requirements (**S**) (**Level II**).
5. Long-term opioid use is a dose-dependent risk factor for sleep-disordered breathing, which requires appropriate perioperative assessment, monitoring and management (**S**) (**Level III-2 SR**).
6. Long-term opioid use is associated with dose-dependent increased risks of injuries (**N**) (**Level III-2**) including fractures (**N**) (**Level III-2 SR**) and overdose (**N**) (**Level III-2**).
7. Preoperative opioid use is associated with worse outcomes after a variety of operations (**N**) (**Level III-2**).
8. Preoperative opioid tapering may ameliorate the risk of postoperative complications and morbidity (**N**) (**Level III-2**)
9. Preoperative opioid use is a risk factor for prolonged postoperative opioid use (**N**) (**Level III-2**).
10. Opioid-tolerant patients report higher pain scores, have slower pain resolution leading to longer hospital stay and increased readmissions but have a lower incidence of opioid-induced nausea and vomiting (**U**) (**Level III-2**).
11. Opioid-tolerant patients may have significantly higher opioid requirements and interpatient variation in the doses needed than opioid-naïve patients (**U**) (**Level III-2**).

☑ Usual preadmission opioid regimens should be maintained where possible or appropriate substitutions made (**S**).

☑ Liaison with all health care professionals involved in the treatment of the opioid-tolerant patient is important (**S**).

☑ Opioid-tolerant patients are at risk of opioid withdrawal if nonopioid analgesic regimens, tramadol or tapentadol alone are used (**U**).

☑ PCA settings may need to include a background infusion or other background opioid to replace the usual opioid dose and a higher bolus dose (**U**).

☑ Neuraxial opioids can be used effectively in opioid-tolerant patients, although higher doses may be required and these doses may be inadequate to prevent withdrawal (**U**).

☑ Adjuvants are used for their antitolerance, antihyperalgesic, and antiallodynic effects and there is some evidence upon which to base the choice of agent (**S**).

☑ In patients with escalating opioid requirements, management considerations are the development of tolerance or opioid-induced hyperalgesia (**S**).

☑ Following short-term opioid dose escalation for acute pain, a "reverse analgesic ladder" approach, using stepwise reduction to the patient's usual opioid regimen is recommended (**S**).

☑ For assessment of withdrawal reactions, the use of a validated withdrawal tool in opioid-tolerant patients is recommended; management strategies vary and include weaning, rotation and adjuvant use (**N**).

The patient with a substance use disorder

1. Benzodiazepines are effective for alcohol-withdrawal symptoms, in particular reducing seizures (**U**) (**Level I** [Cochrane Review]).
2. Opioid substitution therapy with methadone or buprenorphine is better than clonidine and lofexidine in ameliorating withdrawal symptoms (**N**) (**Level I** [Cochrane Review]).
3. Methadone and buprenorphine maintenance regimens should be continued throughout acute pain episodes wherever possible (**S**) (**Level III-2 SR** [PRISMA]).
4. Poorly managed acute pain episodes may decrease retention in opioid-maintenance programs (**U**) (**Level III-2**).
5. To achieve better analgesic efficacy, daily methadone maintenance doses should be divided and given 8 to 12 hourly (**S**) (**Level IV SR** [PRISMA]).

☑ Pain management in patients with substance use disorder often presents significant challenges for both clinicians and patients. Patients fear being stigmatised or discriminated against, are concerned about inadequate pain relief with their past experiences leading to physician distrust; they fear experiencing withdrawal (before their usual drugs are prescribed) and relapse precipitated by acute opioid exposure. The challenges for the clinician Include mistrust, concerns about drug seeking, fear of overtreatment with adverse events, concerns about diversion, and risk of discharge against medical advice (**N**).

☑ A "universal precautions" approach is increasingly recommended for patients with substance use disorder in acute pain settings; it may include use of multimodal analgesia, abuse-deterrent formulations, urine drug screening, use of prescription drug monitoring programs and risk management strategies (**N**).

☑ An acute admission offers opportunity to engage with patients with substance use disorder as well as to treat the acute issues (**N**).

☑ There is no cross-tolerance between alcohol or benzodiazepines or central nervous system stimulants and opioids (**U**).

☑ Oral naltrexone should be stopped at least 24 hours, ideally 72 hours, prior to elective surgery (**U**); naltrexone implants may need surgical removal in cases of severe acute pain where opioid responsiveness is required (**U**).

☑ Patients who have ceased naltrexone therapy should be regarded as opioid naïve; in the immediate post-treatment phase they may be more opioid sensitive (**U**).

☑ To achieve better analgesic efficacy, daily buprenorphine maintenance doses could be divided and given 8 to 12 hourly (**U**).

☑ Nicotine has a small to medium analgesic effect in volunteers and smoking abstinence increased self-reported pain (**N**).

10.0 | Paediatric

Developmental neurobiology of pain

1. Following birth, even the most preterm neonate responds to nociceptive stimuli (**U**) (**Level IV**).
2. In early development, more generalised reflex nociceptive responses occur in response to lower intensity stimuli (**U**) (**Level IV**).

Consequences of early pain and injury

1. Pain and injury in early life cause structural changes in cortical and subcortical pathways and are associated with alteration in somatosensory thresholds in later life (**U**) (**Level III-2**).
2. Analgesia may modulate the long term effects of pain and injury in early life but more information is required to determine the optimal dosing and type of agents to avoid negative impact of the pharmacological intervention itself (**U**) (**Level III-2**).
3. Improving quality of infant pain management delivery in neonatal intensive care (including pharmacological and nonpharmacological interventions) may result in improved neurodevelopmental outcomes (**U**) (**Level III-2**).
4. Understanding of the epigenetic factors that contribute to the behavioural pain trajectory is evolving; this may lead to enhanced developmentally targeted care to reduce stress exposure and long term impacts for infants (**N**) (**Level IV SR** [PRISMA]).

Paediatric pain assessment

1. Pain measurement tools are available for children of all ages (**S**) (**Level IV SR**).
2. Paediatric pain measurement tools must be matched to the age and development of the child (**U**) (**Level IV SR**).
3. Adoption of written guidelines or pain management algorithms improves both assessment and management of pain in neonates and children (**N**) (**Level IV SR**).

☑ Pain assessment and measurement are important components of paediatric pain management (**U**).

☑ Pain scores generated from different pain scales may not be congruent and this should be considered when used clinically and in research (**N**).

☑ Pain scores and pain score subdivisions (cut-offs) should not be used as a sole guide to administration of analgesia (**N**).

☑ Children with neurodevelopmental disorders (with and without cognitive impairment and varying levels of physical disability) may be more susceptible to pain and communicate it in different ways (**N**).

☑ Pain measurement tools must be appropriate for the clinical context, be explained and used consistently (**U**) and be validated when translated into other languages (**Q**).

☑ Facial recognition software applications may reduce clinician bias and become useful bedside tools in neonates and children with and without cognitive impairment (**N**).

Analgesic agents

Paracetamol (acetaminophen)

1. Post tonsillectomy in children, paracetamol (alone or combined with opioids) administered as required compared to fixed schedule achieved similar pain scores over 3 days; with lower dosing administered in the as required groups (**N**) (**Level I** [Cochrane Review]).
2. For pain of acute otitis media in children, paracetamol is similar to ibuprofen and both are superior to placebo in achieving pain freedom at 48 hours, but not other time points (**N**) (**Level I** [Cochrane Review]).
3. Paracetamol is effective for moderately severe pain and decreases opioid requirements after major and minor surgery in children (**U**) (**Level I** [PRISMA]).
4. Paracetamol has a similar safety and tolerability profile compared with ibuprofen and placebo if prescribed and administered at recommended doses in children (**U**) (**Level IV SR**).
5. Retrospective epidemiological studies linking paracetamol use in pregnancy or infancy to later development of childhood asthma are inherently confounded (**U**); when adjusted for respiratory tract infections in the child the association is lost (**Q**) (**Level III-2 SR** [PRISMA]).
6. Retrospective epidemiological studies report modest association of paracetamol use in pregnancy with childhood neurodevelopmental disorders such as attention deficit and hyperkinetic disorders; this is strengthened when adjusted for longer term use (>28 days) and disappears for short term use (<8 days) (**Q**) (**Level III-2 SR** [PRISMA]).
7. Paracetamol has unclear vasoactive effects; in critically ill children, hypotension is reported with both IV formulations (**N**) (**Level IV SR**).

☑ Safe dosing of paracetamol requires consideration of the age and body weight of the child and the duration of therapy (**U**).

☑ Paracetamol related hepatotoxicity generally occurs in children who have received doses greater than 120 mg/kg, as single or repeated daily dosing; with contributions from rounding up or 10-fold dosing error and formulation substitution or confusion by prescribers and parents (**N**).

☑ Paracetamol is recommended routinely following tonsillectomy and pharmacokinetic/pharmacodynamic simulation is exploring the optimal combinations of multimodal analgesia in this surgical model (**N**).

☑ There is insufficient pharmacokinetic/pharmacodynamic and safety data of use of paracetamol in preterm and term neonates; use for patent ductus arteriosus closure in preterm neonates provides limited data in this age group of an improved safety profile compared with nsNSAIDs (**N**).

☑ Emerging evidence suggests that maternal paracetamol use may influence premature closure of the fetal ductus arteriosus (**N**); use in pregnancy should be limited to the minimum dose and duration that is clinically necessary.

☑ Intravenous paracetamol in haemodynamically unstable patients has been associated with hypotension (**N**).

Nonselective NSAIDs

1. Nonselective NSAIDs do not increase the risk of either surgical or nonsurgical intervention for bleeding after paediatric tonsillectomy (**U**) (**Level I** [Cochrane Review]); however this was not supported by a large non-inferiority RCT where surgical intervention was increased with ibuprofen versus paracetamol (**Q**) (**Level II**).
2. Nonselective NSAID (ibuprofen) use for acute otitis media reduces pain (at 48 hours) vs placebo, with similar efficacy to paracetamol (**N**) (**Level I** [Cochrane Review]).
3. Nonselective NSAIDs are effective for moderately severe pain and decrease opioid requirements after major paediatric surgery (**U**) (**Level I** [PRISMA]) and postoperative nausea and vomiting (**U**) (**Level I** [QUOROM]).
4. Serious adverse effects after nonselective NSAIDs are rare in children over 6 months of age (**U**) (**Level II**).
5. Ibuprofen may increase severity of haemorrhage post tonsillectomy in patients returning to theatre (**N**) (**Level III-3**).
6. Short term use of ketorolac or ibuprofen do not increase bone healing complications in children undergoing posterior spinal fusion, osteotomy, or fractures managed surgically (**S**) (**Level III-3**) or conservatively (**N**) (**Level III-3**).

☑ Aspirin for acute pain indications should be avoided in children (**U**).

☑ Combined population pharmacokinetic-pharmacodynamic modelling is required to inform targeted dosing recommendations of analgesics in children (**U**).

Coxibs

1. Parecoxib use in children reduces early postoperative pain scores, PONV (compared to tramadol and fentanyl) and postoperative opioid consumption (**N**) (**Level I** [PRISMA]).
2. Parecoxib may have a ceiling analgesic effect in children in doses less than 1 mg/kg (**N**) (**Level II**).

☑ The safety profile of coxibs in the setting of allergy or contraindication to nonselective NSAID in adults and children is encouraging; but safety data specific to short term use in the perioperative period is limited (**Q**).

☑ Celecoxib for 3 days reduces pain and additional analgesic requirement post-tonsillectomy in children (**N**).

☑ Some paediatric centres retain the 1 mg/kg (40 mg) maximum daily dosing schedule for Parecoxib for off license use (**N**).

Conventional and atypical opioids

Opioids

1. Young and obese children with history of obstructive sleep apnoea/sleep-disordered breathing are at higher risk of developing serious opioid-induced ventilatory impairment and death (**U**) (**Level IV**).
2. Opioid-induced ventilatory impairment and death occur rarely with therapeutic dosing in children taking opioids at home (**N**) (**Level IV**).
3. Safe dosing of opioids requires consideration of the child's age, body weight, comorbidities and ethnicity (**U**) (**Level IV**).

Fentanyl

4. Intranasal fentanyl is an effective treatment for paediatric acute pain management, with an acceptable adverse effect profile and ease of delivery (**N**) (**Level I**).

Codeine

5. The efficacy of oral codeine in children is unpredictable due to genetic differences in the ability to generate the active metabolite morphine (**U**) (**Level II**), as are adverse effects and serious toxicity (**U**) (**Level IV**).
6. Codeine should not be used in children, especially after adenoidectomy or tonsillectomy, due to an increased risk of opioid-induced ventilatory impairment and death (**S**) (**Level IV**).

Tramadol

7. Tramadol provides superior analgesia to placebo and has similar efficacy to conventional opioids in children of all ages administered by various routes for multiple surgery types (**S**) (**Level I** [Cochrane]).
8. It is unclear if tramadol causes less ventilatory impairment than other opioids in children due to insufficient trial size (**N**) (**Level I** [Cochrane]).

Buprenorphine

9. Buprenorphine administered IV or caudally has similar efficacy to morphine or caudal local anaesthetic in children for different surgery types (**N**) (**Level II**).

Nalbuphine

10. Nalbuphine intravenously is effective for postoperative pain relief in children in several low quality heterogeneous trials (**N**) (**Level I** [Cochrane]).

☑ Careful titration of opioids is advised according to the individual child's response (analgesia and adverse effects) (**U**).

☑ Despite the regulatory response with boxed warning and upscheduling of codeine, prescription continues in at risk patients (with obstructive sleep apnoea/sleep-disordered breathing or post adenotonsillectomy) or has been replaced by prescription of potent conventional opioids such as oxycodone and hydrocodone which present similar or greater hazard (**N**).

☑ The practice of applying an occlusive dressing to the skin surface of a transdermal fentanyl delivery system does not limit dose delivery (**U**).

☑ Tramadol shares some adverse effects with the conventional opioid class in children, with similar or reduced rates of nausea and vomiting, sedation and fatigue but less constipation

and pruritus (**U**). Sedation (not necessarily associated with miosis), seizures, ventilatory impairment and deaths have occurred (**N**).

☑ Naloxone has been used to treat tramadol overdose in children with effect (**N**).

☑ CYP2D6 phenotype has been the reason for codeine's black box warning, but the clinical significance in terms of tramadol/M1's analgesic efficacy and adverse-effect profile including safety is still unknown (S). Inadvertent overdose and formulation issues are likely of greater risk than CYP phenotypes resulting in variable drug metabolism; evidence for harm from this second mechanism is lacking (**N**).

☑ Tramadol 100mg/mL concentrated drops formulation use is potentially harmful in children with possible dosing confusion (drops with millilitres) and resultant overdose (**U**).

☑ In paediatric overdose, buprenorphine causes the spectrum of neurocognitive adverse events as seen with conventional opioids which may be reversible with naloxone (**N**).

☑ More studies are required to determine tapentadol's comparative efficacy in paediatric acute pain and if its adverse effect profile in children is improved versus placebo, conventional opioids or tramadol (**N**).

☑ In paediatric overdose, tapentadol causes the spectrum of neurocognitive adverse events seen with conventional opioids, which may be reversible with naloxone (**N**).

Discharge opioid prescribing for children

1. Postoperative opioid therapy in children and adolescents may lead to long term opioid use and misuse in later life (**N**) (**Level III-2**); risk factors include type of surgery, psychological and social factors and other substance use (**N**) (**Level III-2**).
2. Long term opioid use following therapeutic medical prescription is uncommon in children and adolescents (**N**) (**Level IV**). However, prior diagnosis of chronic pain, substance use or mental health conditions are risk factors (**N**) (**Level IV**).
3. Misuse of prescription opioids is common amongst adolescents and young adults either as medical use (self-treatment) or nonmedical use (sensation seeking/recreational) (**N**) (**Level IV**).
4. Leftover prescribed opioids are a common source of nonmedical opioid use in adolescents, with most adolescents gaining access through family or friends (**N**) (**Level IV**).
5. Unsafe storage of prescription opioids in the home and non-disposal of leftover opioids is common (**N**) (**Level IV**).
6. Prescription opioids are a large source of opioid-related poisonings: usually accidental in young children and related to recreational use or with intentional overdose in adolescents (**N**) (**Level IV**).
7. Adverse drug events in children and adolescents sent home with prescription opioids are common (**N**) (**Level IV**).

☑ As for adults, a sensible approach should be used in the setting of prescribing discharge opioid medications for children and to adults with children at home (**N**).

☑ As for adults, prescribing discharge medications for children should be done with consideration of the child's anticipated opioid requirements. The tablet number and volume of opioid solution prescribed should be judicious and individualised (**N**).

☑ Understanding and education is required to determine procedure specific pain trajectories in children (**N**).

☑ Carer/parental, patient and clinical staff education is necessary about risks of opioids and how to safely dispose of unused medication by return to a pharmacy (**N**).

☑ Carer/parental and patient education in case of ongoing pain and analgesic issues is appropriate with follow-up by general practitioners or pain medicine services as indicated (**N**).

☑ Education and guidelines are desirable for adult and paediatric discharge and community opioid prescribers with focus on information provision for staff delivering the advice (ideally written and verbal combined) to carers and families (**N**).

Opioid tolerance in children and adolescents

1. Iatrogenic withdrawal syndrome following prolonged inpatient intravenous opioid therapy in critically ill children is common (**N**) (**Level IV SR** [PRISMA]).

☑ There are groups of paediatric patients who are opioid-tolerant, as in adults. They require special consideration for inpatient pain management and perioperative care. In children with opioid tolerance, inadequate pain relief and withdrawal (if opioids are acutely ceased) are specific risks. Acute pain service input can assist with preadmission planning and use of various adjuvants beyond standard multimodal interventions (**N**).

☑ For assessment of withdrawal reactions, the use of a validated withdrawal tool in paediatric opioid-tolerant patients is recommended; management strategies vary and include opioid weaning, rotation and adjuvant use (**N**).

Systemic NMDA-receptor antagonists

Ketamine

1. Perioperative low-dose intravenous ketamine bolus is similarly effective to opioids and superior to placebo in reducing early pain scores and analgesic requirements in children (**U**) (**Level I** [PRISMA]).
2. Perioperative low-dose intravenous ketamine bolus does not increase the postoperative incidence of nausea and vomiting, sedation, agitation, dreams or hallucinations in children (**S**) (**Level I** [PRISMA]).
3. Peritonsillar infiltration and topical application of ketamine for paediatric tonsillectomy reduces early pain scores and analgesic requirements versus placebo (**S**) (**Level I** [PRISMA]).
4. When added to multimodal analgesia, perioperative ketamine (bolus with or without intra/postoperative infusion) in children is not opioid-sparing vs placebo (**S**), although low postoperative pain scores and small sample sizes mean the meta-analysis is underpowered (**Q**) (**Level I** [PRISMA]).
5. There is low level evidence that combination ketamine and opioid PCA improved pain scores and PCA use post Nuss surgery (**N**) (**Level II**)**.**

☑ High-dose long term ketamine is neurotoxic in animal models. The neurodevelopmental impact in children of subanaesthetic/analgesic doses of ketamine administered by bolus or postoperative infusion is unclear (**U**).

☑ The benefit of perioperative ketamine in preventing remifentanil induced hyperalgesia has not been adequately assessed in paediatric surgery (**U**).

Magnesium

6. Magnesium (intravenous or peritonsillar infiltration) in children for tonsillectomy reduces postoperative rescue medication use, and increases time to first analgesia versus control; magnesium also reduces risk of postoperative emergence agitation and laryngospasm (**N**) (**Level I** [PRISMA]).

7. Magnesium (locally infiltrated) in children reduces late (24 hour) but not early (<1 hour) pain scores post tonsillectomy versus control (**N**) (**Level I** [PRISMA]).

Alpha-2 agonists

1. Preoperative oral clonidine reduces postoperative pain scores and analgesic requirement in children compared to placebo or midazolam but not fentanyl (**U**) (**Level I** [Cochrane Review]).

2. Preoperative oral clonidine reduces postoperative nausea and vomiting in children compared to placebo or midazolam (**U**) (**Level I** [Cochrane Review]).

3. Preoperative intranasal dexmedetomidine reduces postoperative pain scores, rescue analgesic requirements and emergence agitation with minimal adverse effects vs placebo (**N**) (**Level I** [PRISMA]) and mixed comparators (**N**) (**Level I**).

4. Intraoperative dexmedetomidine reduces postoperative pain scores (**U**) (**Level I** [PRISMA]) and need for postoperative rescue analgesia (**Q**) (**Level I**) including opioid (**U**) (**Level I** [PRISMA]) in children compared to placebo, with minimal impact on time to discharge (**N**) (**Level I** [PRISMA]) via intravenous (**S**) (**Level I** [PRISMA]) and intranasal routes (**S**) (**Level I**).

☑ Alpha-2 agonists offer benefits in addition to analgesia in children in the perioperative, intensive care and procedural settings. These benefits include anxiolysis, sedation (MAC sparing), behavioural modification, prevention or treatment of opioid withdrawal (facilitating opioid weaning) (**U**) and reduction of emergence agitation (**S**).

Alpha-2-delta ligands (gabapentinoids)

1. Multi-day perioperative (but not single preoperative) gabapentin dosing reduces postoperative morphine consumption vs placebo following multilevel posterior spinal fusion for adolescents with idiopathic scoliosis (**N**) (**Level II**).

2. Multiday perioperative gabapentin reduces phantom limb pain incidence vs placebo in paediatric oncology amputation surgery (**N**) (**Level II**).

3. Preoperative gabapentin and likely pregabalin improve analgesia after tonsillectomy in children and reduce PONV without increasing adverse effects (**N**) (**Level I** [PRISMA]).

☑ Alpha-2 delta ligands use in children for acute (and chronic) pain conditions is expanding based mostly on expert opinion and case series. The pain indications are similar to those for adults with similar benefit and adverse event profiles (**N**).

☑ Gabapentin and pregabalin are used to manage pruritus and neuropathic pain following burn injury in children (**N**).

☑ The use of alpha-2 delta ligands for the prevention of chronic postsurgical pain in children has not been studied (**N**).

Corticosteroids

1. Single dose intravenous dexamethasone reduces pain post tonsillectomy, postoperative vomiting and time to soft diet commencement in children (**U**) (**Level I** [Cochrane Review]).
2. Intavenous dexamethasone does not increase the overall risk of bleeding post tonsillectomy but increases the risk of reoperation for bleeding in children (S) (**Level I**).
3. Oral dexamethasone (given in addition to antibiotics) shortens the time to onset of pain relief in pharyngitis in children (**U**) (**Level I**).
4. Oral prednisolone multiday course post tonsillectomy does not reduce pain outcomes at day 3 or day 7 or postoperative nausea and vomiting (**N**) (**Level I**).

Systemic lidocaine infusions

1. Perioperative intravenous lidocaine infusion in abdominal surgery in children improved various pain and non-pain related postoperative outcomes (**N**) (**Level II**).

☑ Dosing of perioperative lidocaine infusions have been extrapolated from use in adults and pharmacokinetic study is warranted to determine safe dosing practices in children (**N**).

Opioid infusions and Patient Controlled Analgesia (PCA) in children

1. Addition of a low-dose background infusion to patient controlled analgesia (PCA) bolus results in similar pain scores and total opioid consumption and improves sleep duration in children; numbers are inadequate to assess safety of adding a background (**N**) (**Level I**).
2. In ventilated preterm neonates, routine use of morphine infusions does not affect mortality, duration of ventilation or neurological outcomes (**U**) (**Level I** [Cochrane Review]), including when followed up as older children (**S**) (**Level II**).
3. Postoperative intravenous opioid requirements vary with age in neonates, infants and children (**U**) (**Level II**).
4. Intermittent intramuscular injections are distressing for children and are less effective for pain control than intravenous infusions (**U**) (**Level III-1**).
5. Patient-controlled analgesia (PCA) can provide safe and effective analgesia for children as young as 5 years old (**S**) (**Level III-3**).
6. Intravenous opioids via continuous infusion, nurse-controlled analgesia and parental proxy use of patient controlled analgesia (PCA) devices can be used effectively (**U**) (**Level III-2**) and safely (**N**) (**Level IV**) in children of all ages.
7. Nurse-controlled analgesia (**U**) (**Level III-2**) and parental proxy use of patient controlled analgesia (PCA) devices in children (**U**) (**Level III-3**) may require more rescue interventions (such as naloxone, airway management or intensive care) than PCA, but this may reflect the younger patient population where this technique is offered.
8. Morphine by patient controlled analgesia (PCA) is at least as safe as intermittent nurse administered intravenous morphine (**N**) (**Level IV**).

☑ Initial doses of opioid should be based on the age, weight and clinical status of the child and then titrated against the individual's response (**U**).

☑ Effective patient controlled analgesia (PCA) prescription in children incorporates a bolus that is adequate for control of movement-related pain (**U**).

Paediatric Regional Analgesia

1. Topical local anaesthetic does not adequately control pain associated with circumcision in awake neonates (**U**) (**Level I** [Cochrane Review]).
2. Caudal local anaesthetic, dorsal penile nerve block (**U**) (**Level I** [Cochrane Review]) and ring block (**N**) (**Level II**) provide effective perioperative analgesia for circumcision in infants to adolescents.
3. Caudal local anaesthetic in addition to general anaesthesia for circumcision does not reduce postoperative nausea and vomiting or the need for early rescue or other analgesia in children (infants to adolescents) when compared to parenteral analgesia (**U**) (**Level I** [Cochrane Review]).
4. In acute otitis media, topical local anaesthetic drops are effective in children compared to placebo and equivalent to naturopathic drops (**S**) (**Level I** [Cochrane Review]).
5. For paediatric cleft lip repair, infraorbital nerve block with lidocaine or bupivacaine may reduce postoperative pain versus placebo; duration is increased when opioids are added (with no systemic comparator) (**N**) (**Level I** [Cochrane Review]).
6. Epidural analgesia compared to systemic analgesia after spinal surgery in children improves pain up to 72 hours postoperatively (N) (Level I[Cochrane Review]).
7. Local anaesthetics (by infiltration or nerve block) reduce pain scores post dental procedures (**N**) (**Level I** [PRISMA]).
8. Ketamine added to caudal local anaesthetic for paediatric day-stay surgery prolongs analgesia but not motor block (**U**) (**Level I** [PRISMA]); however concerns regarding neurotoxicity remain.
9. Dexamethasone (caudal, perineural or IV) prolongs the duration of analgesia of local anaesthetic caudal (**N**) (**Level I** [PRISMA]) and peripheral nerve blocks (**N**) (**Level II**).
10. Magnesium added to caudal local anaesthetic blocks improves analgesia in children (**N**) (**Level I** [PRISMA]).
11. Clonidine (**U**) and dexmedetomidine (**N**) improve analgesia in children when added to local anaesthetic caudal blocks, epidural infusions (**Level I** [PRISMA]) and peripheral nerve blocks (**N**) (**Level II**).
12. Peritonsillar dexamethasone or peritonsillar ketamine may reduce pain scores following paediatric tonsillectomy compared to placebo (in trials with no systemic comparator arms) (**N**) (**Level I**).
13. Ultrasound guidance for epidural catheter insertion is a reliable predictor of depth to loss of resistance (or of epidural space), offers visibility of the needle and catheter and may reduce bone contacts (**N**) (**Level IV SR**).
14. In children having cardiac surgery, caudal injections with various medication combinations vs control reduces postoperative analgesia requirements and pain scores (**N**) (**Level IV SR** [PRISMA]).

15. In children having scoliosis surgery, the addition of epidural local anaesthetic infusion to intravenous PCA morphine improves pain scores and patient satisfaction (**U**) (**Level I**) and decreases postoperative nausea (**U**) (**Level II**).
16. Peripheral nerve blocks (**S**) (**Level I** [PRISMA]), wound infiltration and caudal local anaesthetic provide effective analgesia after day-stay paediatric inguinal surgery (**S**) (**Level II**).
17. Epidural infusions of local anaesthetic in children provide similar levels of analgesia compared to systemic opioid infusion (**U**) (**Level II**) and intravenous PCA (**U**) (**Level III-3 SR**).
18. Epidural opioids alone are less effective than epidural local anaesthetic or combinations of local anaesthetic and opioid in children (**U**) (**Level II**).
19. Intrathecal opioids provide prolonged analgesia after surgery in children and reduce blood loss during paediatric spinal fusion (**U**) (**Level II**). High doses of intrathecal morphine in children have been associated with respiratory failure and intensive care admission (**N**) (**Level III-2**).
20. Paediatric regional analgesia (peripheral nerve and neuraxial blocks as single injections and continuous catheters) are effective (**Level II**) and safe analgesic techniques in children (**S**) (**Level IV**); continous peripheral nerve catheters have been used in hospital and following discharge, with low secondary failure rates (**N**) (**Level IV**).
21. Ultrasound guidance to assist peripheral block and catheter placement has increased block success (**Level II**) but not impacted the incidence of local anaesthetic systemic toxicity or neurological complications in children; the latter having decreased independently over time (**N**) (**Level IV**).
22. Continuous wound catheter infusions of local anaesthetic are effective (**N**) (**Level II**) and safe analgesic techniques (**N**) (**Level IV**).
23. Caudal local anaesthetic blocks provide effective analgesia for lower abdominal, perineal and lower limb surgery (**Level II**) and have a low incidence of serious complications (**S**) (**Level IV**).
24. Continuous ultrasound-guided caudal injection versus landmark technique increases success of first puncture and lowers risk of vascular puncture and inadvertent subcutaneous injection (**N**) (**Level II**); while permitting real-time visualisation of injectate spread (**N**) (**Level IV**).
25. Sub Tenon block for paediatric ocular surgery achieved longer time to first analgesic administration versus placebo or intravenous opioid (**N**) (**Level II**).
26. Complications of epidural infusions are rare; the rates are slightly higher in neonates and infants versus older children (S) (**Level III-2**).
27. Continuous epidural infusions provide effective postoperative analgesia in children of all ages (**U**) (**Level III-2**).
28. Continuous epidural infusions are safe in children of all ages (**S**) (**Level III-2**) if appropriate doses and equipment are used by experienced practitioners, with adequate monitoring and management of complications (**U**) (**Level IV**).
29. Thoracic epidural, paravertebral catheters, wound catheters and intercostal nerve blocks all provide effective analgesia for pectus excavatum repair surgery, with longer hospital stays in thoracic epidural recipients (**N**) (**Level III-3**).

30. Placement of paediatric regional analgesia (peripheral nerve and neuraxial blocks as single injections and catheters) in children under general anaesthesia is not associated with an increased rate of complications (**S**) (**Level IV**).

☑ An association between urethral fistula formation complicating hypospadias repair and caudal block has not been consistently reported; variation in anatomical presentation and surgical technique are more biologically plausible risk factors (**N**).

☑ Lipid emulsion (20%) has been used in successful resuscitation of paediatric patients (neonates to 18 years) with local anaesthetic systemic toxicity; dosing recommendations are the same as for adults and higher doses have led to adverse effects (**N**).

☑ Dosing practices for peripheral nerve blocks vary and concerningly doses sometimes approach or exceed the accepted safe dose limit; this occurs more commonly in younger children (**N**).

Management of procedural pain in children

Neonates

1. In term neonates, venipuncture is less painful than heel lance (**N**) (**Level I** [Cochrane Review]).
2. Sucrose (**S**) (**Level I** [Cochrane Review]) and non-sucrose sweet solutions (mostly glucose) (**N**) (**Level I** [PRISMA]) reduce pain scores and behavioural response for skin-breaking procedures in neonates.
3. Providing physical comfort measures, including kangaroo care (maternal or alternative skin to skin provider), non-nutritive sucking (alone or combined with sweet-tasting solutions), facilitated tucking (swaddling) or rocking and holding (**N**) reduces pain experienced by term and preterm neonates having skin-breaking procedures (**S**) (**Level I** [Cochrane Review]).
4. Pain from ocular examination for retinopathy of prematurity is reduced by sucrose and non-nutritive sucking (**N**) (**Level I** [Cochrane Review]) and topical local anaesthetic (**N**) (**Level III-1 SR** [Cochrane Review]).
5. Kangaroo care (or skin to skin contact) in neonates reduces the distress of vaccine injection (**N**) (**Level III-1 SR**).
6. Sucrose reduces distress after gastric tube placement in neonates (**N**) (**Level III-1 SR**).

Infants and children

7. Breastfeeding (<2 years of age) reduces pain intensity and crying duration for skin-breaking procedures including vaccine injection compared to positioning, holding by mother, maternal skin to skin contact (<1 months), topical anaesthetics, music therapy, pacifier use (<4 months), placebo, no intervention and/or oral sucrose (**S**) (**Level I** [Cochrane Review]).
8. Non-nutritive sucking reduces pain after needle-related procedures in infants and young children (<3 years) (**N**) (**Level I** [Cochrane Review]).
9. Oral sucrose and glucose reduce cry incidence and duration (**U**) (**Level III-1 SR** [Cochrane Review]**)** and distress (**N**) (**Level III-1 SR**) of vaccine injection in infants.
10. Distraction in infants and young children (<3 years) reduces vaccine injection pain (**N**) (**Level III-1 SR**).

11. Procedural modifications reduced distress of vaccine injection including injection without aspiration (≤18 months), simultaneous injection of multiple vaccines (≤12 months) and injection of most painful vaccine last (≤6 months) (**N**) (**Level III-1 SR**).
12. Topical local anaesthetic reduces distress of vaccine injection in infants (**N**) (**Level III-1 SR**).
13. Parental presence reduces prevaccine injection distress in infants and children (**N**) (**Level III-1 SR**).
14. Parental education before or on vaccination day increases use of evidence-based pain management strategies and reduces distress in infants and children (**N**) (**Level III-1 SR**).
15. Physical interventions including holding by parent (during or after) and non-nutritive sucking in infants (0–4 months) reduces the distress of vaccine injection (**N**) (**Level III-1 SR**).
16. The efficacy of supplemental/expressed breast milk for procedural pain management is unclear (**N**) (**Level III-1 SR**).
17. Needle-free pressure injected lidocaine is quick in onset and reduces pain from subsequent needle-related procedures in infants and children (**N**) (**Level II**).

Children and adolescents

18. EMLA® is an effective topical local anaesthetic for children but amethocaine is superior for reducing needle-insertion pain (**U**) (**Level I** [Cochrane Review]).
19. Topical local anaesthetic application (**U**) **(Level I** [Cochrane Review]), inhalation of nitrous oxide 50–70% or the combination of both (**U**) (**Level I** [PRISMA]) provides effective and safe analgesia for minor procedures in children.
20. Distraction (including with video, toys, music or stories) and hypnosis reduces needle related pain (**S**) and distress (**N**) in children and adolescents (**Level I** [Cochrane Review]).
21. Buzzy® (which combines vibration and cold) (**N**) (**Level I** [PRISMA]) and vibration by other methods (**S**) (**Level III-1 SR**) reduces needle-related procedure pain, including vaccine injection in children.
22. Active and passive music therapy reduces pain and anxiety associated with various needle-related procedures in children (**U**) (**Level I**).
23. Immersive virtual reality reduces pain of medical procedures including wound dressing care and venipuncture (**N**) (**Level III-1 SR** [PRISMA]).
24. Immersive virtual reality for medical procedures in children reduces self-reported pain and anxiety (**N**) (**Level III-1 SR**).
25. Ketamine is effective for paediatric procedural pain management (**Q**) (**Level IV**).
26. Hospital wide initiatives to implement evidence-based standards of care for needle related procedures can improve service delivery and patient satisfaction (**N**) (**Level IV**).

☑ Using combinations of evidence-supported single pain management strategies for painful procedures is strongly recommended (**N**). Non-pharmacological intervention should always be incorporated (**N**).

☑ It is of concern that minor procedures are still undertaken in children, particularly neonates and infants, in the elective and emergency hospital setting with minimal or no pain management intervention (**N**).

- ☑ Inadequate monitoring, lack of adequate resuscitation skills and equipment, and the use of multiple medicine combinations has been associated with major adverse outcomes during paediatric procedural analgesia and sedation (**U**).
- ☑ Pain caused by injection is a barrier to vaccine uptake; thus managing vaccine injection pain has immediate and long term implications for the wellbeing and health of individuals and society (**N**).
- ☑ Based on data from other specific phobias, exposure-based therapy (*in vivo* or imagined) is recommended for children and adolescents (7–17 years) with needle phobia receiving vaccine injections (**N**).
- ☑ Hypnosis requires teaching by a trained professional, but distraction can be readily provided by staff or parents and should be routinely offered in the paediatric setting (**U**).
- ☑ For children and adolescents, sitting upright may reduce procedural pain and distress (**N**).

Acute pain in children with cancer

1. PCA and continuous opioid infusions are equally effective in the treatment of pain in mucositis in children, but opioid consumption and duration of pain is less with PCA (**U**) (**Level I** [Cochrane Review]).
2. Topical local anaesthetic application for children having central venous port access is effective and analgesia is not further improved by oral analgesics (morphine or paracetamol) (**U**) (**Level II**).
3. Self-reported pain scores by children with cancer were higher in intensity compared with nurse-reported pain scores, with variable agreement with parent/carer-reported pain scores (**N**) (**Level III-2 SR**).
4. There is limited evidence that low-level laser therapy reduces the severity of mucositis in children (**U**) (**Level III-2 SR** [PRISMA]).
5. QT interval prolongation with methadone in children with cancer has been reported without complication; the clinical significance is not clear (**N**) (**Level IV**).
6. Poorly managed pain in children during the terminal stages of cancer is associated with higher levels of long term parental grief (**N**) (**Level IV**).
7. Outpatient intravenous PCA opioid has been used to help children in the terminal stages of cancer stay at home (**N**) (**Level IV**).
8. Transdermal fentanyl patch use may be appropriate in opioid tolerant children with cancer (**N**) (**Level IV**).

- ☑ In paediatric cancer pain management, the same therapeutic approaches as in adults are used, although evidence is limited (**U**).
- ☑ The World Health Organization has removed codeine from the management approach to paediatric cancer pain reducing the number of tiers from three to two: with tier one including nonopioid analgesics and adjuvants and tier two including strong opioids; in 2019 the WHO withdrew the reference document, but it remains endorsed by organisations throughout Australia, New Zealand and internationally until it is replaced (**Q**).

☑ Caution must be taken during uptitration of transdermal systems due to the pharmacokinetic profile of transdermal delivery that has slow penetration and delayed uptake from the stratum corneum (**N**).

Other acute pain conditions in children

Management of pain due to trauma and burns in children

1. For paediatric trauma patients in the prehospital setting, frequency of administration of analgesics is low (**N**) (**Level IV SR**) and documentation of pain assessment is variable (**N**) (**Level IV**).
2. Intranasal fentanyl is equivalent to intravenous or intramuscular morphine in reducing pain associated with paediatric fracture presenting to the emergency department (**U**) (**Level II**).
3. Intranasal ketamine (1–2 mg/kg) achieves similar pain reduction to intranasal fentanyl (1.5–2 mcg/kg) for isolated limb fracture pain, but with an increased frequency of minor side effects (eg dizziness, bad taste) (**N**) (**Level II**).
4. The introduction of an intranasal fentanyl protocol for limb injury can reduce the time to first analgesia in the emergency department, compared to intravenous morphine (**N**) (**Level III-3**).
5. Single shot fascia iliaca compartment block is effective in managing femoral fracture pain (**N**) (**Level III-3**).
6. Methoxyflurane, intranasal or intravenous fentanyl and intravenous morphine are effective and commonly used prehospital to manage pain from trauma (**N**) (**Level IV**); intravenous or intranasal ketamine is also an effective analgesic in the prehospital setting (**U**) (**Level IV**).
7. Younger children (<3 years) with an isolated limb injury receive less analgesia in the emergency department than older children (**N**) (**Level IV**).
8. In children and adolescents admitted to hospital with burns, higher morphine doses during admission predict reduced post-traumatic stress symptoms (**N**) (**Level IV**).
9. Pruritus following burn injury in children is common; predictors for pruritus include greater total body surface area of burn and greater number of days since burn injury (**N**) (**Level IV**).

☑ Administration of analgesia by emergency medical services and emergency departments for trauma patients (including those with burns) is strongly recommended as part of the initial resuscitation along with first aid measures such as cooling and dressings for burns and splint application for trauma (**N**).

☑ Gabapentin and pregabalin are used to manage pruritus and neuropathic pain following burn injury in children (**N**).

Paediatric migraine

1. In children (<12 years), effective acute migraine treatments include ibuprofen and triptans (**Q**) (**Level I** [Cochrane]), however there is a significant placebo response rate in this setting.
2. In adolescents (12–17 years), triptans are effective acute migraine treatments, however there is a significant placebo response rate in this setting. One triptan cannot be recommended over another (**Q**) (**Level I** [Cochrane]).

3. Nonpharmacological preventive therapies including relaxation training and cognitive behavioural therapy reduce the frequency and intensity of headache in adolescents for 1 year (**S**) (**Level I** [Cochrane]). Biofeedback also reduces migraine attack duration (**S**) (**Level I**).

☑ Guidelines for the treatment of migraine in children and adolescents recommend environment modification, paracetamol, ibuprofen, naproxen (or other nonselective NSAIDs), dopamine antagonists (if nausea prominent), fluid therapy and triptans (**U**).

☑ Evidence is limited for standard of care second line therapies (single and multiple IV therapies including fluids and antiemetics) and third line therapies (such as IV dihydroergotamine, magnesium, sodium valproate, lidocaine or propofol) for acute childhood migraine (**N**).

☑ The use of psychological interventions and stress management strategies have not been assessed in acute migraine episodes; it must be recognised that many of these skills need to be developed over time (**N**).

Acute abdominal pain in children

1. Probiotics improve pain in children with recurrent abdominal pain versus placebo (**N**) (**Level I** [Cochrane Review]) with no good evidence for positive effect of various pharmacological treatments (**N**) (**Level I** [Cochrane Review]).

2. Cognitive behavioural therapy (CBT) and hypnotherapy reduce pain short term (over 1 to 3 months) in children and adolescents with recurrent abdominal pain (**N**) (**Level I** [Cochrane Review]).

Acute pain associated with haematological disorders in children

Sickle cell disease

1. Hydroxyurea decreases the frequency of acute vaso-occlusive crises, life-threatening complications and hospitalisations in children with sickle cell disease (**S**) (**Level I** [Cochrane Review]).

2. Intravneous or oral magnesium does not reduce pain of vaso-occlusive crises associated with sickle cell crises or length of hospital stay (**N**) (**Level I** [Cochrane Review]).

3. Attention must be paid to acute kidney injury risk in sicker inpatients with sickle cell disease receiving multiple doses of nsNSAID (**N**) (**Level III-3**).

4. Parenteral corticosteroids reduced the duration of severe pain in children with vaso-occlusive crises in sickle cell disease at the expense of more rebound attacks post cessation (**Q**) (**Level II**).

☑ It is standard of care for oral and IV paracetamol, nsNSAIDs and opioids to form part of an individual at home or hospital care plan for children with vaso-occlusive crises. Upon admission this is escalated to parenteral nsNSAID and opioid therapy (**N**).

☑ There is no evidence that fluid replacement therapy reduces pain in children with VOC, although it is common practice (**N**).

☑ The impact on painful vaso-occlusive crises of oxygen supplementation in patients with and without obstructive sleep apnoea and CPAP in patients with obstructive sleep apnoea requires assessment (**N**).

☑ Most children with sickle cell disease are not on opioids for chronic or frequent recurrent pain (while adolescents are, at similar rates to affected adults). In patients with sickle cell disease, postoperative opioid requirements may be higher (**N**).

☑ Adjunctive low-dose ketamine and IV lidocaine infusions reduce pain intensity and opioid requirements in refractory pain of acute vaso-occlusive crisis in children with sickle cell disease (**N**).

Haemophilia

☑ In children with haemophilia, on demand and preventative use of recombinant factor concentrates has improved pain-related quality of life measures. Otherwise the principles of pain management in acute bleeds in affected children and adults involve rest, ice, compression and elevation and stepwise escalation of analgesia. Parents of young affected children need education regarding analgesic medication (**N**).

The overweight or obese child or adolescent

☑ When dosing medication in the overweight or obese child or adolescent, age of the patient, each individual drug and the dose type (initial or maintenance) must be considered (**N**).

☑ Given the barriers to accurate dosing in overweight and obese children, judicious dosing and titration to effect wherever possible is recommended. This requires consideration of both pharmacokinetic and pharmacodynamic factors (**N**).

☑ Young and obese children with history of obstructive sleep apnoea syndrome/sleep-disordered breathing are at higher risk of developing serious opioid-induced ventilatory impairment and death (**U**) (**Level IV**).

Complementary and alternative medicines and therapies in children

1. Hypnosis for needle-related procedural pain (including for cancer-related procedures) reduces pain intensity (**S**) and distress (**N**) versus control (**Level I** [Cochrane Review]).
2. Preventive use of probiotics does not reduce infantile colic incidence, but does reduce crying duration versus placebo (**N**) (**Level I** [Cochrane Review]).
3. The probiotic *Lactobacillus reuteri* reduces cry/fuss time in breastfed infants with colic; there is insufficient evidence in formula fed infants (**N**) (**Level I** [PRISMA]).
4. Oral administration of honey versus control in children reduces pain and analgesic use after tonsillectomy (**N**) (**Level I** [PRISMA]).
5. Perioperative acupuncture (including electroacupuncture) versus control in children having tonsillectomy reduces postoperative pain intensity (in the first 48 h) and analgesic consumption (**N**) (**Level I** [PRISMA]).
6. Acupuncture (invasive or non-invasive) versus control for preterm and term neonates receiving heel lance does not reduce pain intensity (**N**) (**Level I** [PRISMA]).

☑ Complementary and alternative medicines and therapies encompass a wide variety of interventions with common use in the community; complementary medicines and therapies are increasingly used as part of integrative approaches to hospital-based healthcare in the paediatric population (**N**).

☑ The evidence on complementary and alternative medicines and therapies is characterised by small sample sizes and study designs prone to bias and caution is urged in interpreting results. Additionally, the safety and potential drug interactions of many complementary and alternative medicines and therapies have not been adequately assessed (**N**).

1

Physiology and psychology of acute pain

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1.1 | Applied physiology of acute pain

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1.2 | Psychological aspects of acute pain

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1.3 | Placebo and nocebo effects in acute pain

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1.4 | Progression of acute to chronic pain

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1.5 | Pre-emptive and preventive analgesia

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1.6.1 | Acute pain and the injury response

1.6.2 | Adverse physiological effects

1.6.3 | Pain and analgesia: effects on injury-induced organ dysfunction

Contributor: Prof Mark Hutchinson

1.6.4 | Adverse psychological effects

Contributor: Prof Michael Nicholas

1.7 | Genetics and acute pain

Contributor: Prof Andrew Somogyi

1.1 | Applied physiology of acute pain

1.1.1 | Definition of acute pain

Pain is most commonly described as "*an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage*", (Merskey 1994 **GL**). It should be noted that "*pain is subjective and indicates that each individual learns the application of the word through experiences related to injury in early life, and characterizes the experience as unpleasant, and therefore emotional as well as sensory in nature*" (IASP 2019a **GL**). Chronic pain has gradually emerged as a distinct phenomenon in comparison with acute pain with the IASP currently defining it as *"pain that lasts or recurs for longer than 3 months"* (Treede 2019 **GL**). Although acute pain cannot be precisely distinguished from chronic pain using time-based definitions, for pragmatic purposes recommended definitions continue to be time-based (Kent 2019 **GL**):

"*Acute pain is considered to last up to seven days, with the following qualifications:*

1. *Its duration reflects the mechanism and severity of the underlying inciting event.*
2. *Prolongations from seven to 30 days are common.*
3. *Prolongations beyond the duration of acute pain but not extending past 90 days post onset/-injury are common. This refers to the ill-defined but important period of "subacute" pain that warrants further specification and consideration in future taxonomic, research, and regulatory efforts.*
4. *Our understanding of pain mechanisms is currently insufficient to link these durations to specific physiologic mechanisms*."

This section focuses on the physiology and pathophysiology of pain resulting from nociceptive activity in the sensory nervous system, but also introduces the neurobiology of pain as a beneficial adaptive brain state that responds to and can be altered by psychological factors. A more complete description of the classes of psychological factors that affect the experience of pain is outlined in Section 1.2; for paediatric information se Section 10.1.

1.1.2 | Nociceptive pathways and pain perception

The ability of the somatosensory system to detect noxious and potentially tissue-damaging stimuli (ie nociception) is an important protective feature that involves multiple interacting peripheral and central mechanisms (Sommer 2018 **NR**). In addition to the sensory effects, the perception and experience of pain is multifactorial and will be influenced by genetic, psychological and environmental factors in every individual (Tracey 2019 **NR EH**; Porreca 2017 **NR**; Vardeh 2016 **NR**).

1.1.2.1 | Peripheral nociceptors

The detection of noxious stimuli by peripheral sensory nerve endings (nociceptors) first requires the transduction of noxious stimuli into electrical activity and the conduction of these nociceptive signals in peripheral sensory nerves to the central nervous system (CNS) (Sommer 2018 **NR**; Dubin 2010 **NR**; Woolf 2007 **NR**). Nociceptive primary afferents are widely distributed throughout the body (skin, muscle, joints, viscera, meninges) and comprise both medium-diameter lightly myelinated A-delta fibres and small-diameter, slow-conducting unmyelinated C fibres. Distinct classes of nociceptors are activated by noxious stimuli, which include intense pressure, extreme temperatures (>40 to 45°C or <15°C) and damaging chemicals. The most

prevalent subclass of nociceptor is the C-fibre polymodal type, which responds to mechanical, thermal and chemical stimuli, whereas other subclasses are specialised mechanical, heat or cold nociceptors (Woolf 2007 **NR**).

The physiological properties of nociceptors are determined by the differential expression of a repertoire of transduction molecules (Dubin 2010 **NR**). The particular expression of these transducers determines which modalities are detected by each set of nociceptors. For example, the transient receptor potential (TRP) channel type vanilloid 1 (TRPV1) transduces noxious temperatures from 39–51°C and generates electrical receptor potentials in a class of polymodal C fibres. All nociceptor axons have free terminal endings without anatomically specialised transducers such as the Meissner's corpuscles and Merkel cells used by skin mechanoreceptors. However, it is now known that molecular transducers used by mechanosensitive neurons, such as Piezo1 and Piezo2, are also widely expressed by non-neuronal cells in skin and other organs that can bidirectionally interact with somatosensory terminals including nociceptors (Oetjen 2018 **NR**; Moehring 2018 **NR**). Nociceptors in visceral tissue show differences to those in somatic tissue but are much less well studied. In the viscera, high threshold specific nociceptors are unusual and most mechanosensitive afferents code stimulation in a linear manner, which can reach the noxious range. There is a large proportion of silent nociceptors in viscera, which are unresponsive under basal conditions and respond to heat and chemical stimuli in the presence of inflammation (Grundy 2019 **NR**; Gebhart 2016 **NR**).

Nociceptors may also be classified by their relationship to trophic factors (Denk 2017 **NR**). Some C-fibre nociceptors are dependent on nerve growth factor (NGF) and express tyrosine kinase receptor (TrkA), which is a neurotrophin receptor. Most of these nociceptors also express substance P and calcitonin gene-related peptide (CGRP) and are classed as peptidergic. Another class of C fibres are not peptidergic but have glial cell line-derived neurotrophic factor (GDNF) family receptors (GFRα1, GFRα2; and their co-receptor Ret) and are thereby targets for GDNF or neurturin, respectively**.** Next generation sequencing and transcriptional profiling (by bulk sequencing or single-cell RNA-Seq) has been used for unbiased classification of primary sensory neurons, including nociceptors (Iadorola 2018 **NR**; Emery 2018 **NR**). A large proportion of differentially expressed genes that define classes encode membrane ion channels and receptors that function in nociceptor transduction and transmission (Waxman 2014 **NR**; Gold 2010 **NR**). However, the function of other transcripts identified by this unbiased approach have yet to be determined. This is advancing our understanding and resolving the conflicting alignment between classes previously defined by molecular, neurochemical, developmental and physiological criteria (Gatto 2019 **NR**; Emery 2018 **NR**).

Nociceptor plasticity

Sensitisation is a characteristic of nociceptors (Woolf 2007 **NR**). The phenotypes of the nociceptors change in response to nerve injury and inflammation and are not static. This dynamic neural plasticity lowers the transduction threshold of nociceptors and contributes to primary hyperalgesia, which is defined as abnormal intensity of pain relative to the stimulus (Gold 2010 **NR**; Sandkuhler 2009 **NR**).

Sensitisation is most often produced by chemical signals of tissue damage: such as during infection, inflammation or ischaemia; disruption of cells; degranulation of mast cells; secretions from inflammatory cells; or following induction of enzymes such as cyclooxygenase-2 (COX-2) (Baral 2019 **NR**; Sommer 2018 **NR**; Oetjen 2018 **NR**). A majority of chemical mediators act locally at nociceptor terminals by directly targeting ion channels or indirectly by activating intracellular signalling via calcium-permeable channels (Bourinet 2014 **NR**) or membrane receptors (see Table 1.1). NGF, immune mediators and other chemicals including proteinases, cytokines such as

tumour necrosis factor (TNF) alpha, interleukins, and chemokines such as chemokine (C-C motif) ligand 3 (CC L3) all have an impact on sensitisation of nociceptors (see Table 1.1).

TRPV1 is an example of a nociceptor transducer that contributes to sensitisation in nociceptor terminals. This is achieved when the thermal and chemical sensitivity of TRPV1 is lowered following direct or indirect modulation by local inflammatory mediators or by noxious environmental chemicals such as capsaicin (which causes the perception of heat and pain elicited by chillies) (Henrich 2015 **Level III-1 EH**). Neuropeptides (substance P and CGRP) released from the activated peripheral terminals via peripheral antidromic axonal responses cause neurogenic inflammation by promoting vasodilation and plasma extravasation. This promotes recruitment of serum factors and inflammatory cells at the site of injury (Sousa-Valente 2018 **NR**). Nonsteroidal anti-inflammatory drugs (NSAIDs) modulate peripheral pain by reducing prostaglandin E2 (PGE_2) synthesis from locally induced COX-2. Inflammation also induces changes in protein synthesis in the cell body of neurons in the dorsal root ganglia (DRG) and trigeminal ganglia, and alters the expression and transport of receptors, such as TRPV1 and opioid receptors, to the peripheral nerve terminal (Woolf 2007 **NR**). The latter underlies the peripheral action of opioid agonists in inflamed tissue and could allow nociceptor modulation by immune cells (Stein 2009 **NR**).

Table 1.1 | Examples of receptors and ligands that function in transduction or primary and secondary hyperalgesia of nociceptive primary afferent or spinal cord neurons

	Subtype	Ligand/Stimulus
Ionotropic receptor		
TRP	TRPV1	heat (≥43°C, unsensitised), capsaicin, H^+ (protons)
	TRPV2	heat (≥52°C)
	TRPV3, TRPV4	warm (32 to 39°C)
	TRPA1	environmental irritants (mustard oil, nicotine, formaldehyde, acrolein)
	TRPM8	cool (≤26°C)
acid sensing	ASIC1-4, TRAAK/TREK	H^+ (protons)
glutamate	NMDA, AMPA Kainate, GLurR1-5, NR1-2	glutamate
nicotinic	nACh (multiple subtypes)	acetylcholine
purine	P2X1-6	ATP
serotonin	$5\text{-}HT_3$	5-HT
Metabotropic receptor		
bradykinin	B_I, B_2	bradykinin
cannabinoid	CB_1, CB_2 (TRPs, non-canonical)	anandamide, cannabidiol

	Subtype	Ligand/Stimulus
chemokine	CXCR2,CXCR5, CX3CR1	CXCL1, CXCl13, CCL2 (MCP1), et al.
histamine	H_1	histamine
Interleukin	IL1R, IL-31A/OSMR, et al.	IL-1 alpha, IL-6, IL-31, et al.
LPS	Toll-like receptor 4	lipopolysaccharides
Mas-related GPCRs	MRGPRD, MRGPRA3, MRGPRX1	β-alanine, BAM8-22, other orphan ligands
metabotropic glutamate	$mGLuR_{1,2/3,5}$	glutamate
prostanoids	EP_{1-4} IP	PGE_2 (prostaglandins) PGI_2 (prostacyclin)
proteinase	PAR_{1-4} (TRPs non-canonical)	protease
serotonin	$5\text{-}HT_{1A}$, $5\text{-}HT_{2A,}$ $5\text{-}HT_4$	5-HT (serotonin)
tachykinin	neurokinin-1 (NK_1)	substance P, neurokinin A
tyrosine kinase receptor	TrkA, p75 neurotrophin	NGF (nerve growth factor)
TNR receptor	TNFR1, TNFr2	TNF (tumour necrosis factor)
Pore forming toxins		
haemolysin	α-haemolysin, γ- haemolysin AB	Secreted by gram-positive bacteria (eg *S. aureus*)

Sources: Baral 2019; Sommer 2018; Harding 2018; Oetjen 2018; Gold 2010.

Similarly, NGF increases with inflammation, binds to TrkA, which causes phosphorylation of the TRPV1 and facilitates the sodium channels, which both increase nociceptor activity. In addition, NGF-TrkA complex is transported to the DRG, where it impacts on phenotypic changes resulting in changes to receptors and channels (Denk 2017 **NR**). NGF regulates relative amounts of neuropeptides and the threshold of nociceptors. The number of receptors for NGF (TrkA) is also determined by the functions of the corresponding DRG cells. Visceral primary afferents have a higher proportion of cells containing TrkA compared to somatic primary afferent neurons.

Sodium, potassium, calcium and chloride ion channels also function in nociceptor transduction and transmission. Sodium channels are a prerequisite for conduction of neuronal action potentials to the CNS (Bennett 2019 **NR**). A rapidly inactivating fast sodium current that is blocked by tetrodotoxin is present in all sensory neurons. This is the principal site of action for local anaesthetics but, as the channel is present in all nerve fibres, conduction in sympathetic and motor neurons may also be blocked. Subtypes of slowly activating and inactivating tetrodotoxin-resistant sodium currents are selectively present on nociceptive fibres. Following injury, changes in sodium-channel kinetics and specific alterations in the expression of sodium channels (upregulation or downregulation) contribute to hyperexcitability that occurs in different pain states and may explain part of the mechanism of benefit of systemic local anaesthetics in acute and chronic pain (see Section 4.4.1) . The importance of sodium channels

in pain sensitivity is reflected by the impact of human mutations in the SCN9A gene encoding the $Na_v1.7$ channel (Dib-Hajj 2019 **NR**) (see Section 1.7.1). Loss of function results in insensitivity to pain, whereas gain of function mutations can produce erythromelalgia and other severe pain. These effects are not restricted to sodium channels; functional and expression changes in other classes of calcium, potassium and chloride channels also contribute to nociceptive transmission and processing by nociceptors (Bennett 2019 **NR**).

Medicines that are specific blockers of sodium channel subtypes or cause state-dependent reductions in sodium channel activity are becoming available for evaluation in human clinical trials (Dib-Hajj 2019 **NR**). New ion channel targets are also emerging that, as well as regulators of afferent fibre excitability, include a separate class of ion channels that regulate the transfer of the nociceptive signal (synaptic transmission) from primary afferent fibres to the second-order neurons in the spinal cord (Yekkirala 2017 **NR**).

1.1.2.2 | Nociceptive transmission in the spinal cord

The cell bodies of nociceptive afferents that innervate the trunk, limbs and viscera are found in the DRG, while those innervating the head, oral cavity and neck are in the trigeminal ganglia and project to the brainstem trigeminal nucleus (Dubin 2010 **NR**). The central terminals of C and A-delta fibres convey information to nociceptive-specific areas within laminae I and II of the superficial dorsal horn and to wide dynamic range neurons in lamina V, which encode both innocuous and noxious information (Koch 2018 **NR**; Todd 2010 **NR**). By contrast, large myelinated A-beta fibres transmit light touch or innocuous mechanical stimuli to the deeper laminae III and IV (Moehring 2018 **NR**).

Primary afferent terminals activate dorsal horn neurons by releasing two major classes of neurotransmitter; glutamate as the primary transmitter and neuropeptides such as substance P, CGRP, galanin and somatostatin as cotransmitters (Sandkuhler 2009 **NR**). Depolarisation of the primary afferent terminal results in glutamate release, which activates postsynaptic ionotropic α-amino-3-hydroxyl-5-methyl-4-isoxazole-propionate (AMPA) receptors and rapidly signals information relating to the location and intensity of noxious stimuli. In this “normal mode”, a high-intensity stimulus elicits brief localised pain and the stimulus-response relationship between afferent input and dorsal horn neuron output is predictable and reproducible (Prescott 2014 **NR**; Sandkuhler 2009 **NR**).

Summation of repeated C-fibre inputs results in a progressively more depolarised postsynaptic membrane and removal of the magnesium block from the N-methyl-D-aspartate (NMDA) receptor. This is mediated by glutamate acting on ionotropic (non-NMDA) and metabotropic (mGluR) glutamate receptors, and by substance P acting on neurokinin-1 (NK1) receptors. A progressive increase in action potential output from the dorsal horn cell is seen with each stimulus and this rapid increase in responsiveness during the course of a train of inputs has been termed “wind-up”. Long-term potentiation (LTP) is induced by higher frequency stimuli but the enhanced response outlasts the conditioning stimulus. This mechanism has been implicated in learning and memory in the hippocampus and pain sensitisation in the spinal cord (Sandkuhler 2009 **NR**). Behavioural correlates of these electrophysiological phenomena have been seen in human volunteers as repeated stimuli elicit progressive increases in reported pain (Treede 2016 **NR**).

Intense and ongoing stimuli further increase the excitability of dorsal horn neurons, leading to central sensitisation (Woolf 2014 **NR**; Baron 2013 **NR**; Woolf 2011 **NR**). Increases in intracellular calcium due to influx through the NMDA receptor and release from intracellular stores activate a number of intracellular kinase cascades. Subsequent alterations in ion channel and/or receptor activity and trafficking of additional receptors to the membrane increase the efficacy of synaptic

transmission. As a result of the increased excitability of central nociceptive neurons, their threshold for activation is reduced. In this situation, pain can occur in response to low-intensity previously nonpainful stimuli (ie allodynia) and sensitivity spreads beyond the area of tissue injury (ie secondary hyperalgesia) (Sandkuhler 2009 **NR**). Wind-up, LTP and secondary hyperalgesia may all contribute to central sensitisation and may share some of the same cellular mechanisms but are independent phenomena.

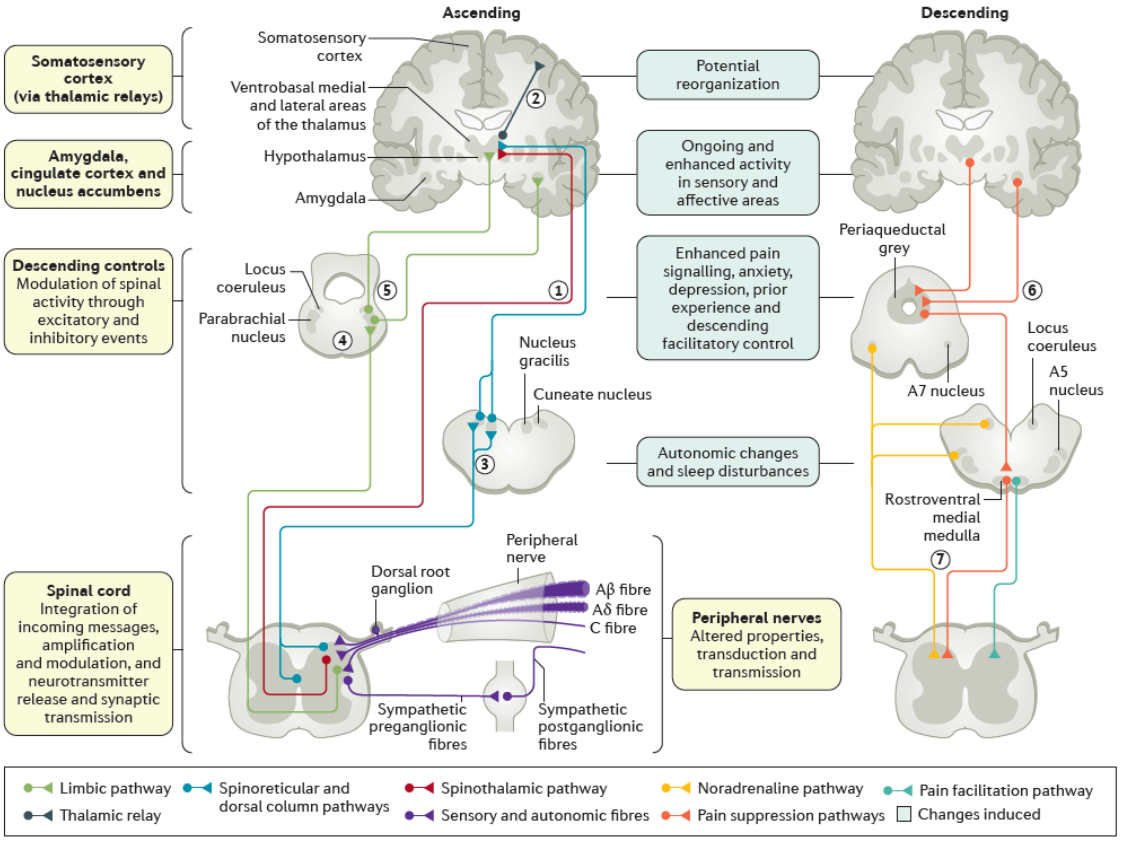
The intracellular changes associated with sensitisation may also activate a number of transcription factors both in DRG and dorsal horn neurons, with resultant changes in gene and protein expression (Ji 2018 **NR**; Simonetti 2013 **NR**). Unique patterns of either upregulation or downregulation of neuropeptides, G-protein coupled receptors, growth factors and their receptors, and many other signalling molecules occur in the spinal cord and DRG in inflammatory, neuropathic and cancer pain. Further elucidation of changes specific to different pain states may allow more accurate targeting of therapy in the future.

In addition to activity in neurons, central neuroinflammation involving surrounding glial and immune cells (including microglia) can also modulate synaptic transmission (Baral 2019 **NR**; Ji 2018 **NR**). Strong evidence has accumulated to suggest glial and neuroimmune mechanisms contribute to sex differences in pain (Mapplebeck 2017 **NR**).

1.1.2.3 | Central projections of nociceptive pathways

Different qualities of the overall pain experience are subserved by five major ascending spinal cord projection pathways; the spinothalamic, spinoreticular, spinomesencephalic, cervicothalamic and spinohypothalamic pathways. The spinothalamic pathway ascends from primary afferent terminals in laminae I and II, via connections in lamina V of the dorsal horn, to the thalamus and then to the somatosensory cortex (Craig 2003 **NR**). This pathway provides information on the sensory-discriminative aspects of pain (ie the site and type of painful stimulus). The spinoreticular and spinomesencephalic (spinoparabrachial) tracts project to the medulla and midbrain and are important for integrating nociceptive information with arousal, homeostatic and autonomic responses as well as projecting to central areas mediating the emotional or affective component of pain (Kobayashi 2012 **NR**; Craig 2009 **NR**; Price 2000 **NR**). Many of the second-order projection neurons in these pathways are superficial dorsal horn lamina I neurons that express the NK1 receptor and are stimulated by peptidergic C-fibre afferents (Todd 2010 **NR**). Other connections include those to cortical areas involved in the affective and motivational components of pain (eg anterior cingulate cortex, insular and prefrontal cortex), projections back to the periaqueductal grey (PAG) region of the midbrain and rostroventromedial medulla (RVM), which are crucial for fight or flight responses and stress-induced analgesia, and projections to the reticular formation that are important for the regulation of descending pathways to the spinal cord. Descending projections from the medullary dorsal reticular nucleus (DRt) are important in facilitating the diffuse noxious inhibitory control (DNIC) (see Figure 1.1) (Treede 2016 **NR**; Ossipov 2010 **NR**; Tracey 2007 **NR**).

Figure 1.1 | The main ascending and descending spinal nociceptive pathways



In the ascending afferent pathways, the sensory components of pain are via the spinothalamic pathway to the ventrobasal medial and lateral areas ①, which then project to the somatosensory cortex allowing for the location and intensity of pain to be perceived ②. The spinal cord also has spinoreticular projections and the dorsal column pathway to the cuneate nucleus and nucleus gracilis ③. Other limbic projections relay in the parabrachial nucleus ④ before contacting the hypothalamus and amygdala, where central autonomic function, fear and anxiety are altered ⑤. Descending efferent pathways from the amygdala and hypothalamus ⑥ drive the periaqueductal grey, the locus coeruleus, A5 and A7 nuclei and the rostroventral medial medulla. These brainstem areas then project to the spinal cord through descending noradrenaline (inhibition via α2 adrenoceptors) and, in neuropathy, there is a loss of this control and increased serotonin descending excitation via 5-HT3 receptors ⑦. The changes induced by peripheral neuropathy on peripheral and central functions are shown.

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1.1.2.4 | Descending modulatory pathways

The brain has a remarkable capacity to modulate pain according to the competing demands of physiological, psychological and social factors. The neural contributors to this modulation are complex and only partly elucidated. Best understood is a descending pain-modulatory circuit that projects to the spinal cord and changes the experience of pain by directly or indirectly modulating (inhibiting or facilitating) nociceptive traffic (Ossipov 2010 **NR**). Descending pathways contribute to the modulation of nociceptive transmission in the spinal cord via presynaptic actions on primary afferent fibres, postsynaptic actions on projection neurons or via effects on interneurons within the dorsal horn. Sources include direct corticofugal and indirect (via

modulatory structures such as the PAG) pathways from the cortex and from the hypothalamus, which is important for coordinating autonomic and sensory information. The RVM receives afferent input from brainstem regions (PAG, parabrachial nucleus and nucleus tractus solitarius) as well as direct ascending afferent input from the superficial dorsal horn and is an important site for integration of descending input to the spinal cord (Ossipov 2010 **NR**). The relative balance between descending inhibition and facilitation varies with the type and intensity of the stimulus and also with time following injury (Chen 2019 **NR**). Serotonergic and noradrenergic pathways in the dorsolateral funiculus (DLF) contribute to descending inhibitory effects and serotonergic pathways have been implicated in facilitatory effects (Bannister 2017 **NR**).

Inhibitory modulation occurs within the dorsal horn and can be mediated by non-nociceptive peripheral inputs, local inhibitory gamma-amino butyric acid (GABA) and glycine interneurons, descending bulbospinal projections and higher-order brain function (eg distraction, cognitive input). These inhibitory mechanisms are activated endogenously through neurotransmitters such as endorphins, enkephalins, noradrenaline (norepinephrine) to reduce the excitatory responses to persistent C-fibre activity. Serotonin (5-HT) has been implicated as both pronociceptive and inhibitory (Bannister 2017 **NR**).

Similar mechanisms are the basis of many exogenous analgesic agents (Bannister 2017 **NR**; Ossipov 2010 **NR**; Sandkuhler 2009 **NR**). Thus, analgesia may be achieved by either enhancing inhibition (eg opioids, clonidine, antidepressants) or by reducing excitatory transmission (eg local anaesthetics, ketamine) (Yekkirala 2017 **NR**).

A feature of sensory processing is that not all of the signals received from receptors are perceived. The limited processing capacity of the brain is optimised by prioritising behaviourally relevant signals, while suppressing less important signals. Advances in human functional brain imaging have provided new evidence of how pain perception is shaped by other sensory modalities and attentional or emotional processing by the cerebral cortex and basal forebrain (Wager 2015 **NR**; Carlino 2014 **NR**). The engagement of attention, expectation and reappraisal mechanisms provides for complex cognitive modulation of pain (Bushnell 2013 **NR**; Wiech 2013 **NR**). This is the basis of placebo-induced analgesia (see Section 1.3) and for using psychological interventions to target endogenous pain modulation (Flor 2014 **NR**; Carlino 2014 **NR**).

1.1.3 | Physiological and pathological pain

As discussed in the introduction, pragmatic working clinical definitions of acute and chronic pain continue to be time-based and do not explicitly identify underlying pathophysiology. However, the development of mechanism-based functional classification schemes and identification of clinically useful pain biomarkers continue to be intensively researched (Tracey 2019 **NR**; Vardeh 2016 **NR**).

The basic framework most commonly used addresses heterogeneity of pain by identifying “nociceptive” and “inflammatory” classes of physiological or adaptive pain, together with “neuropathic” and “CNS dysfunctional (nociplastic)” classes of pathological or maladaptive pain (Tracey 2019 **NR**; Kosek 2016 **NR**; Vardeh 2016 **NR**; Woolf 2010 **NR**). Nociceptive and inflammatory pain are considered to be physiological functions of the nociceptive division of the somatosensory nervous system, which monitors the physical state of the body (Sommer 2018 **NR**). It has been understood from the earliest investigations by Sherrington and later landmark studies by Wall and Melzack that this system does not simply locate and measure the intensity of painful sensory stimulation; it also encodes innate aversive reinforcing signals that drive motivational, emotional and cognitive processing in the brain (as described below) (Seymour 2019 **NR**). In humans and other animals, these systems support escape and defensive behaviours that minimise potential lethal tissue damage, as well as coping behaviours that manage recovery from

such damage and avoidance behaviours that use learning signals to minimise the risk of such damage in the future (Seymour 2019 **NR**). This broad functionality can be shown to engage most of the major functional brain subdivisions (Tracey 2019 **NR**). Their basic physiological importance is shown by the unavoidable tissue damage suffered in humans with rare genetic mutations that render them insensitive to pain (Dib-Hajj 2019 **NR**).

Neuropathic pain is defined as "*pain caused by a lesion or disease in the somatosensory nervous system*" (Scholz 2019 **GL**; Jensen 2011 **GL**). The estimated prevalence of neuropathic pain is much higher than commonly thought and in the range of 7–10% of the population (van Hecke 2014 **NR**). Although commonly regarded as a cause of chronic symptoms, neuropathic pain can also present acutely following trauma and surgery. The incidence has been conservatively estimated as 3% of acute pain service (APS) patients (Hayes 2002 **Level IV**). Similarly, acute medical conditions may present with neuropathic pain (Gray 2008 **NR**) (as discussed further in Section 8.1.4). Nerve injury and associated alterations in afferent input or hyperexcitability associated with central pain (eg caused by stroke, spinal cord injury [SCI], multiple sclerosis) can induce structural and functional changes at multiple points in nociceptive pathways with complex long-term psychobiological consequences (Alles 2018 **NR**; Colloca 2017 **NR**; Treede 2016 **NR**; von Hehn 2012 **NR**).

CNS dysfunctional pain syndromes such as migraine, fibromyalgia and chronic pelvic pain show chronicity that often cannot be reliably linked to clinical pathophysiology in the somatosensory system (Woolf 2010 **NR**). Historically, many terms have been used to refer to clinical CNS dysfunctional pain, including "functional pain syndromes", "maldynia", or "neuroplastic" (Mayer 2009 **NR**). The IASP, however, has recently endorsed "nociplastic pain", defined as "*Pain that arises from altered nociception despite no clear evidence of actual or threatened tissue damage causing the activation of peripheral nociceptors or evidence for disease or lesion of the somatosensory system causing the pain*" (IASP 2019a **GL**; Kosek 2016 **NR**). This new term is matched in ICD-11 by the classification '*chronic primary pain'* (Nicholas 2019 **GL**).

When viewed from this perspective, acute pain will most commonly be linked to nociceptive and inflammatory pain but also to less common neuropathic pain. It is clear, however, that the clinical definition will also capture early stages of chronicity that could leadto neuropathic and nociplastic pain in some patients. It is important to recognise that it is currently not possible to identify in advance specific patients who will undergo this transition (Kent 2019 **NR**). The probability of chronic pain developing is subject to the influences of genetic and physiological factors and how these interact with the accumulated psychological and social experiences of pain (Borsook 2018 **NR**; Flor 2014 **NR**; Denk 2014 **NR**). How these combine will determine how individuals experience pain and is also highly likely to determine their underlying resilience in coping with this experience (Bushnell 2013 **NR**; Elman 2013 **NR**) (see Sections 1.2, 1.4 and 1.5).

1.2 | Psychological aspects of acute pain

A new definition of pain has been proposed by the IASP: "*An aversive sensory and emotional experience typically caused by, or resembling that caused by, actual or potential tissue injury*." (IASP 2019b). The revised definition is broadened to include non-verbal presentations (eg in people with communication deficits and animals). A key part of the definition is the recognition that pain is an experience that has emotional and sensory components (ie it is not just a sensation).

This section emphasises several important points:

- Pain is always a personal experience that is influenced to varying degrees by biological, psychological and social factors;
- Pain and nociception are different phenomena – the experience of pain cannot be deduced from activity in sensory pathways;
- Through their life experiences, individuals learn the concept of pain;
- A person's report of an experience as pain should be respected;
- Although pain usually serves an adaptive role, it may have adverse effects on function and social and psychological well-being.

There is a consensus view that pain is an individual, multifactorial experience influenced, among other things, by culture, previous pain experience, beliefs, expectations, mood and ability to cope. Pain may be an indicator of tissue injury but may also be experienced in the absence of, or out of proportion to an identifiable tissue injury, especially when it becomes chronic. The degree of pain and disability experienced in relation to similar tissue injury varies between people; likewise, there is individual variation in response to methods to alleviate pain (Flor 2012 **NR**).

Factors that might contribute to the individual's pain experience include somatic (physical) and psychological factors as well as contextual factors, such as situational and cultural characteristics. Pain expression, which may include facial expressions, body posture, language, vocalisations and avoidance behaviour, partially represents the complexity of the psychological experience but is not equivalent to it (Kunz 2004 **Level III-2 EH**, n=40; Vervoort 2009 **Level IV EH**, n=62). Engel's enunciation (Engel 1997 **NR**) of a biopsychosocial model of illness has provided a framework for considering pain phenomena.

Biopsychosocial models of pain (Turk 1995 **NR**) are based on the proposition that psychobehavioral processes are mediated via neurobiological processes and that they interact. Biological factors are reflected in physiological and neurophysiological changes in the body and psychological factors are reflected in the appraisal and perception of internal physiological phenomena. These appraisals and behavioural responses are, in turn, influenced by social or environmental factors, such as reinforcement contingencies (Flor 2002 **Level III-2**, n=60). At the same time, the model also proposes that psychological and social factors can affect biological processes (eg hormonal/stress responses, endogenous pain regulation) and brain structures associated with the exacerbation and maintenance of pain symptoms (Turk 2018 **NR**).

1.2.1 | Psychological factors

Psychological factors that influence the experience of pain include the processes of attention, other cognitive processes (eg learning, thinking styles, beliefs, mood), behavioural responses and interactions with the person's environment.

Importantly, psychological factors that contribute to the experience and impact of pain (acute or chronic) can be amenable to change and thus influence outcomes for the individual (Nicholas 2011 **NR**).

1.2.1.1 | Attention

In relation to pain, attention is viewed as an active process and the primary mechanism by which nociception accesses awareness and disrupts current activity (Legrain 2012 **NR**; Eccleston 1999 **NR**). The degree to which pain may interrupt attention depends on factors such as the intensity of pain, its novelty, unpredictability, degree of awareness of bodily information, threat value, catastrophic thinking, presence of emotional arousal, environmental demands (such as task difficulty) and emotional significance.

Concepts like somatosensory amplification and hypervigilance have been used to describe the selective attention of patients towards pain to the detriment of more functional activities. These processes have been characterised as attentional bias (ie the preferential allocation of attention to information that is related to pain) and this has been extensively studied in relation to acute, chronic and experimentally induced pain. The most recent meta-analysis of this literature indicated that attentional bias appears to relate more towards the sensory aspects of the pain experience, rather than the emotional content (Todd 2018 **Level IV SR**, 52 studies, n=4,466). It is important to note that these studies may not be completely representative of clinical acute pain (eg postsurgical pain). The role of attentional mechanisms in pain experience and impact is not uniform and terms like "hypervigilance" should not be used loosely as other processes, particularly emotional ones (eg sense of threat), are likely to be involved as well as attention.

1.2.1.2 | Learning processes

The role of learning processes has primarily been studied in laboratory settings with experimentally induced pain. A number of studies using healthy subjects have demonstrated that reports of pain (eg pain severity ratings) can be conditioned by their consequences and this effect can be reflected in measures of associated skin conductance responses, facial activity and cortical responses (Jolliffe 2004, **Level III-2 EH**, n=46; Flor 2002 **Level III-2**, n=60). Taken together, these studies provide support for the thesis that the experience of pain is not solely due to noxious input but that environmental reinforcement contingencies can also influence this experience (see also Section 1.3).

Learning processes have also been implicated in the development and maintenance of chronic pain (Flor 2012 **NR**).

1.2.1.3 | Beliefs and thought processes

Empirical evidence supports a role for "fear of pain" contributing to the development of avoidance responses following pain and injury, which ultimately lead to disability in many people with persisting pain (Leeuw 2007 **NR**). From this perspective, appraisals of internal and external stimuli as threats (eg catastrophising), negative affectivity and anxiety sensitivity can contribute to the development of pain-related fear and, in turn, lead to escape and avoidance behaviours, as well as hypervigilance to internal and external illness information, muscular reactivity, and physical disuse and behavioural changes.

Studies with a range of patient samples have confirmed that thinking styles that are overly pessimistic, ruminative and helpless (eg catastrophic thinking) are frequently associated with more severe acute pain and associated distress, as well as persisting pain.

In patients who underwent anterior cruciate ligament repair, those with high Pain Catastrophising Scale (PCS) scores assessed prior to surgery reported more pain immediately after surgery and when walking at 24 h compared with those with low scores; however there was no difference in analgesic consumption (Pavlin 2005 **Level IV**, n=48). After breast surgery, catastrophising was associated with increased pain intensity and analgesic use (Jacobsen 1996 **Level IV**, n=59) and after abdominal surgery (Granot 2005 **Level IV**, n=38) and Caesarean section with higher pain scores (Strulov 2007 **Level IV**, n=47). Preoperative PCS scores also predicted pain after total knee arthroplasty (TKA) in the postoperative period (Roth 2007 **Level IV**). After a wide range of surgical procedures , the most important predictors of pain severity up to 5 d following surgery were surgical fear and pain catastrophising (beside preoperative pain and expected pain) (Sommer 2010 **Level IV**, n=1,490). In a clinical sample of aged patients, attentional avoidance of emotionally aversive stimuli prior to surgery predicted acute postoperative pain, measured by the consumption of opioids via patient-controlled analgesia (PCA) (Lautenbacher 2011 **Level IV**, n=58). This measure was a better predictor of postoperative pain than depression, anxiety and pain catastrophising. Subsequently, a systematic review of studies of psychological factors associated with acute postsurgical pain confirmed the most significant correlates are: pain catastrophising, expectation of pain, anxiety (state and trait), depression, optimism, negative affect and neuroticism/psychological vulnerability (Sobol-Kwapinska 2016 **Level IV SR** [PRISMA], 53 studies, n=10,749). This meta-analysis suggests that pain catastrophising is the most strongly associated with acute postsurgical pain (r=0.41; 95%CI 0.28 to 0.52) (see also Section 1.4).

A significant association between anxiety or pain catastrophising and the subsequent development of chronic postsurgical pain (CPSP) was reported in a systematic review in 16 of 29 studies (Theunissen 2012 **Level III-2 SR**, 29 studies, n=6,628). Following TKA, a systematic review found catastrophising is the strongest predictor of chronic pain (Lewis 2015 **Level IV SR**, 32 studies, n=29,993). Another systematic review found patients with acute and subacute back pain with high levels of catastrophising complained of more pain and disability at 6 mth and more disability at 1 y than those with low levels (Wertli 2014a **Level III-2 SR**, 16 studies, n unspecified).

High fear avoidance beliefs in patients with back pain of <6 mth duration are associated with poor outcomes, which may be improved by treatment approaches aimed at fear avoidance (Wertli 2014b **Level I** [PRISMA], 17 RCTs, n=1,153). Early postoperative fear of movement also predicted pain, disability and physical health 6 mth after spinal surgery for degenerative conditions (Archer 2014 **Level III-2**, n=141).

1.2.1.4 | Depression and anxiety

Anxiety and depression have repeatedly been found to contribute to the experience and impact of both acute and chronic pain.

Significant preoperative predictors of poor postoperative pain control included younger age (OR 1.18; 95%CI 1.05 to 1.3) (14 studies), female sex (OR 1.29; 95%CI 1.17 to 1.43) (20 studies), smoking (OR 1.33; 95%CI 1.09 to 1.61) (9 studies), history of depressive symptoms (OR 1.71; 95%CI 1.32 to 2.22) (8 studies), history of anxiety symptoms (OR 1.22; 95%CI 1.09 to 1.36) (10 studies), sleep difficulties (OR 2.32; 95%CI 1.46 to 3.69) (2 studies), higher body mass index (OR 1.02; 95%CI 1.01 to 1.03) (2 studies), presence of preoperative pain (OR 1.21; 95%CI 1.10 to 1.32) (13 studies) and use of preoperative analgesia (OR 1.54; 95%CI 1.18 to 2.03) (6 studies) (Yang 2019 **Level IV SR** [PRISMA], 33 studies, n=53,362). Interestingly, pain catastrophising, American Society of Anesthesiologists (ASA) status, chronic pain, marital status, socioeconomic status, education, surgical history, preoperative pressure pain tolerance and orthopaedic surgery (vs abdominal surgery) were not associated with increased odds of poor pain control.

Anxiety is one of the most significant predictive factors (in addition to pre-existing pain, age and type of surgery) for the severity of postoperative pain (Ip 2009 **Level IV SR**, 48 studies, n=23,037). Psychological distress (besides type of surgery and age) is the most significant predictor of postoperative analgesic consumption, not sex as is commonly believed.

Among other factors, preoperative anxiety predicted pain intensity 48 h after hysterectomy for benign conditions (Pinto 2012 **Level IV**, n=203). Subsequent multivariable analysis revealed that pain catastrophising acted as a full mediator between presurgical anxiety and postsurgical pain intensity. In the late phase after leg injury, anxiety has the only significant relationship to pain (Castillo 2013 **Level IV**, n=545). Anxiety predicted pain over all time periods: 3 to 6 mth (standardised regression weights [SRW] 0.11), 6 to 12 mth (SRW 0.14) and 12 to 24 mth (SRW 0.18).

In opioid-tolerant patients, the anxiety and autonomic arousal associated with withdrawal (Tetrault 2008 **NR**) may also have an impact on acute pain experience and report (see Section 9.7 for further details).

There is a consistent association between chronic postsurgical pain and depression as well as psychological vulnerability and stress (Hinrichs-Rocker 2009 **Level IV**, 50 studies, n≈25,000). Similarly, there is a strong relationship between persistent knee pain and depression (with higher levels of knee pain being positively related to higher levels of depression) but not with anxiety and poor mental health in general (Phyomaung 2014 **Level IV SR**, 16 studies, n=15,113).

1.2.1.5 | Implications

The presence of modifiable psychological factors, especially anxiety, catastrophising and depression, should be considered in acute pain settings and, if identified, should be targeted by treatment. The results of research evaluating psychological interventions for these factors are considered elsewhere (see Section 7.1). These psychological contributors to higher pain levels and interference in daily activities are not universal and there is considerable variability between individuals.

1.2.2 | Patient-controlled analgesia

In general, anxiety seems to be the most important psychological variable that affects PCA bolus use. Preoperative anxiety correlates with increased postoperative pain intensity, the number of PCA demands made by the patient (often "unsuccessful" presses during the lockout interval), degree of dissatisfaction with PCA and lower self-reports of quality of analgesia (Thomas 1995 **Level III-1**, n=110; De Cosmo 2008 **Level IV**, n=80; Hsu 2005 **Level IV**, n=40; Ozalp 2003 **Level IV**, n=99; Brandner 2002 **Level IV**, n=71; Perry 1994 **Level IV**, n=99; Jamison 1993 **Level IV**, n=68). Another study designed to look at predictors of PCA demands made during the lockout interval also found that anxiety and negative affect positively predicted unsuccessful PCA demands and postoperative pain, as did preoperative intrusive thoughts and avoidant behaviours about the impending surgery (Katz 2008a **Level IV**, n=117).

Evidence regarding PCA opioid consumption and psychological variables is however contradictory, with some studies showing no change (Jamison 1993 **Level IV**, n=68; Gil 1992 **Level IV**, n=50; Gil 1990 **Level IV**, n=80) and others showing an increase in analgesia demands (Katz 2008a **Level IV**, n=117; De Cosmo 2008 **Level IV**, n=80; Ozalp 2003 **Level IV**, n=99).

In a study looking at the effect of a number of psychological factors on both pain and IV morphine use (by PCA) in the immediate postoperative period, and on pain 4 wk after surgery, preoperative self-distraction and coping positively predicted postoperative pain levels and morphine consumption; emotional support and religious-based coping positively predicted PCA-morphine consumption; and preoperative distress, behavioural disengagement, emotional

support, and religious-based coping also positively predicted pain levels 4 wk after surgery (Cohen 2005 **Level IV**, n=122).

There was no relationship between locus of control and postoperative pain intensity, satisfaction with PCA or PCA dose-demand ratio (Brandner 2002 **Level IV**, n=71). Preoperative depression was associated with increased pain intensity, opioid requirements, PCA demands and degree of dissatisfaction (Hsu 2005 **Level IV**, n=40; Ozalp 2003 **Level IV**, n=99) (for further details on PCA see also Section 6.0).

KEY MESSAGES

1. High pain-related fear avoidance beliefs in patients with back pain of less than 6 months duration are associated with poor outcomes, which may be improved by treatment approaches aimed at fear avoidance (**U**) (**Level I** [PRISMA]).
2. There is a significant association between high levels of catastrophising in acute and subacute back pain and pain and disability at later points of time (**U**) (**Level III-2 SR**).
3. Psychological factors associated with poor postoperative pain control are in particular anxiety (state and trait) and catastrophising, but also expectation of pain, depression, negative affect and neuroticism/psychological vulnerability (**S**) (**Level IV SR** [PRISMA]).
4. There is significant association between anxiety, pain catastrophising (**U**) (**Level III-2 SR**), depression, psychological vulnerability and stress (**U**) (**Level IV SR**) and the subsequent development of chronic postsurgical pain.
5. Preoperative anxiety and depression are associated with an increased number of PCA demands and dissatisfaction with PCA (**U**) (**Level IV**).

The following tick box represents conclusions based on clinical experience and expert opinion:

☑ Pain is an individual, multifactorial experience influenced by culture, previous pain events, beliefs, mood and ability to cope (**U**).

1.3 | Placebo and nocebo effects in acute pain

The study of placebo is directly relevant to the field of pain management, as it provides further understanding of the mind–brain interaction in the modulation of pain and is a core element of routine clinical management (Finniss 2010 **NR**).

The term "placebo", originally defined as an inert substance having therapeutic response, has been used in the medical literature for over 200 y. Only in the last 50 y, however, has interest grown in responses to placebo administration. The first major systematic review of the topic showed a placebo effect for many interventions but particularly for those interventions aimed at analgesia (Beecher 1955 **Level I**, 15 RCTs, n=1,082). The early studies included in this systematic review of response to placebo were mainly studies of placebo vs active medicine or intervention alone without a control no-treatment group (nonplacebo group).

Placebo effects are psychobiological effects that are attributable to the psychosocial context (or treatment ritual) surrounding the patient. Importantly, these genuine effects must be distinguished from other causes of improvement following administration of a placebo (placebo responses), such as spontaneous remission, regression to the mean and the natural history of acute pain (Price 2008 **NR**). Defining placebo and placebo effects has been difficult, primarily due to the traditional definition, which uses the word "inert", therefore theoretically rendering it as being unable to have any power to elicit an effect (Moerman 2002 **NR**). Recent reconceptualisations of placebo effects have emphasised several key points which are highly relevant to modern pain management practice (Finniss 2010 **NR**; Miller 2008 **NR**).

- Placebo responses refer to all health changes following administration of an inert agent (including natural history and regression to the mean) (Evers 2018 **NR**).
- Placebo effects are changes attributable to specific psychobiological mechanisms, whether a traditional placebo is given or as part of a routine clinical interaction (Evers 2018 **NR**).
- The key aspect of placebo administration is the act of simulating a treatment context or ritual, regardless of the content of the placebo.
- Routine clinical care occurs in a rich therapeutic context and, on this basis, placebo effects exist in everyday practice even though no traditional placebo is given. The overall outcome of a treatment is related to both the treatment itself and the context in which it is given (the component attributable to placebo effects).

The term "nocebo" has been used to express the opposite (negative) response following placebo administration, particularly in relation to development of adverse effects from interventions or, in the case of painful stimuli, with an increased pain response expressed. Nocebo studies in pain show moderate to large nocebo effects of high variability (Petersen 2014 **Level I** [PRISMA], 10 RCTs, n=619). The results are similar to those seen for placebo effects; combinations of verbal suggestions and conditioning (see below) are more effective than verbal suggestions alone. The authors suggest that these results demonstrate "*the importance of minimising nocebo effects in clinical practice*".

1.3.1 | Mechanisms

The study of placebo mechanisms has traditionally been divided into psychological and neurobiological categories, although it is the interplay between the two that is the key to the topic area.

1.3.1.1 | Psychological mechanisms

There are many psychological mechanisms of placebo effects proposed, including expectation, conditioning, learning, reward and anxiety reduction (Price 2008 **NR**).

Expectancy

Expectancy has been one of the most studied psychological mechanisms and relates to patient expectations of a future response. Expectancy can result in increased pain response to nociceptive stimuli as well as a placebo response to an analgesic intervention (Atlas 2012 **NR**). It has been associated with placebo effects in studies, where verbal cue ranges from a simple instruction "*this is a powerful painkiller*" (Price 1999 **Level II**, n=40, JS 4) to the use of conditioning protocols to maximise expectancy (Voudouris 1989 **Level II**, n=20, JS 4; Voudouris 1990 **Level III-1**). Furthermore, a "graded" effect can be seen in studies with variable levels of expectancy (such as the classic "double-blind" instruction, which carries a 50% uncertainty) to more certain information about treatment expectations "*the drug I will give you is a powerful painkiller*" (Vase 2003 **Level II**, n=13, JS 4; Verne 2003 **Level II**, n=10, JS 4; Pollo 2001 **Level II**, n=38, JS 3). More recently, in the setting of chronic low back pain, expectancies were associated with duration and stability of placebo effects following diagnostic injections (Finniss 2019 **Level II**, n=107, JS 5). This underscores the dynamic nature of the construct and emphasises the role of repeated expectancy assessment and modulation over the duration of a healthcare encounter.

Treatment expectations are also involved in studies of the open-hidden paradigm (Finniss 2010 **NR**). Giving a treatment "hidden", without the patient's knowledge (eg by a computerised pump behind a curtain) and comparing the effects when the same treatment is given "open" (in the usual therapeutic context with a health professional present) has shown that open administration of a range of analgesics is, by far, more effective than hidden administration. This approach permits measurement of the placebo effect as "*the difference in effect between the open and hidden administration*". An example of such a trial compared the efficacy of a remifentanil infusion (0.8 ng/mL effect site concentration) on experimental pain in volunteers under three conditions (Bingel 2011 **Level III-3 EH**):

- without expectation of analgesia (hidden administration);
- with expectancy of a positive analgesic effect (open administration by a clinician); and
- with negative expectancy of analgesia (claimed discontinuation of analgesic infusion while infusion continued).

The pain relief achieved by hidden administration of remifentanil was more than doubled by the open administration and completely negated by the claimed discontinuation of the infusion. Functional MRI (fMRI) showed that, during positive expectancy, activity in the endogenous pain modulatory system was increased, while negative expectancy increased activity in the hippocampus.

These findings and the results of other groups suggest that RCTs comparing an analgesic with a placebo may underestimate the efficacy of the analgesic (Lund 2014 **Level II EH**, n=48 [cross over], JS 5). The hypothesis that placebo effect and drug effect are additive, upon which calculation of efficacy is based, is most likely flawed. This is particularly true when the placebo effect is large. Expectations influence placebo and nocebo response to acute pain independently from personality factors (Corsi 2017 **Level III-1 EH**)

In conclusion, expectancy is a powerful determinant of placebo response, with only minor changes in the way information is delivered to the patient having the ability to significantly alter expectancy and the magnitude of the placebo effects.

Classical conditioning

Classical conditioning is a learning phenomenon whereby repeated associations between a neutral stimulus and an active treatment (unconditioned stimulus) can result in the ability of the neutral stimulus itself being able to elicit an effect similar to that of the unconditioned stimulus (Finniss 2010 **NR**). Typically, an opioid analgesic is given on repeated occasions and then replaced with a placebo-treatment simulation. These phenomena have been demonstrated in animals (Pacheco-Lopez 2006 **BS**) and in humans (Voudouris 1989 **Level II EH**, n=20, JS 4; Voudouris 1990 **Level III-1 EH**). In a similar way, treatment history can influence the efficacy of a subsequent treatment (Kessner 2014 **Level III-2 EH**). In an experimental setting, induced negative experience with a first treatment resulted in reduced response to a second analgesic treatment; the size of the effect was modulated by psychological trait variables such as anxiety, depression and locus of control. There is evidence that social or observational learning may also be a determinant of placebo effects (Colloca 2006 **Level III-1 EH**). For example, placebo effects were larger in subjects who had higher empathy after witnessing another volunteer in pain (Colloca 2009 **Level II EH**, n=48, JS 2).

1.3.1.2 | Neurobiological mechanisms

Studies into placebo analgesia have provided a substantial component of the knowledge about placebo mechanisms, although it is now known that there are multiple placebo effects that operate across many different medical conditions (Benedetti 2008 **NR**).

At a biochemical level, pioneering studies have shown that placebo effects in acute pain are either completely or in part mediated by endogenous opioids, by virtue of their reversibility with naloxone (Benedetti 1995 **Level II EH**, n=47, JS 3; Levine 1978 **Level II EH**, n=93, JS 3). The role of cholecystokinin (CCK) was demonstrated through the potentiation of placebo effects using a CCK antagonist (proglumide) (Benedetti 1995 **Level II EH**, n=93, JS 3). Interestingly, CCK has also been shown to be responsible for nocebo effects and this suggests that anxiety and panic mechanisms (also associated with CCK release) may be activated (Benedetti 2007 **NR**).

Using both conditioning and expectancy manipulations with the administration of an opioid analgesic, the resulting placebo effect was mediated by endogenous opioids (Amanzio 1999 **Level II EH**, n=229, JS 3). In contrast, in patients who received a nonopioid analgesic during conditioning, the placebo effect was not reversed by naloxone. These findings are a powerful demonstration that there is not one placebo effect but many. One mechanism for this nonopioid-mediated placebo analgesia was found to be the endogenous cannabinoid system (cannabinoid type 1 [CB_1] receptor) (Benedetti 2011 **Level III-1 EH**).

The neuroanatomy of placebo analgesic effects has been partially unravelled. A positive emission tomography (PET) study demonstrated similar brain changes to placebo as seen with opioid administration (Petrovic 2002 **Level III-2 EH**). Further PET and fMRI studies have supported the involvement of key regions of the brain associated with opioid analgesia (Zubieta 2005 **Level III-3 EH**), including subcortical (Bingel 2006 **Level III-2 EH**) and spinal cord mechanisms (Eippert 2009 **Level III-1 EH**). Taken together, these studies show growing neurobiological evidence of placebo-induced brain and spinal cord modulation of pain, although much more research is needed in this area.

A meta-analysis of 25 neuroimaging studies identified that placebo analgesia and expectancy-based pain modulation resulted in reductions of activity in brain regions involved in pain processing (eg the dorsal anterior cingulate, thalamus and insula) (Atlas 2014 **Level IV EH SR**). Other regions with reduced activity were the amygdala and the striatum; as these are related to affect and valuation, placebo effects involve these components too. In addition, regions such as the prefrontal cortex, the midbrain surrounding the PAG and rostral anterior cingulate showed increased activity with expectations for pain reduction.

There is a link between polymorphisms in the dopamine, opioid and endocannabinoid genes and response to placebo, demonstrating potential genetic determinants of placebo effects (Colloca 2019 **Level III-2 EH**, n=160).

1.3.2 | Clinical findings

Many meta-analyses include studies that also have a control nonplacebo/nocebo group. One of these reveals a relatively small placebo effect size for all clinical conditions (60 assessed) (Hrobjartsson 2010 **Level I** [Cochrane], 234 RCTs, n unspecified), but did not consider nocebo. The majority of studies measured continuous outcomes (158 RCTs, n=10,525) but the results are also consistent in those assessing binary outcomes (44 RCTs, n=6,041). In the studies with continuous outcomes, there is an effect of placebo treatment (SMD -0.23; 95%CI -0.28 to -0.17) (158 RCTs, n=10,525), which is larger for patient-reported (SMD -0.26; 95%CI -0.32 to -0.19) (109 RCTs, n=8,000) than for observer-reported outcomes (SMD -0.13; 95%CI -0.24 to -0.02) (49 RCTs, n=2,513). Overall, larger placebo effects are seen with physical placebo interventions (eg acupuncture), patient-involved outcomes, smaller trials and trials that did not inform patients about the possible placebo intervention.

Importantly, trials aimed at studying placebo effects (rather than assessing responses in placebo-control groups) demonstrate larger placebo effects, particularly in the case of analgesia (Vase 2002 **Level I**, 37 RCTs, n=2,298). Effect sizes can be five times higher in these studies than in analysis of placebo effects on control groups, demonstrating an important difference when understanding placebo effects in clinical trials (where instructions are uncertain and the context does not replicate routine clinical care) (Vase 2009 **Level I** [QUOROM], 24 RCTs, n=602). Consistently positive but highly variable placebo responses are obvious in studies involving analgesia specifically (pooled SMD -0.28; 95%CI -0.36 to -0.19) (60 RCTs [continuous outcome, pain], n=4,154) with a wide range of response in the individual trials from around SMD -1.0 to 0.5. This variability is also seen in targeted studies on placebo (Vase 2009 **Level I** [QUOROM], 24 RCTs, n=602).

1.3.3 | Clinical Implications

The clinical implications of placebo effects are widespread and there is much more research needed to understand how placebo effects operate and how they can be manipulated in clinical practice. However, the notion that placebo effects (and therefore mechanisms) may be a component of routine pain management practice is highly important (Klinger 2014 **NR**; Finniss 2009 **NR**). If one can study how psychosocial factors alter the patient's nociception and the experience of pain (by running experiments in which placebos are given), this has direct implications for clinical care where, even though no placebo is given, placebo effects are present.

In recent times, the ethical debate has shifted somewhat as the concept of placebo is better understood. It is widely accepted that placebos should not be administered in a deceptive manner (Finniss 2010 **NR**; Brody 1982 **NR**). However, there are not the same ethical problems associated with harnessing the placebo effects that coexist with routine "active" treatments, as the outcome of a treatment is attributable to both the treatment itself and the specific context in which it was given (the placebo component). An applied example is that of the PSYHEART trial, where a specific pre-treatment intervention addressing patients expectations pre-cardiac surgery resulted in significant reductions in biological markers (endocrine and immune markers of stress), reduced disability and improved quality of life at 6 mth post-surgery (Rief 2017 **Level II**, n=124, JS 5).

It is suggested that, in a therapeutic interaction, the placebo effect can be clinically utilised by enhancing expectations and using learning components (Klinger 2014 **NR**). Practical examples of this are listed below.

To enhance expectations:

- Assess and manage expectations over the entire time course of a treatment;
- Emphasise positive effects of medicines;
- Avoid stressing adverse effects;
- Explain effects and mechanisms of action of medicines;
- Interact personally with the patient;
- Do not rely only on written handouts; and
- Avoid unrealistic expectations.

To enhance learning components:

- Administer analgesics in an open manner;
- Connect the administration to positive internal states and external conditions;
- Combine analgesics with other pain-relieving approaches, preferably with time-contingent administration of analgesics; and
- Reinforce positive and minimise negative experiences.

KEY MESSAGES

1. Responses to placebo across all clinical conditions are small but consistently positive. They are more prominent, although highly variable in magnitude, in studies of pain (**U**) (**Level I** [Cochrane Review]).
2. Nocebo effects in studies of pain are of moderate to large size and of high variability (**U**) (**Level I** [PRISMA]).
3. Trials aimed at studying placebo effects demonstrate larger placebo effects than those assessing responses in placebo-control groups (**U**) (**Level I** [QUOROM]).
4. Analgesic placebo effects are based upon multiple neurobiological mechanisms, including involvement of endogenous opioid, cholecystokinin (**U**) (**Level II**), endogenous cannabinoid systems (**U**)(**Level III-1**) and genotype (**N**) (**Level III-2**).
5. Analgesic placebo effects are based upon multiple psychological determinants including expectancy, classical conditioning and social and observational learning (**S**) (**Level II**).
6. Placebo and nocebo effects have significant influence on the efficacy of analgesics (**U**) (**Level II**).

The following tick boxes represent conclusions based on clinical experience and expert opinion:

☑ Placebo effects are the consequence of the psychosocial context (or treatment ritual) on the patient's mind, brain and body (**U**).

☑ Placebo effects occur in routine clinical care even when no traditional placebo is given. The outcome of a treatment is attributable to both the treatment itself and the contextual (or placebo) component (**U**).

☑ Nocebo effects occur in routine clinical care and are seen as an increased pain response to a painful stimulus or the development of adverse effects not caused by, or separate from, the intervention (**U**).

☑ Ethical harnessing of placebo and minimisation of nocebo effects will improve response to clinical management interventions (**U**)

1.4 | Progression of acute to chronic pain

Chronic pain is common in the community and is moderate to severe in intensity in approximately 20% of the population (Kennedy 2014 **Level IV**, n≈39,400,000 [chronic pain sufferers]). This inevitably leads to significant personal and economic cost (Breivik 2006 **Level IV**, n=46,394; Deloitte Access Economics 2019 **NR**). Episodes of acute pain may result in chronic pain with subsequent impact on quality of life, employment and mental health (Steyaert 2012 **NR**; Lavand'homme 2011 **NR**; McGreevy 2011 **NR**). The prediction and prevention of transition to chronic pain may therefore convey health and economic benefits (see also Section 3.3).

The 11th revision of the International Classification of Diseases (ICD-11) defines chronic postsurgical pain (CPSP) as pain developing or increasing in intensity after a surgical procedure, in the area of the surgery, persisting beyond the healing process (ie at least 3 mth) and not better explained by another cause such as infection, malignancy, or a pre-existing pain condition (Schug 2019 **GL**).

CPSP is common and although often mild, may be of sufficient severity to interfere with function and quality of life in 1 to 10% of cases (De Kock 2009 **Level IV**). The currently accepted prevalence of CPSP is shown below, however some studies suggest the prevalence may be lower than previously thought (see Table 1.2) (Chan 2016 **Level II**, n=2,924, JS 5; Fletcher 2015 **Level IV**, n=3,120).

CPSP often has identifiable neuropathic characteristics, although this is procedure specific, and is often poorly responsive to opioids (Chan 2011 **Level II**, n=423, JS 5; Wylde 2011 **Level IV**, n=1,334; Haroutiunian 2013 **NR**; Macrae 2008 **NR**; Kehlet 2006 **NR**). The lack of efficacy of opioids for treating CPSP is one factor contributing to the current prescription opioid crisis (Neuman 2019 **NR**; Hollmann 2019 **NR**) (see also Sections 1.4.3, 8.13 and 9.7).

Other well-characterised acute pain events may also lead to chronic pain, such as post-traumatic pain (see below and Section 8.1), acute back pain (see Section 8.7) and herpes zoster (see Section 8.6.2). Although CPSP tends to be associated with major surgery, involving significant acute pain, nerve injury and inflammation, it may also occur following minor operations. The surgical drive towards minimally invasive surgery has reduced acute postsurgical pain but has had a limited effect on the incidence of CPSP (Roth 2018 **Level IV**, n=1,996; Lavand'homme 2017 **NR**).

This section will focus primarily on CPSP, although the underlying mechanisms and risk factors are also relevant to the nonsurgical conditions mentioned above.

1.4.1 | Epidemiology of chronic postsurgical pain

There is a high prevalence of CPSP and chronic pain following trauma; 22.5% of 5,130 patients attending chronic pain clinics in North Britain cited surgery as a cause for their pain and 18.7% felt that trauma was the primary cause (Crombie 1998 **Level IV**, n=5,130). As chronic pain is very common in the population and only a small percentage of people with chronic pain attend pain clinics, data obtained from clinics may not accurately reflect the scale of the problem in the community. A randomised population survey from Portugal found that only 6% of those identified with chronic pain felt that it was due to surgery (Azevedo 2012 **Level IV**, n=2,213). In contrast, a Norwegian population-based study found 40.4% prevalence of pain in the anatomical region of surgery 3 mth to 3 y later (Johansen 2012 **Level IV**, n=2,043). In 18.3% (n=373), the pain was moderate to severe. The prevalence of moderate to severe pain was reduced to 10.5% by excluding all respondents with the same pain before surgery and to 6.2% by excluding all respondents with any pain before surgery. Factors associated with CPSP were sensory abnormalities in the area of surgery (hyperaesthesia [OR 6.27; 95%CI 4.43 to 8.86] or hypoaesthesia [OR 2.68; 95%CI 1.05 to 3.50]) and psychological distress (OR 1.69; 95%CI 1.22 to 2.36).

Chronic pain following trauma is common and approximately 70% of patients without prior pain reported significant pain 6 mth following injury in one UK study (Rockett 2019 **Level II**, n=64, JS 5). Preceding studies found similar high rates of 46% to 85% of polytrauma survivors with subsequent chronic pain (Gross 2011 **Level IV**, n=229) and 72% of some pain in the last 24 h at 1 y after serious trauma (Holmes 2010 **Level III-2**, n=290).

Less is known about CPSP in the paediatric population, but it has been estimated that 20% of children experience CPSP 1 y after spinal and mixed major surgery (Rabbitts 2017 **Level IV SR**, n=628; (Williams 2017 **NR**).

The incidence of CPSP varies with the type of operation and it is particularly common where nerve trauma is inevitable (eg amputation) or where the surgical field is richly innervated (eg chest wall) (see Table 1.2) (Wylde 2011 **Level IV**, n=1,294; Macrae 2008 **NR**; Kehlet 2006 **NR**). In a prospective cross-sectional study at a university-affiliated hospital and level 1 trauma centre, 14.8% of patients described CPSP, in particular those after trauma and major orthopaedic surgery (Simanski 2014 **Level IV**, n=3,020). A similar study, focussing on neuropathic CPSP only following two procedure types, identified an incidence of 3.2% for laparoscopic herniorrhaphy vs 37.1% for breast cancer surgery at 6 mth after surgery (Duale 2014 **Level IV**, n=3,112). Overall, these data support the high incidence of CPSP and the frequent linkage of CPSP to nerve injury.

Table 1.2 | Incidence of chronic pain after surgery

Type of surgery	Any CPSP (%)	Severe CPSP (%)	Neuropathic pain (proportion)*
Abdominal surgery (visceral)	17-21%	Not reported	Not reported
Amputation	30-85%	5-10%	80%
Caesarean section	6-55%	5-10%	50%
Cholecystectomy	3-50%	Not reported	Not reported
Craniotomy	7-30%	25%	Not reported
Dental surgery	5-13%	Not reported	Not reported
Hip arthroplasty	27%	6%	1-2%
Inguinal herniotomy	5-63%	2-4%	80%
Knee arthroplasty	13-44%	15%	6%
Melanoma resection	9%	Not reported	Not reported
Mastectomy	11-57%	5-10%	65%
Sternotomy (CABG)	30-50%	4-28%	Not reported
Thoracotomy	5-65%	10%	45%
Vasectomy	0-37%	Not reported	Not reported

*CABG-Coronary artery bypass graft surgery; * assessed by screening questionnaires in most studies. Adapted from Glare 2019; Schug 2017.*

1.4.2 | Characteristics of chronic postsurgical pain

Efforts are now being made to standardise outcome measures to characterise CPSP in future RCTs and epidemiological studies (Wylde 2014 **Level IV**, n=1,294; VanDenKerkhof 2013 **GL**). CPSP may persist as a continuum from acute postsurgical pain or it may occur following a pain-free interval. CPSP may occur in the skin or deep tissues of the region of surgery, it may be referred to characteristic areas due to viscerosomatic convergence or be related to the course of a nerve injured by surgery.

A significant proportion of patients with CPSP demonstrate sensory abnormalities, suggesting that CPSP often has a neuropathic component (Johansen 2016 **Level IV**, n=81; Aasvang 2008 **Level IV**, n=46). The incidence of acute neuropathic pain has been reported as 1 to 3%, based on patients referred to an APS, primarily after surgery or trauma (Hayes 2002 **Level IV**). The majority of these patients had persistent pain at 12 mth, suggesting that acute neuropathic pain is a risk factor for chronic pain. These qualitative results were confirmed in a subsequent study (Beloeil 2017 **Level III-2**, n=593). Using a screening tool (DN-4), acute neuropathic pain was identified in 5.6% (95%CI 3.6 to 8.3) on the day of surgery and in 12.9% (95%CI 9.7 to 16.7) on POD 1. Postsurgical neuropathic pain was identified in phone follow-up 2 mth postsurgery in 33.3% of patients; acute neuropathic pain was a risk factor for its development (OR 4.2; 95%CI 2.2 to 8.1). Similarly, immediately after thoracotomy or video-assisted thoracic surgery (VATS), 8% of patients scored positively on another screening tool for neuropathic pain (LANSS) and 22% 3 mth later; again acute neuropathic pain was identified as a risk factor for chronic neuropathic pain (RR 3.5; 95%CI 1.7 to 7.2) (Searle 2009b **Level III-2**, n=100). Following VATS, sensory changes suggestive of nerve injury were demonstrated in most patients but there was no difference in sensory abnormalities or measures of central sensitisation between patients with and without CPSP (Wildgaard 2012 **Level IV**). Similarly, changes in sensory thresholds (warmth detection and heat pain) were demonstrated in most pain-free patients following open inguinal herniorrhaphy (Aasvang 2010b **Level IV**). This suggests that, although nerve injury is frequently associated with CPSP, such injury does not inevitably lead to chronic pain. It should be recognised however that numbness might still be distressing to some patients. Additionally, neuroplastic processes termed central sensitisation may occur without nerve injury and may result in altered nociceptor function with a gain (sensitisation) or a loss (desensitisation) of function of nociceptors, resulting in sensory changes superficially resembling neuropathic pain. Assessment of these sensory changes using techniques such as quantitative sensory testing may in the future lead to more individualised treatment and drug development for the prevention and treatment of CPSP (Arendt-Nielsen 2018 **NR**).

The intensity and character of CPSP is variable. Descriptors may relate to neuropathic pain (shooting, burning, tingling) (VanDenKerkhof 2013 **Level IV**) but somatic / nociceptive pain characteristics (aching, tender, stabbing, squeezing) are also commonly reported (Chan 2011 **Level III-1**), especially associated with joint arthroplasty (Wylde 2011 **Level IV**, n=1,294). Typically around 10% of patients describe the CPSP as severe, although this proportion may be higher in some surgical groups (Glare 2019 **NR**). The sequelae of CPSP vary from mild discomfort to a significant impact on quality of life. The negative impact of CPSP is similar to that of other chronic pain conditions and, along with psychological distress, may include the use of multiple analgesics, regular medical attendances, inability to undertake certain activities and difficulty returning to work (Chan 2011 **Level III-1**, n=640; Steyaert 2012 **NR**).

1.4.3 | Opioids and CPSP

In recent years, the use of strong opioids to manage acute and chronic non-cancer pain has been increasing. This has been one factor in the generation of a global opioid crisis, with opioid use

and deaths from overdose of prescription drugs increasing dramatically in many countries (Jones 2018 **NR**). Surgery is a risk factor for both persistent pain and ongoing inappropriate opioid use (Hah 2017 **NR**). Prolonged opioid use after hospital discharge seems to be relatively common, occurring in 10.5% of patients for greater than 90 d after surgery in an Australian study (Stark 2017 **Level IV**, n=970), and in 3% of opioid naïve patients at 90 d in a large cohort study from Canada (Clarke 2014 **Level IV**, n=39,140). In contrast, opioid use by outpatient pain clinics has been decreasing in chronic non-cancer pain due to lack of evidence for their efficacy (Dowell 2016 **GL**; Chou 2009 **GL**). For more details see also Section 8.13.

Not only is CPSP a risk factor for ongoing opioid use, but opioid use may trigger or worsen symptoms of CPSP (see also Section 1.4.4 below). The use of high dose opioids in the acute setting has been shown to activate neuroplastic processes which may result in CPSP (see also Sections 1.1, 4.3.1 and 9.7). Opioid induced hyperalgesia (OIH) is a state of increased sensitivity to noxious stimuli occurring after exposure to high dose opioids (usually remifentanil). Patients exposed to high dose opioids in the perioperative period have higher postoperative pain scores and increased opioid use. OIH may result in spiralling opioid use (Fletcher 2014 **Level I**, 24 RCTs, n=1,494). Endogenous opioid analgesic systems are protective against the development of CPSP (Eippert 2009 **Level III-1 EH**; Yarnitsky 2008 **Level IV**, n=62). Prolonged opioid use leads to internalisation of mu opioid receptors at a cellular level. This may impair the functioning of the endogenous opioid analgesic system and increase sensitivity to pain leading to OIH and potentially CPSP (Glare 2019 **NR**).

1.4.4 | Predictive factors for chronic postsurgical pain

Risk evaluation for CPSP enables clinicians to address identified risk factors before surgery. This guides planning and discussion regarding expectations, the scope of planned surgery and possibility of changed approaches to the anaesthesia, pain management and even the procedure itself. Risk factors for CPSP have been identified in the preoperative, intraoperative and postoperative periods, and cover 6 broad domains: genetic, demographic, psychosocial, pain, clinical, and surgical factors (Schug 2017 **NR**).

Demographic factors such as younger age for adults and female gender influence the frequency of CPSP, as do psychological factors such as anxiety, depression, catastrophising, fear of surgery and hypervigilance (Theunissen 2012 **Level IV SR**, 29 studies, n=6,628; Hinrichs-Rocker 2009 **Level IV SR**, 50 studies, n≈25,000; Weinrib 2017 **NR**). Very young age may be a protective factor as hernia repair in children <3 mth of age did not lead to chronic pain in adulthood (Aasvang 2007 **Level IV**, n=651). In children aged 8–18 y, "*parent pain catastrophising"* was the main risk factor for the development of CPSP (Page 2013 **Level IV**, n-83). The significance of each risk factor varies with the operation but pre-existing psychological factors (high state anxiety and pain magnification as a component of catastrophising) increased the risk across two types of surgery (TKA and breast cancer surgery) (Masselin-Dubois 2013 **Level III-2**, n=189; Weinrib 2017 **NR**).

The intensity of acute postsurgical pain is a consistent predictor of CPSP (Chan 2011 **Level II**, n=640, JS 5; Althaus 2012 **Level IV**, n=150). This has been shown following a wide range of procedures including breast surgery (Bruce 2014 **Level IV**, n=362), thoracic surgery (Yarnitsky 2008 **Level IV**, n=62; Katz 1996 **Level IV**, n=30), gynaecological surgery (VanDenKerkhof 2012a **Level IV**, n=433), Caesarean section (Nikolajsen 2004 **Level IV**, n=220), lower limb amputation (Hanley 2007 **Level IV**, n=57), total hip arthroplasty (THA) (Nikolajsen 2006 **Level IV**, n=1,231) and inguinal herniotomy (Aasvang 2010a **Level IV**, n=464). After thoracic surgery, higher acute pain intensity postoperatively predicted the incidence of CPSP (OR 1.80; 95%CI 1.28 to 2.77), nearly doubling the chance of developing chronic pain for each point increase on a 10-point numerical rating scale (NRS) (Yarnitsky 2008 **Level IV**, n=62). Large scale observational studies have confirmed the

importance of acute pain in the development of CPSP with a 10% increase in the percentage of time in severe acute pain associated with a 30% increase in the incidence of CPSP at 12 mth (Fletcher 2015 **Level IV**, n=3,120). Sensitisation and "wind-up" of nociceptive pathways within the CNS is thought to play a significant role in the establishment and maintenance of chronic pain following an intense nociceptive stimulus. Nociceptive processes occurring in the periphery, including nerve injury, are also implicated in the transition from acute to chronic pain (Baron 2013 **NR**).

Preoperative chronic pain is a universal risk factor (Johansen 2014 **Level IV**, n=12,981; VanDenKerkhof 2012a **Level IV**, n=433; Wylde 2011 **Level IV**, n=1,294; Aasvang 2010a **Level IV**, n=464). This is likely due to the increase in sensitivity of the nociceptive system found in patients with chronic pain. This may partly explain the relatively high rates of CPSP following THA and TKA (25 and 44% respectively) (Wylde 2011 **Level IV**, n=1,294). Preoperative pain was the predictor that most commonly demonstrated a significant relationship with persistent pain following TKA across uni- and multivariate analyses. In a meta-analysis of univariate models, the largest effect sizes were found for preoperative pain at other sites, catastrophising and depression (Lewis 2015 **Level I**, 28 RCTs, n=29,993). For data from multivariate models catastrophising, preoperative pain, mental health and comorbidities had significant effects. Preoperative pain was also a risk factor for CPSP at 3 mth in trauma patients requiring orthopaedic surgery (OR: 1.17; 95% CI: 1.03, 1.32) (Edgley 2019 **Level III-2**, n=229).

Given the potential for opioids to interfere with endogenous analgesic systems, it is perhaps not surprising to find that preoperative opioid use increased the risk of CPSP after gynaecological surgery (RR 2.0; 95%CI 1.2 to 3.3) (VanDenKerkhof 2012a **Level IV**, n=433). In a prospective study of day case orthopaedic surgery, 8% developed CPSP if they were taking pre-operative analgesics with adequate analgesia (Hoofwijk 2015 **Level IV**, n=908). However, patients taking analgesics without relief had a much higher incidence of CPSP of 32%.

Presurgical sensitivity to painful stimuli, identified using some form of quantitative sensory testing (QST), variably accounts for 5–54% of the variance in acute postoperative pain and can predict risk for CPSP (Werner 2010 **Level I** [QUOROM], 15 RCTs, n=962). The relative efficacy of the endogenous descending inhibitory system determined by assessing DNIC partly predicted patients who developed CPSP after thoracotomy (OR 0.52; 95%CI 0.33 to 0.77) (Yarnitsky 2008 **Level IV**, n=62). Widespread pressure pain sensitivity was correlated with worse functional outcome following TKA (Wylde 2013 **Level III-3**, n=51). Sensitivity to noxious heat and mechanical stimuli did not correlate with CPSP in an unselected surgical population, whereas cold sensitivity correlated both with CPSP and comorbid chronic pain conditions (Johansen 2014 **Level IV**, n=12,981). Prior to herniotomy, high pain scores from a 47°C temperature probe were predictive of postherniotomy pain (OR 1.34; 95%CI 1.15 to 1.57) (Aasvang 2010a **Level IV**, n=464).

It is also likely that genetic and epigenetic factors influence both the sensitivity of individuals to analgesics and their risk of CPSP (Mauck 2014 **NR**; Buchheit 2012 **NR**). For example, different haplotypes of the gene for the enzyme catechol-O-methyltransferase (*COMT*), involved in the modulation of pain responses, were associated not only with differences in experimental pain sensitivity but also with the development of chronic temporomandibular joint disorder (TMD) (Nackley 2007 **Level IV**). In women undergoing hysterectomy the polymorphism rs4818 within the *COMT* gene was associated with the presence of CPSP at 3 mth but not 12 mth postoperatively (Hoofwijk 2019 **Level III-2**, n=345). However, opioid receptor mu-1 (*OPRM1*) genotype, but not *COMT* genotype, was associated with the development of CPSP after abdominal surgery (Kolesnikov 2013 **Level IV**, n=102). One prospective study of patients undergoing various surgical procedures did not reveal any correlation between 90 genetic markers and the incidence or severity of CPSP (Montes 2015 **Level IV**,

n=2,929). Overall, heritability estimates suggest that about 50% of the variability in CPSP rates is attributable to genetic variability. In order to apply these findings to individual patients, very large studies analysing tens of thousands of genetic samples will be needed to characterise patients at risk (Clarke 2015 **NR**) (see also Section 1.7).

To date, clinical risk factors remain the most reliable tools for the prediction of CPSP (Althaus 2012 **NR**). Attempts have been made to generate predictive models of CPSP but these do not yet have sufficient sensitivity and specificity to prove clinically useful. Using a training set of 150 patients with an incidence of CPSP of about 50%, five factors were independently predictive of developing CPSP, of which four can be assessed pre-operatively: pain in the surgical field, comorbid chronic pain at other sites, capacity overload and comorbid stress. Moderate to severe postoperative pain at POD 5 was the only significant postoperative factor. Patients with three to five risk factors were more likely to go on to develop CPSP than were those with zero to two factors (sensitivity 74%, specificity 65%).

Screening tools based on specific types of surgery have demonstrated better specificity, but identify many false positives. For example, for breast cancer surgery four factors were predictive of CPSP: preoperative pain at the site of surgery, high body mass index, axillary lymph node dissection and severity of acute pain on the 7th d after surgery (Meretoja 2017 **NR**). At the 20% risk level, the model had 32.8% and 47.4% sensitivity and 94.4% and 82.4% specificity in two cohorts from Denmark and Scotland, respectively. A predictive model for CPSP after inguinal hernia repair, hysterectomy or thoracotomy has been developed (Montes 2015 **Level IV**, n=2,929). The model included six clinical factors: surgical procedure, age, physical health, mental health, preoperative pain in the surgical field, and preoperative pain in another area. This model was a good fit (c-statistic 0.731; 95%CI 0.705 to 0.755). Interestingly, the same study found that 90 genetic markers did not predict CPSP.

The trajectory of daily pain scores after surgery has also been investigated as a predictor of CPSP (Chapman 2011 **Level IV**, n=502). Following TKA, 4 distinct acute pain trajectories were identified. Patients with a constantly high acute pain trajectory were at higher risk of CPSP (Page 2015 **Level IV**, n=173). Subacute pain after orthopaedic surgery at 10 d and 6 wk also predicted CPSP at 12 mth in one study (Andersson 2015 **Level IV**). Trajectories of anxiety and depression over time have also been assessed as a potential risk factor for CPSP, and patients with unremitting high levels of anxiety, but not depression were found to be more likely to experience CPSP following cardiac surgery (Page 2017 **Level IV**, n=173).

A summary of risk factors identified for the development of CPSP is presented in Table 1.3.

Table 1.3 | Risk factors for chronic postsurgical pain

Preoperative factors	Pain, moderate to severe, lasting >1 mth Repeat surgery Psychological vulnerability (eg catastrophising) Preoperative anxiety Female sex Younger age (adults) Workers' compensation Genetic predisposition Inefficient diffuse noxious inhibitory control Opioid use (particularly if ineffective)
Intraoperative factors	Surgical approach with risk of nerve damage
Postoperative factors	Pain (acute, moderate to severe and subacute) Radiation therapy to area Neurotoxic chemotherapy Depression Psychological vulnerability Neuroticism Anxiety Pain and anxiety trajectories

Sources: Adapted from Page 2017; Schug 2017; Johansen 2014; Wylde 2011; Hinrichs-Rocker 2009; Macrae 2008; Kehlet 2006.

1.4.5 | Mechanisms for the progression from acute to chronic pain

Central and peripheral sensitisation are the most likely underlying factors in the development of CPSP (Richebe 2018 **NR**; Lavand'homme 2017 **NR**). There is limited trial data to infer mechanisms and therefore most evidence relating to likely mechanisms is based on laboratory animal or epidemiological data (Peirs 2016 **NR BS**). Initiation of these processes is most likely in a situation where an individual is "primed" (eg by pre-existing pain) or susceptible (eg inefficient DNIC, psychological state or genetic predisposition) (Lavand'homme 2017 **NR**; Denk 2014 **NR**; Lavand'homme 2011 **NR**). The imposition of an intense surgical stimulus induces both central and peripheral changes (Baron 2013 **NR**). Maintenance of these intense nociceptive inputs by poorly controlled postoperative pain, peripheral nerve damage (D'Mello 2008 **NR**) and complications (eg wound infection) then lead on to a chronic pain state. It is proposed that these all lead to neuroplastic processes such as peripheral and central sensitisation. Such processes include inflammation at the site of tissue damage as well as ectopic discharges after nerve injury and lead to a barrage of afferent input that produces changes in the peripheral nerves, spinal cord, higher central pain pathways, somatosensory cortex and the sympathetic nervous system (see Section 1.1). Evidence for sensitisation includes the presence of larger area of secondary hyperalgesia at 48 h (88 vs 33 cm^2) in patients having iliac crest bone harvesting who developed CPSP with higher neuropathic pain scores on the Doleur Neuropathique 4 (DN4) questionnaire (4.3/10 vs 2.3) (Martinez 2012 **Level IV**). Similarly, following abdominal surgery, patients with analgesic regimens resulting in smaller areas of wound hyperalgesia (indicating less sensitisation) had a lower incidence of CPSP (Lavand'homme 2005 **Level II**, n=85, JS 5). Punctuate hyperalgesia

around a surgical incision could be shown in a large area, suggesting central sensitisation, which was suppressed by IV ketamine injection (Stubhaug 1997 **Level II**, n=20, JS 5).

The relative degree of ongoing inflammation or intraoperative nerve injury resulting in peripheral and central sensitisation may explain the variation in risk and, to an extent, the characteristics of CPSP for different operations (Simanski 2014 **Level IV**).

Psychological factors (depression, psychological vulnerability and stress) are important in the development of CPSP (Hinrichs-Rocker 2009 **Level IV SR**, 50 RCTs, n≈25,000) and cortical processing of nociceptive information and descending inhibitory and excitatory pathways provides a plausible mechanism for some of these effects. Functional connectivity and anatomical differences of corticolimbic structures involved in emotion and motivation predict chronic pain in some circumstances (Vachon-Presseau 2016 **Level IV EH**; Baliki 2012 **NR**).

1.4.6 | Prevention of chronic postsurgical pain

Effective prevention of CPSP is limited by an incomplete understanding of the mechanisms that generate it. However, some recognised risk factors are modifiable in the perioperative period. These include, body mass index, opioid use, preoperative pain and some psychological factors. In the postoperative period, attention to effective management of acute pain, limiting exposure to opioids and psychological support in rehabilitation and recovery of normal functioning are all likely to play a role.

Interventions evaluated thus far are divided into four broad groups and include regional and neuraxial analgesia, pharmacotherapy, surgery and multidisciplinary nonpharmacological interventions. Analgesic strategies for which the clinical efficacy outlasts the pharmacological activity are described as “preventive analgesia” (defined as analgesia that persists more than 5.5 half-lives of the medicine) and most likely rely on reducing peripheral and central sensitisation (Katz 2011 **NR**) (see also Section 1.5).

1.4.6.1 | Regional or neuraxial analgesia

Meta-analysis on the prevention of CPSP by regional anaesthesia found benefits for three procedure types: thoracotomy, breast cancer surgery and Caesarean section (Weinstein 2018 **Level I** (Cochrane), 63 RCTs, n=3,027). Following open thoracotomy (7 RCTs, n=499), epidural anaesthesia reduces the incidence of CPSP 3 to 18 mth following surgery compared to systemic analgesia (OR 0.52; 95%CI 0.32 to 0.84) (number-needed-to-treat [NNT] 7). For breast cancer surgery any form of regional anaesthesia (18 RCTs, n=1,297) reduces CPSP 3 to 12 mth after surgery compared with systemic analgesia (OR 0.43; 95%CI 0.28 to 0.68) (NNT 7); specifically paravertebral block (PVB) (6 RCTs, n=419) is effective (OR 0.61; 95%CI 0.39 to 0.97) (NNT 11). For Caesarean section (4 RCTs, n=551), a mixture of regional analgesia techniques, reduces CPSP from 3 to 8 mth (OR 0.46; 95%CI 0.28 to 0.78) (NNT 19). There is insufficient data to make clear recommendations regarding the timing of various local anaesthetic interventions (21 RCTs) and the impact on CPSP, but earlier administration of epidural prior to incision vs post amputation (4 RCTs, n=334) may provide benefit (Humble 2015 **Level I**, 32 RCTs, n=2,834).

For many procedures, studies investigating the effect of regional anaesthesia and analgesia on chronic pain outcomes are limited in number and have differing designs, which prevents meta-analysis due to high levels of heterogeneity. In patients undergoing open colonic resection, continuous perioperative epidural analgesia led to a lower risk of developing chronic pain up to 1 y after surgery compared with IV analgesia (Lavand'homme 2005 **Level II**, n=85, JS 5). In a case-control study, epidural anaesthesia reduced chronic pain at 6 mth after surgery (OR 0.19; 95%CI 0.05 to 0.76) (Bouman 2014 **Level III-2**). Spinal anaesthesia in comparison to general anaesthesia

reduced the risk of CPSP after Caesarean section (Nikolajsen 2004 **Level III-2**) and hysterectomy (OR 0.42; 95%CI 0.21 to 0.85) (Brandsborg 2007 **Level III-2**). The latter study found no difference in risk between abdominal and vaginal hysterectomy.

A systematic review on phantom limb pain prophylaxis showed that perioperative (pre, intra and postoperative) epidural analgesia reduced the incidence of severe phantom limb pain 12 mth after surgery (NNT 5.8) (Gehling 2003 **Level III-2 SR**, 9 studies, n=836). The use of epidural analgesia to prevent the development of phantom pain or CPSP following limb amputation may be a useful component of multimodal therapy in patients with severe preoperative pain (Karanikolas 2011 **Level II**, n=65, JS 5). See also Section 8.1.5.

The use of IV lidocaine for prevention of CPSP is discussed in Section 1.4.6.3 below.

1.4.6.2 | Local anaesthetic infiltration

Meta-analysis on the prevention of CPSP by local infiltration finds benefits for breast cancer surgery and iliac crest bone graft (ICBG) harvest (Weinstein 2018 **Level I** [Cochrane], 39 RCTs, n=3,027). For breast cancer surgery (6 RCTs, n=379), local anaesthetic infiltration reduces CPSP 3 to 12 mth after surgery vs systemic analgesia (OR 0.29; 95%CI 0.12 to 0.73) (NNT 7). For ICBG harvest (4 RCTs, n=159), continuous local anaesthetic infiltration reduces CPSP 3 to 12 mth after surgery vs systemic analgesia (OR 0.1; 95%CI 0.01 to 0.59) (NNT 3).

Local anaesthetic wound infiltration reduced the proportion of patients with chronic pain and neuropathic pain 2 mth following intracranial tumour resection (Batoz 2009 **Level II**, n=52, JS 3).

1.4.6.3 | Pharmacotherapy

Ketamine

Ketamine is commonly used to treat both acute and chronic pain. When used as a preventive analgesic, perioperative ketamine compared to placebo significantly reduces CPSP at 3 mth (5 RCTs, n unspecified) but only when administered for >24 h (OR 0.37; 95%CI 0.14 to 0.98) (Chaparro 2013 **Level I** [Cochrane], 14 RCTs [ketamine], n=1,388). At 6 mth (10 RCTs, n=516), perioperative ketamine reduces CPSP (OR 0.63; 95%CI 0.47 to 0.83), which remains significant when infused for <24 h (OR 0.45; 95%CI 0.26 to 0.78). These effects were predominantly in abdominal surgery. Another meta-analysis found a benefit of perioperative IV ketamine vs placebo in reducing the incidence of CPSP at 3 mth (RR 0.74; 95%CI 0.60 to 0.93) (NNT 12), 6 mth (RR 0.70; 95%CI 0.50 to 0.98) (NNT 14) but not at 12 mth postoperatively (McNicol 2014 **Level I**, 14 RCTs [IV route], n=1,586) (11 RCTs overlap); such beneficial effects were not found with epidural administration of ketamine (3 RCTs, n=302).

A network meta-analysis investigating multiple pharmacological interventions to reduce CPSP identified ketamine as the highest ranked in terms of efficacy and safety (Ning 2018 **Level I** [NMA], 24 RCTs, n unspecified). In thoracic surgery, low dose ketamine infusion (0.1 mg/kg/hr) reduced opioid use for 24 h and pain at 48 h, but did not affect CPSP at 3, 6 or 12 mth (Chumbley 2019 **Level II**, n=70, JS 5).

Opioids

High dose intra-operative opioids, particularly remifentanil, have been shown to result in opioid induced hyperalgesia, increased pain and 24 h opioid use in the postoperative period which may be associated with CPSP (Fletcher 2014 **Level I**, 27 RCTs, n=1,494). The intra-operative use of remifentanil in cardiac surgery also resulted in a higher incidence of CPSP at 1 y (OR 8.9; 95%CI 1.6 to 49.0) (van Gulik 2012 **Level III-2**, n=90).

Alpha-2-delta ligands (gabapentinoids)

Two previous parallel meta-analyses (10 RCT overlap) and a correction of one of these investigated the use of perioperative gabapentin or pregabalin in reducing CPSP across a diverse range of procedures (Chaparro 2013 **Level I** [Cochrane], 15 RCTs [gabapentin and pregabalin], n=1,300; Clarke 2012 **Level I** [PRISMA], 11 RCTs, n=930; Clarke 2013 **Level I**, 5 RCTs, n=875). The overall conclusion was that there was limited or no benefit in the setting of significant heterogeneity.

In addressing the issue of potential bias due to unpublished data, a meta-analysis of pregabalin and CPSP included 79% unpublished trials (Martinez 2017 **Level I** [PRISMA], 18 RCTs, n=2,485). There was no benefit with pregabalin use in the prevention of CPSP overall at 3, 6 or 12 mth postoperatively, in cardiac, visceral or orthopaedic surgery (OR 0.87 [at 3 mth]; 95%CI 0.66 to 1.14). There was, however, a reduction in chronic postsurgical neuropathic pain in four published trials (4 RCT, n=451) (OR 0.16; 95%CI 0.04 to 0.73). These results reflect weak evidence due to the small size of most included studies, the variability in existing study design, doses used, duration of treatment and measured outcomes, and positive publication bias.

IV lidocaine (lignocaine)

IV lidocaine has preventive effects on acute postoperative pain (Barreveld 2013 **Level I**, 16 RCTs [lidocaine], n=847) (see Section 1.5) and reduces CPSP following breast cancer surgery at 3 mth compared to systemic analgesics alone (OR 0.24; 95%CI 0.08 to 0.69) (Weinstein 2018 **Level I** [Cochrane], 2 RCTs, n=97 [IV lidocaine]) (1 RCT overlap). A meta-analysis of IV lidocaine versus placebo in the prevention of CPSP at 3 mth across a range of surgeries (predominantly mastectomy), identified a significant benefit (OR 0.29; 95%CI 0.18 to 0.48) (NNT 5), although numbers were too small to specifically identify safety concerns (Bailey 2018 **Level I**, 6 RCTs, n=420) (2 RCT overlap with Weinstein 2018).

Others

Following mastectomy, 10 d treatment with venlafaxine (37.5 mg/d) commencing preoperatively was associated with significantly lower burning and stabbing pain after 6 mth (Amr 2010 **Level II**, n=150, JS 3).

Planned subgroup analysis of the intraoperative use of nitrous oxide (ENIGMA-2) revealed that this intervention prevents CPSP in Chinese patients and those with variants in the methylene tetrahydrofolate reductase gene (RR 0.70; 95%CI 0.50 to 0.98) suggesting that there may be a genetic component to vulnerability to CPSP (Chan 2016 **Level II**, n=674, JS 5); there was no benefit in non-Chinese patients overall.

1.4.6.3 | Modification of surgical approach

Minimally invasive and laparoscopic surgery has made a significant impact on the severity of acute postsurgical pain but has resulted in little impact on the prevalence of CPSP (Aasvang 2010a **Level III-2**, n=464). While VATS vs open thoracic surgery reduced the risk of post-thoracotomy pain (aOR 0.33; 95%CI 0.13 to 0.86) and neuropathic pain (aOR 0.18; 95%CI 0.04-0.85), it still carries a significant risk (35% incidence) (Shanthanna 2016 **Level III-3**, n=106); this is confirmed in another study (VATS 13.3% vs thoracotomy 32.2%) (Wang 2017 **Level III-2**, n=298).

Deliberate neurectomy (of the ilioinguinal nerve) for inguinal hernia repair reduced the incidence of CPSP (from 21 to 6%) in one RCT (Malekpour 2008 **Level II**, n=100, JS 4) and in another study (Smeds 2010 **Level III-2**), while an earlier nonrandomised multicentre prospective study found this approach increased CPSP risk (Alfieri 2006 **Level III-2**, n=973). Intraoperative nerve identification of the iliohypogastric, ilioinguinal and genitofemoral nerves did not reduce the risk of development of sensory loss or postherniotomy pain syndrome compared with nonidentification (Bischoff 2012 **Level III-3**, n=244). International

guidelines for the reduction in CPSP following inguinal herniorrhaphy have been developed, recommending preservation of all three nerves (Alfieri 2011 **GL**).

Sparing of the intercostobrachial nerve during mastectomy with axillary dissection reduces the likelihood of a patient having hyposensitivity but not hypersensitivity (Warrier 2014 **Level I** [PRISMA], 3 RCTs, n=309). Cryoanalgesia of the intercostal (IC) nerves at the time of thoracotomy results in an increase in chronic pain in comparison to IV PCA or epidural analgesia or in conjunction with epidural analgesia (Humble 2015 **Level I**, 6 RCTs [cryoanalgesia], n=186).

1.4.6.4 | Multidisciplinary approaches

The impact of psychological interventions delivered in the perioperative period to prevent CPSP has been assessed by a systematic review (Wang 2018 **Level I** [PRISMA], 15 RCTs, n=2,220). Perioperative education has no effect on CPSP, while perioperative cognitive-behavioural therapy and/or relaxation training reduce the severity of CPSP based on evidence of moderate quality (MD -1.06/10; 95%CI -1.56 to -0.55). Preemptive and preventive pain psychoeducation decrease the length of stay and improve quality of acute postsurgical pain relief (Horn 2020 **Level I** [PRISMA], 43 RCTs, n unspecified). The authors concluded that preemptive pain psychoeducation would result in a decreased incidence of CPSP given that severe acute postsurgical pain and catastrophising were both significant risk factors.

Transitional pain services

New models of acute pain services have been suggested to manage pain and opioid use in the perioperative period. The '*Transitional Pain Service*' aims to optimise pain and opioid use prior to surgery, devise individualised intraoperative opioid sparing analgesic plans and manage pain postoperatively beyond the time of discharge from hospital (Katz 2015 **NR**). This approach is intended to reduce CPSP and inappropriate long-term opioid use. Psychological strategies including Acceptance and Commitment Therapy (ACT) are employed to assist in rehabilitating patients and treat or prevent CPSP (Huang 2016 **NR**). A similar model of '*Acute Pain Service Outpatient Clinic*' has been established in Finland (Tiippana 2016 **Level III-3**). Of the first 200 high risk patients referred to the clinic, 70% had evidence of neuropathic CPSP. The median time to referral to the clinic from surgery was 2 mth and patients were followed up for a median of 2.8 mth. At discharge from hospital, half the patients were using weak opioids, one third strong opioids and 70% were taking gabapentinoids. At discharge from the clinic, use of these drugs was approximately halved. One fifth of the patients were referred to the chronic pain clinic for ongoing management.

See also the following Section 1.5 for more examples of the use of preemptive and preventive analgesic interventions in attempts to reduce the risk of chronic pain after surgery and Sections 8.1.5 to 8.1.6 for more details on prevention of phantom pain after limb amputation and other postoperative pain syndromes.

KEY MESSAGES

1. Perioperative IV ketamine reduces the incidence of chronic postsurgical pain in selected procedures (**S**) (**Level I** [Cochrane Review]).
2. Following thoracotomy, epidural analgesia reduces the incidence of chronic postsurgical pain (**S**) (**Level I** [Cochrane Review]).
3. Following breast cancer surgery, paravertebral block (**S**), local infiltration (**N**) (**Level I** [Cochrane Review]) and IV lidocaine reduce the incidence of chronic postsurgical pain (**N**) (**Level I** [PRISMA]).
4. For iliac crest bone graft harvest, continuous local anaesthetic infiltration reduces the incidence of chronic postsurgical pain (**N**) (**Level I** [Cochrane Review])
5. Pregabalin reduces the incidence of chronic postsurgical neuropathic pain, but does not affect non-neuropathic chronic postsurgical pain (**N**) (**Level I** [PRISMA]).
6. Sparing of the intercostobrachial nerve during mastectomy does not decrease chest wall hypersensitivity (**U**) (**Level I** [PRISMA]).
7. Cryoanalgesia of the intercostal nerves at the time of thoracotomy results in no improvement in acute pain but an increase in chronic pain (**U**) (**Level I**).
8. There is significant association between anxiety, pain catastrophising (**U**) (**Level III-2 SR**), depression, psychological vulnerability and stress (**U**) (**Level IV SR**) and the subsequent development of chronic postsurgical pain.
9. Other risk factors that predispose to the development of chronic postsurgical pain include the severity of presurgical chronic pain and postsurgical acute pain and intraoperative nerve injury (**U**) (**Level IV SR**).
10. Spinal anaesthesia in comparison to general anaesthesia reduces the risk of chronic postsurgical pain after hysterectomy and Caesarean section (**U**) (**Level III-2**).
11. Chronic postsurgical pain is common and may lead to significant disability (**S**) (**Level IV**).
12. Chronic postsurgical pain often has a neuropathic component (**S**) (**Level IV**).

The following tick boxes represent conclusions based on clinical experience and expert opinion:

☑ Gabapentin has no demonstrated effect in preventing chronic postsurgical pain; considerable uncertainty exists regarding efficacy with contradictory meta-analyses of a few, usually small, studies with a large degree of heterogeneity (**Q**).

☑ Implementation of transitional pain services may help manage the complex issues of prolonged postoperative opioid use and chronic postsurgical pain (**N**).

1.5 | Pre-emptive and preventive analgesia

The terms 'pre-emptive' and 'preventive' analgesia have a highly specific meaning with respect to pain neurophysiology and sensitisation. The understanding of pre-emptive analgesia has evolved since the term was first coined in early 1988 (Wall 1988 **NR**). In laboratory studies, administration of an analgesic prior to an acute nociceptive stimulus more effectively minimised dorsal horn changes associated with central sensitisation than the same analgesic given after the pain state was established (see Section 1.1) (Woolf 1983 **BS**). This led to the hypothesis that pain relief prior to surgery may enhance postoperative pain management when compared with the same analgesia administered during or following surgery; that is, "pre-emptive preoperative analgesia" (Wall 1988 **NR**). However, individual clinical studies have reported conflicting outcomes when comparing "preincisional" with "postincisional" interventions. In part this relates to variability in definitions, deficiencies in clinical trial design and differences in the outcomes available to laboratory and clinical investigators (Rosero 2014a **NR**; Katz 2002 **NR;** Kissin 1994 **NR**).

Central and peripheral sensitisation affects both the intensity of acute pain and the persistence of pain well into the postoperative period and beyond (see also Section 1.4). This is complex and relates not only to the skin incision but also to the extent of intraoperative tissue and nerve injury, postoperative inflammation and the nervous system's response. The research focus has shifted from the "timing" of a single analgesic intervention to the concept of modifying sensitisation and thus having a longer-term impact on pain relief. This is termed "preventive" analgesia (Kissin 1994 **NR**) rather than pre-emptive analgesia. The differences between these two terms relate to the timing and outcomes being described, because both aim to minimise sensitisation. "Pre-emptive" analgesia, as described above, relates to the timing of administration of the analgesic intervention prior to the insult and is measured in terms of pain intensity or related outcomes. "Preventive" analgesia is the persistence of analgesic treatment efficacy beyond its expected duration of effect (see Table 1.4). This had been defined as analgesia that persists for >5.5 half-lives of a medicine, to ensure complete washout of any direct pharmacological effect (Katz 2011 **NR**). A useful summary of medicines and their criterion value of 5.5 half-lives has been published (Katz 2008b **NR**). In clinical practice, preventive analgesia appears to be the most relevant and, of pharmacological options, holds the most hope for minimising chronic pain after surgery or trauma because it decreases central sensitisation and "wind-up". An important consideration to maximise the benefit of any analgesic strategy is that the active intervention should be continued for as long as the sensitising stimulus persists (ie well into the postoperative period) (Pogatzki-Zahn 2006 **NR**; Dahl 2004 **NR**). However, from a "preventive" perspective, the critical aspect is that the effect of the intervention is sufficient to modify sensitisation and hence longer-term outcomes; the timing and duration for specific interventions still require clarification.

Table 1.4 | Definitions of pre-emptive and preventive analgesia

Pre-emptive analgesia	Preoperative treatment is more effective than the identical treatment administered after incision or during surgery. The key clarification point is the timing of administration "pre" insult/surgery. A treatment given pre-emptively can also be preventive if it satisfies the below definition.

Preventive analgesia	Postoperative pain and/or analgesic consumption is reduced relative to another treatment, a placebo treatment or no treatment with the effect observed at a point in time beyond the expected duration of action of the intervention (eg 5.5 half-lives of the medicine). The intervention may or may not be initiated before surgery.

Sources: Moiniche 2002; Katz 2002; Katz 2011; Rosero 2014b

1.5.1 | Pre-emptive analgesia

The benefits of pre-emptive analgesia have been questioned (Katz 2008b **Level I**, 27 RCTs, n unspecified; Moiniche 2002 **Level I**, 80 RCTs, n=3,761; Dahl 2004 **NR**). However, one meta-analysis provided support for pre-emptive analgesia (Ong 2005 **Level I**, 66 RCTs, n=3,261). The efficacy of different pre-emptive analgesic interventions (epidural analgesia, local anaesthetic wound infiltration, systemic NMDA antagonists, systemic opioids and systemic NSAIDs) was analysed in relation to different analgesic outcomes (pain intensity scores, supplemental analgesic consumption, time to first analgesic). The effect size is most marked for epidural analgesia, with improvements found in all outcomes (13 RCTs, n=653) (overall effect size 0.38; 95%CI 0.28 to 0.47). Pre-emptive effects of local anaesthetic wound infiltration and NSAID administration were also suggested but reanalysis is required as one of the positive studies for each of these treatments has subsequently been withdrawn (White 2011 **NR**). As a result of this withdrawal, evidence supporting the pre-emptive effects of nonselective NSAIDS (nsNSAIDs) and COX-2 inhibitors is equivocal (White 2009 **NR**). Reductions in analgesic consumption ranged from 44–58%, which the authors regarded as clinically significant, but associated changes in adverse effects were not analysed. Pain score results were equivocal for systemic NMDA antagonists (effect size [ES] 0.00; 95%CI -0.19 to 0.20) (7 RCTs, n=418) and there was no clear evidence for a pre-emptive effect of opioids (ES -0.24; 95%CI -0.46 to -0.01) (7 RCTs, n=324).

Following thoracotomy, pre-emptive thoracic epidural analgesia (local anaesthetic ± opioid prior to surgery) reduces the severity of acute pain on coughing for up to 48 h, with a marginal effect on pain at rest compared with the same therapy initiated postoperatively (Bong 2005 **Level I**, 6 RCTs, n=458). Acute pain intensity was a predictor of chronic pain at 6 mth in two studies but there was no statistically significant difference in the incidence of chronic pain between the pre-emptive epidural (39.6%) vs control epidural (48.6%) groups. Pre-emptive analgesia with epidural use in thoracotomy identified lower postoperative pain scores, reduced pro-inflammatory biomarkers and shortened hospital LOS (Yang 2015 **Level II**, n=90, JS 3).

In single-stage TKA, pre-emptive epidural analgesia was associated with lower postoperative pain scores, fewer days with pain following surgery (mean ± SD 64.3 d ± 21.3 vs 142.4 d ± 80.0) and less CPSP at 3 mth (24 vs 56.5%) (Rao 2020 **Level II**, n=50, JS 3); there were no differences in morphine consumption or LOS.

A Cochrane review investigated opioids commenced prior to incision compared to those commenced following incision; this review uses the term “preventive” to indicate the continued use of opioids into the postoperative period and so its findings are actually more in line with the above definition of “pre-emptive” (Doleman 2018 **Level I** [Cochrane], 20 RCTs, n=1,343). There were no differences in 6 h or 24 to 48 h pain score outcomes, but a small reduction was found in 24 h morphine consumption in the pre-incision group (MD -4.9 mg; 95%CI -9.4 to -0.4).

Across a range of procedures, IV paracetamol given before incision is more effective than post incision in reducing pain at 1 h (MD -0.50/10; 95%CI -0.98 to -0.02) and 2 h (MD -0.34/10; 95%CI - 0.67 to -0.01), 24 h opioid consumption (SMD 0.52; 95%CI -0.98 to -0.06) and

postoperative vomiting (RR 0.50; 95%CI 0.31 to 0.83) (Doleman 2015 **Level I** [PRISMA], 7 RCTs, n=544). IV paracetamol reduces PONV when administered before recovery from anaesthesia (Apfel 2013 **Level I** [PRISMA], 30 RCTs, n=2,364). This effect is correlated to pain relief achieved but not to reduced opioid consumption.

In total abdominal hysterectomy, gabapentin given only prior to surgery compared to gabapentin given pre- and postoperatively found both interventions decreased 24 h morphine requirements compared to placebo (preoperatively only SMD -0.69; 95%CI -1.20 to-0.07; pre and postoperatively -1.45; 95% CI -1.79 to -1.11) (Alayed 2014 **Level I SR**, 14 RCTs, n=891); the effect of gabapentin in reducing morphine consumption was stronger in the preoperative only group than in the preoperative and postoperative group. The design of the studies in this meta-analysis did not allow for evaluation of a true pre-emptive effect because all active treatments were given preoperatively.

Dexketoprofen administered 30 min pre- vs 10 min post-incision in patients having abdominal hysterectomy resulted in lower pain scores for up to 4 h postoperatively and reduced morphine consumption for up to 24 h (Gelir 2016 **Level II**, n=50, JS 3); all patients received intraoperative ketamine infusions and there was no difference in time to first analgesic request.

A combination of paracetamol, ketoprofen and pregabalin administered 4 h pre-surgery vs control, with all drugs being then given to both groups post-incision for at least 48 h, resulted in improved pain scores for up to 48 h and reduced PCA opioid requirements (Raja 2019 **Level II**, n=97, JS 4).

The reason for there being a limited number of valid clinical studies investigating 'pre-emptive' analgesia is that investigators often fail to compare the same technique pre- and post-incision or they apply the intervention after sensitisation has occurred eg in trauma or injury. The variability in clinical trial design coupled with the complexity of clinical pain management means that, with the exception of epidural analgesia, benefits remain unclear regarding pre-emptive analgesia in a clinical setting.

1.5.2 | Preventive analgesia

A true preventive analgesic effect needs to be assessed many days or even months after the analgesic intervention has ceased. A large number of studies published use the term 'preventive' where the investigation often simply compares the addition of a preoperative dose of an analgesic to a preoperative placebo (possibly continuing the medications postoperatively) with analgesic outcomes assessed for a relatively short period – this is not 'preventive' in the neurophysiological sense and such studies are not discussed here.

A systematic review analysed dichotomous trial outcomes (overall positive or negative outcomes) (Katz 2008b **Level I**, 39 RCTs, n unspecified) and identified overall beneficial acute preventive effects following the use of a range of different medicines (28 positive RCTs, 11 negative RCTs). Again, results of this meta-analysis might be affected by the subsequent withdrawal of some of the studies included (White 2011 **NR**). The methodology was unable to identify specific therapeutic techniques that may be of benefit.

The use of local anaesthetics (neuraxial, perineural or systemic) demonstrates a preventive analgesic effect in the perioperative period whether given pre- or postincision (Weinstein 2018 **Level I** (Cochrane), 63 RCTs, n=3,027; Barreveld 2013 **Level I**, 89 RCTs, n unspecified). Meta-analysis on the prevention of CPSP by regional anaesthesia found benefits for three procedure types: thoracotomy, breast cancer surgery and Caesarean section (Weinstein 2018 **Level I** (Cochrane), 63 RCTs, n=3,027). IV lidocaine versus placebo provides a significant benefit in prevention of CPSP at 3 mth across a range of surgeries (Bailey 2018 **Level I**, 6 RCTs, n=420) (2 RCTs overlap with Weinstein 2018 **Level I** [Cochrane]) 2 RCTs, n=97 [IV lidocaine]) (see Section 1.4 for details).

Activation of the NMDA receptor plays an important role in central sensitisation and many studies have focussed on the ability of NMDA-receptor antagonists to produce pre-emptive or preventive analgesic effects. A medicine which, when used perioperatively, reduces CPSP has by definition a preventive analgesic effect (see Section 1.4). The preventive effects of perioperative ketamine, dextromethorphan and magnesium on CPSP are described in Sections 1.4 and 4.6. Analgesic benefit is seen in the acute postoperative period with ketamine following a range of doses, timings and procedures (Laskowski 2011 **Level I** [PRISMA], 70 RCTS, n=4,701) supported by a network meta-analysis investigating multiple pharmacological interventions to reduce CPSP which identified ketamine as the highest ranked in terms of efficacy and safety (Ning 2018 **Level I** [NMA], 24 RCTs, n unspecified) (see also Section 4.6.1). However, in the immediate postoperative period, it is difficult to separate persistence of direct pharmacological effects from preventive actions, as many studies continued treatment for over 24 h. Expanding potential indications for ketamine in depression have led to exploration of its potential 'metaplastic' effects on synaptic transmission whereby a brief exposure may result in persisting changes in neuronal long term potentiation (Izumi 2014 **BS**); this may explain in part its effect in CPSP.

The alpha-2-delta ligands, gabapentin and pregabalin, reduce opioid requirements and improve analgesia when given perioperatively (see Section 4.8). However, even though some of these studies used only single-dose therapy, the range of doses, duration of follow-up and long half-life of gabapentin (6 to 7 h) means that an early preventive benefit is difficult to discern from a direct pharmacological effect. Longer term preventive effects on CPSP are discussed in Sections 1.4 and 4.8.

In a study of multimodal epidural analgesia (local anaesthetic, opioid, ketamine and clonidine) in four groups of patients having colonic resection, a clear preventive effect on the development of residual pain up to 1 y after surgery was demonstrated with continuous perioperative epidural analgesia (Lavand'homme 2005 **Level II**, n=85, JS 5). Residual pain at 1 y was lowest in patients who received intraoperative vs postoperative epidural analgesia. Epidural analgesia commenced pre-incision versus post-incision for TKA resulted in less CPSP at 3 mth (24 vs 56.5%) (Rao 2020 **Level II**, n=50, JS 3) indicating a possible preventive effect (see Section 1.5.1 above for other details).

Epidural calcitonin, bupivacaine and fentanyl versus epidural bupivacaine and fentanyl alone reduced phantom pain, allodynia and hyperalgesia at 6 and 12 mth following proximal or distal amputation in the lower limb (Yousef 2017 **Level II**, n=60, JS 3).

KEY MESSAGES

Pre-emptive analgesia

1. The timing of opioid administration (preincision rather than postincision) may reduce further opioid consumption over 24 h, but has no effect on pain scores **(N)** (**Level I** [Cochrane Review])
2. Pre-emptive use of paracetamol across a range of procedures reduces pain scores up to 2 h, opioid consumption for up to 24 h and postoperative nausea and vomiting (**N**) (**Level I** [PRISMA]).
3. Pre-emptive epidural analgesia has a significant effect on postoperative pain relief (**S**) (**Level I**).

Preventive analgesia

4. Epidural, regional and systemic local anaesthetic administration shows preventive analgesic effects in reducing chronic postsurgical pain (**S**) (**Level I** [Cochrane Review])
5. NMDA-receptor antagonists (ketamine) reduce the incidence of chronic postsurgical pain in selected procedures (**S**) (**Level I** [Cochrane Review]).

The following tick box represents conclusions based on clinical experience and expert opinion:

☑ In clinical trials assessing acute postoperative pain for many systemic medicines, the range of doses administered, the variable durations of follow-up and variable half-lives following infusion or repeated dosing means that "early" preventive effects, although possible, are difficult to discern from persistence of direct pharmacological effects (**U**).

1.6 | Adverse physiological and psychological effects of acute pain

1.6.1 | Acute pain and the injury response

Acute pain, and its associated injury and treatment, triggers a complex haemodynamic, metabolic, neurohumoral, immune as well as somatosensory response (see Figure 1.2) (Manou-Stathopoulou 2019 **NR**). Clinically, acute pain is commonly associated with actual tissue damage. This tissue damage may be due to trauma or surgery. The complete physiological response to the insult has a quantifiable molecular and cellular response. Importantly, this response is generated in a range of anatomical compartments. These include rapid adaptations at the site of injury, along ascending neuronal projections, within the spinal cord, at higher brain centres and within distal organs. These disparate events are triggered by a coordinated array of neuronal, autocrine and paracrine signalling events. Many of these events do not result in nociceptive outcomes but may detrimentally impact an individual's injury recovery or increase risk of secondary complications. Importantly, all of these events can occur in a conscious individual whose prior life experience may prime or protect them from the molecular consequences and perception-processing of a painful response.

Figure 1.2 | The injury response

Triggers and predisposing factors	Mediators	Injury response
Surgical trauma or injury	Neural	Pain experience, primary and secondary hyperalgesia (peripheral and central sensitisation)
Preoperative pain	Immune factors Proteins and other molecules: growth factors eicosanoids nitric oxide others	Inflammation Haemodynamic
Psychological factors	Endocrine	Catabolism
Social and environmental factors	Metabolic	Physical deconditioning
Genetic factors		Psychological effects
Anaesthesia and analgesia, other medications		Other adaptations systemic

Source: Modified from NHMRC 1999.

It is difficult to separate the complex array of potential individual or interacting triggers associated with pain from other aspects of the broader physiological response observed clinically (see Figure 1.2). However, some data have been obtained with experimental pain in the absence of injury. For example, electrical stimulation of the abdominal wall results in a painful experience

(intensity 8/10) and an associated hormonal/metabolic response, which includes increased levels of cortisol, catecholamines and glucagon, and a decrease in insulin sensitivity (Greisen 2001 **Level II EH**). A systematic review of the effect of experimental pain on the autonomic nervous system, assessed by heart rate variability, determined that experimental pain increases baroreflex activity and decreases parasympathetic activity (Koenig 2014 **Level IV EH SR**, 20 studies, n unspecified). Factors such as time of day, possibly owing to nociceptive control by diurnally active hormones, contribute to reported differences in thermal pain (both cold and heat) (Aviram 2015 **Level II EH**, n=48, JS 3). Some of these environmental conditioning factors may change the perception rather than the nociceptive signal itself eg sleep deprivation in healthy controls causes hyperalgesia which may be caused by a reduction in cortical cognitive or perceptual mechanisms, rather than sensory nociceptive amplification (Odegard 2015 **Level II EH**, n=33, JS 4).

Although acute pain is only one of the important triggers of the "injury response" (see Figure 1.2), as the magnitude and duration of the response is related to the magnitude and duration of the nociceptive stimulus, effective pharmacological pain relief may have a significant impact on this response (Moselli 2011 **Level II**, n=35, JS 3), although this may be variable (Fant 2013 **Level II**, n=26, JS 3; Liu 2008 **NR**; Carli 2008 **NR**). Beyond pharmacological interventions, mere distraction of attention away from the pain protects against experimental pain-induced changes in heart rate variability (Koenig 2014 **Level IV EH SR**, 20 studies, n unspecified). Importantly, negative expectations in patients created by verbal suggestions can lead to the "nocebo" response, defined as experiencing greater pain to the same nociceptive stimulus (Petersen 2014 **Level III-1 EH SR** [PRISMA], 10 studies, n=344).

As noted above, the release of systemic factors such as proinflammatory cytokines as a result of pain and trauma associated with surgery or injury may contribute to multiple physiological responses that hamper the recovery of a patient (Manou-Stathopoulou 2019 **NR**). Limiting these effects by analgesic techniques may affect some surgical outcomes. A group of patients having abdominal surgery were randomised to receive intraoperative epidural analgesia or IV opioid analgesia, with both groups receiving postoperative epidural analgesia (Moselli 2011 **Level II**, n=35, JS 3). In the intraoperative epidural group, inflammatory markers were lower up to 24 h postoperatively and minor complications were reduced in number (39 vs 76%), although there was no difference in major complications or LOS. Postoperative ileus is attenuated in patients receiving IV lidocaine infusions compared to saline in patients undergoing colonic surgery (Sun 2012 **Level I** [PRISMA], 21 RCTs, n=1,108; Vigneault 2011 **Level I** [PRISMA], 29 RCTs, n=1,754) (15 RCT overlap). Analgesic and bowel motility benefits of lidocaine were more marked when administered via the thoracic epidural route than by IV infusion (Kuo 2006 **Level II**, n=60, JS 5); however, both lidocaine groups were associated with reduced opioid consumption compared with saline. The postoperative decreases in proinflammatory cytokines, such as interleukin (IL)-6, IL-8 and IL-1RA (a competitive inhibitor of IL-1β), were associated with more rapid return of bowel function following abdominal surgery. Ketamine, administered intraoperatively, is associated with reduced IL-6 levels post operatively, suggesting an anti-inflammatory effect in addition to analgesic benefits (Dale 2012 **Level I** [PRISMA], 6 RCTs, n=331).

In addition to the stress responses to surgery and analgesia, aberrant neuronal firing during acute pain creates a state of altered cell function in nociceptive pathways. This may not be perceived as pain by higher brain centres (eg under general anaesthesia) nor acknowledged consciously by the individual. Cellular adaptations to acute nociceptive inputs in primary and secondary fibres are well established to drive peripheral and central sensitisation (Baron 2013 **NR**; von Hehn 2012 **NR**; Woolf 2011 **NR**; Kuner 2010 **NR**). Critically, these result in multiple changes to gene transcription and protein translation (see also Section 1.1).

1.6.2 | Adverse physiological effects

Clinically significant injury responses that are often associated with nociceptive stimuli trigger diffuse physiological responses such as stress and inflammation, which leads to hyperalgesia, hyperglycaemia, protein catabolism, increased free fatty acid levels (lipolysis) and changes in water and electrolyte flux (Manou-Stathopoulou 2019 **NR**; Carli 2008 **NR**; Liu 2008 **NR**) (see Table 1.5). In addition, increased sympathetic activity has diverse effects on the cardiovascular, gastrointestinal and respiratory systems and on coagulation, endocrine, immune and psychological function (Prabhakar 2014 **NR**; Cardinale 2011 **NR**; Blackburn 2011 **NR**).

Table 1.5 | Metabolic immunological and endocrine responses to injury

Endocrine	↑Catabolic hormones	ACTH, cortisol, ADH, growth hormone, catecholamines, angiotensin II, aldosterone, glucagons,
	↓Anabolic hormones	Insulin, testosterone
Immune	Mitochondrial initiation	Alarmins (DAMP molecules)
	Proinflammatory followed by compensatory response	IL-1, TNFα, IL-6, IL4, IL8, IL10 Chemokines
Metabolic		
Carbohydrate	Hyperglycaemia, glucose intolerance, insulin resistance	Glycogenolysis, gluconeogenesis (cortisol, glucagon, growth hormone, adrenaline, free fatty acids) Insulin secretion/activation
Protein	Muscle protein catabolism, synthesis of acute phase proteins	Cortisol, adrenaline, glucagon, IL-1, IL-6, TNF
Lipid	Lipolysis and oxidation	Catecholamines, cortisol, glucagon, growth hormone
Water and electrolyte flux	Retention of water and sodium, excretion of potassium and functional ECF with shifts to ICF	Catecholamine, aldosterone, ADH, cortisol, angiotensin II, prostaglandins and other factors

Note: *ACTH: adrenocorticotrophic hormone; ADH: antidiuretic hormone; DAMP: damage-associated molecular pattern; ECF: extracellular fluid; ICF: intracellular fluid; IL: interleukin; TNF: tumour necrosis factor.*

Source: *Modified from Manou-Stathopoulou 2019; NHMRC 1999.*

1.6.3 | Pain and analgesia: effects on injury-induced organ dysfunction

Pain from injury activates a range of adverse physiological effects (Manou-Stathopoulou 2019 **NR**; Prabhakar 2014 **NR**; Cardinale 2011 **NR**; Blackburn 2011 **NR**). Increased sympathetic efferent nerve activity increases heart rate, contractility and blood pressure. As sympathetic activation increases myocardial oxygen demand and reduces myocardial oxygen supply, the risk of cardiac ischaemia, particularly in patients with pre-existing cardiac disease, is increased. Enhanced sympathetic activity can also reduce gastrointestinal motility and contribute to ileus. Perioperative neurocognitive disorders such as postoperative delirium are exacerbated by

under-treated pain and associated factors such as stress and inflammation. In patients with fractured neck of femur, delirium was associated with lack of analgesic use (Thompson 2018 **Level IV**, n=688). In elderly patients, postoperative delirium is decreased with the use of multi-component interventions, which include effective analgesia (Siddiqi 2016 **Level I** [Cochrane], 39 RCTs, n=16,082).

Severe pain after upper abdominal and thoracic surgery contributes to an inability to cough and a reduction in functional residual capacity, resulting in atelectasis and ventilation-perfusion abnormalities, hypoxaemia and an increased incidence of pulmonary complications. The injury response also contributes to a suppression of cellular and humoral immune function and a hypercoagulable state following surgery, both of which can contribute to postoperative complications (Lord 2014 **NR**). Alterations to glucose metabolism and accelerated protein breakdown also contribute to the injury response. These factors need to be considered when evaluating analgesic interventions. Patients at greatest risk of adverse outcomes from unrelieved acute pain include very young or elderly patients, those with concurrent medical illnesses and those undergoing major surgery (Liu 2008 **NR**). Analgesic technique may reduce adverse physiological impact and improve surgical outcomes. Often a multimodal approach to anaesthesia, pain management, the surgical stress response and perioperative care is undertaken, making it difficult to separate individual factors involved in outcome; especially with multifaceted strategies such as with enhanced recovery after surgery (ERAS) protocols (Kehlet 2018 **NR**). The influence of epidural anaesthesia and analgesia on outcome has been evaluated (Popping 2014 **Level I** [PRISMA], 125 RCTs, n=9,044) (see also Section 5.6).

There is also limited evidence that stress and opioid analgesia in some circumstances may inhibit immune function, promoting tumour growth or metastasis. Regional anaesthetic and opioid-sparing analgesic techniques might have a beneficial effect on rates of cancer recurrence after tumour resection but overall study results are still unclear (Meserve 2014 **NR**; Colvin 2012 **NR**).

KEY MESSAGES

1. Recognition of the importance of postoperative rehabilitation including pharmacological, physical, psychological and nutritional components has led to enhanced recovery (**U**) (**Level I** [PRISMA]).

The following tick box represents conclusions based on clinical experience and expert opinion:

☑ Acute pain and injury of various types are inevitably interrelated and, if severe and prolonged, the injury response becomes counterproductive and can have adverse effects on outcome (**U**).

1.6.4 | Adverse psychological effects

Psychological changes associated with acute pain have received less clinical attention than those associated with chronic pain, however they have been well-studied in experimental contexts, especially regarding interference with attention and cognitive processes such as learning and memory. Clinically, sustained acute nociceptive input, as often occurs after surgery, trauma or burns, can also have a major influence on psychological function, which may in turn increase the risk of progression to chronic pain (Glare 2019 **NR**). In addition, pre-operative psychological characteristics, in concert with other factors (eg genetic factors and pre-operative pain), have

also been found predictive of adverse reactions to postoperative pain (Yang 2019 **Level III-2 SR**, 33 studies, n=53,362; Lindberg 2017 **Level IV**, n=188; Schug 2017 **NR**).

Failure to relieve acute pain may result in increasing anxiety, inability to sleep, demoralisation, a feeling of helplessness, loss of control, and an inability to think and interact with others; in the most extreme situations, where patients can no longer communicate, effectively they have lost their autonomy (VanDenKerkhof 2012b **Level IV**, n=76; Cousins 2004 **NR**). In turn, these psychological responses in the acute phase may be major determinants of progression to chronic pain conditions, such as chronic postsurgical pain (CPSP), typically in combination with other known risk factors (Jenewein 2009 **Level III-2**, n=90; Williamson 2009 **Level III-2**, n=1,290; Schug 2017 **NR**; Young Casey 2008 **NR**). In breast cancer surgery patients, anxiety and low psychological robustness (positive affect and dispositional optimism) emerged as significant predictors of acute pain with distress being the strongest predictor of chronic pain (McCowat 2019 **Level IV SR**, 12 studies, n=3,452). However, the relationship between depression and CPSP was uncertain

In acute pain, attention has also focussed on perioperative neurocognitive disorders (PND), including delirium and the research outcome of postoperative cognitive dysfunction (POCD). Both pain itself and analgesic drugs can exacerbate PND, especially delirium (Scottish Intercollegiate Guidelines Network 2019 **GL**). Although the aetiology of PND (and POCD) is unclear, factors include dysregulation of cerebral neurotransmitters, patient factors (age, preoperative cognitive function), and perioperative pharmacological therapy (Evered 2018 **NR**). Neurotransmitters involved in PND include acetylcholine and serotonin, especially in the elderly (Inouye 2014 **NR**); hence analgesics and adjuvants with anticholinergic or sedative effects should be avoided where possible in at-risk patients (Scottish Intercollegiate Guidelines Network 2019 **GL**; American Geriatrics Society 2015 **GL**). Effective non-opioid-based acute pain management in older patients helps reduce delirium (Scottish Intercollegiate Guidelines Network 2019 **GL**; Mahanna-Gabrielli 2019 **NR**) (see also Sections 1.2, 1.4, 9.2).

KEY MESSAGES

1. Postoperative delirium is exacerbated by unrelieved acute pain and by overuse of sedating analgesics, in particular opioids (**N**) (**Level IV**).

The following tick box represents conclusions based on clinical experience and expert opinion:

☑ Failure to relieve acute pain can lead to psychological distress (**N**).

1.7 | Genetics and acute pain

An increasing number of genetic variants modulating nociception, susceptibility to pain conditions, as well as response to pharmacotherapy are being discovered.

Pharmacogenomics deals with the influence of variations in the human genome on response (both beneficial and undesirable) to medicines in patients. By correlating gene alterations with a medicine's efficacy or toxicity, it is possible to gain a better understanding of the causes of interpatient variability in response to a specific medicine and so to develop a rational means to optimise pharmacological therapy with respect to the patient's genotype and ensure maximum efficacy with minimal adverse effects. For example, genetic factors regulating opioid pharmacokinetics (metabolising enzymes, transporters) and pharmacodynamics (receptors and signal transduction elements, ion channels, enzymes) contribute to the large interpatient variability in postoperative opioid requirements (De Gregori 2016 **NR**; Trescot 2014 **NR**). Information from genotyping may help in selecting the analgesic medicine and the dosing regimen for an individual patient (Packiasabapathy 2018 **NR**; Allegri 2010 **NR;** Lotsch 2006 **NR**). Nevertheless, given the complexity of pain pathways, in very few cases is a single gene variant contributing substantially to response variability, but rather there are a large number of small contributions from multiple genes.

Although there is increasing information from studies, often small numbers of subjects are involved and therefore translation into clinical practice is still limited (Trescot 2014 **NR**; Stamer 2007b **NR**). Nevertheless, some preliminary estimates for dose adaptations are possible (Allegri 2010 **NR**; Lotsch 2006 **NR**). Importantly however, genetic factors must be considered within the context of the multiple interacting physiological, psychological, age-related, cultural, ethnic and environmental factors that influence individual responses to pain and analgesia (Sadhasivam 2014 **NR**; Searle 2009a **NR**; Kim 2009 **NR**).

1.7.1 | Single gene pain disorders

A number of rare pain-related conditions have been identified through family linkage mapping, which are due to single gene mutations (Mendelian gene).

Recognised hereditary syndromes associated with reduced pain sensation include the following.

- Channelopathy-associated insensitivity to pain (CAIP) is caused by variants in the *SCN9A* gene, which codes for the alpha-subunit of the voltage-gated sodium channel $Na_v1.7$. $Na_v1.7$ is located in peripheral (dorsal root and sympathetic ganglion) neurones and plays an important role in action potential generation in these cells. Mutations that result in loss of $Na_v1.7$ function cause affected individuals to be unable to feel physical pain (Bennett 2014 **NR**). Patients with a single-nucleotide polymorphism (SNP) in *SCN9A* (3312T; 5.5% frequency) had lower postoperative pain sensitivity after pancreatectomy, lower PCA requirements and a lower likelihood of developing inadequate analgesia than those carrying the 3312G allele (OR 0.10; 95%CI 0.01 to 0.76) (Duan 2013 **Level III-2**, n=200).
- Hereditary sensory and autonomic neuropathy (HSAN) I–V syndromes are associated with a range of genetic abnormalities and produce varying patterns of sensory and autonomic dysfunction and peripheral neuropathy (NTRK1 gene) (Vetter 2017 **NR**; Auer-Grumbach 2013 **NR**; Mogil 2012 **NR**). These syndromes present as various combinations of loss or reduced sensitivity to pain accompanied by other autonomic and sensory deficits. HSAN type IV is also known as congenital insensitivity to pain with anhydrosis (CIPA).

Recognised hereditary syndromes associated with increased pain sensation include (Mogil 2012 **NR**):

- Erythromelalgia and paroxysmal extreme pain disorder, also known as familial rectal disorder, both of which are due to different gain-of-function mutations of sodium channel Nav1.7 (SCN9A) (Dabby 2012 **NR**);
- Familial hemiplegic migraine;
- Hereditary neuralgic amyotrophy;
- Hereditary pancreatitis (Rebours 2012 **NR**).

1.7.2 | Genetic influences on sensitivity to pain

Apart from these rare Mendelian inherited conditions, "pain sensitivity" variability is thought to vary up to 50% in the general population due to genetic differences, with environmental influences responsible for the remainder of variability (Norbury 2007 **Level IV**, n=196). Twin studies have helped identify inheritable traits for development of back pain, postherpetic neuralgia, fibromyalgia and other common painful conditions (Mogil 2012 **NR**).

While several hundred genes have been identified as associated with pain expression in mice, they are not necessarily relevant to humans (LaCroix-Fralish 2011 **SR BS**) and have been studied in chronic and not acute pain (Kringel 2018 **Level IV**; Zorina-Lichtenwalter 2016 **NR**). Evidence for a genetic association with more common pain conditions has come from association studies, which require large cohorts (Mogil 2012 **NR**). Studies often suffer from low sample sizes and the restricted number of potential genotype variants studied. Many findings of an association of a particular gene allele with pain sensitivity have not been replicated in subsequent studies, so caution is needed in this area.

Many genetic variants have been associated with pain sensitivity (Crist 2014 **NR**); the most commonly studied genes include:

- Mu opioid receptor (*OPRM1*);
- Catechol-O-methyltransferase (*COMT*);
- Guanosine triphosphate cyclohydrolase 1;
- Transient receptor potential (*TRPV1*);
- Melanocortin-1 receptor (*MC1R*).

Other gene variants that have been associated with alterations in pain sensitivity in acute pain states include *ADRB2, HTR2A, IL1RN, KCNJ6, MAOA* and *MAOB* (Mogil 2012 **NR),** *P2RX7* (Kambur 2018 **Level III-2**, n=3,847) and *TAOK3* (Cook-Sather 2014 **Level III-2**, n=617). Often studies have addressed postoperative analgesic requirements as the index of pain sensitivity rather than use of experimental pain models.

1.7.2.1 | OPRM1

A variant of the gene encoding the mu opioid receptor *OPRM1,* A118G SNP, was targeted as a very promising candidate for modulation of analgesia and has been the most studied variant (Crist 2014 **NR**).

Overall findings on the effects of this SNP remain contradictory (Crist 2014 **NR**). In a random-effects meta-analysis in the postoperative setting, *OPRM1* 118G-allele carriers have higher mean opioid requirements than *OPRM1* 118AA homozygotes (SMD -0.18; p=0.003) (Hwang 2014 **Level III-2 SR**, 18 studies, n=4,607). These findings were robust in a subgroup analysis of Asian patients, whose frequency of the G variant is about 40% compared to about 15% for Caucasians (SMD -0.21; p=0.001), morphine users (SMD -0.29; p<0.001) and patients after bowel surgery (SMD -0.20; p=0.008). A preceding systematic review found a similar but smaller effect (SMD 0.096;

95%CI 0.025 to 0.167) of *OPRM1* 118G with increased opioid requirements in the perioperative and postoperative period (Walter 2013 **Level III-2 SR**, 14 studies, n=3,346); there was no significant association of *OPRM1* 118G with opioid requirements, when using the random-effects environment (Cohen's d 0.044; 95%CI -0.113 to 0.202). A positive finding was obtained in 1,000 women undergoing breast cancer surgery in which the GG cohort required about 33% more oxycodone than the AA cohort (Cajanus 2014 **Level III-2 SR**, n=1,000). For epidural analgesia using fentanyl during labour however, G-allele (AG+GG) carriers of the *OPRM1* 118 polymorphism required lower (not higher) fentanyl doses to achieve adequate pain relief compared to those with the AA homozygote (SMD -0.24; 95%CI -0.44 to -0.03) (Song 2013 **Level III-2 SR**, 6 studies, n=838). *OPRM1* 304A/G polymorphism did not influence the duration of effect or the requirement for breakthrough analgesia after intrathecal (IT) opioid administration for labour pain (Wong 2010 **Level III-2**, n=293). There was also no effect of A118G mu-opioid receptor polymorphism on duration of analgesia found in a subsequent study, but patients of Hispanic/African origin had increased duration of analgesia and pruritus vs Jewish/Arabic patients in labour (Ginosar 2013 **Level III-2**, n=125).

OPRM1 A118G seems to modulate effects of opioids given in experimental pain; in the clinical setting it has limited impact with no clinical relevance in Caucasians, but explains increased opioid requirements in Asians. Studies that assessed different haplotypes of the *OPRM1* and combinations of genetic variants, eg *OPRM1*, COMT and ESR1, found greater predictability suggesting more complexity (De Gregori 2016 **Level III-2**, n=201; Reyes-Gibby 2007 **Level III-2**, n=207; Mura 2013 **NR**). Overall *OPRM1* 118 polymorphisms may be too complex to be used as a predictive tool for individual opioid dosing (Mogil 2012 **NR**).

1.7.2.2 | COMT

COMT metabolises noradrenaline, adrenaline, and dopamine and has been implicated in the modulation of pain. COMT inhibition or low activity via genetic polymorphisms may lead to increased pain sensitivity via beta-adrenergic receptor-dependent mechanisms (Nackley 2007 **NR**). Haplotypes with high COMT activity are associated with low pain sensitivity to mechanical and thermal stimuli (Diatchenko 2005 **NR**). The Val158Met polymorphism influences the activity of the COMT enzyme with the Met158 allele associated with low COMT activity and increased pain sensitivity (Vuilleumier 2012 **NR**), leading to greater morphine requirements post-surgery in adults (Dai 2010 **Level IV**, n=69) and children (Sadhasivam 2014 **Level IV**, n=149).

A large study undertaken to address influence of *COMT* polymorphism on postoperative pain in a homogenous ethnic sample of 1,000 women having breast surgery showed no association with any *COMT* polymorphism and postoperative oxycodone requirements (Kambur 2013 **Level III-2**, n=1,000). Furthermore, the most studied *COMT* mutation, Val158Met, showed no association with pain levels in these patients, but two previously unstudied mutations did. In contrast, in 152 patients undergoing nephrectomy, the 31 patients with Val/Val genotype consumed more IV morphine than 61 Met/Met patients (36%; 95%CI 31 to 41) (Candiotti 2014 **Level III-2**, n=152). Combinations of several genetic mutations act together to determine pain sensitivity associated with COMT (Smith 2014 **Level III-2**, n=398). Similarly, genetic association studies using COMT variants have also revealed conflicting results (Belfer 2011 **NR**).

1.7.2.3 | TRPA1

Emerging evidence suggests that epigenetic variations of the TRPA1 receptor may be responsible for some of the genetically determined individual differences in pain sensitivity (Gombert 2017 **Level III-2 EH**, n=75; Bell 2014 **Level III-2 EH**, n=100).

There is considerable complexity associated with genetic mutations influencing pain sensitivity and much to be unravelled before clear evidenced-based conclusions can be drawn.

1.7.3 | Drug metabolism

Drug-metabolising enzymes represent a major target for identifying associations between an individual's genetic profile and drug response (pharmacogenetics) (Trescot 2014 **NR**; Stamer 2007c **NR**). The polymorphic cytochrome P450 enzymes metabolise most medicines and show interindividual variability in their catalytic activity. There are 57 enzymes in this family of which 9 are clinically relevant to drug metabolism: CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4/3A5, all of which have different and often overlapping activity. Medicines can be substrates, inhibitors or inducers of metabolism of analgesic medications.

CYP2D6, CYP2C19, and CYP2C9 are highly polymorphic and are involved in approximately 40% of CYP-mediated drug metabolism. Of these, CYP2D6 is the most relevant to analgesic medications. Those who have the genetic variants resulting in poor metabolism by CYP2D6 are likely to have more severe postoperative pain than those who have other variants (Yang 2012 **Level III-2**, n=236).

CYP2D6 gene influences the metabolism of many medications including codeine, tramadol, oxycodone, hydrocodone, dextromethorphan, amitriptyline, nortriptyline, duloxetine, metoclopramide and venlafaxine. Specifically, CYP2D6 metabolises codeine, dihydrocodeine, hydrocodone, oxycodone and tramadol to their more potent hydroxyl metabolites, which have a higher affinity for the mu receptor (Somogyi 2007 **NR**). For additional detail related to individual opioids see Section 4.3.1.

Over 100 allelic variants of *CYP2D6* have been identified, resulting in wide variability in function. Individuals carrying two wild type alleles display normal enzyme activity and are known as normal metabolisers; intermediate metabolisers are heterozygotes with one reduced function and one nonfunctional allele; poor metabolisers have no functionally active alleles and have minimal or no enzyme activity (Crews 2014 **NR**; Vuilleumier 2012 **NR**; Zhou 2009a **NR**; Zhou 2009b **NR**). Ultrarapid metabolisers have multiple copies of the wildtype *CYP2D6* alleles (Crews 2014 **NR**; Vuilleumier 2012 **NR**; Stamer 2007b **NR**).

There are large interethnic differences in the frequencies of the variant alleles. For example, in Caucasian populations, 8–10% of people are poor metabolisers and 1-3% are ultrarapid metabolisers (Crews 2014 **NR**; Vuilleumier 2012 **NR**; Stamer 2007b **NR**). The proportion of ultrarapid metabolisers is higher (up to 29%) in Middle Eastern and Northern African populations and lower (0.5%) in Asian populations (Stamer 2007c **NR**). The proportion of poor metabolisers is lower in Asian and African American populations (Zhou 2017 **Level IV SR**, 5 population-scale sequencing projects, n=56,945; Yee 2013 **Level IV**, n=75; Holmquist 2009 **NR**).

Other genetic factors indirectly affecting the metabolism or effect of analgesics are liver cell transporter proteins: organic cation transporter (OCT1) (Fukuda 2013 **Level III-2**, n=146); ABCC3 (Venkatasubramanian 2014 **Level III-2**, n=220) and ATP-binding cassette subfamily member B1 (also known as multidrug resistance protein [MDR]1 or p-glycoprotein) (Sadhasivam 2015 **Level III-2**, n=263). The latter affects efflux transport of morphine at the blood-brain barrier and thereby cerebral pharmacokinetics.

Further considerations are the differential risk with genetic differences and varying prevalence of racial/ethnic phenotypes (Anderson 2014 **NR**) and consequent variability in sensitivity to efficacy and adverse effects (Jimenez 2012 **Level III-3**, n=68**;** Fukuda 2013 **Level IV**, n=146**;** Palada 2018 **NR**).

1.7.3.1 | Codeine and CYP2D6

In children and adults receiving codeine for postoperative pain, very low or undetectable plasma morphine levels have been noted in those with poor metaboliser or intermediate metaboliser genotypes, but with variable impact on analgesia (Williams 2002 **Level II**, n=96, JS 3; Poulsen 1998 **Level IV**, n=81; Persson 1995 **Level IV**, n=11).

CYP2D6 genotypes predicting ultrarapid metabolism resulted in about 50% higher plasma morphine and its glucuronides concentrations following oral codeine compared with the extensive metaboliser (Kirchheiner 2007 **Level IV**). Both the impaired renal clearance of these metabolites and genetic background (CYP2D6 ultrarapid metaboliser status) have been implicated in reports of respiratory depression due to codeine in adults and children (Friedrichsdorf 2013 **Level IV**; Kelly 2012 **Level IV**; Stamer 2007b **Level IV**). (See also Sections 4.3.1.3 and 10.4.4.5)

1.7.3.2 | Tramadol and CYP2D6

O-demethylation of tramadol by the enzyme CYP2D6 produces the active metabolite (+)-O-demethyltramadol (M1), which has an affinity for mu-opioid receptors that is approximately 200 times higher than the parent drug (Lai 1996 **BS**). Poor metabolisers have significantly lower plasma concentrations of M1 compared with both homozygous and heterozygous extensive metabolisers (Fliegert 2005 **Level II**, n=26, JS 2; Kirchheiner 2008 **Level III-2**, n=22; Stamer 2003 **Level III-3**, n=300) and experience less analgesia (Stamer 2007a **Level III-3**, n=174; Stamer 2003 **Level III-3**, n=300). As with codeine, impaired renal clearance of metabolites and genetic background (CYP2D6 ultrarapid metaboliser status) have been implicated in cases of respiratory depression after tramadol (Desmeules 1996 **Level II**, n=10, JS 3**;** Stamer 2008 **CR**) (see also Section 4.3.1.3).

1.7.3.3 | Methadone

Genetic polymorphisms in genes coding for methadone-metabolising enzymes, transporter proteins (p-glycoprotein) and mu-opioid receptors may explain part of the observed interindividual variation in the pharmacokinetics and pharmacodynamics of methadone; blood concentrations may vary up to 20-fold for a given dose (Somogyi 2014 **NR**; Li 2008 **NR**).

Methadone is metabolised primarily by CYP2B6 and to a minor extent by CYP3A4 (Kharasch 2017 **NR**; Kapur 2011 **NR**). Differing effects for isomers of methadone have also been reported; genetic variability in CYP2B6 influenced (S)-methadone (less active isomer) and, to a lesser extent, (R)-methadone (more active isomer) plasma concentrations (Somogyi 2014 **NR**). In addition, genetic polymorphisms in *CYP2C19* gene (responsible for a minor role in methadone metabolism) have effects on methadone-maintenance dosing, (R)-methadone/methadone ratio and cardiotoxicity of methadone (prolonged QT interval) (Wang 2013 **NR**) (see also Section 4.3.1.5).

1.7.3.4 | Oxycodone

Oxycodone is metabolised primarily to noroxycodone by CYP3A4 (≈80%) and by CYP2D6 to oxymorphone (Lalovic 2006 **Level IV EH**). The O-demethylated metabolite oxymorphone has up to 40-fold higher affinity for the mu receptor and eight-fold higher potency than oxycodone and represents about 11% of its overall metabolism (Crews 2014 **NR**). Oxymorphone may contribute significantly to the overall analgesic effect of oxycodone in experimental pain (Samer 2010 **EH**); noroxycodone, the major metabolite, is only a weak mu-receptor agonist (Lalovic 2006 **EH**; Coluzzi 2005 **NR**).

The dependence of oxymorphone concentrations on CYP2D6 activity and its high potency explains why oxycodone's pharmacodynamics and pharmacokinetics are dependent on *CYP2D6* polymorphism (Soderberg Lofdal 2013 **NR**), at least in experimental pain (Samer 2010 **EH**).

However, in acute postoperative pain, *CYP2D6* genotype had either no influence on oxycodone requirements (Zwisler 2010 **Level III-2**, n=270) or a small difference in dosage that was not gene-dose related (Stamer 2013 **Level III-2**, n=121). Overall, the data on the association of *CYP2D6* pheno/genotype and oxycodone response in acute pain are unconvincing (Huddart 2018 **NR**) (see also Section 4.3.1.2).

1.7.3.5 | NSAIDs

Wide variability in gene expression and functional polymorphisms in the COX-2 gene (*PTGS2*) may explain part of the interindividual variations in acute pain and the analgesic efficacy of nsNSAIDs and coxibs; this may be useful to predict patient risk and benefit from medicines based on individual genetic variations (Somogyi 2007 **NR**; Lee 2006 **Level III-2**).

NSAIDs such as ibuprofen, diclofenac and celecoxib are metabolised by CYP2C9 (Rollason 2014 **NR**). Between 1 and 3% of Caucasians are poor metabolisers. Homozygous carriers of the *CYP2C9*3* allele may accumulate celecoxib and ibuprofen in blood and tissues and be at risk of increased adverse effects (Kirchheiner 2003 **Level III-3**, n=26; Kirchheiner 2002 **Level IV**; Rollason 2014 **NR**; Stamer 2007b **NR**), but this is unlikely to affect acute pain response.

KEY MESSAGES

1. CYP2D6 polymorphisms affect plasma concentrations of active metabolites of codeine, oxycodone and tramadol with variable effects on analgesic efficacy (**U**) (**Level II**).
2. The mu opioid receptor OPRM1 polymorphism is unlikely to be clinically relevant as a single gene mutation in Caucasian populations and is more likely to be of clinical relevance in Asian populations (**U**) (**Level III-2 SR**).
3. CYP2D6 ultrarapid metabolisers are at increased risk of codeine and tramadol toxicity (**U**) (**Level IV**).

The following tick box represents conclusions based on clinical experience and expert opinion:

☑ Genetic polymorphisms contribute to the wide interindividual variability in plasma concentrations of a given dose of methadone (**U**).

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2

Assessment and measurement of pain and pain treatment

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2.1 | Assessment

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2.2 | Measurement

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2.3 | Outcome measures in acute pain management

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2.0 | Assessment and measurement of pain and pain treatment

Reliable and accurate assessment of acute pain is necessary to ensure safe and effective pain management and to provide effective research outcome data. The assessment and measurement of pain is fundamental to the process of assisting in the diagnosis of the cause of a patient's pain, selecting an appropriate analgesic therapy and evaluating then modifying that therapy according to the individual patient's response. Pain should be assessed within a sociopsychobiomedical model that recognises that physiological, psychological and environmental factors influence the overall pain experience. Likewise, the decision regarding the appropriate intervention following assessment needs to be made with regard to a number of factors, including recent therapy, potential risks and side effects, any management plan for the particular patient and the patient's own preferences. A given pain 'rating' should not automatically trigger a specific intervention without such considerations being undertaken (van Dijk 2012a **Level IV**, n=2,674; van Dijk 2012b **Level IV**, n=10,434). Care must be undertaken with pain assessment to avoid the process of assessment itself acting as a nocebo (see Section 1.3).

2.1 | Assessment

The assessment of acute pain should include a thorough general medical history and physical examination, a specific "pain history" (see Table 2.1) and an evaluation of associated functional impairment (see Section 2.3). In acute pain management, assessment must be undertaken at appropriate frequent intervals. At these times, evaluation of pain intensity, functional impact and adverse effects of treatment must be undertaken and recorded using tools and scales that are consistent, valid and reliable (Scott 2008 **NR**). In addition, pain assessment must lead to changes in management and re-evaluation of the patient to ensure improvements in the quality of care (Gordon 2005 **GL**).

Although not always possible in an acute setting, a complete pain history provides important diagnostic information that may help distinguish different underlying pain states such as nociceptive (somatic and visceral) or neuropathic pain (Victor 2008 **Level III-2**, n=823). Somatic pain may be described as sharp, hot or stinging, is generally well localised and is associated with local and surrounding tenderness. By contrast, visceral pain may be described as dull, cramping or colicky, is often poorly localised and may be associated with tenderness locally or in the area of referred pain, or with symptoms such as nausea, sweating and cardiovascular changes (Scott 2008 **NR**).

While nociceptive pain typically predominates in the acute pain setting, neuropathic pain may also be present (Guastella 2011 **Level IV**, n=54) (see also Section 1.1 and 8.1.4). Features in the pain history that may suggest a diagnosis of neuropathic pain include (Dworkin 2007 **Level III-2**, n=618; Haanpaa 2011 **GL**; Gray 2008 **NR**):

- Clinical circumstances associated with a high risk of nerve injury (eg thoracic or chest wall procedures, amputations or hernia repairs);
- Pain descriptors such as burning, shooting and stabbing;
- The paroxysmal or spontaneous nature of the pain which may have no clear precipitating factors;
- The presence of dysaesthesias (spontaneous or evoked unpleasant abnormal sensations), hyperalgesia (increased response to a normally painful stimulus), allodynia (pain due to a stimulus that does not normally evoke pain such as light touch) or areas of hypoaesthesia;

- Regional autonomic features (changes in colour, temperature and sweating) and phantom phenomena.

The IASP definition of neuropathic pain is "*pain caused by a lesion or disease of the somatosensory system*" (IASP 2019 **GL**; Jensen 2011 **NR**). This has been subdivided into 'central' and 'peripheral' neuropathic pain (IASP 2019 **GL**). Symptoms consistent with neuropathic pain may occur without nerve injury (nociplastic pain) (IASP 2019 **GL**; Kosek 2016 **NR**). To determine if pain is neuropathic, further quantitative sensory testing (QST) may be needed (Haanpaa 2011 **GL**; Garcia-Larrea 2012 **NR**).

It is useful to draw the distinction between the different types of pain because the likely duration of the pain and the response to analgesic strategies may vary. The concept of "*mechanism-based pain diagnosis*" has been promoted (Woolf 2001 **NR**) and although the correlation between symptoms, mechanisms and response to therapy is not fully defined, specific therapy targeted at, for example neuropathic pain, may be of benefit (Gray 2008 **NR**).

Table 2.1 | Fundamentals of a pain history (not necessarily applicable to all settings of acute pain)

1 Site of pain a. primary location: description ± body map diagram b. radiation
2 Circumstances associated with pain onset including details of trauma or surgical procedures
3 Character of pain a. sensory descriptors eg sharp, throbbing, aching (Victor 2008) b. McGill Pain Questionnaire: includes sensory and affective descriptors (Melzack 1987) c. neuropathic pain characteristics (eg NPQ; DN4; LANSS; PainDETECT; ID Pain)
4 Intensity of pain a. at rest b. on movement c. temporal factors i duration ii current pain, during last week, highest and lowest level iii continuous or intermittent d. aggravating or relieving factors
5 Associated symptoms (eg nausea)
6 Effect of pain on activities and sleep a. Functional assessment tools i Acute (eg Functional Activity Scale) ii Recent (eg Brief Pain Inventory – Short Form (BPI-SF))
7 Treatment a. current and previous medications — dose, frequency of use, efficacy, adverse effects b. other treatment eg transcutaneous electrical nerve stimulation c. health professionals consulted

8 Relevant medical history

a. prior or coexisting pain conditions and treatment outcomes
b. prior or coexisting medical conditions

9 Factors influencing the patient's symptomatic treatment

a. belief concerning the causes of pain
b. knowledge, expectations and preferences for pain management
c. expectations of outcome of pain treatment
d. reduction in pain required for patient satisfaction or to resume "reasonable activities"
e. typical coping response for stress or pain, including presence of anxiety or psychiatric disorders (eg depression or psychosis)
f. family/cultural expectations and beliefs about pain, stress and postoperative course

Notes: *NPQ - Neuropathic Pain Questionnaire; DN4 - Douleur Neuropathique en 4; LANSS - Leeds Assessment of Neuropathic Symptoms and Signs.*

2.2 | Measurement

The definition of pain underlies the complexity of its measurement. As described in Chapter 1, pain is an individual and subjective experience modulated by physiological, psychological and environmental factors such as previous events, culture, prognosis, coping strategies, fear and anxiety. Therefore, most measures of pain are based on self-report. These measures lead to sensitive and consistent results if administered properly (Moore 2003 **NR**). Self-report measures may be influenced by mood, sleep disturbance and medications (Scott 2008 **NR**).

In some instances, it may not be possible to obtain reliable self-reports of pain eg patients with impaired consciousness or cognitive impairment, young children (see Section 10.3), elderly patients (see Section 9.2) or where there are failures of communication due to language difficulties, inability to understand the measures, unwillingness to cooperate or severe anxiety. In these circumstances, other methods of pain assessment will be needed.

There are no objective measures of "pain" but associated factors such as hyperalgesia (eg mechanical withdrawal threshold), the stress response (eg plasma cortisol concentrations), behavioural responses (eg facial expression), functional impairment (eg coughing, ambulation) or physiological responses (eg changes in heart rate) may provide additional information. Analgesic requirements (eg patient-controlled opioid doses delivered) are commonly used as *post hoc* measures of pain experienced (Moore 2003 **NR**).

Regular and repeated measurements of pain and its impact should be made to assess ongoing adequacy of analgesic therapy. An appropriate frequency of reassessment will be determined by the duration and severity of the pain, patient needs and response, and the type of medicine or intervention (Gordon 2005 **GL**). Such measurements should incorporate different components of pain, and assessment for analgesic side effects, especially sedation (Macintyre 2011 **NR**). For example, in the postoperative patient this should include assessments of static (rest) and dynamic (on sitting, coughing or moving the affected part) pain. Whereas static measures may relate to the patient's ability to sleep, dynamic measures can provide a simple test for mechanical hyperalgesia and determine whether analgesia is adequate for recovery of function (Breivik 2008 **NR**).

Recording pain intensity as "*the fifth vital sign*" was a program advocated by the USA Department of Veteran Affairs, which aimed to increase awareness and utilisation of pain

assessment (Mularski 2006 **Level III-3**, n=600), with the intention of leading to improved acute pain management (Gould 1992 **Level III-3**, n=2,035). However, an over-reliance on sometimes unrealistic aims (such as "pain free") and an excessive use of opioids is leading to a more moderate and balanced approach to intervention (Levy 2018 **NR**).

Aiming to reduce suffering and improve function rather than targeting 'zero pain' is more in keeping with patient expectations (Lee 2016 **NR**). In 2018, the USA Joint Commission (JCAHO) implemented new and revised pain assessment and management standards for accredited hospitals, emphasising patient engagement, multimodal therapy and improving pain assessment by concentrating more on how pain affects patients' physical function (JCAHO 2017 **GL**).

Uncontrollable or escalating pain should always trigger a reassessment of the diagnosis and consideration of alternatives such as developing surgical or other complications, or the presence of neuropathic pain. Review by an acute pain service (APS) or other specialist group should be considered.

2.2.1 | Unidimensional measures of pain

A number of scales are available that measure either pain intensity or the degree of pain relief following an intervention. Pain relief scales, although less commonly used, have some advantage when comparing the response to different treatments as all patients start with the same baseline "relief" score (zero), whereas they may have differing levels of baseline pain intensity (Breivik 2008 **NR**; Moore 2003 **NR**).

2.2.1.1 | Categorical scales

Categorical scales use words to describe the magnitude of pain or the degree of pain relief (Moore 2003 **NR**). The verbal descriptor scale (VDS) is the most common example (eg using terms such as none, mild, moderate, severe and excruciating or agonising) typically using four or five graded descriptors.

These terms can then be converted to numeric scores (eg 0, 2, 5, 8, 10) for charting and easy comparison over time. There is a good correlation between descriptive verbal categories and visual analogue scales (VAS) (Banos 1989 **Level III-2**, n=212), but the VDS is a less sensitive measure of pain treatment outcome than the VAS (Jensen 2002 **Level IV**, n=247). Pain "relief" may also be graded as none, mild, moderate or complete using a VDS.

Categorical scales have the advantage of being quick and simple and may be useful in the elderly or visually impaired patient and in some children. However, the limited number of choices in categorical compared with numerical scales may make it more difficult to detect differences between treatments (Breivik 2000 **Level III-2**). Other limitations include personal, cultural or linguistic differences in interpretation of the specific words chosen as descriptors both between patients and between patients and their clinicians.

2.2.1.2 | Numerical rating scales

Numerical rating scales (NRS) have both written and verbal forms. Patients rate their pain intensity on the scale of zero to ten where zero represents "no pain" and ten represents "worst pain imaginable". The Verbal NRS (VNRS) is typically administered using a phrase such as: "On a scale of zero to ten, with zero being no pain at all and ten being the worst pain you could imagine, where would you rate the pain you are experiencing right now?". VNRS are often preferred because they are simpler to administer, give consistent results and correlate well with the VAS (Karcioglu 2018 **Level I**, 19 RCTs, n=853; Hjermstad 2011 **Level IV SR**, 54 studies, n unspecified; Safikhani 2018 **NR**). Recall of pain intensity using the VNRS over the previous 24 h was a reasonable

indicator of average pain experienced by the patient during that time (Jensen 2008 **Level III-2**). VNRS may reflect pain interference as well as pain intensity (Thong 2018 **Level III-3**, n=101; Jensen 2017 **Level IV**, n=807).

It is important that scales are consistent, and it is recommended that the "no pain" point be represented as zero rather than one (Scott 2008 **NR**). Pain relief may be measured in the reverse direction with zero representing "no relief" to ten representing "complete relief". A visual form of the 11-point NRS with tick marks on a line or boxes with numbers may also be used (Breivik 2008 **NR**). Although NRS are widely used, some patients have difficulty representing their pain in numerical terms and are better suited to a categorical scale. A value of four or more is often used as a threshold to guide clinical intervention (Hartrick 2003 **Level IV**, n=222).

2.2.1.3 | Visual analogue scales

Visual analogue scales (VAS) consist of a 100 mm horizontal line with verbal anchors at both ends and no tick marks. The patient is asked to mark the line and the "score" is the distance in millimetres from the left side of the scale to the mark. VAS are the most commonly used scales for rating pain intensity in research, with the words "no pain" at the left end and "worst pain imaginable" at the right. Pictorial versions also exist. VAS can also be used to measure other aspects of the pain experience (eg affective components, patient satisfaction, adverse effects).

Assessment of pain immediately after surgery can be more difficult and lead to greater interpatient variability in pain scores because of transient anaesthetic-related cognitive impairment and decreases in visual acuity. A "pain meter" (PAULA), which used five coloured emoticon faces on the front of a ruler and corresponding VAS scores on the back and allowed patients to move a slider to mark the pain they were experiencing, resulted in less variance than pain scores obtained from a standard VAS (Machata 2009 **Level III-2**, n=48).

VAS ratings ≥70 mm are indicative of "severe pain" (Aubrun 2003 **Level IV**, n=3,045; Jensen 2003 **Level IV**, n=248) and 0–5 mm "no pain", 5–44 mm "mild pain" and 45–69 "moderate pain" (Aubrun 2003 **Level IV**, n=3,045). A reduction in pain intensity by 30–35% has been rated as clinically meaningful by patients with postoperative pain (Cepeda 2003 **Level IV**, n=700; Jensen 2003 **Level IV**, n=248), acute pain in the emergency department (ED) (Lee 2003 **Level IV**, n=143), breakthrough cancer pain (Farrar 2000 **Level IV**, n=1,268 [episodes of breakthrough pain]) and chronic pain (Farrar 2001 **Level IV**, n=2,724).

These scales have the advantage of being simple and quick to use, allow for a wide choice of ratings and avoid imprecise descriptive terms (Scott 2008 **NR**). However, the scales require concentration and coordination, need physical devices, are unsuitable for children aged <5 y and may be unsuitable in up to 26% of adult patients (Cook 1999 **NR**).

The VAS has been shown to be a linear scale for patients with postoperative pain of mild to moderate intensity (Myles 1999 **Level IV**, n=52) and severe pain (Myles 2005 **Level IV**, n=22). Therefore, results are equally distributed across the scale, such that the difference in pain between each successive increment is equal.

2.2.2 | Functional impact of acute pain

Analgesia should be titrated to achieve both decreased pain intensity and the ability to undertake appropriate functional activity (Breivik 2008 **NR**). This will enable analgesia to optimise recovery. Most tools for measuring the functional impact of pain are based on chronic pain assessment and therefore are not routinely applicable to the acute pain environment.

Measurement of pain intensity scores on movement or with coughing is a useful guide; however, this reflects the subjective pain experience and not the capacity to undertake the

specific activity. The Functional Activity Scale (FAS) score is a simple three-level ranked categorical score designed to be applied at the point of care (Scott 2008 **NR**). Its fundamental purpose is to assess whether the patient can undertake appropriate activity at their current level of pain control and to act as a trigger for intervention should this not be the case. The patient is asked to perform the activity or is taken through the activity in the case of structured physiotherapy (eg joint mobilisation) or nurse-assisted care (eg ambulation, turned in bed). The ability to complete the activity is then assessed using the FAS as:

A — no limitation	the patient is able to undertake the activity without limitation due to pain (pain intensity score is typically zero to three);
B — mild limitation	the patient is able to undertake the activity but experiences moderate to severe pain (pain intensity score is typically four to ten); and
C — significant limitation	the patient is unable to complete the activity due to pain, or pain treatment-related adverse effects, independent of pain intensity scores.

This score is then used to track effectiveness of analgesia on function and trigger interventions if required. Disadvantages of the FAS score are that it has not been independently validated and clinical staff need to be educated in its application.

A four-level scale (no interference, interference with some vs most activities vs unable to do any activity) has been evaluated against NRS in a pilot study and identified a correlation with NRS in cognitively intact but not impaired patients (Halm 2019 **Level III-2**, n=68).

2.2.3 | Multidimensional measures of pain

Rather than assessing only pain intensity, multidimensional tools provide further information about the characteristics of the pain and its impact on the individual. Examples include the Brief Pain Inventory (BPI), which assesses pain intensity and associated disability (Daut 1983 **Level IV**), and the McGill Pain Questionnaire (MPQ), which assesses the sensory, affective and evaluative dimensions of pain (Melzack 1987 **NR**). The MPQ also exists in a 15-item short-form (SF-MPQ), which is well validated and has a VAS item for pain intensity and a VRS for rating the overall pain experience. The role of the McGill Pain questionnaire (and its Short Form variants) has been reviewed; with a conclusion that, while still useful, it provides little information regarding mechanism, nor the broader social and functional impact of the pain and so should not be used as a single measure to guide research or therapy (Main 2016 **NR**) . The BPI also exists in a short form (BPI-SF and -SF2) which includes functional impact of the pain over the previous 24 h (Dworkin 2009 **Level IV**, n=1,008).

2.2.3.1 | Neuropathic Pain

Neuropathic pain is not easily identified using unidimensional tools such as the VAS (Haanpaa 2011 **GL**). Specific scales have been developed that identify (and/or quantify) descriptive factors specific for neuropathic pain (Dworkin 2007 **Level III-2**, n=618; Bouhassira 2005 **Level III-2**, n=160; Bouhassira 2004 **Level IV**, n=176; Cruccu 2004 **GL**; Freynhagen 2006 **NR**) and may also include sensory examination (Bouhassira 2005 **Level III-2**, n=160; Cruccu 2004 **GL**) and allow evaluation of response to treatment (Bouhassira 2004 **Level IV**, n=176).

Screening tools in common use for identifying neuropathic pain include:

- Leeds Assessment of Neuropathic Symptoms and Signs (LANSS) has five symptom items and two clinical assessment items — a subjective-only form also exists (Bennett 2001 **Level III-3**, n=100);
- Douleur Neuropathique en 4 (DN4) has ten items — seven symptomatic and three from clinical examination (Bouhassira 2005 **Level III-3**, n=160);
- Pain DETECT has nine self-reported items that do not require a clinical examination and gives a likelihood scoring for neuropathic pain (Freynhagen 2006 **NR**); its use has been reviewed in over 300,000 patients (Freynhagen 2016 **NR**)
- Neuropathic Pain Questionnaire (NPQ) comprises twelve items and can be self-reported - a three-item short-form also exists (Krause 2003 **Level III-2**, n=528; Backonja 2003 **NR**);
- ID Pain has six self-reported items (Portenoy 2006 **Level IV**, n=586).

These scales have similar specificity and sensitivity (except for the ID Pain, which has lower values than the others), have mostly been validated and are often available in validated translations in many languages (Haanpaa 2011 **GL**)**.** In assessing the criterion validity and reliability of the above screening questionnaires, the DN4 and NPQ were found to be most suitable for clinical use overall, noting that cross-cultural adaptations had less evidence than the original versions (Mathieson 2015 **Level IV SR**, 37 studies, n unspecified).

Clinical questionnaires for neuropathic pain show that subjective pain assessments are essential for diagnosis and assessment of neuropathic pain, with screening questionnaires being effective at leading to more formal diagnosis (aided by assessment questionnaires), and also are valuable in research (Attal 2018 **NR**).

2.2.3.2 | Global scales and satisfaction

Global scales are designed to measure the effectiveness of overall treatment (see Section 2.3.1). They are more suited to outcome evaluation at the end of treatment than to modifying treatment in the acute stage (Moore 2003 **NR**). Questions such as "*How effective do you think the treatment was?*" recognise that unimodal measures of pain intensity cannot adequately represent all aspects of pain perception.

Satisfaction is often used as a global indicator of outcome; however, patients may report high levels of satisfaction even if they have moderate to severe acute pain (Svensson 2001 **Level IV**, n=191). Satisfaction may also be influenced by preoperative expectations of pain, effectiveness of pain relief, the patient–provider relationship (eg communication by medical and nursing staff), interference with function due to pain and number of opioid-related adverse effects (Jensen 2004 **Level IV**, n=191; Carlson 2003 **Level IV**, n=787; Svensson 2001 **Level IV**, n=191). Although complete absence of pain is not required for patients to report high levels of satisfaction, moderate pain (VAS >50/100) has been associated with dissatisfaction (Jensen 2005 **Level III-2**, n=207).

2.2.4 | Patients with special needs

Validated tools are available for measuring pain in neonates, infants and children but must be both age and developmentally appropriate (see Section 10.3). These include behavioural assessments, pictorial scales (eg faces) and response to treatment. Adult patients who have difficulty communicating their pain (eg patients with cognitive impairment or who are critically unwell in the ED or intensive care unit [ICU]) require special attention as do patients whose language or cultural background differs significantly from that of their health care team. Communication aids and behavioural scales such as the modified Faces, Legs, Activity, Cry and

Consolability (FLACC) scale (Erdek 2004 **Level III-3**) can be particularly useful in these situations (see Section 9.2.3).

NRS are considered the best tool for measurement of pain intensity for adult ICU patients who may be non-verbal, sedated or ventilated. If they are not feasible, then the Behavioural Pain Scale (BPS) or Critical-Care Pain Observation Tool (CPOT) should be used (Varndell 2017 **Level III-3 SR**, 26 studies, n unspecified; Barr 2013 **GL**; Azevedo-Santos 2018 **NR**; Gelinas 2013 **NR**). The CPOT has been validated in neurosurgical patients (Echegaray-Benites 2014 **Level III-3**, n=43) and in different countries (Rijkenberg 2015 **Level III-3**, n=68; Li 2014 **Level III-3**, n=63). The CPOT appears to be more specific for pain than the BPS (Rijkenberg 2015 **Level III-3**, n=68).

In patients with dementia, similar challenges often require the use of non-verbal tools. Overall, in assessing reviews of multiple tools there is limited evidence about the reliability, validity and clinical utility of any specific tool (Lichtner 2014 **Level IV SR**, 23 reviews [28 tools]).

A systematic review of the effect of the use of pain assessment tools in critically ill patients on patient outcomes concluded that it improves pain management, but evidence was too heterogeneous to draw firm conclusions regarding outcomes such as length of mechanical ventilation or ICU stay (Georgiou 2015 **SR Level III-2**, 10 studies, n unspecified)

Surveys in the UK and Netherlands show that pain assessment tools were underutilised in many ICUs (Kemp 2017 **Level IV**, n=750 [patients assessed by 362 UK physicians]; van der Woude 2016 **Level IV**, n=107 [adult ICUs in the Netherlands]) (see also Section 8.10).

KEY MESSAGES

1. There is good correlation between the visual analogue and verbal numerical rating scales (**S**) (**Level I**).
2. Regular assessment of pain leads to improved acute pain management (**U**) (**Level III-3**).
3. Appropriate assessments (including screening tools) are required to determine the presence of neuropathic pain (**N**) (**Level III-2**).

The following tick boxes represent conclusions based on clinical experience and expert opinion:

- ☑ Functional outcomes rather than pain scores alone should be used to guide acute pain management, including non-pharmacological approaches (**N**).
- ☑ Self-reporting of pain should be used whenever appropriate as pain is by definition a subjective experience (**U**).
- ☑ The pain measurement tool chosen should be appropriate to the individual patient and the clinical context (eg intensive care, ward, community). Developmental, cognitive, emotional, language and cultural factors should be considered (**U**).
- ☑ Scoring should incorporate different components of pain including the functional capacity of the patient. In the postoperative patient, this should include static (rest) and dynamic (eg pain on sitting, coughing) pain (**U**).
- ☑ Uncontrolled or unexpected pain requires a reassessment of the diagnosis and consideration of alternative causes for the pain (eg new surgical/ medical diagnosis, neuropathic pain) (**U**).

2.3 | Outcome measures in acute pain management

What follows is a brief guide to some of the outcome measures used particularly in the acute pain literature. A comprehensive review is beyond the scope of this document and more detail may be found elsewhere (Breivik 2008 **NR**). Concerns have been raised regarding trial design limitations resulting in type II errors (failure to identify a difference when one truly exists) and recommendations have been made for the design of chronic pain RCTs that include patient numbers, study site and outcome measurements to reduce this problem (Dworkin 2012 **GL**). Similar issues are of relevance to studies in acute pain interventions.

2.3.1 | Outcome measures

2.3.1.1 | Pain

The aim of many clinical trials is to determine whether a medicine or intervention provides adequate pain relief for the majority of participants or is equivalent or noninferior to an existing accepted treatment. This can be achieved by repeated single measures at fixed time points, which may encompass only a proportion of the total illness. When comparison is made with a placebo, a statistically significant result can be achieved with a relatively small number of patients (eg n=40) (Collins 2001 **Level I**, 11 SRs [151 RCTs], n unspecified). The primary outcome is chosen by the researcher and may not be of direct importance to the individual patient, particularly if it relates to only a proportion of the total time he/she was in pain. It is also important to consider that statistically significant differences in pain scores may not reflect clinically significant differences, although these are harder to define (see above).

Data derived from categorical and VAS of pain intensity or relief produce a range of summary outcomes that can be used to assess (Moore 2003 **NR**):

- the degree of analgesic effect:
  - difference between the baseline and post-intervention score of pain intensity or pain relief (summed pain intensity difference [SPID]);
  - the area under the time-analgesic effect curve for a given time (total pain relief [TOTPAR]);
  - dose of rescue analgesic consumption required in a given time period (eg PCA use);
- the time to analgesic effect:
  - the time to onset of analgesic effect;
  - time to maximum reduction in pain intensity or to peak relief;
- the duration of effect:
  - time for pain to return to at least 50% of baseline;
  - time for pain intensity to return to baseline or for pain relief to fall to zero; and
  - time to re-medication/rescue analgesia.

A widely used method of describing the effectiveness of an analgesic intervention is the number needed to treat (NNT). In this setting it is commonly defined as the number of patients that need to be treated to achieve at least 50% pain relief (eg at least 50% maximum TOTPAR) in one patient compared with a placebo over a 4–6 h treatment period (Moore 2003 **NR**). Analysis at other cut-off points (30–70% max TOTPAR) has shown the same relative efficacy of different treatments (McQuay 2003 **NR**).

In acute pain research, using TOTPAR to assess pain relief may be more sensitive to treatment effects than SPID which is assessing intensity (Singla 2015 **Level I** [PRISMA], 45 RCTs, n unspecified).

The validity of this approach as a true method of comparison may be questioned as there is no standardisation of the acute pain model or patient and only single doses of the analgesic agents are used. However, it may sometimes be reasonable to extrapolate estimates of analgesic efficacy from one pain model to another (Barden 2004 **Level I**, 160 RCTs, n=14,410).

The use of supplemental analgesic consumption as an outcome measure has been questioned in situations where pain scores are not similar (McQuay 2008 **Level I**, 18 RCTs, n=1,217).

2.3.1.2 | Physical functioning

Measures of physical functioning quantify many aspects of a patient's life including their ability to sleep, eat, think, deep breathe, cough, mobilise, perform activities of self-care and daily living, undertake their usual vocation and to enjoy leisure activities and sport (Williams 1999 **NR**). In acute pain, this may be measured by pain intensity scores with movement or other functional activity scores (see above).

Global or multidimensional measures of function attempt to combine various abilities or disabilities to derive a summary measure. Scales that employ a large number of items might be comprehensive but risk patient exhaustion or error, while scales with fewer items might be patient friendly but risk becoming insensitive to state or change (Williams 1999 **NR**). These scales have been used in some studies of acute spinal pain and cancer-related pain:

- *Disability scales* — generic scales include the Short Form 36 of Medical Outcomes Study (SF-36), the Sickness Impact Profile (SIP) and Roland & Morris Short SIP (Williams 1999 **NR**);
- *Quality of life (QOL) measures* — these measures are not widely used in acute pain studies, but have relevance for chronic or cancer-related pain (Higginson 1997 **NR**).

Disease-specific measures quantify the impact of a specific pain problem on function and can be used to track changes after an intervention (eg ability to cough after thoracotomy, ability to lift a baby after Caesarean section) (Garratt 2001 **Level IV**, n=187). Generic measures facilitate comparisons among the functional limitations of different conditions and treatments and may have advantages for audit of an APS that includes patients with a range of conditions (Patrick 1989 **NR**).

2.3.1.3 | Emotional functioning

Acute pain is an unpleasant sensory and emotional experience. The unpleasantness of the experience and its meaning for the individual may have short term (anxiety, depression, irritability) and long term (lost confidence or self-efficacy or post-traumatic stress disorder) consequences for the individual's emotional functioning.

2.3.1.4 | Adverse effects

In trials of efficacy, adverse effects are usually considered to be of secondary importance and inadequate reporting has been found in as many as half of randomised trials reviewed (Ioannidis 2001 **Level I**, 192 RCTs, n=130,074; Edwards 1999 **Level I**, 52 RCTs, n unspecified). If adverse effects are sufficiently common (eg nausea with opioids), they may be quantifiable in trials of efficacy and specifically measured using dichotomous (present or absent), categorical (none, mild, moderate, severe) or interval (analogue or Likert) scales. Analogous to NNTs, the number needed to harm (NNH) may be used to describe the incidence of adverse effects.

Most efficacy trials will have inadequate power to detect rare adverse effects and therefore they are also absent from systematic reviews. Large clinical trials specifically designed to detect adverse effects are required (eg the Vioxx Gastrointestinal Outcomes Research [VIGOR] study

investigated gastrointestinal toxicity of NSAIDs) (Bombardier 2000 **Level II**, n=8,076, JS 5). Case reports and post-marketing epidemiological research and surveillance (eg the Australian Adverse Drug Reactions Advisory Committee) remain important for detection of delayed effects occurring after the initial trial period. Results from comprehensive large prospective audits and database reviews have provided a sufficiently reliable denominator for incidence and risk factor evaluation in rare but serious adverse effects in acute pain management (Wijeysundera 2008b **Level IV**, n=259,037; Cameron 2007 **Level IV**, n=8,210; Wijeysundera 2008a **NR**).

Besides the adverse effects attributed to acute pain management interventions, another area of interest is whether the adverse effects of trauma and surgery might be prevented by effective acute pain management. Outcomes such as mortality, morbidity due to derangements of the cardiovascular, respiratory, gastrointestinal and coagulation systems and progression to chronic pain have also been reported (see Chapter 1).

KEY MESSAGE

1. Assessment of pain relief (with total pain relief [TOTPAR]) may be more sensitive to treatment effects than assessment of intensity (with summed pain intensity difference [SPID]) (**N**) (**Level I** [PRISMA]).

The following tick box represents conclusions based on clinical experience and expert opinion:

☑ Multiple outcome measures are required to adequately capture the complexity of the pain experience and how it may be modified by pain management interventions (**U**).

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3

Provision of safe and effective acute pain management

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3.1 | Education

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3.2 | Organisational requirements

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3.3 | Economic considerations in acute pain management

Contributor: Dr Melanie Zeppel

3.1 | Education

3.1.1 | Patients

Patients and carers who learn about assessment of pain, the risks and adverse effects of treatment, and who are informed that they should communicate both the effectiveness of treatment and any adverse effects, will have greater control over the quality of their pain relief. Information on treatment options, goals, likely benefits and probability of success should be available; this advice is found in most published recommendations and guidelines. Despite this, many patients still feel uninformed about pain, particularly in the perioperative period (Macintyre 2015 **NR**; Counsell 2008 **NR**). A national survey of patients who were undergoing total hip arthroplasty (THA) revealed that 70% did not believe they had been given adequate information about their procedure (including pain relief) and those who had higher levels of education perceived a larger deficit (Johansson Stark 2014 **Level IV**, n=320). A survey of health professionals acknowledged that perioperative pain management knowledge and other aspects of colonic surgery were deficient in patients undergoing the procedure (Sjostedt 2011 **Level IV**, n=49 [health care professionals]).

3.1.1.1 | General principles

A systematic review of systematic reviews (using the AMSTAR 1 tool) pertaining to methods of patient education, in general, concludes that teaching strategies that increase patient knowledge decrease anxiety and improved patient satisfaction (Friedman 2011 **Level IV SR**, 23 systematic reviews & meta-analyses, n unspecified). This comprised those using computer technology, audio and videotapes, written materials and demonstrations. While only one systematic review addressed pain management, the more general results are relevant to this topic. Educational strategies were better when combined, structured, culturally appropriate and patient-specific, rather than generic or *ad hoc*. Verbal teaching and discussions were found to be the least effective strategies. Web-based teaching improved patient knowledge, anxiety, and satisfaction, as did audiotapes, videotapes, written materials and lectures, all of which were more effective than verbal teaching and discussions. Demonstrations had the highest effect of any of the teaching strategies evaluated. Multiple teaching strategies are better than single ones, with one systematic review finding that 67% of patients who received patient education using several different strategies had better outcomes than those who received routine care.

Patient education regarding the procedure or recovery provided a small improvement in postoperative pain (SMD -0.21; 95%CI -0.02 to -0.39) (12 RCTs, n=1,242), pre-operative anxiety (SMD -0.27; 95%CI -0.10 to -0.44) (12 RCTs, n=1,260) and postoperative anxiety (SMD -0.26; 95%CI -0.08 to -0.43) (11 RCTs, n=921), but had no impact on analgesic use (SMD -0.06; 95%CI 0.13 to -0.24) (10 RCTs, n=860) (Szeverenyi 2018 **Level I** [PRISMA], 62 RCTs, n=4,908). Pain psychoeducation undertaken before surgery (pre-emptive) or throughout the perioperative period (preventive) is an underutilised component of multimodal analgesia with data showing reduced pain intensity, analgesic use, LOS, return to ED, patient anxiety and possibly chronic postsurgical pain (Horn 2020 **Level IV SR**, 33 studies, n unspecified).

There is evidence that written information is better than verbal education. Written information resulted in more satisfaction, lower pain scores and lower analgesic use after gynaecological cancer surgery (Angioli 2014 **Level II**, n=190, JS 2). Knowledge was lower in those given non-standardised verbal information vs those given written information, including information regarding pain management, at the time of preoperative anaesthetic review

(Binhas 2008 **Level III-3**, n=180). Patients receiving education favoured the combination of verbal plus written information over verbal information alone, as it allowed them to refresh their memory (Andersson 2015 **Level III-1**, n=18). A study of emergency department patients found that the provision of patient information leaflets improved doctor-patient communication and patient satisfaction levels and reduced rates of reattendance for the same condition, as well as the number of drug prescriptions by doctors (Sustersic 2019 **Level III-2**, n=324). This aligns with the findings of a previous systematic review of systematic reviews which determined that patient information leaflets improve patient knowledge, satisfaction and adherence to treatment recommendations (Sustersic 2017 **Level IV SR**, 24 SRs, n unspecified).

A systematic review of studies of postoperative education (conducted between 1986 and 2007) which aimed at improvement in self-knowledge and symptom experience (including pain) evaluated the best type and amount of postoperative education (Fredericks 2010 **Level III-3 SR**, 58 studies, n=5,271). All types of surgery were included with 46% assessing cardiac surgery, 26% general surgery, 4% abdominal/ colorectal surgery and 5% hip and knee surgery. Individualised education with the patient having input into their educational requirements, use of combined media for delivery, provision of one-on-one education and multiple sessions were associated with improvement in educational and/or health outcomes. Individuals <50 y and those with higher educational level showed the highest benefit.

3.1.1.2 | Effects in specific postoperative settings

PCA use

Structured vs brief patient education prior to PCA use resulted in improved patient knowledge of PCA (Yankova 2008 **Level III-1 SR**, 5 RCTs & 1 study, n=592). No studies demonstrated that structured education about PCA improved postoperative pain scores.

Total joint arthroplasty

Three overlapping reviews draw similar conclusions as to the limited effect of preoperative patient education in addition to standard care on pre and postoperative outcomes after total hip and knee arthroplasty (THA/TKA) (McDonald 2014 **Level I** [Cochrane], 18 RCTs, n=1,463; Aydin 2015 **Level I** [PRISMA], 12 RCTS, n=1,567; Louw 2013 **Level III-1 SR**, 12 RCTs & 1 study, n=1,021) (10 & 8 RCTs overlap). The included RCTs are heterogeneous in terms of the patient population and teaching methods applied. There is some reduction in preoperative anxiety for THR (MD -5.10/60; 95%CI -7.17 to -3.03) (4 RCTs, n=333) and LOS for TKR (MD -1.86 d; 95% CI -3.40 to -0.32) (2 RCTs, n=183); but little or no evidence for any other outcomes including postoperative anxiety, mobility, pain, function or postoperative complications.

Preoperative education does not improve postoperative pain scores after either THA (up to 3 mth after surgery) or TKA (up to 12 mth after surgery) (McDonald 2014 **Level I** [Cochrane], 18 RCTs, n=1,463). However, education has a low risk of adverse effects, and may be beneficial for certain patients with depression, anxiety or unrealistic expectations about their surgery.

Interviews with focus groups of patients following THA and TKA identified patient requests for increased education on pain management in the postoperative period (Kennedy 2017 **Level IV**, n=32). Patients reported that they would have preferred more information regarding expected levels of postoperative pain, the purpose, administration and expected side effects of analgesic medication, and specific weaning instructions. Among the patients interviewed, there was a wide range of preference for content, mode of delivery (web-based or traditional methods), and timing of education. It is acknowledged in the literature that a more personalised education program that allows patients to ask questions may translate to improved outcomes following preoperative education (Aydin 2015 **Level I** [PRISMA], 12 RCTs, n=1,567). However, a randomised controlled trial that involved personalised preoperative information sessions prior

to TKA did not demonstrate any difference in pain at any time point vs a group receiving standard care (Wilson 2016 **Level II**, n=143, JS 4). The authors suggest that this may reflect a requirement for increased education for healthcare providers as well as patients in order to achieve significant benefits in postoperative analgesia. Online resources available for patients to read about pain control after TKA are generally of limited utility, with more than 90% of websites containing information directed at patients written in language that exceeds average reading levels (Schairer 2017 **NR**). This has the potential to limit patient understanding of postoperative pain management and highlights an opportunity for orthopaedic, anaesthetist and pain medicine specialists to develop and encourage access to appropriate patient-focused online resources.

Cardiac surgery

Preoperative education reduces anxiety (6 RCTs, n=829) in patients undergoing mixed types of cardiac surgery, but there was limited evidence for any effect on pain (4 RCTs, n=704) (Ramesh 2017 **Level I** [PRISMA], 14 RCTs, n=2,071). This is consistent with a preceding systematic review which found no effect of preoperative education on pain levels or other outcome measures in patients after coronary artery bypass graft (CABG) surgery (Guo 2015 **Level I**, 6 RCTs, n=1,406 [2 RCTs pain, n=762]) (2 RCTs overlap).

Spinal surgery

Patients receiving neuroscience education (including a conversation with a physical therapist for 30 min plus a neuroscience booklet) prior to lumbar spinal surgery for radicular pain had the same pain levels and function 12 mth following surgery vs controls who received routine care (Louw 2014 **Level II**, n=67, JS 3). However, those in the experimental group exhibited 45% less healthcare expenditure in the 12 mth following surgery and viewed their surgical experience more positively. At 3 y follow-up, this reduction in health care costs was maintained; the group that received preoperative neuroscience education spent 37% less on medical expenses (Louw 2016 **Level III-2**, n=50). The authors postulated this could be a result of the educational emphasis on neurobiology and neurophysiology (central and peripheral sensitisation, facilitation and inhibition) as opposed to the pathoanatomical explanation previously utilised for education in patients undergoing lumbar spinal surgery.

A preoperative educational intervention (provision of a detailed information booklet and 30 to 40 min guided explanation by a nurse) vs control in spinal surgery lowered preoperative anxiety and postoperative pain scores (6.1/10 to 5.3/10) (Lee 2018 **Level II**, n=86, JS 3) (see also Section 7.1.1).

Other types of surgery

The provision of a detailed information sheet to parents after tonsillectomy in children provided postoperative benefit (Bailey 2015 **Level II**, n=60, JS 5). The information sheet contained specific instructions regarding the dose and timing of oxycodone and resulted in higher parental satisfaction and knowledge and some improvements in pain scores up to POD 7 vs standard verbal instructions.

After cosmetic day-surgery procedures, preoperative education reduced postoperative opioid requirements and pain intensity and duration (Sugai 2013 **Level II**, n=135, JS 2). Preoperative written and verbal education (two sessions by the same surgeon) on the adverse and negative effects of opioids resulted in 90% of the treatment group declining an opioid prescription vs 100% filling their opioid prescription in the control group.

Patients undergoing modified radical mastectomy, who had received a specific 20 min education about their analgesia management and medications, reported less pain and mobilised earlier than those who had not received the education (Sayin 2012 **Level III-1**, n=84).

3.1.1.3 | Effects in other acute pain settings

The effect of patient education has also been studied in patients with acute non-surgical pain.

Education programs, depending on their approach, may not be effective in the prevention and treatment of neck pain or low back pain in a widely heterogeneous patient and community groups (including children and at-risk workers) (Ainpradub 2016 **Level I**, 15 RCTS, n=10,488); these findings were cautioned against in a letter (Hurley 2016), because they were based excessively on a "biomedical education" approach which emphasises "*protecting the injured back*". This type of education has now been supplanted by the effective "biopsychosocial education" approach, which in contrast, emphasises the robustness of the back, and is in agreement with pain physiology. Another systematic review shows a beneficial outcome from patient education in the management of acute lumbar back pain when a "biopsychosocial/neuroscience" education-based approach is used (Traeger 2015 **Level I** [PRISMA], 14 RCTs, n=4,872). In this review, the outcomes were "*reassurance*" (which was a composite of anxiety, fear, worry, distress) and healthcare utilisation (number of primary care visits for LBP over 12 mth). The effect size for a benefit on reassurance at 4 mth was SMD -0.21 (95%CI -0.36 to -0.07), and the effect on reduction in healthcare utilisation was SMD -0.14 (95%CI -0.28 to 0.00).

Regarding acute back pain, there is moderate to high quality evidence that patient education provided by primary care practitioners can reassure patients for up to 12 mth, and lead to reductions in low back pain related healthcare utilisation, with a NNT of 17 to prevent one subsequent primary care visit (Traeger 2015 **Level I** [PRISMA], 14 RCTs, n=4,872). Patient reassurance is heightened with education provided by a physician rather than by other health professionals. Conversely, a subsequent RCT found that the addition of two sessions (1 h each) of patient education (focusing on biopsychosocial contributors to pain as well as self-management techniques) to standard practice did not improve pain intensity or disability vs a placebo educational intervention (Traeger 2019 **Level II**, n=202, JS 4).

An earlier systematic review of pain education strategies for neck pain was unable to find good evidence for the benefit of patient education, apart from one RCT (n=348) showing that an educational video of advice about being active was more beneficial in the medium term (Gross 2012 **Level I** [Cochrane], 15 RCTs, n=5,305) (3 RCTs overlap with Ainpradub 2016). After acute whiplash injury specifically, short educational interventions reduce pain and disability and enhance recovery and mobility (Meeus 2012 **Level I** [PRISMA], 10 RCTs, n=1,594) (2 RCTs overlap). Educational interventions for patients with whiplash (neurophysiology content) have demonstrated improvements in both pain behaviours and pain threshold (Rebbeck 2017 **NR**). It is also recommended that patients receive advice regarding the course of recovery and education about coping strategies and unhelpful beliefs.

Antenatal education regarding epidural analgesia led to more primigravid women indicating that they would request epidural analgesia for pain relief in labour (Alakeely 2018 **Level III-3**, n=81). Antenatal teaching about postnatal nipple pain and trauma resulted in reduced nipple pain and improved breastfeeding (Duffy 1997 **Level II**, n=70, JS 3).

An emergency department nurse-delivered opioid education intervention (verbal and written communication strategies) increased patient understanding of appropriate use of discharge opioids (Waszak 2018 **Level III-3**). However, this relied on nurses' ability to take extra steps in their usual discharge routine, including printing information sheets and conducting verbal 'teach-back' sessions.

3.1.1.4 | Web-based education for acute pain management

The internet and mobile devices are being increasingly used for pain education. There are few published studies that have evaluated these types of interventions for patients with acute pain. A systematic review of web-based pain education included only two RCTs that evaluated educational websites with information on acute postoperative pain (Bender 2011 **Level I**, 17 RCTs, n=2,503): one aimed to prepare adolescents for tonsillectomy and demonstrated improvements in satisfaction and knowledge, but no difference in pain scores or anxiety (O'Conner-Von 2008 **Level II**, n=69, JS 3); the other prepared adults for postoperative self-care after outpatient surgical procedures and found reductions in postoperative pain intensity the night and day afterwards (Goldsmith 1999 **Level II**, n=195 [only 80 at follow-up], JS 2). An innovative web technology used an assessment process to individualise the content of education and use persuasive educational techniques to effect changes in response to pain after cardiac surgery (Martorella 2012 **Level II**, n=60, JS 3). The 30 min web-based intervention used a virtual nurse to guide the patient, followed by two face-to-face 5-min booster sessions. In the experimental group, patients did not experience less intense pain, but they reported significantly less pain interference when breathing/coughing and used more analgesia. A web-based intervention program providing daily postural advice and exercise instructions with daily email reminders and personalised log over 9 mth to office workers with sub-acute low-back pain (of 6 wk duration) was effective in improving quality of life, behaviour change, function and pain vs standard care (del Pozo-Cruz 2013 **Level II**, n=100, JS 2).

A systematic review found no additional benefit for tailored vs standardised web-based patient education for patients with chronic pain (Martorella 2017 **Level I** [PRISMA], 16 RCTs [15 chronic], n=4,304).

The readability of web-based educational materials regarding epidural analgesia was well above the recommended reading level for patient education, which may limit the ability of patients to make informed choices (Patel 2015 **Level IV**, n=101 [educational materials on 128 websites in English and Spanish]). An assessment of online patient education material about regional anaesthesia produced by USA teaching hospitals found the mean (SD) Flesch-Kincaid Grade Level for patient education material was high at hospitals offering and not offering regional fellowship teaching programs: 13.8 (2.9) vs 10.8 (2.0) ie well above the recommended sixth-grade level (Kumar 2017 **Level III-3**, n=32 [websites]). Similarly, a review of patient education material about safe opioid use after surgery found the online information from the websites of selected North American academic medical centres to have the reading grade level 7.84 (SD 1.98) (Kumar 2019 **Level III-3**, n=38 [websites]).

3.1.2 | Staff

Appropriate education of medical and nursing staff is essential if more sophisticated forms of analgesia (eg PCA or epidural analgesia) are to be managed safely and effectively and if better results are to be gained from conventional methods of pain relief (Macintyre 2015 **NR**). Medical and health professional staff education may take several forms; the evidence for any benefit for the best educational technique is varied and inconsistent. Education may also include organisational approaches, the provision of guidelines and accompanying changes to practice to enable good outcomes.

3.1.2.1 | Nursing staff

Improvements in nursing knowledge and ability to manage epidural analgesia followed the reintroduction of an epidural-education program using an audit/guideline/problem-based teaching approach, accompanied by practical assessments (Richardson 2001 **Level III-3**). A more

recent simulation-based educational workshop (4 h) relating to epidural assessment improved knowledge and confidence of participating nursing staff and increased the number of correct procedures performed in a post-workshop assessment (Sawhney 2018 **Level III-3**). However, translation to practice changes in the clinical environment was not assessed, and educational workshops of this type require significant time and monetary investments. Pain documentation in surgical wards (Ravaud 2004 **Level III-1**, n=2,278; Karlsten 2005 **Level III-2**) and intensive care units (ICUs) (Erdek 2004 **Level III-3**; Arbour 2003 **Level IV**) was also improved by education programs. A quality-improvement system, which included education and guidelines as well as systems to improve practice, resulted in significant improvements in postoperative pain, nausea, vomiting and fatigue (Usichenko 2013 **Level III-3**, n=520). Implementation of a quality-improvement program led to improvements in nurses' knowledge and assessment of pain using pain-rating scales; however, while the number of patients assessed increased, there was no improvement in pain relief (Hansson 2006 **Level III-2**).

There are possible reasons why education programs may not always be successful in improving nursing staff knowledge or attitudes (Dahlman 1999 **Level III-3**) or pain relief (Knoblauch 1999 **Level IV**). In rural and remote settings, distance and professional isolation could affect the ability of healthcare staff to receive up-to-date education about pain relief. However, similarities between urban and rural nurses' knowledge and knowledge deficits relating to acute pain management have been reported (Kubecka 1996 **Level IV**, n=123 [nurses]) and a tailored education program in a rural hospital improved the management of acute pain (Jones 1999 **Level III-3**, n=126). An education program delivered to nurses in rural and remote locations and focusing on acute, chronic and cancer pain improved understanding of pain management (Linkewich 2007 **Level III-2**). Early attempts at using online education for nurses to improve pain management were not widely accessed. A proposed model involving e-learning and problem-based approaches have had some initial success (Keyte 2011 **NR**).

A range of didactic and interactive teaching methods have been applied in nursing pain management education (Drake 2017 **Level IV SR** [PRISMA], 12 studies, n≈726 [staff] & n≈8,124 [patients]). Overall, nurses showed an improvement in pain documentation after participating in a pain management education program. However, there was no assessment of the nurses' associated behavioural change, and failure to account for the challenges of daily nursing practice, such as the requirement to frequently shift attention, which may interfere with assessment and ability to empathise with patients in pain). The provision of information and skills has limited ability to improve patient outcomes if these practical barriers to pain management are not addressed.

3.1.2.2 | Physiotherapists

Physiotherapists have recognised the need for more education about acute and subacute pain incorporating a biopsychosocial approach to prevent long-term disability and pain. However, an 8 d university course about how to identify and address psychosocial risk factors attended by practicing musculoskeletal physiotherapists led to no improvement in their patients being treated for musculoskeletal problems (Overmeer 2011 **Level II**, n=42, JS 2). The authors suggest that this type of teaching may be more effective if incorporated at an earlier stage of learning or by other methods if an impact on practice is to be made.

3.1.2.3 | Medical staff

Education of junior emergency department medical staff improved patient pain relief (Jones 1999 **Level III-3**, n=126). Additionally, the implementation of an education program with guidelines for pain management improved analgesia and patient satisfaction (Decosterd 2007 **Level III-2**, n=441).

A number of studies have shown the benefits of education and/or guidelines on improved prescribing patterns both in general terms (Ury 2002 **Level III-3**, n=1,006; Humphries 1997 **Level III-3**) and specifically for NSAIDs (Ray 2001 **Level II**, n=209, JS 2; Figueiras 2001 **Level III-2**, 495 [doctors in north-western Spain]; May 1999 **Level III-3**, n=210 [doctors in South Australia]), paracetamol (acetaminophen) (Ripouteau 2000 **Level III-3**, n=35 [French anaesthetists and nurses]) and pethidine (meperidine) (Gordon 2000 **Level III-3**).

A pilot program facilitated within Stanford University's Clinical Pain Medicine Fellowship program has implemented simulation as a method of medical education in opioid prescription (Heirich 2019 **Level III-3**, n=27).

3.1.2.4 | Interprofessional

Interprofessional education programs involving medical and nursing staff may improve collaboration and communication between health care team members and patients, and therefore encourage active self-management techniques and limit the implementation of passive pain management strategies (Hogans 2018 **NR**). An educational program (2 h) consisting of an interactive e-learning module and simulation session to both nursing and medical staff improved knowledge, but did not change analgesic administration or pain reduction for patients during an emergency department admission (Friesgaard 2017 **Level III-3**, n=2,140). The authors suggest that achieving behavioural change in healthcare professionals is complex, requiring repeated education, changes in workplace attitudes towards pain management, modification of daily practice environments and continuous support and follow-up.

Junior medical staff education over 3 y in an Australian tertiary hospital reduced inappropriate oxycodone IR prescriptions from 28% to 10% (Stevens 2019 **Level III-2**). The education package included junior medical and anaesthetic staff group and individual education (with feedback from audit data on individual prescribing), implementation of pharmacist-monitored prescription guidelines, an educational patient pamphlet and education sessions for surgical nursing staff regarding how to discuss opioid weaning and disposal.

3.1.2.5 | Web-based

There is growth in web-based delivery of education programs for health professionals. Online educational resources improve knowledge and skills, but not confidence and competence, (Liossi 2018 **Level IV SR** [PRISMA], 13 RCTs & 19 studies, n unspecified). Notably, there was significant heterogeneity among studies and relevant health outcomes for patients were not assessed. A survey of clinicians who completed an interactive online learning module regarding opioid prescription determined that clinician knowledge, the likelihood of adherence to prescription guidelines, and perceived competence in opioid prescription improved following participation (Langford 2020 **Level III-3**, n=167).

3.1.2.6 | Guidelines

When combined with education, the introduction of medical and nursing guidelines may contribute to improvements in pain management and prescribing practices (Gould 1992 **Level III-2**, n=2,035; Harmer 1998 **Level III-3**, n=2,738). Several initiatives have been described which employ guidelines with the aim of safe opioid prescription:

- A targeted medical, nursing and patient education initiative significantly reduced the median quantity of opioid analgesics provided at discharge for trauma patients (Oyler 2018 **Level III-3**, n=913);

- An emergency department opioid prescribing guideline reduced the number of discharge opioid prescriptions for dental, neck, back or chronic pain presentations from 53% (6 to 12 mth prior to introduction) to 34% (12 to 18 mth following introduction) (del Portal 2016 **Level III-3**, n=13,187);
- An Australian tertiary hospital introduced discharge analgesia prescribing guidelines which initially improved discharge prescribing practices, but diminished over time (Stewart 2019 **Level III-3**, n=170 [discharge prescriptions]). Maintaining education of junior medical staff can be a resource and time intensive proposition and is often maintained in an informal manner by pharmacists and other healthcare team members.

Advances in pain education require the engagement of healthcare professionals, patients, stakeholders, and ultimately a better understanding of pain education research (Hogans 2018 **NR**). Pain education research continues to present multiple challenges in terms of definition of content, ethical and practical study design, and consideration of appropriate outcome measures.

The importance of pain medicine education at an undergraduate medical level has also been recognised. A cross-sectional study of medical school curricula across Europe (Advancing the Provision of Pain Education and Learning [APPEAL] study) demonstrated that current undergraduate medical pain education is not consistent with that which would be expected given the current prevalence of pain conditions and their associated public health burden (Briggs 2015 **Level IV**, n=242 [curricula of medical schools]). Of 242 medical schools, only 31% offered a dedicated pain module and only 18% of these were compulsory, while 7% lacked any pain education. In response to the prescription opioid epidemic, American medical schools have implemented curriculum changes to include pain management and opioid prescribing (Barth 2017 **NR**). Furthermore, a systematic review of all articles that examined the content of pain education in medical school curricula found that the number of teaching hours was limited, and most had no mandatory formal pain medicine program (Shipton 2018 **Level IV SR**, 14 studies, n=383 [medical schools]); this did not reflect the healthcare needs for pain management in the population. Anaesthetists and acute pain services are central to the education of junior medical staff and development of hospital and state-wide prescription guidelines, and thus it is important that anaesthetists themselves receive appropriate exposure to acute pain medicine during their training (Macintyre 2014 **NR**).

KEY MESSAGES

1. There is no good evidence in favour of general education for acute neck pain having significant effects on any relevant outcomes (**U**) (**Level I** [Cochrane Review]).
2. Short educational interventions in acute whiplash injury reduce pain and disability and enhance recovery and mobility (**U**) (**Level I** [PRISMA])
3. There is limited evidence that preoperative education may lead to small improvements in postoperative outcomes such as pain, preoperative and postoperative anxiety, but not in analgesic requirements (**Q**) (**Level I** [PRISMA]).
4. General “biomedical” education in patients with acute back pain does not reduce pain or improve other outcomes (**S**) (**Level I**); however, education using a “biopsychosocial/ neuroscience” approach reduces a composite of anxiety, fear, worry, distress and healthcare utilisation (**N**) (**Level I** [PRISMA]).

5. Targeted reassurance in acute back pain by physicians in primary care can result in improved changes in psychological factors such as fear, worry, anxiety, catastrophisation and healthcare utilisation (**U**) (**Level I** [PRISMA].
6. Preoperative education improves patient or carer knowledge of pain and encourages a more positive attitude towards pain relief (**U**) (**Level II**).
7. Specific pain neuroscience education in specific surgical settings may result in less healthcare utilisation (**U**) (**Level II**).
8. Written information given to patients is better than verbal information given at the time of the interview (**S**) (**Level II**).
9. Educational interventions in cancer pain patients improve knowledge, attitudes and pain control (**U**) (**Level III-1 SR**).
10. While evidence for the benefit of patient education in terms of better pain relief is inconsistent, structured preoperative education may be better than routine information (**U**) (**Level III-2**).
11. Staff education and the use of guidelines improve pain assessment, pain relief and prescribing practices (**S**) (**Level III-3**).
12. Pain psychoeducation undertaken before surgery (pre-emptive) or throughout the perioperative period (preventive) is an underutilised component of multimodal analgesia which may reduce pain intensity, analgesic use, length of stay, return to the emergency department, patient anxiety and possibly chronic postsurgical pain (**N**) (**Level IV SR**).
13. Pain score documentation improves with various forms of nursing education, but the impact of this behaviour change has not been adequately assessed (**N**) (**Level IV SR**).
14. Pain medicine education in medical school curricula is restricted in scope and content (**N**) (**Level IV SR**).

The following tick boxes represent conclusions based on clinical experience and expert opinion:

☑ Successful management of acute pain requires close liaison between all personnel involved in the care of the patient (**U**).

☑ More effective acute pain management will result from appropriate education and organisational structures for the delivery of pain relief rather than the analgesic techniques themselves (**U**).

3.2 | Organisational requirements

It is recognised that patients should be able to access best-practice care, including appropriate assessment of their pain and effective pain management strategies (ASA 2012 **GL**; ANZCA 2010 **GL**). However, effective acute pain management will, to a large extent, depend not only on the medicines and techniques available, but also on the systems involved in their delivery (Macintyre 2015 **NR**). Even simple methods of pain relief can be more effective if proper attention is given to education (see Section 3.1 before), prescribing, administration, documentation, monitoring of patients and the provision of appropriate policies, protocols and guidelines (Gould 1992 **Level III-3**, n=2,035). The incorporation of pain measurement into clinical assessment for all patients, not only those under the care of an Acute Pain Service (APS), will aid pain management for all the patients throughout an institution (Gordon 2008 **NR**). Standardised clinical observation charts which include pain, sedation and function scores with other vital signs are an important step in ensuring safe provision of effective analgesia (Macintyre 2015 **NR**). In many institutions, an APS will assume responsibility for managing complex patients and more advanced methods of pain relief such as PCA, epidural analgesia and perineural infusions.

3.2.1 | General requirements

Guidelines to enhance patient outcomes and standardise analgesic techniques (eg selection of medicines and their concentrations, dose and dose intervals), monitoring requirements, choice of equipment, and responses to inadequate or excessive analgesic doses or other complications lead to consistency of practice. This can potentially improve patient safety and analgesic efficacy, regardless of the technique used (Macintyre 2015 **NR**; Counsell 2008 **NR**). These guidelines should be evidence-based wherever possible.

Marked improvements in conventional methods of pain relief have followed the introduction of guidelines for parenteral opioid administration (Humphries 1997 **Level III-3**, n=242; Gould 1992 **Level III-3**, n=2,035). However, it is the implementation of guidelines, not their development that remains the greatest obstacle to their use. Compliance with available guidelines is highly variable and may be better in larger and university-affiliated hospitals (Nasir 2011 **Level IV**, n=301 [USA hospitals]; Carr 1998 **Level IV**, n=400 [USA hospitals]). Resource availability, particularly staff with pain management expertise, and the existence of formal quality-assurance programs to monitor pain management are positive predictors of compliance with guidelines (Jiang 2001 **Level IV**, n=220 [USA hospitals]).

Different types of surgery require different types of analgesic regimens. Common and minor surgical procedures often result in high pain scores, which are frequently undertreated (eg laparoscopic appendicectomy, cholecystectomy, and haemorrhoidectomy) (Gerbershagen 2013 **Level IV**, n=70,764). The adoption of procedure-specific methods and the use of analgesic combinations may help to optimise analgesia and reduce adverse effects (Joshi 2013 **NR**) (see Section 8.1.3). A hospital-wide approach can be incorporated into postoperative enhanced-recovery programs (White 2010 **NR**) (see Section 3.2.3 below).

Professional bodies in a number of countries have issued guidelines for the management of acute pain (RCoA 2020 **GL**; Agency for Clinical Innovation NSW 2016 **GL**; Faculty of Pain Medicine RCoA 2015 **GL**; ANZCA 2013 **GL**; ASA 2012 **GL**).

While there is widespread agreement about the value of clinical guidelines, they do have limitations. Some of these include reliance on the population-wide aggregation of patient outcomes, which may not be optimal on an individual patient level. Individual patient

variability arises from complex interactions between genetic and environmental exposures over the life of the patient (Fillingim 2017 **NR**). A method that can incorporate standardised care but allow for individual patient variation is the SCAMP approach – Standardised Clinical Assessment and Management Plans (Beverly 2017 **NR**). This process is a clinician-engaged approach that promotes standardisation but accommodates patient preferences, includes clinician experience and incorporates recent medical knowledge. Benefits include reduced variability in medical care (Farias 2013 **NR**).

The success of an APS and patient treatment depends not only on good clinical care but also on a positive organisational culture(Powell 2009 **NR**; Bate 2008 **NR**). This should follow the key principles of effective change management. A series of semi-structured interviews of healthcare professionals identified key areas that need to be addressed for well-organised care. These include structural issues, political issues, cultural change, educational challenges, leadership and motivation, and technological challenges.

3.2.2 | Acute pain services

There is a very wide diversity of APS structures, with no consensus as to the best model and no agreed definition of what might constitute such a service (Counsell 2008 **NR**). Some are "low-cost" nurse-based (Shapiro 2004 **Level IV**, n=4,617; Rawal 2005 **NR**), others are anaesthetist-led but rely primarily on APS nurses as there may not be daily clinical participation by an anaesthetist (Nagi 2004 **NR**; Harmer 2001 **NR**). In contrast, others are comprehensive and multidisciplinary services with APS nursing staff, sometimes pharmacists or other staff (eg clinical psychologists) (Katz 2015 **NR**) and daily clinical input from and 24 h cover by anaesthetists (Macintyre 1990 **Level IV**, n=1,053; Ready 1988 **Level IV**, n=820; Schug 1993a **NR**). The development of specific paediatric pain services has also been described (Kost-Byerly 2012 **NR**) and is an emerging field (Finley 2014 **NR**).

Larger hospitals and those with university affiliations are more likely to have a formal APS and use protocols (Nasir 2011 **Level IV**, n=301 [USA hospitals]). When advanced modalities such as epidural analgesia and continuous peripheral nerve block (CPNB) are used, the APS is most commonly anaesthetist-led. An economic evaluation of a physician-led APS has shown it to be cost-effective even for patients having IV PCA after intermediate grade surgical procedures (Lee 2010 **Level II**, n=423, JS 2).

The degree of medical input varies enormously. A UK survey reported that while 90% of hospitals reported having an APS, dedicated medical staff sessions did not exist in 37%, were limited to one or two per wk in 40% and in only 4% were there five or more sessions (Nagi 2004 **NR**). In training hospitals in Australia, 91% of hospitals accredited for anaesthetic training had an APS run from the department of anaesthesia with daily input from medical staff. Consultant anaesthetist sessions (one session is 0.5 d) varied from zero in 27%, just one or two a wk in a further 22%, four to six per wk in 22% and ten per wk in 15% (Roberts 2008 **Level IV**, n=67 [AUS and NZ hospitals]). A UK survey of 141 acute pain services found variation in the structure, function and staffing of the APSs between the responding hospitals (Rockett 2017 **Level IV**, n=209 [UK hospitals]). The mean number of consultant hours per wk was only 5.5 h. 35% of the APSs also had other roles in addition to acute pain management. Only half of the teams (49%) had members that also worked in an integrated multidisciplinary pain service. A Dutch survey showed again that 90% of hospitals have an APS of variable organisational structure; important tasks of the APS were regular patient rounds and checking complex pain techniques (100%), supporting quality improvement of pain management (87%), pain education (100%) and pain research (21%) (van Boekel 2015 **Level IV**, n=96 [Dutch hospitals]). However, a survey repeated in Denmark from 2000–2009 showed a surprising decline of APSs in parallel to the

increased usage of enhanced-recovery programs (Nielsen 2012 **Level IV**). In the USA, APSs were more common in university/academic hospitals (96%) than in Veterans' Affairs hospitals (69%), with the lowest rate in private hospitals (47%) (Nasir 2011 **Level IV**, n=301 [USA hospitals]). Formal written postoperative pain protocols were more common in hospitals with an APS but overall only 55% of hospitals had such protocols. In Germany, 81% of the hospitals surveyed stated that they had an APS; however, only 45% met quality criteria defined by the authors (Erlenwein 2014 **Level IV**, n=403 [German hospitals]). In contrast to the USA data above, 97% of the hospitals had written acute pain protocols for surgical patients, but only 51% on nonsurgical wards.

Some APSs supervise primarily "high-tech" forms of pain relief and/or complex patients, while others have input into all forms of acute pain management in an institution and will work towards optimising traditional methods of pain relief so that all patients in that institution benefit (Macintyre 2015 **NR**; Counsell 2008 **NR**; Breivik 2002 **NR**). Increasingly, APSs are also called on to deal with much more complex pain management issues (eg acute-on-chronic pain, acute pain after SCI or other major trauma, and resulting from a multitude of medical illnesses) and more complex patients (eg opioid-tolerant patients, older patients) (Counsell 2008 **NR**).

Individual publications assessing the benefits of an APS have reported that the presence of an APS reduced pain scores (Stadler 2004 **Level III-3**, n=1,975; Bardiau 2003 **Level III-3**, n=2,283; Salomaki 2000 **Level III-3**, n=400; Sartain 1999 **Level III-3**, n=605; Harmer 1998 **Level III-3**, n=2,783; Gould 1992 **Level III-3**, n=2,035; Miaskowski 1999 **Level IV**, n=5,837) and adverse effects (Sartain 1999 **Level III-3**, n=605; Stacey 1997 **Level III-3**, n=40; Miaskowski 1999 **Level IV**, n=5,837; Schug 1993a **Level IV**, n=3,016). A review of publications (primarily audits) looking at the effectiveness of APSs (77% were physician-based, 23% nurse-based) concluded that the implementation of an APS is associated with a significant improvement in postoperative pain and a possible reduction in postoperative neurological symptoms (PONS), but that it was not possible to determine which model was superior (Werner 2002 **Level IV SR**, 48 studies, n=84,097). The authors comment, however, that it is not possible to assess the contribution of factors such as an increased awareness of the importance of postoperative analgesia, the use of more effective analgesic regimens (eg epidural analgesia), the effects of APS visits and better strategies for antiemetic therapy. The benefits of an APS can be enhanced when its role is expanded beyond its traditional postoperative realm and into the entire patient journey – preoperative, intraoperative, postoperative and posthospital discharge (Zaccagnino 2017 **NR**).

Possible benefits of an APS are summarised in Table 3.1.

Given the heterogeneity of APS models and types of patients and pain treated, as well as variation in the quality of published studies, it is difficult to meaningfully analyse the benefits or otherwise of an APS. Although systematic reviews have been attempted (McDonnell 2003 **Level III-3 SR**, 15 studies, n unspecified; NICS 2003 **Level III-3 SR**, 32 studies, n unspecified) (4 Studies overlap), the poor quality of the studies looking at the effectiveness or otherwise of APSs and the many different types of APSs, means that a meta-analysis cannot be performed.

In addition, the above studies looked at outcome in terms of immediate pain and adverse effects in postoperative patients only. It is possible that an APS may benefit patients in other ways.

Combination of an APS with a physician-based critical-care outreach team, which systematically reviewed high-risk postoperative patients for 3 d after their return to a general ward, showed a significant improvement in postoperative outcome with a decrease in serious adverse effects from 23 to 16 events per 100 patients and 30 d mortality from 9 to 3% (Story 2006 **Level III-2**, n=590). Finally, members of an APS may also be more likely to recognise the early onset of neuropathic pain associated with surgery, trauma or medical disease and institute the appropriate treatment (Counsell 2008 **NR**).

Table 3.1 | Possible benefits of an acute pain service

Benefit	References
Better pain relief	Stadler 2004; Bardiau 2003; Werner 2002; Salomaki 2000; Sartain 1999; Gear 1999; Harmer 1998; Gould 1992
Lower incidence of adverse effects	Werner 2002; Sartain 1999; Miaskowski 1999; Stacey 1997; Schug 1993b
Lower postoperative morbidity/mortality	Story 2006
Management of analgesic techniques that may reduce the incidence of persistent pain after surgery	Gehling 2003; Senturk 2002; Obata 1999
Cost-effective patient care	Lee 2010
Reduced persistent pain and discharge opioid use after surgery	Tiippana 2016; Katz 2015

The role of an APS can be extended into the pre-admission (elective cases) and post-acute phase of recovery. This approach can bridge the gap between ward-based acute pain care and outpatient chronic pain management. Descriptions of this type of extended and proactive care suggests a reduction in the occurrence of persistent pain and excessive opioid use after hospital discharge, which may also be cost-effective (Tiippana 2016 **Level IV**, n=200; Katz 2015 **NR**) (see also 3.3 Economic Considerations).

3.2.2.1 | Safety

Unidimensional management of acute pain can lead to adverse outcomes including opioid-induced ventilatory impairment (OIVI) (Vila 2005 **Level III-3**; Macintyre 2011 **NR**). Structural changes in an APS can minimise such effects (Story 2006 **Level III-2**, n=590). Implementation of root-cause analysis for critical incidents improved the safety of patients looked after by an APS; this approach reduced the overall event rate (1.47% vs 2.35) with specific effects on the rate of respiratory depression (0.41% vs 0.71), severe hypotension (0.78% vs 1.34) and PCA pump programming errors (0.0% vs 0.08) (Paul 2014 **Level III-3**, n=35,384) (see also Sections 6.6 and 6.8).

Standardised written documentation of APS treatment can potentially improve the safety of patient care. An agreed and consistent format for prescribing, observation and documentation of care can reduce unnecessary clinical variation, which is beneficial (Agency for Clinical Innovation NSW 2016 **GL**). The use of an electronic medical record (EMR) can facilitate the function and safety of an institution's APS. Specifically, these benefits can include clear documentation, organisation of ward rounds, billing, analysis of patient safety and outcomes, and integration with research (Goldstein 2014 **NR**). It is important that the design of an EMR has features that facilitate usability, efficiency, safety and mobility (Telenti 2018 **NR**; Mandl 2012 **NR**; Grams 2009 **NR**). The integration of electronic smart-pumps directly into the EMR greatly increased the accuracy and completeness of recording PCA episode of care vs paper-based records (38% to 91) (Suess 2019 **Level III-3**, n=113).

KEY MESSAGES

1. Implementation of an acute pain service may improve pain relief and reduce the incidence of adverse effects (**U**) (**Level III-3**).
2. Even "simple" techniques of pain relief can be more effective if attention is given to education, documentation, patient assessment and provision of appropriate guidelines and policies (**U**) (**Level III-3**).
3. Implementation of root-cause analysis to follow up critical incidents improved the safety of patients under care of an acute pain service (**U**) (**Level III-3**).

The following tick boxes represent conclusions based on clinical experience and expert opinion:

☑ Successful management of acute pain requires close liaison between all personnel involved in the care of the patient (**U**).

☑ More effective acute pain management will result from appropriate education and organisational structures for the delivery of pain relief rather than the analgesic techniques themselves (**U**).

☑ Appropriate institutional support and engagement is important for the effective implementation of an acute pain service (**U**).

☑ Procedure-specific analgesic protocols can help optimise analgesia for the individual patient while reducing adverse effects (**U**).

☑ The adoption of individualised care pathways (eg SCAMPS) can improve patient outcomes and reduce clinical variation (**N**).

☑ The benefit of an acute pain service can be enhanced when acute pain management is integrated into the pre, intra and postoperative periods (**N**).

☑ The recruitment of patients 'at-risk' for persistent pain and/or excessive opioid use into a post-discharge treatment service for early review can improve outcomes (**N**).

☑ Appropriately designed, implemented and integrated Electronic Medical Records (EMR) can improve the standards of clinical care (**N**).

3.3 | Economic considerations in acute pain management

An economic evaluation of healthcare can be described as the "*comparative analysis of alternative courses of action in terms of their costs and consequences*" (Drummond 2008 **NR**). Health economics aims to maximise health benefits relative to the resources available. This approach is particularly crucial in a growing and ageing population, with fewer people in the workforce paying taxes, and a more substantial proportion with chronic conditions and aged care, requiring health services. An economic assessment of acute pain can be of the overall service provision (eg an APS), or a specific technique (eg PCA). Areas where acute pain management may affect the economics of healthcare include: patients, hospitals, and payers/insurers. These impacts may be direct or indirect, where the costs of delivering pain management may result in savings in other areas of patient treatment. Limited data indicate potential areas of cost savings arising from improved acute pain care. These include shorter ICU admissions, decreased cardiac and respiratory adverse events, decreased risk of postoperative infections, and potentially reduced risk of the development of chronic pain (Gray 2017 **NR**; Schug 2017 **NR**).

While the costs of healthcare are relatively easy to measure, the value of healthcare is harder to quantify (Goldman 2014 **NR**). Often, the benefits of healthcare are limited to those occurring within the healthcare system; however, there may be other significant benefits in society that should also be included eg return to full employment, long-term disability due to pain, or mental health related to ongoing pain (Drummond 2008 **NR**). The impact on a patients' family and carers in their workforce participation and their psychological well-being are further considerations (Schofield 2019 **Level IV**).

There are several types of economic assessment that are commonly used in the literature. These have important differences; there is a consensus agreement on their definitions (Husereau 2013 **GL**; Drummond 2005 **NR**) (see Table 3.2). The most commonly used is cost-effectiveness analysis, which examines the cost in dollars per additional life-year gained.

In the literature, these terms may be used interchangeably, without correct adherence to their definitions. No one assessment measure is superior to another, and health economists debate the merits of each. In addition, issues of social equity, needs, and priorities should also be part of the decision making process (Schlander 2009 **NR**; Phillips 2009 **NR**; McGregor 2003 **NR**).

In contrast to most commodities, healthcare is a "*credence good*" (Emons 1997 **NR**) ie patients or consumers/stakeholders find it difficult or impossible to determine the utility of a treatment prior to its consumption. They have to rely on the knowledge of healthcare experts when choosing a treatment. This situation is also referred to as "*asymmetry of knowledge*".

Patients value pain relief highly; a survey of two million USA inpatients found that "*how well their pain was controlled*" was the second most important factor in recommending a hospital (PressGaney 2009 **Level IV**). When healthcare funding occurs without regard to patient's values, then funding for formal acute pain services becomes limited (Sun 2010 **NR**).

A consistent risk factor for the development of chronic postsurgical pain (CPSP) is poorly controlled postoperative pain (see Section 1.4). CPSP is an economic burden on society. An economic report in 2019 found that the total cost of chronic pain in Australia was $73.2 billion, and that much of chronic pain originates as acute pain (Deloitte Access Economics 2019 **NR**). Chronic pain interferes with the return to employment, requires ongoing medical treatment with its inherent costs, and may require carers at an additional cost, or require informal care from a family member or friend, influencing their workforce participation (Schofield 2019 **IV**) .

Table 3.2 | Definitions of health economic assessment measures

Cost-effectiveness analysis	Consequences are measured in natural units, such as life years gained, disability days avoided, or cases detected
Cost-utility analysis	Consequences are measured in terms of preference-based measures of health, such as quality adjusted life years (QALY) or disability adjusted life years (DALY).
Cost-benefit analysis	Consequences are valued in monetary units
Cost-minimisation analysis	Consequences of compared interventions are equivalent (in terms of clinical efficacy and tolerability), and only relative costs are compared
Cost-outcome description	Costs measured in monetary value and health effects measured in natural units (eg intensive care unit days saved, patient satisfaction etc.)
Value of statistical life	A method to assign a monetary value to a person's life (or a proportion if a disability) using a willingness to pay approach. This is similar to a QALY. (Office of Best Practice Regulation 2014 **GL**)

Economic assessment of pain relief requires direct and indirect evaluation of both the costs and the benefits. Assessment of subjective experiences, such as a reduction in pain scores, can be assigned a monetary value using techniques such as 'willingness to pay', and 'human capital approaches' (Kumar 2006 **NR**). These monetary values can then be used in performing a cost-benefit analysis. Economic analysis needs to include the assessment of a treatment in comparison with the alternatives eg IV PCA vs prn opioid analgesia. Direct costs can include the cost of equipment, drugs and staff. Indirect costs can include the duration of hospital stay, use of ICU, development of persistent pain and treatment of adverse effects. Potential benefits include: reduction in pain intensity, minimisation of pain-related adverse effects, improved fast-track recovery and compliance with rehabilitation, as well as earlier return to work of both the patient and their informal carer (White 2007 **NR**).

3.3.1 | Economic evaluation of PCA

The direct and indirect costs of PCA for pain relief after three common types of surgery have been assessed (Palmer 2014 **Level III-3**, n=11,805,513). This evaluation used data from a large administrative healthcare database (Premier 2015 **Level IV**). Further cost estimates of adverse events were derived from the literature. The use of PCA after TKA, THA and open abdominal surgery was evaluated. The costs included PCA pump usage, setup costs, and costs of IV extension set, drug, fluid for IV co-infusion and the pump. The total of these costs (standardised to US$ in 2012) during the first 48 h after surgery, were US$204, US$196, and US$243 respectively. Additionally, cost estimates for particular adverse events in the first 48 h of PCA use were calculated. These costs were: phlebitis (US$2.18), healthcare worker needle stick injury (US$1.67), and IV PCA programming error (US$35.52). The assessment of costs for PCA programming errors did not include newer pumps that have software for the mitigation of programming errors (ie 'smart pumps'). The cost of other adverse events, such as respiratory depression or nausea and vomiting, were not included in this assessment.

The costs and rates of harmful and non-harmful errors due to the use of IV PCA were estimated from two large safety-reporting databases in the USA (Meissner 2009 **Level IV**): the datasets included medication errors (MEDMARX) and device errors (MAUDE). A cost-accounting methodology was used, which included direct, indirect and opportunity costs. These were estimated from published literature, expert consensus, physician billing-charges and staff labour-rates (standardised to US$ in 2006). The estimated average cost of a PCA adverse event in the medication error dataset was US$733, whereas the cost related to a pump error was US$552. If an error led to patient harm, then the cost was 120 to 250 times more costly than a non-harmful error. For medication incidents, the most expensive harm-causing error was due to poor communication (US$8,984 per incident). For pump-related errors, the two most expensive were operator error (US$5,756) and those of indeterminate cause (US$6,120). The estimated annual USA error rates per 10,000 patients treated with PCA were 407 for PCA medication errors, and 17 for PCA device errors (see also Section 6.6).

3.3.2 | Economic evaluation of Acute Pain Services

A narrative review (Gray 2017 **NR**) examined the economic aspects of an APS from within a USA healthcare perspective. Assessment included the areas of the patient, the hospital and the payer (insurer). Indirect benefits may include improved outcome over a range of postoperative measures. This may be relevant for a hospital within an 'activity-based funding' agreement. The use of continuous regional anaesthesia/analgesia techniques can be made more cost-effective by instigating a single regional block service that covers multiple operating rooms. This service model could reduce the cost of time delays associated with the initiation of regional anaesthesia. The treatment options used by a specialised acute pain service could ensure there is greater use of non-opioids, and mitigation of excess opioid prescribing with that resultant long-term health cost.

A systematic review of the economic evaluations of APSs has been performed (Lee 2007 **Level IV SR**, 9 studies, n=14,774). Five of the studies were of nurse-based, anaesthetist-supervised services. Out-of-pocket expenses and loss of productivity due to absence from work were not included. No study went beyond five d. Monetary values were standardised to $US in 2005. The cost of an anesthetist-led APS ranged from US$31.73 to US$100.37 per patient per d. The cost of a nurse-based/anaesthetist supervised APS ranged from US$3.70 to US$50.77 per patient per d. The cost-savings from a shorter ICU stay were US$9.90 per patient per d. The cost-savings from a shorter duration of hospital stay were US$11.40 per patient per d. Savings from reduced nursing time were also identified. Data were not available to compare the economics of a nurse-based/anaesthetist supervised APS with an anaesthetist-led APS. No studies were of high quality or included all costs and benefits associated with APS care.

An RCT for the cost-effectiveness of APS care (anaesthetist-led, nurse-based) compared APS patient care (IV PCA plus adjuvants) with conventional ward analgesia for patients having major surgery (Lee 2010 **Level II**, n=423, JS 2). Regional analgesic techniques were not included. Of patients in the APS group, 86% had one or more d of highly effective pain relief vs 75% in the conventional care group. Costs were higher in the APS group when compared with the conventional group by US$46/d. Cost-effectiveness was determined using a 'willingness-to-pay' methodology which assigns a monetary value to pain relief. This analysis showed that to be 95% certain of obtaining one d of highly-effective pain relief per patient, the benefit was valued at US$546.

The cost-utility analysis of a nurse-based APS has been performed (Stadler 2004 **Level III-3**, n=1,975). The interventions used in this APS were: implementation of guidelines, use of multimodal analgesia, optimum use of systemic opioids as well as NSAIDs and paracetamol,

along with information pamphlets to patients. In 1.5% of patients, PCA was used; patients receiving epidural analgesia were not included. The patient population was a large tertiary hospital that included all surgical subspecialties. Cost-utility was assessed using a measure of 'Postoperative Pain Days Averted (PPDA)', which is a health state scale conceptually similar to quality adjusted life years (QALY). The PPDA measure summarises treatment outcome in terms of time spent with lower pain scores. A value of "1" represents a state of "no pain", whereas a value of "0" represents "worst pain imaginable". For POD 1 to 3, PPDA values were 0.075 (1.8 h), 0.05 (1.2 h) and 0.0375 (0.9 h) respectively. The incremental cost of pain management by the APS vs no APS, was 19 Euro per patient per d. The effectiveness of the APS may have been different if more advanced methods of pain relief had been used. Measuring PPDA alone may have missed other benefits from improved pain relief (ie quality of life surveys such as SF-12).

3.3.3 | Economic benefit related to improved patient outcome and reduced chronic postsurgical pain.

While not intended as economic assessments, there are studies that have measured patient outcomes, other than pain, which are related to an economic outcome. These are similar to a cost-effectiveness analysis (see Table 3.2). For example, the mental health issues following chronic pain, inability to return to the workforce for a patient or informal carers, and the resultant isolation and psychological distress are all non-monetary considerations. Monetary considerations of pain outcomes can be considered either from the health system or patient perspective, depending on whether the issue in question is the impact of pain on the individual or the health systems. From an individual perspective, out-of-pocket costs, travel, parking and accommodation for rural patients are considerations, particularly for those with chronic pain. From the health system perspective, cost includes Medicare costs such as the Pharmaceutical Benefits Scheme (PBS) or Medicare Benefits Scheme (MBS), outpatient visits, as well as other hospital costs.

The pattern of opioid prescribing (dose, duration and type) while in hospital and after discharge are significant instigators of opioid misuse and its resultant economic burden (Neuman 2019 **NR**; Lowenstein 2018 **NR**; Shah 2017 **Level IV**). This important public health problem can be mitigated by appropriate acute pain strategies in the hospital setting. These may include analgesic techniques that minimise the dose and duration of opioid use; this includes using non-opioid analgesic strategies. At the time of patient discharge there needs to be appropriate limitations on the dose and duration of the prescribed opioids (Lowenstein 2018 **NR**) (see Sections 8.13 and 10.4.5). The estimated financial cost of prescription opioid misuse in Australia comprises the costs related to deaths, hospitalisation, and pharmacotherapy. The estimated annual (2018) costs of these three areas are $4.7 billion, $13.4 million and $60.2 million respectively (Deloitte Access Economics 2019). These costs may be further mitigated by a real-time prescription monitoring program which can reduce deaths and the issue of multiple prescribers ("*doctor shopping*") (Finklea 2014 **NR**; Winters 2013 **NR**).

A systematic review of patient outcomes after epidural analgesia showed a reduction in the incidence of costly adverse events. These included a reduced risk of atrial fibrillation, supraventricular tachycardia, deep vein thrombosis, respiratory depression, atelectasis, pneumonia, ileus, postoperative nausea and vomiting and improved recovery of bowel function (Popping 2014 **Level I** [PRISMA], 125 RCTs, n=9,044) (see section 5.6). These must be balanced against the increase in adverse events associated with epidural analgesia such as hypotension, pruritus, urinary retention and motor block.

One study examined the effect on patient outcome when an APS provided additional advice on patient care during their usual ward round (Story 2006 **Level III-3**, n=590). Examples of advice include oxygen therapy, IV fluid management, physiotherapy, analgesia, or calling the medical emergency team. This APS intervention resulted in a reduction of serious adverse events (from 23 to 16 per 100 patients) and reduced 30 d mortality (9% to 3%).

Chronic postsurgical pain (CPSP) has a significant prevalence, which is typically 1 to 10% at one year after surgery. This is dependent on the nature of surgery. A consistent predictor for the development of CPSP is the severity and duration of postoperative pain. The provision of effective acute pain management can reduce this costly public health problem. Examples include limb amputation, thoracotomy, craniotomy, joint arthroplasty, breast surgery and inguinal hernia repair. (Glare 2019 **NR**). Once CPSP is established, it may be challenging to treat, resulting in ongoing costs. Additionally, there are indirect costs, including impairment of return to employment. The annual cost per patient (2018) with chronic pain was estimated at A$42,979 (Deloitte Access Economics 2019 **NR**). A potential strategy to reduce the transition from acute to chronic postsurgical pain, along with its economic costs, is the use of a transitional pain clinic. Patients at this clinic are reviewed and managed in the early period after hospital discharge to prevent the progression from acute to chronic pain and reduce opioid usage (Huang 2016 **Level IV**; Katz 2015 **NR**) (see also Section 1.4).

Quantifying the health outcomes of patients immediately after surgery as well as over the longer term will allow improved assessments of cost-effectiveness of new strategies.

KEY MESSAGES

1. Long term economic consequences from the progression of acute to chronic postsurgical and post-traumatic pain can be significant (**S**) (**Level IV**).
2. Strategies to optimise acute and subacute pain management (including involvement of transitional pain services) may reduce the economic burden of chronic pain and inappropriate prescription opioid use (**N**) (**Level IV**).
3. The early pattern of prescription opioid use after surgery may increase the risk of chronic use with significant direct and indirect economic costs (**N**) (**Level IV**).
4. Patients' willingness to pay for good pain relief is high (**S**) (**Level IV**).
5. Costs from PCA errors can be considerable; the most common high cost errors arise from staff communication error and operator error (**S**) (**Level IV**).

The following tick boxes represent conclusions based on clinical experience and expert opinion:

☑ There are different measures of economic assessment and analysis used in healthcare; no one method is the most appropriate (**U**).

☑ Prescription drug monitoring may reduce the economic burden through its impact on inappropriate opioid prescribing (**N**).

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4

Analgesic medicines

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Prof Stephan A Schug

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4.1 | Paracetamol

Paracetamol and its intravenous prodrug propacetamol are the only remaining aniline derived drugs used in clinical practice; it is an effective analgesic (see below) and antipyretic. It is absorbed rapidly and well from the small intestine after oral administration with a bioavailability of between 63 and 89% (Oscier 2009 **NR**). It can also be given rectally and IV (see below and Chapter 5).

4.1.1 | Mechanism of action

Despite extensive use since its discovery in the 19th century the mechanism of action of paracetamol is still not fully understood. In contrast to opioids, paracetamol has no known endogenous binding sites and, unlike NSAIDs, causes only weak inhibition of peripheral cyclooxygenase (COX) activity, with apparent selectivity for COX-2 (Graham 2013a **NR**). Given its limited peripheral actions the most likely mechanism is a central effect and may involve multiple pathways:

- When paracetamol is de-acetylated to p-aminophenol it can undergo conjugation with arachidonic acid by fatty acid amide hydrolase to AM404 in the CNS (Ghanem 2016 **NR**). AM404 has multiple potential mechanisms of action in the CNS. Firstly, it is a weak cannabinoid receptor agonist as well as a reuptake inhibitor of the endocannabinoid anandamide. Secondly, it is a potent TRPV1 receptor agonist and a TRPV1 mutation is associated with paracetamol non-responsiveness in healthy humans volunteers (Pickering 2020 **Level II EH**, n=47, JS 4);
- Paracetamol has been shown to prevent prostaglandin production at the cellular transcriptional level predominantly in the CNS, independent of COX activity (Mancini 2003 **BS**). This may also be AM404 mediated as AM404 reduces PGE-2 release from activated microglia (Saliba 2017 **BS**). This effect is independent of cannabinoid and TRPV1 receptor effects;
- Indirect effects on the serotonergic system appear to be important. In volunteers, coadministration of tropisetron or granisetron blocked the analgesic effects of paracetamol (Pickering 2008 **EH**; Pickering 2006 **EH**). In children undergoing tonsillectomy who all received paracetamol, a fixed dose of morphine and betamethasone, administration of ondansetron was associated with significantly more morphine in recovery vs droperidol, but no change in codeine over the first 24 h (Ramirez 2015 **Level II**, n=69, JS 4).

4.1.2 | Efficacy

For paediatric specific information see 10.4.1.1

Perioperative use

Single doses of paracetamol are effective in the treatment of postoperative pain. The NNTs for a variety of doses, as well as combinations of paracetamol with other analgesic medicines such as codeine, are discussed in Chapter 5 and listed in Table 5.1.

There is no good evidence for a dose-dependent analgesic effect of oral paracetamol; the effects of 500 mg (NNT 3.5; 95%CI 2.7 to 4.8), 600/650 mg (NNT 4.6; 95%CI 3.9 to 5.5) and 1,000 mg (NNT 3.6; 95%CI 3.2 to 4.1) show no statistically significant difference (Moore 2015b **Level I** [Cochrane], 53 RCTs, n=5,679). Although in clinical practice there is no clear evidence of a dose-response relationship, experimental surgical models have shown that the maximal

effective dose is 1000 mg. Paracetamol by all routes of administration has an opioid-sparing effect on PCA-morphine consumption (MD over 24 h -6.3 mg; 95%CI -9.0 to -3.7), although this effect is inferior to nsNSAIDs and coxibs (Maund 2011 **Level I**, 60 RCTs, n unspecified).

Oral paracetamol given 1 h prior to surgery reduced the pain intensity of propofol injection: by a median NRS of 2/10(IQR 0 to 3) for 500 mg and 4/10 (2 to 5) for 1,000 mg vs placebo 8/10 (7 to 10) (Nimmaanrat 2019 **Level II**, n=324, JS 5).

IV paracetamol is also an effective analgesic after surgery with an NNT of 4.0 (95%CI 3.5 to 4.8) over 4 h and an NNT of 5.3 (95%CI 4.2 to 6.7) over 6 h (Tzortzopoulou 2011 **Level I** [Cochrane], 36 RCTs, n=3,896). When paracetamol is used as an adjuvant to opioid analgesia, opioid requirements are reduced by 30% over 4 h after a single IV dose. For hip and knee arthroplasty, there is a reduction in pain scores for each of the first 3 PODs (POD 1: WMD -0.95; 95%CI -1.2 to -0.7) and opioid consumption (POD 1: WMD -3.1; 95%CI -4.1 to -2.1) (Yang 2017a **Level I** [PRISMA], 4 RCTs, n=865).

IV paracetamol given perioperatively reduces PONV when administered before recovery from anaesthesia (Apfel 2013 **Level I** [PRISMA], 30 RCTs, n=2,364). This effect is correlated to pain relief achieved, but not to reduced opioid consumption. IV paracetamol given before incision is more effective than post incision in reducing pain at 1 h (MD -0.50; 95%CI -0.98 to -0.02) and 2 h (MD -0.34; 95%CI - 0.67 to -0.01), 24 h opioid consumption (SMD 0.52; 95%CI -0.98 to -0.06) and PONV (RR 0.50; 95%CI 0.31 to 0.83) (Doleman 2015b **Level I** [PRISMA], 7 RCTs, n=544).

Other acute pain indications

Paracetamol is superior to placebo for migraine (NNT 12 for pain-free response at 2 h) and reaches the efficacy of sumatriptan when combined with 10 mg metoclopramide (Derry 2013a **Level I** [Cochrane], 11 RCTs, n=2,942). In episodic tension-type headache (TTH), paracetamol is mildly effective at 2 h (NNT for mild pain or pain free 10; 95%CI 7.9 to 14) (Stephens 2016 **Level I** [Cochrane], 23 RCTs, n=8,079). Paracetamol is also superior to placebo for postpartum perineal pain (OR 2.14; 95%CI 1.59 to 2.89) (Chou 2013 **Level I**, 10 RCTs, n=1,377) but less effective than NSAIDs (Wuytack 2016 **Level I** [Cochrane], 3 RCTs, n=342). Paracetamol does not appear to be effective for acute low back pain (Saragiotto 2016 **Level I** [Cochrane], 3 RCTs, n=1,825).

Paracetamol in combinations

The combination of paracetamol and NSAIDs is more effective than either paracetamol or NSAID alone (Martinez 2017 **Level I** [NMA], 2 RCTs, n=85 [paracetamol/NSAID]; 60 RCTs, n=3,259 [NSAIDs]; 20 RCTs, n=699 [paracetamol]; Ong 2010 **Level I**, 21 RCTs, n=1,909). This in particular is shown for the combination of paracetamol and ibuprofen in the setting of wisdom tooth removal (Bailey 2013 **Level I** [Cochrane], 7 RCTs, n=2,241).

A combination of 1,000 mg paracetamol with 130 mg caffeine is more effective than paracetamol alone (OR 1.12; 95%CI 1.05 to 1.19) in a range of painful conditions with no safety concerns (Palmer 2010 **Level I** [QUOROM], 8 RCTs, n=2,510).

Combinations of paracetamol with opioids such as codeine, tramadol or hydrocodone show increased efficacy (see Section 5.1.3.1.).

4.1.3 | Adverse effects

For paediatric specific information see 10.4.1.3

Paracetamol has fewer adverse effects than NSAIDs and can be used when the latter are contraindicated (eg patients with a history of renal impairment, asthma or peptic ulcers).

4.1.3.1 | Hepatic effects

The risk of hepatotoxicity from therapeutic doses (maximum 4 g/24 h) is not supported by current data (Dart 2007 **Level IV SR**, 791 studies, n=40,202). The higher number of findings in the retrospective vs the prospective studies suggests that some of these cases may be inadvertent overdoses. Similar safety has also been shown in a paediatric population with no cases of liver disease, need for antidote or transplantation, or death (95%CI 0.000 to 0.009) and only 0.031% of cases (95%CI 0.015 to 0.057) with major or minor hepatic adverse effects (Lavonas 2010 **Level IV SR**, 62 studies, n=32,414). In conclusion, hepatotoxicity from therapeutic doses of paracetamol is extremely rare (Caparrotta 2018 **NR**; Graham 2013a **NR**).

Guidelines based on individual case reports only recommend that paracetamol should be used with caution or in reduced doses in patients with low body weight (<50 kg), active liver disease, history of heavy alcohol intake, older age, malnutrition, Gilbert's syndrome and glucose-6-phosphate dehydrogenase deficiency (NPS MedicineWise 2015 **GL**; Queensland Health 2014 **GL**; NSW TAG 2008 **GL**); however, consistent evidence of increased risk in these settings is lacking (Caparrotta 2018 **NR**; Graham 2013a **NR**). Therapeutic doses of paracetamol are an unlikely cause of hepatotoxicity in patients who ingest moderate to large amounts of alcohol. In subjects who consume alcohol, no elevation of alanine aminotransferase levels was noted with up to 4 g/d of paracetamol for at least 4 d (Rumack 2012 **Level I** [PRISMA], 5 RCTs, n=551); no cases of hepatic failure or death were observed in any published prospective trial of moderate to heavy alcohol drinkers. In patients newly abstinent after abusing alcohol, therapeutic doses of paracetamol had no effect on parameters of liver function (Dart 2010 **Level II**, n=142, JS 5).

There is no evidence that patients who have depleted glutathione stores (eg patients who are malnourished or who have cirrhosis, hepatitis C or HIV) are at increased risk of liver dysfunction when exposed to therapeutic doses of paracetamol (Caparrotta 2018 **NR**; Graham 2013a **NR**). However, there is a potential association between acute liver failure and therapeutic paracetamol doses in paediatric patients with myopathies (Ceelie 2011 **Level IV**, n=2).

Paracetamol overdose is a common cause of acute liver failure (Caparrotta 2018 **NR**; Graham 2013a **NR**); in the USA 30,000 patients are hospitalised every year for paracetamol overdose, of which >50% are unintentional and 17% result in hepatotoxicity (Blieden 2014 **NR**). In a multiethnic Asian population, the hepatotoxicity rate was lower at 7.3% (Marzilawati 2012 **Level IV**, n=1,024). Treatment should be with acetylcysteine; there is no obvious advantage of IV over oral administration (Green 2013 **Level III-3 SR**, 16 studies, n=5,164). Treatment delays increase the incidence of hepatotoxicity; a detailed systematic review on interventions for treatment of paracetamol poisoning (Chiew 2018 **Level I** [Cochrane], 11 RCTs, n=700) and treatment guidelines have been published (Chiew 2020 **GL**).

4.1.3.2 | Renal effects

Newly diagnosed chronic kidney disease patients had an increased risk of end-stage renal disease with paracetamol use (OR 2.92; 95%CI 2.47 to 3.45) and higher risk with increasing dose exposure (Kuo 2010 **Level III-2**, n=19,163).

4.1.3.3 | Cardiovascular effects

There is a potential association between premature closure of ductus arteriosus and maternal paracetamol use in pregnancy (Allegaert 2019 **Level IV SR**, 12 studies, n=25). Given paracetamol has been shown to be as effective as ibuprofen for closure of a patent ductus arteriosus in preterm neonates (Ohlsson 2018 **Level I** [Cochrane], 8 RCTs, n=916), it seems reasonable to recommend that (as with all medications) use should be limited to the minimum dose and duration that is clinically necessary.

The overall effect of oral paracetamol on long term blood pressure remains unclear; observational studies (4 studies, n=155,910) show a variable association between paracetamol use and increased hypertension, but RCTs (6 RCTS, n=152) have inconsistent results (Turtle 2013 **Level III-3 SR**, 6 RCTs and 4 studies, n=156,062).

Paracetamol may interact with warfarin to increase the International Normalised Ratio (INR) (Hughes 2011 **Level IV SR**, 5 studies (& 5 case reports), n=345; Pinson 2013 **Level IV SR**, 6 studies (& 2 case reports); n=365) (5 studies and 2 case reports overlap).

For information on IV paracetamol and hypotension of see Section 5.2.1.

4.1.3.4 | Respiratory effects

In children, exposure to paracetamol was associated with an increased incidence of asthma (pooled OR 1.63; 95%CI 1.46 to 1.77) (Etminan 2009 **Level III-3 SR**, 19 studies, n=425,140). There are also claimed associations between the use of paracetamol in pregnancy and subsequent asthma in childhood (OR 1.19; 95%CI 1.12 to 1.27) (Fan 2017 **Level III-3 SR**, 13 studies, n=1,043,109). For details see Section 10.4.1.3.

4.1.3.5 | Carcinogenic effects

A review of epidemiological studies of paracetamol and cancer found mixed studies with respect to renal cell carcinoma and very limited positive studies with plasma cell disorders and leukaemia and otherwise a null effect on other types of cancer (Weiss 2016 **NR**).

4.1.3.6 | Neurodevelopmental effects

Epidemiological studies show an association between attention deficit disorder and paracetamol usage in pregnancy: for longer >29 d (HR 2.2; 95%CI 1.50 to 3.24), but not short duration use <8 d (HR 0.90; 95%CI 0.81 to 1.00) (Ystrom 2017 **Level III-3**, n=112,973). For details see Section 9.1.1.1 and 10.4.1.3.

Caution should be used with interpretation of all these retrospective analyses because of the possible effect of unknown or unmeasured confounding factors; the relevance to use limited to an acute situation is also unclear.

KEY MESSAGES

1. Paracetamol is an effective analgesic for acute pain; the incidence of adverse effects is comparable to placebo (**U**) (**Level I** [Cochrane Review]).
2. Paracetamol given in addition to PCA opioids reduces opioid consumption but does not result in a decrease in opioid-related adverse effects (**U**) (**Level I**).
3. Hepatotoxicity with therapeutic doses of paracetamol is extremely rare (**U**) (**Level IV**) and not associated with alcohol consumption (**U**) (**Level I** [PRISMA]).

The following tick boxes represent conclusions based on clinical experience and expert opinion:

☑ Emerging evidence suggests that maternal paracetamol use may influence premature closure of the fetal ductus arteriosus **(N).**

4.2 | Nonselective NSAIDs and coxibs

4.2.1 | Systemic nonselective nonsteroidal anti-inflammatory drugs

The term NSAIDs refers to both nonselective NSAIDs (nsNSAIDs) and coxibs (COX-2 selective inhibitors). NSAIDs have a spectrum of analgesic, anti-inflammatory and antipyretic effects and are effective analgesics in a variety of acute pain states. Many effects of NSAIDs can be explained by inhibition of prostaglandin synthesis in peripheral tissues, nerves and the CNS (Botting 2006 **NR**). However, NSAIDs and aspirin may have other mechanisms of action independent of any effect on prostaglandins, including effects on basic cellular and neuronal processes. Prostaglandins are produced by the enzyme prostaglandin endoperoxide synthase, which has both COX and hydroperoxidase sites. Subtypes of the COX enzyme have been identified; the "constitutive" COX-1 and the "inducible" COX-2; COX-3 does not appear to play a significant role in fever or inflammation in humans (Kam 2009 **NR**; Botting 2006 **NR**; Gajraj 2005 **NR**; Simmons 2004 **NR**).

Prostaglandins regulate many physiological functions including gastric mucosal protection, bronchodilation, renal tubular function and intrarenal vasodilation. Production of endothelial prostacyclin leads to vasodilation and prevents platelet adhesion, whereas thromboxane, produced from platelets by COX, results in platelet aggregation and vasoconstriction. With the exception of prostacyclin synthesis (mediated largely through COX-2), such physiological roles are mainly regulated by COX-1 and this is the basis for many of the adverse effects associated with nsNSAID use. Tissue damage induces COX-2 production leading to synthesis of prostaglandins that result in inflammation, peripheral sensitisation of nociceptors and consequently increased pain perception. COX-2 induction within the spinal cord plays a role in central sensitisation. COX-2 may also be "constitutive" in some tissues, including the kidney, cardiovascular system and brain and is overexpressed in some cancers (Kam 2009 **NR**).

NSAIDs are reversible COX inhibitors with the exception of aspirin, which binds covalently and acetylates the enzyme irreversibly. In platelets, the enzyme cannot be replenished leading to prolonged inhibition of platelet function with minimal inhibition of endothelial prostacyclin; this confers cardiovascular protection at low dosages of aspirin. NsNSAIDs are "nonselective" COX inhibitors that inhibit both COX-1 and COX-2. The coxibs have been developed to inhibit selectively, but not specifically, COX-2 (Botting 2006 **NR**; Gajraj 2005 **NR**; Simmons 2004 **NR**).

4.2.1.1 | Efficacy

Single doses of oral nsNSAIDs are effective in the treatment of pain after surgery (Moore 2015b **Level I** [Cochrane], RCTs ≈460, n≈50,000). For a list of NNTs for each medicine see Table 5.1. However, while useful analgesic adjuvants, they are often inadequate as the sole analgesic agent in the treatment of severe postoperative pain (Cepeda 2005 **Level II**, n=1,003, JS 5).

They are also effective analgesics in chronic low-back pain (Enthoven 2016 **Level I** [Cochrane], 13 RCTs, n= 4,807), renal colic (Afshar 2015 **Level I** [Cochrane], 50 RCTs, n=5,734), primary dysmenorrhoea (Marjoribanks 2015 **Level I** [Cochrane], 80 RCTs, n=5,820), migraine (Rabbie 2013 **Level I** [Cochrane], 9 RCTs, n=4,473); Derry 2013b **Level I** [Cochrane], 5 RCTs, n=1,356), acute ankle sprains (van den Bekerom 2015 **Level I**, 28 RCTs, n unspecified), biliary colic (Colli 2012 **Level I**, 11 RCTs, n=1,076) and acute muscle injury (Morelli 2018 **Level I** [PRISMA], 41 RCTs, n= 5,343).

For more information on use in migraine see Section 8.6.5.2 and in paediatrics Section 10.9.3.

Nonselective NSAIDs are integral components of multimodal analgesia (Young 2012 **NR**; Buvanendran 2009 **NR**; Kehlet 1997 **NR**). When given in combination with IV PCA morphine after surgery, nsNSAIDs result in better analgesia, reduced opioid consumption (MD over 24 h -10.2 mg; 95%CI -11.7 to -8.7) and a lower incidence of PONV (OR 0.70; 95%CI 0.53 to 0.88) (Maund 2011 **Level I**, 60 RCTs, n unspecified). Similar findings were made in the paediatric setting (Michelet 2012 **Level I**, 27 RCTs, n=985).

The combination of paracetamol and NSAIDs is more effective than paracetamol or NSAID alone (Martinez 2017 **Level I** [NMA], 2 RCTs, n=85 [Paracetamol/NSAID]; 60 RCTs, n=3,259 [NSAIDs]; 20 RCTs, n=699 [paracetamol]; Ong 2010 **Level I**, 21 RCTs, n=1,909). This is particularly well documented for the combination of paracetamol and ibuprofen in the setting of wisdom tooth removal (Bailey 2013 **Level I** [Cochrane], 7 RCTs, n=2,241).

Administration of ketorolac to patients with rib fractures reduced the incidence of pneumonia (OR 0.14; 95%CI 0.04 to 0.46) and reduced requirements for ICU admission and ventilation (Yang 2014 **Level III-2**, n=619). The perioperative use of nsNSAIDs, predominantly rectal diclofenac and indomethacin, for endoscopic retrograde cholangiopancreatography (ERCP) reduces the risk of post-ERCP pancreatitis vs placebo (RR 0.54; 95%CI 0.45 to 0.64) (Liu 2019 **Level I** [PRISMA], 19 RCTs, n=5,031).

In cancer surgery, initial data suggested benefits of intraoperative use of nsNSAIDs in breast cancer patients (reduced recurrence rate and lower mortality) and in lung cancer patients (lower metastases risk and longer survival) (Forget 2013 **Level III-2**, n=720). In breast cancer surgery, intraoperative administration of nsNSAIDs (ketorolac or diclofenac) was associated with an improved disease-free survival (HR 0.57; 95%CI 0.37 to 0.89) and better overall survival (HR 0.35; 95%CI 0.17 to 0.70) (Forget 2014 **Level III-2**, n=720). However, a more recent case control study found a reduction of distant recurrences with ketorolac, but not diclofenac (Desmedt 2018 **Level III-2**, n=1,834). Despite epidemiological associations with NSAIDs reducing prostate cancer risk, pre-operative courses of celecoxib 400mg BD did not appear to increase tumor cell apoptosis in surgical specimens (Flamiatos 2017 **Level II**, n=28, JS 5). NSAID administration (primarily ibuprofen) after colorectal surgery was associated with reduced recurrence in a historical case series (aHR 0.84; 95%CI 0.72 to 0.99) (Schack 2019 **Level III-3**, n=2,308).

4.2.1.2 | Adverse effects

Adverse effects of nsNSAID are more common with long-term use; the major concerns relate to the gastrointestinal, renal and cardiovascular systems. In the perioperative and acute period, the main concerns are renal impairment, interference with platelet function, wound and bone healing and peptic ulceration or bronchospasm in individuals at risk. Certain risks are accentuated in the perioperative period because of pre-existing comorbidities, concurrent medications, haemodynamic disturbances, fluid shifts, activation of the neurohumoral stress response and deficient enteral feeding.

In general, the risk and severity of nsNSAID-associated adverse effects is increased in elderly people (Juhlin 2005 **Level II**, n=14, JS 4; Pilotto 2003 **Level III-2**, n=2,251). For this reason, opioids are sometimes used in preference to NSAIDs. A cohort study of elderly patients with arthritis (mean age 80 y) started on nsNSAIDs, coxibs or opioids challenges the assumption that opioids are safer in that population, showing increased rates of fracture, hospital admission and all-cause mortality in the opioid cohort and similar or higher rates of cardiovascular, renal and gastrointestinal adverse effects (Solomon 2010 **Level III-2**; n=12,840). Overall the nsNSAID cohort appeared to have the lowest risk for adverse effects.

Gastrointestinal effects

Chronic nsNSAID use is associated with peptic ulceration and bleeding and the latter may be exacerbated by the antiplatelet effect (Bhala 2013 **Level I**, 754 RCTs, n=353,809). All long-term nsNSAID regimens increase the risk of upper gastrointestinal complications (diclofenac RR 1.89; 95%CI 1.16 to 3.09; ibuprofen RR 3.97; 95%CI 2.22 to 7.10; naproxen RR 4.22; 95%CI 2.71 to 6.56). The combination of an nsNSAID with an SSRI further increases the risk of upper gastrointestinal bleeding (Anglin 2014 **Level III-2 SR**, 19 studies, n>393,268). In patients with rheumatoid arthritis, steroids and NSAIDs appear to be additive in increasing gastric ulceration (Tsujimoto 2018 **Level III-2**, n=1,704).

Acute gastroduodenal damage and bleeding can also occur with short-term nsNSAID use; the risk is increased with higher doses, a history of peptic ulceration, use for >5 d and in patients >75 years of age (Strom 1996 **Level III-3**, n=10,272 [uses of parenteral ketorolac]). After 6.5 d of naproxen and 5 d of ketorolac use in healthy elderly subjects (65 to 75 y of age), ulcers were found on gastroscopy in 18 and 23% of cases respectively (Goldstein 2003 **Level II**, n=168, JS 4; Stoltz 2002 **Level II**, n=94, JS 4; Harris 2001 **Level II**, n=17 [terminated due to high incidence of gastrointestinal ulcers in both nsNSAID groups], JS 4). Importantly, such endoscopic findings do not correlate with dyspeptic symptoms; these consequently cannot be relied upon as an indicator of potential harm (Dib 2014 **Level III-2**, n=1,231).

The relative risk of hospital admission for perforations, ulcers and bleeds associated with nsNSAIDs is estimated as 5.3 vs people not consuming nsNSAIDs (Lanas 2003 **Level III-2**, n=3,532). Use of ketorolac and piroxicam carried the highest risk. Concurrent use of a proton-pump inhibitor (PPI) significantly reduced the incidence of nsNSAID-related peptic ulcer disease (Targownik 2008 **Level III-2**, n=35,339). However, concurrent use of a PPI and nsNSAID (diclofenac) was still associated with an increased risk of clinically significant upper or lower gastrointestinal adverse effects vs coxib alone (RR 4.3; 95%CI 2.6 to 7.0) (Chan 2010b **Level II**, n=4,484, JS 5). Suppression of gastric acid by PPI to reduce nsNSAID-induced gastropathy may increase the risk of enteropathy lower in the gastrointestinal tract (Blackler 2014 **NR**), possibly from changes in gut flora (Minalyan 2017 **NR**).

Colonic diverticular bleeding is also increased by aspirin (RR 1.73; 95%CI 1.31 to 2.30) and other nsNSAIDs (RR 2.24; 95%CI 1.63 to 3.09) (Yuhara 2014 **Level III-2 SR**, 6 studies, n≈52,000).

Renal effects

Renal prostaglandins regulate tubular electrolyte handling, modulate the actions of renal hormones and maintain renal blood flow and glomerular filtration rate in the presence of circulating vasoconstrictors. The adverse renal effects of chronic nsNSAID use are common and well recognised. In some clinical conditions, including hypovolaemia, dehydration and major surgery, high circulating concentrations of the vasoconstrictors angiotensin II, noradrenaline and vasopressin increase production of intrarenal vasodilators including prostacyclin; maintenance of renal function may then depend on prostaglandin synthesis and thus can be sensitive even to brief nsNSAID administration (McDowell 2014 **NR**).

In patients with normal preoperative renal function, NSAIDs vs placebo may slightly increase serum creatinine (MD 3.23 micmol/L; 95%CI -0.80 to 7.26), however effects on acute kidney injury and need for renal replacement therapy are uncertain (Bell 2018 **Level I** [Cochrane], 26 RCTs, n=8,943). The risk of adverse renal effects of nsNSAIDs and coxibs is increased in the presence of factors such as pre-existing renal impairment, hypovolaemia, hypotension, use of other nephrotoxic agents including angiotensin-converting enzyme (ACE) inhibitors (Juhlin 2005 **Level II**, n=14, JS 4), IV contrast media and aminoglycosides (RCA 1998 **Level IV**). Of note, a trial of naproxen following cardiac surgery was stopped because of an increased rate of renal failure (7.3 vs 1.3%) (Horbach 2011 **Level II**, n=161, JS 5). This is confirmed by an analysis of a French pharmacovigilance database, which showed that acute renal failure caused by drug interactions between NSAIDs

and ACE inhibitors, angiotensin-receptor blockers or diuretics was a common issue (Fournier 2014 **Level IV**, n=11,442 [notifications of adverse drug reactions]).

After nephrectomies, evidence is limited and contradictory with a continuous infusion of ketorolac for 24 h after laparoscopic donor nephrectomy having no significant effect on renal function for up to 18 mth postoperatively (Grimsby 2014 **Level II**, n=111, JS 3), but a retrospective case series of donor nephrectomies found a reduction in renal function at 12 mth despite less pain and a shorter LOS (Takahashi 2017 **Level III-2**, n=251). Another retrospective case series found no associations at 1 wk, 1 y or 5 y (Tabrizian 2019 **Level III-2**, n=862).

In the PRECISION trial, long-term use of ibuprofen for treatment of arthritis was associated with significantly more serious renal events than celecoxib (HR 0.61; 95%CI 0.44 to 0.85), but not naproxen (HR 0.79; 95% CI, 0.56 to 1.12) (Nissen 2016 **Level II**, n=24,081, JS 5).

Overall in the general population, NSAID (including coxib) usage is associated with an increased risk of AKI (OR 1.73; 95%CI 1.44 to 2.07) as well as exacerbation in patients with CKD (OR 1.63; 95%CI 1.22 to 2.19) (Zhang 2017a **Level III-3 SR**, 10 studies, n=1,609,163).

For more information on paediatric effects see Section 10.4.2.3.

Cardiovascular effects

Most publications looking at the risk of cardiovascular adverse effects associated with nsNSAID use also include information relating to risks with coxibs (see the more detailed discussion under Section 4.3.2 below).

For some years it has been known that ibuprofen may impede access of aspirin to platelet COX-1 and may abrogate the protective effect of aspirin (Hudson 2005 **Level III-2**, n=18,503; MacDonald 2003 **Level III-2**, n=7,107). Subsequent research indicates that a degree of inhibition may occur with most nsNSAIDs and even some coxibs; while not blocking COX-1, they may block aspirin from reaching it (Nalamachu 2014 **NR**). This is backed up by an ad hoc analysis of PRECISION trial data which showed worse cardiovascular outcomes of aspirin/ibuprofen vs aspirin/celecoxib (HR 1.27; 95%CI 1.06 to 1.51) (Reed 2018 **Level III-2**, n=23,953). Impaired aspirin inhibition of platelet function is described in multiple studies for ibuprofen, flufenamic acid, mefenamic acid, piroxicam, nimesulide and dipyrone, while there is conflicting evidence with respect to naproxen, celecoxib, rofecoxib and sulindac, and no inhibition was seen with diclofenac, etoricoxib, ketorolac, ketoprofen, meloxicam or paracetamol (Polzin 2013 **Level III-2**; Meek 2013 **EH**; Saxena 2013 **EH**). The FDA issued a caution specifically about the concomitant use of aspirin and ibuprofen, which states that ibuprofen should be "*given at least 8 hours before or at least 30 minutes after immediate release aspirin*" (FDA 2006 **GL**).

Platelet effects and bleeding

Nonselective NSAIDs inhibit platelet function on aggregometry with naproxen and ibuprofen showing a mild antiplatelet effect for up to 72 and 48 h respectively where meloxicam and celecoxib show essentially no antiplatelet activity (Scott 2014 **BS**).

More recent studies and meta-analyses seem to show less impact of perioperative nsNSAIDs on bleeding compared to older ones, perhaps reflecting improvements in surgical technique and reduced total blood loss. A recent meta-analysis found no increased haematoma risk in plastic surgery (OR 1.39; 95%CI 0.82 to 2.37) (Walker 2019 **Level I** [PRISMA] 15 studies, n=3,064) and in another meta-analysis ketorolac did not increase the rate of postoperative bleeding (OR 1.1; 95%CI 0.61 to 2.06) (Gobble 2014 **Level I**, 27 RCTs, n=2,314). In a cohort study in paediatric neurosurgery, ketorolac was not associated with an increase in clinically significant bleeding events (OR 0.69; 95%CI 0.15 to 3.1) or radiographic haemorrhage (OR 0.81; 95%CI 0.43 to 1.51) (Richardson 2016 **Level III-2**, n=1,451). In contrast, in a previous meta-analysis the rate of surgery-related bleeding was 2.4% after nsNSAIDs vs 0.4% with placebo (Maund 2011 **Level I**, 6 RCTs [bleeding], n=695). In another meta-analysis the use of nsNSAIDs showed a significant increase in

risk of severe bleeding from 0 to 1.7% vs placebo (NNH 59) (Elia 2005 **Level I**, 52 RCTs, n=4,893). A retrospective analysis using data from 2003 to 2016 looking at transfusion risk for hip fractures found a small increase in risk of transfusion with preoperative nsNSAID use within 90 d of surgery (RR 1.07; 95%CI 1.04 to 1.10) (Glassou 2019 **Level III-2**, n=74,791). Other older evidence showing an increased risk of bleeding includes ibuprofen in total hip arthroplasty (THA) (Fransen 2006 **Level II**, n=902, JS 5), tenoxicam in otorhinolaryngological surgery (Merry 2004 **Level II**, n=1,001, JS 5) and diclofenac vs rofecoxib in gynaecological and breast surgery (Hegi 2004 **Level II**, n=50, JS 5).

Bleeding after tonsillectomy is of clinical significance but occurs infrequently; nsNSAID use and post tonsillectomy bleeding remains controversial with conflicting evidence. The most recent meta-analysis found no statistically significant increase of any outcome related to bleeding with the perioperative use of nsNSAIDs in tonsillectomy (Riggin 2013 **Level I**, 36 RCTs, n=3,193). This was found for most severe bleeding outcome (OR 1.30; 95%CI 0.90 to 1.88), bleeding requiring reoperation (OR 1.32; 95%CI 0.59 to 2.95), bleeding requiring readmission (OR 1.08; 95%CI 0.54 to 2.15), bleeding managed conservatively (OR 1.56; 95%CI 0.91 to 2.66) and secondary haemorrhage (OR 0.90; 95%CI 0.40 to 2.01). There is also no increased bleeding outcome in the paediatric subgroup of this meta-analysis (19 RCTs, n=1,747), which is in line with another meta-analysis in children only (OR 1.69; 95%CI 0.71 to 4.01) (Lewis 2013 **Level I** [Cochrane], 15 RCTs, n=1,101) (see also Section 10.4.2.3 for details). However, neither of these meta-analyses include a subsequent multicentre RCT which was unable to show non-inferiority of ibuprofen to paracetamol with respect to bleeding requiring surgery in paediatric patients (1.2% vs 2.9%; p=0.12 for noninferiority) (Diercks 2019 **Level II**, n=741, JS 5). The above meta-analysis (Riggin 2013 **Level I**, 46 RCTs, n=4,878) could not identify a specific risk for any nsNSAID including aspirin (OR 4.23; 95%CI 0.64 to 27.66) (3 RCTs, n=1,610) and ketorolac (OR 2.01; 95%CI 0.62 to 6.54) (8 RCTs; n=579). These findings are contradicted by a previous larger meta-analysis on aspirin (OR 1.94; 95%CI 1.09 to 3.42) (Krishna 2003 **Level I**, 7 RCTs, n=1,368) and a systematic review on ketorolac (Chan 2014 **Level III-2 SR** [PRISMA], 10 studies, n=1,357). The latter found an overall increased risk of bleeding post tonsillectomy with ketorolac (RR 2.04; 95%CI 1.32 to 3.15), which was also found in adults (RR 5.64; 95%CI 2.08 to 15.27) (3 studies, n=246) but not in children (RR 1.39; 95%CI 0.84 to 2.30) (7 studies, n=1,111).

For more information on paediatric effects see Section 10.4.2.3 and on post-tonsillectomy pain see Sectioin 8.6.7.3.

Hypersensitivity and NSAID-exacerbated respiratory disease (NSAID-ERD)

NSAIDs, especially nsNSAIDs, are one of the most common causes of drug-induced hypersensitivity reactions. Acute reactions include rhinitis, asthma, urticaria, angioedema and anaphylaxis, while delayed reactions include fixed drug eruptions, Stevens-Johnson syndrome, toxic epidermal necrolysis, maculopapular reactions, pneumonitis, nephritis or aseptic meningitis (Kowalski 2019 **GL**). This guideline advises on classification, diagnosis and management.

NSAID-ERD has a community prevalence of 1.8% and affects 10-20% of adults with asthma and 5% of children with asthma (Kowalski 2019 **GL**). Bronchospasm usually occurs within 1 to 2 h of exposure and precipitation is related to COX-1 activity, while both COX-2 selective NSAIDs (eg celecoxib and etoricoxib) and COX-2 preferential inhibitors (eg nimesulide and meloxicam) being usually well tolerated. See also Section 4.2.2.2 below.

Bone and ligament healing

Ever since the first study in 1976 showed impaired osteoblastic activity with indomethacin in rodent bone models of fracture there has been concern about the effect of NSAIDs on bone healing. The most recent meta-analysis of cohort studies shows an association between long-term NSAID usage and delayed union or disunion (OR 2.07; 95%CI 1.19 to 3.61), but not with low dose or short duration (<2 wk) (OR 1.68; 95%CI 0.63 to 4.46) or in paediatric populations (OR

0.58; 95%CI 0.27 to 1.21) (Wheatley 2019 **Level III-2 SR**, 19 studies, n=15,242 bones). Given the non-randomised cohort nature of this evidence, it may be that patients are taking NSAIDs for longer for a painful non-healing fracture rather than NSAIDs being a causative agent and a firm conclusion is unlikely without a large and well-designed randomised control trial.

In a meta-analysis which included primarily anterior cruciate ligament (ACL) reconstructions (93%) no difference in surgical failure was seen (3.6 vs 3.7%) (Constantinescu 2019 **Level III-2 SR**, 4 studies, n=4,451)

Anastomotic leakage and colorectal surgery

Rodent models of anastomotic leakage have for some time shown reduced collagen formation in rodents given diclofenac leading to concerns about the effect of NSAIDs on anastomotic leak rate in humans (Klein 2012 **BS**). The two most recent meta-analyses of primarily cohort studies show an increased anastomotic leak rate with nsNSAIDs (OR 2.02; 95%CI 1.62 to 2.50 and OR 1.79; 95%CI 1.47 to 2.18 respectively) (Modasi 2019 **Level III-2 SR** [PRISMA], 8 studies, n=9,835; Huang 2018 **Level III-2 SR**, 17 studies, n=26,098) (4 studies overlap). Subgroup analysis was unable to show any increase with either selective COX-2 inhibitors (OR 1.17; 95%CI 0.50 to 2.74) or ketorolac (OR 1.36; 95%CI 0.89 to 2.06)). A high risk of publication bias was detected.

NSAIDs do, however, improve recovery of gastrointestinal function with evidence for faster return of flatus (MD -17.73 h; 95%CI -21.26 to -14.19), stool passage (MD -9.52 h; 95%CI -14.74 to -4.79), and oral feeding tolerance (MD -12.00 h; 95%CI -18.01 to -5.99 h) (Chapman 2019 **Level I** [PRISMA], 6 RCTs, n=563). NSAIDs also reduce the recurrence rate of colorectal adenomas after endoscopic resection (RR 0.68; 95%CI 0.63 to 0.73) (Wang 2015a **Level I**, 9 RCTs, n=8,521).

Central nervous system effects

CNS effects of NSAIDs are poorly defined, but range from symptomatic adverse effects such as headache or dizziness through to possible disease modification in conditions such as Parkinson's disease and dementia (Auriel 2014 **NR**). Evidence on effects on cognitive decline is conflicting with long-term NSAID use showing a small protective effect in one metanalysis of cohort studies (RR 0.87; 95 %CI 0.81 to 0.94) (Wang 2016b **Level III-2 SR** [PRISMA], 11 studies, n=36,165), but no protective effect in another looking at low dose aspirin (Veronese 2017 **Level III-2 SR** [PRISMA], 3 RCTs & 5 studies, n=36,196).

4.2.2 | Systemic cyclooxygenase-2 selective inhibitors (Coxibs)

Coxibs selectively inhibit the inducible COX enzyme, COX-2, and relatively spare constitutive COX-1 (see above). The coxibs available at present are celecoxib, etoricoxib, polmacoxib and parecoxib (the injectable prodrug of valdecoxib). By sparing physiological tissue prostaglandin production while inhibiting inflammatory prostaglandin release, coxibs offer the potential for effective analgesia with fewer adverse effects than nsNSAIDs. However, as noted above, some constitutive physiological synthesis of prostaglandins is also mediated through COX-2, and coxibs may still inhibit COX-1 to some extent.

4.2.2.1 | Efficacy

Coxibs are as effective as nsNSAIDs for postoperative pain (Moore 2015b **Level I** [Cochrane], ≈460 RCTs, n≈50,000), osteoarthritis of the knee (Smith 2016 **Level I** [PRISMA], 9 RCTs, n= 2,937) and chronic low-back pain (Chung 2013 **Level I** [PRISMA], 25 RCTs, n=5,935). NNTs are comparable to those for nsNSAIDs for the treatment of moderate to severe acute pain. For a list of NNTs for each mediciation see Table 5.1.

When given in combination with opioids after surgery, coxibs show reduced opioid consumption similar to nsNSAIDs (MD over 24 h -10.9 mg; 95%CI -12.8 to -9.1) but no significant reductions in pain scores or opioid-related adverse effects (Maund 2011 **Level I**, 60 RCTs, n unspecified). When given as a single dose preoperatively, coxibs provide a reduction in mean postoperative analgesic requirements at 24 h (MD -0.68; 95%CI -0.95 to -0.33) (Nir 2016 **Level I** [PRISMA], 13 RCTs, n=1,079).

After total knee arthroplasty (TKA), use of coxibs in the perioperative period reduces pain scores, opioid consumption, PONV and pruritus and improves range of motion without increased blood loss (Lin 2013 **Level I**, 8 RCTs, n=571). Continuation of coxibs for 6 wk postoperatively resulted in ongoing improved analgesia and reduced opioid consumption with improved rehabilitation conveying benefits on knee flexion for up to 1 y (Schroer 2011 **Level II**, n=107, JS 5). The risk-benefit ratio for coxibs as a discharge medication after orthopaedic surgery is superior to that for nsNSAIDs (Roberts 2012 **Level I** [PRISMA], 23 RCTs, n unspecified).

Pain relief at rest and on movement and satisfaction were improved when oral celecoxib was added to thoracic PCEA using local anaesthetic and opioid (Senard 2010 **Level II**, n=40, JS 5).

Celecoxib given pre-operatively is effective at reducing 24 h parenteral MED consumption (MD 4.13 mg; 95%Cl 5.58 to 2.67), pain scores at 24 h (MD -1.02/10; 95%CI -1.54 to -0.50) and reducing postoperative nausea and vomiting by 44% and 38% respectively (Khan 2016 **Level I**, 14 RCTs, n=994).

A meta-analysis of parecoxib in orthopaedic surgery in elderly patients shows a reduction in perioperative cognitive dysfunction up to 7 d (RR 0.32; 95%CI 0.16 to 0.63), but not at 3 mth (RR 0.40; 95%CI 0.16 to 1.02) (Huang 2019 **Level I** [PRISMA], 2 RCTs, n=200); these results should be viewed with caution as outcome measures were not robust. A similar effect was shown with celecoxib after arthroplasty (Zhu 2018b **Level II**, n=178, J 5).

4.2.2.2 | Adverse effects

Gastrointestinal effects

In the PRECISION trial, celecoxib/esomeprazole was associated with significantly less gastrointestinal events than ibuprofen/esomeprazole (HR 0.43; 95%CI 0.27 to 0.68) and naproxen/esomeprazole (HR 0.51; 95%CI 0.32 to 0.81) (Yeomans 2018 **Level II**, n=24,081, JS 5). Despite a possible dosing inequality this is supported by a trial of naproxen 500 mg BD + PPI vs Celecoxib 100 mg BD + PPI in patients with a recent GI bleed (Chan 2017 **Level II**, n=514, JS 5). Rebleed rates were 5.6% (95%CI 3.3 to 9.2) in the celecoxib group and 12.3% (95%CI 8.8 to 17.1) in the naproxen group (HR 0.44; 95%CI 0.23 to 0.82). Etoricoxib in osteoarthritis similarly shows superiority to nsNSAIDs in terms of GI event rates (RR 0.67; 95%CI 0.59 to 0.76) (Feng 2018 **Level I** [PRISMA], 9 RCTs, n=39,442).

Short-term use (< 7 d) of parecoxib/valdecoxib, as required to treat acute pain, results in gastroscopic ulcer rates similar to placebo in elderly patients (65 to 75y) at increased risk (Goldstein 2003 **Level II**, n=168, JS 4; Stoltz 2002 **Level II**, n=94, JS 4; Harris 2001 **Level II**, n=17 [terminated due to high incidence of gastrointestinal ulcers in both nsNSAID groups], JS 4). This contrasts with increased rates of ulceration with nsNSAIDs in the same setting.

Despite relative safety in comparison to nsNSAIDs, long term usage of COX-2 inhibitors is still associated with an increased GI event rate in cohort studies of non-use versus etoricoxib (RR 4.85; 95%CI 2.64 to 8.93), rofecoxib (RR 2.02; 95%CI 1.56 to 2.61) and celecoxib (RR 1.53; 95%CI 1.19 to 1.97) (Martin Arias 2019 **Level III-2 SR** [PRISMA], 28 studies, n=1,255,401). These results might be unexpected given that both rofecoxib and etoricoxib are more COX-2 selective than celecoxib, however current understanding of gastrointestinal injury includes multiple mechanisms such as mitochondrial uncoupling and ion-trapping that may be unrelated to COX inhibition (Bjarnason 2018 **NR**). In a pooled analysis of COX-2 inhibitor use in osteoarthritis an increase in

gastrointestinal events is seen vs placebo (RR 1.19, 95% CI 1.03 to 1.38) (Curtis 2019 **Level I** [PRISMA], 40 RCTs, n unspecified).

Renal effects

COX-2 is constitutively expressed in the kidney and is highly regulated in response to alterations in intravascular volume. COX-2 has been implicated in maintenance of renal blood flow, mediation of renin release and regulation of sodium excretion (Cheng 2004 **NR**; Kramer 2004 **NR**).

A meta-analysis of perioperative parecoxib found no increase in renal failure vs placebo (Schug 2017 **Level I**, 26 RCTs, n=9,282). In contrast (and as with nsNSAIDs), a statistically significant increased risk of renal failure was reported following administration of coxibs in cardiac surgery patients (NNH 73) (Elia 2005 **Level I**, 3 RCTs [cardiac surgery], n=803).

In the PRECISION trial, long-term ibuprofen was associated with significantly more serious renal events than celecoxib (HR 0.61; 95%CI 0.44 to 0.85), but naproxen was not worse than celecoxib (HR 0.79; 95%CI 0.56 to 1.12) (Nissen 2016 **Level II**, n=24,081, JS 5).

Analysis of the effects of different coxibs on renal function showed heterogeneity within the class as rofecoxib was associated with increased risk of renal dysfunction, while celecoxib was not (Zhang 2006 **Level I**, 114 RCTs, n=116,094).

A subsequent meta-analysis of cohort studies of the general population showed little evidence of lower AKI incidence with increasing COX-2 selectivity (OR 1.84; 95%CI 1.54 to 2.19 [no COX-2 selectivity] vs OR 1.41; 95%CI 1.07 to 1.87 [≥5 fold COX-2 selectivity]) (Zhang 2017a **Level III-2**, 10 studies, n=1,609,163).

Cardiovascular effects

Cardiovascular risk with coxibs seems very dependent on the coxib in question. This may reflect non-COX dependent effects that NSAIDs may have on the cardiovascular system (Walker 2018 **NR**).

In acute pain management, short-term use of parecoxib (< 7 d) after noncardiac surgery does not increase the risk of cardiovascular adverse effects (Schug 2017 **Level I**, 26 RCTs, n=9,282). Similarly, short-term use of other NSAIDs (meloxicam, ketorolac, celecoxib for a mean of 3 d) after lower limb total joint replacement did not increase the risk of myocardial infarction postoperatively vs nonuse (aOR 0.95; 95%CI 0.5 to 1.8) (Liu 2012 **Level III-2**, n=10,873). However, an increase in the incidence of cerebrovascular and cardiovascular events has been reported in patients given parecoxib, then valdecoxib, after CABG surgery (Furberg 2005 **Level I**, 2 RCTs, n=2,098). The FDA has contraindicated the use of all NSAIDs in the immediate postoperative period following CABG surgery (FDA 2007 **GL**). A subsequent retrospective observational study with ketorolac has not confirmed these concerns (Oliveri 2014 **Level III-2**, n=1,309).

Absolute long-term cardiovascular risk with chronic usage of NSAIDs remains unclear as the recent large prospective studies were non-inferiority trials without a placebo arm. Studies are conflicting as to cardiovascular risk with individual drugs.

In a review of epidemiological data, rofecoxib showed increased cardiovascular risks vs other coxibs and nsNSAIDs (Gunter 2017 **Level III-2 SR**, 26 studies, n=228,389). In the PRECISION trial in patients with arthritis, there was no difference in cardiovascular event rates between long-term celecoxib vs ibuprofen (HR 0.81; 95%CI 0.65 to 1.02) or vs naproxen (HR 0.90; 95%CI 0.71 to 1.15) (Nissen 2016 **Level II**, n=24,081, JS 5). The SCOT trial randomised patients over 60 y with arthritis to either continue their current NSAID or be changed to celecoxib and found no difference in cardiovascular risk (HR 1.1; 95%CI 0.81 to 1.55) (MacDonald 2017, **Level II**, n=7,297, JS 3).

A Bayesian meta-analysis found no increased risk of myocardial infarction for celecoxib (OR 1.24; 95%CI 0.91 to 1.82) or ibuprofen (OR 1.48; 95%CI 1.00 to 2.26), but increased risk for diclofenac (OR 1.50; 95%CI 1.06 to 2.04), naproxen (OR 1.53; 95%CI 1.07 to 2.33) and rofecoxib

(OR 1.58; 95%CI 1.07 to 2.17) (Bally 2017 **Level III-2**, n=446,763 [61,460 myocardial infarctions]). This data directly conflicts with a previous meta-analysis that found no increased cardiovascular risk with naproxen, diclofenac or etoricoxib (Trelle 2011 **Level I**, 31 RCTs, n=116,429).

Once daily administration of celecoxib eg 400 mg (RR 1.1; 95%CI 0.6 to 2.0) was associated with a lower cardiovascular risk than giving 400 mg as divided doses of 200 mg twice daily (RR 1.8; 95%CI 1.1 to 3.1) (Solomon 2008 **Level I**, 6 RCTS, n=7,950).

All NSAIDs approximately double the risk of congestive heart failure (Bhala 2013 **Level I**, 54 RCTs, n=353,809). However, this analysis pooled all coxib data so that data from rofecoxib and celecoxib was not differentiated. A subsequent meta-analysis of coxibs which looked at heart failure in osteoarthritis found no increase in congestive heart failure (RR 1.18; 95%CI 0.24 to 5.71) (4 RCTs), but increased risk of peripheral oedema (RR 1.61; 95%CI 1.09 to 2.40) (15 RCTs) and generalised oedema (RR 1.91; 95%CI 1.08 to 3.39) (8 RCTs) (Curtis 2019 **Level I** [PRISMA], 40 RCTs, n unspecified). In a nested cohort study which matched 92,163 heart failure admissions with 8,246,403 controls, all NSAIDs except celecoxib were associated with an increased risk of heart failure (Arfe 2016 **Level III-2**, n=8,566,955).

A small increase in the risk of atrial fibrillation with NSAID usage (RR 1.12; 95%CI 1.06 to 1.18) has been documented (Krijthe 2014, **Level III-2**, n=8,423).

In comparison with a historical cohort, the use over a subsequent 10 mth period of parecoxib and valdecoxib 40 mg daily for 2 to 3 wk was associated with an increase in the rate of vascular free flap failure from 7 to 29%, which fell to 4% after the coxibs were no longer used (Al-Sukhun 2006 **Level III-3**, n=180). These retrospective data, which are subject to potential confounding factors, are supported by one study in rats showing a harmful effect of parecoxib on flap survival (Ren 2013 **BS**), which did not occur with celecoxib (Wax 2007 **BS**). A retrospective cohort study using ketorolac after head and neck free flaps found no bleeding complications and no increased risk of free flap failure (Schleiffarth 2014 **Level III-2**, n=138 [free flaps]).

Platelet effects and bleeding

Platelets express only COX-1, not COX-2, and as a consequence, coxibs do not impair platelet function (Munsterhjelm 2006 **Level II EH**, n=18, JS 4). This is consistent with a study on platelet aggregometry with meloxicam and celecoxib show essentially no antiplatelet activity (Scott 2014 **BS**). COX-2 selective NSAIDs show no difference in the risk of postoperative bleeding events (RR 0.92; 95%CI 0.63 to 1.33), intraoperative blood loss (WMD -4.38 mL; 95%CI -14.69 to 5.92), postoperative blood loss (WMD -13.89 mL; 95%CI -30.24 to 2.47), and 24 h postoperative haemoglobin loss (WMD 0.47 g/dL; 95%CI 0.14 to 1.09) vs nsNSAIDs, other analgesics, or placebo (Teerawattananon 2017 **Level I**, 16 RCTs, n=1,704).

Allergic reactions and NSAID-exacerbated respiratory disease

Patients with anaphylactoid reactions to dipyrone and nsNSAIDs (mainly propyphenazone and diclofenac) tolerated oral challenges with rofecoxib and celecoxib (Quiralte 2004 **Level IV**, n=33).

Coxibs, administered at analgesic doses, do not produce bronchospasm in patients with NSAID-exacerbated respiratory disease (Morales 2013 **Level I** [PRISMA], 14 RCTs, n=426).

Bone and ligament healing

At present, data on the effect of coxibs on bone healing are mainly restricted to animal models, where they undoubtedly affect bone remodelling (Kurmis 2012 **NR BS**). Celecoxib after THA reduced the frequency and severity of heterotopic bone formation (Lavernia 2014 **Level III-2**, n=170**;** Oni 2014 **Level III-2**, n=214). There is no good evidence of any clinically significant inhibitory effect of coxibs on bone healing (Kurmis 2012 **NR**; Gerstenfeld 2004 **NR**; Bandolier 2004 **NR**).

In a small single centre trial, re-tear rates were increased following rotator cuff repairs in celecoxib(11/30 [37%]) vs ibuprofen (2/27 [7%]) and tramadol treated patients (1/25 [4%]) groups (Oh 2018 **Level II**, n=180, JS 5). This matches animal model data from rabbits (Lu 2015 **BS**).

Anastomotic leakage

There is no increased leakage rate with perioperative coxibs (Modasi 2019 **Level III-2 SR** [PRISMA], 8 studies, n=9,835; Huang 2018 **Level III-2 SR**,17 studies, n=26,098) (4 studies overlap). See 4.2.1.2 for more detail.

KEY MESSAGES

Efficacy of systemic NSAIDs

1. Nonselective NSAIDs are effective in the treatment of acute postoperative pain, renal colic, migraine, primary dysmenorrhoea (**S**) (**Level I** [Cochrane Review]), acute muscle injury (**N**) (**Level I** [PRISMA]), chronic low-back pain (**U**) (**Level I** [PRISMA]) and acute ankle sprain (**U**) (**Level I**).
2. Coxibs are as effective as nonselective NSAIDs in the treatment of acute pain (including postoperative pain) (**S**) (**Level I** [Cochrane Review]), chronic low-back pain (**U**) (**Level I** [PRISMA]) and osteoarthritis of the knee (**N**) (**Level I** [PRISMA]).
3. Nonselective NSAIDs given in addition to paracetamol improve analgesia compared with either medicine given alone (**S**) (**Level I**), in particular ibuprofen combined with paracetamol (**U**) (**Level I** [Cochrane Review]).
4. The risk-benefit ratio for coxibs as a discharge medication after orthopaedic surgery is superior to that for nonselective NSAIDs (**U**) (**Level I** [PRISMA]).
5. Nonselective NSAIDs given in addition to PCA opioids reduce opioid consumption and the incidence of nausea and vomiting (**U**) (**Level I**).
6. Coxibs given in addition to PCA opioids reduce opioid consumption but do not result in a decrease in opioid-related adverse effects (**U**) (**Level I**), except after total knee arthroplasty, where they reduce pain scores and adverse effects and improve outcomes (**U**) (**Level I**).
7. Celecoxib given as a single pre-operative dose is effective at reducing opioid usage, pain scores at 24 hours and postoperative nausea and vomiting (**N**) (**Level I**).

Adverse effects of systemic NSAIDs

8. In patients with normal preoperative renal function nonselective NSAIDs slightly increase serum creatinine, but effects on acute kidney injury and need for renal replacement therapy are uncertain due to lack of evidence (**W**) (**Level I** [Cochrane Review]).
9. Nonselective NSAIDs may increase the risk of any bleeding-related outcome after tonsillectomy in adults (**U**) (**Level I**); however, not in paediatric patients (**U**) (**Level I** [Cochrane Review]) except in a large non-inferiority RCT where need for surgical intervention was increased with ibuprofen versus paracetamol (**Q**) (**Level II**). There is an increase in bleeding complications with aspirin in adults and children (**U**) (**Level I**) and with ketorolac in adults only (**U**) (**Level III-2** [PRISMA]).
10. Nonselective NSAIDS, but not coxibs, may cause bronchospasm in individuals known to have NSAID-exacerbated respiratory disease (**U**) (**Level I** [PRISMA]).
11. Coxibs and nonselective NSAIDs exert individual (non-class) adverse effects on the cardiovascular system with rofecoxib appearing to be worse than other coxibs and nonselective NSAIDs (**N**) (**Level I**). Celecoxib is no worse than naproxen or ibuprofen (**N**) (**Level II**) and better than ibuprofen when combined with aspirin (**N**) (**Level II**).

12. Short-term use of parecoxib (**S**) (**Level I**) and other NSAIDs (**U**) (**Level III-2**) compared with placebo does not increase the risk of cardiovascular adverse effects after noncardiac surgery.
13. Use of parecoxib followed by valdecoxib after coronary artery bypass graft surgery increases the incidence of cardiovascular and cerebrovascular effects and is therefore contraindicated (**U**) (**Level I**).
14. Perioperative nonselective NSAIDs may increase the risk of minor and major bleeding after surgery compared with placebo (**W**) (**Level I**).
15. Coxibs do not impair platelet function and are not associated with increased perioperative blood loss (**S**) (**Level I**).
16. In patients with normal renal function, parecoxib perioperatively does not increase renal failure (**N**) (**Level I**).
17. NSAIDs hasten bowel recovery after colorectal surgery (**N**) (**Level I**).
18. With regard to renal function, celecoxib and naproxen are safer than ibuprofen with long-term use (**N**) (**Level II**).
19. Short-term use (5–7 days) of coxibs results in gastric ulceration rates similar to placebo and lower than nonselective NSAIDs (**U**) (**Level II**).
20. The cardiovascular protective effects of low-dose aspirin are reduced by concomitant administration of some NSAIDs, in particular ibuprofen (**S**) (**Level II**).
21. Nonselective NSAIDs, but not coxibs increase the risk of anastomotic leak after colorectal surgery (**N**) (**Level III-2**).
22. Short term use of ketorolac or ibuprofen do not increase bone healing complications in children undergoing posterior spinal fusion, osteotomy, or fractures managed surgically (**S**) (**Level III-3**) or conservatively (**N**) (**Level III-3**).
23. Chronic administration of nsNSAIDs or coxibs is associated with an increased risk of renal impairment (**N**) (**Level III-3 SR**).

The following tick box represents conclusions based on clinical experience and expert opinion:

☑ The risk of adverse renal effects of nonselective NSAIDs and coxibs may be increased in the presence of factors such as pre-existing renal impairment, hypovolaemia, hypotension and use of other nephrotoxic agents including angiotensin-converting enzyme inhibitors (**W**).

4.2.3 | Nonsystemic administration of nonsteroidal anti-inflammatory drugs

Non-systemic (transdermal patch or gel, wound infiltration) for non-ophthalmic (intra- or abdominal wall, mastectomy and skin graft) surgery as part of multimodal analgesic regimens may improve pain control and postoperative function vs placebo or systemic administration based on low to moderate quality evidence (Brubaker 2016 **Level I** [PRISMA], 9 RCTs, n=532).

4.2.3.1 | Intra-articular

Following arthroscopy, intra-articular (IA) nsNSAIDs (tenoxicam and ketorolac) result in improved pain relief (Romsing 2000 **Level I**, 16 RCTs, n=844 [7 RCTs IA]). Compared with systemic administration, IA nsNSAIDs (4 RCTs) showed a pain reduction of 20/100 (95%CI 13 to 26) and a 50 to 65% reduction in supplementary analgesic requirements over 24 h. In contrast, when IA nsNSAIDs were compared with IA placebo, two of three RCTs showed no significant analgesic benefit. More recent studies do not permit differentiation of the effect of IA NSAIDs from other components in the injected solution.

In human chondrocytes, single-dose equivalent concentrations of ketorolac caused significant chondrotoxicity (Abrams 2017 **BS**). Intraarticular ketorolac for THA showed no increased risk of prosthetic loosening, even with long-term follow-up (mean 7.3 y) (Nizam 2015 **Level IV**, n=100).

4.2.3.2 | Wound infiltration

Infiltration of the surgical wound with local anaesthetic/nsNSAID vs local anaesthetic and IV nsNSAID showed no difference in analgesia in three of five RCTs (overall WMD -6/100; 95%CI -19 to 6); similarly, wound infiltration with local anaesthetic/nsNSAID vs local anaesthetic/ placebo showed no analgesic benefit in four of five studies (Romsing 2000 **Level I**, 16 RCTs, n=844 [10 RCTs wound]). This lack of a local effect was confirmed with lornoxicam after thyroidectomy (Kilbas 2015 **Level II**, n=80, JS 4).

4.2.3.3 | Local infiltration analgesia

Local infiltration analgesia (LIA) involves the intraoperative periarticular infiltration of large volumes of local anaesthetic combined with a variety of adjuvants typically including an alpha-2 agonist/vasoconstrictor, an opioid and/or an anti-inflammatory agent. The majority of investigations into the effectiveness of LIA in acute pain management following THA/TKA fail to separate out the components of the mixture and some protocols also use catheter-based “top-up” regimens of varying composition. The lack of appropriate systemic comparators further complicates analysis of the role of the individual components. Ketorolac is the most frequently used nsNSAID in the LIA mixture. A systematic review identified no RCTs enabling a comparison of the efficacy of systemic vs periarticular administration of nsNSAIDs as a component of LIA in THA (Andersen 2014a **Level I** [PRISMA], 27 RCTs [THA], n=756).

The peak plasma concentrations of ketorolac after use of 30 mg as a component of LIA were comparable to those of similar doses administered IM (0.3-2.2 mg/L) (Affas 2014 **PK**).

4.2.3.4 | Intravenous regional analgesia

Ketorolac 60 mg in combination with local anaesthetic for IV regional analgesia (IVRA) demonstrated longer time to first analgesia request vs local anaesthetic IVRA with either IV ketorolac or IV placebo following minor upper limb procedures (Reuben 1995 **Level II**, n=60, JS 2).

However, pain scores were low overall and this study was not blinded. Ketorolac 60 mg added to local anaesthetic for IVRA or infiltrated into the wound provided superior analgesia for up to 2 h following tourniquet release vs no ketorolac use (Reuben 1996 **Level II**, n=60, JS 3). Again, pain scores were low for all groups and there was no separate parenteral ketorolac arm for comparison. When varying doses of ketorolac were added to IVRA for hand surgery, a linear dose-response relationship from 5 to 20 mg was found; between 20 and 60 mg, there appeared to be no additional analgesic benefit (Steinberg 1998 **Level II**, n=75, JS 3). With IVRA doses of ≥20 mg vs doses <20 mg, time to first analgesia was prolonged and pain scores were lower for up to 2 h following tourniquet release. There was no comparison with ketorolac administered as a separate parenteral dose.

Overall, no conclusion can be drawn regarding a specific benefit of adding ketorolac to IVRA over parenteral administration by a separate route.

4.2.3.5 | Nerve block

Parecoxib/ropivacaine improved quality and duration of brachial plexus block vs placebo/ropivacaine and ropivacaine/IV parecoxib (Liu 2013 **Level II**, n=150, JS 5).

4.2.3.6 | Topical

Application to skin

In adult patients with acute pain resulting from strains, sprains or sports injuries, topical diclofenac, ibuprofen, ketoprofen, piroxicam and indomethacin are effective vs placebo, whereas benzydamine is not better than placebo (Derry 2015a **Level I** [Cochrane] 61 RCTs, n=8,386). Topical compounds with good efficacy are diclofenac with an NNT (for 50% pain reduction over placebo) of 3.7 (95%CI 3.2 to 4.3), ketoprofen of 3.9 (95%CI 3.0 to 5.3), piroxicam of 4.4 (95%CI 3.2 to 6.9) and ibuprofen of 4.6 (95%CI 3.3 to 8.0). Different formulations may differ in efficacy; gels seem to be superior to creams with a diclofenac gel preparation having the lowest NNT of 1.8 (95%CI 1.5 to 2.1) and ketoprofen gel one of 2.5 (95%CI 2.0 to 3.4). The rate of systemic adverse effects with the topical NSAIDs is low and does not differ from placebo. The rate was also lower than with the same NSAID by oral route, although there was limited data on direct comparison.

Topical NSAIDs were of limited efficacy in lateral elbow pain, providing short-term functional improvement for up to 2 wk (Pattanittum 2013 **Level I** [Cochrane], 8 RCTs, n=301). The overall quality of included studies was poor and findings heterogeneous. No comparisons with oral NSAIDs were included.

There is insufficient evidence to differentiate between routes of administration of NSAIDs in the treatment of acute low back pain (Roelofs 2008 **Level I** [Cochrane], 65 RCTs, n=11,237).

Topical application of diclofenac results in tissue levels that are higher and plasma levels that are lower vs oral administration (Zacher 2008 **Level I**, 19 RCTs, n>3,000). Topical NSAIDs were associated with fewer gastrointestinal adverse effects but more local skin irritation than systemic NSAIDs (Klinge 2013 **Level I**, 6 RCTs, n=600).

Ophthalmological applications

There is no strong evidence for pain reduction with topical NSAIDs for traumatic corneal abrasions, but some evidence for a reduced requirement for rescue analgesia at 24 h as a proxy for pain reduction (RR 0.46; 95%CI 0.34 to 0.61) (Wakai 2017 **Level I** [Cochrane], 9 RCTs, n=637). After cataract surgery, topical NSAIDs reduce anterior chamber inflammation and thereby provide postoperative analgesia (Duan 2017 **Level I** [PRISMA], 19 RCTs, n=7,234); diclofenac, nepafenac,

ketorolac and bromfenac are in particular effective. After a number of other ophthalmological procedures, multiple studies show contradictory results with topical NSAIDs.

Mucosal applications

Microgranules containing flurbiprofen 8.75 mg provided better pain relief and reductions in difficulty in swallowing for sore throat than placebo, with fast onset (1 min) and long duration (6 h) (Russo 2013 **Level II**, n=373, JS 5). Flurbiprofen spray (8.75 mg/dose) rapidly reduced symptoms of sore throat after upper respiratory tract infection and provided significantly more relief for up to 6 h vs placebo, with no difference in adverse effects vs placebo over 3 d (de Looze 2016 **Level II**, n=505, JS 5); similar results (non-inferior to the spray) were found with use of a 8.75 mg flurbiprofen lozenge (Radkova 2017 **Level II**, n=440, JS 5). Flurbiprofen was also useful in post-tonsillectomy pain with reduction in pain scores and reduced requirement for additional analgesia (Muderris 2016 **Level II,** n=84, JS 4).

KEY MESSAGES

1. Topical NSAIDs are effective in treating acute strains, sprains or sports injuries with systemic adverse effects comparable to placebo; gel formulations show superior efficacy over creams (**S**) (**Level I** [Cochrane Review]).
2. Topical NSAIDs are of limited analgesic efficacy for traumatic corneal abrasions, but reduce rescue analgesia requirements (**W**) (**Level I** [Cochrane Review]).
3. Topical NSAIDs reduce anterior chamber inflammation and thereby pain after cataract surgery (**N**) (**Level I** [PRISMA])**.**
4. The efficacy of NSAIDs for peri- or intra-articular injection as a component of local infiltration analgesia compared with systemic administration remains unclear (**U**) (**Level I** [PRISMA]).
5. Intra-articular nonselective NSAIDs may provide more effective analgesia following arthroscopy than intravenous administration (**U**) (**Level I**).
6. Mucosal administration of flurbiprofen provides long-lasting pain relief for sore throat (**N**) (**Level II**).

4.3 | Opioids

Opioids can bind to receptors in the brain, spinal cord and periphery, and can be administered systemically or locally (eg intrathecal, intra-articular).

4.3.1 | Systemic opioids

Opioids remain the mainstay of systemic analgesia for the treatment of moderate to severe acute pain.

While opioids are conventionally regarded as acting on opioid receptors, some opioids achieve analgesic effects by additional mechanisms or via alternate interactions with opioid receptors (Raffa 2014a **NR**). The first of this class to be labelled as an "atypical opioid" was tramadol with its effects on noradrenergic and serotonergic inhibitory systems on top of a weak mu-agonism (by an active metabolite) (Raffa 1992 **BS**). The term atypical opioids (although another term "multigesics" has also been suggested) (Pergolizzi Jr 2017 **NR**) is increasingly used for buprenorphine, cebranopadol, tapentadol and tramadol (Schug 2019 **NR**); of these cebranopadol is undergoing early clinical investigations (Lambert 2015 **NR BS**), while the other three are approved in many countries.

4.3.1.1 | Choice of systemic opioid

All full conventional opioid agonists can produce the same level or analgesia once the dose is appropriately adjusted (McQuay 1991 **NR**), although accurate determination of equianalgesic doses is difficult due to interindividual variabilities in kinetics and dynamics (Gammaitoni 2003 **NR**). Equianalgesic conversion dose tables are often used to assist in the change from one opioid to another. However, such tables are based largely on single-dose studies in opioid-naïve subjects and may not be as relevant when conversions are made after repeated doses of an opioid have been given (either in the acute or chronic pain setting) and do not consider incomplete cross-tolerance and patient-specific factors (Weschules 2008a **NR**). Care must be taken when opioid rotations are undertaken based on such tables alone without consideration of clinical factors because this carries a significant risk of toxicity and even fatality (Webster 2012 **NR**). When healthcare professionals (physicians, pharmacists, and nurse practitioners/physician assistants) were surveyed, there was a large variation in mean opioid conversions (Rennick 2016 **Level IV**, n=319). A detailed analysis of equianalgesic doses and suggestions for opioid rotations based on these calculations has been published (Treillet 2018 **Level IV SR**, 20 studies, n unspecified). FPMANZCA provides an opioid calculator including references and background material on a website (FPMANZCA 2019a **GL**), which is also available as an app ("Opioid Calculator") for smartphones. Opioid rotations to methadone require particular care due to the risk of accumulation and subsequent toxicity (McLean 2015 **Level IV SR**, 25 studies, n=1,229).

In general, there is little evidence, on a population basis, to suggest that there are any major differences in efficacy or the incidence of adverse effects between any of the pure agonist opioids, although the results of individual studies are inconsistent. However, for pharmacokinetic and other reasons, some opioids may be better in some patients (Woodhouse 1999 **Level II**, n=82, JS 4). Comparisons of the different opioids are commonly done in patients using PCA (see Section 6.3.1 for these comparisons).

While the data to support the concept of opioid rotation originate from cancer pain (Mercadante 2011 **Level III-2 SR**, 31 studies, n unspecified; Quigley 2004 **Level IV SR** [Cochrane], 52 studies, n unspecified), it may be a useful strategy in the management of acute pain in patients with

intolerable opioid-related adverse effects, who are unresponsive to treatment and in opioid-tolerant patients (see also Section 9.7).

The efficacy of various opioids administered by the different routes used in the management of acute pain is discussed in detail in Chapter 5. The following sections describe other relevant aspects of selected atypical and conventional opioids.

4.3.1.2 | Conventional opioids

Codeine

Codeine is classified as a weak opioid. However, it is only a very weak mu-receptor agonist and its analgesic action depends on the metabolism of about 10% of the dose to morphine, via the CYP2D6 cytochrome P450 isoenzyme (Lotsch 2005 **NR**). The principal metabolite of codeine is codeine-6-glucuronide, which has a similar low potency to the parent medicine and is renally excreted.

Over 100 allelic variants of CYP2D6 have been identified, resulting in wide variability in enzyme activity (Somogyi 2007 **NR**). Individuals carrying two wild-type alleles display normal enzyme activity and are known as extensive metabolisers; intermediate metabolisers are heterozygotes with two variant alleles known to decrease enzymatic capacity; and poor metabolisers have no functionally active alleles and have minimal or no enzyme activity (Stamer 2007a **NR**). In Caucasian populations, 8 to 10% of people are poor metabolisers; however, 3 to 5% are ultrarapid metabolisers (Madadi 2009 **Level III-2**, n=72; Stamer 2007a **NR**). Those who are ultrarapid metabolisers (carriers of the *CYP2D6* gene duplication) have significantly higher levels of morphine and morphine metabolites after the same dose of codeine (Kirchheiner 2007 **Level IV**, n=23).

There are large interethnic differences in the frequencies of the variant alleles. For example, the proportion of ultrarapid metabolisers is higher (up to 29%) in Middle Eastern and Northern African populations and lower (0.5%) in Asians (Stamer 2007b **NR**); the proportion of poor metabolisers is lower in Asians and African Americans (Yee 2013b **Level IV**, n=75; Holmquist 2009 **NR**).

A case-control study including a case of a newborn dying while breastfed by a mother taking codeine has highlighted that breastfed infants of mothers who are ultrarapid metabolisers are at increased risk of life-threatening CNS depression (Madadi 2009 **Level III-2**, n=72). A number of similar cases have been reported and health professionals and mothers of breastfeeding infants should be aware of this risk (Madadi 2008 **Level IV**, n=35). CYP2D6 genotyping predicts subjects with reduced or increased metabolism to morphine but must be combined with additional phenotyping to accurately predict patients at risk of morphine toxicity (Lotsch 2009 **Level III-2**, n=57)

Death or OIVI has occurred after codeine treatment. Although rare, the risk is highest in children who are ultrarapid metabolisers, after they have undergone tonsillectomy, adenoidectomy, or both, as many of these have sleep-disordered breathing and are therefore more sensitive to opioids (Friedrichsdorf 2013 **Level IV**, n=3; Kelly 2012 **Level IV**, n=4; Racoosin 2013 **NR**). The USA Food and Drug Administration (FDA) now requires a boxed warning of the risk posed by codeine after a child has undergone tonsillectomy or adenoidectomy (FDA 2013 **GL**). The European Medicines Agency has responded similarly (EMA 2013 **GL**); as has the WHO in removing codeine from its tiered analgesic ladder for treatment of (persistent) pain in children (WHO 2012 **GL**). Guidelines on this issue have been published (Crews 2014 **GL**). See also Sections 1.7.3.2 and 10.4.4.5.

Dextropropoxyphene

Oral dextropropoxyphene 65 mg alone is a poorly effective analgesic in postoperative pain (NNT 7.7) (Collins 2000 **Level I** [Cochrane], 6 RCTs [dextropropoxyphene only], n=440). Dextropropoxyphene is often used in combination with paracetamol but this combination does not lead to better pain relief vs paracetamol alone and increases the incidence of dizziness (Li Wan Po 1997 **Level I**, 26 RCTs, n=2,231).

The use of this compound is discouraged, not only because of its low efficacy but also because of a number of risks related to its use (Barkin 2006 **NR**). These include QT-interval prolongation and possibility of Torsades des Pointes (TdP) and cardiogenic death. This is exacerbated by complex pharmacokinetics (particularly in the elderly) with the risk of accumulation of dextropropoxyphene and its metabolite nordextropropoxyphene, leading to CNS, respiratory and cardiac depression (Davies 1996 **NR**). However, in therapeutic doses (125±25 mg) no prolongation of the QT-interval >500 ms was observed (Keller 2018 **Level IV**, n=92).

In line with many other developed countries including New Zealand, the Therapeutics Goods Administration (TGA) in Australia decided in November 2011 to remove the registration of dextropropoxyphene (Buckley 2013 **NR**). Despite a number of appeals by the manufacturer, the medication has since been withdrawn from sale in Australia.

Diamorphine

Diamorphine (diacetylmorphine, heroin) is rapidly hydrolysed to monoacetylmorphine (MAM) and morphine (Miyoshi 2001 **NR**); diamorphine and MAM are more lipid-soluble than morphine and penetrate the CNS more rapidly. It is MAM and morphine that are thought to be responsible for the analgesic effects of diamorphine.

There was no difference between parenteral diamorphine and morphine in terms of analgesia and adverse effects after hip surgery (Robinson 1991 **Level II**, n=40, JS 4) and between parenteral diamorphine and pethidine for labour analgesia (Wee 2014 **Level II**, n=484, JS 4). Epidurally administered diamorphine resulted in a longer time to first PCA use and lower total 24 h morphine requirements vs the same dose given by intramuscular (IM) injection (Green 2007 **Level II**, n=60, JS 4). Intranasal (IN) diamorphine has been used as an analgesic for acute pain in children attending EDs (Kendall 2015 **Level IV**, n=226). Here peak morphine plasma concentrations were higher and occurred earlier when diamorphine was administered IV vs IN (Kidd 2009 **Level III-1**, n=24).

Dihydrocodeine

Dihydrocodeine is a semisynthetic derivative of codeine and has similar mu-opioid agonist activity. However, unlike codeine, inhibition of CYP2D6 by quinine does not alter its analgesic effect, even though the CYP2D6-dependent active metabolite, dihydromorphine, has a much higher mu-opioid receptor affinity than the parent medicine (Lotsch 2005 **NR**). Orally administered, it has around twice the potency of codeine and one-sixth the potency of morphine (Leppert 2010 **NR**).

Fentanyl

Fentanyl is a highly potent phenylpiperidine derivative, structurally related to pethidine. It is metabolised almost exclusively in the liver to minimally active metabolites. Less than 10% of unmetabolised fentanyl is renally excreted. Fentanyl is commonly used in the treatment of acute pain, especially when its lack of active metabolites and fast onset of action may be of clinical benefit (Grape 2010 **NR**). The fast onset is the result in particular of its high lipophilicity (octanol:water partition coefficient >700); this leads to a transfer half-life of 4.7 to 6.6 min between plasma and CNS (Lotsch 2013 **NR**) (see also Section 5.4.1). The pharmacokinetics of fentanyl are influenced by impaired liver function and CYP3A4 inhibitor and inducer use (Kuip 2017 **NR**). Data on fentanyl causing opioid-induced hyperalgesia (OIH) are limited and conflicting

with 4 RCTs supporting the induction and 2 RCTs opposing it (Lyons 2015 **Level I**, 6 RCTs, n=340).

There is insufficient evidence to judge the efficacy of fentanyl in neuropathic pain (Derry 2016b **Level I** [Cochrane], 1 RCT, n=163).

There is an increasing rate of fentanyl (and its analogues) abuse, primarily in the USA, but also now seen in other countries (Jannetto 2019 **NR**). This is paralleled by an increase in fentanyl overdose deaths; in the USA there was a 72% increase from 2014 to 2015 reaching 9,580 deaths caused by synthetic opioids, primarily fentanyl (including illicitly manufactured/non-pharmaceutical). The high mortality is partially due to admixture of fentanyl with other drugs of abuse, in particular heroin; sources are illegal importation and diversion of fentanyl-containing medication (Kuczynska 2018 **NR**). In 2015, a cluster of fentanyl-laced heroin deaths was reported in Melbourne, Australia, the first report of this nature outside North America (Rodda 2017 **Level IV**, n=9 [fentanyl related deaths out of ≈ 4,000 deaths investigated]).

Hydromorphone

Hydromorphone is a derivative of morphine that is approximately five times as potent as morphine. The main metabolite of hydromorphone is hydromorphone-3-glucuronide (H3G), a structural analogue of morphine-3-glucuronide (M3G). Like M3G (see below), H3G is dependent on the kidney for excretion, has no analgesic action and can lead to dose-dependent neurotoxic effects (Smith 2000 **NR**; Wright 2001 **NR**; Murray 2005 **NR**).

Hydromorphone is an effective opioid analgesic with similar efficacy and adverse effects as other strong opioids (Quigley 2002 **Level I** [Cochrane], 36 RCTs [acute pain], n=2,521). It provides slightly better clinical analgesia than morphine with similar adverse effects (Felden 2011 **Level I**, 8 RCTs, n=1,004). In cancer pain, its efficacy is similar to oxycodone and morphine (Bao 2016 **Level I** [Cochrane], 4 RCTs, n=504). There is insufficient evidence to judge the efficacy of hydromorphone in neuropathic pain (Stannard 2016 **Level I** [Cochrane], 4 RCT, n=604).

Methadone

Methadone is a synthetic opioid commonly used for the maintenance treatment of patients with an addiction to opioids and in patients with chronic non cancer and cancer pain. It is commercially available as a racemic mixture of R- and L-enantiomers but it is the R-enantiomer that is responsible for most, if not all, its mu-opioid receptor-mediated analgesic effects (Fredheim 2008 **NR**; Lugo 2005 **NR**).

It has good oral bioavailability (70 to 80%), high potency and long duration of action and a lack of active metabolites (Lugo 2005 **NR**). It is also a weak NMDA-receptor antagonist and monoamine (5HT and noradrenaline [norepinephrine]) reuptake inhibitor and has a long and unpredictable half-life (mean of 22 h; range 4 to 190 h) leading to an increased risk of accumulation (Weschules 2008b **NR**). Therefore, it is of limited use for acute pain treatment. Its use as an analgesic in general requires caution and guidelines have been published (ACMT 2016 **GL**). Recommendations include that it should not be prescribed on an as-needed basis, that the risk of overdose during the initial induction period for chronic use is high and that titration should be very slow. A baseline ECG and a follow-up ECG at 30 d should be obtained in patients at risk for QT prolongation (eg on other medications that prolong QT interval, with structural heart disease or a history of arrhythmias). Patients need extra education on potential risks of methadone treatment.

Dose conversion is complex and depends on many factors including absolute doses of other opioids and duration of treatment (McLean 2015 **Level IV SR**, 25 studies, n=1,229). In cancer pain management, methadone has similar analgesic effects to morphine (Nicholson 2017 **Level I** [Cochrane], 6 RCTs, n=388) (see also 10.4.4.9). There is very limited, very low-quality evidence supporting the efficacy and safety of methadone for chronic neuropathic pain (McNicol 2017 **Level I** [Cochrane], 3 RCTs, n=105).

Methadone is metabolised primarily by the cytochrome P450 group of enzymes, in particular 3A4 and to a lesser extent by CYP 1A2, 2D6, 2D8, 2C9/2C8, 2C19 and 2B6 (Kapur 2011 **NR**). Over 50 drug-drug interactions with methadone are described. Concurrent administration of other medicines that are CYP450 inducers may increase methadone metabolism and lower methadone blood levels (eg carbamazepine, rifampicin, phenytoin, St John's wort [*Hypericum perforatum*] and some antiretroviral agents) leading to potential reduced efficacy or even withdrawal. Conversely, medicines that inhibit CYP450 (eg other antiretroviral agents, some selective serotonin-reuptake inhibitors [SSRIs], grapefruit juice and antifungal agents) may lead to raised methadone levels and an increase in adverse effects or overdose (Fredheim 2008 **NR**) See also Section 8.6.8.2 for interactions in patients with human immunodeficiency virus (HIV).

Methadone use, but not use of other opioids, was associated with an increased incidence of hypoglycaemia in a dose-dependent fashion (for doses >80 mg/d OR 3.1; 95%CI 2.5 to 3.6) (Flory 2016 **Level III-2**, n=641). This was also found in an analysis of reports from the USA's Food and Drug Administration Adverse Event Reporting System, which showed an association between methadone use and hypoglycaemia in comparison to all other opioids except tramadol (Makunts 2019 **Level IV**, n=12,004,552).

High-dose methadone (eg >100 mg/d) has been associated with prolonged QT intervals and other cardiac complications: Torsade de pointes, changes in QT dispersion, pathological U waves, Taku-Tsubo syndrome (stress cardiomyopathy), Brugada-like syndrome, and coronary artery diseases (Alinejad 2015 **NR**) (see below Section 4.3.1.5).

In the setting of postoperative pain (spinal surgery), low-dose methadone was associated with high rates of postoperative complications with the use of a mean dose of 0.14 (±0.07) mg/kg (11.5±4.6 mg) in mostly non opioid naïve patients (72.3%) with BMI 30.3 (±0.9) (Dunn 2018 **Level IV**, n=1,478). Respiratory depression was recorded in 36.8%, hypoxemia in 79.8%, naloxone administered 2.3% and 1.5% required reintubation. QTc prolongation occurred in 58.8% and arrhythmias in 29.9% as well as two in-hospital deaths (0.14%). In contrast, a meta-analysis of small trials in various surgery types (cardiac, abdominal, hysterectomy, day case, orthopaedic, and spinal) of low to intermediate dose methadone 0.1 to 0.43 mg/kg vs morphine (7 RCTs), morphine and placebo (1 RCT), hydromorphone (1 RCT) and fentanyl (1 RCT) controls reported low power and did not detect a difference in risk for sedation (OR 0.62; 95% CI 0.27 to 1.45), respiratory depression/hypoventilation (OR 1.03; 95% CI 0.20 to 5.25) or hypoxaemia (OR 1.56, 95% CI 0.67 to 3.61) (D'Souza 2020 **Level I** [PRISMA], 10 RCTs, n=617). Current data are inadequate to support the routine use of long acting single intraoperative methadone doses in surgical patients where, as already emphasised, opioid requirements vary and titration is warranted. Further, large scale randomised trials are needed to overcome detection bias and define the efficacy and safety of both single and multiple low-dose methadone use in the perioperative period, with consideration of opioid naive and opioid tolerant patient groups (Murphy 2019 **NR**). The ANZCA position paper on the role of slow release (SR) opioid formulations in acute pain includes methadone due to its long half-life and recommends that its use should be avoided (ANZCA 2018 **GL**)

Morphine

Morphine remains the standard against which other opioids are compared. Morphine-6-glucuronide (M6G) and M3G, the main metabolites of morphine, are formed by morphine glucuronidation, primarily in the liver. M6G is a mu-opioid receptor agonist that crosses the blood-brain barrier more slowly than morphine (De Gregori 2012 **NR**). It contributes such a large extent to morphine analgesia in patients with both normal (85% of the effect after parenteral and up to 95% after oral administration) and impaired (98% of the effect) renal function, that morphine could be regarded as a prodrug to M6G (Klimas 2014 **NR**). M6G also has other morphine-

like effects including respiratory depression (van Dorp 2006b **NR**; Dahan 2008b **NR**). M3G has very low affinity for opioid receptors, has no analgesic activity and animal studies have shown that it may be responsible for the neurotoxic symptoms (not mediated via opioid receptors), such as hyperalgesia, allodynia and myoclonus, sometimes associated with high doses of morphine (Lotsch 2005 **NR**).

Clinical trials have investigated M6G as an analgesic agent after a variety of different types of surgery. It was more effective than placebo (Smith 2009 **Level II**, n=201, JS 4; Romberg 2007 **Level II**, n=42, JS 3) and in some trials as effective as morphine (Cann 2002 **Level II**, n=144, JS 4; Hanna 2005 **Level II**, n=100, JS 3), although withdrawal due to insufficient analgesia was higher in another (Binning 2011 **Level II**, n=249, JS 5); this is possibly due to a slower onset of effect of M6G. However, in the clinical setting of titration of IV morphine to postoperative analgesia, which is an effective approach to early postoperative pain (Aubrun 2012 **NR**), the kinetics of morphine and its metabolites had only limited value in explaining the analgesic effects of morphine (Hammoud 2011 **Level IV**, n=214).

Excellent pain relief was also obtained after IT administration of 100 or 125 mcg M6G in patients after hip replacement surgery, but there was a high incidence (10%) of late respiratory depression (9 to 12 h after the dose was given) requiring treatment with naloxone, and a high incidence of nausea (76 to 88%) and vomiting (60 to 64%) (Grace 1996 **Level II**, n=75, JS 5).

The incidence and severity of nausea and vomiting as well as the need for antiemetics was less with lV M6G than with IV morphine (Binning 2011 **Level II**, n=249, JS 5; Cann 2002 **Level II**, n=144, JS 4). In healthy volunteers, IV morphine 0.15 mg/kg and IV M6G 0.2 mg/kg resulted in similar reductions in ventilatory response to carbon dioxide (CO_2) (Romberg 2003 **Level III-1 EH**).

Both M6G and M3G are dependent on the kidney for excretion. Impaired renal function, the oral route of administration (first-pass metabolism), higher doses and increased patient age are predictors of higher M3G and M6G concentrations (Faura 1998 **Level IV PK SR**, 57 studies, n=1,232; Klepstad 2003 **Level IV**, n=300) with the potential risk of severe long-lasting sedation and respiratory depression.

There is insufficient evidence to judge the efficacy of morphine in neuropathic pain (Cooper 2017 **Level I** [Cochrane], 5 RCTs, n=236). Oral morphine is effective in treating cancer pain with similar efficacy vs other opioids (Wiffen 2016 **Level I** [Cochrane], 62 RCTs, n=4,241).

Oxycodone

Oxycodone is a semisynthetic opioid and directly contributes the majority of drug effect itself while being metabolised primarily to noroxycodone by CYP3A4 (≈45%) and by CYP2D6 to oxymorphone (≈19%) (Kinnunen 2019 **NR PK**). Oxymorphone is more potent than oxycodone as a mu-receptor agonist (14 times) and has a higher receptor affinity (40 times) and may contribute to the overall analgesic effect of oxycodone (Samer 2010b **Level II EH**, n=10 [5-arm cross over], JS 5); noroxycodone, the major metabolite, is only a weak mu-receptor agonist (Lalovic 2006 **NR**; Coluzzi 2005 **NR**).

The dependence of oxymorphone concentrations on CYP2D6 activity and its high potency explains the impact of CYP2D6 polymorphism on oxycodone's pharmacodynamics and pharmacokinetics (Samer 2010b **Level II EH**, n=10 [5-arm cross over], JS 5). Ultrafast metabolisers experience better analgesic effects and higher toxicity, while poor metabolisers experience less analgesic effect. However, in acute postoperative pain, CYP2D6 genotype had no influence on oxycodone requirements (Zwisler 2010 **Level III-3**, n=270; Crews 2014 **GL**).

These findings mean also that drug-drug interactions can influence the efficacy of oxycodone (Samer 2010a **Level II EH**, n=10 [cross over], JS 5). This is particularly true for CYP2D6 ultrafast metabolisers but also can be influenced by CYP3A inhibitors such as ketoconazole, which increases the efficacy and toxicity of oxycodone. Therefore, use of a CYP3A inhibitor in an ultrafast CYP2D6 metaboliser is a potentially dangerous combination.

Animal studies have shown that oxycodone is actively taken up into the brain, resulting in a brain concentration that is up to six times that of free plasma levels (Bostrom 2008 **PK**); this may explain the discrepancies between its poorer mu-receptor affinity compared to morphine but its higher potency (Olkkola 2013 **NR**). In general anaesthesia, oxycodone showed a significant dose-dependent respiratory depressant effect measured by reduced minute ventilation, which was significantly more than that of comparable doses of morphine (Chang 2010 **Level II**, n=54, JS 4).

Overall oxycodone has a faster onset of action than morphine, better oral bioavailability, longer duration of action, fewer concerns about metabolites and a lower rate of adverse effects (Olkkola 2013 **NR**). There is increasing use of oxycodone in the perioperative setting based on these pharmacological properties (Kokki 2012 **NR**). With regard to analgesic efficacy in acute pain, IV oxycodone seems superior to fentanyl (6 RCTs) and sufentanil (2 RCTs) and comparable to morphine (3 RCTs), but these results may partially reflect use of doses which were not equianalgesic (Raff 2019 **Level I**, 11 RCTs, n=721). The incidence of adverse effects was lower with oxycodone vs fentanyl (possibly also a reflection of non-equianalgesic doses) and comparable for oxycodone vs morphine and sufentanil. Patient satisfaction was comparable for all opioids except for sufentanil, which showed consistently lower patient satisfaction vs oxycodone. Similar results are reported by a parallel systematic review which also acknowledges similar limitations (Tan 2018 **Level I**, 8 RCTs, n=506) (6 RCTs overlap). In cancer pain management, oxycodone is comparable in efficacy and adverse effects to other strong opioids; very low-level evidence suggests lower risk of hallucinations with oxycodone vs morphine (Schmidt-Hansen 2018 **Level I** [Cochrane], 23 RCTs, n=2,144). With regard to adverse effects in the setting of cancer pain treatment, there were no differences between oxycodone vs other opioids except for less sleepiness with oxycodone vs morphine (Ma 2016a **Level I** [PRISMA], 11 RCTs, n=1,211) (5 RCTs overlap). In neuropathic pain, there is very low-quality evidence that oxycodone is effective in the treatment of painful diabetic neuropathy (4 RCTs, n=637) and postherpetic neuralgia (1 RCT, n=50) (Gaskell 2016b **Level I** [Cochrane], 5 RCTs, n=687).

Pethidine

Pethidine (meperidine) is a synthetic opioid with decreasing use worldwide due to multiple disadvantages compared to other opioids, and equally effective analgesic alternatives. Despite a common belief that it is the most effective opioid in the treatment of renal colic, it was no better than morphine (O'Connor 2000 **Level II**, n=103, JS 5) or hydromorphone (Jasani 1994 **Level II**, n=73, JS 4). Pethidine and morphine also had similar effects on the sphincter of Oddi and biliary tract and there was no evidence that pethidine was better in the treatment of biliary colic (Latta 2002 **NR**).

Pethidine induced more nausea and vomiting than morphine when used parenterally in the ED (Silverman 2004 **Level III-3**, n=193) and in the first 2 h after gynaecological surgery (Ezri 2002 **Level II**, n=200, JS4). Pethidine use postoperatively was associated with an increased risk of delirium in the postoperative period in comparison to other opioids (Swart 2017 **Level III-2 SR**, 3 studies [pethidine], n=877).

Accumulation of its active metabolite, norpethidine (normeperidine), is associated with neuroexcitatory effects that range from nervousness to tremors, twitches, multifocal myoclonus and seizures (Simopoulos 2002 **Level IV**, n=355). Impaired renal function increases the half-life of norpethidine; therefore, patients with poor renal function are at increased risk of norpethidine toxicity. Naloxone does not reverse and may increase the problems related to norpethidine toxicity.

Overall, the use of pethidine should be discouraged in favour of other opioids in adults (Latta 2002 **NR**) and in the paediatric setting (Benner 2011 **NR**).

Remifentanil

Remifentanil is an unusual opioid with a very fast onset of effect (<1 min) and an extremely short duration of action due to rapid metabolism by nonspecific esterases (Parashchanka 2014 **NR**). It is mainly used as a component of anaesthesia and carries a high risk of OIH; its use as an analgesic has primarily been studied in the setting of labour analgesia (Devabhakthuni 2013 **NR**) (see Section 9.1.3.1).

Sufentanil

Sufentanil (a derivative of fentanyl with rapid onset, short duration of action and no active metabolites) was originally used in the anaesthetic setting; its use has been introduced into the postoperative acute pain setting by the development of SL PCA (Frampton 2016 **NR**) (see Section 6.5.3).

4.3.1.3 | Atypical opioids

Buprenorphine

Buprenorphine is a semisynthetic derivative of thebaine, an alkaloid of opium and a potent, but *in vitro* partial, mu-opioid receptor agonist (Raffa 2014b **NR**) with high receptor affinity and slow dissociation from the mu-receptor and different downstream effects (G protein and adenylcyclase activation) than conventional opioids (Ehrlich 2019 **NR**; Davis 2012 **NR**; Pergolizzi 2010 **NR**). Furthermore, buprenorphine is a potent kappa-opioid receptor antagonist, a weak agonist at the nociceptin or opioid-receptor-like 1 (ORL-1) receptor and binds to the delta-opioid receptor. Buprenorphine, in particular the SL formulation, is increasingly used in the setting of acute pain management (Macintyre 2017 **NR**).

Buprenorphine shows biphasic pharmacokinetics with an initial distribution half-life of around 2–3 h and a terminal half-life of around 24 h; two-thirds of the medicine is excreted unchanged, mainly in faeces, while the remaining one-third is metabolised predominantly in the liver and gut wall via glucuronidation to an inactive metabolite, buprenorphine-3-glucuronide, and via CYP3A4 to norbuprenorphine, which has 40 times less analgesic effect than buprenorphine (Kress 2009 **NR**). However, in line with findings in animal experiments, an exploratory clinical investigation found respiratory depression more strongly associated with norbuprenorphine than with buprenorphine (Strang 2018 **EH PK**, n=11). Onset of effect is slower than for many other opioids; using experimental pain stimuli, the time to peak effect after administration of an IV bolus dose of buprenorphine was 70 to 90 min (Yassen 2006 **Level III-3 EH**).

The debate on buprenorphine being a partial or full mu-opioid receptor agonist in clinical practice continues (Holyoak 2019 **NR**) and is complicated by its multiple mechanisms of action. While *in-vitro* experiments have characterised buprenorphine as a partial agonist, clinically it behaves like a full mu-receptor agonist; in 23 of 24 studies identified in a systematic review, buprenorphine achieved analgesia comparable to full mu-opioid agonists (morphine, fentanyl, sufentanil and oxycodone) (Raffa 2014b **Level I**, 24 studies, n>1,270). The authors conclude that in clinically relevant doses, buprenorphine behaves like a full mu-opioid receptor agonist *in-vivo*. A subsequent systematic review found SL buprenorphine comparable to IM or IV morphine in acute pain management without any differences in pain control achieved, need for rescue analgesia or secondary outcomes (Vlok 2019 **Level I** [PRISMA], 9 RCTs, n=826) (3 RCTs overlap). This is confirmed in a paediatric population with IV buprenorphine vs IV morphine showing similar analgesic effects, but a longer duration of analgesia with buprenorphine (Murray 2018 **Level I**, 4 RCTs, n=193). An overarching meta-analysis of buprenorphine vs morphine by any route of administration in any population finds no difference in pain intensity at <1 h (WMD 0.18; 95%CI -0.45 to 0.81), conflicting evidence for other points of time (1 to 48 h) and no difference overall at all time points combined (WMD 0.29; 95%CI -0.62 to 0.03) (White 2018 **Level I** [PRISMA], 28 RCTs,

n=2,210) (all 9 RCTs overlap with Vlok 2019 and all 4 RCTs with Murray 2018). All other outcomes for analgesia and adverse effects (including respiratory depression) are not different except for less pruritus with buprenorphine (OR.0.31; 95%CI 0.12 to 0.84).

In animals as well as humans, in therapeutic doses there also appears to be no antagonism of other concurrently administered mu-agonist medicines and combined use should be effective (van Niel 2016 **NR**; Pergolizzi 2010 **NR**). In patients on opioid substitution therapy (OST) with daily SL buprenorphine (12 to 16 mg), high doses of IV hydromorphone (16 and 32 mg) and to a lesser extent IV buprenorphine (32 mg) achieved analgesic effects in an acute pain model (cold pressor test) (Huhn 2019 **Level II EH**, n=17, JS 4). In contrast, patients on OST with SL buprenorphine (2 to 22 mg/d) achieved no relief of experimental pain (cold pressor or electrical stimulation) with IV morphine (55 mg achieving plasma concentrations of 92 to 201 ng/mL), but reduced respiratory rates (Athanasos 2019 **Level II EH**, n=12, JS 2).

There is a ceiling effect for respiratory depression but not for analgesia in healthy volunteers (in the dose range tested of 200 to 400 mcg) (Dahan 2006 **Level III-2 EH**; Dahan 2005 **Level III-2 EH**). In clinical practice, transdermal (TD) buprenorphine has not been associated with any fatality in the National Poison Data System of the USA (Coplan 2017 **Level IV**, n=117 [TD burenorphine]). When used for OST, methadone use increased the risk of overdose death vs buprenorphine (RR 6.23; 95%CI 4.79 to 8.10) (Marteau 2015 **Level III-2**, n=2,418 [overdose deaths] in n=19,935,537 [prescriptions]). However, even with buprenorphine the overdose death rate was not zero, but 0.022/1000 prescriptions (vs 0.137/1000 prescriptions of methadone). In an analysis of overdose deaths, buprenorphine alone can cause fatal respiratory depression, although in most cases (90%) other medications, in particular benzodiazepines and other sedatives, were found (Selden 2012 **Level IV**, n=97). Similarly, in elderly opioid-naïve patients acute pain treatment with titration of SL buprenorphine (200 mcg steps with total doses of 200 to 3,000 mcg) resulted in cases of OIVI without a fatal outcome; all patients had risk factors such as advanced age, concurrent comorbidities, or the ingestion of other potential central nervous system depressants (Richards 2017 **Level IV**, n=6). A meta-analysis comparing buprenorphine with morphine finds no difference in the incidence of respiratory depression (defined as respiratory rate <8 to 12/min) (OR.2.07; 95%CI 0.78 to 5.51) or sedation (OR.1.44; 95%CI.0.76 to 2.74) (White 2018 **Level I** [PRISMA], 28 RCTs, n=2,210).

Should buprenorphine-induced respiratory depression occur, then complete reversal with naloxone is possible (Pergolizzi 2010 **NR**), although higher than usual doses and a longer duration infusion of naloxone are required (van Dorp 2006a **Level III-2 EH**; Yassen 2006 **Level III-3 EH**; Boom 2012 **NR**). This is confirmed in the case series referred to above, where naloxone bolus doses up to 2.2 mg and infusions for up to 20 h were used (Richards 2017 **Level IV**, n=6).

In animal models of pain, buprenorphine appears to have good efficacy for neuropathic pain (Hans 2007 **NR**). In the clinical setting, case reports have suggested that buprenorphine is effective in peripheral (Licina 2013 **Level IV**, n=4) and central neuropathic pain (Guetti 2011 **Level IV**). However, a specific effect cannot be supported or refuted based on current evidence (Wiffen 2015 **Level I** [Cochrane], 0 RCTs, n=0).

Buprenorphine may also have a reduced tendency to cause opioid-induced hyperalgesia (OIH) (Lee 2011 **NR**). In patients in opioid-substitution programs, buprenorphine reduced pain thresholds less than methadone (Compton 2001 **Level III-2 EH**, n=54). Using experimental pain stimuli in humans, buprenorphine, unlike conventional mu-opioid agonists, has been shown to be antihyperalgesic, which may be related in part to its kappa-opioid antagonist activity (Koppert 2005 **Level II EH**, n=15, JS 4). During major lung surgery under remifentanil infusion, perioperative buprenorphine infusion (25 mcg/h for 24 h) vs equianalgesic morphine infusion resulted in less hyperalgesia and allodynia around the incision and longer time until rescue analgesia requirements, with no long-term benefits at 3 mth (Mercieri 2017 **Level II**, n=64, JS 5).

However, in healthy volunteers, IV infusions of buprenorphine (0.3 mg) and morphine (10 and 20 mg) showed no differences in antihyperalgesic or analgesic effects; only IV buprenorphine (0.6 mg) enhanced the descending nociceptive inhibitory control (Ravn 2013 **Level II EH**, n=32, JS 5). Similarly, patients on OST with SL buprenorphine (2 to 22 mg/d) were hyperalgesic in the cold pressor test vs controls (buprenorphine 17±2 s vs control 34±6 s) (Athanasos 2019 **Level II EH**, n=12, JS 2).

Withdrawal symptoms, which may be seen if the medicine is ceased after long-term treatment, are milder and more delayed in onset (≥72 h) than other opioids (Kress 2009 **NR**). In a direct comparison of buprenorphine vs morphine withdrawal, withdrawal symptoms were far less with buprenorphine (subjectively and objectively) (Tompkins 2014 **Level III-1**, n=7). There is also less neonatal abstinence syndrome (NAS) in babies of mothers receiving buprenorphine vs methadone substitution (Jones 2012 **NR**). In the USA National Poison Data System, calls describing intentional abuse of an opioid were lower for TD buprenorphine than any conventional opioid; specifically, prescription adjusted rates for abuse were much higher for TD fentanyl vs TD buprenorphine (aRR 10.8; 95%CI 4.46 to 25.9) (Coplan 2017 **Level IV**, n= 2,687 [calls]).

Buprenorphine can be safely used in patients with renal impairment and has less immunosuppressive effect in animal experiments than pure mu-opioid agonists (Davis 2012 **NR**; Pergolizzi 2010 **NR**). However, buprenorphine has the potential to prolong the QT interval (Klivinyi 2018 **NR**). High doses of buprenorphine patch (above 40mcg/h) may cause QT wave prolongation that is reversible with a MOR antagonist; clinical significance of this is unclear (Merivirta 2015 **Level III-1**, n=110).

For use in OST and implications for perioperative management see Section 9.8.3.2

Tapentadol

Tapentadol is a combined mu-agonist and noradrenaline-reuptake inhibitor (Tzschentke 2014 **NR**). In contrast to tramadol, it has no relevant functional serotonin-reuptake inhibition and no active metabolites (Raffa 2012 **NR**). Therefore, serotonin syndrome with its use alone has not been reported in 2 systematic reviews (Channell 2018 **Level IV SR**, 13 RCTs & 3 studies & 8 CRs, n=21,995 [tapentadol-treated]; Gressler 2017 **Level IV SR**, 13 RCTs & 9 studies, n=12,138) (significant overlap). However, in spontaneous adverse drug event (ADE) reporting to the TGA, 16 cases consistent with serotonin syndrome were reported (14 with coadministration of serotonergic medications) (Abeyaratne 2018 **Level IV**, n=104 [reports for tapentadol]). A probable serotonin syndrome in the setting of tapentadol overdose in combination with amitriptyline and duloxetine has also been published (Walczyk 2016 **CR**). There is no effect on heart rate or blood pressure due to noradrenaline-reuptake inhibition in doses up to the maximum recommended 500 mg/d, even in patients with hypertension and/or on antihypertensives (Biondi 2014 **Level I**, 3 RCTs [*post hoc* analysis], n=1,464).

Elimination is by glucuronidation; severely impaired hepatic function may require dose adjustment (Xu 2010 **PK**).

Although in humans tapentadol has 18-fold lower affinity for the mu-receptor than morphine, it is only three times less potent as an analgesic due to its dual mechanism of action with synergy shown in site-specific administration studies (Christoph 2013 **BS**). With regard to tapentadol, the concept of "mu-load" (the % contribution of the opioid component to the adverse effect magnitude relative to a pure/classical mu-opioid at equianalgesic doses) has been discussed, suggesting that while conventional opioids have by definition a mu-load of 100%, atypical opioids have a mu-load <100%; for tapentadol using respiratory depression and constipation the mu-load is calculated ≤ 40% (Raffa 2018 **NR**).

The effect of tapentadol as a noradrenaline-uptake inhibitor on descending pathways of pain inhibition has been confirmed in diabetic neuropathy, where tapentadol use increased

conditioned pain modulation (Niesters 2014b **Level II**, n=24, JS 5). This mechanism of action suggests benefits in neuropathic pain (Vinik 2014 **Level II**, n=318, JS 5; Freo 2019 **NR**), but tapentadol also showed efficacy in nociceptive and inflammatory-pain models (Schiene 2011 **NR**) including postoperative pain (Lee 2014b **Level II**, n=352, JS 5) and cancer pain (Mercadante 2017 **Level IV SR**, 8 studies, n=792). In the setting of acute pain, tapentadol IR achieves similar analgesia to oxycodone IR, mostly in a 5:1 dose ratio, but with oxycodone resulting in an increased incidence of the gastrointestinal adverse effects nausea (OR 2.23; 95%CI 1.72 to 2.90), vomiting (OR 2.19; 95%CI 1.09 to 4.42) and constipation (OR 3.16; 95%CI 1.42 to 7.01) (each in 3 RCTs) (Hartrick 2010 **Level I**, 5 RCTs, n=2,831). A subsequent systematic review confirmed these results; tapentadol IR in doses of 50, 75 and 100 mg (with 75 mg being superior to 50 mg) provides similar analgesia to oxycodone IR 10 mg (Xiao 2017 **Level I** [PRISMA}, 9 RCTs, n=3,961) (4 RCTs overlap). The rate of nausea (RR 0.64; 95%CI 0.48 to 0.85), vomiting (RR 0.37; 95%CI 0.24 to 0.56) and constipation (RR 0.44; 95%CI 0.32 to 0.62) was lower with tapentadol IR 50 mg and nausea (RR 0.41; 95%CI 0.41 to 0.93) and constipation (RR 0.38; 95%CI 0.25 to 0.54) with 75 mg.

Data in the setting of a number of chronic pain conditions show similar or superior efficacy to conventional opioids with reduced rates of gastrointestinal adverse effects such as nausea, vomiting and constipation leading to reduced rates of treatment discontinuation (Riemsma 2011 **Level I**, 42 RCTs [8 RCTs tapentadol, n=6,698]). In a network meta-analysis of opioids for chronic pain treatment, tapentadol was identified as top-ranking due to low rates of overall adverse effects, in particular constipation, and lowest withdrawal rate for adverse effects (Meng 2017 **Level I** [PRISMA] [NMA], 32 RCTs, n unspecified).

Despite increasing use of this analgesic in many countries of the world (in particular the USA [approved 2008], Australia [2010] and Europe [2011]), only 4 (possibly 5 as double reporting of one case could not be excluded) single drug tapentadol overdose deaths could be identified (Channell 2018 **Level IV SR**, 13 RCTs, 3 studies & 8 CRs, n=21,995 [tapentadol treated]). Relative safety of tapentadol vs conventional opioids has been confirmed by data from the USA Researched Abuse, Diversion and Addiction-Related Surveillance (RADARS®) System Poison Center Program; there was no reported death due to tapentadol between 2010 and 2016 and it had the lowest rate of overdose deaths, major medical effects, serious adverse events and hospitalisations (data corrected for amounts dispensed) (Murphy 2018 **Level IV**, n=64,538 [reports]). Post-marketing surveillance by the manufacturer could also not identify any overdoses with fatal outcomes (Stollenwerk 2018 **Level IV**, n=10,758 [case reports]). In an experimental setting, tapentadol (100 mg) vs oxycodone (20 mg) (equianalgesic doses) had less respiratory depressant effects, but not 150 mg (van der Schrier 2017 **Level II EH**, n=18, JS 5).

Although a controlled medicine in all countries, tapentadol shows a lower rate of abuse and diversion than oxycodone and hydrocodone and a rate comparable to tramadol (Dart 2012 **Level IV**). Diversion rates of tapentadol in the USA (monitored by RADARS® - note that the SR preparation in the USA is tamper resistant) adjusted for amounts used were lower for tapentadol IR (0.03/1,000 prescriptions) and tapentadol SR (0.016) than all other scheduled oral opioids (0.172) (Dart 2016 **Level III-2**, n=38,388 [cases of diversion]). A subsequent analysis by the same system (adjusted for dosing units dispensed) confirms the lowest rate of diversion (comparable to tramadol) and lower, but not the lowest, rate of intentional abuse in reports to poison centres (tramadol and hydrocodone being lower) (Vosburg 2018 **Level III-3**, n multiple denominators). Rates of doctor shopping (sourcing from multiple providers) were higher for oxycodone vs tapentadol (OR 3.5; 95%CI 2.8 to 4.4) (Cepeda 2013b **Level III-2**) and rates of abuse lower for tapentadol vs oxycodone (OR 0.35; 95%CI 0.21 to 0.58) (Cepeda 2013a **Level III-2**).

Tramadol

Tramadol is commonly referred to as an atypical centrally acting analgesic because of its combined effects as an opioid agonist and a serotonin- and noradrenaline-reuptake inhibitor (Bravo 2017 **NR**; Raffa 2012 **NR**; Raffa 1992 **NR**). Although an effective analgesic, it may not provide adequate pain relief if used as the sole agent for the management of moderate to severe acute pain at the currently recommended doses (Thevenin 2008 **Level III-1**). However, compared to a variety of strong opioids (morphine, fentanyl, oxycodone, pethidine) when administered by PCA, tramadol had comparable analgesic efficacy (Murphy 2010 **Level I**, 12 RCTs, n=782). As discharge medication after surgery, the risk of prolonged tramadol use was similar, if not slightly higher than other short acting opioids (Thiels 2019 **Level III-2**, n= 444,764).

Limited low-quality evidence supports tramadol's analgesic effect in cancer pain, although it is not as effective as morphine in this indication (Wiffen 2017b **Level I** [Cochrane], 10 RCTs, n=958). Tramadol is an effective treatment for neuropathic pain with NNT of 4.4 (95%CI 2.9 to 8.8) (Duehmke 2017 **Level I** [Cochrane], 6 RCTs, n=438).

IV tramadol/IV morphine vs IV morphine has a minor opioid-sparing effect (WMD 6.9 mg; 95%CI 211.3 to 22.5), but does not reduce pain intensity (WMD -0.9/100; 95%CI -7.2 to 5.2) nor adverse effects (nausea, vomiting, sedation) (Martinez 2015 **Level I** [PRISMA], 14 RCTs, n=713).

The (+) enantiomer of tramadol is the stronger inhibitor of serotonin reuptake and the (-) enantiomer the more potent inhibitor of noradrenaline reuptake; tramadol is metabolised by CYP2D6 and the resultant active metabolite O-desmethyltramadol (M1) is a more potent mu-opioid receptor agonist than the parent drug (Lee 1993 **NR**). Patients who are poor metabolisers get less analgesic effect from tramadol (Stamer 2003 **Level III-2**), while ultrarapid metabolisers may be at increased risk of opioid-induced adverse effects including OIVI (Desmeules 1996 **Level II**, n=10, JS 3; Stamer 2008 **CR**). See also Section 1.7.3.2.

Coadministration with other medicines that inhibit CYP2D6 may also influence the effectiveness of tramadol. For example, pretreatment with paroxetine in healthy extensive metabolisers reduced the hypoalgesic effect of tramadol in an experimental pain model (Laugesen 2005 **Level II EH**, n=16 [4-way cross over], JS 5). Inhibition of $5HT_3$ receptors by ondansetron also decreased the analgesic effect of tramadol, as measured by increased tramadol requirements, in particular early after ondansetron administration (Stevens 2015 **Level I** [PRISMA] 6 RCTs, n=340), although this may also be a pharmacokinetic interaction (Hammonds 2003 **NR**). This has been confirmed in a subsequent RCT in hemithyroidectomy patients; here co-administration of IV tramadol (1.5 mg/kg) with ondansetron (0.1 mg/kg) vs tramadol alone reduced time to request for rescue analgesia (76.3 min vs 164.1) and analgesic efficacy at 0 to 60 min postoperatively (at 60 min: 2.51/10 (SD ± 0.66) vs 1.16/10 (± 0.68), but improved PONV scores (Murmu 2015 **Level II**, n=134, JS 4)

Tramadol's adverse-effect profile is different from other opioids. In the RADARS® System Poison Center Program, tramadol had the second-lowest rates of overdose deaths, major medical effects, serious adverse events and hospitalisations (data corrected for amounts dispensed) (Murphy 2018 **Level IV**, n=64,538 [reports]). The risk of respiratory depression is lower than with conventional opioids at equianalgesic doses (Mildh 1999 **Level II EH**, n=8 [cross over], JS 5; Tarkkila 1998 **Level II**, n=36, JS 4; Tarkkila 1997 **Level II**, n=36, JS 4) and it does not depress the hypoxic ventilatory response (Warren 2000 **Level II EH**, n=20 [cross over], JS 5). However, in a large series of tramadol overdoses in Iran, mainly due to deliberate self-harm or abuse, 3.6% experienced apnoea and required respiratory support or naloxone use (Hassanian-Moghaddam 2013 **Level IV**, n=525 [overdoses]). The mean time to presentation was 7.7 h (range 1 to 24 h); the mean dose causing apnoea was 2,125 mg (range 200 to 4,600 mg), significantly higher than in those not experiencing apnoea (1,383 mg; range 100 to 6,000 mg). One death in each group was reported. A further series of tramadol overdoses reported hypertension (38.4%), tachycardia (24.8%),

respiratory depression (20%) (median dose 2,750 mg), seizure (14.5%) and no serotonin toxicity (Habibollahi 2019 **Level IV**, n=359 [overdoses]). Similar findings are reported from the USA; respiratory depression with relatively higher doses than other symptoms (median dose 2,500 mg) and seizures, tachycardia, mild hypertension, but no serotonin toxicity (Ryan 2015 **Level IV**, n=71). Significant respiratory depression has also been described in a patient with severe renal failure, most likely due to accumulation of the metabolite M1 (Barnung 1997 **CR**).

There is a risk of inducing serotonin toxicity when tramadol is combined with other serotonergic medicines, in particular SSRIs (Nelson 2012 **Level IV SR**, 1 study & 9 CR, n=14). However, despite the widespread use of both medicines, there are only very few case reports (14 cases in above SR) on this interaction. The interaction might be complex, as SSRIs are often CYP2D6 inhibitors (eg sertraline, paroxetine and fluoxetine) and can thereby increase tramadol concentrations (Miotto 2017 **NR**). This might also mean that poor CYP2D6 metabolisers are at an increased risk of this interaction (Nelson 2012 **Level IV SR**, 1 study & 9 CR, n=14). Furthermore, administration of tramadol to elderly patients in the postoperative period was a risk factor for delirium (Swart 2017 **Level III-2 SR**, 1 study [tramadol]: Brouquet 2010 **Level IV**, n=133).

Tramadol has less effect on gastrointestinal motor function than morphine (Lim 2001 **Level II**, n=101, JS 5; Wilder-Smith 1999b **Level II**, n=62, JS 5; Wilder-Smith 1999a **Level II**, n=30, JS 5; Wilder-Smith 1997 **Level II**, n=10 [cross over], JS 5). Nausea and vomiting are the most common adverse effects and occur at rates similar to morphine (Lim 2001 **Level II**, n=101, JS 5; Radbruch 1996 **NR**), although an increased rate in comparison to a variety of strong opioids (morphine, fentanyl, oxycodone, pethidine) occurs with PCA use (OR 1.52; 95%CI 1.07 to 2.14) (Murphy 2010 **Level I**, 12 RCTs, n=782). The incidence of pruritus was reduced with tramadol (OR 0.43; 95%CI 0.19 to 0.98).

Tramadol did not increase the incidence of seizures compared with other analgesic agents in two observational studies (Gasse 2000 **Level III-2**, n=11,383; Jick 1998 **Level III-2**, n=10,916). Seizures were reported in tramadol intoxication, mainly due to deliberate self-harm or abuse, with recurrent seizures in 7 and 11.7% of patients (Hassanian-Moghaddam 2013 **Level IV**, n=525; Shadnia 2012 **Level IV**, n=100). Potential risk factors for seizure, other than overdose, were a history of traumatic brain injury, seizure activity secondary to hypoxia and use in combination with medications that lower seizure threshold (Miotto 2017 **NR**). Calls to the National Poison Data System of the American Association of Poison Control Centers were more likely to report seizures with tramadol vs tapentadol (RR 7.94; 95%CI 2.99 to 20.91) (Tsutaoka 2015 **Level III-2**, n=8,783 [calls]). The low rate of recurrence does not justify the prophylactic use of an anticonvulsant after an initial seizure (Shadnia 2012 **Level IV**, n=100).

An analysis of reports from United States Food and Drug Administration Adverse Event Reporting System showed an association between tramadol use and hypoglycaemia in comparison to all other opioids except methadone (Makunts 2019 **Level IV**, n=12,004,552).

Although withdrawal from tramadol is uncommon, abrupt cessation can lead to withdrawal symptoms, which can have features of classical opioid withdrawal or atypical withdrawal seen with SNRI antidepressants (similar to those described with venlafaxine withdrawal); gradual tapering is recommended and treatment with lorazepam and clonidine if necessary (Miotto 2017 **NR**).

Finally, tramadol has a lower abuse and misuse potential than conventional opioids, as reconfirmed by an expert committee on drug abuse of the German government (Radbruch 2013 **GL**); this is in line with previous findings and tramadol's status as a noncontrolled drug in most countries. However, in countries with low availability of conventional opioids, tramadol has a higher rate of abuse. This has been reported from China (Wang 2018b **Level III-2 SR**, 80 studies, n= 118,904) and Africa (Salm-Reifferscheidt 2018 **NR**): eg Egypt (Bassiony 2018 **Level IV**, n=1,135), Ghana (Fuseini 2019 **NR**) and Nigeria (Idowu 2018 **Level IV**, n=249). A detailed assessment of issues related to tramadol use and abuse internationally has been released by the WHO (WHO 2018 **NR**).

4.3.1.4 | Determinants of opioid dose

Interpatient opioid requirements vary greatly (Macintyre 1996 **Level IV**) and opioid doses therefore need to be titrated to suit each patient. Reasons for variation include patient age and gender, genetic differences and psychological factors as well as opioid tolerance.

Patient age

Age, rather than patient weight, appears to be a better determinant of the amount of opioid an adult is likely to require for effective management of acute pain. There is clinical and experimental evidence of a two-fold to four-fold decrease in opioid requirements as patient age increases (Gagliese 2008 **Level IV**, n=246; Coulbault 2006 **Level IV**, n=74; Gagliese 2000 **Level IV**, n=99; Macintyre 1996 **Level IV**, n=1,010; Burns 1989 **Level IV**, n=100). The decrease in opioid requirement is not associated with reports of increased pain (Macintyre 1996 **Level IV**, n=1,010; Burns 1989 **Level IV**, n=100).

This age-related decrease in opioid requirement appears mainly due to differences in pharmacodynamics or brain penetration rather than systemic pharmacokinetic factors (Minto 1997 **Level IV**, n=65; Scott 1987 **Level IV PK**; Macintyre 2008b **NR**). See also Section 9.2.3.

Sex-based differences

In general, females report more severe pain than males with similar disease processes or in response to experimental-pain stimuli (Hurley 2008 **NR**). This is more complicated than initially thought; in experimental-pain settings, women have lower pressure pain thresholds than men with no difference for cold and ischaemic pain (Racine 2012a **Level IV SR**, 122 studies, n unspecified). Temporal summation, allodynia and secondary hyperalgesia may be more pronounced in women than in men (Racine 2012b **Level IV SR**, 129 studies, n unspecified). In acute pain, there is more of a difference in pain perception than pain sensitivity (Ravn 2012 **Level IV EH**, n=100).

Evidence for differences of opioid responses in the acute pain setting varies. Across all studies in acute clinical pain with mu-opioids there is no association between sex and opioid response, however with PCA use there is greater analgesic effect in women (ES 0.22; 95%CI 0.02 to 0.42) (Niesters 2010 **Level I**, 25 RCTs, n unspecified). The effect is even more pronounced with morphine PCA (ES 0.36; 95%CI 0.17 to 0.56) and is similar in experimental-pain settings (ES 0.35; 95%CI 0.01 to 0.69). Likely explanations are interactions between oestrogen and opioid receptors (Lee 2013b **NR**). This is supported by preclinical data which show that hormones interact with the opioid system and that these interactions may produce meaningful sex-based differences in the subjective experience of opioids, but the direction of effect is variable and inconsistent (Huhn 2018 **BS SR**).

While response to opioids may differ, both the degree and direction of variation depend on many variables (Campesi 2012 **NR**; Dahan 2008a **NR**). This variation as well as other known and unknown factors involved in the very large interpatient differences in opioid requirements seen clinically, means that biological sex cannot be used as a basis for opioid-dose alteration and confirms the need to titrate doses to effect for each patient.

Genetics

Genetic variability may also affect a patient's response to opioids (see Section 1.7.3).

Psychological factors

The effect of psychological factors such as anxiety on opioid requirements is contradictory (see Section 1.2). Behavioural and psychological aspects associated with opioid tolerance and addiction are discussed in Sections 9.7 and 9.8.

Common opioid-related adverse effects are sedation, pruritus, nausea, vomiting, slowing of gastrointestinal function and urinary retention. A network meta-analysis has assessed frequencies for the various opioids at equianalgesic doses relative to morphine by PCA (Dinges 2019 **Level I** [NMA], 63 RCTs, n unspecified) (for more details see Section 6.3.2). Meta-analysis has also shown that the risk of adverse effects from opioids administered by PCA is similar to the risks from traditional methods of systemic opioid administration, with the exception of pruritus, which is increased in patients using PCA (Hudcova 2006 **Level I** [Cochrane] 55 RCTs, n=3,861).

However, there may be differences in the routine clinical setting (Dolin 2005 **Level IV SR**, 165 studies, n≈20,000; Cashman 2004 **Level IV SR**, 165 studies, n≈20,000). The following incidences (means) were associated with the use of PCA opioids: respiratory depression 1.2 to 11.5% (using decreased respiratory rate and oxygen desaturation, respectively, as indicators), nausea 32%, vomiting 20.7%, pruritus 13.8% and excessive sedation 5.3%. The incidences reported for IM opioid analgesia were: respiratory depression 0.8 to 37% (using the same indicators), nausea 17%, vomiting 21.9%, pruritus 3.4% and excessive sedation 5.2%.

Clinically meaningful opioid-related adverse effects are dose-related. There was an increased risk of 0.9% for nausea and 0.3% for vomiting for every 1 mg increase in PCA-morphine consumption after surgery (Marret 2005 **Level I**, 22 RCTs, n=2,307). In a prospective evaluation of elderly surgical inpatients (requiring a length of stay (LOS) >2 d and no PONV prophylaxis), increasing opioid dose also correlated directly with both nausea and vomiting incidence (Roberts 2005 **Level IV**, n=193). After laparoscopic cholecystectomy, once a threshold dose was reached (≈10 mg MED/d), every further 3–4 mg increase of MED/d was associated with one additional meaningful adverse effect or patient-day with such an event (Zhao 2004 **Level II**, n=193, JS 5).

Opioid-related adverse effects in surgical patients were associated with increased LOS in hospital and total hospital costs; the use of opioid-sparing techniques can be cost-effective (Oderda 2007 **Level III-2**; Barletta 2012 **NR**; Philip 2002 **NR**). Postsurgical patients who experienced an opioid-related adverse effect had a 55% longer LOS, 47% higher costs, 36% increased risk of readmission and 3.4 times higher risk of inpatient mortality (Kessler 2013 **Level III-2**, n=37,031). Similar results were found in the analysis of a large national hospital database (Oderda 2013 **Level III-2,** n=319,898). More specific information was reported subsequently where 10.6% of surgical patients experienced an opioid-related adverse event (Shafi 2018 **Level III-2**, n=135,379). Risk factors were higher opioid doses (MED 46.8 mg vs 30.0 mg) and opioid use for a longer duration (median 3.0 vs 2.0 d). Opioid-related adverse events were associated with increased inpatient mortality (OR 28.8; 95%CI 24.0 to 34.5 [2.9% increase in absolute mortality]), prolonged LOS (OR 3.1; 95%CI 2.8 to 3.4), high cost of hospitalisation (OR 2.7; 95% CI 2.4 to 3.0), higher rate of 30 d readmission (OR 1.3; 95%CI 1.2 to 1.4) and US$ 8,225 per event increase in cost. Similarly, in previously opioid-naïve patients receiving opioids after surgery, 9.1% experienced opioid-related adverse effects with an increased risk with prolonged IV administration and resulted in 29% higher costs of hospitalisation, 55% longer postoperative LOS, 29% lower odds of discharge home and 2.9 times the odds of death (Urman 2019 **Level III-2**, n= 12,218 [patients receiving opioids]).

Identifying patients at high risk of opioid-related adverse effects using clinical and demographic parameters is possible (Minkowitz 2014a **Level III-2**, n=6,285; Minkowitz 2014b **Level III-3**, n=3,697); identification of such high-risk patients enabled reduction of adverse effects and hospital costs.

Opioid-induced ventilatory impairment

OIVI is a more appropriate term to describe the effects of opioids on ventilation than respiratory depression alone (Macintyre 2011 **NR**). It encompasses the respiratory depression caused by

opioids (decreased central CO_2 responsiveness resulting in hypoventilation) and elevated partial pressure of CO_2 in arterial blood [$PaCO_2$]) (Boom 2012 **NR**) but also the depressed consciousness (decreased arousal and protection) and the subsequent upper airway obstruction (associated with lower airway motor tone) resulting from excessive opioid use. This combination is the most feared adverse effect of opioids, potentially with fatal consequences.

The most frequently reported risk factors for OIVI were older age, female gender, sleep-disordered breathing, obesity, renal impairment, pulmonary disease (in particular COPD), cardiac disease, diabetes, hypertension, neurologic disease, two or more comorbidities, opioid dependence, concomitant administration of sedatives, different routes of opioid administration and CYP450 enzyme polymorphisms, but patients without such risk factors can also develop OIVI (Gupta 2018b **Level IV SR**, 13 studies, n=871,912; Overdyk 2014 **Level IV**, n=134 [case reports]). Postoperative OIVI occurred in 5/1,000 cases with 85% in the first 24 h (95% CI 4.8 to 5.1) (Gupta 2018a **Level IV SR** [PRISMA], 12 studies, n=841,424). Increased risk is linked to cardiac disease (OR 1.7; 95%CI 1.2 to 2.5), pulmonary disease (OR 2.2; 95%CI 1.3 to 3.6), OSA (OR 1.4; 95%CI 1.2 to 1.7) and higher daily MED (24.7±14 mg vs 18.9±13.0 mg). Age, gender, BMI and ASA status are not identified as risk factors in this systematic review. In a closed claims study of postoperative OIVI, 88% of events occurred within 24 h postoperatively; risk factors included multiple prescribers (33%), concurrent administration of sedating medications (34%), and inadequate nursing assessments or response (31%) (Lee 2015b **Level IV**, n=92 [episodes of OIVI]). Other studies confirm that most postoperative events of OIVI occur in the first 24 h: within 24 h 88% (within 12 h 58%) (Weingarten 2015 **Level III-2**, n=134 [naloxone administrations]), 81% (34% within 6 h) (Ramachandran 2011 **Level IV**, n=33 [episodes of OIVI]) and 78% (57% within 12 h) (Taylor 2005 **Level III-2**, n=62 [episodes of OIVI]).

OIVI can usually be avoided by careful titration of the dose against effect and careful observation and monitoring. A variety of clinical indicators have been used to indicate OIVI caused by opioids; not all may be appropriate or sensitive.

A number of studies investigating hypoxia in the postoperative period in patients receiving opioids for pain relief have found that measurement of respiratory rate as an indicator of respiratory depression may be of limited value and that hypoxaemic episodes often occur in the absence of a low respiratory rate (Kluger 1992 **Level III-2**, n=40; Wheatley 1990 **Level III-2**, n=30; Catley 1985 **Level III-2**, n=32; Jones 1990 **NR**). As respiratory depression is almost always preceded by sedation, the best early clinical indicator is increasing sedation (Jungquist 2017 **NR**; Macintyre 2011 **NR**; Vila 2005 **NR**; Ready 1988 **NR**). This has also been acknowledged in recommendations of current guidelines (Jungquist 2020 **GL**; Chou 2016 **GL**).

Introduction of a numerical pain treatment algorithm in a cancer setting was followed by a review of opioid-related adverse effects (Vila 2005 **Level III-3**, n=25). Use of this algorithm, in which opioids were given to patients in order to achieve satisfactory pain scores, resulted in a two-fold increase in the risk of respiratory depression. Importantly, the authors noted that respiratory depression was usually not accompanied by a decrease in respiratory rate. Of the 29 patients who developed respiratory depression (either before or after the introduction of the algorithm), only 3 had a respiratory rate of <12 breaths/min but 27 (94%) had a documented decrease in their level of consciousness (Vila 2005 **Level III-3**, n=29). This study highlights the risk of titrating opioids to achieve a desirable pain score without appropriate patient monitoring.

In a review of PCA, case reports of respiratory depression in patients with obstructive sleep apnoea (OSA) were examined (Macintyre 2008a **NR**). It would appear that the development of respiratory depression might have been missed because of an apparent over-reliance on the use of respiratory rate as an indicator of respiratory depression; the significance of excessive sedation was not recognised.

In an audit of 700 acute pain patients who received PCA for postoperative pain relief, respiratory depression was defined as a respiratory rate of <10 breaths/min and/or a sedation score of 2 (defined as "asleep but easily roused") or more. Of the 13 patients (1.86%) reported with respiratory depression, 11 had sedation scores of at least 2 and, in contrast to the statements above, all had respiratory rates of <10 breaths/min (Shapiro 2005 **Level IV**, n=700). In a closed claims report, 62% of patients with postoperative OIVI (with 77% fatality or severe brain injury) experienced somnolence before the event (Lee 2015b **Level IV**, n=92 [events of OIVI]): the authors emphasise that assessment of sedation levels by nurses needs to be improved; 97% were judged preventable with better monitoring and response. These studies confirm that assessment of sedation is a more reliable way of detecting opioid-induced respiratory depression, although monitoring respiratory rate is still important.

Oxygen saturation levels may not be a reliable method of detecting respiratory depression in the postoperative setting. In addition to the use of supplemental oxygen delaying OIVI diagnosis, there may be reasons other than opioids for hypoxaemia. For example, when measurement of oxygen saturation was used as an indicator of respiratory depression, the incidence was reported to be 11.5% in patients receiving PCA and 37% in those given IM opioids (Cashman 2004 **Level IV SR**, 165 studies, n≈20,000). However, the same authors showed that patients given IM opioids reported more pain (moderate to severe pain in 67.2% and severe pain in 29.1% vs 35.8% and 10.4% respectively in PCA patients), suggesting that these patients received much lower doses of opioids (Dolin 2002 **Level IV SR**, 165 studies, n≈20,000). Continuous pulse oximetry (1 RCT, 3 studies) improves recognition of desaturations (<90%) (OR 15.7; 95% CI 10.6 to 23.2), with no effect on transfers to the ICU (RR 0.66; 95%CI 0.42 to 1.01) (Lam 2017 **Level IV SR** [PRISMA}, 2 RCTs & 7 studies, n>6,579).

Increases in $PaCO_2$ are the most reliable way of detecting respiratory depression. Continuous monitoring of transcutaneous CO_2 for 24 h after major abdominal surgery showed that patients given IV PCA morphine had higher CO_2 levels than those receiving epidural local anaesthetic/fentanyl infusions (McCormack 2008 **Level III-2**, n=30; Kopka 2007 **Level III-2**, n=28). Continuous capnography vs continuous pulse oximetry (1 RCT & 2 studies) identifies more events of respiratory depression (OR 5.83; 95%CI 3.54 to 9.63) (11.5% vs 2.8%) (Lam 2017 **Level IV SR** [PRISMA}, 2 RCTs & 7 studies, n>6,579).

Alternative monitors include continuous non-invasive respiratory-volume monitoring, which was described as identifying at-risk patients with a significant drop in minute ventilation or apnoeic/hypopnoeic episodes with high sensitivity (93%) and specificity (86%) (Voscopoulos 2014 **Level IV**, n=132).

Pharmacological strategies to reduce OIVI without affecting analgesia, eg by respiratory stimulants, have been investigated (Kimura 2014 **NR**; van der Schier 2014 **NR**).

Cardiac effects

The use of methadone has been linked to the development of prolonged QT interval with a risk of TdP and cardiac arrest (Alinejad 2015 **NR**; Mujtaba 2013 **NR**). Methadone has this effect due to inhibition of the cardiac-ion channel KCNH226 and the effect is dose-dependent. Most case reports of TdP in patients taking methadone have identified the presence of at least one other risk factor in addition to methadone (Justo 2006 **Level IV**, n=40 [TdP cases in 14 reports]; Fredheim 2008 **NR**). Risk factors include female sex, heart disease, other medicines with effects on the QT interval (eg tricyclic antidepressants [TCAs], antipsychotics, diuretics) or methadone metabolism, congenital or acquired prolonged QT syndromes, liver impairment and hypokalaemia (Mujtaba 2013 **NR**; Fredheim 2008 **NR**).

Of patients receiving substitution therapy of 60 to 100 mg/d methadone, 23% developed prolonged QT intervals during treatment vs none of the buprenorphine patients taking 16 to

32 mg 3 times/wk (Wedam 2007 **Level II**, n=165, JS 5). In the methadone group, the QT interval continued to increase over time, even with stable doses.

There is as yet no consensus regarding the benefits or otherwise of obtaining an electrocardiogram (ECG) in patients prior to starting methadone, although it may be that the threshold for doing so should be lower in patients with other concomitant risk factors, including those receiving higher doses of methadone (Cruciani 2008 **NR**). Overall, guidelines targeting the prevention of death from methadone can only offer weak recommendations due to lack of good data (Chou 2014 **GL**); a Cochrane review was unable to identify any studies suitable for inclusion (Pani 2013 **Level I** [Cochrane] 0 RCTs, n=0). No adverse cardiac events related to intraoperative methadone administration have been reported so far, although methadone (given along with other perioperative medications) has been associated with QT-prolongation in the post-operative period in over 50% of patients (Murphy 2019 **NR**).

The use of dextropropoxyphene also carries a risk of TdP (Barkin 2006 **NR**) (see above). Similarly, higher doses of oxycodone were linked to prolonged QT intervals (Fanoe 2009 **Level III-2**). Beside these opioids, buprenorphine and pethidine have also been associated with prolonged QT intervals (Klivinyi 2018 **NR**).

Nausea and vomiting

Nausea and vomiting are frequent adverse effects of opioid analgesia in a range of settings. PONV and its prevention have been studied the most extensively; hence the following discussion will focus on this data. PONV is common and related to opioid administration in a dose-dependent manner (Marret 2005 **Level I**, 22 RCTs, n=2,307; Roberts 2005 **Level IV**, n=193), although many other more relevant risk factors for PONV have also been identified (Apfel 2012 **Level IV SR**, 22 studies, n=95,154). Opioids are a risk factor for PONV (OR 1.39; 95%CI 1.20 to 1.60) but less so than female sex, history of previous PONV or motion sickness, inhalational anaesthesia and nonsmoking status. The biological mechanisms of PONV have not yet been completely unravelled (Horn 2014 **NR**).

Guidelines on the prevention and management of PONV have been published (Gan 2014 **GL**).

Medications used as components of multimodal analgesia and that are opioid-sparing may also reduce PONV. Opioid-sparing effect and PONV reduction occurs with concurrent administration of gabapentin (Grant 2016b **Level I** [PRISMA], 44 RCTs, n=3,489) and pregabalin (Grant 2016a **Level I** [PRISMA], 23 RCTs, n=1,693), nsNSAIDs (Maund 2011 **Level I**, 43 RCTs [PONV], n unspecified), ketamine (Assouline 2016 **Level I** [PRISMA], 19 RCTS, n=1,453) and lidocaine (Weibel 2018 **Level I** [Cochrane], 68 RCTs, n=4,525). See also sections covering these medications.

Opioid-sparing effect with no decrease in PONV is reported for paracetamol and coxibs (Maund 2011 **Level I**, 43 RCTs [PONV], n unspecified). However, paracetamol given IV preoperatively or intraoperatively reduces PONV; this effect is associated with improved analgesia, not reduced opioid requirements (Apfel 2013 **Level I** [PRISMA], 30 RCTs, n=2,364). Preoperative vs postoperative paracetamol reduces postoperative vomiting (RR 0.50; 95%CI 0.31 to 0.83) (Doleman 2015b **Level I** [PRISMA], 7 RCTs, n=544) (see also Section 4.1).

Antiemetic medications

Eight antiemetic medications effectively prevent PONV vs placebo: droperidol, metoclopramide, ondansetron, tropisetron, dolasetron, dexamethasone, cyclizine and granisetron (Carlisle 2006 **Level I** [Cochrane], 737 RCTs, n=103,237). The authors conclude that evidence for differences between the medications was unreliable due to publication bias. Despite limited data to compare adverse effects, droperidol was more sedative and headache more common after ondansetron.

Scientific fraud by Yoshitaka Fujii has influenced this meta-analysis on the efficacy of antiemetics, in particular the efficacy of granisetron and ramosetron is overestimated by inclusion of 168 fraudulent RCTs by his group (Carlisle 2012 **Level I**, 534 RCTs, n unspecified).

Ramosetron remains effective vs placebo (but less than reported previously) and maintains a statistical, but clinically questionable, advantage over ondansetron (Mihara 2013 **Level I**, 12 RCTs, n=1,372).

The efficacy of various single compounds in reducing incidence of PONV in the first 24 h has been confirmed in updated meta-analyses; dexamethasone 4–5 mg IV (NNT 3.7), 8–10 mg IV (NNT 3.8) (De Oliveira 2013b **Level I** [PRISMA], 60 RCTs, n=6,696); droperidol ≤1 mg IV (NNT 3.5 to 5 for high-risk patients) (Schaub 2012 **Level I**, 25 RCTs, n=2,957); metoclopramide 10 mg IV (NNT 7.8) (De Oliveira 2012b **Level I** [PRISMA], 30 RCTs, n=3,328); perphenazine (Schnabel 2010 **Level I**, 11 RCTs, n=2,081); $5HT_3$-antagonists ondansetron, granisetron, tropisetron and dolasetron (Tang 2012 **Level I**, 85 RCTs, n=15,269), palonosetron (Singh 2016a **Level I** [PRISMA], 22 RCTs, n unspecified) and TD hyoscine (scopolamine) (Apfel 2010 **Level I**, 25 RCTs, n=3,298). All 5-HT_3 antagonists are superior to placebo in reducing incidence of PONV (125 RCTs, n=16,667 patients) (Tricco 2015a **Level I** [NMA], 450 RCTs, n=80,410).

NK1 receptor antagonists are also used in treatment and prophylaxis of PONV (George 2010 **NR**). Aprepitant (80 mg) reduces the incidence of nausea vs placebo (pooled RR 0.60; 95%CI 0.47 to 0.75) (3 RCTs, n=224) and vomiting (pooled RR 0.13; 95%CI 0.04 to 0.37) (3 RCTs, n=224) (Liu 2015 **Level I** [PRISMA], 14 RCTs, n=4,322). However, neither 40 mg (3 RCTs, n=1,171) nor 125 mg (2 RCTs, n=1,085) are superior to ondansetron 4 mg. After craniotomy, IV fosaprepitant 150 mg was significantly more effective than IV ondansetron 4 mg (6 vs 50% vomiting) (Tsutsumi 2014 **Level II**, n=64, JS 5) and more effective than IV droperidol 1.25 mg (Atsuta 2017 **Level II**, n=200, JS 5).

Propofol (1 mg/kg) close to the end of surgery reduced PONV significantly vs placebo (Kim 2014a **Level II**, n=107, JS 4). Caffeine 500 mg IV was ineffective in preventing PONV and increased rates of nausea (Steinbrook 2013 **Level II**, n=136, JS 3).

Combinations of antiemetics may be more effective than one medication given alone. Prophylaxis with the combination of a $5HT_3$-receptor antagonist and dexamethasone was associated with lower use of rescue antiemetics than $5HT_3$-receptor antagonist or dexamethasone alone (Tricco 2015a **Level I** [NMA], 450 RCTs, n=80,410; Kovac 2006 **Level I**, 49 RCTs, n=12,752), also after strabismus surgery in children (Shen 2014 **Level I**, 13 RCTs, n=2,006). Similarly, the combination of droperidol and ondansetron was additive (Chan 2006 **Level II**, n=400, JS 5). Other combinations that were more effective than either medicine given alone were cyclizine/granisetron (Johns 2006 **Level II**, n=960, JS 5), dexamethasone/haloperidol (Chu 2008 **Level II**, n=400, JS 5) and dexamethasone/dolasetron (Rusch 2007 **Level II**, n=242, JS 5). The addition of metoclopramide to dexamethasone also led to better PONV prophylaxis but, compared with dexamethasone 8 mg alone, only if doses of 25 mg and 50 mg metoclopramide were used, not 10 mg (Wallenborn 2006 **Level II**, n=3,140, JS 4). Oral aprepitant 80 mg added to ondansetron reduced the rate of postoperative vomiting in bariatric surgery patients for 72 h (Sinha 2014 **Level II**, n=125, JS 5).

Droperidol and, to a lesser extent, ondansetron may lead to prolonged QT intervals. Concerns about the potential for serious cardiac arrhythmias secondary to QT prolongation associated with droperidol led to a "black box" warning by the USA FDA in 2001. Following this there has been a significant reduction in the use of this medication, even though the warning was felt by many to be unwarranted (Habib 2008b **NR**). Mild QT prolongation can occur with anaesthesia and surgery. Saline administration vs 0.625 and 1.25 mg IV droperidol were associated with similar QT prolongation in the postoperative period (White 2005 **Level II**, n=120, JS 5). Similarly, 1.25 mg droperidol did not prolong QT interval (Toyoda 2013 **Level II**, n=72, JS 3). A large review of surgical patients in the periods 3 y before (n=139,932) and 3 y after (n=151,256) the FDA black box warning merged anaesthesia database information with information from ECG and other databases as well as patients' case notes, and recorded all patients who had documented prolonged QT

intervals, TdP or death within 48 h of their surgery (Nuttall 2007 **Level III-3**). Despite a reduction in droperidol use from 12 to 0% of patients following the warning, there was no difference in the incidence of QT prolongation, ventricular tachycardia, or death within 48 h of surgery and no clearly identified case of TdP related to use of droperidol. The authors concluded that for low-dose droperidol, the "black box" warning was "*excessive and unnecessary*". The scientific basis of the decision in favour of a "black box" warning has been questioned as a range of data show that the incidence of QT prolongation and TdP development is similar for low-dose droperidol and other compounds used to treat PONV (Halloran 2010 **NR**). The authors of guidelines for the management of PONV also express concerns about the FDA caution and state "*due to the 2001 black box warning, droperidol is not the first choice for PONV prophylaxis in many countries*" (Gan 2014 **GL**).

Haloperidol has also been associated with QT prolongation and TdP (Habib 2008a **NR**). Using data from studies published up until 1988, a meta-analysis showed that haloperidol is also an effective antiemetic (Buttner 2004 **Level I**, 23 RCTs, n=1,468). Subsequent studies have confirmed its effectiveness vs placebo (Aouad 2007 **Level II**, n=93, JS 4), ondansetron (no differences in efficacy, adverse effects or QT intervals) (Rosow 2008 **Level II**, n=244, JS 2; Aouad 2007 **Level II**, n=93, JS 4; Lee 2007 **Level II**, n=90, JS 5) and droperidol (equally effective) (Wang 2008 **Level II**, n=150, JS 5). Haloperidol/ondansetron was more effective than ondansetron alone (Grecu 2008 **Level II**, n=268, JS 3) and haloperidol/dexamethasone was also more effective than either medication given alone (Wang 2012 **Level II**, n=135, JS 3; Chu 2008 **Level II**, n=400, JS 5), again with no difference in adverse effects or QT intervals. Compared with droperidol, the only advantage of haloperidol may be "*that there is no black box warning*" (Ludwin 2008 **NR**).

Dolasetron (IV and oral formulations) is contraindicated by the Canadian authorities for any therapeutic use in children and adolescents aged <18 y and the prevention or treatment of PONV in adults because of the risk of QT prolongation (Health Canada 2006 **GL**). This age restriction is not limited to Canada but applies in a number of other countries including the UK. The effect of therapeutic doses of dolasetron (and ondansetron) on QT prolongation is, however, minimal (6% from baseline) (n=1,429) (Obal 2014 **Level III-3**, n=1,429); a case of prolonged QT interval has been reported after overdose (Rochford 2007 **CR**). More patients receiving granisetron/dexamethasone experience an arrhythmia vs placebo (OR 2.96; 95 %CI 1.11 to 7.94), ondansetron (OR 3.23; 95 %CI 1.17 to 8.95), dolasetron (OR 4.37; 95% CI 1.51 to 12.62), tropisetron (OR 3.27; 95 %CI 1.02 to 10.43), and ondansetron/dexamethasone (OR 5.75; 95% CI 1.71-19.34) (Tricco 2015b **Level I** [NMA], 31 RCTs, n=6,623).

Other antiemetic interventions

Low-dose naloxone (≤ 1 mcg/kg/h) reduces opioid-related postoperative nausea (RR 0.80; 95%CI 0.67 to 0.95), but has no effect on vomiting (RR 0.83; 95%CI 0.63 to 1.09) (Barrons 2017 **Level I** [PRISMA], 9 RCTs, n=946).

Mirtazapine vs placebo reduces PONV (RR 0.44; 95%CI 0.32 to 0.62) (3 RCTs) and has similar effects to ondansetron (1 RCT), while it also reduces anxiety (Bhattacharjee 2019 **Level I** [PRISMA], 7 RCTs, n=581).

Supplemental IV crystalloid infusions reduce the risk of PONV and the need for rescue antiemetics (Jewer 2019 **Level I** [Cochrane], 41 RCTs, n=4,424). IV dextrose perioperatively vs control does not reduce the risk of PONV, but does reduce the need for rescue antiemetics (Kim 2018 **Level I** [PRISMA], 7 RCTs, n=701).

Supplemental oxygen (FiO_2 80%) in the postoperative period does not reduce PONV (Orhan-Sungur 2008 **Level I**, 10 RCTs, n=1,729), but high inspired oxygen concentrations intraoperatively reduce PONV in patients receiving inhalational anaesthetics without prophylactic antiemetics (Hovaguimian 2013 **Level I**, 22 RCTs, n=7,001).

PC6 acupoint stimulation (by any means: acupuncture, electro-acupuncture, transcutaneous electrical acupoint stimulation, transcutaneous nerve stimulation, laser stimulation, capsicum plaster, acu-stimulation device and acupressure) reduces the incidence of nausea (RR 0.68; 95%CI 0.60 to 0.77) (40 RCTs, n=4,742), vomiting (RR 0.60; 95%CI 0.51 to 0.71) (45 RCTs, n=5,147) and rescue antiemetic requirements (RR 0.64; 95%CI 0.55 to 0.73) (39 RCTs, n=4,622) based on low quality evidence (Lee 2015a **Level I** [Cochrane], 59 RCTs, n=7,667). PC6 acupoint stimulation vs antiemetics (metoclopramide, cyclizine, prochlorperazine, droperidol, ondansetron and dexamethasone) is similarly effective on all three above outcomes. Acupuncture/acupressure is the only nonpharmacological intervention included in the PONV management guideline developed by the Society for Ambulatory Anesthesiology, endorsed by ANZCA (Gan 2014 **GL**).

Ginger (*Zingiber officinale*) reduces the severity (SMD −0.25; 95%CI −0.46 to −0.04), but not the incidence of PONV (Toth 2018 **Level I** [PRISMA], 10 RCTs, n=918).

Aromatherapy vs placebo has no effect on incidence of PONV, but may reduce need for rescue antiemetic requirements; both statements are based on low-quality evidence (Hines 2018 **Level III-1 SR** [Cochrane], 16 RCTs and CCTs, n=1,036).

In a pilot RCT, chewing gum was not inferior to ondansetron 4 mg for PONV treatment after laparoscopic or breast surgery in females (Darvall 2017 **Level II**, n=94, JS 3).

Impairment of gastrointestinal motility

Opioids are well described as inducing constipation with chronic use (Ahmedzai 2006 **NR**). Opioids impair return of bowel function after surgery (Barletta 2012 **NR**). A daily dose of hydromorphone IV >2 mg was the most obvious risk factor for postoperative ileus (Barletta 2011 **Level IV**, n=279). Another risk factors was longer IV opioid use and postoperative ileus was a risk factor for prolonged hospital LOS. After laparotomy and laparoscopic cholecystectomy and colectomy, patients with postoperative ileus received higher opioid doses (median MED 285 mg vs 95 mg); in postoperative patients with an ileus, opioid doses above the median were associated with increased LOS (3.8 d to 7.1 d), total costs (US$ 8,458 to 19,562), and readmission after laparoscopic surgeries (4.8% to 5.2%) (Gan 2015 **Level III-3**, n= 138,068).

Overall, treatment of opioid-induced constipation due to chronic intake with opioid antagonists (methylnaltrexone, naloxone, naloxegol, alvimopan, axelopran, or naldemedine) (NNT 3.4 to 7) (23 RCTs) is more effective than laxatives (lubiprostone [NNT 15] or prucalopride) (4 RCTs) (Nee 2018 **Level I** [PRISMA], 27 RCTs, n=8,881); the effects of the various opioid antagonists are similar, while the two laxatives are only slightly better than placebo. A network meta-analysis identified SC methylnaltrexone as the most effective opioid antagonist to treat opioid-induced constipation (Sridharan 2018 **Level I** [NMA], 23 RCTs, n unspecified) (17 RCTs overlap).

The peripheral-acting opioid antagonists alvimopan and methylnaltrexone are effective in reversing opioid-induced slowing of gastrointestinal transit time and constipation and alvimopan is an effective treatment for postoperative ileus (McNicol 2008 **Level I** [QUOROM], 22 RCTs, n=2,358) (4 RCTs overlap with Nee 2018); insufficient evidence exists about the efficacy or safety of naloxone or nalbuphine. The efficacy of alvimopan has been confirmed in subsequent studies summarised in a review (Kraft 2010 **NR**). After radical cystectomy in an RCT not included in any of the above systematic reviews, alvimopan resulted in faster gastrointestinal recovery, shorter hospital LOS and reduced incidence of postoperative ileus (7 vs 26%) with reduced resulting morbidity (8.4 vs 29.1%) without increased adverse effects (Lee 2014a **Level II**, n=280, JS 3).

A combined formulation of controlled-release (CR) oxycodone and naloxone is available in many jurisdictions. Compared with CR oxycodone alone in patients with chronic non-cancer pain, the combination formulation resulted in similar analgesic efficacy but less bowel dysfunction (Lowenstein 2010 **Level II** [pooled analysis of 2 RCTs], n=578, JS 5). It has been suggested that these benefits were transferable to acute pain settings (Kuusniemi 2012 **NR**). This was not confirmed

after laparoscopic hysterectomy where oxycodone/naloxone CR had no beneficial effect on constipation or other opioid adverse effects vs oxycodone CR (Comelon 2013 **Level II**, n=85, JS 5). IV administration of the crushed combination resulted in reduced drug liking and other subjective effects (Colucci 2014 **Level II EH**, n=24, JS 3).

Urinary retention

Opioids cause urinary retention due to presumed central and peripheral mechanisms. Opioid antagonists reverse this effect; naloxone reversed opioid-induced urinary retention in 100% of patients, while the peripheral opioid antagonist methylnaltrexone IV was effective in 42% of study participants (Rosow 2007 **Level III-1 EH**, n=13). These data suggest that at least part of the bladder dysfunction caused by opioids is peripherally mediated.

Premedication with gabapentin reduces urinary retention caused by opioids (NNT 7) (Tiippana 2007 **Level I** [QUOROM], 22 RCTs, n=1,909). This effect is most likely related to the opioid-sparing effect of gabapentin.

Pruritus

The mechanism of opioid-induced pruritus, which is particularly common after neuraxial opioid administration, is not fully understood but central mu-opioid receptor-mediated mechanisms are thought to be the primary cause (Ganesh 2007 **NR**). However, a serotonergic mechanism has also been suggested (Aly 2018 **Level II,** n=40, JS 4) (see also Section 4.3.1.5).

Naloxone, naltrexone, nalbuphine and droperidol are effective in the treatment of opioid-induced pruritus, although minimum effective doses remain unknown (Kjellberg 2001 **Level I**, 22 RCTs, n=1,477 patients); doses >2 mcg/kg/h of naloxone are more likely to lead to reversal of analgesic effects. Low-dose continuous naloxone (0.25–1 mcg/kg/h) has the best evidence (Miller 2011 **NR**). Nalbuphine specifically is more effective than placebo (3 RCTs), control (3 RCTs) and diphenhydramine (1 RCT) in reducing pruritus (Jannuzzi 2016 **Level I**, 9 RCTs, n=1,128). Furthermore, ondansetron reduces the incidence of opioid-induced pruritus after neuraxial administration only in non-obstetric patients (RR 0.63; 95%CI 0.45 to 0.89) (3 RCTs, n=235) and not in obstetric patients (RR 0.84; 95%CI 0.69 to 1.03) (7 RCTs, n=576) (Wang 2017b **Level I** [PRISMA], 10 RCTs, n=811).

Cognitive function and confusion

While opioids can be the cause of cognitive dysfunction, confusion and delirium, it is surprising that, after cardiac surgery, IM morphine 5 mg was superior to IM haloperidol 5 mg in treating delirium (Atalan 2013 **Level II**, n=53, JS 2). This suggests that undertreated pain is a relevant consideration. Similarly, in elderly patients after hip fracture repair, opioids were not an important predictor of postoperative delirium (Sieber 2011 **Level IV**, n=236).

The risk of delirium and/or changes in cognitive function has been compared in patients receiving different PCA opioids. There was no statistically significant difference in the rates of confusion between morphine and fentanyl (14.3 vs 14.3%) but there was less depression of cognitive function with fentanyl (Herrick 1996 **Level II**, n=96, JS 2). No differences in cognitive function were reported in patients receiving tramadol vs morphine (Silvasti 2000 **Level II**, n=60, JS 4) or fentanyl (Ng 2006 **Level II**, n=30, JS 5) but cognition has been found to be poorer with hydromorphone vs morphine (Rapp 1996 **Level II**, n=61, JS 4).

Pethidine use postoperatively was associated with an increased risk of delirium in the postoperative period in comparison to other opioids (Swart 2017 **Level III-2 SR**, 3 studies [pethidine], n=877). Tramadol has been identified as a risk factor for postoperative delirium in the elderly following abdominal surgery (Swart 2017 **Level III-2 SR**, 1 study [tramadol]: Brouquet 2010 **Level III-2**, n=118).

Tolerance and hyperalgesia

In the absence of disease progression, a decrease in the effectiveness of opioid analgesia has traditionally been attributed to opioid tolerance. It is now known that administration of opioids can lead to both opioid-tolerance (a desensitisation of antinociceptive pathways to opioids) and, paradoxically, to opioid induced hyperalgesia (OIH: a sensitisation of pronociceptive pathways leading to pain hypersensitivity) and that both these phenomena can significantly reduce the analgesic effect of opioids (Mao 2015 **NR**; Low 2012 **NR**; Lee 2011 **NR**). The mechanisms underlying the development of tolerance and OIH are still not fully understood but, as with neuropathic pain, are thought to include activation of the glutaminergic system via the NMDA receptor, GABA receptors and possibly the innate neuroimmune system (Arout 2015 **BS NR**) as well as peripheral mu-opioid receptors (Weber 2017 **NR**).

It may be useful here to distinguish "pharmacological tolerance" (ie tolerance, as defined in Section 9.7.1 "the predictable and physiological decrease in the effect of a drug over time") and "apparent tolerance", where both tolerance and OIH contribute to a decrease in the effectiveness of opioids (Chang 2007 **NR**; Mao 2008 **NR**). The clinical significance of this mix, and the relevant contribution of pharmacological tolerance and OIH to apparent tolerance in any particular patient is difficult, if not impossible, to determine (Low 2012 **NR**). However, inadequate pain relief because of pharmacological tolerance may improve with opioid dose escalation, while improvements in analgesia in the presence of OIH may follow a reduction in opioid dose (Mao 2008 **NR**; Chu 2008 **NR**; Chang 2007 **NR**).

A formal diagnosis of hyperalgesia may require quantitative sensory testing (QST), that is, serial assessment of the responses to varying intensities of a nociceptive stimulus, in order to determine pain thresholds (Mitra 2008 **NR**). QST before and after starting chronic opioid therapy may assist in the differentiation between OIH and pharmacological tolerance (Chu 2008 **NR**) but this is unlikely to become common practice in the acute pain setting. OIH is identified by reduced pain tolerance to noxious thermal (hot and cold) stimuli, but not electrical stimuli, in patients with chronic opioid exposure for pain management and for opioid use disorder treatment (here more evident) (Higgins 2019 **Level III-3 EH SR** [PRISMA], 26 studies, n=2,706); pain detection thresholds remain unchanged. However, an attempt to identify a QST method to detect hyperalgesia in chronic pain patients on long-term opioids failed, as none of the measures could be used as a definitive standard (Katz 2015 **Level IV EH SR**, 14 studies, n unspecified). The pain types investigated include cold, heat, pressure, electrical, ischaemic and injection; only heat pain sensitivity showed promise.

Studies of OIH are confounded by factors such as pain modality tested, route of administration and type of opioid (Weber 2017 **NR**). Psychological factors such as pain-related distress and catastrophising might also affect pain sensitivity in those taking opioids for chronic pain (Edwards 2011 **Level III-2**, n=276; Eyler 2013 **NR**). Illicit substance use, affective characteristics, or coping styles may also play a role here (Higgins 2019 **Level III-3 EH SR** [PRISMA], 26 studies, n=2,706). Additionally, increasing opioid dose will worsen OIH (Colvin 2019 **NR**). Practical clinical challenges include lack of consensus on "the" diagnostic test, and overlap with tolerance, drug withdrawal and neuropathic pain.

It is probable that the degree of OIH varies between opioids. Remifentanil in particular (Fletcher 2014 **Level I** [PRISMA], 27 RCTs, n=1,494; Kim 2014b **Level IV EH SR**, number of studies unspecified, n unspecified; Rivosecchi 2014 **Level IV SR**, 35 studies, n unspecified) (significant overlap between all three SRs), but also morphine, in high doses, may be more likely to result in OIH than some other opioids; experimental data and a very limited number of case reports have shown an improvement when morphine doses were reduced or a change to methadone, fentanyl or sufentanil was made (Angst 2006 **NR**). Similarly, it appears that opioids differ in their ability to induce tolerance. Medications such as methadone, fentanyl and sufentanil promote receptor internalisation and thereby receptor

recycling; in contrast, the activation of opioid receptors by morphine leads to little or no receptor internalisation and thereby increased risk of development of tolerance (Joo 2007 **NR**). The difference between opioids is one reason why opioid-rotation may be a useful strategy in the clinical setting in attempts to improve pain relief (see Section 9.7.6.4).

In the setting of postoperative pain, high intraoperative doses of opioids resulted in higher postoperative pain intensity than controls at 1 h (MD 9.4/100; 95%CI 4.4 to 14.5), 4 h (MD 7.1/100; 95%CI 2.8 to 11.3) and 24 h (MD 3/100; 95%CI 0.4 to 5.6) and higher postoperative morphine use over 24 h (SMD 0.7; 95%CI 0.37 to 1.02) (Fletcher 2014 **Level I** [PRISMA], 27 RCTs, n=1,494). These results are mainly influenced by remifentanil due to limited data with other opioids. Overall, the effect of remifentanil is dose dependent (Angst 2015 **NR**).

Compared with abrupt cessation, gradual withdrawal from a target concentration 2.5 ng/mL of a remifentanil infusion for 30 min (by 0.6 ng/mL target concentration every 5 min) induced no OIH (pain similar to placebo) measured with the heat pain test, but not the cold pressor test (Comelon 2016 **Level II EH**, n=19, JS 5). This was confirmed in a clinical setting of thyroidectomy, where gradual tapering of a remifentanil infusion (from 0.3 to 0.1 mcg/kg/min over at least 30 min) reduced postoperative pain at 1 and 2 h and rescue analgesia requirements (Han 2015 **Level II**, n=62, JS 5).

NMDA-receptor antagonists (mainly ketamine [8 RCTs] but also magnesium [5 RCTs] and amantadine [1 RCT]) reduce the development of acute tolerance/OIH associated with remifentanil use (Wu 2015 **Level I** [QUOROM], 14 RCTs, n=729). Attentuation occurs with pregabalin (Lee 2013a **Level II**, n=93, JS 5; Jo 2011 **Level II**, n=60, JS 5), propofol (subgroup analysis: 6 RCTs, n=341) (Fletcher 2014 **Level I** [PRISMA], 27 RCTs, n=1,494) and N_2O (Wehrfritz 2016 **Level II EH**, n=21, JS 5; Echevarria 2011 **Level II**, n=50, JS 4). Low-dose naloxone (0.25 mcg/kg/h intraoperatively) also reduced postoperative opioid requirements when combined with high dose remifentanil (and improved time to bowel recovery) (Xiao 2015 **Level II**, n=75, JS 5). In an experimental setting, propranolol infusion reduced the size of area of secondary hyperalgesia induced by remifentanil to being not significantly different from baseline (Chu 2012 **Level II EH**, n=10 [cross over], JS 4). In animal experiments, the effects of gabapentin and ketamine on fentanyl-induced hyperalgesia were supra-additive (Van Elstraete 2011 **BS**).

The challenge faced by the health professional is that if inadequate pain relief is due to OIH, a reduction in opioid dose may help; if it is due to opioid tolerance, increased doses may provide better pain relief (Colvin 2019 **NR**; Huxtable 2011 **NR**; Mao 2008 **NR**). There are case reports of patients with cancer and chronic noncancer pain taking high doses of opioid who developed OIH and whose pain relief improved following reduction of their opioid dose (Chang 2007 **CR**; Angst 2006 **CR**); there are no data in the acute pain setting.

When a patient who has been taking opioids for a while (either legally prescribed or illicitly obtained) has new and ongoing tissue injury with resultant acute pain, a reasonable initial response to inadequate opioid analgesia, after an evaluation of the patient and in the absence of evidence to the contrary, is a trial of higher opioid doses (Huxtable 2011 **NR**; Chang 2007 **NR**). If the pain improves, this would suggest that the inadequate analgesia resulted from tolerance; if pain worsens, or fails to respond to dose escalation, it could be a result of OIH (Chang 2007 **NR**). Fortunately, some of the strategies that may be tried in an attempt to attenuate opioid tolerance in the acute pain setting may also moderate OIH (see below).

Other reasons for increased pain and/or increased opioid requirements should also be considered. These include acute neuropathic pain, pain due to other causes including postoperative complications, major psychological distress and aberrant drug-seeking behaviours (see Sections 9.7 and 9.8) (Edwards 2011 **Level III-2**; Macintyre 2015 **NR**; Gourlay 2008 **NR**).

The clinical relevance of the phenomena of opioid tolerance and OIH in the setting of perioperative analgesia remains under discussion (Colvin 2019 **NR**) (See also Section 9.7.2 and 9.8.1).

Tolerance to adverse effects of opioids

Tolerance to the adverse effects of opioids also occurs; tolerance to sedation, cognitive effects, nausea and respiratory depression can occur reasonably rapidly but there is little, if any, change in miosis or constipation (Chang 2007 **NR**).

KEY MESSAGES

1. Dextropropoxyphene has low analgesic efficacy (**U**) (**Level I** [Cochrane Review]).
2. Tramadol is an effective treatment for neuropathic pain (**S**) (**Level I** [Cochrane Review]).
3. Droperidol, metoclopramide, ondansetron, tropisetron, dolasetron, dexamethasone, cyclizine, granisetron (**U**) (**Level I** [Cochrane Review]), supplemental crystalloid infusions (**N**) (**Level I** [Cochrane Review]), palonosetron and mirtazapine (**N**) (**Level I** [PRISMA]) are effective in the prevention of postoperative nausea and vomiting.
4. PC6 acupoint stimulation by multiple techniques reduces postoperative nausea and vomiting (**S**) (**Level I** [Cochrane Review]).
5. Neurokinin-1 receptor antagonists aprepitant (**S**) (**Level I** [PRISMA]) and fosaprepitant (**U**) (**Level II**) are effective in the prevention of postoperative nausea and vomiting.
6. Intraoperative administration of the long acting opioid methadone reduces consumption of shorter acting opioids in the 24 hours after surgery (**N**) (**Level I** [PRISMA]). Safety data suggest an increased risk of opioid induced ventilatory impairment due to the long and unpredictable half-life of methadone (**N**) (**Level IV**).
7. Opioids in high doses, in particular remifentanil, can induce hyperalgesia and/or acute tolerance (**S**) (**Level I** [PRISMA]).
8. Propofol (**U**) (**Level I** [PRISMA]), NMDA-receptor antagonists (**U**) (**Level I** [QUOROM]), pregabalin (**U**) (**Level II**), nitrous oxide (**N**) (**Level II**) and gradual tapering of remifentanil dose (**N**) (**Level II**) attenuate acute tolerance and/or hyperalgesia induced by remifentanil.
9. NSAIDs, gabapentin, pregabalin, systemic lidocaine and ketamine are opioid-sparing medications and reduce opioid-related adverse effects (**S**) (**Level I** [PRISMA]).
10. Paracetamol given preoperatively and intraoperatively reduces postoperative nausea and vomiting; this effect is associated with improved analgesia, not reduced opioid requirements (**S**) (**Level I** [PRISMA]).
11. Opioid antagonists (methylnaltrexone, naloxone, naloxegol, alvimopan, axelopran, or naldemedine) are effective (more so than laxatives) and safe to treat opioid-induced constipation (**S**) (**Level I** [PRISMA]).
12. Alvimopan is an effective treatment for postoperative ileus (**U**) (**Level I** [QUOROM]).
13. Haloperidol, perphenazine and transdermal scopolamine are effective in the prevention of postoperative nausea and vomiting (**U**) (**Level I**).
14. The incidence of clinically meaningful adverse effects (nausea, vomiting) of opioids is dose-related (**U**) (**Level I**).

15. Paired combinations of $5HT_3$ antagonists, droperidol or dexamethasone provide superior prophylaxis of postoperative nausea and vomiting than either compound alone (**U**) (**Level I**).
16. Naloxone, naltrexone, droperidol (**U**), nalbuphine (**S**) (**Level I**) and ondansetron (**N**) (**Level I** [PRISMA]) are effective treatments for opioid-induced pruritus.
17. Opioids administered by PCA, in particular morphine, show higher analgesic efficacy in females than in males (**U**) (**Level I**).
18. Tapentadol has similar efficacy to conventional opioids with a reduced rate of gastrointestinal adverse effects (nausea, vomiting, constipation) (**S**) (**Level I**).
19. Tramadol has a lower risk of respiratory depression and impairs gastrointestinal motor function less than other opioids at equianalgesic doses (**U**) (**Level II**).
20. Pethidine is not superior to morphine or hydromorphone in treatment of pain of renal colic (**U**) (**Level II**).
21. Morphine-6-glucuronide is an effective analgesic (**U**) (**Level II**).
22. In the management of acute pain, one opioid is not superior to others but some opioids are better in some patients (**U**) (**Level II**).
23. High doses of methadone can lead to prolonged QT interval (**U**) (**Level II**).
24. Opioid antagonists are effective treatments for opioid-induced urinary retention (**U**) (**Level III-1**).
25. Pethidine use is associated with an increased risk of delirium in the postoperative period compared to other opioids (**S**) (**Level III-2 SR**).
26. In clinically relevant doses, there is a ceiling effect for respiratory depression with buprenorphine but not for analgesia (**U**) (**Level III-2**).
27. Tapentadol has lower rates of abuse and doctor shopping than oxycodone (**S**) (**Level III-2**).
28. Opioid-related adverse effects in the postoperative period are associated with increased inpatient mortality, length of hospital stay, costs and rates of readmission (**S**) (**Level III-2**).
29. Assessment of sedation is a more reliable way of detecting early opioid-induced ventilatory impairment than a decreased respiratory rate (**S**) (**Level III-3**).
30. The evidence for significant QT prolongation and risk of cardiac arrhythmias following low-dose droperidol, haloperidol and dolasetron is weak (**U**) (**Level III-3**).
31. Opioid-induced ventilatory impairment occurs in particular in the first 24 h after surgery and important risk factors are cardiac and pulmonary disease, obstructive sleep apnoea and use of higher opioid doses (**N**) (**Level IV SR** [PRISMA]).
32. Continuous pulse oximetry in patients receiving opioids postoperatively increases detection rate of desaturation, but continuous capnography is superior in identifying episodes of opioid-induced ventilatory impairment (**N**) (**Level IV SR** [PRISMA]).
33. In adults, patient age rather than weight is a better predictor of opioid requirements, although there is a large interpatient variation (**U**) (**Level IV**).

34. Impaired renal function and the oral route of administration result in higher levels of the morphine metabolite morphine-6-glucuronide with increased risk of sedation and respiratory depression (**U**) (**Level IV**).

34. CYP2D6 ultrarapid metabolisers are at increased risk of codeine toxicity (**N**) (**Level IV**).

The following tick boxes represent conclusions based on clinical experience and expert opinion:

☑ Opioid-induced ventilatory impairment is a more appropriate term to describe the effects of opioids on ventilation as it encompasses the central respiratory depression caused by opioids and also the depressed consciousness and the subsequent upper airway obstruction resulting from excessive opioid use (**U**).

☑ The use of pethidine and dextropropoxyphene should be discouraged in favour of other opioids (**S**).

☑ Drug interactions relevant for opioids include pharmacodynamic considerations (eg coadministration of sedative agents) and pharmacokinetic effects (eg CYP 450 enzyme inducers or inhibitors [antidepressants for CYP2D6 and antifungals, antibiotics for CYP3A4 and complementary medicines for both]) (**N**).

4.3.2 | Neuraxial opioids

Opioid receptors were described in the spinal cord of the rat in 1976 (Pert 1976 **BS**) and the same year a potent analgesic effect of directly applied IT morphine was reported in these animals (Kontinen 2019 **NR**; Yaksh 1976 **BS**). Opioid analgesia is spinally mediated via presynaptic and postsynaptic receptors in the substantia gelatinosa in the dorsal horn (Yaksh 1981 **BS**). Spinal opioid receptors are 70% mu, 24% delta and 6% kappa (Treman 2001 **NR**); with 70% of all mu and delta receptors being presynaptic (predominantly small primary afferents) and commonly co-located, with kappa being more commonly postsynaptic. Opioid-mediated antinociception may be further augmented by descending inhibition from mu-opioid-receptor activation in the periaqueductal area of the brain, which may be potentiated by neuraxial opioids. In addition to this, a local anaesthetic action has been described for pethidine (meperidine) that may contribute to the clinical effect when administered IT (Jaffe 1996 **BS**). The first clinical use of IT morphine was for analgesia in cancer patients (Wang 1979 **Level IV**).

The use of neuraxial opioids has been reviewed in paediatric patients (Berger 2019 **NR**) (see sections 10.6.4 for use in paediatric cardiac and general surgery and section 10.6.6 for use in paediatric scoliosis surgery) and obstetric populations (Armstrong 2016 **NR**). Its use is widespread in the obstetric and gynaecological setting for provision of analgesia in labour, Caesarean section and hysterectomy (Hein 2017 **Level IV**, n=32 [obstetric units in Sweden]). See also Section 9.1.3.3.

Although dose-response analyses are not always clear, it is suggested that neuraxial opioids have a ceiling effect for analgesia, with optimal single-injection morphine doses (balancing risk-benefit) of 50 to 150 mcg IT and 2.5 to 3.75 mg via epidural route (Saltan 2011 **NR**).

4.3.2.1 | Efficacy of intrathecal opioids

IT opioids have been used for surgical procedures ranging from lower limb orthopaedic surgery to CABG surgery because of their ability to provide prolonged postoperative analgesia following a single dose vs systemic administration. IT opioids may be given alone or in conjunction with a local anaesthetic. In acute pain, the use of continuous subarachnoid infusions of opioids for postoperative analgesia is uncommon.

The lipid solubility of opioids largely determines the speed of onset and duration of IT analgesia; hydrophilic opioids (eg oxycodone, morphine, hydromorphone) have a slower onset of action and longer half-lives in CSF with greater dorsal horn bioavailability and greater cephalad migration vs lipophilic opioids (eg fentanyl) (Bujedo 2014 **NR**; Bernards 2003 **NR**).

Single injection IT opioids

Early clinical studies used very high IT morphine doses (ie ≥500 mcg). However adequate postoperative analgesia with fewer adverse effects may be obtained with significantly less morphine; although at lower doses there is not a clear dose-response relationship for pain relief or some adverse effects (see below) (Meylan 2009 **Level I**, 27 RCTs, n=1,205).

Low doses of IT morphine are effective in prolonging local anaesthetic block or reducing the dose of local anaesthetic required for spinal anaesthesia with reduced adverse effects and improved recovery (Popping 2013 **Level I** [PRISMA], 28 RCTs; n=1,393; Popping 2012 **Level I** [PRISMA], 55 RCTs; n=3,338).

When combined with low-dose bupivacaine for Caesarean section, 100 mcg IT morphine produced analgesia comparable with doses as high as 400 mcg, with significantly less pruritus (Girgin 2008 **Level II**, n=100, JS 4). A single dose of IT morphine (100 mcg) added to a spinal anaesthetic for Caesarean section prolongs the time to first postoperative analgesic administration by 16 to 20 h (Dahl 1999 **Level I**, 15 RCTs, n=535). Sufentanil (2 RCTs) and fentanyl (8 RCTs) showed little or no analgesic benefit in doses of 25 mcg or less. No differences in pain reported or analgesia use was detected when comparing 100 mcg to 50 mcg IT morphine for Caesarean section, although pruritus was more common in the higher-dose group (Carvalho 2013 **Level II**, n=130, JS 4).

IT morphine 100, 200 and 300 mcg added to bupivacaine for postoperative analgesia following abdominal hysterectomy reduced IV PCA morphine consumption vs placebo, with no additional benefit of 300 mcg vs 200 mcg (Hein 2012 **Level II**, n=144, JS 5).

The addition of IT fentanyl 25 mcg to low-dose spinal bupivacaine for anorectal surgery resulted in more pruritus but lower mean recovery and discharge times, with fewer analgesic requests in the fentanyl group (Gurbet 2008 **Level II**, n=40, JS 3). Tramadol 10 and 25 mg administered IT with bupivacaine produces extension of spinal analgesia and prolonged postoperative analgesia similar to comparative doses of fentanyl 10 and 25 mcg for Caesarean section (Subedi 2013 **Level II**, n=80, JS 5) and appendectomy (Afolayan 2014 **Level III-1**, n=186).

Added to hyperbaric bupivacaine 10 mg (2 mL 0.5%), IT sufentanil 5 mcg provided shorter postoperative analgesia (mean 6.3 h) than IT morphine 200 mcg (mean 19.5 h) with no difference in adverse effects (Karaman 2006 **Level II**, n=54, JS4).

In a non-blinded comparison, following Caesarean section IT morphine 100 mcg recipients had longer analgesia and fewer intraoperative adverse effects vs IT pethidine 10 mg recipients but experienced more pruritus (Kumar 2007 **Level II**, n=60, JS 2). IT pethidine 25 mg added to lidocaine with adrenaline for spinal anaesthesia had quicker onset with higher sensory block and more prolonged time to significant pain (≥4/10) (9.6 h) vs IT fentanyl 25 mcg (6.3 h) or placebo (2.1 h) (Farzi 2014 **Level II**, n=195, JS 5).

Combination IT opioids

The addition of 10 mcg sufentanil to 400 mcg IT morphine did not potentiate postoperative analgesia or reduce intraoperative opioid requirements in patients undergoing major colorectal surgery (Culebras 2007 **Level II**, n=80, JS 5).

IT opioid infusions

In the ICU, IT infusion of morphine has been reported as a method to control burns pain and thereby avoiding the adverse effects of systemic opioids (Zuehl 2018 **CR**). IT morphine has also been administered in bolus doses via a 22-g IT catheter placed at L 3/4 to provide analgesia after thoracotomy (mean dose over 48 h 2.56 mg ± SD 0.88) with no serious complications or sequelae at 6 mth follow-up (Ward 2014 **Level IV**, n=84).

For further details on effectiveness and adverse effects related to the use of IT opioids see Section 4.3.2.3 below and 5.7.1.2.

4.3.2.2 | Efficacy of epidural opioids

The behaviour of epidural opioids is governed largely by their lipid solubility. The greater sequestration of lipid soluble opioids into epidural fat and slow rerelease back into the epidural space means that elimination from the epidural space is prolonged, resulting in relatively smaller fractions of medication reaching the CSF (Bernards 2003 **NR**). Lipophilic opioids (eg fentanyl) have a faster onset but shorter duration of action vs hydrophilic opioids (eg morphine) (Bujedo 2014 **NR**; Bernards 2004 **NR**; de Leon-Casasola 1996 **NR**).

A meta-analysis of randomised studies involving epidural opioids, mostly in combination with local anaesthetics, found no differences in VAS pain scores at any time after surgery between opioids, although there was a higher rate of nausea and vomiting (OR 1.95; 95%CI 1.14 to 3.18) with morphine vs fentanyl (Youssef 2014 **Level I** [PRISMA], 24 RCTs, n=1,513). No studies directly compare epidural morphine and fentanyl alone for postoperative analgesia.

Epidural diamorphine

Diamorphine (diacetylmorphine, heroin) is rapidly hydrolysed to 6-mono-acetylmorphine (6-MAM) and morphine. Diamorphine and 6-MAM are more lipid soluble than morphine and penetrate the CNS more rapidly, although it is 6-MAM and morphine that are thought to be responsible for the analgesic effects of diamorphine (Miyoshi 2001 **NR**). Epidural administration of diamorphine is common in the UK and is effective whether administered by intermittent bolus dose or infusion (McLeod 2005 **Level II**, n=62, JS 5).

Epidural fentanyl

The evidence that epidural fentanyl acts via a spinal rather than systemic effect is conflicting and it has been suggested that any benefit when comparing epidural with systemic fentanyl alone is marginal (Bernards 2004 **NR**; Wheatley 2001 **NR**). However, the conflicting results may be due to differing techniques of administration. A lumbar epidural infusion of fentanyl appears to produce analgesia by uptake into the systemic circulation, whereas a bolus dose of fentanyl produces analgesia by a selective spinal mechanism (Ginosar 2003 **Level IV EH**, n=10). Thoracic epidural administration does appear to produce greater spinal analgesia, an effect more pronounced with coadministration with adrenaline, which provides a supra-additive effect possibly via both pharmacokinetic (via vasoconstriction, increasing the amount of epidural fentanyl available to spinal cord site of action) and pharmacodynamic (via alpha-2 adrenoceptor antinociceptive) mechanisms (Niemi 2013 **NR**). Less intraoperative fentanyl is required when administered via a thoracic epidural catheter vs IV administration for colon surgery, with longer time to first

postoperative analgesia request (Sadurni 2013 **Level II**, n=30, JS 4). There is no evidence of benefit of epidural vs systemic administration of alfentanil or sufentanil (Bernards 2004 **NR**).

Epidural hydromorphone

The quality of epidural analgesia with hydromorphone is similar to morphine (Chaplan 1992 **Level II**, n=55, JS 5). In a comparison of epidural and IV hydromorphone, patients required twice as much IV hydromorphone to obtain the same degree of analgesia (Liu 1995 **Level II**, n=16, JS 3).

Epidural morphine

Morphine is the least lipid soluble of the opioids administered epidurally; it has the slowest onset and offset of action (Cousins 1984 **NR**) and the highest bioavailability in the spinal cord after epidural administration (Bernards 2004 **NR**). As morphine has a prolonged analgesic effect, it can be given by intermittent bolus dose or infusion; the risk of respiratory depression may be higher and analgesia less effective with bolus dose regimens (de Leon-Casasola 1996 **NR**). The low lipid solubility makes level of administration of epidural morphine less relevant after blunt chest wall trauma with no difference in any outcome between thoracic and lumbar epidural morphine administration (Hakim 2012 **Level II**, n=55, JS 3).

Extended-release epidural morphine

An extended-release (ER) suspension of morphine has been developed for epidural use (Depodur™) consisting of morphine molecules suspended in liposome complexes (lipofoam). ER epidural morphine (EREM) was effective vs placebo after THA (Martin 2006 **Level II**, n=126, JS 5; Viscusi 2005 **Level II**, n=200, JS 5) and, using doses of ≥10 mg, to lead to better pain relief vs standard epidural morphine (4 or 5 mg) and reduced need for supplemental analgesics up to 48 h after THA (Viscusi 2006 **Level III-1**, n=39), lower abdominal surgery (Gambling 2005 **Level II**, n=541, JS 4) and Caesarean section (Carvalho 2007 **Level II**, n=70, JS 5; Carvalho 2005 **Level II**, n=79, JS 3). A pooled analysis of six clinical studies described consistent prolonged pharmacokinetics vs standard epidural morphine, with 25% higher peak plasma concentrations in women, mainly explained by differences in body weight (Viscusi 2009 **PK**).

EREM has provided superior analgesia vs continuous femoral nerve block (FNB) after TKA; however, only at rest at 24 h (Johnson 2011 **Level II**, n=65, JS 3). There were no differences in functional outcomes and adverse effects except for more pruritus with EREM but patients reported greater satisfaction with EREM. In two patients, EREM was used successfully after multiple rib fractures (Ford 2012 **Level IV**). After lumbar spinal surgery, EREM provided similar analgesia with fewer adverse effects than epidural morphine (Vineyard 2014 **Level II**, n=60, JS 3). IT morphine 7.5 mcg/kg vs EREM 150 mcg/kg had similar time to first PCA use and similar postoperative morphine IV use over 0 to 48 h in children (8 to 17 y) undergoing posterior spinal fusion for scoliosis repair (Cohen 2017 **Level II**, n=71, JS 4). Pain scores differed relating to the kinetics of the epidural preparation and were lower with IT morphine from 0 to 4 h, similar from 8 to 24 h, and lower with extended release epidural morphine from 28 to 36 h.

OIVI is more likely with EREM than IV PCA opioids (OR 5.74; 95%CI 1.08 to 30.5) (Sumida 2009 **Level I**, 3 RCTs, n=464). It has been recommended that the liposome preparation of EREM not be administered while local anaesthetics are present in the epidural space as this may cause early release of the morphine (Viscusi 2009 **PK**). When EREM was administered within 3 to 15 min of a 3 mL test dose of 1.5% lidocaine with adrenaline, higher serum morphine maximum concentration (C_{max}) values were reported vs C_{max} values when no lidocaine was administered; there was no difference in morphine C_{max} if the interval was >30 min. The C_{max} of morphine was unchanged when EREM doses were given 15, 30 and 60 min after an anaesthetic dose of epidural bupivacaine 0.25% 20 mL (Gambling 2009 **PK**) although, in a later study, peak plasma morphine concentrations were increased when administered 1 h post a high volume anaesthetic dose (2%

lidocaine with adrenaline, 20 to 35 mL) after Caesarean section, with associated increased morphine-related adverse effects (Atkinson Rallis 2011 **Level II**, n=30, JS 3).

Epidural oxycodone

There is limited safety data for neuraxial oxycodone (Lamminsalo 2019 **Level III-1 PK**, n=30; Olczak 2017 **Level IV**, n=11; Kokki 2016 **BS).** After Caesarean section, patients given epidural oxycodone 3 mg vs epidural morphine 3 mg had higher pain scores up to 24 h with slightly less pruritus (Sng 2016 **Level II**, n=100, JS 4). Epidural oxycodone was superior to IV oxycodone in gynaecological laparotomy, resulting in less rescue analgesia up to 4 h (Piirainen 2018 **Level II**, n=30, JS 5). The addition of epidural oxycodone to ropivacaine in labour analgesia was superior to ropivacaine alone, with lower pain scores for 4 h and longer duration of analgesia (Zhong 2020 **Level II**, n=80, JS 5).

Epidural pethidine

Pethidine is effective when administered epidurally by bolus dose, continuous infusion and by patient-controlled epidural analgesia (PCEA). It is more lipid soluble than morphine (but less than fentanyl and its analogues); thus its onset and offset of epidural analgesic action is more rapid than morphine (Ngan Kee 1998 **NR**). The analgesic effect of smaller doses appears to be spinally mediated but systemic effects are likely after larger doses; in the smaller doses it is not known whether the local anaesthetic properties of pethidine contribute significantly to pain relief (Ngan Kee 1998 **NR**). Epidural pethidine has been used predominantly in the obstetric setting. After Caesarean section epidural pethidine resulted in better pain relief and less sedation than IV pethidine (Paech 1994 **Level II**, n=45, JS 5) but inferior analgesia vs IT morphine, albeit with less pruritus, nausea and drowsiness (Paech 2000 **Level II**, n=144, JS 5).

Epidural sufentanil

Epidural sufentanil has been mainly used in labour analgesia; for details see Section 9.1.3.3.

Epidural buprenorphine

Epidural buprenorphine has been used in a limited number of studies in the past with no recent publications; a detailed review of the neuraxial use of buprenorphine has been published (Kosel 2016 **NR**).

Epidural tramadol

For lumbar epidural analgesia after thoracotomy, tramadol 100 mg vs morphine 4 mg resulted in comparable analgesia quality of shorter duration with less sedation and less decrease in arterial oxygenation (Turker 2005 **Level II**, n=40, JS 4). For epidural analgesia in labour, tramadol 5 mg/mL vs fentanyl 3 mcg/mL added to ropivacaine 0.125% had similar efficacy and adverse effects (Fan 2011 **Level II**, n=61, JS 5).

For paediatric use see Section 10.4.4.12.

4.3.2.3 | Adverse effects of neuraxial opioids in general

Opioid-induced ventilatory impairment

The prevalence of OIVI (author-reported) with use of neuraxial diamorphine and morphine after Caesarean section is 61/10,000 (95%CI 51 to 74) (Sharawi 2018 **Level IV SR**, 78 studies [54 RCTs, 21 studies & 3 case reports], n=18,455). However, when classified as clinically significant OIVI, highest prevalence with all doses of neuraxial opioids was 8.67/10,000 (95%CI 4.20 to 15.16) and lowest was 5.96/10,000 (95%CI 2.23 to 11.28). These rates dropped even further with the use of lower but clinically relevant doses of neuraxial morphine: IT dose ≤150 mcg 1.63/10,000 (95%CI 0.62 to 8.77) (31 RCTs [IT]) or epidural dose ≤3 mg 1.08/10,000 (95%CI 0.24 to 7.22) (32 RCTs

[epidural]). No cases were reported for IT diamorphine ≤400 mcg or epidural diamorphine ≤5 mg.

Practice guidelines for the prevention, detection and management of respiratory depression caused by neuraxial opioids have been published (ASA 2016 **GL**).

Nausea and vomiting

IV dexamethasone reduces the need for rescue antiemetics for PONV caused by long-acting neuraxial opioids (RR 0.44; 95%CI 0.35 to 0.56) (Grape 2018 **Level I** [PRISMA], 13 RCTs, n=1,111).

4.3.2.4 | Adverse effects of intrathecal opioids

Depending on type and dose of the opioid, a combination of spinal and systemic (supraspinal) mechanisms may be responsible for adverse effects associated with intrathecal opioids. Many of these effects are more frequent with morphine and are to some extent dose-related (Dahl 1999 **Level I**, 15 RCTs, n=535; Cole 2000 **Level II**, n=38, JS 4).

Opioid-induced ventilatory impairment

Late onset respiratory depression (>2 h after administration), which is believed to be a result of the cephalad spread of opioids to the medulla within the cerebrospinal fluid (CSF), is also seen more commonly with hydrophilic opioids such as morphine and hydromorphone and appears to match the time taken for trigeminal analgesia, which is approximately 6 to 12 h after administration (Bujedo 2014 **NR**; Saltan 2011 **NR**; Cousins 1984 **NR**).

A single dose of IT morphine 100 mcg added to a spinal anaesthetic for Caesarean section was associated with low rate of respiratory depression (Dahl 1999 **Level I**, 15 RCTs [12 respiratory depression], n=535). A meta-analysis comparing IT morphine doses <300 mcg, ≥300 mcg and placebo reported a greater risk of respiratory depression with the higher vs the lower doses of morphine (Gehling 2009 **Level I,** 28 RCTs, n=1,314). In combination with bupivacaine, IT morphine 50 to 2,000 mcg was associated with more respiratory depression than IT fentanyl 10 to 50 mcg (3.4% vs 0.4%) (Popping 2013 **Level I** [PRISMA], 28 RCTs; n=1,393; Popping 2012 **Level I** [PRISMA], 55 RCTs; n=3,338).

The incidence of respiratory depression with the lipophilic opioid fentanyl given via the epidural route has been reported to be 1.4% (with 0.4% requiring naloxone) (Scott 1995a **Level IV**, n=1,297) but, when given IT, fentanyl or sufentanil are likely to be lower risk than the hydrophilic opioids morphine and hydromorphone (Horlocker 2009 **GL**).

Risk factors for respiratory depression include higher doses (>300 mcg morphine), increasing age, obesity and coadministration of systemic opioids or sedatives (Saltan 2011 **NR**). A detailed analysis of sustained hypercapnia events (transdermal CO_2 >50 mm Hg for ≥2 min) after IT administration of hyperbaric bupivacaine 12 mg , fentanyl 15 mcg and morphine 150 mcg for Caesarean section revealed an incidence of 32% (Bauchat 2017 **Level IV**, n=120). Events occurred at a median of 300 min after IT administration with a median number of 3 events and longest duration of 26 min.

Nausea and vomiting

A meta-analysis comparing IT morphine doses <300 mcg vs ≥300 mcg and placebo reports increased nausea (RR 1.4; 95%CI 1.1 to 1.7) and vomiting (RR 3.1; 95%CI 1.5 to 6.4) in the higher dose group (Gehling 2009 **Level I,** 28 RCTs, n=1,314). A single dose of morphine 100 mcg added to a spinal anaesthetic for Caesarean section was associated with nausea (10%) and vomiting (12%) (Dahl 1999 **Level I**, 15 RCTs [11 nausea & 8 vomiting], n=535).

Pruritus

A meta-analysis comparing IT morphine doses <300 mcg vs ≥300 mcg and placebo reports increased pruritus (RR 1.8; 95%CI 1.4 to 2.2) in the higher dose group (Gehling 2009 **Level I,** 28 RCTs,

n=1,314). A single dose of morphine 100 mcg added to a spinal anaesthetic for Caesarean section was associated with pruritus (43%) (Dahl 1999 **Level I**, 15 RCTs [11 pruritus], n=535). For Caesarean section, IT morphine 50 mcg vs IT morphine 100 mcg resulted in a lower rate of pruritus (70% vs 87%) (Carvalho 2013 **Level II**, n=130, JS 4).

Neurotoxicity

Clinical experience with morphine, fentanyl and sufentanil has shown no neurotoxicity or behavioural changes at clinically used IT doses (Hodgson 1999 **Level IV**). Other opioid agonists or partial agonists do not have animal or human safety data.

Tolerance

Tolerance to spinal opioid analgesia can develop rapidly. Low-dose mu and delta opioid antagonists can prevent tolerance development and restore morphine IT analgesia in animals (Abul-Husn 2007 **BS**). In an animal model, bolus doses increased nociceptive thresholds for 3 to 5 h followed by delayed hyperalgesia with a lower threshold lasting 1 to 2 d, an effect prevented by coadministration of ketamine (Van Elstraete 2005 **BS**). The clinical implications of single-dose neuraxial opioid administration in regard to the potential development of OIH or tolerance is uncertain. IT fentanyl added to bupivacaine and morphine for Caesarean section was associated with higher pain scores (the authors suggesting acute tolerance) but no difference in 24 h morphine consumption (Carvalho 2012 **Level II**, n=40, JS 5). Adding fentanyl to IT local anaesthesia for Caesarean section improved anaesthesia conditions but was associated with a 60% increase in morphine consumption between 6 and 24 h (Cooper 1997 **Level II**, n=60, JS 2). IT sufentanil was associated with wound hyperalgesia (at 48 h), with a preventive effect demonstrated by addition of 150 mcg IT clonidine (Lavand'homme 2008 **Level II**, n=96, JS 5). Ondansetron is assumed to ameliorate opioid-induced hyperalgesia and tolerance in animal studies; however, IV ondansetron 8 mg vs placebo administered before spinal anaesthesia for Caesarean section (IT bupivacaine 15 mg, IT fentanyl 20 mcg and IT morphine 100 mcg) had no effect on postoperative pain scores or opioid consumption (Greer 2017 **Level II**, n=86, JS 5).

For more details on epidural opioid use see Section 5.6. and in particular 5.6.2.2 and 5.6.2.3.

KEY MESSAGES

Intrathecal opioids

1. Intrathecal morphine and intrathecal fentanyl prolong spinal local anaesthetic block, with fentanyl being associated with fewer adverse effects (**U**) (**Level I** [PRISMA]).
2. Intrathecal morphine produces better postoperative analgesia than intrathecal fentanyl or sufentanil after Caesarean section (**U**) (**Level I**).
3. Intrathecal morphine doses of 300 mcg or more increase the risk of respiratory depression (**U**) (**Level I**).

Epidural opioids

4. Epidural morphine provides similar analgesia to epidural fentanyl when combined with local anaesthetic, although the incidence of nausea is greater with morphine (**U**) (**Level I** [PRISMA]).
5. Extended-release epidural morphine provides analgesia for up to 48 hours (**U**) (**Level II**), however it is associated with more respiratory depression than intravenous PCA following abdominal surgery (**U**) (**Level I**).

6. Epidural pethidine produces better pain relief and less sedation than intravenous pethidine after Caesarean section (**U**) (**Level II**).

The following tick boxes represent conclusions based on clinical experience and expert opinion:

☑ No neurotoxicity has been shown at normal clinical intrathecal doses of morphine, fentanyl and sufentanil (**U**).

☑ Neuraxial administration of bolus doses of hydrophilic opioids carries an increased risk of delayed sedation and respiratory depression compared with lipophilic opioids (**U**).

4.3.3 | Peripheral opioids

Opioid receptors are expressed in peripheral sensory neurons in both animals and humans (Stein 2013 **NR**; Stein 2011 **NR**). Multiple mechanisms have been proposed to explain the clinical observation that peripheral opioids are more effective in the presence of tissue injury or inflammation. Further research into the role of peripheral opioids in clinical models of inflammatory pain is recommended; the acute postoperative period may not allow sufficient time for the upregulation of peripheral opioid receptors.

Peripherally applied opioids (excluding IA, perineural and mucosal administration) for post-operative pain relief vs placebo or systemic administration do not have any clinically relevant effects (Nielsen 2015a **Level I** [PRISMA], 26 RCTs, n=1,531).

However, peripherally applied opioids had an analgesic effect, when injected into areas with preoperative inflammation (Stein 2013 **NR**; Stein 2011 **NR**). Consequently, submucosal injection of morphine 2 mg into inflamed tissue after tooth extraction (under a standard local anaesthesia) resulted in lower pain on swallowing and prolonged post-operative analgesia vs IM injection and vs injection into non-inflamed tissue of the same dose of morphine (Akural 2016 **Level II**, n=81, JS 5).

4.3.3.1 | Intra-articular

Morphine

IA administration is the most extensively examined clinical application of peripheral opioid therapy (Stein 2013 **NR**). In experimentally induced synovitis in horses, IA morphine reduced clinical and biological signs of inflammation vs IV administration (Lindegaard 2010 **BS**).

IA bupivacaine was less effective than morphine in providing analgesia in patients having "high inflammatory arthroscopic knee surgery", whereas bupivacaine was more effective than morphine in those having "low inflammatory surgery" (Marchal 2003 **Level II**, n=53, JS 5).

IA morphine in a dose of 1 mg is not better than placebo at reducing pain at early, medium or late stages post arthroscopy (7 RCTs, n=297) (Zou 2016 **Level I** [Cochrane], 28 RCTs, n=2,564). IA morphine 1 mg was not more effective than IA bupivacaine, NSAIDs, sufentanil, fentanyl and pethidine. There was no difference in pain relief between IM morphine vs IA morphine at any time point (2 RCTs, n=73); the latter results are in line with another RCT not included in the meta-analysis (Cepeda 1997 **Level II**, n=112, JS 5).

Morphine/bupivacaine vs bupivacaine alone leads to reduced pain scores (WMD −1.15/10; 95% CI −1.67 to −0.63) without an effect on time to first analgesic request and requirements for supplementary analgesia and with no increase in side effects (Yang 2017b **Level I** [PRISMA], 29 RCTs,

n=1,116). However following arthroscopy, morphine/bupivacaine increased postoperative analgesia requirements and side effects vs tenoxicam/bupivacaine (Sanel 2016, **Level II**, n=240, JS 5).

Other opioids

IA tramadol 50-100 mg administered as an adjunct to bupivacaine reduces postoperative pain and increases time to breakthrough analgesia requirements without increasing side effects after arthroscopy (Ryan 2019 **Level I**, 6 RCTs, n=334). The combination of IA pethidine (meperidine)/bupivacaine had synergistic analgesic effect vs either medication alone (Imani 2015 **Level II**, n=60, JS 5). IA fentanyl/bupivacaine did not reduce reported pain scores and postoperative analgesia requirement vs bupivacaine alone or midazolam/bupivacaine in an underpowered RCT (Nahravani 2017, **Level II**, n=45, JS 5). IA administration of morphine/levobupivacaine/tenoxicam provided superior analgesia to a combination of tramadol/levobupivacaine/tenoxicam or saline placebo (Oral 2015 **Level II**, n=90, JS 5). Levobupivacaine 0.25% for arthroscopic knee surgery combined with either fentanyl or tramadol provided superior analgesia vs levobupivacaine alone for day case arthroscopic knee surgery (Sayin 2015 **Level II**, n=80, JS 4). The addition of IA sufentanil to a mixture of ropivacaine and clonidine following anterior cruciate ligament repair provided no additional analgesic benefits (Armellin 2008 **Level II**, n=120, JS 5).

The evidence for IA morphine, tramadol, buprenorphine, fentanyl and NSAIDs was inconclusive due to a small number of low-quality studies for temporomandibular joint arthrocentesis (Gopalakrishnan 2018 **Level IV SR** [PRISMA], 6 studies, n=433 [3 RCTs, n=91]).

There are no comparisons between IA and systemic administration of these opioids alone.

4.3.3.2 | Perineural

An initial meta-analysis found no evidence for analgesic efficacy of peripheral opioids with perineural block by local anaesthetics (Picard 1997 **Level I**, 26 RCTs, n=952). Since this publication, more research has been conducted.

Buprenorphine

The addition of perineural buprenorphine 0.1 to 0.3 mg to local anaesthetics prolongs the duration of analgesia provided by nerve blocks vs placebo (MD 8.64 h; 95%CI 6.44 to 10.85) (9 RCTs, n= 510), but is associated with significant increases in PONV (RR 5.0; 95%CI 1.12 to 22.27) (3 RCTs, n=210) (Schnabel 2017 **Level I** [PRISMA], 13 RCTS, n=685). In comparison to systemic (IM) administration of buprenorphine, perineural administration prolongs duration of analgesia (MD 6.87 h, 95%CI 4.02 to 9.71) (5 RCTs, n=294) without increasing PONV. The findings are qualified by the description of high risk of publication bias and heterogeneity in the results obtained. A subsequent RCT found no difference in time to first rescue analgesia comparing a femoral nerve block for TKA with either perineural or SC buprenorphine 0.3 mg (van Beek 2017 **Level II**, n=65, JS 5). Adjuvant buprenorphine 0.3 mg vs adjuvant dexamethasone 4 mg added to levobupivacaine 0.25% 20 mL transverse abdominis plane block (TAPB) for inguinal hernia repair demonstrated longer times to rescue analgesia and lower mean postoperative tramadol consumption in the first 24 h vs placebo (saline 1 mL) (Seervi 2019 **Level II**, n=93, JS 4). Perineural administration of buprenorphine 0.15 mg and dexamethasone 4 mg vs IV administration of the same doses in conjunction with sciatic and adductor canal blocks for foot and ankle surgery resulted in longer block duration, lower scores for 'worst pain' and less nausea, but no difference in pain scores at 24 h (YaDeau 2015 **Level II**, n=90, JS 5).

Sufentanil

The addition of sufentanil 10 mcg to bupivacaine for ultrasound guided brachial plexus block for upper limb procedures prolonged the duration of both sensory and motor block in chronic opioid users and non-users (Azimaraghi 2015 **Level II**, n=120, JS 5). No difference was found in postoperative pain scores or supplemental analgesic requirements when fentanyl 100 mcg was administered with ropivacaine 0.75% in a femoral nerve block and then per perineural catheter infusion (3 mcg/mL fentanyl/ropivacaine 0.75%: basal rate 10 mL/h) vs ropivacaine alone (Heo 2016 **Level II**, n=82, JS 5).

Tramadol

Tramadol 100 mg as an adjuvant to brachial plexus block vs placebo prolonged analgesia (MD 125.5 min; 95% CI 73.3 to 175.8), but also sensory and motor block (Shin 2017 **Level I** [PRISMA], 16 RCTS, n=751); there were no comparisons to systemic administration.

Preoperative femoral nerve block for TKA with ropivacaine 0.375% 20 mL and adjuvant tramadol 100 mg was superior with lower pain scores (from 8 to 72 h), longer sensory and motor blockade and reduced requirement for postoperative PCA vs no femoral nerve block, femoral nerve block with ropivacaine only or femoral nerve block with ropivacaine/ tramadol 50 mg (Tang 2016 **Level II**, n=60, JS 1).

4.3.3.3 | Topical

While opioid receptors have been identified in the cornea and skin, topically applied opioids have not consistently demonstrated efficacy in pain states such as corneal ulceration (fentanyl) (Zollner 2008 **Level II**, n=40, JS 4), partial thickness burns (morphine) (Welling 2007 **Level II**, n=49, JS 5) or chronic skin ulceration (morphine) (Vernassiere 2005 **Level II**, n=18, JS 4).

The clinical use of topical opioids in palliative care for pain control in cutaneous lesions is reported as beneficial in three of six RCTs (Graham 2013b **Level IV SR**, 26 studies, n unspecified). A greater benefit was reported with inflammatory lesions than with vascular ulcers, suggesting an anti-inflammatory role of topical opioids may be as important as a peripheral analgesic benefit. Topical morphine (0.2% gel) and ointment for mucosal and skin lesions in palliative cancer patients reduced base line pain after 7 d of treatment ($NNT_{50\%}$ 1.67) with minimal side effects (Cialkowska-Rysz 2019, **Level II**, n=35, JS 4).

In chemotherapy-induced mucositis an analgesic dose-dependent effect was seen in a small pilot study using 1 mg/mL and 2 mg/mL morphine mouthwash (Cerchietti 2003 **Level III-1**). Benefit was also evident for morphine mouthwash 30 mg every 3 h, with a local anaesthetic-based solution, in mucositis associated with chemoradiotherapy in head and neck cancer patients (Cerchietti 2002 **Level II**, n=26, JS 3). With oral morphine mouthwash 2% (30 mg in 15 mL) for the treatment of mucositis pain, the act of mouth washing was beneficial, with early termination due to recruitment difficulty and indaequate power to detect benefit with morphine vs quinine placebo solution (Vayne-Bossert 2010 **Level II**, n=11, JS 5). Topical morphine mouthwash 2% (10 mL) for patients with severe mucositis associated with head and neck cancer treatment was more effective than a combination mouthwash (containing viscous lidocaine, magnesium aluminium hydroxide and diphenhydramine) 10 mL 3 hly over 6 d (Sarvizadeh 2015 **Level II**, n=30, JS 5). WHO grading scores for mucositis decreased in both groups at 6 d, but were lower in and with increased satisfaction in morphine recipients. See also Section 8.6.7.7 and 8.9.8.2.

KEY MESSAGES

1. Intra-articular morphine (1 mg) following knee arthroscopy does not improve analgesia compared with placebo (**S**) (**Level I** [Cochrane Review]).
2. Intra-articular morphine/bupivacaine following knee arthroscopy compared to bupivacaine alone improves analgesia without increasing adverse effects (**N**) (**Level I** [PRISMA]).
3. Perineural buprenorphine/local anaesthetic for peripheral nerve blocks compared to local anaesthetic and to systemic buprenorphine/local anaesthetic prolongs duration of analgesia (**N**) (**Level I** [PRISMA]).
4. Perineural tramadol/local anaesthetic for brachial plexus block compared to local anaesthetic alone prolongs duration of analgesia (**N**) (**Level I** [PRISMA]).
5. Peripherally applied opioids (excluding intra-articular, perineural and mucosal administration) show no clinically relevant analgesic effect (**N**) (**Level I** [PRISMA]).
6. Intra-articular tramadol/bupivacaine following knee arthroscopy compared to bupivacaine alone improves analgesia without increasing adverse effects (**N**) (**Level I**).
7. Morphine mouthwash may have analgesic effects in chemotherapy-induced mucositis (**N**) (**Level II**).
8. Evidence for intra-articular analgesic administration is inconclusive for temporomandibular joint arthrocentesis (**N**) (**Level IV SR** [PRISMA]).

4.4 | Local anaesthetics and other membrane stabilisers

Local anaesthetics (LA) act primarily by reversibly blocking neuronal voltage-gated sodium channels (VGSC) and thereby temporarily interrupting nerve impulse propagation. LA also have additional systemic effects which may be independent of action on the VGSC due to interaction with potassium channels, calcium channels, N-methyl-D-aspartate (NMDA) receptors, and G-protein coupled receptors (van der Wal 2016 **NR BS**; Lirk 2014 **BS**). The latter, via the $G_{q/11}$ subfamily, may contribute to the anti-inflammatory effects of LAs (Hollmann 2000 **NR**). Thus, the use of LAs beyond perineural applications is expanding.

Both amide and ester local anaesthetics have been found to have antimicrobial activity in concentrations used in clinical practice, with tetracaine, bupivacaine and lidocaine having the most marked activity (Razavi 2019 **NR BS**); these are not primary effects and are modified by a range of factors including the admixture of other drugs.

4.4.1 | Systemic local anaesthetics and other membrane stabilisers

IV lidocaine has analgesic, anti-inflammatory and antihyperalgesic properties and attenuates the neuroinflammatory response in perioperative pain and chronic neuropathic pain (van der Wal 2016 **Level IV SR**, 36 in vitro studies, 31 animal studies & 21 clinical studies [3 SRs & 7 RCTs in acute pain; 1 SR, 6 RCTs & 4 studies in chronic pain]). The safe dose and duration of perioperative IV lidocaine infusions has not been clearly established, with only limited total patient numbers and few adverse reactions having been reported in the literature to date (Bailey 2018 **Level I**, 6 RCTs, n=420; Masic 2018 **Level IV SR**, 13 studies, n= 512).

4.4.1.1 | Acute pain

A Cochrane review on IV lidocaine and analgesia (Kranke 2015 **Level I** [Cochrane], 45 RCTs, n=2,802) has been updated with a further 23 RCTs (Weibel 2018 **Level I** [Cochrane], 68 RCTs [66 vs placebo/no comparator; 2 vs epidural], n=4,525) finding small effects and uncertain outcomes. Lidocaine infusions at varying doses (1-5 mg/kg/h) for varying duration in various surgery types (open [22 RCTs] or laparoscopic [20 RCTs] abdominal and others [26 RCTs]) vs placebo or no treatment) reduces pain intensity to a limited extent 1 to 4 h postoperatively (SMD −0.50; 95%CI −0.72 to −0.28; 0.37/10 to 2.48/10) (29 RCTs, n=1,656), at 24 h (SMD −0.14; 95%CI −0.25 to −0.04) (33 RCTs, n=1,847) and at 48 h (SMD −0.11; 95%CI −0.25 to 0.04) (24 RCTs, n=1,404), noting that the results for these later time points represent less than a 1 point reduction in a 10 point pain scale. There is also a reduction of postoperative ileus (RR 0.37; 95%CI 0.15 to 0.87) (4 RCTs, n=273), time to first defaecation (MD −7.92 h; 95%CI −12.71 to −3.13) (12 RCTs, n=684), postoperative nausea 0 to 2 h (RR 0.78; 95%CI 0.67 to 0.91) (35 RCTs, n=1,903), opioid requirements (MD −4.52 MME; 95%CI −6.25 to −2.79) (40 RCTs, n=2,201) and LOS (MD −0.37 d; 95%CI −0.60 to −0.15) (32 RCTs, n=2,077). Vomiting overall was not impacted (OR 0.83; 95% CI 0.63 to 1.08) (19 RCTs, n=1026). IV lidocaine vs TEA has no effect on pain intensity and other outcomes (2 RCTS, n=102). The authors describe all these results as "*uncertain*" due to the quality of the evidence being limited by inconsistency, imprecision, and study quality.

In breast surgery, IV lidocaine administered intraoperatively and continued for up to 2 h is not associated with improved pain scores up to 72 h vs placebo controls, but opioid requirements were lower in the lidocaine group (Chang 2017 **Level I** [PRISMA], 3 RCTs, n=167); however, benefit was found in chronic postsurgical pain prevention. See Section 4.4.1.2 below.

After colonic surgery, IV lidocaine was associated with improved pain relief vs controls and also with decreases in proinflammatory cytokines, including interleukin-6 (IL-6), IL-8 and IL-1RA (a competitive inhibitor of IL-1β) (Kuo 2006 **Level II**, n=60, JS 5). For radical prostatectomy, a combination of intraoperative IV and postoperative SC lidocaine for up to 24 h vs saline reduced pain, morphine consumption and LOS (Weinberg 2016 **Level II**, n=76, JS 5). Following open nephrectomy, intraoperative IV lidocaine or IV ketamine continued for 24 h were both superior to placebo in reducing pain scores and 24 h opioid consumption (lidocaine 27.8 mg ± 5.5 and ketamine 32 mg ± 7.0 vs placebo 47.6 mg ± 5.0) (Jendoubi 2017 **Level II**, n=60, JS 4); IV lidocaine was associated with significantly lower pain scores at rest and with movement over 24 h vs IV ketamine. In radical cystectomy patients, the addition of perioperative IV lidocaine infusion for 6 h resulted in lower pain scores for up to 18 h (Moeen 2019 **Level II**, n=111, JS 5); recovery of bowel function was also improved.

Perioperative IV administration of lidocaine also has a preventive analgesic effect (extending beyond 5.5 half-lives of lidocaine, ie >8 h after cessation of administration) after a wide range of operations (Barreveld 2013a **Level I**, 16 RCTs, n=678) (15 RCTs overlap with Weibel 2018). See also Sections 1.4 and 1.5.

In the emergency department (ED), the efficacy of IV lidocaine in the treatment of nonsurgical acute pain has been reviewed, noting that dosing was not standardised and individual studies were small (Silva 2018 **Level IV SR**, 6 RCTs & 2 studies, n=536; Masic 2018 **Level IV SR** 4 RCTs & 9 studies, n= 512) (4 RCTs overlap); analgesic benefit is superior to placebo or comparable to active controls in renal colic (2 RCTs) and limb ischemia (1 RCT), but inconsistently in acute migraine (2 RCTs) and not in acute radicular low back pain (1 RCT). Although most non-randomised studies demonstrated improved analgesia with IV lidocaine, certainty with these findings is low. Safety data is limited with 20 adverse events (19 nonserious, 1 classified serious: overall rate 8.9%; 95%CI 5.5% to 13.4%) (6 studies, n=225) reported with IV lidocaine use in the ED (Silva 2018 **Level IV SR**, 6 RCTs and 2 studies, n=536).

IV lidocaine has a potentially analgesic effect in procedural pain in burns (Wasiak 2012 **Level I** [Cochrane], 1 RCT: Wasiak 2011 **Level II**, n=45, JS 5), however its role in this indication requires further investigation.

The use of IV lidocaine in an obese population undergoing laparoscopic gastric reduction surgery reduced pain scores, opioid consumption and improved quality of recovery (Sherif 2017 **Level II**, n=150, JS 5; De Oliveira 2014a **Level II**, n=50, JS 5).

Results for IN lidocaine are conflicting showing significant benefit (Maizels 1996 **Level II**, n=53, JS 2) and no effect (Blanda 2001 **Level II**, n=49, JS 4).

Mexiletine improved pain relief and reduced analgesic requirements after breast surgery (Fassoulaki 2002 **Level II**, n=75, JS 3).

4.4.1.2 | Chronic pain and transition to chronic pain

A meta-analysis found that IV lidocaine reduces chronic postsurgical pain at 3 mth vs placebo (OR 0.29; 95%CI 0.18 to 0.48) (Bailey 2018 **Level I** [PRISMA], 6 RCTs, n=420). In breast surgery patients, IV lidocaine administered intraoperatively and continued for up to 2 h has a lower risk for the development of chronic pain at 3 to 6 mth (RR 0.33; 95%CI 0.14 to 0.78) (Chang 2017 **Level I** [PRISMA], 2 RCTs, n=97) (2 RCTs overlap). See also Sections 1.4 and 1.5.

The membrane stabilisers IV lidocaine and mexiletine have a similar analgesic effect on neuropathic pain of various origins, which is superior to placebo (WMD 10.6; 95%CI -14.5 to -6.7) (Tremont-Lukats 2005 **Level I,** 19 RCTs, n=706) and similar to various comparators (Challapalli 2005 **Level I** [Cochrane], 30 RCTs, n=1,142). There was strong evidence of benefit for use of membrane stabilisers in pain due to peripheral nerve trauma (Kalso 1998 **Level I**, 17 RCTs, n=450). However, in

the guidelines for pharmacotherapy for neuropathic pain by the Special Interest Group on Neuropathic Pain (NeuPSIG) of the IASP, there is a strong recommendation against the use of mexiletine because of negative trials on efficacy and safety concerns (Finnerup 2015 **GL Level I** [PRISMA], 229 RCTs, n unspecified).

Currently, the use of membrane stabilisers for acute neuropathic pain can only be based on extrapolation of the above data.

KEY MESSAGES

1. Perioperative intravenous lidocaine reduces pain and opioid requirements to a limited extent following a range of surgery types, as well as nausea, but not vomiting, incidence and duration of ileus and length of hospital stay (**W**) (**Level I** [Cochrane Review]).
2. In breast surgery, perioperative lidocaine infusion does not improve pain scores for up to 72 hours, but is associated with lower acute opioid requirements and less chronic postsurgical pain at 3 to 6 months (**N**) (**Level I** [PRISMA])
3. Perioperative intravenous lidocaine has a preventive analgesic effect (extending beyond 5.5 half-lives of lidocaine, ie > 8 hrs after cessation of administration) after a wide range of operations (**U**) (**Level I**).

Chronic neuropathic pain and transition to chronic postsurgical pain

4. Both intravenous lidocaine and mexiletine are effective in the treatment of chronic neuropathic pain (**U**) (**Level I** [Cochrane Review]); however, guidelines advise against the use of mexiletine for this indication (**N**) (**GL Level I** [PRISMA]).
5. Perioperative IV lidocaine reduces chronic postsurgical pain at 3 months compared to placebo (**N**) (**Level I** [PRISMA]).

The following tick box represents conclusions based on clinical experience and expert opinion:

☑ The optimal and safe dose and duration of perioperative intravenous lidocaine infusions has yet to be clearly established (**N**).

☑ Based on the experience in chronic neuropathic pain states, it would seem reasonable to use membrane stabilisers including systemic lidocaine in the management of acute neuropathic pain (**U**).

☑ The role and safety of IV lidocaine for analgesia in the emergency department still requires clarification (N).

4.4.2 | Regional local anaesthetics

LAs exert their effect as analgesics by blocking sodium channels and hence impeding neuronal excitation and/or conduction. LAs differ predominantly by potency, duration of action and systemic toxicity.

4.4.2.1 | Short-duration local anaesthetics

Lidocaine is the most widely used short-duration LA in acute pain management. Although the plasma half-life is approximately 90 min, the duration of the LA effect depends very much on site of administration, dose administered and the presence or absence of vasoconstrictors. Although lidocaine is hydrophilic, it is delivered in high concentrations and therefore usually diffuses well into nerve bundles, resulting in little separation of sensory and motor blocking actions (Covino 1998 **NR**).

The use of lidocaine in ongoing acute pain management is usually restricted to the short-term re-establishment of a LA infusion block. It is generally considered unsuited to long-term (ie days) use because of the development of tachyphylaxis or acute tolerance, although the existing literature documenting the phenomenon of tachyphylaxis with neuraxial use of local anaesthetics is scarce and the mechanisms behind this phenomenon should it occur, is unclear (Kongsgaard 2016 **Level III-3** [PRISMA], 6 RCTs & 7 studies, n unspecified). Continuous perineural infusions of lidocaine for 24 h resulted in less effective analgesia and more motor block than infusions of the long-acting LA ropivacaine (Casati 2003c **Level II**, n=40, JS 4).

Mepivacaine is a short- to intermediate-duration LA agent, structurally related to bupivacaine and ropivacaine. Its use is largely restricted to intraoperative anaesthesia.

4.4.2.2 | Long-duration local anaesthetics

The three commonly used long-duration LAs, bupivacaine, levobupivacaine and ropivacaine, are structurally related (McLeod 2001 **NR**; Markham 1996 **NR**). Whereas bupivacaine is a racemic mixture of S- and R-enantiomers, levobupivacaine is the S(+)- (or levo-) enantiomer of bupivacaine; ropivacaine is likewise an S-enantiomer.

The issue with relative potency emerges with lower doses and concentrations of LAs. When doses are carefully titrated, a minimum local anaesthetic concentration (MLAC) can be found at which 50% of patients will achieve a satisfactory analgesic block. In obstetric epidural analgesia, two separate studies found the MLAC of bupivacaine was 0.6 times that of ropivacaine (Capogna 1999 **Level II**, n=87, JS 4; Polley 1999 **Level II**, n=83, JS 4). The motor-blocking potency showed a similar ratio of 0.66 (Lacassie 2003 **Level II**, n=60, JS 4).

When comparing bupivacaine with levobupivacaine, the “percentage” bupivacaine solution is by weight of bupivacaine hydrochloride, whereas the percentage levobupivacaine solution is for the active molecule alone. This means that the molar dose of equal “percentage concentration” is 13% higher for levobupivacaine (Schug 2001 **NR**). The sensory MLAC potency ratio of levobupivacaine to bupivacaine is 0.98, although if correction is made for molar concentrations this falls to 0.87 (neither value being significantly different from unity) (Lyons 1998 **Level II**, n=60, JS 3). Levobupivacaine has been shown to have slightly less motor-blocking capacity than bupivacaine with a levobupivacaine/bupivacaine potency ratio for epidural motor block of 0.87 (95%CI 0.77 to 0.98) (Lacassie 2003 **Level II**, n=60, JS 4). Another labour epidural analgesia study has found no difference in MLAC between levobupivacaine and ropivacaine with a ropivacaine/levobupivacaine potency ratio of 0.98 (95%CI 0.80 to 1.20) (Polley 2003 **Level II**, n=83, JS 4).

4.4.2.3 | Epidural local anaesthetics

For postoperative analgesia using epidural infusions, dose-ranging studies established that 0.2% ropivacaine was a suitable concentration (Schug 1996 **Level II**, n=36, JS 5; Scott 1995b **Level II**, n=30, JS 5). Therefore, most investigators compare infusions of bupivacaine or levobupivacaine at 0.1% or 0.125% with ropivacaine 0.2%, which removes any imbalance in comparative potency. In obstetric epidural analgesia, lower concentrations of epidural ropivacaine, typically 0.1%, are used in labour to avoid dense sensory and motor block (Zhang 2018 **SR Level IV**, 30 studies, n=2,851).

The majority of studies find similar analgesic outcomes with postoperative epidural infusions based on these strengths (Casati 2003b **Level II**, n=45, JS 5; Macias 2002 **Level II**, n=80, JS 5; Jorgensen 2000 **Level II**, n=60, JS 3). Motor block is of clinical relevance in low-thoracic or lumbar epidural infusions and has been reported to be less intense with epidural ropivacaine than with bupivacaine (Merson 2001 **Level II**, n=68, JS 4; Muldoon 1998 **Level II**, n=52, JS 4; Zaric 1996 **Level II**, n=37, JS 3). However, this finding has not been supported by another study (Casati 2003b **Level II**, n=45, JS 5).

The relevance of dose, not concentration or volume of LA infused, was confirmed in two trials. The same dose of a mixture of levobupivacaine in three different concentrations (0.5%, 0.25% and 0.15%) and sufentanil administered during continuous thoracic epidural infusion for thoracotomy resulted in similar efficacy and adverse effects (Mendola 2009 **Level II**, n=138, JS 3) as did two concentrations (0.15 and 0.5%) of levobupivacaine in another RCT (Dernedde 2006 **Level II**, n=82, JS 4). Neither infusions of bupivacaine 0.125% nor ropivacaine 0.2% interfered with neurophysiological assessments after scoliosis surgery (Pham Dang 2008 **Level II**, n=18, JS 4). At concentrations of ≥0.5%, there were no significant differences in onset time and intensity or duration of sensory block between bupivacaine, levobupivacaine or ropivacaine used for epidural analgesia (Casati 2003b **Level II**, n=45, JS 5; Cheng 2002 **Level II**, n=45, JS 3).

Local anaesthetic/opioid combinations

The quality of pain relief from low-dose epidural infusions of plain LA consistently benefits from the addition of opioids, most commonly fentanyl (Walker 2002 **Level I**, 4 RCTs [epidural local anaesthetic/opioid combinations], n=226; Curatolo 1998 **Level I**, 18 RCTs [fentanyl/local anaesthetic], n unspecified); this was confirmed by additional RCTs (Senard 2002 **Level II**, n=60, JS 3; Hubler 2001 **Level II**, n=109, JS 4; Crews 1999 **Level II**, n=64, JS 3; Scott 1999 **Level II**, n=182, JS 5;). For addition of other adjuvants see Sections 4.9, 4.12.2 and 4.13.

Potential dose-sparing benefits are more obvious for LA adverse effects (hypotension and motor block) than for opioid-related adverse effects (Walker 2002 **Level I**, 4 RCTs [epidural LA/opioid combinations], n=226).

Comparisons of PCEA using ropivacaine 0.2%, ropivacaine 0.125% and levobupivacaine 0.125%, all with sufentanil 1 mcg/mL (6 mL/h background plus 2 mL bolus), showed no differences in pain relief or motor block; patients given 0.2% ropivacaine used similar volumes, thus receiving more total dose of local anaesthetic and the same amount of sufentanil (Sitsen 2007 **Level II**, n=63, JS 4). Similarly, there was no difference in analgesia and no motor block reported in a PCEA comparison of ropivacaine 0.05%, 0.075% and 0.1%, with fentanyl 4 mcg/mL and droperidol 25 mcg/mL added to all solutions (Iijima 2007 **Level II**, n=272, JS 4). In another comparison of PCEA bupivacaine 0.625% with fentanyl 3 mcg/mL and 0.15% ropivacaine alone, there was no difference in pain relief; patient satisfaction was lower with PCEA ropivacaine, even though it led to fewer opioid-related adverse effects (Pitimana-aree 2005 **Level II**, n=70, JS 3).

No studies directly compare fentanyl to morphine when added to LA epidural infusions, although a single retrospective audit of the use of high-thoracic epidural following cardiac surgery suggested improved pain control and lowered infusion rate using ropivacaine 0.2% with

morphine 20 mcg/mL vs fentanyl 2 mcg/mL (Royse 2005 **Level III-3**, n=200). For information relating to the use of epidural LA or LA/opioid combinations for postoperative pain see Section 5.6.2 and for labour pain see Section 9.1.3.3.

4.4.2.4 | Peripheral local anaesthetics

A number of studies have compared different LAs or doses of LAs used for peripheral nerve block (PNB) and continuous peripheral nerve block (CPNB). Specific regional and local anaesthetic techniques are discussed in Section 5.8

In a meta-analysis comparing ropivacaine to levobupivacaine for peripheral nerve block, there was no difference in time to onset of anaesthesia or patient satisfaction, but levobupivacaine provides longer block (WMD -2.94 h; 95%CI -5.56 to -0.32) and a lower incidence of postoperative rescue analgesia (OR 2.11; 95%CI 1.18 to 3.74) (Li 2017a **Level I** [PRISMA], 12 RCTs, n=556); concentrations included ranged from 0.5% to 1.0% and non-equipotent comparisons were included.

At concentrations of 0.5% or greater, there were no significant differences in onset time and intensity or duration of sensory block between bupivacaine, levobupivacaine or ropivacaine in sciatic (Casati 2002 **Level II**, n=50, JS 4), interscalene (Casati 2003a **Level II**, n=47, JS 5) or axillary brachial plexus blocks (McGlade 1998 **Level II**, n=61, JS 5). In a comparison of three concentrations (0.1%, 0.2%, 0.3%) of ropivacaine for continuous FNB following TKA, infusions of 0.2% and 0.3% ropivacaine had equivalent quality of postoperative analgesia (Brodner 2007 **Level II**, n=102, JS 4). After similar surgery, there was no difference in pain relief or motor block between patient-controlled FNB with levobupivacaine 0.125% and ropivacaine 0.2% (Heid 2008 **Level II**, n=60, JS 4).

Comparisons of two different patient-controlled CPNB regimens found different results depending on the location of the block; the regimens were ropivacaine at 4 mL/h 0.4% (bolus 2 mL) or 8 mL/h 0.2% (bolus 4 mL). For continuous popliteal nerve block, the larger volumes of the dilute LA were more likely to cause an insensate limb (Ilfeld 2008 **Level II**, n=50, JS 3); for continuous interscalene nerve block there was no difference between the two solutions (Le 2008 **Level II**, n=50, JS 2) and for continuous infraclavicular nerve block the smaller volumes of the more concentrated LA were more likely to cause an insensate limb (Ilfeld 2009 **Level II**, n=50, JS 3).

In another RCT of patient-controlled continuous interscalene block comparing levobupivacaine 0.25%, ropivacaine 0.25% and ropivacaine 0.4%, the lower concentration of ropivacaine achieved less effective pain relief (Borghi 2006 **Level II**, n=72, JS 5).

Continuous popliteal sciatic nerve block using ropivacaine 0.2% vs levobupivacaine 0.2% and levobupivacaine 0.125% resulted in similar pain relief after foot surgery but fewer patients had complete recovery of motor function at 24 and 48 h with 0.2% levobupivacaine (Casati 2004 **Level II**, n=60, JS 5). Many continuous perineural infusion techniques now use low concentrations of ropivacaine (approx. 0.1%) in order to minimise motor block while still providing effective analgesia (see Section 5.8).

Skin infiltration

Increasing the pH of commercial lidocaine (to ≥7.35 by the addition of sodium bicarbonate prior to injection) reduces pain scores on injection for invasive procedures in cross-over studies (WMD -2/10; 95%CI -2.6 to -1.3) (10 RCTs) and in parallel design studies (WMD -1/10; 95%CI -1.4 to -0.4) (7 RCTs) (Cepeda 2010 **Level I** [Cochrane], 23 RCTs, n=1,067). The magnitude of the decrease in pain is larger when the solution contains adrenaline (WMD -2.5/10; 95%CI -3.2 to -1.7) (6 RCTs, n=232).

Warming the solution (to 37–43°C), assessed mostly in adults, reduces pain on SC or intradermal injection overall (WMD -11/100; 95%CI -14 to -7) (18 RCTs, n=831) and when the local anaesthetic is buffered (WMD -7/100; 95%CI -12 to -3) (8 RCTs, n=412) (Hogan 2011 **Level I** [PRISMA], 18 RCTs, n=831).

Local infiltration analgesia

Two main strategies using large volume, low concentration local anaesthetic infiltration techniques are described: tumescent local anaesthesia and local infiltration analgesia (LIA). Tumescent local anaesthesia has been described for soft-tissue surgery such as varicose vein sclerosis, liposuction or cosmetic breast surgery.

The term LIA typically refers to the systematic intraoperative injection of LAs in the periarticular and intra-articular regions. LIA may also be referred to as periarticular infiltration. A "cocktail" is most commonly used for periarticular LIA comprising a local anaesthetic, an alpha-2 agonist/vasoconstrictor, an opioid and an anti-inflammatory agent. The majority of investigations into the effectiveness of LIA in acute pain management following THA or TKA fail to separate out the components of the mixture and some protocols use "top-up" regimens of varying composition (Andersen 2014a **Level I** [PRISMA], 27 RCTs, n=1,644). In THA (n=756), multimodal systemic analgesia or neuraxial techniques (IT morphine or epidural analgesia) have similar analgesic efficacy vs LIA; however in TKA, LIA provided superior analgesia to placebo (n=328). Compared with FNB, epidural analgesia or IT morphine, LIA provided similar or improved analgesia in the early postoperative period, but most trials had a high risk of bias due to different systemic analgesia regimens between groups. Overall, the use of wound catheters for postoperative administration of local anaesthetic following LIA was not supported in the included trials.

Despite the many studies of LIA, final interpretation is hindered by methodological insufficiencies in most studies, especially because of differences in use of systemic analgesia between groups. For more detail see also Section 5.8.7.1.

There is limited data regarding local anaesthetic systemic toxicity (LAST) in patients receiving LIA with hip and knee joint surgery. In a case series of 39 patients receiving up to 300 mg ropivacaine as LIA, there was no clinical toxicity and peak plasma concentrations did not exceed 1.7 mcg/mL; peak concentrations occurred at ≈6 h post administration (Affas 2016 **Level IV**, n=39).

In volunteers receiving 41 exposures to tumescent subcutaneous infiltration of lidocaine with epinephrine, recommendations were made for up to 28 mg/kg lidocaine without liposuction and 45 mg/kg with liposuction with peak concentrations occurring 8–16 h after infiltration (Klein 2016 **Level IV EH**, n=14).

Slow-release preparations of local anaesthetics

Encapsulation of bupivacaine within liposomes in clusters of <100 microns diameter (liposomal bupivacaine) results in drug release into adjacent tissues for a number of days following injection, with peak plasma concentrations occurring 12–36 h after injection (Skolnik 2014 **NR**). Current indications from trial data have not raised any specific safety concerns (Viscusi 2014 **Level I**, 10 RCTs, n=823).

A limited number of RCTs have been conducted with wound infiltration, periarticular infiltration, perineural block and epidural administration (see Section 4.3.2.2 for ER epidural opioid preparations); most RCTs have demonstrated analgesic superiority over placebo for up to 72 h, however benefit over normal formulations of bupivacaine has not been shown (Tong 2014 **Level III-2 SR**, 5 studies, n unspecified). When comparing wound infiltration with liposomal bupivacaine to either ropivacaine or plain bupivacaine, no difference was seen with analgesic outcomes up to 48 h (Kendall 2018 **Level I** [PRISMA], 9 RCTs, n=779).

A systematic review of liposomal bupivacaine for periarticular infiltration in TKA (Yayac 2019 **Level IV SR** [PRISMA], 6 SRs & 17 RCTs & 25 studies, n unspecified) finds:

- vs conventional LA single injection PNB (3 RCTs, n=555), pain relief is better with PNB (SMD 0.45, 95%CI 0.08 to 0.82), largely driven by benefits on POD 0 and 1; there is no

difference in opioid consumption. Differences in complication rates, including falls, are mixed;

- vs conventional LA LIA (13 RCTs, n=1,155), slightly lower pain scores are found using AUC over 5 d (SMD = -0.08, 95%CI -0.14 to -0.03), but not using pain scores by time-point up to 3 d (-5.21/100; 95%CI -12.1 to 1.65). There are no differences in opioid consumption nor functional recovery;
- vs conventional LA IA infiltration (2 RCTs, n=345), only one study included a direct comparison and found no difference in pain outcomes.

Also in TKA, two overlapping meta-analyses compared liposomal bupivacaine by periarticular infiltration to conventional LA FNB (Liu 2017a **Level III-2 SR** [PRISMA], 1 RCT & 7 studies, n=2,407; Ma 2016b **Level III-2 SR**, 1 RCT & 5 studies, n=1,289) (all 6 studies overlap); 2 FNB studies used continuous infusions. There is no difference between groups in pain scores to 72 h, PONV or range of motion, but liposomal bupivacaine is associated with decreased LOS (MD -0.43 d; 95%CI -0.60 to -0.27) and reduced total morphine requirements (MD -29.3 mg; 95% CI -57.6 to -1.1) (Liu 2017a **Level III-2 [PRISMA]**, 1 RCT & 7 studies, n=2,407).

In THA, LIA with liposomal bupivacaine vs conventional bupivacaine showed no difference up to 72 h in postoperative opioid consumption, pain scores, opioid-related side effects, time to first ambulation, or LOS (Perets 2018 **Level II**, n=107, JS 4).

Following day-case retropubic sling placement, pain scores were low but liposomal bupivacaine infiltration vs saline improved scores slightly at 4 h post-discharge and the following morning (Mazloomdoost 2017 **Level II**, n=109, JS 4).

4.4.3 | Local anaesthetic toxicity

4.4.3.1 | Direct toxicity

Nerve injury following perineural LA injection may be a consequence of many factors including needle trauma, haematoma, pressure injury, or direct local anaesthetic toxicity (Verlinde 2016 **NR**). In clinical practice it is difficult, if not impossible to separate out these elements, and the likely contribution of direct neurotoxicity is small. All local anaesthetics exhibit neurotoxicity if nerves are exposed to sufficiently high concentrations for a sufficiently long period (Verlinde 2016 **NR BS**). Lidocaine 5% infused via lumbar subarachnoid microcatheters has been associated with case reports of cauda equina syndrome (Rigler 1991 **Level IV**, n=4; Schell 1991 **Level IV**, n=2). This suggested that high local concentrations of lidocaine were potentially neurotoxic and led to the technique falling into disfavour. The precise mechanisms of direct LA neurotoxicity remain unclear, but are concentration-dependent, and may involve the intrinsic caspase-pathway, PI3k-pathway, and MAPK-pathways (Verlinde 2016 **NR BS**).

Transient neurological symptoms (TNS) is a clinical syndrome associated with spinal (IT) anaesthesia. Patients experience pain or muscle spasms in the buttocks or lower limbs following initial recovery from the spinal anaesthetic. The onset of symptoms is usually within 24 h of the procedure and it fully resolves spontaneously within a few days. Despite its name, there is no evidence that this condition is associated with actual neurologic pathology. A network meta-analysis showed that the risk of TNS was lower for bupivacaine, levobupivacaine, prilocaine, procaine, and ropivacaine with RRs in the range of 0.10 to 0.23 vs lidocaine; while 2-chloroprocaine and mepivacaine did not differ to lidocaine (Forget 2019 **Level I** [Cochrane] [NMA], 24 RCTs, n=2,226). The quality of evidence was considered moderate to low, and the overall incidence of TNS was 10.7%.

Other tissues are susceptible to direct toxicity from local anaesthetics. Myotoxicity has been described clinically (Zink 2004 **NR**) and reproduced experimentally (Yildiz 2011 **BS**), especially for bupivacaine, but is rare and reversible. Local anaesthetics have chondrotoxic effects on articular cartilage, which are worsened by coadministration of corticosteroids (Jayaram 2019 **Level III-2 BS** [PRISMA], 16 studies, n unspecified); ropivacaine at concentrations of 0.5% or less was found to be the least chondrotoxic LA.

4.4.3.2 | Local anaesthetic systemic toxicity (LAST)

There is consistent laboratory data showing that the S-enantiomers of the long-acting amide LAs exhibit less CNS or cardiac toxicity than the R-enantiomers or the racemic mixtures for doses resulting in equivalent sensory nerve conduction block. Defining relative toxicities for these agents is complex because it depends on the parameters measured (eg cardiac, CNS), the dose, route and species studied. There is lack of scientific data available to determine a safe maximal dose of local anaesthetic. However, the upper limit of a dose should take into account patient weight, age and comorbidities. There is a pharmacokinetic rationale to support fractional dosing by incremental injection of local anaesthetic in addition to identifying unintended intravascular injection.

The incidence of local anaesthetic systemic toxicity (LAST) has been quantified using registry databases at 0.03% or 0.27/1,000 PNBs (95%CI 0.21 to 0.35) (Gitman 2018 **Level IV**, n=251,325). Factors associated with increased LAST events were paravertebral (OR 9.20; 95%CI 2.24 to 37.8) and upper limb blocks (OR 4.80; 95%CI 1.23 to 18.7), the use of lidocaine vs ropivacaine (OR 5.64; 95%CI 2.02 to 15.7) and larger doses of local anaesthetic (Barrington 2013 **Level IV**, n=25,336 [PNBs in n=20,021 patients]).

The use of ultrasound and LAST

The use of ultrasound (US) was associated with a reduced incidence of LAST (OR 0.23; 95%CI 0.088 to 0.59) (Barrington 2013 **Level IV**, n=25,336 [PNBs] in n=20,021 [patients]); this may be due to increased precision of needle placement with US guidance (minimising intravascular placement) (Neal 2016 **Level IV SR**, 27 studies, n=1,867), or the use of lower doses of local anaesthetic. A meta-analysis identifies a significantly decreased risk of vascular puncture using US (RR 0.16; 95%CI 0.05 to 0.47) (Abrahams 2008 **Level I**, 13 RCTs, n=946). These data form the basis for the current Class I-B ASRA recommendations for the use of US to reduce LAST (Neal 2018 **GL**). It should be noted that LAST episodes continue to occur despite precautionary measures, including US use (Gitman 2018 **Level IV SR**, n=47 [episodes of LAST]).

Seizures related to LAST

The most common presenting feature of LAST was seizure (53% and 61%; from case reports and registries respectively) (Gitman 2018 **Level IV**, n=251,325). In blinded human-volunteer studies, CNS symptoms were detected at IV doses and plasma concentrations that were 25% higher for ropivacaine vs bupivacaine (Scott 1989 **Level II EH,** n=12, JS 2) and 16% higher for levobupivacaine than bupivacaine (Bardsley 1998 **Level II EH**, n=14, JS 3). Although these data show that CNS toxicity might occur less frequently or be less severe with the S-enantiomers, all local anaesthetics are toxic. A rapid IV bolus of any of these agents may overwhelm any of the more subtle differences found at lower plasma concentrations.

Cardiac events related to LAST

Severe myocardial depression and refractory ventricular fibrillation have been described as the hallmark of accidental IV administration of moderately large doses of bupivacaine. This has been attributed to the slow dissociation of bupivacaine from the myocardial sodium channel, which is less marked with levobupivacaine and ropivacaine (Mather 2001 **NR**). Animal studies confirm that

higher systemic doses of ropivacaine and levobupivacaine are required to induce ventricular arrhythmias, circulatory collapse or asystole (Ohmura 2001 **BS**), with the ranking of toxicity risk being bupivacaine > levobupivacaine > ropivacaine (Groban 2001 **NR**).

Controlled human studies are only possible when looking at surrogate endpoints such as ECG changes or myocardial depression and suggest a similar ranking of adverse effects (Bardsley 1998 **Level II EH**, n=14, JS 5; Knudsen 1997 **Level II EH**, n=12, JS 5; Scott 1989 **Level II EH**, n=12, JS 5), with bupivacaine being the most toxic and levobupivacaine being less toxic and similar to ropivacaine (Stewart 2003 **Level II EH**, n=14, JS 5).

Successful resuscitation from a massive overdose is of greater relevance in clinical practice. A canine study investigating resuscitation (not using lipid emulsion) and survival following local anaesthetic-induced circulatory collapse showed survival rates of 50%, 70% and 90% with bupivacaine, levobupivacaine and ropivacaine respectively (Groban 2001 **BS**).

Case reports of accidental toxic overdose with ropivacaine suggest that outcomes are more favourable and resuscitation more straightforward (in particular requiring less cardiovascular support) than with racemic bupivacaine (Weiss 2014 **CR**; Hubler 2010 **CR**; Kimura 2007 **CR**; Khoo 2006 **CR**; Soltesz 2003 **CR**; Chazalon 2003 **CR**; Huet 2003 **CR**; Klein 2003 **CR**; Pham-Dang 2000 **CR**). This data is prior to the widespread use of guidelines and lipid emulsion therapy, and a review of case-series and registry data over 33 mth from March 2014 identified only 2 reported deaths out of 47 events, one case having delayed therapy and the other related to lidocaine (Gitman 2018 **Level IV SR,** n=47 [episodes of LAST]).

Total plasma concentrations of LAs tend to rise during the first 48 h of postoperative infusion, although free levels remain relatively low (Scott 1997 **Level IV**, n=11; Emanuelsson 1995 **EH PK**). Thus, in published studies, toxicity due to systemic absorption from epidural or perineural infusions has not been a problem. However, the risk of accidental absolute overdose with postoperative infusions and the increasing use of fascial plane infusions, suggests that the less toxic agents should be used in preference and that the doses administered should be the minimum needed for efficacy.

Lipid emulsion therapy

Lipid emulsion therapy is advocated for in the treatment of LAST (Neal 2018 **GL**; AAGBI 2010 **GL**). Animal experimental data (Weinberg 2003 **BS**; Weinberg 1998 **BS**) has been supported by case reports of successful resuscitation following bupivacaine (Rosenblatt 2006 **CR**), ropivacaine (Litz 2006 **CR**), levobupivacaine (Foxall 2007 **CR**), mepivacaine/prilocaine (Litz 2008 **CR**) and mepivacaine/bupivacaine (Warren 2008 **CR**) toxicity and published case series of use of IV lipid emulsion therapy (Gitman 2018 **Level IV SR**, n=47 [LAST episodes]; Cave 2014 **Level IV**, n=10 (LAST episodes]; Felice 2008 **Level IV**, n=4).

The mechanism of action of the lipid emulsion may be due to partitioning of local anaesthetic within the emulsion itself (acting as a “lipid sink” or “shuttling”) (Fettiplace 2018 **NR**), mitochondrial substrate enhancement in the myocardium (Weinberg 2000 **BS**) and/or a direct inotropic effect (Fettiplace 2014 **BS**). Uncertainties relating to dosage, efficacy and adverse effects (Cave 2014 **Level IV**, n=10 (LAST episodes]) still remain, however, lipid administration appears safe. The ASRA Practice Advisory on Local Anesthetic Systemic Toxicity recommends the administration of IV lipid emulsion therapy at the first signs of LAST but following airway management (Class I-B recommendation) (Neal 2018 **GL**). In suspected LAST, it is also recommended to administer lipid emulsion immediately after airway support has commenced and ventilation is controlled (convulsions may or may not need control at this point in order to ventilate) (Neal 2018 **GL**); this prevents hypoxia, hypercapnia, and acidosis which are known to potentiate LAST. It should be noted that local anaesthetic toxicity might recur following

successful initial resuscitation, suggesting a need for continued intensive observation if a large dose of local anaesthetic has been administered (Marwick 2009 **GL**).

The ASRA guidelines are also available as an app for mobile phones and tablets ('*ASRA LAST*') (Neal 2018 **GL**).

LAST is also discussed in Section 5.8.11.3 and in paediatric patients in Section 10.6.3.5 (including adverse effects of lipid emulsion use).

KEY MESSAGES

1. Lidocaine intrathecal is more likely to cause transient neurologic symptoms than bupivacaine, prilocaine and procaine (**S**) (**Level I** [Cochrane Review NMA]).
2. Local anaesthetics have chondrotoxic effects on articular cartilage, with ropivacaine the least toxic (**N**) (**Level I** [PRISMA]).
3. Wound infiltration with liposomal preparations of bupivacaine is no more effective than ropivacaine or plain bupivacaine for analgesic outcomes up to 48 hours (**N**) (**Level I** [PRISMA]).
4. The quality of epidural analgesia with local anaesthetics is improved with the addition of opioids (**U**) (**Level I**).
5. Ultrasound guidance reduces the risk of vascular puncture during the performance of regional blocks (**S**) (**Level I**).
6. Local anaesthetic systemic toxicity is reduced by the use of ultrasound guidance for regional anaesthesia (**S**) (**Level I**).
7. Continuous perineural infusions of lidocaine result in less effective analgesia and more motor block than long-acting local anaesthetic agents (**U**) (**Level II**).
8. There are no consistent differences between ropivacaine, levobupivacaine and bupivacaine in terms of quality of analgesia or motor block, when given in low doses for regional analgesia (epidural and peripheral nerve block) (**U**) (**Level II**).
9. Cardiovascular and central nervous system toxicity of the stereospecific isomers ropivacaine and levobupivacaine is less severe than with racemic bupivacaine (**U**) (**Level II**).
10. Local anaesthetic systemic toxicity is increased in paravertebral and upper limb blocks, with the use of lidocaine and higher doses of local anaesthetics (**U**) (**Level IV**).
11. Lipid emulsion is effective in resuscitation of circulatory collapse due to local anaesthetic toxicity (**S**) (**Level IV SR**); however, uncertainties relating to dosage, efficacy and adverse effects still remain; therefore, it is appropriate to administer lipid emulsion only once ventilatory support has begun and convulsions are controlled (**S**) (**Level IV**).

The following tick box represents conclusions based on clinical experience and expert opinion:

☑ Case reports following accidental overdose with ropivacaine, levobupivacaine and bupivacaine suggest that resuscitation is less likely to be successful with bupivacaine (**U**).

4.5 | Inhalational agents

4.5.1 | Nitrous oxide

N_2O has been used since the inception of anaesthesia for its modest analgesic and sedative properties. It has minimal respiratory and cardiovascular depression. In many countries it is available as a 50% N_2O /50% oxygen mixture called Entonox®. While it has a long history of use, there is a paucity of good studies examining its effectiveness in comparison with other analgesics (Buhre 2019 **NR**).

In a meta-analysis of inhaled analgesics in labour, subgroup analysis of N_2O shows minimal analgesic difference vs placebo (RR 0.06; 95%CI 0.01 to 0.34) (MD 3.5/100; 95%CI -3.75 to -3.25) (Klomp 2012 (**Level I** [Cochrane], 3 RCTs [N_2O], n=819). A systematic review shows that N_2O in oxygen has some analgesic efficacy in labour (Likis 2014 **Level IV SR**, 58 studies, n=20,266). Only two studies were of good quality. N_2O provides less analgesia than epidural analgesia but more than pethidine, or bath and shower. Maternal satisfaction with the birth experience using N_2O for analgesia is higher than for pethidine or epidural analgesia. The reports of maternal adverse effects in this review are nausea, vomiting, dizziness and drowsiness. Apgar scores are no different for N_2O vs no analgesia. A subsequent systematic review vs multiple comparators, was overall of low quality and did not add to the previous information (Sheyklo 2017 **Level I** [PRISMA], 14 RCTs, n=2,158) (See also Section 9.1.3.2).

N_2O was effective during painful procedures such as venous cannulation (Gerhardt 2001 **Level II**, n=10, JS 5), sigmoidoscopy (Harding 2000 **Level II**, n=77, JS 5), dermatological procedures (Brotzman 2018 **Level IV SR**, 8 studies, n=438), extraction of gauze packing strips after Caldwell-Luc operation (Dong 2017 **Level II**, n=47, JS 4), lumbar puncture (Moisset 2017 **Level II**, n=66, JS 5), transrectal prostate biopsy (Cazarim 2018 **Level II**, n=84, JS 4), liver biopsy (Castera 2001 **Level II**, n=100, JS 5), in relieving acute ischaemic chest pain (O'Leary 1987 **Level II**, n=12, JS 2) and in trauma patients in the prehospital setting (Ducasse 2013 **Level II,** n=60, JS 4). In elderly patients (median age 84 y), N_2O provided better analgesia than morphine during bed sore and ulcer care (Paris 2008b **Level II**, n=34, JS 3). For colonoscopy, there was no difference in pain intensity between continuous and as-required 50% N_2O use (Ball 2015 **Level II**, n=108, JS 5).

While a previous study reported benefits in bone marrow aspiration (Gudgin 2008 **Level III-3**, n=16), a subsequent RCT found no difference in pain and anxiety scores between 50% N_2O in oxygen and an oxygen/air mixture (Kuivalainen 2015 **Level II**, n=60, JS 3). Similarly, for intrauterine device insertion, there was no analgesic effect of 50% N_2O vs oxygen (Singh 2016b **Level II**, n=80, JS 5) and there was no pain relieving or opioid-sparing effect of 65% N_2O vs oxygen for burns dressing changes (do Vale 2016 **Level III-1**, n=15).

For lower gastrointestinal endoscopy, there is no difference in pain scores between N_2O and IV opioid/midazolam, or the ability to successfully complete the procedure (Welchman 2010, **Level I**, 11 RCTs, n=623). The N_2O group has a shorter time to achieve fitness for discharge. Self-administration of 50% N_2O combined with PO morphine vs the same dose of PO morphine alone resulted in better pain control of breakthrough pain in cancer patients at 5 and 15 min (Liu 2018 **Level II**, n=240, JS 5).

As no RCTs compare N_2O and methoxyflurane, an indirect comparison for pain relief in the ED showed no significant differences in efficacy between the two agents (Porter 2018b **Level I** [NMA], 2 RCTs, n=263).

For use in paediatrics see Section 10.7.2 and 10.7.4.

In an experimental setting, a study measuring changes in detection and pain thresholds to electrical tooth stimulation reported the development of acute and chronic tolerance in

response to single and repeated administration of N_2O (38% or 35%) for 30 min (Ramsay 2005 **EH**). The significance of this finding in the clinical setting is unknown.

A *post-hoc* analysis of an RCT (ENIGMA) using telephone interviews at a median of 4.5 y following (mostly abdominal) surgery found that the intraoperative use of N_2O reduced the risk of chronic postsurgical pain in an Asian population (OR 0.48; 95%CI 0.33 to 0.93) (Chan 2011 **Level II**, n=423, JS 5); factors increasing risk included severity of acute postoperative pain, wound length, wound infection and anxiety. These findings were confirmed in a planned subgroup analysis in Asian vs non-Asian patients (RR 0.70; 95%CI 0.50 to 0.98) of a subsequent RCT (ENIGMA II) (Chan 2016 **Level II**, n=2,924 [phone interviews at 12 mth postop], JS 5).

N_2O attenuated remifentanil induced tolerance/hyperalgesia (Wehrfritz 2016 **Level II EH**, n=21, JS 5; Echevarria 2011 **Level II**, n=50, JS 4).

N_2O diffuses more rapidly than nitrogen and can expand enclosed air-containing spaces within the body. Its use is therefore contraindicated in the presence of a pneumothorax, obstruction of middle ear and sinus cavities, recent vitreoretinal surgery, pneumocephalus, bowel obstruction and gas embolism (Shaw 1998 **NR**).

4.5.1.1 | Toxicity

N_2O oxidises the cobalt ion of cobalamin (vitamin B_{12}) preventing it from acting as a coenzyme for methionine synthetase; methionine synthetase also requires 5-methyltetrahydrofolate as a coenzyme (Sanders 2008 **NR**). Methionine synthetase is required for the synthesis of deoxyribonucleic acid and ribonucleic acid and therefore the production of cells in rapidly dividing tissues such as bone marrow and gastrointestinal mucosa, as well as the synthesis of myelin (Sanders 2008 **NR**). Exposure of young children (median age 11 mth) to N_2O anaesthesia for more than 2 h leads to a statistically significant but small increase in total homocysteine plasma concentrations on the first postoperative morning with unclear clinical relevance (Pichardo 2012 **Level IV**, n=32).

Bone marrow and neurological complications have been reported in patients exposed to N_2O. A systematic review identified 100 cases of neurological toxicity, of which 57% resulted from recreational use (Oussalah 2019 **Level IV SR**, 85 studies, n=100 [cases]). Other reasons for exposure were surgery in 25%, occupational exposure in 9%, pain control in 6% and procedural sedation in 1%. Clinical symptoms included paraesthesia in 80%, unsteady gait in 58% and weakness in 43%. The most common diagnoses were subacute combined degeneration (SACD) of the spinal cord in 28%, myelopathy in 26% and generalized demyelinating polyneuropathy in 23%; a T2 signal hyperintensity in the MRI of the spinal cord was seen in 68%. Pathological haematological findings occurred in 72%. The most relevant factor was possible or probable vitamin B_{12} deficiency (diagnosed on the combined indicator of vitamin B_{12} status [cB_{12}] scoring system [Fedosov 2015 **BS**]) in 85%. In a univariate risk analysis, the following risk factors were identified: age ≥40 y (OR 23.3; 95%CI 6.8 to 79.6), vitamin B_{12} level ≤74 pmol/L (OR 6.06; 95%CI 2.05 to 17.9) and MCV >100 fL (OR 9.8; 95%CI 1.9 to 49.1). The dose of N_2O was not associated with any outcome.

A parallel systematic review of SACD excluded recreational users (Patel 2018 **Level IV SR**, 32 studies, n=39 [cases]) (significant overlap). Again in 84% of cases vitamin B_{12} malabsorption secondary to a gastrointestinal disorder was the underlying causation. Classical symptoms were proprioceptive and vibratory sensation loss in 67% and burning or tingling paraesthesia in 59%. Again, there was no association to exposure duration. Most notably, supplementation with vitamin B_{12} resulted in complete recovery in 33% and partial improvement in 64%. Mean time to complete resolution was 37 wk (4 wk to 3 y).

The risk may be greater in critically ill patients with increased metabolic demands or poor nutrition (Amos 1982 **Level IV**, n=70). N_2O-induced bone marrow toxicity leading to megaloblastic anaemia is usually progressive but reversible. The bone marrow changes were almost completely prevented by administration of folinic acid (Amos 1982 **Level IV**, n=70).

The following case reports are included in the systematic reviews above, but highlight specific risk factors: those at risk of vitamin B_{12} deficiency include some vegetarians (in particular vegans) (Rosener 1996 **CR**), the newborns of vegetarian mothers (McNeely 2000 **CR**), patients with gastrointestinal pathology (Schilling 1986 **Level IV**) or phenylketonuria (Walter 2011 **NR**), being elderly (Nilsson-Ehle 1998 **NR**), patients taking PPIs (Schenk 1999 **Level IV**) or H2 blockers and alcoholics (Sanders 2008 **NR**; Carmel 2000 **NR**). Cases have also been reported in those abusing the drug (eg obtained from whipped cream chargers) or being exposed to N_2O for medical purposes after longer periods of abuse (Lin 2011 **Level IV**, n=3; Rheinboldt 2014 **CR**; Hu 2014 **CR**; Chiang 2013 **CR**; Cheng 2013 **CR**; Ghobrial 2012 **CR**; Sanders 2008 **NR**).

The neuropathy appears to be the result of decreased methionine and subsequent defective myelin formation. Involvement of peripheral, autonomic and central nervous systems may also lead to incontinence, diplopia, confusion or impaired cognitive function (Weimann 2003 **NR**). Despite the lack of any good data assessing efficacy in humans, and even though the bone marrow changes are usually reversible, it may be reasonable to give patients repeatedly exposed to N_2O, vitamin B_{12} and folic or folinic acid supplements (Weimann 2003 **NR**).

Another consequence of N_2O-induced inactivation of methionine synthetase is elevation of plasma homocysteine (a known risk factor for coronary artery and cerebrovascular disease), the levels of which rise after anaesthesia using N_2O (Myles 2008 **Level II**, n=59, JS 3; Badner 1998 **Level II**, n=20, JS 2; Nagele 2008 **Level III-3**, n=140). Patients who are homozygous for polymorphisms in the gene encoding the enzyme that is an antecedent to methionine synthetase are at a higher risk of developing abnormal plasma homocysteine concentrations after N_2O anaesthesia (Nagele 2008 **Level III-3**, n=140). However, the large ENIGMA II study, comparing oxygen 30% with or without N_2O (70%) in patients with known or risk factors for ischaemic heart disease, found no difference in serious adverse effects in the N_2O group vs the non-N_2O group (Myles 2014 **Level II**, n=7,112, JS 3). However, as this study examined patients who were undergoing major surgery that lasted for at least 2 h, the applicability to the setting of analgesia may be limited.

Methionine given preoperatively to patients undergoing N_2O anaesthesia improved the rate of recovery of methionine synthetase and prevented the prolonged postoperative rise in plasma homocysteine concentrations (Christensen 1994 **Level IV**, n=14). Preoperative administration of oral B vitamins (folate, B_6 and B_{12}) (Badner 2001 **Level II**, n=53, JS 3) and of vitamin B_{12} infusions (Kiasari 2014 **Level II**, n=60, JS 5) also prevented the postoperative increase in homocysteine following N_2O anaesthesia.

The information about the complications of N_2O derives from case reports only. There are no controlled studies that evaluate the safety of repeated intermittent exposure to N_2O in humans and no data to guide the appropriate maximum duration or number of times a patient can safely be exposed to N_2O. Nevertheless, the potential problems require highlighting. The suggestions for the use of N_2O outlined below are extrapolations only from the information above.

4.5.1.2 | Suggestions for the use of nitrous oxide as an analgesic

When N_2O is to be used repeatedly for painful short procedures, it may be reasonable to:

- Exclude patients with persistent vitamin B_{12} deficiency;
- Screen patients at risk of vitamin B_{12} deficiency by examination of the blood picture and serum B_{12} concentrations before using N_2O repeatedly;

- Exclude asymptomatic patients with macrocytic anaemia or hypersegmentation of neutrophils until it is established that vitamin B_{12} or folate deficiency is not the cause;
- Exclude females who may be in the early stages of pregnancy, although this will depend on the relative harm of any alternative methods;
- Limit exposure to N_2O to the briefest possible time — restricting the duration of exposure may require strict supervision and limited access to the gas;
- Administer methionine, vitamin B_{12} (both with a good safety profile) and possibly folic or folinic acid to patients repeatedly exposed to N_2O (doses that may prevent the complications of exposure to N_2O have not been established);
- Monitor for clinical signs and symptoms of neuropathy on a regular basis and start treatment with vitamin B_{12} early.

4.5.2 | Methoxyflurane

Methoxyflurane is a volatile anaesthetic agent with analgesic properties. It was first marketed in 1962 and later withdrawn from sale in 2001. The FDA withdrew the medicine because of the risk of nephrotoxicity and hepatotoxicity and stated that it would not consider reintroduction into the market until new clinical trials were undertaken (FDA 2005). Methoxyflurane is no longer licensed for anaesthesia in humans.

Although no longer used as an anaesthetic, methoxyflurane has been registered in Australia and New Zealand (as well as now a number of other countries) for use as an analgesic in low doses since 1975 for relief of trauma-associated acute pain as well as procedural pain (Porter 2018a **NR**; Jephcott 2018 **NR**; Medical Devices International 2009). It is available as a self-administered "Penthrox®" inhaler, which dispenses 0.2 to 0.4% methoxyflurane (Medical Devices International 2009).

As an analgesic in prehospital and ED settings, methoxyflurane has been reported as effective (Yeung 2018 **Level III-2 SR** [PRISMA], 2 SRs & 2 studies, n>43,823 [methoxyflurane recipients]; Grindlay 2009 **Level IV SR,** 6 studies [analgesia], n=293). Methoxyflurane provided inferior analgesia to IV morphine and IN fentanyl in the prehospital setting with minimal adverse effects (1 study, n=42,844) (Yeung 2018 **Level III-2 SR**, 2 SRs & 2 studies, total n unspecified). In ED patients aged ≥12 y, it was significantly more analgesic than placebo, with only mild transient adverse effects such as dizziness and headache (Wells 2018 **Level I** [PRISMA, 1 RCT: Coffey 2014 **Level II**, n=300, JS 4). The median time to onset of analgesia was rapid at 4 min and time to peak analgesia was 15 min. Safety was assessed over 14 d following administration and no significant adverse effects were found, including no renal impairment. Use of the Penthrox® inhaler in children reduced pain associated with extremity injuries (Babl 2006 **Level IV**, n=15) but did not provide adequate analgesia for subsequent fracture manipulation (Babl 2007 **Level IV**, n=14). It also provided effective pain relief for adult patients in the prehospital setting, as shown in adults travelling by ambulance to an urban teaching hospital (Buntine 2007 **Level IV**, n=83). Adverse effects included hallucinations, vomiting, confusion and dizziness, and sedation/drowsiness was common (26%) in children (Buntine 2007 **Level IV**, n=83; Babl 2006 **Level IV**, n=15).

As an analgesic for painful procedures outside of the ED, methoxyflurane was first described for obstetric analgesia in 1966 (Bodley 1966 **Level IV**, n=62) and then used as an analgesic for burns dressing (Marshall 1972 **Level IV**, n=60 [procedures in 10 patients]; Firn 1972 **Level IV**, n=94 [procedures in 36 children]; Packer 1969 **Level IV**, n=60 [procedures in 11 patients]). Methoxyflurane was effective for prostate biopsies achieving a low pain score (median 3/10), mild adverse effects and high patient acceptance (Grummet 2012 **Level IV**, n=42). However, methoxyflurane combined with periprostatic infiltration of local analgesia provided superior analgesia vs methoxyflurane alone (Huang 2016 **Level III-1**, n=72). In patients having colonoscopies, methoxyflurane vs IV

fentanyl/midazolam resulted in similar pain scores but shorter recovery and fitness for discharge times, no respiratory depression, and high degree of patient satisfaction (Nguyen 2013 **Level II** n=250, JS 3). Ten patients in the methoxyflurane group required supplementation with IV sedation.

In patients having bone-marrow biopsies, local anaesthetic infiltration plus methoxyflurane vs placebo inhaler resulted in lower worst pain scores (4.9 vs 6.0/10) (Spruyt 2014 **Level II**, n=97, JS 4). Adverse effects were mild and of short duration. The overall efficacy was also confirmed in an audit of methoxyflurane use for procedural analgesia in a variety of procedures with reported success in 97% and minimal adverse effects (Gaskell 2016a **Level IV**, n=173 [procedures in 123 patients]).

As no RCTs compare methoxyflurane and N_2O, an indirect comparison for pain relief in the ED showed no significant differences in efficacy between the two agents (Porter 2018b **Level I** [NMA], 2 RCTs, n=263). In an unblinded comparison between self-administered methoxyflurane and IV PCA ketamine/midazolam for burns dressing both achieved similar analgesia with patient preference for methoxyflurane (Gaskell 2016a **Level II**, n= 8 [cross over], JS 3).

4.5.2.1 | Toxicity

Methoxyflurane causes dose-dependent renal toxicity and, as noted above, renal failure was a key reason behind the withdrawal of the medicine from use. Use of an analgesic device delivering higher concentrations of methoxyflurane was reported to have led to two fatalities from renal toxicity (Toomath 1987 **Level IV**). However, the amount of methoxyflurane delivered using the Penthrox® inhaler is said to be significantly less than the dose that has been associated with subclinical nephrotoxicity (Grindlay 2009 **NR**). There have been no reports of toxicity (Grindlay 2009 **NR**) with dosing limited to 6 mL/d or 15 mL/wk (Medical Devices International 2009). A large population database study found no long-term (up to 14 y) adverse effects (heart disease, renal disease, hepatic disease, diabetes, or cancer) in patients who had been given methoxyflurane by an ambulance service (Jacobs 2010 **Level IV**; n=17,629). The maximum dose approved (6 mL/d and 15 mL/wk) is calculated to achieve a minimum alveolar concentration (MAC) of 0.59 MAC-h (Dayan 2016 **NR**). Methoxyflurane ≤2.0 MAC-h results in serum fluoride ≤40 micmol/L, which has not been associated with renal tubular toxicity, thereby suggesting a safety margin of at least 2.7 to 8-fold of the approved dose limits.

There has been one documented case report of acute hepatitis following three administrations of methoxyflurane in an otherwise healthy woman for procedural analgesia (O'Rourke 2011 **CR**).

Methoxyflurane is contraindicated in patients with known or at genetic risk of malignant hyperpyrexia as well as in patients with renal impairment (Medical Devices International 2009).

KEY MESSAGES

1. Nitrous oxide has some analgesic efficacy in labour pain (**U**), increases maternal adverse effects (nausea, vomiting, dizziness) (**U**), with no adverse effects on the newborn (**U**) (**Level I** [Cochrane Review]) and increases maternal satisfaction compared to pethidine and epidural analgesia (**U**) (**Level IV SR**).
2. Nitrous oxide has equivalent effectiveness and more rapid recovery compared with intravenous sedation in patients having lower gastrointestinal endoscopy (**U**) (**Level I**).
3. Methoxyflurane, in low doses, is an effective analgesic with rapid onset in the prehospital setting, and a range of procedures in the hospital setting (**U**) (**Level II**) with good safety data (**S**) (**Level IV**); it may have comparable efficacy to nitrous oxide (**N**) (**Level I** [NMA]), but is inferior to IV morphine and IN fentanyl (**N**) (**Level III-2 SR**).
4. Nitrous oxide is an effective analgesic agent in a variety of other acute pain situations (**U**) (**Level II**).
5. Intraoperative use of nitrous oxide reduces the incidence of chronic postsurgical pain in Asian populations (**N**) (**Level II**).
6. Subacute combined degeneration of the spinal cord, myelopathy and generalised demyelinating polyneuropathy are rare but potentially serious complications of nitrous oxide use including in those abusing nitrous oxide (**S**) (**Level IV SR**).
7. Vitamin B_{12} deficiency (identified by vitamin B_{12} level $\leq$74 pmol/L and MCV >100 fL) and age $\geq$40 years are relevant risk factors in nitrous oxide neurotoxicity; total nitrous oxide exposure may not be a risk factor (**N**) (**Level IV SR**).
8. Early supplementation with Vitamin B_{12} in subacute combined degeneration of the spinal cord exacerbated by nitrous oxide use improves neurological recovery (**N**) (**Level IV SR**).

The following tick boxes represent conclusions based on clinical experience and expert opinion:

☑ In patients receiving nitrous oxide repeatedly, supplementation with vitamin B_{12}, methionine and folic or folinic acid is a consideration, in particular in those with risk factors (**Q**).

☑ If nitrous oxide is used with other sedative or analgesic agents, appropriate clinical monitoring should be used (**U**).

4.6 | NMDA-receptor antagonists

NMDA-receptor/ion-channel complexes are located peripherally and centrally within the nervous system (Gonda 2012 **NR**). These ionotropic receptors are an important component of glutamergic neurotransmission and thereby involved in multiple functions within the nervous system including learning and memory, cognitive functions, neural development, neuroplasticity, excitotoxicity, addiction, psychiatric disorders and nociception (Li 2016a **NR**).

At the spinal level, NMDA-receptor activation results in the development of central sensitisation manifested clinically as hyperalgesia and allodynia (Petrenko 2014 **NR**; Hocking 2007 **NR**). Activation of NMDA receptors via glutamate release from excitatory synapses augments the propagation of nociceptive information and is therefore linked to acute and chronic pain states as well as opioid-induced tolerance and hyperalgesia.

The NMDA-receptor antagonists ketamine, dextromethorphan, amantadine, memantine and magnesium have been investigated for the management of acute pain (Kreutzwiser 2019 **NR**; Jonkman 2017 **NR**).

4.6.1 | Systemic NMDA-receptor antagonists

4.6.1.1 | Ketamine

In low (subanaesthetic) doses, ketamine acts primarily as a noncompetitive antagonist of the NMDA receptor, although it also binds to many other sites in the peripheral and central nervous systems (Petrenko 2014 **NR**; Sleigh 2014 **NR**; Mion 2013 **NR**). In more detail it is a "high-trapping" antagonist with a slow off-rate, causing a prolonged tonic block; therefore it has higher adverse effect rates than "low-trapping" antagonists with a fast off-rate such as memantine (Sleigh 2014 **NR**). Consequently, ketamine's main role is as an adjuvant in the treatment of pain associated with central sensitisation (Persson 2013 **NR**), such as in severe acute pain, neuropathic pain (Zhou 2011 **NR**) (see Section 8.1.4) and "opioid-resistant" pain (Kreutzwiser 2019 **NR**; Tawfic 2013 **NR**). See also Section 9.7 and for paediatric use Section 10.4.7.

In experimental pain, low-dose ketamine (<1 mg/kg) reduces the area of hyperalgesia (SMD 0.54; 95% CI 0.34 to 0.74) and pain intensity (MD -1.2/10; 95%CI -0.88 to -1.44) (54 RCTs [ketamine]: 43 RCTs [IV administration]) (Thompson 2019 **Level I EH** (PRISMA), 70 RCTs, n=1,069).

In Australia and New Zealand, ketamine is supplied as a racemic mixture (S- and R- enantiomers), although a number of other countries have the more potent pure S-ketamine enantiomeric form available which has twice the analgesic potency, and slightly less adverse cognitive effects in adults (Mion 2013 **NR**).

Perioperative use

Perioperative IV ketamine (IV bolus pooled with IV infusion) used in a large number of operations performed under general anaesthesia vs placebo reduces postoperative opioid consumption over 24 h by 19 % (MD 8 mg morphine equivalents; 95%CI 6 to 9) (65 RCTs, n=4,004) and over 48 h by 19 % (MD 13 mg; 95%CI 10 to 15) (37 RCTs, n=2,449) (Brinck 2018 **Level I** [Cochrane], 130 RCTs, n=8,341). Pain at rest is reduced by 19% at 24 h (MD -5/100; 95%CI -4 to -7) (82 RCTs; n=5,004) and at 48 h by 22 % (MD -5/100; 95%CI -3 to -7) (49 RCTs, n=2,962). Pain during movement is reduced in a similar way. Furthermore, PONV is reduced to a minor degree (23 % vs 27 %; RR 0.88; 95%CI 0.81 to 0.96) (NNT 24; 95%CI 16 to 54) (95 RCTs, n=5,965). The incidence of adverse events with ketamine (5%) vs placebo (4%) is similar (RR 1.2; 95%CI 0.95 to 1.4) (105 RCTs, n=6,538). A dose-dependent analgesic effect is not apparent.

Multiple further systematic reviews in subgroups have been performed with significant overlap of RCTs included.

Adding ketamine to an opioid in the PCA pump has similar benefits to the pooled data above on pain at rest at 24 h (WMD 21.1/100; 98%CI 21.8 to 20.39) (9 RCTs, n=595), opioid consumption (-28%) (7 RCTs, n=495) and PONV (-44%) (7 RCTs, n=435) (Assouline 2016 **Level I** [PRISMA], 19 RCTS, n=1,453). Respiratory depression (RR 0.31; 98%CI 0.06 to 1.51) (9 RCTs, n=871) and hallucinations (OR 1.16; 98%CI 0.47 to 2.79) (7 RCTs, n=690) are not increased. A parallel meta-analysis on ketamine added to morphine or hydromorphone PCA confirms these results (Wang 2016a **Level I** [PRISMA], 36 RCTs, n=2,502) (12 RCTs overlap).

Morphine/ketamine vs higher doses of morphine alone improves analgesia (MD 2.19/10; 95%CI 1.24 to 3.13) and wakefulness (MD -1.53/10; 95%CI -2.67 to -0.40) and reduces PONV (OR 3.71; 95%CI 2.37 to 5.80) and need for non-opioid rescue analgesia (Ding 2014 **Level I**, 7 RCTS, n=492).

Subanaesthetic doses of IM ketamine (escalating from 5 to 25 mg) injected two to three times 17 h to 4 h before cancer surgery reduced postoperative pain and morphine consumption in comparison to a single injection 4 h before surgery and placebo (Rakhman 2011 **Level II**, n=120, JS 5).

Results with regard to specific types of surgery:

- After thoracotomy, addition of ketamine to IV morphine PCA is opioid-sparing and improved analgesia in all RCTs and increases patient satisfaction in one (Mathews 2012 **Level I**, 5 RCTs, n=243). Improved respiratory outcomes (oxygen saturations and $PaCO_2$) are found in the RCTs assessing these parameters (2 RCTs, n=89). IV ketamine/fentanyl PCA resulted in comparable analgesia to thoracic epidural analgesia (Tseng 2019 **Level II**, n=70, JS 3);
- After knee arthroscopy, IV ketamine reduces pain intensity and opioid requirements as well as malonaldehyde levels as a measure of reperfusion injury (SMD -0.63; 95%CI -1.05 to -0.2) (2 RCTs, n=90), but not PONV (Pan 2019 **Level I** [PRISMA], 7 RCTs, n=300);
- After laparoscopic cholecystectomy, IV ketamine reduces pain intensity and opioid requirements at all time points up to 48 h, while reducing the incidence of PONV, pruritus and ileus (Zhu 2018a **Level I**, 6 RCTs, n=294; Ye 2017 **Level I**, 5 RCTs, n=212) (5 RCTs overlap);
- After Caesarean section under spinal anaesthesia (7 RCTs, n=562), but not under general anaesthesia (5 RCTs, n=391), parenteral ketamine improves pain intensity at 2 h, prolongs time to first analgesic request and reduces opioid requirements without increasing adverse effects except for diplopia in one RCT and nystagmus in 2 RCTs (Heesen 2015 **Level I** [PRISMA], 12 RCTs, n=953);
- After spinal surgery, ketamine reduces pain intensity and opioid requirements for 24 h without increased adverse effects (Pendi 2018 **Level I**, 14 RCTs, n=649). After spinal fusion surgery, perioperative IV ketamine bolus and infusion vs placebo resulted in improved long-term outcomes 1 y after surgery with reduced oral morphine (0 mg vs 20 mg) and other analgesic use, better pain relief at rest and on mobilisation (MD -17/100; 95%CI −30 to −3) and higher rate of return to work (43% vs 28%) (Nielsen 2019 **Level II**, n=147, JS 4);
- After laparoscopic gastric banding in obese patients, intraoperative ketamine infusion reduced pain and PCA opioid requirements (Andersen 2014b **Level I**, 1 RCT: Hasanein 2011, **Level II**, n=60, JS 3).

Subsequent to these meta-analyses, multiple further RCTs studying the same issue have been performed; overall the outcomes from these studies do not affect the existing conclusions and they are therefore not referenced here.

Low-dose parenteral ketamine may also improve analgesia in patients with opioid-induced tolerance or hyperalgesia. After spinal fusion in opioid-tolerant patients, use of a continuous ketamine infusion resulted in significantly less pain but did not reduce PCA opioid requirements in one RCT (Urban 2008 **Level II**, n=24, JS 4), however its use reduced opioid requirements and pain scores in the early postoperative period and at 6 wk in another (Loftus 2010 **Level II**, n=101, JS 4). Another trial in the same setting found reduced morphine requirements over 24 h (MD -42 mg; 95%CI -59 to -25), reduced sedation and improved function and disability at 6 mth (Nielsen 2017 **Level II**, n=150, JS 5). Similar results were found after noncancer surgery (Barreveld 2013b **Level II**, n=64, JS 5). A preoperative ketamine bolus for extracorporeal shock-wave lithotripsy reduced opioid requirements in chronic opioid users on low and high doses (Gharaei 2013 **Level II**, n=190, JS 4). However, when opioid-tolerant patients had epidural analgesia and IV PCA after spinal surgery, the addition of ketamine bolus and 24 h infusion conveyed no further benefit vs placebo (Subramaniam 2011 **Level II**, n=30, JS 5); the patients in this study also received gabapentin and antidepressants.

After remifentanil based anaesthesia, perioperative systemic ketamine reduces the development of acute tolerance/OIH associated with remifentanil use (Garcia-Henares 2018 **Level I** [PRISMA], 12 RCTs, n=569). This assessment is based on reduced postoperative pain scores and opioid requirements and increased time to first analgesic request and satisfaction scores in the ketamine vs the placebo groups but not on QST.

Use of a low-dose IV ketamine infusion 0.05 mg/kg/h for 24 h postoperatively reduced pain scores (over 48 h) in patients receiving epidural ropivacaine and morphine analgesia following thoracotomy (Suzuki 2006 **Level II**, n=49, JS 5). However, this was not confirmed by a subsequent study, where the addition of IV ketamine infusion 0.09 mg/kg/h for 48 h to epidural analgesia added no benefit (Joseph 2012 **Level II**, n=60, JS 5).

Perioperative ketamine vs placebo reduces the incidence of CPSP at 3 mth (5 RCTs, n unspecified) but only when administered for >24 h (OR 0.37; 95%CI 0.14 to 0.98) (Chaparro 2013 **Level I** [Cochrane] 14 RCTs [ketamine], n=1,388). At 6 mth (10 RCTs, n=516), perioperative ketamine reduces CPSP (OR 0.63; 95%CI 0.47 to 0.83), including when infused for <24 h (OR 0.45; 95 %CI 0.26 to 0.78). These effects were predominantly in abdominal surgery. Another meta-analysis found a benefit of perioperative IV ketamine vs placebo in reducing the incidence of CPSP at 3 mth (RR 0.74; 95%CI 0.60 to 0.93) (NNT 12), 6 mth (RR 0.70; 95%CI 0.50 to 0.98) (NNT 14) but not at 12 mth postoperatively (McNicol 2014 **Level I**, 14 RCTs [IV route], n=1,586) (11 RCTs overlap); such beneficial effects were not found with epidural administration of ketamine (3 RCTs, n=302). A subsequent meta-analysis found a benefit only at one mth, but is based on a much smaller number of included RCTs and speculates about the potential benefits of ketamine infusion >72 h and the role of epidural administration (Klatt 2015 **Level I** [PRISMA], 10 RCTs, n=784) (6 RCTs overlap with Chaparro 2013, all 10 RCTs overlap with McNicol 2014).

Ketamine has an effect on the regulation of inflammation by inhibiting inflammatory cell recruitment, cytokine production and downregulating inflammatory mediators (Loix 2011 **NR**). Intraoperative administration of ketamine has an inhibitory effect on the early postoperative IL-6 inflammatory response (MD -71 pg/mL; 95%CI -101 to -41) (Dale 2012 **Level I** [PRISMA], 6 RCTs, n=331).

Other acute pain indications

IV ketamine pretreatment reduces pain from propofol injection vs no pretreatment (OR 0.52; 95%CI 0.46 to 0.57) (Jalota 2011 **Level I**, 7 RCTs, n=910).

Ketamine has also some analgesic efficacy in burns patients (McGuinness 2011 **Level I**, 4 RCTs, n=67) (see also Section 8.5).

In the ICU, ketamine acts as a potent analgesic, sedative agent and bronchodilator with positive effects on haemodynamics (Patanwala 2017 **Level IV SR** [PRISMA], 6 RCTs, n=223 & 6 studies).

See also Section 8.10.5.5.

Low dose ketamine 0.1 to 0.3 mg/kg IV is considered a safe and efficacious analgesic in the ED either as single therapy or in combination with IV morphine 0.1 mg/kg (Karlow 2018 **Level I** [PRISMA], 3 RCTs, n=261; Ghate 2018 **Level IV SR** [PRISMA], 6 RCTs, n=544 & 2 studies, n=65) (2 RCTs overlap). See also Section 8.11.1.4.

Ketamine is also a safe and effective analgesic for pain due to trauma in the prehospital setting (Jennings 2011 **Level IV SR**, 2 RCTs & 4 studies, n=340). See also Section 8.12.2.4.

Guidelines for the use of ketamine infusions in acute pain support its use in painful surgery, for opioid-dependent or opioid-tolerant patients undergoing surgery or with acute or chronic sickle cell pain and possibly for patients with sleep apnoea to limit opioid use (Schwenk 2018 **GL**).

Adverse effects with short-term systemic administration of ketamine

Overall, CNS adverse events (eg hallucinations and nightmares) were increased vs placebo in 52 studies, while 53 studies reported no increase (Brinck 2018 **Level I** [Cochrane], 130 RCTs, n=8,341). Pooled incidence of CNS adverse effects is not increased (RR 1.2; 95%CI 0.95 to 1.4) (105 RCTs, n=6,538). The incidence of hallucinations is reported as not increased when ketamine is combined with the opioid in a PCA pump (OR 1.16; 98%CI 0.47 to 2.79) (7 RCTs, n=690) (Assouline 2016 **Level I** [PRISMA], 19 RCTS, n=1,453).

The incidence can be reduced with a gradual dose increase (Okamoto 2013 **Level IV**, n=46). For IV administration, slow IV infusion of 0.3 mg/kg ketamine resulted in lower rates of CNS adverse effects than IV bolus injection (Clattenburg 2018 **Level II**, n=62, JS 5; Motov 2017 **Level II**, n=48, JS 5).

Contrary to common beliefs, IV ketamine does not increase intracranial pressure or reduce cranial perfusion pressure vs opioids (Wang 2014 **Level I**, 5 RCTs, n=198). This is also true for patients with nontraumatic neurological diseases (Zeiler 2014 **Level IV SR**, 16 studies, n=127 [adult] & n=87 [children]).

Chronic pain

Ketamine has efficacy in treatment of chronic neuropathic pain (15 of 23 RCTs positive [ketamine]) (Aiyer 2018 **Level I** [PRISMA], 58 RCTs, n unspecified).

IV ketamine is superior to placebo and comparable to IV lidocaine and IV alfentanil in the treatment of pain after SCI (Teasell 2010 **Level I**, 2 RCTs [ketamine], n=19). See also Section 8.2.1.

IV ketamine reduces phantom limb pain short-term with some possible long-term benefit (Alviar 2016 **Level I** [Cochrane], 2 RCTs [ketamine], n=31; McCormick 2014 **Level I**, 4 RCTs, n=107) (2 RCTs overlap). See also Section 8.1.5.2.

Ketamine by various routes of administration (IV, oral, topical) is also a successful treatment for Complex Regional Pain Syndrome (CRPS) based on limited evidence (Zhao 2018 **Level III-2 SR**, 1 RCT & 14 studies, n=258; Azari 2012 **Level IV SR**, 3 RCTS & 16 studies, n unspecified).

In view of the risks described below, current use of ketamine to treat chronic pain should be restricted to therapy-resistant severe neuropathic pain (Niesters 2014a **NR**; Tawfic 2013 **NR**); recent evidence-based guidelines outline a cautious approach with possibly best indications in spinal cord injury pain and CRPS (Cohen 2018 **GL**). A draft of a practice guideline has been published by FPMANZCA (FPMANZCA 2020 **GL**).

Cancer pain

Ketamine is a viable therapeutic option in treating refractory cancer pain despite limitations in the data available (Bredlau 2013 **Level IV SR**, 5 RCTs and 6 studies, n=483); however, the largest RCT included showed no clinical benefit when ketamine was added to opioids for cancer-pain treatment (Hardy 2012 **Level II**, n=187, JS 5). A subsequent Cochrane review of ketamine as an adjunct to opioids in cancer pain excluded most of the RCTs considered above and regards the current evidence as insufficient to assess the benefits and harms of ketamine as an adjuvant to

opioids for the relief of refractory cancer pain (Bell 2017 **Level I** [Cochrane] 3 RCTs, n=217). See also Section 8.9.3.3.

Adverse effects with long-term systemic administration of ketamine

Ketamine has an abuse potential (Morgan 2012 **NR**) with highest abuse rates in South-East Asia and China (Liu 2016 **NR**; Kalsi 2011 **NR**). Heavy use of ketamine has consequences on cognitive and emotional function (Morgan 2010 **NR**) and there are increasing consequences including traffic accidents when under its influence (Liu 2016 **NR**). Acute toxicity leads to confusion, drowsiness, or transient loss of consciousness, while symptoms of chronic toxicity are "ketamine cystitis" and chronic abdominal pain (Yiu-Cheung 2012 **NR**) as well as hepatotoxicity. The latter issues need to be considered when using ketamine in a chronic setting therapeutically (Bell 2012 **NR**) and may limit its indications (Cohen 2018 **GL**; Niesters 2014a **NR**).

Other routes of systemic administration and bioavailability

Ketamine is most commonly administered as a continuous low-dose IV infusion, however SC infusion is also used, especially in palliative care, with a bioavailability (similar to IM) of approximately 90% (Clements 1982 **PK**). Sublingual (SL), IN and TD routes have also been used for acute pain management (Peltoniemi 2016 **NR PK**) (see Chapter 5).

A pharmacokinetic study in healthy volunteers calculated the bioavailability of oral ketamine as 20%, SL 30% and IN 45%; the pharmacodynamic effects of the active metabolite norketamine were thought to be of potential significance (Yanagihara 2003 **PK**). The bioavailability of a 25 mg ketamine lozenge was 24% when given by both SL and oral routes; peak plasma levels were seen at 30 min and 120 min respectively and terminal half-lives were similar at around 5 h (Chong 2009 **PK**). For both routes, norketamine concentrations exceeded the concentrations of ketamine and, given its pharmacological activity profile, norketamine is therefore likely to be a major contributor to the overall analgesic effect. A SL ketamine wafer achieved rapid absorption with a bioavailability of 29% (Rolan 2014 **PK**).

4.6.1.2 | Dextromethorphan

In a meta-analysis of experimental studies (oral administration 11 RCTs; IV administration 1 RCT) (mean dose 0.92 mg/kg [range 0.17 to 2.71 mg/kg]), dextromethorphan has no effect on area of hyperalgesia (4 RCTs) nor on pain intensity (SMD 0.07; 95%CI -0.21 to 0.34) (10 RCTs, n=132) (Thompson 2019 **Level I EH** [(PRISMA]), 70 RCTs, n=1,069). However, PO dextromethorphan 30 mg in a model of primary and secondary hyperalgesia (freeze-injury pain model) had antihyperalgesic effects on both phenomena, while it has no anti-nociceptive effect in areas of healthy skin (Martin 2019a **Level II EH**, n=20, JS 5).

In postoperative pain, dextromethorphan reduces pain at 1 h (MD -1.60/10; 95%CI -1.89 to -1.31) (13 RCTs, n=884), 4 to 6 h and 24 h as well as opioid requirements (IV MED MD -10.51 mg; 95%CI -16.48 to -4.53) (14 RCTs, n=848) (King 2016 **Level I**, 21 RCTs, n=1,520).

As dextromethorphan is metabolised by CYP2D6 to the inactive metabolite dextrorphan, the effect of the CYP2D6 inhibitor quinidine before PO dextromethorphan 50 mg administration has been assessed in knee ligament surgery (Ehret 2013 **Level II**, n=48, JS 4). Dextromethorphan concentrations were higher after quinidine than after placebo and resulted in lower rescue analgesia requirements. PO dextromethorphan/quinidine provided superior pain relief vs placebo in diabetic polyneuropathy (Shaibani 2012 **Level II**, n=379, JS 3).

PO dextromethorphan 120 to 180 mg reduces chronic phantom limb pain vs placebo (Alviar 2016 **Level I** [Cochrane], 1 RCT [dextromethorphan]: Ben Abraham 2003 **Level II**, n=10 [triple phase cross over], JS 3).

Dextromethorphan may have efficacy in chronic neuropathic pain (4 of 6 RCTs), possibly with less benefit in PHN (Aiyer 2018 **Level I** [PRISMA], 58 RCTs, n unspecified). After IV ketamine treatment of neuropathic pain, PO dextromethorphan extended treatment effects for one mth vs placebo (Martin 2019b **Level II**, n=60, JS 4).

PO dextromethorphan therapy (titrated to 480 mg/d) for 5 wk was not effective in reversing methadone-induced hyperalgesia (Compton 2008 **Level III-1**).

4.6.1.3 | Magnesium

Magnesium is regarded as an NMDA-receptor antagonist as its primary mechanism of action; however, magnesium also blocks calcium channels and modulates potassium channels and may have an antinociceptive effect through the activation of the nitric oxide (NO) pathway (Srebro 2016 **NR**). It has also anti-inflammatory effects by reducing IL-6 and TNF-alpha plasma levels in the postoperative setting, which might contribute to the effects described here (Aryana 2014 **Level II**, n=90, JS 4).

Magnesium IV as an adjunct to morphine IV analgesia has an opioid-sparing effect (MED WMD -7.4 mg; 95%CI -9.4 to -5.4) without reducing PONV but with improved pain scores at 4 to 6 h (Murphy 2013 **Level I**, 22 RCTs, n=1,177). This is in line with two parallel meta-analyses: one also describes an opioid-sparing effect (MED WMD -10.52 mg; 99%CI -13.50 to -7.54) and reduction of pain at rest (4 and 24 h) and on movement (24 h) (De Oliveira 2013c **Level I** [PRISMA], 20 RCTs, n=1,257) (most RCTs overlap); the second draws similar conclusions and found no significant adverse effects (Albrecht 2013 **Level I**, 25 RCTs, n=1,461) (most RCTs overlap).

Subsequent to these three meta-analyses, multiple further meta-analyses and RCTs exploring the same issues after different types of surgery or anaesthesia with significant overlap of included RCTs conclude:

- After orthopaedic surgery, IV magnesium reduces postoperative analgesic consumption, PONV and shivering (Peng 2018 **Level I** [PRISMA], 11 RCTs, n=535). Pain intensity is reduced in 6 of 11 RCTs;
- After laparoscopic cholecystectomy, IV magnesium reduces pain intensity at 2 and 8 h and analgesic consumption (Chen 2018a **Level I**, 4 RCTs, n=463);
- After Caesarean section, a qualitative systematic review showed that IV magnesium may reduce postoperative pain intensity (McKeown 2017 **Level I**, 7 RCTs, n=530);
- In paediatric tonsillectomy, magnesium administered by local infiltration or IV (bolus ± infusion) has analgesic effects (Xie 2017 **Level I** [PRISMA], 10 RCTs n=665; Cho 2018 **Level I** [PRISMA], 10 RCTs, n=615) (9 RCTs overlap). See also Section 10.4.7.2;
- After spinal anaesthesia, IV magnesium prolonged the duration of sensory block for abdominal hysterectomy and reduced postoperative pain scores in the first 4 h after surgery (Kahraman 2014 **Level II**, n=40, JS 5). After spinal anaesthesia for umbilical hernia repair, IV magnesium prolonged time to first rescue analgesia and was opioid-sparing in the first 24 h after surgery (Kumar 2013 **Level II**, n=60, JS 5). This was also found after spinal anaesthesia for THA, where IV magnesium reduced postoperative pain scores and opioid requirements for 48 h, while increasing serum magnesium concentrations (Hwang 2010 **Level II**, n=40, JS 5). However, IV magnesium did not change magnesium concentrations in the CSF (Mercieri 2012 **Level II**, n=45, JS 3).

Subsequent to these meta-analyses, multiple further RCTs studying the same issue have been performed; overall the outcomes from these studies do not affect the existing conclusions and they are therefore not referenced here.

Magnesium reduces the development of acute tolerance/OIH associated with remifentanil use (Wu 2015 **Level I** [QUOROM], 5 RCTs [magnesium], n=729).

Combining ketamine with IV magnesium reduced 48 h morphine consumption by 30% vs ketamine alone after scoliosis surgery (Jabbour 2014 **Level II**, n=50, JS 5). While pain scores were not different, sleep quality and patient satisfaction were improved with the combination treatment.

IV magnesium may also have other beneficial effects on postoperative recovery; after segmental mastectomy in an outpatient setting, patients receiving IV magnesium had better quality of recovery (QoR) scores at 24 h vs saline (MD 24/40; 99%CI 3 to 33) and reduced opioid requirements after discharge (De Oliveira 2013a **Level II**, n=50, JS 5). There were significant linear relationships between the postoperative systemic magnesium concentrations and 24 h postoperative QoR scores as well as with pain burden (inverse).

IV magnesium sulphate 4 g attenuated tourniquet pain in healthy volunteers (Satsumae 2013 **Level II EH**, n=24, JS 5).

IV magnesium in treatment of acute migraine attacks vs placebo or active comparators is superior at time points 15-45 min (OR 0.23; 95%CI 0.09 to 0.58) (6 RCTs), 2 h (OR 0.20; 95%CI 0.10 to 0.40) [5 RCTs] and 24 h (OR 0.25; 95%CI 0.10 to 0.60) [4 RCTs] (Chiu 2016 **Level I** [PRISMA], 11 RCTs, n=948).

IV magnesium was non-inferior to IV dexamethasone for the prevention of postoperative sore throat after lumbar spinal surgery in the prone position (Park 2015 **Level II**, n=146, JS 5).

IV magnesium has only at best anecdotal evidence for an effect on any outcome of Irukandji syndrome, caused by jellyfish sting in Northern Queensland (Rathbone 2017 **Level IV SR** 1 RCT & 8 studies, [n=291 Mg recipients]); the only RCT included showed no beneficial effect (McCullagh 2012 **Level II**, n=39, JS 5).

Oral magnesium daily for 4 wk had no beneficial effect in the treatment of neuropathic pain (Pickering 2011 **Level II**, n=45, JS 5). IV or oral magnesium therapy has been shown to have no effect on reducing painful crisis and hospital LOS in treating sickle cell disease (Than 2019 **Level I** [Cochrane], 5 RCTs, n=386). Oral magnesium (65 mg elemental/d) was also not improving analgesia when added in cancer pain patients treated with oral morphine (Baaklini 2017 **Level II**, n=43, JS 5). IV magnesium vs IV lidocaine provided inferior analgesia for propofol injection pain; IV magnesium/IV lidocaine offered no advantage over IV lidocaine alone (Galgon 2015 **Level II**, n=200, JS 5).

See Section 5.7.1.4 for magnesium use via the IT route and Section 10.4.7.2 for paediatric use.

4.6.1.4 | Amantadine and memantine

A bolus dose of IV amantadine had no effect on postoperative analgesia after abdominal hysterectomy (Gottschalk 2001 **Level II**, n=30, JS 4). However, after radical prostatectomy, perioperative oral amantadine reduced morphine consumption, wound pain on palpation and bladder spasms (Snijdelaar 2004 **Level II**, n=24, JS 4). After spinal surgery, premedication with oral amantadine reduced not only intraoperative fentanyl requirements but also postoperative pain intensity and opioid requirements in the first 48 h by 25% (Bujak-Gizycka 2012 **Level II**, n=60, JS 5).

Oral memantine shows analgesic effects in acute [4 studies, n=24], but not in chronic phantom limb pain [4 RCTs, n=104] (Loy 2016 **Level IV SR**, 5 RCTs, 2 case series & 1 case report, n=128).

Memantine administered perioperatively was not effective in reducing the incidence of postmastectomy pain syndrome (Eisenberg 2007 **Level II**, n=22, JS 5); however, a subsequent trial showed a reduction in postmastectomy pain, analgesic consumption and better emotional state at 3 mths (Morel 2016 **Level II**, n=43, JS 5).

Memantine may have some benefits in neuropathic pain (Pickering 2018 **NR**).

KEY MESSAGES

1. Perioperative IV ketamine reduces opioid consumption, pain intensity and postoperative nausea and vomiting compared to placebo (**S**) (**Level I** [Cochrane Review]); similar outcomes are achieved when ketamine is added to an opioid in a PCA pump (**S**) (**Level I** [PRISMA]).
2. Perioperative IV ketamine reduces the incidence of chronic postsurgical pain in selected procedures (**S**) (**Level I** [Cochrane Review]).
3. NMDA-receptor antagonists reduce the development of acute tolerance/opioid-induced hyperalgesia associated with remifentanil use (**S**) (**Level I** [PRISMA]).
4. IV ketamine reduces ischaemic pain intensity in critical limb ischaemia (**N**) (**Level I** [PRISMA]).
5. IV magnesium as an adjunct to morphine analgesia has an opioid-sparing effect and improves pain scores (**S**) (**Level I** [PRISMA]).
6. IV magnesium is effective in treatment of acute migraine attacks (**N**) (**Level I** [PRISMA]).
7. IV ketamine is effective in the treatment of neuropathic pain following spinal cord injury (**U**) (**Level I**).
8. Morphine/ketamine compared with higher doses of morphine alone improves analgesia and reduces sedation and postoperative nausea and vomiting in postoperative patients (**U**) (**Level I**).
9. IV ketamine does not increase intracranial pressure or reduce cranial perfusion pressure compared to opioids (**U**) (**Level I**).
10. Perioperative dextromethorphan reduces opioid consumption and pain intensity compared to placebo (**N**) (**Level I**)
11. Ketamine is a safe and effective analgesic in the prehospital setting (**U**) (**Level II**).
12. Ketamine reduces postoperative pain and opioid requirements in opioid-tolerant patients (**S**) (**Level II**).
13. IV magnesium extends the duration of sensory block with spinal anaesthesia and reduces subsequent postoperative pain (**N**) (**Level II**).

The following tick box represents conclusions based on clinical experience and expert opinion:

☑ Increasing rates of ketamine abuse are reported, in particular from South-East Asia and China (**S**).

☑ Ketamine toxicity leads to cognitive impairment and abuse to chronic organ toxicity (bladder, liver) (**U**).

4.6.2 | Regional NMDA-receptor antagonists

4.6.2.1 | Ketamine

Neuraxial

Some commercially available preparations of ketamine have a low pH (3.5 to 5.5) and contain an untested preservative (benzethonium chloride) and thus cannot be recommended for IT use in humans (de Lima 2000 **NR**; Hodgson 1999 **NR**). Subarachnoid administration of S(+)-ketamine without preservative caused histological lesions on the spinal cord and meninges in dogs (Gomes 2011 **BS**). Concerns of local neurotoxicity *in vitro* continue to limit the use of neuraxial ketamine, in particular when combined with lidocaine (Werdehausen 2011 **NR**).

The addition of IT racemic ketamine to bupivacaine did not prolong postoperative analgesia or reduce analgesic requirements but led to significantly more nausea and vomiting, sedation, dizziness, nystagmus and "strange feelings" (Kathirvel 2000 **Level II**, n=30, JS 2). IT S(+)-ketamine with bupivacaine for Caesarean section decreased time to onset and increased spread of the block but did not prolong duration vs fentanyl (Unlugenc 2006 **Level II**, n=90, JS 5). However, IT ketamine/morphine/bupivacine was superior to IT morphine/bupivacaine or IT ketamine/bupivacaine for major abdominal cancer surgery with regard to pain intensity, opioid requirements and time to rescue analgesia (Abd El-Rahman 2018b **Level II**, n=90, JS 3).

The combination of epidural ketamine with epidural opioid-based (±local anaesthetic) solutions improves pain relief and may reduce overall opioid requirements without increasing the incidence of adverse effects (Subramaniam 2004 **Level I,** 8 RCTs [epidural], n=513; Walker 2002 **Level I**, 4 RCTs [epidural], n=211). Ketamine IV may be as effective as epidural ketamine in reducing hyperalgesia. Epidural racemic ketamine improved early postoperative analgesia when used with bupivacaine for lower limb amputations, although pain at 1 y was not different; perioperative opioids were not used (Wilson 2008 **Level II**, n=47, JS 5).

Ketamine 0.25 to 0.5 mg/kg added to caudal local anaesthetic prolongs time to first analgesic request by a median difference of 5.6 h without prolonged motor block (Schnabel 2011 **Level I** [PRISMA], 13 RCTs, n=884); 0.5 mg/kg increases block duration and reduces postoperative analgesic requirements (Dahmani 2011 **Level I** [QUORUM], 10 RCTs [caudal], n=686) (6 RCT overlap). Although some adverse effects are more frequent in the ketamine group (eg sedation), there was no significant difference to placebo. Caudal ketamine prolonged analgesia when administered with caudal bupivacaine but was less effective than midazolam or neostigmine as caudal adjuvants (Kumar 2005 **Level II**, n=80, JS 5). See also Section 10.4.7.1 and 10.6.3.3.

Peripheral sites

Use of ketamine alone or with local anaesthesia for PNB or local infiltration shows contradictory results, possibly due to systemic effects. Systemic comparators are not included in most RCTs.

No analgesic benefit for PNB was shown in brachial plexus block for arm surgery (Lee 2002 **Level II**, n=51, JS 4), IA injection (where IV ketamine provided better analgesia) (Rosseland 2003 **Level II**, n=77, JS 5) or wound infiltration such as following Caesarean section (Zohar 2002 **Level II**, n=50, JS 5) or inguinal hernia repair (Clerc 2005 **Level II**, n=36, JS 2). Adding ketamine to lidocaine IVRA did not result in better pain relief vs IV ketamine (Viscomi 2009 **Level II**, n=36, JS 4). When added to lidocaine for axillary brachial plexus block, ketamine 50 mg only modestly increased duration of sensory and motor block vs placebo (114.8 ± 12.5 min v. 106.2 ± 7.9 min), much less than dexamethasone (174.4 ± 13.1 min) (Zaman 2017 **Level II**, n=78, JS 5). Significant nystagmus, increased heart rate and blood pressure were observed in the ketamine group.

However, in pectoral block for mastectomy, ketamine 1 mg/kg added to bupivacaine 0.25% 30 mL vs bupivacaine alone prolonged time to first analgesic request and reduced opioid

requirements (Othman 2016 **Level II**, n=60, JS 3). IA ketamine 1 mg/kg provided analgesia superior to placebo, but inferior to IA ketamine 0.5 mg/kg in levobupivacaine 0.25% 20 mL after arthroscopic meniscectomy (Isik 2015 **Level II**, n=6, JS 3). In circumcision, pain scores were lower with preincisional ketamine vs saline (Tan 2007 **Level II**, n=40, JS 4). Adding ketamine 2 mg/kg to bupivacaine 0.25% 40 mL resulted in comparable analgesia to adding dexmedetomidine 2 mcg/kg to local wound infiltration after abdominal hysterectomy; both mixtures were superior to bupivacaine alone (Mohamed 2018 **Level II**, n=90, JS 5). Following thyroidectomy, wound infiltration with ketamine 1 mg/kg provided superior analgesia to IM ketamine 1 mg/kg and both groups were superior to placebo (Abd El-Rahman 2018a **Level II**, n=90, JS 5). After rhinoplasty, the addition of ketamine 0.5 mg/kg to lidocaine for submucosal infiltration provided superior analgesia to lidocaine alone with both being superior to placebo (Sanli 2016 **Level II**, n=90, JS 4).

Topical administration

Ketamine gargle vs placebo or no treatment reduces the incidence of postoperative sore throat up to 24 h postoperatively (RR 0.42 to 0.52 over time points 0 to 24 h) based on high-quality evidence (Mayhood 2015 **Level I** [PRISMA], 5 RCTs, n=291); systemic absorption is an unknown factor.

After mandibular molar extraction, topical administration (to the extraction sockets on resorbable gelatin sponges) of ketamine 0.5 mg/kg vs tramadol 1 mg/kg and vs saline achieved the lowest pain scores and rescue analgesic use for the first 24 h after surgery (Gonul 2015 **Level II**, n=90, JS 2). In a similar setting, the addition of ketamine 0.3 mg/kg to lidocaine 2% for the local anaesthesia (Inferior alveolar, lingual and buccal nerve blocks) reduced pain at 1 and 4 h and facial swelling at 1 d, while improving mouth opening up to 7 d (Kumar 2015 **Level II**, n=60, JS 1).

Topical ketamine-amitriptyline did not reduce chemotherapy-induced peripheral neuropathic pain (Gewandter 2014 **Level II**, n=462, JS 5).

4.6.2.2 | Magnesium

Magnesium influences neuronal calcium influx and may exert an analgesic effect on NMDA receptors in the spinal cord (Bailard 2014 **NR**). The long-term effects of perineural or neuraxial magnesium have not been clarified.

Neuraxial magnesium for Caesarean section prolongs duration of sensory and motor block, time to first rescue analgesic requirement and reduces pain intensity and analgesic requirements without an effect on PONV, pruritus, hypotension, shivering or sedation (Wang 2017a **Level I** [PRISMA], 9 RCTs, n=827).

IT magnesium combined with lipophilic opioid, with or without local anaesthetic, prolongs the duration of spinal analgesia in nonobstetric populations also (SMD 1.38; 95%CI 0.6 to 2.11) (Morrison 2013 **Level I**, 15 RCTs, n=980). There is no increase in adverse effects. There was a high degree of heterogeneity, including magnesium dose, making any firm conclusion difficult. This was supported by a parallel meta-analysis (Pascual-Ramirez 2013 **Level I**, 12 RCTs, n=817) (9 RCTs overlap).

Epidural magnesium 50 mg added to bupivacaine 12.5 mg/morphine 2 mg improved analgesia after thoracotomy for the first 4 h and reduced rescue analgesia requirements vs placebo/ bupivacaine 12.5 mg/morphine 2 mg (Farzanegan 2018 **Level III-1**, n=80).

Magnesium added to perineural block prolongs analgesia (MD 125 min; 95%CI 65 to 184), sensory and motor block (Li 2016b **Level I** [PRISMA], 7 RCTs, n=493). Subsequent RCTs have confirmed these findings in femoral nerve block in the prehospital setting (Jebali 2018 **Level II**, n=48, JS 4), TAPB after abdominal hysterectomy (Abd-Elsalam 2017 **Level II**, n=60, JS 4) and sciatic nerve block for toe amputation (Sun 2017a **Level II**, n=70, JS 5). The mechanism of action of magnesium at perineural sites is uncertain and safety and outcome data are limited suggesting caution should be exercised (Bailard 2014 **NR**).

Oral topical magnesium reduces postoperative sore throat incidence (RR 0.22; 95%CI 0.12 to 0.39 [at 24 h postoperatively]) and severity after orotracheal intubation (Singh 2019 **Level I** [PRISMA] 7 RCTs, n=726).

IA magnesium versus placebo after arthroscopic surgery improves pain control [5 RCTs] and prolongs time to first analgesic request [4 RCTs] (Zeng 2016 **Level I** [PRISMA], 8 RCTs, n=513). The combination magnesium/bupivacaine versus bupivacaine only prolongs time to first analgesic request only [4 RCTs]. Magnesium vs bupivacaine results in similar analgesia [3 RCTs]. No relevant adverse effects were described in any study. Magnesium/levobupivacaine vs levobupivacaine alone and vs placebo after arthroscopic meniscectomy reduced pain intensity and rescue analgesic requirements (Kizilcik 2017 **Level II**, n=96, JS 4).

Magnesium added to lidocaine IVRA improved intra and postoperative analgesia and tourniquet tolerance (Kashefi 2008 **Level II**, n=40, JS 4; Turan 2005 **Level II**, n=30, JS 4).

KEY MESSAGES

1. Neuraxial magnesium reduces pain intensity and analgesic requirements after Caesarean section (**N**) (**Level I** [PRISMA].
2. Oral topical magnesium or ketamine (as gargle or lozenge) reduce the incidence of postoperative sore throat (**N**) (**Level I** [PRISMA].
3. Intra-articular magnesium improves analgesia after arthroscopic surgery compared to placebo (**N**) (**Level I** [PRISMA].
4. Magnesium added to local anaesthetics in peripheral nerve blocks prolongs sensory block and analgesic effects (**N**) (**Level I** [PRISMA].
5. Epidural ketamine (without preservative) added to opioid-based epidural analgesia regimens improves pain relief without reducing adverse effects (**U**) (**Level I**).
6. Caudal ketamine in children, in combination with local anaesthetic or as the sole medication, improved and prolonged analgesia with few adverse effects (**U**) (**Level I**).

The following tick box represents conclusions based on clinical experience and expert opinion:

☑ Variable results for regional and topical administration of ketamine and magnesium may reflect systemic effects (**N**).

4.7 | Antidepressant medicines

4.7.1 | Acute pain

There are limited published data on the use of antidepressants in the management of acute nociceptive and neuropathic pain.

4.7.1.1 | Tricyclic antidepressants

Amitriptyline given to patients with acute herpes zoster reduced the incidence of postherpetic neuralgia at 6 mth (Bowsher 1997 **Level II**, n=80, JS 5). Amitriptyline given after orthopaedic surgery did not improve opioid analgesia vs placebo (Kerrick 1993 **Level II**, n=28, JS 5).

Desipramine, but not amitriptyline, given prior to dental surgery increased and prolonged the analgesic effect of a single dose of morphine, but both had no analgesic effect on their own (Levine 1986 **Level II**, n=30, JS 3). When used for a fortnight in experimental pain, desipramine had no effect on pain or hyperalgesia (Wallace 2002 **Level II EH**, n=13, JS 4).

4.7.1.2 | Serotonin–norepinephrine-reuptake inhibitors

After TKA, duloxetine 60 mg (preoperative and on POD 1) had an opioid-sparing effect (35%) vs placebo (Ho 2010 **Level II**, n=50, JS 5). In patients with an increased Central Sensitisation Inventory (CSI), duloxetine 30 mg (before surgery and daily for 6 wk thereafter) improved pain control, physical and emotional functioning and patient satisfaction with analgesia for 2 to 12 wk after TKA vs control (Koh 2019 **Level II**, n=40, JS 5). However, duloxetine 60 mg (for 2 wk) had no effect on subacute pain with ambulation after TKA vs placebo, when used as a component of a multimodal analgesia regimen (YaDeau 2016 **Level II**, n=106, JS 5). Venlafaxine 37.5 mg was as effective as gabapentin 300 mg in reducing pain at rest and analgesic requirements, when given perioperatively for 10 d in mastectomy vs placebo (Amr 2010 **Level II**, n=150, JS 4). Venlafaxine was inferior to gabapentin in reducing pain on movement; however, at 6 mth postoperatively, fewer patients in the venlafaxine group reported chronic pain or analgesic use.

4.7.1.3 | Selective serotonin-reuptake inhibitors

In patients with high preoperative pain catastrophising scale (PCS) scores, escitalopram 10 mg (preoperatively and for 6 d postoperatively) did not reduce pain on mobilisation at 24 h after total knee replacement vs placebo (Lunn 2015 **Level II**, n=120, JS 5). On POD 2 to 6, pain at rest and mobilisation was lower in the treatment group.

4.7.2 | Chronic pain

Treatment guidelines for chronic neuropathic pain recommend TCAs and SNRIs, but not SSRIs, as first-line treatment in this indication (Finnerup 2015 **GL Level I** [PRISMA], 229 RCTs, n unspecified).

4.7.2.1 | Tricyclic antidepressants

While TCAs are seen as the first-line therapy in neuropathic pain treatment, data are of disappointing quality. None of the supportive studies are of high quality and low risk of bias (Moore 2015a **Level I** [Cochrane], 17 RCTs, n=1,342). Adverse events are increased with amitriptyline (RR 1.5; 95%CI 1.3 to 1.8) (NNH 5.2; 95%CI 3.6 to 9.1). Similarly, imipramine (Hearn 2014 **Level I**

[Cochrane], 5 RCTs, n=168) and nortriptyline are supported only by very low-quality evidence in this indication (Derry 2015b **Level I** [Cochrane], 6 RCTs, n=310). For fibromyalgia, the evidence is also low quality for amitriptyline (NNT 4.1 for ≥50% pain relief and NNH 3.3) (Moore 2015a **Level I** [Cochrane] 9 RCTs, n=649).

In elderly patients, TCAs should possibly be avoided as the use of medications with anticholinergic activity increases risk of cognitive impairment and even mortality in this patient group (Fox 2011 **Level III-2**, n=13,004).

4.7.2.2 | Serotonin–norepinephrine-reuptake inhibitors

Duloxetine 60 to 120 mg/d provides analgesia for diabetic neuropathy (Lunn 2014 **Level I** [Cochrane], 8 RCTs, n=2,728; Hossain 2016 **Level I** [PRISMA], 8 RCTs, n=4,084) (7 RCTs overlap). RCTs supporting the use of venlafaxine in neuropathic pain have a high risk of bias (Gallagher 2015 **Level I** [Cochrane], 6 RCTs, n=460; Aiyer 2017 **Level I** [PRISMA], 13 RCTs, n=851) (6 RCTs overlap). There is no evidence for an effect of milnacipran in neuropathic pain (Derry 2015b **Level I** [Cochrane], 1 unpublished RCT: [NCT01225068], n=40).

SNRIs also have limited analgesic effects in fibromyalgia (NNT 5-11 vs placebo depending on outcome assessed) (Welsch 2018 **Level I** [Cochrane], 18 RCTs, n=7,903). This has been confirmed specifically for milnacipran (Cording 2015 **Level I** [Cochrane], 6 RCTs, n=4,238). Duloxetine and milnacipran have comparable efficacy in this indication (Lee 2016 **Level I** [NMA], 9 RCTs, n=5,140) (4 RCTs overlap).

4.7.2.3 | Selective serotonin-reuptake inhibitors

There is only limited evidence for the effectiveness of SSRIs in neuropathic pain (Saarto 2007 **Level I** [Cochrane] 61 RCTs, n=3,293). Similarly, there is only biased evidence that SSRIs are superior to placebo in treating the key symptoms of fibromyalgia: namely pain, fatigue and sleep problems (Walitt 2015 **Level I** [Cochrane], 7 RCTs, n=383).

4.7.3 | Specific pain conditions

In postherpetic neuralgia, TCAs are less effective than pregabalin and 5% lidocaine medicated plaster (Snedecor 2014 **Level I**, 28 RCTs, n=4,317). In diabetic polyneuropathy, amitriptyline is the least effective of the medications studied with the worst benefit-risk balance, while venlafaxine and duloxetine were the superior antidepressants here (Rudroju 2013 **Level I**, 21 RCTs, n=4,219).

In fibromyalgia, amitriptyline (NNT 4.9) and the serotonin–norepinephrine-reuptake inhibitors (SNRIs) duloxetine and milnacipran (NNT 10) were the most effective antidepressants (Hauser 2012 **Level I**, 35 RCTs, n=6,766).

In chronic headaches, antidepressants are effective in treatment and prophylaxis with better efficacy of TCAs than SSRIs (Jackson 2017 **Level I** [PRISMA], 21 RCTs, n=2,751; Jackson 2010 **Level I** [PRISMA], 37 RCTs, n=3,176). Use of SSRIs and SNRIs for migraine prophylaxis (Banzi 2015 **Level I** [Cochrane], 12 RCTs, n=585) and prevention of chronic tension type headache is not supported by evidence (Banzi 2015 **Level I** [Cochrane], 8 RCTs, n=412).

In chronic low-back pain, antidepressants neither improve pain nor depression (Urquhart 2008 **Level I** [Cochrane], 10 RCTs, n=706); this was confirmed in a subsequent systematic review of pharmacological interventions in this indication (Kuijpers 2011 **Level I**, 5 RCTs, n=303). However, these results are challenged as they did not differentiate between different antidepressants; SNRIs like duloxetine (Williamson 2014 **Level I**, 3 RCTs, n=982) and TCAs may be effective, while SSRIs are not (Staiger 2003 **Level I**, 7 RCTs, n=440).

There is only poor evidence for an analgesic effect of any antidepressant in orofacial pain disorders (Martin 2012 **Level I**, 6 RCTs, n=208) and for an analgesic effect of TCAs or SSRIs in rheumatoid arthritis (Richards 2011 **Level I** [Cochrane], 8 RCTs, n=652).

Duloxetine improves WOMAC scores in osteoarthritis to an extent comparable to other first-line treatments for osteoarthritis (eg NSAIDs) (Myers 2014 **Level I**, 3 RCTs, n=775). Duloxetine results in a greater reduction in pain, improved function and patient rated impression of improvement for treatment of osteoarthritis of the knee after 10 to 13 wk of treatment (Wang 2015b **Level I**, 3 RCTs, n=1,011) (2 RCTs overlap). Therefore, duloxetine is a recommended treatment in updated guidelines for osteoarthritis (eg McAlindon 2014 **GL**).

Currently the use of antidepressants for acute neuropathic pain is mainly based on extrapolation of the above data. Clinical experience in chronic pain suggests that TCAs should be started at low doses (eg amitriptyline 5 to 10 mg at night) and subsequent doses increased slowly if needed, in order to minimise the incidence of adverse effects.

KEY MESSAGES

1. In chronic neuropathic pain and fibromyalgia, tricyclic antidepressants and serotonin–noradrenaline-reuptake inhibitor are effective analgesics (**W**) and more effective than selective serotonin-reuptake inhibitors (**U**) (**Level I** [Cochrane Review]).
2. Tricyclic antidepressants are effective in the treatment of chronic headaches (**U**) (**Level I** [PRISMA]).
3. Duloxetine is as effective as other first-line treatments for pain and disability of osteoarthritis (**U**) (**Level I**).
4. Some antidepressants, in particular duloxetine, may be effective in the treatment of chronic low-back pain (**U**) (**Level I**).
5. Perioperative serotonin-noradrenaline reuptake inhibitors reduce acute pain and opioid requirements in a limited number of studies (**U**) (**Level II**).

The following tick boxes represent conclusions based on clinical experience and expert opinion:

☑ Based on the experience in chronic neuropathic pain states, it would seem reasonable to use tricyclic antidepressants and serotonin–noradrenaline-reuptake inhibitors in the management of acute neuropathic pain (**U**).

☑ To minimise adverse effects, it is advisable to initiate treatment with tricyclic antidepressants at low doses (**U**).

4.8 | Anticonvulsant medicines

4.8.1 | Acute pain

4.8.1.1 | Alpha-2-delta ligands (gabapentinoids)

Efficacy

Gabapentin 250 mg as the sole analgesic reduces the intensity of postoperative pain (NNT 11; 95%CI 6.4 to 35) and requirements for rescue analgesia (NNT 5.8) vs placebo (Straube 2010 **Level I** [Cochrane], 4 RCTs, n=387). This is the only anticonvulsant which has been shown to be effective in acute postoperative pain on its own; the high NNT, inferior to most analgesics used in this setting, suggests that gabapentin is clinically not useful as a sole analgesic for postoperative analgesia.

Single 100 to 1200 mg and multiple 900 to 2400 mg/d doses of gabapentin (similar to pregabalin [see below]) reduce 24 h opioid consumption (MD -7.31 mg; 95%CI -9.74 to -5.98) (73 RCTs, n=5,630), but less so when analysing only RCTs with a low risk of bias (MD -3.1 mg; 95%CI -5.6 to -0.5) (13 RCTs, n=1,362) (Fabritius 2016 **Level I** [PRISMA], 132 RCTs, n=9,498). The opioid-sparing effect is not significant as an add-on to other non-opioids in trials with low risk of bias; in these the risk of serious adverse events (SAEs) is not significantly increased (RR 1.61; 95%CI 0.91 to 2.86). Similar results were found in an earlier meta-analysis of all RCTs of prophylactic gabapentin with an opioid-sparing effect in the first 24 h (8.44 mg; 95%CI 7.26 to 9.62) and reduced postoperative pain scores at multiple time points between 1 and 24 h by 0.71/10 to 1.68/10 (Doleman 2015a **Level I**, 133 RCTs, n=8,655) (significant overlap). These effects increased with increasing pain scores in the control group suggesting more benefit in more painful surgeries. The analysis also identified reduced pre-operative anxiety, postoperative nausea, vomiting and pruritus, and increased patient satisfaction, but also increased sedation. The authors acknowledge that the absolute effects may be overestimated by publication bias and small study effects.

Single 50 to 300 mg and multiple 100 to 600 mg/d doses of pregabalin for postoperative analgesia reduce 24 h IV morphine consumption (MD 10.8 mg; 95%CI –13.19 to –8.46) (37 RCTS, n=2,423) across all RCTs assessing this outcome, but less so when analysing only RCTs with a low risk of bias (MD 5.8 mg; 95%CI -8.5 to -3.2) (11 RCTs, n=705) (Fabritius 2017 **Level I** [PRISMA], 97 RCTs, n=7,201). In low risk of bias studies, the opioid sparing effect is more pronounced when no other non-opioids are used (MD -13.7 mg; 95%CI -9.6 to -17.8) (2 RCTs, n=120) and for single dose (MD -10.1mg; 95% CI -2.4 to -18.0) (6 RCTs, n=399) more so than with multiple dosing (MD 2.4mg; 95%CI -0.5 to -4.9) (5 RCTs, n=306).

In a preceding meta-analysis, operations were classified by the authors according to association with 'pronociceptive' mechanisms (acute hyperalgesia) (eg spine surgery, joint arthroplasty, amputations) and those without such mechanisms (eg abdominal laparoscopic surgery, gynaecological procedures) (Eipe 2015 **Level I** [PRISMA], 43 RCTs, n=3,378) (39 RCTs overlap). Pregabalin 150 to 300 mg reduces pain at rest and on movement more in the pronociceptive surgical group than in the other surgical group (MD -1.09/10; 95%CI -0.37 to -1.80 vs MD -0.45/10; 95%CI 0.13 to -1.03 and MD -0.94/10; 95%CI -0.65 to -1.23 vs MD -0.31/10; 95%CI 0.15 to -0.77). Across all RCTs, there is a reduction of mean analgesic consumption by 16% (pooled ratio of means 0.84; 95%CI 0.79 to 0.91). PONV is reduced (NNT 11; 95%CI 7 to 28).

Multiple meta-analyses have looked at perioperative gabapentin and pregabalin (single and multiple doses) in specific types of surgery with significant overlap with the overarching meta-analyses described above:

- In breast cancer surgery, preoperative use of gabapentin or pregabalin reduces acute postoperative pain and opioid consumption with low to very low quality of evidence of no effect on the rate of CPSP (Rai 2017 **Level I** [PRISMA], 12 RCTs, n=516);
- After open hysterectomy, gabapentin reduces postoperative opioid consumption and pain scores (Li 2017d **Level I** [PRISMA], 14 RCTs, n=879);
- After Caesarean section, gabapentin improves pain scores on movement at 24 h (MD -11.58/100; 95%CI -23.04 to -0.12) and increases satisfaction scores, with no other benefits (Felder 2019 **Level I** [PRISMA], 6 RCTs, n=656);
- After spinal surgery, gabapentin reduces pain scores and morphine consumption over the first 24 h (Han 2017a **Level I** [PRISMA], 10 RCTs, n=827);
- After laparoscopic cholecystectomy, gabapentin decreases analgesic requirements, pain scores and PONV (Sun 2016 **Level I** [PRISMA] 12 RCTs, n=1,192); pregabalin in the same setting has similar effects, except no effect on PONV (Zhang 2017c **Level I** [PRISMA], 6 RCTs, n=434);
- After TKA and THA, a number of meta-analyses with significant overlap are published:
    - After TKA and THA, pregabalin reduces pain scores, opioid consumption and PONV (Li 2017b **Level I** [PRISMA], 7 RCTs, n=823);
    - Specifically in TKA, meta-analyses identify similar benefits with pregabalin reducing opioid requirements and PONV and pruritus, but not pain scores (Han 2017b **Level I** [PRISMA], 7 RCTs, n=962) and gabapentin reducing opioid requirements and pruritus (Han 2016 **Level I** [PRISMA], 6 RCTs, n=859);
    - Specifically in THA, gabapentin reduces pain scores and opioid requirements, but no effect on any adverse effect (Han 2016 **Level I** [PRISMA] 5 RCTs, n=573). Pregabalin 150 mg preoperatively and 75 mg BD postoperatively for 7 d reduced pain and opioid requirements for 7 d with no effects on pain or physical function at 6 wk or 3 mth (Clarke 2015 **Level II**, n=184, JS 5);
    - A combined meta-analysis on the effects of pregabalin and gabapentin found only clinically insignificant reductions of pain (pregabalin only) at 24 h (0.5/10; 95%CI 0 to 1.0) and at 48 h (0.3/10; 95%CI 0 to 0.6) and a reduction in cumulative opioid consumption at 48 h (MD -23.2mg; 95%CI -40.9 to -5.4mg); the latter effect was only significant with pregabalin (MD -33.14 mg; 95%CI -53.98 to -12.29mg) There was no difference in knee flexion at 48 h, but a reduction in the incidence of PONV (RR 0.7; 95%CI 0.6 to 0.9) and an increase in the risk of sedation (only with pregabalin) (RR 1.4; 95% CI 1.1 to 1.9) (NNH 8.7) (Hamilton 2016 **Level I** [PRISMA], 12 RCTs, n=1,493) (4 RCTs [gabapentin] overlap with Han 2016 and all 7 RCTs [pregabalin] overlap with Han 2017b).

Used as an adjunct to epidural analgesia, perioperative gabapentin reduced pain scores and epidural analgesic requirements and improved patient satisfaction, despite an increase in dizziness (Turan 2006 **Level II**, n=54, JS 5) but these benefits were not confirmed with thoracic epidural analgesia for thoracotomy (Kinney 2012 **Level II**, n=120, JS 5).

Alpha-2-delta ligands were also studied in the setting of acute burns pain (see Section 8.5.2), acute herpes zoster pain (see Section 8.6.2.2) and acute pain due to Guillain-Barre Syndrome (see Section 8.10.6.7).

The effects of alpha-2-delta ligands on the prevention of CPSP are presented in Section 1.4.6.3.

Dose dependency of effect

A network meta-analysis reports a dose-dependent effect of single-dose preoperative pregabalin and gabapentin on reduction of pain scores and opioid consumption vs placebo (Hu 2018a **Level I**

[NMA], 79 RCTs, n=6,201). With regard to pain reduction, pregabalin in a dose ≥150mg and gabapentin ≥900 mg are more effective.

Effects on PONV

In RCTs designed with PONV as a primary endpoint (8 RCTs, n=838), preoperative gabapentin reduces PONV (RR 0.60; 99%CI 0.50 to 0.72), nausea (RR 0.34; 99%CI 0.20 to 0.56), and vomiting (RR 0.34; 99%CI 0.19 to 0.61) at 24 h (Grant 2016b **Level I** [PRISMA], 44 RCTs, n=3,489). These findings are similar in an analysis of all 44 RCTs; this is accompanied by an increased rate of sedation (RR 1.22; 95%CI 1.02 to 1.47).

In RCTs designed to report PONV, preoperative pregabalin reduces PONV (RR 0.53; 95%CI 0.39 to 0.73), nausea (RR 0.62; 95%CI 0.46 to 0.83), and vomiting (RR 0.68; 95%CI 0.52 to 0.88) at 24 h (Grant 2016a **Level I** [PRISMA], 23 RCTs, n=1,693). There is no increased sedation reported (RR 0.97; 95%CI 0.71 to 1.33), but an increase of postoperative visual disturbance (RR 3.11; 95%CI 1.34 to 7.21).

Adverse effects

Serious adverse effects (SAEs) in the studies with low risk of bias were rare (22/730) and occurred more with pregabalin than placebo (RR 2.9; 95%CI: 1.2 to 6.8); nausea, sedation and headache were not significantly different between the groups (Fabritius 2017 **Level I** [PRISMA], 97 RCTs, n=7,201).

Adverse effects of perioperative pregabalin include somnolence (RR 1.72; 95%CI 1.08 to 2.72), sedation (RR 1.51; 95%CI 1.16 to 1.96; absolute risk 41/1,000) and visual disturbances (RR 3.08; 95%CI 1.91 to 4.96; absolute risk 10/1,000) (Eipe 2015 **Level I** [PRISMA], 43 RCTs, n=3,378) (39 RCTs overlap). These adverse effects must be weighed against the benefits, which might not be clinically relevant in all postoperative settings. They may also compromise enhanced recovery strategies as outlined in ERAS guidelines eg for elective colorectal surgery (Gustafsson 2019 **GL**).

Toxicity

Overdose toxicity from gabapentin or pregabalin alone is rarely fatal, but the risk is increased when taken in combination with other agents that cause sedation, particularly opioids (then leading to OIVI). Another contributing factor to the interaction with opioids may be that pregabalin reversed the tolerance to opioids (Lyndon 2017 **BS**).

After laparoscopic surgery, preoperative gabapentin (300 to 600 mg) use as a component of multimodal analgesia increased the risk of respiratory depression in general (OR 1.47; 95% CI 1.22 to 1.76) (Cavalcante 2017 **Level III-3**, n=8,567 [n=1,311 episodes of respiratory depression]). In combination with systemic opioids in particular, the risk of OIVI was increased (OR 1.26; 95%CI 1.02 to 1.58) (n=965), in particular in older patients (>50 y) or those having received higher opioid doses. After joint arthroplasty, preoperative gabapentin (>300 mg) increased the risk of respiratory depression (Weingarten 2015 **Level IV**, n=11,970 [n=2,836 episodes of respiratory depression]). Use of alpha-2-delta ligands in combination with opioids was a risk factor for increased need for naloxone administration in hospital patients (Minhaj 2020 **Level III-2**, n=867 [n=275 naloxone administrations; n=105 alpha-2-delta ligand exposures]; Weingarten 2015 **Level III-2**, n=134 [naloxone administrations; n=15 alpha-2-delta ligand exposures]). This was also shown in patients after colorectal surgery (OR 1.58; 95%CI 1.11 to 2.26) despite an opioid-sparing effect (Ohnuma 2019 **Level III-**2; n=175,787 [4,677 alpha-2-delta ligand exposures]). Continuation of alpha-2-delta ligands into the postoperative period in patients receiving this therapy chronically was associated with increased need for naloxone administration (RR 6.30; 95%CI 2.4 to 16.7) but not in those receiving this as a new postoperative intervention (Deljou 2018 **Level III-2**, n=110,019 [n=128 naloxone administrations; n=39 alpha-2-delta ligand exposure). However, in a further study in hospitalised patients receiving opioids (where >60% received opioid for acute pain treatment only and 17% had surgery in the preceding 24 h), alpha-2-delta ligand use vs non-

use did not increase frequency of naloxone requirement (Savelloni 2017 **Level III-2**, n=128 [n=153 naloxone administrations; n=36 alpha-2-delta exposures]).

Data from many countries (USA, UK, Germany, Finland, India, South Africa and France) show that over 75% of deaths attributable to alpha-2-delta ligands also involve opioids (Smith 2016 **Level IV SR**, 34 studies & 23 case reports, n unspecified). This is in line with findings that the combination of gabapentin and opioid vs opioid alone increased the risk of opioid overdose death (OR 1.99; 95%CI 1.61 to 2.47) (Gomes 2017 **Level III-2**, n=5,875).

The combination of alpha-2-delta ligands with conventional opioids in postoperative patients may be associated with an increased risk of OIVI, in particular in certain patient subgroups (chronic users, obese patients, patients with OSA, older patients, higher dosing of opioids and/or alpha-2-delta ligands, combinations with other sedating medications). This is in line with warnings by regulatory authorities (FDA 2019 **GL**; MHRA 2017 **GL**). More data is required to delineate their role in ERAS and multimodal analgesic protocols (Gupta 2018b **NR**).

Abuse potential

Alpha-2-delta ligands have a potential for misuse, abuse and toxicity in overdose (Evoy 2017 **Level IV SR** [PRISMA], 59 studies [24 epidemiological, 3 clinical abuse liability, 16 case series or reports of abuse or misuse or dependence, 17 case series or reports of acute overdose]; Bonnet 2017 **Level IV SR** [PRISMA], 106 studies [17 rewarding behaviour, 14 clinical, 38 case series or reports on abuse and dependence, 37 on overdose toxicity or fatalities]; Schjerning 2016 **Level IV SR** [PRISMA], 76 studies [pregabalin only] [17 preclinical, 19 clinical, 13 epidemiological, 27 case series or reports]) (all with significant overlap of studies). Preclinical studies suggest that modulation of the GABA and glutamate systems, with resulting anxiolysis and in particular euphoria, underpin the abuse potential. The prevalence of abuse in the UK general population is 1.1% for gabapentin and 0.5% for pregabalin; consistently patients with opioid use disorder have higher rates: gabapentin 15 to 22% and pregabalin 3 to 68%. Substance use disorder and psychiatric comorbidities are the most important risk factors. Abuse typically involves the intake of supratherapeutic doses to achieve euphoria, with pregabalin appearing more addictive than gabapentin.

4.8.1.2 | Sodium valproate

A single dose of sodium valproate IV did not improve acute nociceptive pain after surgery (Martin 1988 **Level II**, n=39, JS 3). There are conflicting results on IV sodium valproate in treating acute migraine; it was ineffective in one study (Tanen 2003 **Level II**, n=40, JS 2) and superior to metoclopramide plus sumatriptan in another (Bakhshayesh 2013 **Level II**, n=60, JS 3).

4.8.2 | Chronic pain

Among all anticonvulsants, there is good evidence only for the use of alpha-2-delta ligands in chronic pain conditions including neuropathic pain states such as diabetic polyneuropathy, postherpetic neuralgia and central neuropathic pain as well as fibromyalgia (Wiffen 2013b **Level I** [Cochrane], 91 RCTs, n=17,995). For most other anticonvulsants, the evidence was non-existent, so little or of so low quality that conclusions could not be drawn, or of reasonable quality showing no or very little effect. This is in line with treatment guidelines for chronic neuropathic pain which recommend alpha-2-delta ligands, but no other anticonvulsants, as first-line treatment in this indication (Finnerup 2015 **GL Level I** [PRISMA], 229 RCTs, n unspecified).

4.8.2.1 | Alpha-2-delta ligands (gabapentin/pregabalin)

Gabapentin

At doses of 1,800 mg to 3,600 mg/d, gabapentin is effective in treating neuropathic pain, in particular caused by postherpetic neuralgia (NNT 6.7; 95%CI 5.4 to 8.7) (8 RCTs, n= 2,260) and diabetic polyneuropathy (NNT 5.9; 95% CI 4.6 to 8.3) (6 RCTs, n=1,277) (Wiffen 2017a **Level I** [Cochrane], 37 RCTs, n=5,914). Withdrawals due to adverse events were more common with gabapentin (NNH 30; 95%CI 20 to 65) (22 RCTs, n=4,346), while serious adverse events were not more common with gabapentin than with placebo. Pain relief in 20 to 40% of patients is accompanied by improvement of sleep, fatigue, depression, quality of life and function.

Gabapentin was also effective for the treatment of neuropathic pain caused by traumatic or postsurgical nerve injury (Gordh 2008 **Level II,** n=120, JS 5).

Pregabalin

Pregabalin is effective in a dose-dependent fashion in postherpetic neuralgia, painful diabetic neuropathy, central neuropathic pain due to spinal cord injury (SCI) and mixed or unclassified post-traumatic neuropathic pain, but only with limited evidence in neuropathic back pain or sciatica, neuropathic cancer pain or polyneuropathy and no effect in HIV neuropathy (2 RCTs, n=674) (Derry 2019 **Level I** [Cochrane], RCTs=45, n=11,906):

- Postherpetic neuralgia: 300 mg/d pregabalin (NNT 5.3; 95%CI 3.9 to 8.1) (4 RCTs, n=713) and 600 mg/d (NNT 3.9; 95%CI 3.1 to 5.5) (4 RCTs, n=732);
- Painful diabetic neuropathy: 600 mg/d pregabalin (NNT 7.8; 95% CI 5.4 to 14) (5 RCTs, n=1,015);
- Mixed or unclassified post-traumatic neuropathic pain: 600 mg/d pregabalin (NNT 7.2; 95%CI 5.4 to 11) (4 RCTs, n=1,367);
- Central neuropathic pain (mainly SCI): 600 mg/d pregabalin (NNT 9.8; 95%CI 6.0 to 28) (3 RCTs, n=562).

In all studies, somnolence and dizziness occurred more in pregabalin than placebo arms in a dose-dependent pattern, but serious adverse events were not different between arms: pregabalin 300 mg (RR 1.2; 95%CI 0.8 to 1.7) (17 RCTs, n=4,112) and pregabalin 600 mg (RR 1.1; 95%CI 0.8 to 1.5) (16 RCTs, n=3,995).

Pregabalin 300 to 600 mg/d has also beneficial effects in fibromyalgia; substantial pain relief is achieved over 12 to 26 wk of treatment in about 10% more patients than in the placebo arm, accompanied by improvements of other symptoms, quality of life and function (Derry 2016a **Level I** [Cochrane], 8 RCTs, n=3,283).

Alpha-2-delta ligands are also used in chronic pain due to SCI (see Section 8.2.2.5), phantom limb pain (see Section 8.1.5.2) and in patients who are opioid-tolerant (see Section 9.7) or have a substance use disorder (see Section 9.8).

4.8.2.2 | Carbamazepine

Carbamazepine for the treatment of chronic neuropathic pain has possibly some analgesic efficacy in some patients, but the quality of data is insufficient to draw meaningful conclusions or make comparisons (Wiffen 2014 **Level I** [Cochrane], 10 RCTs, n=480).

4.8.2.3 | Oxcarbazepine

Only very-low level evidence supports limited effectiveness of oxcarbazepine in painful diabetic neuropathy, neuropathic pain from radiculopathy and a mixture of neuropathies (Zhou 2017 **Level I** [Cochrane], 5 RCTs, n=862).

4.8.2.4 | Phenytoin

No study supports the use of phenytoin in chronic neuropathic pain or fibromyalgia (Birse 2012 **Level I** [Cochrane], 0 RCTs, n=0).

4.8.2.5 | Valproate

Valproate may reduce pain in diabetic polyneuropathy based on very small RCTs of poor quality (Gill 2011 **Level I** [Cochrane] 2 RCTs, n=84). Valproate is effective for the prevention of episodic migraine (Linde 2013 **Level I** [Cochrane], 10 RCTs, n=652).

4.8.2.6 | Lamotrigine

Lamotrigine shows no analgesic benefit in neuropathic pain in large, high-quality, long-duration RCTs (Wiffen 2013a **Level I** [Cochrane] 12 RCTs, n=1,511).

4.8.2.7 | Lacosamide

Lacosamide is not beneficial for the treatment of neuropathic pain and fibromyalgia (Hearn 2012 **Level I** [Cochrane] 6 RCTs, n=2,022).

KEY MESSAGES

1. Alpha-2-delta ligands (gabapentinoids) are the only anticonvulsants with proven efficacy in the treatment of chronic neuropathic pain (**S**) (**Level I** [Cochrane Review]).
2. Pregabalin is the only anticonvulsant with proven but limited efficacy in chronic pain due to fibromyalgia (**S**) (**Level I** [Cochrane Review]).
3. Perioperative alpha-2-delta ligands (gabapentinoids) reduce postoperative pain and opioid requirements, in particular after more painful surgery (**Q**) and reduce the incidence of postoperative nausea and vomiting (**S**) as well as pruritus (**S**), but increase the risk of sedation (**S**) and visual disturbances (**N**) (**Level I** [PRISMA]).
4. Overdose toxicity of alpha-2-delta ligands is increased when taken in combination with other agents that cause sedation, particularly opioids (**N**) (**Level III-2**).
5. Alpha-2-delta ligands have the potential for misuse and abuse, in particular in patients with opioid use disorder or psychiatric comorbidity (**N**) (**Level IV SR**).

The following tick box represents conclusions based on clinical experience and expert opinion:

☑ Based on the experience in chronic neuropathic pain states, it would seem reasonable to use alpha-2-delta ligands in the management of acute neuropathic pain (**U**).

4.9 | Alpha-2 agonists

4.9.1 | Systemic alpha-2 agonists

4.9.1.1 | Clonidine

Clonidine is a selective alpha-2 agonist with an alpha-2 to alpha-1 ratio of 200:1 (Chan 2010a **NR**). Systemic perioperative administration of clonidine 1 to 5 mcg/kg vs placebo does not reduce pain scores, but has an opioid-sparing effect at 24 h (MD 24%; 95%CI 16 to 32) (4 RCTs, n=313) and reduces incidence of PONV (RR 0.35; 95%CI 0.25 to 0.51]) (6 RCTs, n=412) (Sanchez Munoz 2017 **Level I** [PRISMA], 57 RCTs, n=14,790 [PO 29 arms, IM 4 arms, IV 24 arms, TD 2 arms]).

After non-cardiac surgery, PO clonidine 200 mcg given preoperatively and continued as 200 mcg/d transdermal clonidine patch for 72 h did not reduce pain scores or opioid consumption vs placebo over these 72 h (Turan 2016 **Level II**, n=624, JS 5). An updated meta-analysis adding this and two further RCTs to a preceding one (Blaudszun 2012 **Level I** [PRISMA], 30 RCTs [clonidine 19 RCTs], n=1,792 [clonidine n=1,156]) confirms no effect of clonidine vs placebo on pain scores at 24 h (7 RCTs, n=802) or 48 h (4 RCTs, n=562) (Turan 2016 **Level I**, 7 RCTs, n=802).

Alpha-2 agonists such as clonidine are more effective than placebo in the management of opioid-withdrawal symptoms (Gowing 2014 **Level I** [Cochrane], 25 RCTs, n=1,668).

4.9.1.2 | Dexmedetomidine

Dexmedetomidine is a highly selective alpha-2 adrenoceptor agonist with an alpha-2 to alpha-1 ratio of 1,620:1 (Chan 2010a **NR**). Systemic intraoperative only administration of dexmedetomidine vs placebo reduces pain intensity at 6 h (WMD −0.93/10; 95%CI −1.34 to −0.53) and at 24 h (WMD=−0.47/10; 95%CI −0.83 to −0.11) as well as opioid consumption (WMD −6.76 mg; 95% CI −10.16 to −3.35) (Wang 2018c **Level I** [PRISMA], 40 RCTs, n=2,401). Dexmedetomidine also reduces the need for rescue analgesia (7 RCTs, n=290) and extends the time to first rescue analgesia (4 RCTs, n=220), without impact on PONV (5 RCTs, n=262). Dexmedetomidine used perioperatively (12 RCTs [intraoperative use only]) in spinal surgery reduces postoperative pain at 2 h postoperatively and reduces analgesic requirement at 12 h (2 RCTs) and 48 h (3 RCTs), but not 24 h (3 RCTs) (Tsaousi 2018 **Level I** [PRISMA], 15 RCTs, n=913) (4 RCTs overlap).

Findings in paediatric RCTs are similar, see Section 10.4.8.

4.9.1.3 | Effects of systemic dexmedetomidine on neuraxial and peripheral blocks

The use of IV dexmedetomidine in patients receiving spinal anaesthesia prolongs time to first analgesic request by at least 60% as well as duration of sensory and motor block by 34% respectively 17% (Abdallah 2013 **Level I** [PRISMA], 7 RCTs, n=364). These results were in principle confirmed by a subsequent systematic review, which separately analysed 8 RCTs published since the previous review (Johnson 2016 **Level I**, 8 RCTs, n=480) and by one subsequent RCT (Kumari 2017 **Level II**, n=60, JS 5). Most of the RCTs utilised an initial bolus dose and a subsequent maintenance infusion for the duration of surgery (11 of the overall 16 RCTs). IN dexmedetomidine had a significant opioid-sparing effect after THA (Uusalo 2019 **Level III-3**, n=120).

IV dexmedetomidine 0.5 mcg/kg but not IV midazolam prolonged spinal bupivacaine sensory block and also provided sedation and additional analgesia in patients undergoing transurethral resection of the prostate (Kaya 2010 **Level II**, n=75, JS 2).

IV dexmedetomidine 2 mcg/kg significantly prolonged analgesia and reduced postoperative

opioid requirements after single-shot interscalene brachial plexus block vs placebo and lower doses of dexmedetomidine (0.5 and 1 mcg/kg) (Kang 2018a **Level II**, n=72, JS 5).

See also Sections 4.9.2.1 and 4.9.2.2 below.

KEY MESSAGE

1. Alpha-2 agonists such as clonidine are more effective than placebo in the management of opioid-withdrawal symptoms (**U**) (**Level I** [Cochrane Review]).
2. The perioperative use of clonidine systemically (excluding transdermal administration) does not reduce pain intensity (at 24 or 48 hours) (**Q**) (**Level I**) but reduces opioid consumption and postoperative nausea and vomiting versus placebo (**Q**) (**Level I** [PRISMA]).
3. The perioperative use of the systemic dexmedetomidine reduces postoperative pain intensity, opioid consumption and requirements for rescue analgesia (**S**) without effect on postoperative nausea and vomiting (**N**) (**Level I** [PRISMA]).
4. The IV administration of dexmedetomidine combined with intrathecal local anaesthetic prolongs time to first analgesic request (**N**) (**Level I** [PRISMA]).

4.9.2 | Regional alpha-2 agonists

Alpha-2 adrenoceptor agonists act as an analgesic at the level of the dorsal horn of the spinal cord, although there may be peripheral effects as well (Chan 2010a **NR**). Systemic adverse effects are predominantly centrally mediated sedation and hypotension.

4.9.2.1 | Neuraxial

Clonidine

There is no human or animal evidence of neurotoxicity when preservative-free clonidine is administered IT (Hodgson 1999 **NR**). Epidural clonidine is approved by the FDA for relief of chronic cancer pain.

In volunteers, significant analgesia to experimental heat pain was detected with IT doses >25 mcg clonidine: with 50 mcg having similar effects on heat threshold to 5 mg bupivacaine (Ginosar 2013 **Level II EH**, n=11, JS 4). IT clonidine given in doses from 15 to 150 mcg, combined with IT local anaesthetic does not affect the rate of onset of a local anaesthetic block, but significantly prolongs the time to two-segment block regression and prolongs the time to first analgesic request (median 101 min, range 35–310 min) (Elia 2008 **Level I**, 22 RCTs, n=1,445). Treatment effects were noted to be heterogeneous and dose responsiveness could not be demonstrated. IT clonidine also reduces intraoperative pain, but hypotension was more frequent (RR 1.8; 95%CI 1.4 to 2.3) (Elia 2008 **Level I**, 22 RCTs, n=1,445).

The addition of IT clonidine to IT morphine causes a small increase in duration of analgesia (MD 1.63 h; 95%CI 0.93 to 2.33) and reduced the amount of systemic morphine consumption over 24 h (MD 4.45 mg; 95%CI -1.40 to -7.49) (Engelman 2013 **Level I**, [PRISMA], 7 RCTs, n=503). Hypotension is also increased (OR 1.78; 95%CI 1.02 to 3.12).

IT clonidine 30 to 150 mcg as an adjuvant to neuraxial anaesthesia during Caesarean section prolongs the duration of sensory block (MD 128 min; 95%CI 82 to 175) and motor block (MD 45 min; 95%CI 9 to 81) (Crespo 2017 **Level I** [PRISMA], 12 RCTs, n=1,280). IT clonidine increases sedation (RR 3.92; 95%CI 1.17 to 13.14), but does not increase the risk of hypotension, affect

pruritus or PONV. Neuraxial clonidine 50 to 150 mcg (epidural and IT) modestly enhances postoperative analgesia in women having Caesarean section under neuraxial anaesthesia (Allen 2018 **Level I** [PRISMA], 12 RCTs [IT administration] [9 RCT overlap with Crespo 2017] & 6 RCTs [epidural administration: 2 RCTs bolus followed by infusion, 2 RCTs repeated bolus, 2 RCTs single bolus], n=1,169). Neuraxial clonidine reduces morphine consumption (MD -8.7 mg; 95% CI -15.3 to -2.0); this effect is less with IT administration (MD -4.3 mg; 95%CI -7.0 to -1.5) than with epidural administration (MD -18.9 mg; 95%CI -34.8 to -3.0). It also increases the time to first analgesic request (MD 150 min; 95%CI 110 to 190) vs placebo, but does not improve pain scores on movement at 0 to 6 h. Neuraxial clonidine increases the risk of intraoperative hypotension (49%) vs placebo (33%) and of intraoperative sedation. Risks for bradycardia, nausea/vomiting and pruritus are inconclusive. There was no case of respiratory depression and neonatal outcome was not different in control and study group.

In obstetrics patients, the time to achieve highest sensory and complete motor block was less and duration of analgesia was longer when clonidine and hyperbaric bupivacaine were administered sequentially, compared to the mixing of the two medicines in a single syringe (Sachan 2014 **Level II**, n=60, JS 4).

Low-dose infusion of clonidine alone via thoracic epidural catheters after spinal surgery reduced systemic opioid requirements and nausea without causing significant sedation or hypotension (Farmery 2009 **Level II**, n=65, JS 5). The addition of clonidine to PCEA with ropivacaine and morphine after TKA decreased opioid requirements and improved analgesia without increasing adverse effects (Huang 2007 **Level II**, n=80, JS 3). The addition of clonidine to epidural anaesthesia with ropivacaine after haemorrhoidectomy improved analgesia without causing adverse effects (Baptista 2014 **Level III-2**, n=80).

Dexmedetomidine

Dexmedetomidine is not approved for epidural or IT administration and animal studies on its neurotoxicity via these routes are contradictory (Ozdamar 2018 **BS**; Konakci 2008 **BS**).

Epidural single-shot dexmedetomidine 0.5 to 1.5 mcg/kg as an adjuvant to epidural analgesia prolongs analgesia (SMD 3.50 h; 95%CI 1.86 to 5.13) (8 RCTs) and reduces rescue analgesia requirements (SMD -2.00; 95% CI -2.80 to -1.21) (6 RCTs) and pain scores (SMD -0.76; 95%CI -1.46 to -0.06) (4 RCTs) (Zhang 2017b **Level I** [PRISMA]; 12 RCTs, n=660). It increases sedation scores and reduces heart rate minimally with no other significant adverse effects, and reduces postoperative shivering. Pain relief was improved with 0.5 mcg/kg epidural dexmedetomidine versus 0.5 mcg/kg IV administration for open thoracotomy (Zeng 2017 **Level II**, n=73, JS 5).

IT dexmedetomidine 3 to 100 mcg vs IT clonidine 30 mcg to 2 mcg/kg as adjuvants for IT local anaesthetics results in a minor prolongation of the sensory block (WMD 24.2 min; 95%CI 12.8 to 35.6) and a prolongation of time to first analgesic request (WMD 65.8 min; 95%CI 14.7 to 116.9) with no difference in incidence of adverse effects (Zhang 2016 **Level I** [QUOROM], 7 RCTs, n=354).

IT dexmedetomidine 3 to 10 mcg vs IT fentanyl 15 to 25 mcg prolongs the pain free period (SMD 2.98 h; 95%CI 1.69 to 4.27) without increasing the incidence of adverse events, including hypotension and bradycardia (Sun 2017b **Level I**, 9 RCTs, n=639). Similarly, after lower limb orthopaedic surgery, the addition of IT dexmedetomidine 5 mcg vs IT fentanyl 25 mcg to IT bupivacaine significantly prolonged duration of sensory, motor block and postoperative analgesia vs saline (Rahimzadeh 2018 **Level II**, n=90, JS 4). In patients undergoing lower limb surgery, IT dexmedetomidine 5 mcg was associated with prolonged motor and sensory block, haemodynamic stability and reduced demand of rescue analgesics at 24 h vs IT clonidine 30 mcg, fentanyl 25 mcg, or saline with bupivacaine (Mahendru 2013 **Level II**, n=60, JS 4).

In patients having lower abdominal surgery using IT bupivacaine 0.5%, IT dexmedetomidine 5 mcg vs IT buprenorphine 60 mcg prolonged anaesthesia and analgesia with a reduced need for

sedation and rescue analgesics (Gupta 2014 **Level II**, n=60, JS 5). Similarly, in patients undergoing lower abdominal surgery, the quality of anaesthesia was superior with low-dose bupivacaine/dexmedetomidine 5 mcg vs bupivacaine/fentanyl 25mcg (Nayagam 2014 **Level II**, n=150, JS 4). Dexmedetomidine facilitated the spread of the block and prolonged postoperative analgesia. For major abdominal cancer surgery, the addition of IT dexmedetomidine 5 mcg to IT morphine 500 mcg/bupivacaine did not improve analgesia vs IT morphine/bupivacaine (Abdel-Ghaffar 2016 **Level II**, n=90, JS 5). Both groups with adjuvants experienced better analgesia than bupivacaine alone.

Adrenaline (epinephrine)

Adding IT adrenaline to IT local anaesthetics (27 RCTs, n=1,660) prolongs motor block (WMD 64 min; 99%CI 37 to 91), analgesia (WMD 34 min; 99%CI 6 to 62) and time to 2 segments regression (WMD 20 min; 99%CI 11 to 28) (Tschopp 2018 **Level I** [PRISMA] [trial sequential analysis], 70 RCTs, n=3,644). For epidural analgesia (37 RCTs, n=1,781), no effects can be identified either due to lack of an effect (pain intensity, hypotension) or insufficient numbers (motor block, urinary retention). These findings are in line with those of a preceding meta-analysis which also presented dose dependent effects of IT adrenaline (de Oliveira 2012a **Level I** [PRISMA], 24 RCTs, n=1,271) (significant overlap). Doses of ≤100 mcg prolong sensory and motor block duration but are also associated with more hypotension and PONV than higher doses. IT adrenaline at doses >100 mcg prolongs sensory and motor block more than the lower dose but is not associated with a greater incidence of hypotension and PONV vs IT local anaesthetic alone. The effect of IT adrenaline in prolonging analgesia duration was not seen when added to IT local anaesthetic/opioid combinations (de Oliveira 2012a **Level I** [PRISMA], 24 RCTs, n=1,271).

The influence of caudal adrenaline and/or clonidine on the absorption characteristics of caudal levobupivacaine were evaluated in children (Chalkiadis 2013 **PK**, n=240). Adrenaline 5 mcg/mL decreased the rate of levobupivacaine systemic absorption, reducing peak concentrations by half. Clonidine 2 mcg/mL resulted in faster systemic absorption of levobupivacaine and a similar concentration time profile to levobupivacaine alone.

In postoperative thoracic epidural infusion, the addition of adrenaline to fentanyl and ropivacaine or bupivacaine improved analgesia (Niemi 2003 **Level II**, n=33, JS 5; Niemi 2002 **Level II**, n=12, JS 5; Sakaguchi 2000 **Level II**, n=77, JS 2). The efficacy of thoracic epidural pethidine infusions after thoracotomy was not improved by addition of adrenaline (Bryson 2007 **Level II**, n=50, JS 5).

With lumbar epidural infusions, no analgesic benefit was seen with added adrenaline at 2 mcg/mL or 4 mcg/mL (Forster 2008 **Level II,** n=63, JS 3; Forster 2003 **Level II**, n=46, JS 5).

In labour epidural analgesia, adrenaline 5 mcg/mL added to low-dose bupivacaine infusions decreased pain scores and resulted in longer redosing intervals with no change in labour duration (Connelly 2011 **Level II**, n=60, JS 4).

See also Section 5.7.1.4, for obstetric use Section 9.1.3.3 and for paediatric use Sections 10.4.8.1 and 10.6.3.3.

4.9.2.2 | Peripheral nerve block

Clonidine

A meta-analysis evaluated the benefits of clonidine as an adjuvant to local anaesthetics for various peripheral nerve and plexus blocks (Popping 2009 **Level I**, 20 RCTs, n=1,054). Clonidine doses ranged from 30 to 300 mcg with most patients receiving 150 mcg. Clonidine prolongs the duration of postoperative analgesia (WMD 122 min; 95%CI 74 to 169), sensory block (WMD 74 min; 95%CI 37 to 111) and also prolongs motor block. However, clonidine increases the risk of hypotension (OR 3.61; 95%CI 1.52 to 8.55), bradycardia (OR 3.09; 95%CI 1.10 to 8.64) and sedation (OR 2.28; 95%CI 1.15 to 4.51). There was a lack of evidence of dose-responsiveness for

beneficial or harmful effects. Subsequent studies in supraclavicular blocks report similar findings (Nasir 2017 **Level II**, n=97, JS 4; Chakraborty 2010 **Level II**, n=70, JS 4; Singh 2010 **Level II**, n=50, JS 4). However, the addition of 150 mcg clonidine to levobupivacaine 0.5% 20 mL in posterior gluteal (Labat) sciatic nerve block did not prolong the duration of analgesia and resulted in more hypotension vs the control group (Fournier 2012 **Level II**, n=60, JS 4).

In an experimental setting controlling for systemic effects of clonidine using bilateral adductor canal blocks, the addition of 150 mcg clonidine to ropivacaine for one side resulted in no difference in block characteristics (quality and duration) on either side (Andersen 2017 **Level II EH**, n=21, JS 5).

Evidence is lacking for the use of clonidine as an adjuvant to local anaesthetics for continuous catheter techniques, with no studies showing benefit (McCartney 2007 **Level I**, 3 RCTs [continuous], n=110).

Dexmedetomidine

Animal studies suggest potential dose-dependent neurotoxic effects when dexmedetomidine is combined with ropivacaine for 48 h of continuous FNB in rabbits (Wang 2019 **BS**) and for brachial plexus injection in high doses in rats (Kang 2018b **BS**).

Dexmedetomidine 25 to 150 mcg added to local anaesthetics for various peripheral nerve and plexus blocks increases duration of postoperative analgesia (MD 4.87 h; 95%CI 4.02 to 5.73) (Schnabel 2018 **Level I** [PRISMA], 46 RCTs, n=3,149). Dexmedetomidine increases the risk of intraoperative bradycardia (RR 2.83; 95%CI 1.50 to 5.33) and hypotension (RR 3.42; 95%CI 1.24 to 9.48). Perineural and IV administration of dexmedetomidine results in a similar prolongation of duration of analgesia (MD 0.98 h; 95%CI -0.12 to 2.08) (2 RCTs, n=107). However, for ulnar nerve blocks, perineural 100 mcg administration was superior to systemic dexmedetomidine in prolonging block duration: perineural 14.4 h (95%CI 13.1 to 15.6) vs systemic administration 9.2 h (95%CI 8.6 to 9.8) vs without dexmedetomidine 7.1 h (95%CI 6.6 to 7.6) (Andersen 2019 **Level II EH**, n=22, JS 5).

Meta-analyses of data on specific blocks have significant overlap with the overarching meta-analysis (Schnabel 2018 **Level I** [PRISMA], 46 RCTs, n=3,149) and show similar results:

- For thoracic paravertebral blocks (PVB), dexmedetomidine 1mcg/kg combined with local anaesthetics reduces pain at rest and with movement; for the latter the results were (SMD -1.63/10; 95%CI -2.92 to -0.34) and at 24 h (SMD -1.78/10; 95% CI -2.66 to -0.90) (Wang 2018a **Level I** [QUORUM], 7 RCTs [2 RCTs infusion, 5 RCTs single shot 1 mcg/kg], n=350). It extends duration of analgesia (202 min; 95% CI 33.5 to 369.6) and reduces postoperative analgesic consumption, while increasing the incidence of hypotension (OR 4.40; 95% CI 1.37 to 14.17);
- For TAPB, dexmedetomidine 0.5 to 1 mcg/kg as an adjuvant increases duration and quality of analgesia, while being opioid sparing (WMD −13.71; 95%CI −17.8 to −9.6) without increasing adverse effects (Sun 2019 **Level I** [PRISMA], 20 RCTs, n=1,212);
- As part of a brachial plexus block, perineural dexmedetomidine reduces time to onset of sensory and motor block, and prolongs sensory, motor block and analgesia duration by at least 57, 58 and 63% respectively (the latter by 266 min; 95%CI 191 to 343) (Vorobeichik 2017 **Level I** [PRISMA], 32 RCTs, n=2,007; Hussain 2017 **Level I**, 18 RCTs, n=1,092 [17 RCTs overlap]; Ping 2017 **Level I** [QUOROM], 18 RCTs, n=1,014 [10 RCTs overlap]). In addition, dexmedetomidine has an opioid sparing effect (MED 10.2 mg; 95%CI -15.3 to -5.2) in the first 24 h, improves pain control and enhances patient satisfaction, but increases the incidence of bradycardia and hypotension.

A dose-finding study for dexmedetomidine as an adjunct to interscalene brachial plexus block identified 2 mcg/kg as superior over 1 and 1.5 mcg/kg with regard to duration of analgesia

(placebo: 808 min ± 180; 1 mcg/kg: 1,033 min ± 288; 1.5 mcg/kg: 1,042 min ± 188; 2 mcg/kg: 1,224 min ± 238 min), but with an increased risk of hypotension for the two highest dose groups (Jung 2018 **Level II**, n=100, JS 5).

Compared with clonidine 1 to 2 mcg/kg, the perineural application of dexmedetomidine ≈1 to 2 mcg/kg as a local anaesthetic adjuvant in single-injection supraclavicular block produces significant prolongation of sensory block, motor block, and postoperative analgesia (on average by a factor of 1.2), while increasing the incidence of transient bradycardia (OR 7.4; 95%CI 1.3 to 40.8) and postoperative sedation (OR 11.8; 95%CI 1.9 to 73.6) (El-Boghdadly 2017 **Level I** [PRISMA], 14 RCTs, n=868).

Compared with dexamethasone 1 to 8 mg, dexmedetomidine 30 to 100 mcg as a perineural adjuvant for supraclavicular plexus block was inferior with regard to duration of analgesia (MD -148 min; 95%CI -259 to -37), while causing more hypotension (RR 6.3; 95%CI 1.5 to 27.5) and sedation (Albrecht 2019 **Level I** [PRISMA], 49 RCTs, n=3,019).

Adrenaline

Adrenaline added to local anaesthetics for locoregional anaesthesia (6 RCTs, n=203) prolongs analgesia (WMD 66 min; 98%CI 32 to 100) (Tschopp 2018 **Level I** [PRISMA] [trial sequential analysis], 70 RCTs, n=3,644).

For paediatric use see Section 10.6.2.6.

4.9.2.3 | Intravenous regional anaesthesia

Clonidine

Clonidine 150 mcg was inferior to magnesium sulphate (1.5 g of 50% MgSO4) as an adjuvant to IVRA with shorter time to first analgesic request (169.5 ± 33.3 vs 193.9 ± 38.4 min) and greater requirements for rescue analgesia (2.1 ± 0.8 vs 1.6 ± 0.7) (Kaur 2017 **Level II**, n=40, JS 5). Similarly, no analgesic benefit was found in a dose-finding study with clonidine (0 to 1.5 mcg/kg) added to IVRA (Ivie 2011 **Level II**, n=52, JS 5).

Dexmedetomidine

Addition of dexmedetomidine (most frequently 0.5 mcg/kg) to lidocaine or prilocaine IVRA increased duration and quality of analgesia (Subramanya 2017 **Level II**, n=60, JS 5; Kumar 2012 **Level II**, n=72, JS 5; Kol 2009 **Level II**, n=75, JS 5; Esmaoglu 2005 **Level II**, n=40, JS 4; Memis 2004 **Level II**, n=30, JS 4).

In patients having carpal tunnel repairs under IVRA, dexmedetomidine IV was compared with dexmedetomidine added to the local anaesthetic for IVRA and with placebo (Mizrak 2010 **Level II**, n=45, JS 5). Both routes of dexmedetomidine had similar effects, with improved postoperative pain scores up to 30 min.

Dexmedetomidine 1 mcg/kg vs midazolam (50 mcg/kg) as an adjuvant to IVRA resulted in similar duration of analgesia (Subramanya 2017 **Level II**, n=60, JS 4).

4.9.2.4 | Intra-articular

Clonidine

Intra-articular (IA) clonidine vs placebo after arthroscopic knee surgery reduces pain scores for 4 h, the need for rescue analgesia and postoperative nausea, but increases the risk of hypotension (Sun 2014 **Level I** [PRISMA] 7 RCTs, n=230). Combined femoral-sciatic nerve block offered better analgesia with fewer adverse effects than IA infiltration with bupivacaine/clonidine/morphine in children undergoing anterior cruciate ligament reconstruction (Tran 2005 **Level II**, n=36, JS 2).

Dexmedetomidine

IA dexmedetomidine 100 mcg when added to ropivacaine resulted in a longer time to analgesic request than ropivacaine alone (mean 10.8 h [SD 2.6] vs 5.4 h [SD 1.4]) (Paul 2010 **Level II**, n=30, JS 5). Compared with IV route, IA dexmedetomidine resulted in a longer time to first analgesia (IA 312.0 min [SD 120.7]; IV 102.1 min [SD 54.4]; placebo 71.0 min [SD 50.1]) (Al-Metwalli 2008 **Level II**, n=60, JS 5). When IA dexmedetomidine 100 mcg, fentanyl 50 mcg and ropivacaine each alone were compared following knee arthroscopy, time to first analgesia was longest with ropivacaine, followed by fentanyl and then dexmedetomidine (mean: 380 min [SD 22], 327 min [SD 17] and 244 min [SD 20] respectively) (Manuar 2014 **Level II**, n=99, JS 2). Added to bupivacaine, IA dexmedetomidine 1 mcg/kg resulted in similar prolongation and quality of analgesia as IA dexamethasone 8 mg vs bupivacaine alone after meniscal surgery (Moeen 2017 **Level II**, n=60, JS 5).

KEY MESSAGES

1. Neuraxial clonidine improves duration and quality of analgesia and is opioid sparing when used as an adjuvant to neuraxial local anaesthetics (in particular after Caesarean section) (**S**) (**Level I** [PRISMA]) or to morphine (**U**) (**Level I** [PRISMA]), but increases the risk of hypotension and sedation (**N**) (**Level I** [PRISMA]).
2. Neuraxial dexmedetomidine improves duration and quality of analgesia when used as an adjuvant to neuraxial local anaesthetics (**S**) (**Level I** [PRISMA]).
3. Intrathecal adrenaline (epinephrine) when combined with local anaesthetic, but not with intrathecal opioids, prolongs analgesia duration (**U**) (**Level I** [PRISMA]).
4. Dexmedetomidine when added to local anaesthetics for peripheral nerve blocks improves duration and quality of analgesia, but is associated with increased hypotension and bradycardia (**S**) (**Level I** [PRISMA]).
5. Intra-articular clonidine reduces pain scores for 4 hours, need for rescue analgesia and incidence of nausea, but increases hypotension (**N**) (**Level I** [PRISMA])
6. Clonidine improves duration of analgesia and anaesthesia when used as an adjuvant to local anaesthetics for peripheral nerve and plexus blocks but is associated with increased hypotension and bradycardia (**U**) (**Level I**).
7. Dexmedetomidine added to intravenous regional anaesthesia improves and prolongs analgesia (**U**) (**Level II**).
8. Epidural adrenaline (epinephrine) in combination with a local anaesthetic improves the quality of postoperative thoracic epidural analgesia (**U**) (**Level II**).

The following tick boxes represent conclusions based on clinical experience and expert opinion:

☑ The benefits of perineural adjuvant administration of alpha-2-agonists over systemic administration remains unclear (**N**).

4.10 | Salmon calcitonin and bisphosphonates

4.10.1 | Calcitonin

Calcitonin is a 32-amino acid peptide hormone that regulates calcium homeostasis in vertebrates. It also has analgesic properties, primarily through receptor-mediated modulation of serotonergic activity in pain pathways of the CNS (Visser 2005 **NR**). Salmon calcitonin has a greater potency than mammalian forms of the hormone and is therefore reproduced as a synthetic medicine for pharmaceutical use. The adverse effects of calcitonin therapy such as sedation, nausea, skin flushing and diarrhoea may reflect increased serotonergic activity. In rodents, the $5HT_3$ antagonist tropisetron reduced its analgesic efficacy, which may be relevant in humans during the treatment of its adverse effects – nausea and vomiting (Visser 2005 **NR**).

In patients with osteoporotic vertebral compression fractures, salmon calcitonin (IV, SC, IM, IN or rectal) administered within <10 d reduces acute pain at rest and on movement within 1 wk and improves mobilisation (in 7 to 28 d); adverse effects are usually minor and mainly gastrointestinal (Knopp-Sihota 2012 **Level I** [PRISMA], 13 RCTs, n=589). Weekly IM injections of eel calcitonin (elcatonin 20 Units) were more effective than NSAIDs in controlling pain and improving mobility in new (<2 wk) thoracolumbar osteoporotic fractures (Endo 2017 **Level II**, n=228, JS 3). In chronic pain (>3 mth) from pre-existing osteoporotic vertebral compression fractures, the effect was minimal and only statistically significant on movement at 6 mth. In a case series, IN salmon calcitonin reduced pain due to fracture of the coccyx (Foye 2014 **Level IV**, n=8).

In acute phantom limb pain, IV (and likely SC) salmon calcitonin was more effective than placebo (Jaeger 1992 **Level II**, n=21 (cross over), JS 3; Bornemann-Cimenti 2017 **CR**; Turek 2012 **CR**). However, it was not effective for chronic phantom limb pain (Eichenberger 2008 **Level II**, n=20 [cross over], JS 5). While epidurally administered calcitonin reduced the incidence of chronic phantom limb pain, allodynia and hyperalgesia at 6 and 12 mth in diabetic patients undergoing lower limb amputation (Yousef 2017 **Level II**, n=60, JS 5).

In CRPS, a meta-analysis concluded that salmon calcitonin (IN, IV) is beneficial (Perez 2001 **Level I**, 5 RCTs [calcitonin], n=260). However, the only two placebo-controlled RCTs in this meta-analysis produced conflicting results. A subsequent RCT found that calcitonin was no more effective than paracetamol in improving pain and function in CRPS over a 2 mth period in patients already receiving physical therapy following upper limb trauma (Sahin 2006 **Level II**, n=35, JS 2). A network meta-analysis recommended short term (<2 mth) calcitonin by all routes of administration in CRPS over 12 mth in duration (Wertli 2014 **Level I** [NMA], 3 RCTs [calcitonin], n=116); the RCTs included did not use IASP or Budapest diagnostic criteria for CRPS and the quality of the data have been questioned by other authors (Benzon 2016 **NR**).

Neuropathic pain after SCI was responsive to SC salmon calcitonin (Humble 2011 **Level IV**, n=3).

In lumbar spinal stenosis, salmon calcitonin (IN, IM, SC) has no effect on pain or walking distance vs placebo or paracetamol regardless of method of administration (Peng 2015 **Level I**, 6 RCTS, n=232).

The limited evidence available does not support the effectiveness of SC salmon calcitonin in the treatment of acute and persistent metastatic bone pain (Martinez-Zapata 2006 **Level I** [Cochrane], 2 RCTs, n=90).

With long-term use of salmon calcitonin for treatment of chronic osteoporosis (with unproven efficacy), there is a suggested association with increased cancer incidence; however, this is based on studies with poor-quality cancer assessment methodology (Overman 2013 **NR**). A subsequent meta-analysis further weakened the association and found little biological plausibility linking cancer risk and long-term calcitonin use (Wells 2016 **Level I**, 22 RCTs, n= 11,489).

The FDA has decided to continue the registration of salmon calcitonin, including for chronic use (FDA 2014b).

4.10.2 | Bisphosphonates

IV pamidronate 30 mg daily (for 3 d) vs placebo, rapidly reduced pain associated with acute osteoporotic vertebral compression fractures (<21 d after incident) for up to 30 d post treatment (Armingeat 2006 **Level II**, n=35, JS 5). Pamidronate IV was as effective as IV human synthetic calcitonin for this indication (Laroche 2006 **Level II**, n=27, JS 3).

Bisphosphonates reduce subacute and chronic bone pain associated with metastatic carcinoma of the breast (Wong 2012 **Level I** [Cochrane], 9 RCTs, n=2,810). In multiple myeloma, there is high quality evidence for benefit in reduction of vertebral fractures and skeletal related events, and low-quality evidence for pain reduction (Mhaskar 2017 **Level I** [Cochrane], 24 RCTs, n=7,293). In advanced prostate cancer, there is no clear benefit to the use of bisphosphonates for reducing pain, but they may prevent further skeletal related events (Macherey 2017 **Level I** [Cochrane], 18 RCTs, n=4,843). Bisphosphonates improve pain control in patients with metastatic bone disease from lung cancer (Lopez-Olivo 2012 **Level I**, 12 RCTs, n=1,767). Zoledronate specifically reduces the likelihood of experiencing a bone pain event in metastatic bone disease in comparison to placebo (RR 0.83; 95%CI 0.76 to 0.89) (Zhu 2013 **Level I**, 12 RCTs, n=4,450). See also Section 8.9.7.7.

There is poor quality evidence for the use of bisphosphonates outside of the aforementioned cancer states (breast, multiple myeloma, prostate, lung), nor is it warranted in patients with short life expectancy (<3 mth) (Porta-Sales 2017 **Level I**, 40 RCTs, n = 16,105).

Bisphosphonates reduce pain in patients with CRPS Type 1, in particular in the early phases of the syndrome (<12 mth) (Chevreau 2017 **Level I**, 4 RCTs, n=181).

In Paget's disease, bisphosphonate use tripled the proportion (31% vs 9%) of participants whose bone pain disappeared (RR 3.42; 95%CI 1.31 to 8.90) (NNT 5) (2 RCTs, n=205) (Corral-Gudino 2017 **Level I** [Cochrane], 20 RCTs [pain], n=3,168). The evidence was limited regarding benefit of specific bisphosphonates, but zoledronate appeared to have marginally better efficacy vs pamidronate and risedronate (2 RCTs, n=436).

In acute pain due to osteoarthritis of the knee, bisphosphonates have no effect on pain, function or radiological progress (Vaysbrot 2018 **Level I**, 7 RCTs, n=3,013).

KEY MESSAGES

1. Bisphosphonates reduce bone pain associated with metastatic breast cancer (**U**), multiple myeloma (**S**) and Paget's disease (**N**) (**Level I** [Cochrane Review]), but have no beneficial effect for knee arthritis (**N**) (**Level I**).
2. Salmon calcitonin reduces pain and improves mobilisation in the acute phase after osteoporosis-related vertebral compression fractures (**U**) (**Level I** [PRISMA]).
3. Bisphosphonates reduce pain in patients with CRPS Type 1 in the early phase of the disease (**N)** (**Level I**).
4. Salmon calcitonin reduces acute, but not chronic, phantom limb pain (**U**) (**Level II**).
5. Pamidronate reduces pain associated with acute osteoporotic vertebral compression fractures (**U**) (**Level II**).

4.11 | Cannabis, cannabinoids and cannabimimetics

4.11.1 | Pharmacology

Medicinal preparations made from the cannabis plant contain several hundred chemical substances, which occur in varying concentrations in different plant strains and growth environments. Cannabis plants and their extracts are uniquely rich in phytocannabinoids (Russo 2011 **NR**), of which delta^9-tetrahydrocannabinol (Δ^9-THC) is the best characterised substance and induces most of the psychogenic effects attributed to cannabis. Tetrahydrocannabinolic acid is the nonpsychotropic phytochemical precursor of THC and is of therapeutic interest for the prevention of nausea (Rock 2013 **BS**) and the selective inhibition of COX-2 (Takeda 2008 **BS**). Other prominent THC congeners include cannabidiol and cannabinol. Cannabidiol (CBD) is of interest because it opposes the psychotropic activity of THC and is currently being developed for anticonvulsant therapy (Schubart 2011 **Level IV**, n=1,877; Devinsky 2014 **NR**; Borgelt 2013 **NR**). Cannabinol is also of interest for possible antitumour actions (Guindon 2011 **NR**).

"Cannabinoids" refers to both the phytocannabinoid congeners of Δ^9-THC and to a wide range of synthetic substances that act on a family of G-protein coupled receptors, which are presently designated subtypes CB_1 and CB_2. CB_1 receptors are predominantly distributed throughout the central and peripheral nervous system, where they mediate inhibition of neurochemical transmitter release and are associated with analgesic and mood modifying effects. CB_2 receptors predominantly occur on immune cells, including microglia, and are associated with modulation of cytokine release and have an anti-inflammatory effect (Mackie 2006 **NR**).

The endogenous cannabinoid system can be considered complementary to the endogenous opioid system (Wilson-Poe 2013 **BS**). Endogenous cannabinoid ligands (endocannabinoids) are derived from arachidonic acid. It is postulated that some (chemically noncannabinoid) analgesic agents (including paracetamol and various NSAIDs) may act, at least in part, via cannabinoid receptor mediation, either directly or indirectly via modulation of endocannabinoid metabolism (Graham 2013a **NR**; Manzanares 2006 **NR**) although much of this evidence is from pre-clinical data and some effects may be species-specific (McPartland 2014 **BS SR**).

It is difficult to group together cannabis-derived preparations and other cannabinoids. This is because plant-extract formulations comprise a mixture of active ingredients (eg the oral mucosal metered-dose spray nabiximols [Sativex®; containing THC:CBD≈1:1] in comparison to pure single ingredient cannabinoid preparations, such as dronabinol [Marinol®, synthetic THC, oral capsules] and nabilone [Cesamet®, synthetic analogue of THC, oral capsules]). Nabiximols are registered in Australia and New Zealand among other countries for treatment of spasticity associated with multiple sclerosis (MS).

The acute toxicity of phytocannabinoids is extremely low; nevertheless, clinical studies of the effect-adverse effect profile of cannabis and cannabinoids have demonstrated that desirable actions may be limited in a proportion of patients due to adverse effects, including dysphoria, sedation and impaired psychomotor performance, memory and concentration (Robson 2011 **NR**).

Many patients self-administer cannabis by smoking; the traditional route popularised by nonmedical users (Wilsey 2013 **Level II**, n=39, JS 4; McQuay 2010 **NR**). Transpulmonary administered phytocannabinoids are rapidly and efficiently absorbed; however, newer vaporising delivery techniques are supplanting smoking with its attendant health risks (Zuurman 2008 **Level II**, n=12, JS 4; Eisenberg 2014 **Level IV PK**; Hazekamp 2006 **EH**) including emerging concerns regarding severe pulmonary toxicity and 'vaping' (Schier 2019 **GL**). Oral cannabis and cannabinoid preparations have a poor and highly variable systemic bioavailability (Huestis 2007 **NR**). Likewise, the oromucosal spray (of nabiximols) does not achieve a rapid systemic absorption, with a profile

resembling oral administration (Karschner 2011a **Level II PK**, n=9, JS 3; Karschner 2011b **Level II EH**, n=22, JS 3; Zuurman 2008 **Level II EH**, n=12, JS 4; Hazekamp 2006 **EH**).

4.11.2 | Efficacy

4.11.2.1 | Acute Pain

A volunteer study considering acute pain used electrical and heat stimuli in healthy young adult female volunteers found 20 mg oral standardised cannabis extract to be no different to 5 mg oral diazepam (active placebo) in a variety of endpoint measures (Kraft 2008 **Level II EH**, n=18, JS 4). The authors concluded that "*cannabinoids are not effective analgesics for the treatment of acute nociceptive pain in humans*". The authors determined the plasma concentrations of the Δ^9-THC and CBD components and found that they varied more than seven-fold between subjects.

Similarly, in the clinical setting, there is no evidence for a role of synthetic or purified cannabinoids in the management of acute pain (Stevens 2017 **Level I** [PRISMA], 7 RCTs, n=310). Five RCTs found cannabinoids to be equivalent to placebo, one inferior and one superior. There were no synergistic or additive analgesic effects when used in combination with opioids.

4.11.2.2 | Chronic Pain

In a variety of chronic pain conditions, including neuropathic pain, fibromyalgia, arthritis and other mixed groups, the efficacy of all commercially available cannabinoids in all study designs and considering all IMMPACT recommended outcomes were analysed (Stockings 2018 **Level IV SR** [PRISMA], 47 RCTs & 57 studies, n=9,958). Across the RCTs, the pooled event rate for 30% pain reduction is 29.0% for cannabinoids vs 25.9% for placebo (OR 1.46; 95%CI 1.16 to 1.84) ($NNT_{30\%}$ 24; 95%CI 15 to 61) (8 RCTs, n=1,734); this outcome is achieved in 72% of patients (95%CI 66%-78%) in observational studies with no comparison group. Across the RCTs, the benefit is lost for 50% pain reduction with pooled event rate of 18.2% vs 14.4% (OR 1.43; 95%CI 0.97 to 2.11) (5 RCTs, n=753). With regard to other outcomes in RCTs, there were no effects on physical functioning, quality of life, overall emotional functioning or depression or anxiety symptoms, but some low level evidence for reduction in sleep problems (moderate level evidence with nabiximols only) and an improved Global Impression of Change (GIC) (perceived "much" to "very much" improved 18.9% vs 11.8%) (OR 1.62; 95%CI 1.34 to 1.96) (NNT 38; 95%CI 27 to 62) (13 RCTs [4 continuous & 9 dichotomous], n=1,896 [1,595 dichotomous]). There is moderate- to high-grade evidence supporting use of nabiximols to achieve modest reductions in pain as adjuvant therapy in MS-related pain. Adverse events occurred in 81.2% of cannabinoid-treated patients vs 66.2% of placebo-treated patients (OR 2.33; 95%CI 1.88 to 2.89) (NNH 6; 95%CI 5 to 8) (10 RCTs, n=1,959); severe adverse events resulting in study withdrawal occurred in 15.8% vs 4.6% (OR 3.47; 95%CI 2.64 to 4.56) (NNH 40; 95%CI 35 to 49) (19 RCTs, n=3,265).

These findings are largely consistent with a preceding meta-analysis with significant overlap of included RCTs (Aviram 2017 **Level I** [PRISMA], 43 RCTs, n=2,437) and an overview of systematic reviews not including the above meta-analyses (Hauser 2018 **Level I** [PRISMA], 10 SRs, unspecified number of RCTs).

In addition to these meta-analyses of effects on all chronic pain conditions, there are also assessments of specific conditions published (with significant overlap of included RCTs):

- In neuropathic pain, there is no high-quality evidence for the efficacy of any cannabis-based medicine (Mucke 2018a **Level I** [Cochrane], 16 RCTs, n=1,750). Low quality evidence shows a 50% or greater pain reduction versus placebo in 21% vs 17% (RD 0.05; 95%CI 0.00 to 0.09) ($NNT_{50\%}$ 20; 95%CI 11 to 100) (8 RCTs, n=1,001). Moderate quality evidence shows a 30% or greater pain reduction in 39 vs 33% (RD 0.09; 95%CI 0.03 to 0.15)

($NNT_{30\%}$ 11; 95%CI 7 to 33) (10 RCTs, n=1,586). For adverse events, evidence is of low quality and shows an increase in nervous system adverse events 61% versus 29% (RD 0.38; 95%CI 0.18 to 0.58) (NNH 3; 95%CI 2 to 6) (9 RCTs, n=1,304) and psychiatric disorders 17% vs 5% (RD 0.10; 95%CI 0.06 to 0.15) (NNH 10; 95% CI 7 to 16) (9 RCTs, n=1,314);

- In fibromyalgia, there is no convincing evidence that nabilone (the only cannabinoid in both RCTs) is of any value in treating this condition (Walitt 2016 **Level I** [Cochrane], 2 RCTs, n=72);
- In cancer pain, very low-quality evidence shows no benefit of nabiximols or THC (the only cannabinoids in the included RCTs) on any outcome including pain, sleep problems and opioid consumption with increased adverse events (GI and nervous system) (Hauser 2019 **Level I** [PRISMA], 5 RCTs, n=1,534). Even for improvement of anorexia or cachexia in a palliative care setting, there is no convincing, unbiased, high quality evidence for an effect of cannabinoids (Mucke 2018b **Level I** [PRISMA], 9 RCTs, n=1,561);
- In MS, cannabinoids may have modest effects for pain or spasticity based on high quality evidence (Nielsen 2018 **Level III-3 SR** [PRISMA], 11 SRs based on 32 studies).

Smoking cannabis has only short-term effects in RCTs of painful HIV associated sensory neuropathy (Phillips 2010 **Level I** [PRISMA], 14 RCTs n=1,764 [2 smoked cannabis, n=111]). Specific to smoked cannabis, the authors caution re potential bias due to difficulties in patient blinding; in one RCT 92% guessed treatment allocation correctly.

A 4 y prospective cohort study of people with chronic non-cancer pain taking opioids identified that those using non-prescribed cannabis had increased pain severity, pain interference and generalised anxiety disorder scores and decreased pain self-efficacy scores (Campbell 2018 **Level III-2**, n=1,514). Cannabis use did not have an opioid-sparing or opioid cessation effect.

4.11.3 | Adverse effects

Transient adverse effects of cannabis and cannabinoids are variable and include impaired cognition, dizziness and sedation. In short-term exposure (mean treatment duration of 2 wk) medical cannabis was not associated with a higher incidence of serious adverse effects vs control (RR 1.04; 95%CI 0.78 to 1.39), with dizziness being reported as the most commonly reported nonserious event in cannabinoid-treated patients (15.5%) (Wang 2008a **Level I**, 23 RCTs, n=3,141).

Longer-term studies in patients with MS have indicated no new safety concerns after several years of administration. Nabiximols (Sativex®) treatment in patients with MS was not associated with psychopathology or impaired cognition (Aragona 2009 **Level II**, n=17, JS 5). Similarly, its adverse effects were assessed in an open-label study following a trial for treating spasticity in MS patients for a mean duration of 334 d (Serpell 2013 **Level IV**, n=146). Adverse effects typically reported as "dizziness", "fatigue" and "headache" caused treatment withdrawal in 14% of patients and were serious (eg psychosis) in 4.3%. A further 9% of these patients withdrew due to lack of efficacy.

There is widespread concern about chronic exposure to cannabis and the development of psychosis in susceptible individuals. Whilst a causal link is yet to be established, one meta-analysis concluded that there is a dose-response relationship between the level of cannabis use and the risk for psychosis (Marconi 2016 **Level III-3** [PRISMA], 10 studies, n=66,816). The risk for schizophrenia and other psychosis-related symptoms is highest in the heaviest cannabis users vs non-users (OR 3.90; 95%CI 2.84 to 5.34). Others have argued that there is little evidence that, at a population level, cannabis use is a primary contributing factor in the development of psychiatric illness (Hamilton 2014 **Level III-3**; Gage 2013 **NR**; Macleod 2010 **NR**).

Rapidly absorbed cannabis (eg by smoking) produces a tachycardia by a beta-adrenergic mechanism (Beaconsfield 1972 **NR**). A detailed literature review identifies an increased risk of acute coronary syndrome and chronic cardiovascular disease associated with cannabis use through other mechanisms postulated as vascular inflammation, platelet activation and carboxyhaemoglobin formation (Richards 2019 **Level IV SR** [PRISMA], 85 studies, n=541,518). However, in patients surviving acute myocardial infarction there was no association between cannabis use and mortality (Frost 2013 **Level IV**, n=519). There are emerging concerns regarding severe pulmonary toxicity related to "vaping", with unclear trigger factors but many reports involve cannabinoids (Schier 2019 **GL**). Overall, cardiovascular and pulmonary effects of cannabinoids need to be considered (Pacher 2018 **NR**).

Acute cannabis intake impairs driving, but the increase in accident risk is of low to medium magnitude (increase in accident risk pooled OR 1.28; 95%CI 1.16 to 1.40 and in culpable accident risk pooled OR 1.42; 95%CI 1.11 to 1.75) (Rogeberg 2019 **Level III-3 SR**, 13 studies [culpability], n=78,023).

After trauma, marijuana use, in particular chronic use, leads to higher pain scores and higher opioid requirements (Salottolo 2018 **Level III-2**, n=261).

Epidemiological evidence of harms is typically derived from "recreational" users where the "cannabis" is defined neither chemically nor posologically (dose) and its relevance to the medical use, particularly of pharmaceutical grade cannabis, in supervised patients, is questionable.

4.11.4 | General considerations

It should be noted that all clinical studies to date have various design limitations, most involving small numbers of patients and most using only nonselective highly lipophilic cannabinoids, often of unknown composition. It should also be noted that several RCTs with negative results are yet to be published. The possible benefits from more selective agonists have yet to be investigated in the clinical setting, along with more innovative or reliable modes of administration.

Many leading stakeholder institutions world-wide, which hold either scientific, best practice or regulatory interests in the use of pharmacological agents for the treatment of pain, express a universal concern for the proliferation of cannabis related products for the indications of acute or chronic pain (FPMANZCA 2019b **GL**). This concern is largely underpinned by the current lack of quality and robust evidence for its efficacy and the significant adverse effects both in the short and long terms. These same institutions welcome further dialogue within the framework of well-designed clinical studies to better determine usefulness of cannabinoids and their side-effect profile.

KEY MESSAGES

1. Adverse effects including dizziness, cognitive changes and psychiatric symptoms (eg psychosis) may limit the usefulness of cannabinoids in pain treatment (**S**) (**Level I** [Cochrane Review]).
2. Current evidence does not support the use of cannabinoids in acute pain management (**S**) (**Level I** [PRISMA]).
3. Smoking cannabis has short-term efficacy in neuropathic pain in patients with HIV/AIDS, although potential study bias means that this is not recommended as routine treatment (**Q**) (**Level I** [PRISMA]).
4. Cannabinoids appear to be mildly effective when used in the treatment of pain and spasticity associated with multiple sclerosis and HIV (**W**) (**Level III-2 SR** [PRISMA]).
5. Smoked cannabis increases the risk of acute coronary syndrome and chronic cardiovascular disease (**N**) (**Level IV SR**).

4.12 | Corticosteroids

4.12.1 | Systemic corticosteroids

Surgical tissue trauma leads to the conversion of arachidonic acid to prostaglandins and leukotrienes. NSAIDs inhibit the formation of prostaglandins, whereas corticosteroids also inhibit the production of leukotrienes and cytokines (Royse 2017 **NR**; Gilron 2004 **NR**). The anti-inflammatory effects of corticosteroids account for some, but not all, of the antinociceptive effects of corticosteroids seen in clinical practice. It is likely that the analgesic actions of systemically administered corticosteroids are attributable predominantly to rapid-onset nongenomic mechanisms. However, the well-documented anti-inflammatory actions may contribute to a more delayed analgesic effect and may be due to genomic effects (Rijsdijk 2014 **NR**; Lowenberg 2008 **NR**). See also paediatric Section 10.4.10.

4.12.1.1 | Efficacy

Perioperative administration of corticosteroids reduces the severity of postoperative pain and decreases analgesic requirements as discussed below. However, corticosteroids are not only administered in the perioperative setting for their analgesic effects but also for other reasons. These include (but are not limited to) a reduction of PONV (De Oliveira 2013b **Level I** [PRISMA], 60 RCTs, n=6,696), decreased swelling in dental and maxillofacial surgery (Dan 2010 **Level I**, 12 RCTs, n=574) and an improvement in quality of recovery and decreased postoperative fatigue (Yue 2017 **Level I**, 11 RCTs, n=774; Murphy 2014 **Level II**, n=200, JS 5; Murphy 2011a **Level II**, n=120, JS 5; Murphy 2011b **Level II**, n=117, JS 5) with facilitation of earlier hospital discharge (Murphy 2011a **Level II**, n=120, JS 5).

Corticosteroids have also been shown to have antihyperalgesic effects in animals and humans (Romundstad 2007 **NR**; Brandsborg 2007 **NR**). In experimental burn injury pain, both methylprednisolone and ketorolac reduced secondary hyperalgesia and increased pain pressure tolerance threshold vs placebo, although the increase in pain pressure tolerance threshold was greater with ketorolac (Romundstad 2007 **Level II EH**, n=12, JS 4). In surgical patients, preoperative administration of methylprednisolone resulted in significantly less hyperalgesia vs parecoxib and placebo but there was no reduction in persistent spontaneous or evoked pain (Romundstad 2006 **Level II**, n=204, JS 4).

Dexamethasone 1.25–20 mg administration to surgical patients decreases postoperative pain scores, opioid consumption, time to first analgesia, requirements for rescue analgesia and PACU LOS (Waldron 2013 **Level I** [PRISMA], 45 RCTs, n=5,796). However, the differences are small and, while statistically significant, unlikely to confer clinically relevant analgesic benefit (eg 13% reduction in postoperative opioid consumption equals 3 mg morphine equivalent over the first 24 h). Preoperative dexamethasone administration is superior to later administration. When steroid doses were classified into three levels, an optimal dose of 0.1 to 0.2 mg/kg dexamethasone was identified (De Oliveira 2011 **Level I** [PRISMA], 24 RCTs, n=2,751); however, a subsequent metaregression did not identify any dose-response relationship for an opioid-sparing effect (Waldron 2013 **Level I** [PRISMA], 45 RCTs, n=5,796).

Systemic dexamethasone 4–40 mg improves quality of analgesia after spinal anaesthesia, with reduced 24 h morphine consumption (6 RCTs, n=326) and prolonged time to first analgesia request (Heesen 2019 **Level I** [PRISMA], 17 RCTs, n=1,133). Systemic 0.5 mg/kg and caudal dexamethasone 0.1–0.2 mg/kg doubles to triples the duration of analgesia from caudal blockade after paediatric surgery to a similar extent (Chong 2018 **Level I** [PRISMA], 14 RCTs, n=1,315).

Orthopaedic surgery

After THA and TKA, glucocorticoids in a dose greater than 0.1 mg/kg dexamethasone equivalent seem to be required to achieve reduction of PONV and pain severity within the first 24 h only (Yue 2017 **Level I**, 11 RCTs, n=774); in addition, systemic steroids are associated with faster functional rehabilitation and greater inflammation control. This is supported by another parallel meta-analysis of elective primary THA with perioperative glucocorticoid administration (dexamethasone 8 to 40 mg, methylprednisolone 125 mg or hydrocortisone 200 mg) (Li 2017c **Level I**, 6 RCTs, n=449).

In patients undergoing elective TKA, perioperative dexamethasone 5–10 mg administration decreases postoperative pain scores at 12, 24, and 48 h, and decreases opioid consumption up to 12 h only vs placebo or control (Zhou 2018 **Level I**, 6 RCTs, n=576). Similar effects are achieved with dexamethasone 10–40 mg in THA (Fan 2018 **Level I** [PRISMA] 3 RCTs, n=207).

High-dose methylprednisolone (dexamethasone equivalent >10 mg), but not low-dose systemic perioperative corticosteroid administration improves analgesia in patients undergoing elective knee or hip surgery (Lunn 2013 **Level I** [PRISMA], 17 RCTs [15 vs placebo], n=1,081). After orthopaedic surgery, there was no difference in the analgesic effect of IV methylprednisolone 125 mg vs IV ketorolac 30 mg, with both being better than placebo; IV methylprednisolone led to greater opioid-sparing but there was no difference in the incidence of adverse effects (Romundstad 2004 **Level II**, n=75, JS 5).

Tonsillectomy

Dexamethasone in doses >10 mg over 24 h given to adults undergoing tonsillectomy appears to decrease postoperative pain, an effect further improved by repeated administration in the postoperative period (Diakos 2011 **Level I**, 7 RCTs, n=580). This has been confirmed by a subsequent meta-analysis, which shows pain reduction by 23% at 4 h (MD -1.4/10; 95% CI -1.6 to -1.2) (Tolska 2019 **Level I** [PRISMA], 10 RCTs [dexamethasone], n=590) (6 RCTs overlap).

In a mixed meta-analysis of tonsillectomy in adults and children, all steroids reduce pain severity at all time points up to 7 d with a peak benefit on POD 1 (SMD -0.99/10; 95%CI -1.32 to -0.67) (41 RCTs, n=3,477) (Titirungruang 2019 **Level I** [PRISMA], 64 RCTs, n=6,327) (8 RCTs overlap with Tolska 2019). These effects are similar for systemic vs local steroid administration. Furthermore, steroids reduce PONV (OR 0.31; 95%CI 0.24 to 0.40) (46 RCTs, n=4,784), while not increasing the risk of primary (OR 0.96; 95%CI 0.55 to 1.67) (15 RCTs, n=1,736) or secondary haemorrhage (OR 1.05; 95%CI 0.74 to 1.51) (23 RCTs, n=2,440).

Thyroidectomy

Dexamethasone in adults undergoing thyroidectomy reduces postoperative pain scores and analgesic requirements vs control (Chen 2012 **Level I** [PRISMA], 5 RCTs, n=497) and the need for rescue analgesia vs placebo (Zou 2014 **Level I**, 13 RCTs, n=2,180). Only higher dose dexamethasone (8 to 10 mg) appeared to confer this analgesic benefit.

Maxillofacial surgery

Similarly, after maxillofacial surgery, the perioperative administration of corticosteroids (dexamethasone equivalent >5 mg) results in significant analgesic effects vs placebo in addition to decreased swelling (Dan 2010 **Level I**, 12 RCTs, n=574).

In rhinoplasty surgery, dexamethasone/pregabalin showed significant analgesic benefits up to 24 h vs placebo/pregabalin vs placebo/placebo (Demirhan 2013 **Level II**, n=60, JS 3).

Other surgery

In lumbar disc surgery, PO dexamethasone 16 mg preoperatively reduced pain with mobilisation in the first 24 h postoperatively vs placebo (Nielsen 2015b **Level II**, n=160, JS 5).

After mixed ambulatory surgery, ketorolac provided better pain relief than either dexamethasone or betamethasone in the immediate postoperative period but there were no differences in pain relief or analgesic use in the 4 to 72 h period after surgery (Thagaard 2007 **Level II**, n=179, JS 5).

A combination of dexamethasone/gabapentin provided better pain relief and led to less PONV than either medicine given alone after varicocoele surgery; both the combination and the individual medicines were more effective than placebo (Koç 2007 **Level II**, n=80, JS 5). In contrast, there was no difference in pain scores or PCA-morphine requirements during the first 24 h postoperatively in patients given pregabalin, dexamethasone/pregabalin or placebo after hysterectomy (Mathiesen 2009 **Level II**, n=116, JS 5).

Nonetheless, not all of the procedure-specific trials demonstrate benefit. Dexamethasone 0.1 mg/kg did not decrease the severity of pain nor opioid consumption up to 72 h in patients undergoing thoracotomy vs placebo (Joung 2018 **Level II**, n=40, JS 4). Likewise, in patients undergoing elective bowel surgery, dexamethasone 8 mg did not improve the quality of recovery, fatigue nor pain severity at 120 h postoperatively vs control (Dreams Trial Collaborators 2017 **Level II**, n=1,350, JS 5). When added to a multimodal analgesic combination including intrathecal morphine for Caesarean section under spinal anaesthesia, dexamethasone 8 mg did not decrease opioid consumption up to 24 h postoperatively (Ituk 2018 **Level II**, n=52, JS 4).

After breast augmentation, IV methylprednisolone 125 mg and IV parecoxib 40 mg provided comparable analgesia; however, PONV and fatigue scores were lower in the patients given methylprednisolone (Romundstad 2006 **Level II**, n=204, JS 4). In cardiac surgery, IV methylprednisolone 250 mg at induction and repeated immediately prior to cardiopulmonary bypass did not reduce the incidence of delirium nor improve the quality of recovery vs placebo (Royse 2017 **Level II**, n=555, JS 5). Oral prednisolone 50 mg preoperatively did not improve pain, fatigue, nausea or vomiting in patients undergoing laparoscopic cholecystectomy vs placebo (Bisgaard 2008 **Level II**, n=200, JS 3). In total abdominal hysterectomy, methylprednisolone 125mg did not confer analgesic benefit vs placebo (Aabakke 2014 **Level II**, n=49, JS 4).

Sore throat

Corticosteroids administered in a single dose (most commonly PO dexamethasone 10 mg) provide pain relief for sore throat including pharyngitis more effectively and faster than placebo (8 RCTs, n=907) (Sadeghirad 2017 **Level I**, 10 RCTs, n=1,426).

Dexamethasone 0.1–0.2 mg/kg decreases incidence (9 RCTs, n=983) and severity (4 RCTs, n=431) of sore throat after extubation when administered IV at induction vs placebo (Kuriyama 2019 **Level I**, 15 RCTs, n=1,849).

Acute gout

In acute gout, corticosteroids provide similar analgesic effects to non-corticosteroid treatments (Liu 2017b **Level I** [PRISMA], 7 RCTs, n=929).

4.12.1.2 | Adverse effects

The principal safety concerns of perioperative corticosteroid administration relate to the development of hyperglycaemia, increased infection and bleeding risk and the risk of recurrence of malignancy (Ali Khan 2013 **NR**; Yee 2013a **NR**; Turan 2011 **NR**; Ho 2011 **NR**).

Two meta-analyses have examined these safety issues with similar conclusions, although with significant methodological differences and including all corticosteroids (Toner 2017 **Level I**,

11 RCTs [hyperglycaemia], n=685; Polderman 2018 **Level I** [Cochrane], 38 RCTs, n=4,931) (17 RCTs overlap). However, the RCTs summarised in these meta-analyses are essentially efficacy studies of the antiemetic and anti-inflammatory effects of dexamethasone. Few trials have examined long-term effects or patient outcomes and those that have, were not adequately powered to do so. In consequence, a large RCT (PADDI) has completed recruitment, the results of which will address many of the safety issues relating to the administration of intraoperative dexamethasone (Corcoran 2019 **Trial Protocol**, n=8,880).

Hyperglycaemia

In non-cardiac surgical patients, glucocorticoids increase blood glucose concentrations (WMD 1.1 mmol/L; 95%CI 0.6 to 1.6) up to 12 h postoperatively (Toner 2017 **Level I**, 11 RCTs [hyperglycaemia], n=685). When only trials which excluded patients with diabetes were examined, the observed increase in blood glucose is smaller (WMD 0.7 mmol/L). These findings are confirmed by the subsequent meta-analysis of dexamethasone only, which finds a similar increase in non-diabetic patients (10 RCTs, n=595) and a more pronounced increase (1.8 mmol/L) in diabetic patients (2 RCTs, n=74) (Polderman 2018 **Level I** [Cochrane], 38 RCTs, n=4,931).

A large dose of dexamethasone (1 mg/kg at induction) in cardiac surgery patients, not excluding diabetic patients, resulted in a higher maximum postoperative blood-glucose concentration (MD 0.9 mmol/L) vs placebo (Dieleman 2012 **Level II**, n=4,494, JS 5). As all patients received glucose-lowering therapy in the ICU postoperatively, the dexamethasone effect may have been mitigated.

Infection risk

The administration of dexamethasone to patients undergoing surgery is not associated with an increase in the risk of any infection (OR 1.01; 95%CI 0.80 to 1.27) (Polderman 2018 **Level I** [Cochrane] (27 RCTs [infection], n=4,931]). This is also shown for all corticosteroids (OR 0.9; 95%CI, 0.6 to 1.3) (Toner 2017 (**Level I** [PRISMA], 18 RCTs [infection], n=2,138). There is also no increase in impaired wound healing or anastomotic leakage.

In cardiac surgery, a single intraoperative high dose of dexamethasone (1 mg/kg) did not significantly increase the incidence of postoperative wound infection; there was actually a reduction in total infection complications, due mainly to a reduction in pneumonia (Dieleman 2012 **Level II**, n=4,494, JS 5).

Bleeding risk

Perioperative corticosteroids do not increase the risk of postoperative haemorrhage in non-cardiac surgery (OR, 1.4; CI, 0.7 to 2.7) (Toner 2017 (**Level I** [PRISMA], 18 RCTs [bleeding], n=2,138).

Specifically, in paediatric tonsillectomy dexamethasone does not increase the overall bleeding risk; however, its use increases the need for operative intervention for bleeding (Plante 2012 **Level I**, 29 RCTs, n=2,674).

See paediatric section 10.4.10.3 for details of corticosteroid effects on bleeding risk.

Malignancy recurrence

There are limited and contradictory results on recurrence of malignancy; after colorectal surgery there was an increase in one small RCT (Singh 2014 **Level II**, n=43, JS 4), while a propensity-matched study failed to confirm such an association following ovarian cancer surgery (De Oliveira 2014b **Level III-2**, n=260).

KEY MESSAGES

1. Mild increase in blood glucose concentration follows perioperative administration of dexamethasone (**S**) (**Level I** [Cochrane Review]) and all corticosteroids (**S**) (**Level I** [PRISMA), particularly in patients with diabetes mellitus.
2. Perioperative administration of dexamethasone (**N**) (**Level I** [Cochrane Review]) and all corticosteroids (**N**) (**Level I** [PRISMA]) does not increase the risk of infection.
3. Perioperative administration of dexamethasone reduces postoperative pain and opioid requirements to a limited extent but also reduces nausea and vomiting, fatigue, and improves the quality of recovery compared with placebo (**U**) (**Level I** [PRISMA]).
4. Preoperative dexamethasone appears to be more effective than intraoperative or postoperative administration (**U**) (**Level I** [PRISMA]).
5. Perioperative corticosteroids do not increase the risk of impaired wound healing, anastomotic leakage or postoperative haemorrhage (**N**) (**Level I** [PRISMA]).
6. A single dose of corticosteroids provides more effective and faster relief of pain from sore throat than placebo (**N**) (**Level I**) and decreases incidence and severity of sore throat after extubation when administered at induction (**N**) (**Level I** [PRISMA]).
7. Systemic dexamethasone reduces pain intensity and opioid requirements after spinal anaesthesia (**N**) (**Level I** [PRISMA].

The following tick box represents conclusions based on clinical experience and expert opinion:

☑ As all adverse event data on corticosteroid use in surgical populations are based to date on efficacy trials (with methodological differences), their long-term safety awaits further evaluation (**N**).

4.12.2 | Regional corticosteroids

4.12.2.1 | Neuraxial

Caudal 0.1 to 0.2 mg/kg and IV dexamethasone (mostly 0.5 mg/kg) doubles to triples the duration of analgesia from caudal blockade after paediatric surgery to a similar extent (Chong 2018 **Level I** [PRISMA], 14 RCTs, n=1,315).

Dexamethasone when added to bupivacaine/fentanyl solution in epidural analgesia prolonged duration of analgesia in abdominal or thoracic surgery (372 min ± 58.1 vs 234.6 min ± 24.3) and decreased opioid requirements in the first 24 h (Naghipour 2013 **Level II**, n=72, JS 5). In patients having lower abdominal surgery, single-dose epidural bupivacaine/dexamethasone had similar prolongation of time to first analgesia, opioid-sparing and antiemetic effects as bupivacaine/fentanyl when compared with epidural bupivacaine alone (Khafagy 2010 **Level II**, n=90, JS 5). Preoperative single-dose epidural administration of dexamethasone, with or without bupivacaine, reduced postoperative pain and morphine consumption following laparoscopic cholecystectomy (Thomas 2006 **Level II**, n=94, JS 5). Epidural dexamethasone/ropivacaine reduced postoperative pain in patients undergoing gastrectomy under epidural analgesia vs ropivacaine alone in a dose-dependent way with 10 mg superior to 5 mg (Hong 2017 **Level II**, n=120, JS 5). Use

of epidural methylprednisolone resulted in no difference in morphine requirements or pain scores following thoracotomy vs epidural saline (Blanloeil 2001 **Level II**, n=24, JS 4).

Epidural corticosteroids (triamcinolone, methylprednisolone or dexamethasone) applied by the surgeons intraoperatively for microdiscectomy or laminectomy reduce pain at 24 h and 1 mth postoperatively, as well as opioid requirements and hospital LOS vs placebo (Wilson-Smith 2018 **Level I** [PRISMA], 17 RCTs, n=1,727; Arirachakaran 2018 **Level I** [PRISMA], 12 RCTs, n=1,006) (10 RCTs overlap). There is no difference in complications; a meta-analysis looking specifically for complications found no significant difference in overall complications (RR 1.94; 95%CI 0.72 to 5.26) nor infectious complications (RR 4.58; 95%CI 0.75 to 27.95) (Akinduro 2015 **Level III-2 SR**, 16 RCTs & 1 study, n=1,933).

Lumbar epidural steroid injections (ESI) for acute sciatica provide small but significant short-term relief (≤3 mth) from acute radicular pain (MD -6.2/100; 95%CI -3.0 to -9.4) and reduce disability but do not provide significant longer-term benefits beyond this time (Pinto 2012 **Level I,** 23 RCTs, n=2,334). Results specifically for transforaminal ESI vs saline or local anaesthetic are similar, with modest but significant pain reduction at 3 mth (MD−0.97/10; 95% CI −1.42 to −0.51) but no benefit on disability or need for later surgery (Bhatia 2016 **Level I** [PRISMA] 8 RCTs, n=771) (4 RCTs overlap).

Several meta-analyses overlapping for multiple studies with each other and the above have analysed specific questions. ESI is superior to saline (6 RCTs) with regard to improved function and pain control and superior to local anaesthetic with regard to improved pain control (2 RCTs), but these findings are only maintained at 1 mth with no significant long-term advantage (Lee 2018a **Level I**, 14 RCTS, n=1,502). Fluoroscopically guided lumbar ESI provide significant short-term improvement of radicular pain caused by lumbar disc herniation and stenosis, but not for axial back pain, based on low-quality evidence (Sharma 2017 **Level IV SR**, 41 studies, n unspecified). Non-image guided ESI provides inferior short-term improvement based on low-quality evidence and should only be performed if image-guidance is not available (Vorobeychik 2016 **Level IV SR**, 39 studies, n unspecified). Transforaminal ESI compared to interlaminar ones result in better short-term pain control (2 to 4 wk) based on weak evidence with no other significant benefits (Lee 2018c **Level III-2 SR**, 10 RCTs & 2 studies, n=876). There is no significant difference between transforaminal and caudal ESI based on very weak evidence (Lee 2018b **Level III-2 SR**, 4 RCTs & 2 studies, n=567). Preganglionic (supraneural, retrodiscal) ESI increases the chance of effectiveness vs postganglionic injection (Pairuchvej 2018 **Level III-2 SR**, 3 RCTs & 1 study, n=412). Particulate steroids compared to non-particulate ones result in statistically significant, but clinically questionable improved pain control (MD -0.53/10; 95%CI -0.14 to -0.92) (Makkar 2016 **Level III-2 SR**, 4 RCTs & 3 studies, n=4,398). For fluoroscopically guided cervical transforaminal epidural steroid injections, the response rate for <50% pain reduction is 48% (95%CI 34 to 61%) at 1 mth (5 studies, n=164) and 62% (95%CI 49 to 75%) at 3 mth (4 studies, n=259), based on very low-quality studies with no control group comparison (Conger 2020 **Level IV SR** [PRISMA], 17 studies, n unspecified).

The FDA issued a warning in April 2014 that injection of corticosteroids into the epidural space of the spine may result in rare but serious adverse effects, including loss of vision, stroke, paralysis and death (FDA 2014a **GL**). These concerns have been subsequently addressed in a number of consensus statements by multiple organisations (Rathmell 2015 **GL**; Kennedy 2015 **GL**). Recommendations particularly address image-guidance and use of particulate vs non-particulate steroids and have led to subsequent discussions in the literature.

Furthermore, repeat ESI (mean 1 to 14.7 injections with cumulative methyl-prednisolone equivalent doses of 80 to 8,130 mg) are associated with reduced bone mineral density and increased risk of vertebral fractures (Kerezoudis 2018 **Level IV SR**, 8 studies, n=7,233).

When compared with local anaesthetic PNB alone, the addition of dexamethasone 4–10mg to local anaesthetic prolongs the duration of sensory block (MD 6.70 h; 95%CI 5.54 to 7.85), and reduces postoperative pain intensity at 12 h (MD -2.08/10; 95%CI -2.63 to -1.53) and 24 h (MD -1.63/10; 95%CI -2.34 to -0.93) (Pehora 2017 **Level I** [Cochrane]**,** 35 RCTs, n=2,702). Another meta-analysis has similar results for analgesia outcomes and also finds a decrease in PONV (RR 0.36; 95%CI 0.19 to 0.70) (Huynh 2015 **Level I** [PRISMA]**,** 12 RCTs, n=1,054) (9 RCTs overlap). Specifically in brachial plexus block, there were similar findings for dexamethasone 1–10 mg, with low quality evidence of a ceiling effect of dexamethasone at 4 mg (Kirkham 2018 **Level I** [PRISMA]**,** 33 RCTs, n=2,138) (23 RCTs overlap with Pehora 2017). The effect on duration of sensory block is more pronounced with bupivacaine (MD 4.0 h; 95%CI 2.8 to 5.2) (4 RCTs, n=429) than with ropivacaine (MD 2.0 h; 95%CI -0.5 to 4.5 h) (5 RCTs, n=357) (Baeriswyl 2017 **Level I** [PRISMA]**,** 11 RCTs, n=914) (10 RCTs overlap with Pehora 2017).

IV dexamethasone vs placebo (8 RCTs, n=499) increases the duration of sensory block (MD 6.21 h; 95%CI 3.53 to 8.88) and reduces postoperative pain intensity at 12 h (MD -1.24/10; 95%CI -2.44 to -0.04) and 24 h (MD -1.26/10; 95% CI -2.23 to -0.29) as well as postoperative opioid consumption to 24 h (MD -6.58 mg; 95% CI -10.56 to -2.60) (Pehora 2017 **Level I** [Cochrane]**,** 35 RCTs, n=2,702).

Perineural vs IV dexamethasone (9 RCTs, n=720) increases the duration of sensory block (MD 3.14 h; 95%CI 1.68 to 4.59), but improves analgesia only in a clinically insignificant way and has no opioid-sparing effect (Pehora 2017 **Level I** [Cochrane]**,** 35 RCTs, n=2,702). However, a subsequent meta-analysis using the Hartung-Knapp-Sidik-Jonkman (HKSJ) methodology, which the authors claim to provide a more conservative estimate of effect, does not confirm the extended duration of sensory block with perineural vs IV dexamethasone 4–10mg (Hussain 2018 **Level I**, 14 RCTs, n=1,007) (9 RCTs overlap).

Adding dexamethasone 4 mg perineurally as an adjuvant to saphenous nerve block increased the duration of analgesia vs placebo (Bjorn 2017 **Level II**, n=40, JS 5). However, time to first rescue analgesia was similar with dexamethasone 4 mg perineurally for an ankle block vs IV 10 mg administration (Marty 2018 **Level II,** n=100, JS 5). Dexamethasone 8 mg/bupivacaine versus IM dexamethasone 8 mg for sciatic and ankle blocks improved pain scores at 24 h in the sciatic group only, but conferred no other analgesic benefits in either group (Fredrickson 2013 **Level II**, n=126, JS 5).

Perineural dexamethasone 4 to 8 mg for TAPB prolongs sensory block duration (MD 2.98 h; 95%CI 2.19 to 3.78) and reduces pain scores at 2, 6 and 12 h postoperatively (Chen 2018b **Level I** [PRISMA] 9 RCTs, n=575). It also reduces systemic analgesic consumption (SMD -1.29; 95%CI -1.88 to -0.70) and PONV incidence (OR 0.28; 95%CI 0.16 to 0.49) on POD 1.

Dexamethasone 8 mg/bupivacaine vs bupivacaine alone for thoracic paravertebral block improved analgesia and duration of analgesia in patients undergoing nephrectomy (Tomar 2017 **Level II**, n=60, JS 4).

Further addition of dexamethasone 8 mg to local anaesthetics for scalp nerve blocks in the setting of perioperative systemic dexamethasone therapy did not prolong duration of the block (Jose 2017 **Level II**, n=90, JS 5).

Although perineural dexamethasone has been shown to prolong sensory and motor block of perineural local anaesthetics, there is little safety data to support its use. Animal data to date are reassuring, with dexamethasone not increasing ropivacaine-induced sensory nerve toxicity at clinically relevant concentrations (Williams 2011 **BS**) and dexamethasone attenuating bupivacaine-induced neuronal injury (Ma 2010 **BS**). In a meta-analysis, although underpowered for complications, there is no difference in complications or nerve injury (10 RCTs, n=763) (Hussain 2018 **Level I**, 14 RCTs, n=1,007). However, given the lack of human safety data, the practice of

perineural dexamethasone administration needs to be further evaluated (Rahangdale 2014 **NR**). Furthermore, mixtures of ropivacaine and nonparticulate dexamethasone sodium phosphate demonstrated a pH-dependent crystallisation and the use of such combinations may be not advisable (Watkins 2015 **BS**).

4.12.2.3 | Peripheral sites

Periarticular injection of combinations of local anaesthetic, opioid and anti-inflammatory agents including steroids have been studied (LIA), however the range of mixtures makes determination of the effect of individual components difficult. In patients having simultaneous bilateral TKAs, bupivacaine/fentanyl/methylprednisolone were infiltrated by the surgeon around one knee but not the other (Mullaji 2010 **Level II**, n=40, JS 4). Pain scores on the infiltrated side were significantly lower and the joint had greater active flexion up to 4 wk and superior quadriceps recovery up to 2 wk after surgery vs the noninfiltrated knee. Periarticular injection of a mixture of bupivacaine/morphine/adrenaline/clonidine showed a reduced hospital LOS by 24 h without any significant effect on pain relief, motion or function following TKA, when methylprednisolone was added (Christensen 2009 **Level II**, n=76, JS 4). In comparing ropivacaine/adrenaline in three groups with no added steroid, triamcinolone 40 mg and 80 mg, the addition of corticosteroid to periarticular injection of local anaesthetic did not improve pain relief or range of movement outcomes for up to 12 wk of follow-up (Chia 2013 **Level II**, n=126, JS 5).

Intra-articular (IA) corticosteroid injections would be expected to have a direct analgesic effect in inflammatory arthropathies. Following knee joint arthroscopy, IA steroids were more effective than placebo in reducing pain, analgesic consumption and duration of immobilisation, either alone (Wang 1998 **Level II**, n=60, JS 4) or in conjunction with opioids (Kizilkaya 2005 **Level II**, n=72, JS 4; Kizilkaya 2004 **Level II**, n=60, JS 2) and/or local anaesthetics (Moeen 2017, **Level II,** n= 60, JS 5; Rasmussen 2002 **Level II**, n=60, JS 3). Dexamethasone on its own was less effective than pethidine or fentanyl (Saryazdi 2006 **Level II**, n=48, JS 3). A single IA injection of methylprednisolone one wk before TKA did not reduce acute postoperative pain (Luna 2017 **Level II,** n=48, JS 4). There may be a higher risk of septic arthritis with IA steroids (Armstrong 1992 **Level IV**, n=4,256).

Subacromial injections of corticosteroids have been shown to be effective in treating rotator cuff tendonitis for up to 9 mth vs placebo (NNT 3.3; 95%CI 1.8 to 7.7) and are superior to oral NSAIDs (NNT 2.5; 95%CI 1 to 9) (Arroll 2005 **Level I** [QUOROM], 7 RCTs, n=347). In patients with tendonitis of the shoulder or elbow, steroid injections show similar benefits to NSAIDs for early (up to 1 wk) pain relief (Gaujoux-Viala 2009 **Level I**, 20 RCTs, n=1,731).

In patients having hand surgery, IVRA using a combination of lidocaine/dexamethasone resulted in lower pain scores and lower analgesic requirements for 24 h vs lidocaine alone or lidocaine IVRA with IV dexamethasone in the nonoperative arm (Bigat 2006 **Level II**, n=75, JS 2). The addition of dexamethasone to lidocaine/ketorolac IVRA for hand surgery improved intraoperative tourniquet tolerance and postoperative analgesia vs lidocaine IVRA alone (Jankovic 2008 **Level II**, n=45, JS 3).

KEY MESSAGES

1. For brachial plexus blocks, addition of dexamethasone to local anaesthetic prolongs the duration of sensory and motor block and improves postoperative analgesia with only very limited benefits over systemic administration (**S**) (**Level I** [Cochrane Review]).
2. For transverse abdominis plane blocks, addition of dexamethasone to local anaesthetics prolongs the duration of sensory block, improves postoperative analgesia and PONV with no comparison to systemic administration (**N**) (**Level I** [PRISMA]).
3. After spinal surgery, epidural steroid application intraoperatively by the surgeon provides analgesic benefit up to 24 hours and reduces length of stay (**N**) (**Level I** [PRISMA]).
4. For acute radicular pain, lumbar epidural corticosteroid administration is effective for short-term relief (**S**) (**Level I** [PRISMA]).
5. Subacromial injections of corticosteroids are superior to oral NSAIDs in treating rotator cuff tendonitis (**U**) (**Level I** [QUOROM]).
6. For peripheral nerve blocks, addition of dexamethasone to local anaesthetics prolongs the duration of sensory block and improves postoperative analgesia with only limited benefits over systemic administration (**N**) (**Level II**).
7. For epidural analgesia, addition of dexamethasone improves postoperative analgesia and reduces opioid requirements (**N**) (**Level II**).
8. Addition of dexamethasone to intravenous regional anaesthesia with lidoocaine improves analgesia for up to 24 hours (**U**) (**Level II**).
9. Addition of corticosteroid to periarticular injection of local anaesthetic does not improve pain relief or range of movement following total knee arthroplasty (**U**) (**Level II**).
10. Following knee joint arthroscopy, intra-articular steroids in combination with either local anaesthetic or opioids reduce pain, analgesic consumption and duration of immobilisation (**U**) (**Level II**).
11. There is a risk of septic arthritis with intra-articular steroids (**U**) (**Level IV**).
12. Repeat epiudural steroid injections are associated with reduced bone mineral density and increased risk of vertebral fractures (**N**) (**Level IV SR).**

The following tick boxes represent conclusions based on clinical experience and expert opinion:

☑ Concerns have been raised regarding the safety of epidural steroids (**U**).

☑ There is little data in humans regarding the neurotoxicity of perineural corticosteroids (**N**).

4.13 | Other regional analgesic medicines

4.13.1 | Midazolam

Preservative-free midazolam has been proposed as a spinal analgesic due to its action on $GABA_A$ receptors. Robust safety data for the use of intrathecal (IT) midazolam in humans is lacking (Yaksh 2017 **NR**), consequently midazolam is currently not licenced for IT use. Several studies in animal models have raised concern about IT midazolam toxicity (Williams 2011 **BS**; Lavand'homme 2006 **NR**; Yaksh 2004 **NR**; Erdine 1999 **BS**; Malinovsky 1991 **NR**). However, cumulative experience with IT midazolam in human trials confirms beneficial analgesic activity with no demonstrable irreversible side effects vs placebo (Ho 2008 **Level I**, 13 RCTs, n=672; Yaksh 2017 **NR**; Staikou 2014 **NR**). There is insufficient long-term data to unequivocally exclude long-term neurological complications, although none have yet been reported.

IT midazolam added to IT local anaesthetic in perioperative and peripartum patients in comparison with IT local anaesthetic alone shows a reduced incidence of nausea and vomiting and delayed time to request for rescue analgesia (WMD 99 min; 95%CI 76 to 121), but did not affect the duration of motor block (Ho 2008 **Level I**, 13 RCTs, n=672). Multiple subsequent RCTs have confirmed these findings as well as earlier onset and better quality of analgesia for addition of IT midazolam to IT local anaesthetics vs IT local anaesthetic alone (Abdollahpour 2015 **Level II**, n=75, JS 4; Selvaraj 2015 **Level II**, n=100, JS 3; Chattopadhyay 2013 **Level II**, n=90, JS 5; Shadangi 2011 **Level II**, n=100, JS 4), compared to addition of IT dexmedetomidine (Shukla 2016 **Level II**, n=80, JS 3; Samantaray 2015 **Level II**, n=60, JS 4) or IT fentanyl (Codero 2016 **Level II**, n=40, JS 3; Safari 2012 **Level II**, n=90, JS 3) and also when added to IT fentanyl (Gupta 2015 **Level II,** 75 patients, JS 4) or IT sufentanil (Salimi 2014 **Level II**, n=80, JS2). In addition, IT midazolam decreased the incidence of transient neurologic symptoms with IT lidocaine (Selvaraj 2015 **Level II**, n=100, JS 3). Overall, an optimum dose of IT midazolam has not been clearly determined; doses less than 1 mg probably have no effect on prolongation of spinal blockade or analgesia, and the commonly effective doses administered in clinical trials range between 1 to 2 mg (Staikou 2014 **NR**). On the basis of the above meta-analyses, reviews and trials, IT midazolam may cause mild, but not excessive sedation, no additional cardio-respiratory adverse effects or urinary retention.

Specific to the obstetric population, IT midazolam does not seem to have any deleterious effect on infants' Apgar scores (Abdollahpour 2015 **Level II**, n=75, JS 4). IT midazolam 1 mg as a part of combined spinal epidural technique in pre-eclamptic parturients undergoing elective Caesarean section is inferior to IT preservative free magnesium sulphate 50 mg with regard to prolongation of analgesia (Paleti 2018 **Level II**, n=50, JS 4; Sapna 2013 **Level III-2**, n=124).

A single preoperative epidural dose of midazolam combined with ketamine in patients having a gastrectomy improved analgesia and prolonged the time to rescue analgesia vs epidural ketamine or placebo, with no significant adverse effects (Wang 2006 **Level II**, n=44, JS 4). Midazolam added to bupivacaine for epidural infusion improved analgesia but increased sedation (Nishiyama 2002 **Level II**, n=100, JS 1).

Midazolam has been added to caudal epidural analgesia in paediatric surgery, although age-related toxicity issues have not been addressed. In combination with bupivacaine, it prolongs postoperative analgesia (Kumar 2005 **Level II**, n=80, JS 5; Ansermino 2003 **Level I**, 2 RCTs [midazolam], n=60). In infants having hernia repairs, neither midazolam nor fentanyl added to bupivacaine for caudal anaesthesia improved postoperative analgesia or recovery (Baris 2003 **Level II**, n=75, JS 4).

4.13.2 | Neostigmine

Neostigmine acts as a spinal analgesic by potentiation of muscarinic cholinergic activity. In a literature review of animal and human studies, there was no evidence of neurotoxicity with spinal neostigmine (Hodgson 1999 **NR**).

4.13.2.1 | Neuraxial

Adding neostigmine to local anaesthetics (bupivacaine or ropivacaine) ± opioid for neuraxial administration in labour analgesia and postoperative analgesia after Caesarean section permits reduction of local anaesthetic doses (MD -4.08 mg/h; 95% CI -6.7 to -1.5) (Cossu 2015 **Level I**, 16 RCTs, n= 1,186). Only IT neostigmine (5 RCTs), but not epidural neostigmine (11 RCTs), increases risk of nausea (OR 9; 95%CI 4.7 to 17.1). Neuraxial neostigmine reduces risk of pruritus (OR 0.4; 95%CI 0.2 to 0.7) (6 RCTs), but does not increase hypotension, sedation or affect fetal outcome.

4.13.2.2 | Intrathecal

IT neostigmine for perioperative and peripartum analgesia prolongs the time to first analgesia request and results in a slight improvement in pain scores and a reduced need for rescue medication, however, it increases nausea and vomiting (OR 5.0; 95%CI 3.4 to 7.3), bradycardia requiring atropine (OR 2.7; 95%CI 1.4 to 5.4) and anxiety, agitation and restlessness (OR 10.3; 95%CI 3.7 to 28.9) (Ho 2005 **Level I**, 19 RCTs, n=1,019) (4 RCTs overlap with Cossu 2015). The authors conclude that the significant adverse effects outweighed any clinical benefit, a conclusion supported by another systematic review, where a lack of a clear dose-response is also identified (Habib 2006 **Level I,** 17 RCTs [IT neostigmine], n unspecified) (15 RCTs overlap).

Subsequent RCTs not included in these meta-analyses support their findings in principle. In patients having various types of surgery under spinal anaesthesia, IT neostigmine prolonged time to first analgesic request (Kayalha 2015 **Level II** n=68, JS 4; Akinwale 2012 **Level II**, n=60, JS 4) and/or effective postoperative analgesia (Kumari Vasantha 2018 **Level II** n=100, JS 4) and/or reduced analgesic consumption (Jain 2012 **Level II**, n=45, JS 4).

In patients having spinal anaesthesia, IT clonidine 75 mcg had longer time to first analgesic request (MD 62 min) but more hypotension during surgery vs IT neostigmine 50 mcg (Yoganarasimha 2014 **Level II**, n=50, JS 3). Both, IT clonidine 30 mcg and IT neostigmine 75 mcg increased the duration spinal analgesia, but neostigmine caused more nausea and vomiting (Bhar 2016 **Level II**, n=150, JS 4). In patients undergoing orthopaedic surgery under spinal anaesthesia, IT dexmedetomidine 5 mcg was superior to IT neostigmine 50 mcg due to faster onset of anaesthesia, better intra- and postoperative analgesia, and prolonged duration of motor and sensory blockade without significant increases in adverse effects (Singh 2017 **Level II** n=75, JS 4). After elective gynaecological surgery under spinal anaesthesia, IT neostigmine extended postoperative analgesia more than IT magnesium (Joshi-Khadke 2015 **Level II**, n=75, JS 4). After surgery for tibial fracture under spinal anaesthesia, IT neostigmine 150 mcg/bupivacaine vs IT fentanyl 25 mcg/bupivacaine and IT magnesium 50 mg/bupivacaine increased the incidence of hypotension, bradycardia, and nausea and vomiting, and failed to prolong duration of analgesia (Mokaram Dori 2016 **Level II**, n=210, JS 4).

Adverse events of IT neostigmine seem to be dose-dependent. In patients undergoing lower abdominal and lower limb surgery, IT neostigmine 150 mcg vs IT neostigmine 50 mcg as an adjuvant to bupivacaine 12.5 mg caused more nausea and vomiting (Pandey 2016 **Level II**, n=75, JS 4). IT neostigmine 75 mcg caused less nausea and vomiting than IT neostigmine 150 mcg when added to spinal anaesthesia for Caesarean section (Hye 2010 **Level II**, n=90, JS 4). Very low-dose IT neostigmine 1 mcg increased the duration of analgesia and decreased the analgesic consumption

over 24 h post-TKA with no increase in the incidence of adverse effects including nausea or vomiting. (Jain 2012 **Level II**, n=45, JS 4).

4.13.2.3 | Epidural

Epidural neostigmine in the general surgical and obstetric populations improves postoperative analgesia in most studies without increasing the incidence of adverse effects (Habib 2006 **Level I**, 7 RCTs [epidural neostigmine], n unspecified). Epidural neostigmine combined with an opioid reduces epidural opioid requirements but may not decrease opioid-related adverse effects vs the opioid alone (Walker 2002 **Level I**, 6 RCTs [neostigmine], n=370).

See Section 10.6.3.1 for use of neostigmine in paediatric caudal epidural analgesia.

4.13.2.4 | Other

Intra-articular administration of neostigmine produces a useful analgesic effect in the postoperative period and is not associated with an increase in the incidence of adverse effects (Habib 2006 **Level I**, 4 RCTs [intra-articular neostigmine], n unspecified).

Studies investigating the efficacy of adding neostigmine to the local anaesthetics used for brachial plexus block and IVRA report conflicting results (Habib 2006 **Level I,** 4 RCTs [perineural neostigmine], n unspecified).

4.13.3 | Botulinum toxin A

Botulinum toxin (botox) A is an exotoxin produced from clostridium botulinum (Sandrini 2017 **NR**; Shilpa 2014 **NR**). Following direct IM injection, botulinum toxin A irreversibly binds to the acetylcholine receptor inducing chemical denervation with resultant dose-dependent muscular paralysis. The extent and duration of paralysis depends on the dose administered. Systemic weakness may follow high cumulative doses. Reinnervation occurs over weeks to months. Botulinum toxin A does not interfere with acute pain perception, nor does it cause local anaesthesia. The use of botulinum toxin in the treatment of chronic painful conditions is beyond the scope of this section.

In treating pain and related muscle spasm in a range of conditions, botulinum toxin A is effective in reducing limb spasm (Son 2019 **Level I**, 27 RCTs, n=2,793; Dong 2017 **Level I**, 22 RCTs, n=1,804), but evidence relating to spasticity-related pain remains uncertain (Baker 2013 **Level I**, 10 RCTs [in pain], n=971). In a range of neuropathic pain conditions (eg trigeminal neuralgia), Botulinum toxin A reduces pain at 4 wk (MD -1.6/10; 95%CI -3.2 to -0.1), 12 wk (MD -1.5/10; 95%CI -2.1 to -0.9) and 24 wk (MD -1.6/10; 95%CI -2.8 to -0.4) (Meng 2018 **Level I**, 12 RCTs, n=495).

In subacute and chronic neck disorders with or without associated cervicogenic headache, IM botulinum toxin A injections provide no clear benefit (Langevin 2011 **Level I** [Cochrane], 9 RCTs, n=503). There is insufficient evidence for the use botulinum toxin A for the treatment of rare head and neck pain syndromes (cluster headache, chronic paroxysmal hemicrania, trigeminal neuralgia) with varying results from only a few small sized trials (cervicogenic headache, chronic neck pain, temporomandibular disorders) (Sycha 2004 **Level I**, 15 RCTs, n=721).

KEY MESSAGES

1. Intrathecal midazolam combined with a local anaesthetic improves and prolongs analgesia and reduces postoperative nausea and vomiting (**U**) (**Level I**).
2. Intrathecal neostigmine improves perioperative and peripartum analgesia in combination with other intrathecal medications (**S**) (**Level I**) but is associated with dose-dependent significant adverse effects, in particular nausea and vomiting (**Q**) (**Level I**).
3. Epidural neostigmine combined with local anaesthetics improves postoperative and peripartum analgesia without increasing the incidence of adverse effects (**U**) (**Level I**).
4. Epidural neostigmine combined with an opioid reduces the dose of epidural opioid that is required for analgesia (**U**) (**Level I**).

4.14 | Complementary and alternative medicine

Complementary and alternative medicine (CAM) is defined as healthcare practices outside the conventional dominant "orthodox" health system of Western industrialised society (Belgrade 2008 **NR**). The boundary between CAM and conventional medicine overlaps and changes with time. In some cultures, these therapies may be considered conventional mainstream practices.

CAM may be classified into two groups: as natural products, including but not limited to herbs, vitamins, minerals and probiotics, vs mind and body practices such as yoga, meditation, massage, acupuncture, tai chi, qi gong, chiropractic and osteopathic manipulation, hypnotherapy and others (NCCIH 2018 **GL**). Ayurvedic medicine, traditional Chinese medicine, homeopathy and naturopathy are considered CAM. CAM approaches are usually termed "alternative" when used in place of conventional medical treatments and "complementary" when used together. This section covers the use of natural products administered as analgesic medicines for treatment of acute pain only; good data on their use in this indication are limited.

See Section 10.11 for paediatric specific data.

4.14.1 | Vitamins

Several mechanisms have been described to explain the analgesic effect of Vitamin C (Carr 2017 **NR**).

Vitamin C reduces acute postoperative pain (Chaitanya 2018 **Level IV SR** [PRISMA], 4 RCTs & 3 studies, n=12,395) and has moderate evidence for a reduction of postoperative morphine consumption (Chen 2016 **Level I** [PRISMA], 7 RCTs [postoperative], n=854). In subsequent RCTs, oral Vitamin C 1 g/d decreased postoperative pain score and rescue analgesia requirements after foot and ankle surgery (Jain 2019 **Level II**, n=60, JS 5) and after major abdominal surgery vs placebo where Vitamin C 2 g was comparable to melatonin 6 mg (Tunay 2020 **Level II**, n=165, JS 5). In acute herpes zoster, concomitant Vitamin C infusion 5 g did not improve pain relief (Kim 2016 **Level II**, n=87, JS 2).

Vitamin B complex (comprising of thiamine [B1], riboflavin [B2], pyridoxine [B6] and nicotinamide) reduced pain intensity and analgesic consumption after Caesarean section when combined with gabapentin vs gabapentin alone (Khezri 2017 **Level II**, n=128, JS 4). Vitamin B complex (thiamine, pyridoxine and hydroxo- or cyanocobalamin) when combined with ketorolac 15 mg was as effective as ketorolac 30 mg monotherapy after Caesarean section (Beltran-Montoya 2012 **Level II**, n=100, JS 3) or more effective when combined with diclofenac 50 mg in relieving acute low back pain vs diclofenac monotherapy (Mibielli 2009 **Level II**, n=372, JS 5). Also in acute low back pain, combination diclofenac/vitamin B complex TPC (thiamine, pyridoxine, and cyanocobalamin) provides greater analgesia vs diclofenac monotherapy (OR 2.23; 95%CI 1.59 to 3.13) (Calderon-Ospina 2020 **Level I**, 4 RCTs, n=1,108). In patients with acute ophthalmic zoster, Vitamin B 12 1,000 mcg/lidocaine 20 mg SC daily for 12 d into the regions of the affected innervations of V1 achieved better pain relief vs controls (IM vitamin B 12, local lidocaine) (Xu 2016a **Level II**, n=98, JS 3; Xu 2016b **Level II**, n=204, JS 3).

4.14.2 | Herbal Medicines

A meta-analysis on oral homeopathic St John's wort *(Hypericum perforatum)* showed no significant benefit on dental pain; the meta-analysis was limited by marked heterogeneity and poor study quality (Raak 2012 **Level I** [QUOROM], 4 studies, n=325). A subsequent review on topical application of *Hypericum perforatum* found studies on improved pain relief for acute otitis media, herpes skin lesions and wound pain after Caesarean section and suggests that this may be due to its anti-inflammatory effects (Galeotti 2017 **NR**). Oral *Hypericum perforatum* affects the

metabolism of oxycodone through induction of cytochrome P450 3A (CYP3A) and leads to a significant reduction of plasma concentration and half-life reducing efficacy (Nieminen 2010 **Level II**, n=12, JS 3).

Homeopathic preparations of *Arnica montana* (containing sesquiterpenes) in acute postoperative pain have shown variable results. A systematic review and other studies concluded that homeopathic arnica vs placebo is not effective for pain relief after orthopaedic surgery (Roberts 2012 **Level I** [PRISMA], 3 studies (arnica), n=181), hallux valgus surgery (Karow 2008 **Level II**, n=88, JS 4) or abdominal hysterectomy (Hart 1997 **Level II**, n=93, JS 5). In contrast, homeopathic arnica vs placebo reduced pain after tonsillectomy (Robertson 2007 **Level II**, n=190, JS 5) (although a large number of patients in this study were lost to follow-up) and after varicose vein surgery (Wolf 2003 **Level II**, n=60, JS 5). A subsequent review (covering many of the studies above) concluded that arnica in homeopathic dilutions has high tolerability and may have effects in treating inflammation (Iannitti 2016 **NR**). The authors argue that variations in formulation affects the quantity of active sesquiterpenes and hence result in variable clinical effects. Traumeel S (an over-the-counter homeopathic highly diluted preparation of extracts from a combination of plants [including arnica] and minerals) was also ineffective following foot surgery (Singer 2010 **Level II**, n=80, JS 4).

A systematic review of the efficacy and safety of Damask rose *(Rosa damascena Mill*) suggests safe use with some pain relief in acute settings (3 RCTs) (Nayebi 2017 **Level I**, 12 RCTs, n=748). Although most of the studies compared topical or inhalational (aromatherapy) applications, one study used oral extract with greater pain relief after Caesarean section vs placebo. The Damask rose recipients also experienced a longer time to requesting rescue analgesia, with lower total analgesic consumption (Gharabaghi 2011 **Level II**, n=92, JS 3).

Zingiberaceae include turmeric (*Curcuma longa*), ginger (*Zingiber officinale*), Javanese ginger (*Curcuma zanthorrhiza*) and galangal (*Alpinia galanga*). Curcumin (diferuloyl methane) is the principal curcuminoid of Indian spice turmeric, while the anti-inflammatory components of ginger are gingerol and zingerone. Extracts of Zingiberaceae reduce pain intensity in a mix of acute and chronic pain states (SMD -0.67; 95%CI -1.13 to -0.21) (Lakhan 2015 **Level I** [PRISMA], 8 RCTs, n=734). Curcuminoids are effective in reducing pain vs a pooled control group of placebo or NSAID (SMD -0.57; 95%CI -1.11 to -0.03), but not vs either placebo or NSAID in a mix of acute and chronic pain states (Sahebkar 2016 **Level I** [PRISMA], 8 RCTs, n=606) (2 RCTs overlap). The effect was greater when a bioavailability enhancer such as piperine was administered (SMD -0.98; 95%CI -1.81 to -0.15); however, only three RCTs in the review evaluated the effectiveness of curcuminoids in acute pain and were not separately analysed. A combination nutritional supplement containing *Boswellia serrata* (30% boswellic acid) and *Curcuma longa* (95% curcuminoids) lowered pain and tramadol rescue requirements only in the first postoperative wk after arthroscopic supraspinatus tendon repair vs placebo (Merolla 2015 **Level II**, n=104, JS 3). A subsequent RCT found ginger powder 500 mg as effective as ibuprofen 400 mg and superior to placebo with regard to pain relief and rescue analgesic requirements POD 1 in patients after wisdom tooth extraction (Rayati 2017 **Level II**, n=67, JS 4).

There is weak evidence for a reduction of rescue analgesia requirements (RR 0.5; 95%CI 0.1 to 2.1) with use of Damask rose (*Rosa damascena*) and ginger vs placebo after laparoscopic and obstetric/gynaecological surgery (Arruda 2019 **Level III-1 SR** [PRISMA], 10 RCTs & 1 study, n=693).

A transdermal preparation of Fenugreek seeds 10% (*Trigonella foenum-graecum L*.) applied topically for open hernioplasty reduced pain intensity and rescue analgesics consumption vs placebo patch and in the first 6 h vs diclofenac patch (Ansari 2019 **Level II**, n=90, JS 4).

Saffron (*Crocus sativus*) 250 mg as a syrup taken together orally with date-juice vs saffron with artificial sugar and placebo reduced pain intensity and anxiety during labour in primiparous women (Mohammadierad 2018 **Level II**, n=96, JS 5).

Herbal medicines (White willow bark [*Salix alba*] and Devil's claw [*Harpagophytum procumbens*]) for non-specific low-back pain (a mix of acute, subacute and chronic back pain) result in short-term improvement vs placebo (Gagnier 2016 **Level I** [Cochrane], 14 RCTs, n=2,050). The review also reported on the effectiveness of several topical preparations of herbal plaster and ointment-based applications including Cayenne (*Capsicum frutescens*), Comfrey root extract (*Symphytum officinale*) and Brazilian arnica (*Solidago chilensis*). However, the quality of evidence was poor. Side effects were usually mild and transient.

Herbal and dietary supplement combinations are commonly prescribed in CAM treatment. A study using a mixture of homoeopathic preparations (arnica, *Bryonia alba, Hypericum perforatum, Ruta graveolens*) did not show any benefit in postoperative pain relief and morphine consumption after knee ligament reconstruction surgery (Paris 2008a **Level II**, n=158, JS 4). There is also no clear evidence that the combination of oral arnica with *Hypericum perforatum* is effective in pain relief after dental procedures (Galeotti 2017 **NR**). Another herbal combination consisting of anise (*Pimpinella anisum*), celery (*Apium graveolens*) and saffron (*Crocus sativus*) (referred to as PAC), had greater pain reduction and faster onset in patients with post-partum pain vs mefenamic acid in a single-blind study (Simbar 2015 **Level II**, n=108, JS 2).

Puerarin, a Chinese herb extract, was analgesic and anti-inflammatory for burns dressing changes; however, the control group received no analgesia (Zhang 2013 **Level II**, n=32, JS 5).

Rhubarb combined with trypsin inhibitor versus trypsin inhibitor alone improved outcomes of acute pancreatitis including abdominal pain (Hu 2018b **Level I**, 16 RCTs, n=912).

Probiotics reduce the pain and symptom severity in IBS vs placebo (Didari 2015 **Level I**, 15 RCTs, n=1,793).

For dysmenorrhoea, a Cochrane review investigated twelve different herbal medicines German chamomile (*Matricaria chamomilla, M recutita, Chamomilla recutita*), cinnamon (*Cinnamomum zeylanicum, C. verum*), Damask rose (*Rosa damascena*), dill (*Anethum graveolens*), fennel (*Foeniculum vulgare*), fenugreek (*Trigonella foenum-graecum*), ginger (*Zingiber officinale*), guava (*Psidium guajava*), rhubarb (*Rheum emodi*), uzara (*Xysmalobium undulatum*), valerian (*Valeriana officinalis*), and zataria (*Zataria multiflora*) and five non-herbal supplements (fish oil, melatonin, vitamins B1 and E, and zinc sulphate) in a variety of formulations and doses (Pattanittum 2016 **Level I** [Cochrane], 27 RCTs, n=3,101). Very limited evidence of effectiveness vs placebo or no treatment was found for fenugreek (1 RCT, n=101), fish oil (1 RCT, n=120), fish oil plus vitamin B1 (1 RCT, n=120), ginger (4 RCTs, n=335), valerian (1 RCT, n=100), vitamin B1 alone (1 RCT, n=120), zataria (1 RCT, n=99), and zinc sulphate (1 RCT, n=99). Very limited evidence was found that chamomile was more effective than NSAIDs (1 RCT, n=160), while no difference vs NSAIDs was found for dill (1 RCT, n=47), fennel (1 RCT, n=59), guava (1 RCT, n=155), rhubarb (1 RCT, n=45), valerian (1 RCT, n=99) and Damask rose (1 RCT, n=92). Comparisons between CAM for dysmenorrhoea showed that Vitamin B1 may be more effective than fish oil (1 RCT, n=120). Subsequent systematic reviews emphasise again the limited quality of the evidence, the high risk of bias and the difficulties to draw definitive conclusions on efficacy. One systematic review analysed results for fennel (*Foeniculum vulgare*) (4 RCTs, n=295), chamomile (*Matricaria chamomilla)* (3 RCTs, n=220) and zataria (*Zataria multiflora*) (3 RCTs, n=302) (Sharghi 2019 **Level I**, 17 RCTs, n=1,656). Another identified only one RCT with low risk of bias to be considered supportive evidence for use of Damask rose (*Rosa damascena*) (Pellow 2018 **Level I** [PRISMA], 22 RCTs, n=1,937).

4.14.3 | Aromatherapy

Aromatherapy describes the inhalation (or sometimes administration to the skin) of essential oils as part of herbal medicine, possibly affecting emotions through the neuroendocrine and autonomic nervous system.

Aromatherapy (oil inhalation and oil massage) reduces pain of dysmenorrhoea vs no treatment or placebo treatment; however, there is a high risk of bias weakening these results (Lee 2018d **Level III-1 SR**, 19 studies, n=1,787; Song 2018 **Level III-3 SR** [PRISMA], 9 RCTs & 12 studies, n=1,580) (13 studies overlap).

There is no sufficient evidence to support the use of aromatherapy for the treatment of postoperative pain (Dimitriou 2017 **Level I**, 9 RCTs, n=644).

Aromatherapy may reduce pain, anxiety and improve sleep quality in burns patients, but the low quality of trials with regard to randomisation and bias does not permit a conclusion (Choi 2018 **Level I** [PRISMA], 4 RCTs, n=248). The addition of aromatherapy (lavender) to standard treatment of renal colic with parenteral diclofenac improved pain scores at 30 min, but only in female patients (Irmak Sapmaz 2015 **Level II**, n=100, JS 0).

4.14.4 | Melatonin

An experimental study on volunteers observed a dose dependent effect on pain threshold and pain tolerance after sublingual melatonin 0.15 mg/kg or 0.25 mg/kg vs placebo (Stefani 2013 **Level II EH**, n=61, JS 5). Two preoperative melatonin doses of 5 mg led to lower pain and anxiety scores in the first 24 h (NNT 2.20 and 2.53) and reduced IV PCA morphine usage after abdominal hysterectomy (Caumo 2007 **Level II**, n=35, JS 5). Melatonin 6 mg vs Vitamin C 2 g both reduced pain and patient-controlled morphine consumption and supplementary doses of diclofenac in patients after major abdominal surgery vs placebo (Tunay 2020 **Level II**, n=165, JS 5). Melatonin reduced pain during blood taking in children vs placebo (Marseglia 2015 **Level II**, n=60, JS 5).

4.14.5 | Honey

Oral administration of honey has been associated with improved pain relief (3 RCTs, n=201) and reduced need for analgesic intake after tonsillectomy in children vs placebo, especially in the early postoperative period based on RCTs of poor methodological quality (Lal 2017 **Level I** [PRISMA], 8 RCTs, n=545; Hwang 2016 **Level I**, 4 RCTs, n=264) (4 RCTs overlap). An RCT not included in the meta-analyses found that onset to pain relief was faster, pain severity was lower and the need for rescue analgesia was less in the honey recipients vs controls (Mohebbi 2014 **Level II**, n=80, JS 2).

KEY MESSAGES

1. White willow bark (*Salix alba*) and devil's claw (*Harpagophytum procumbens*) are effective in treating acute episodes of low back pain (**U**) (**Level I** [Cochrane Review])
2. A variety of complementary medicines may show efficacy in prevention and treatment of primary dysmenorrhoea based on very limited evidence (**W**) (**Level I** [Cochrane Review]), including aromatherapy (**N**) (**Level III-1 SR**).
3. Curcuminoids and extracts of Zingiberaceae may reduce pain intensity in acute and chronic pain states compared to placebo (**N**) (**Level I** [PRISMA]).
4. Oral administration of honey versus control reduces postoperative pain and analgesic use after tonsillectomy (**N**) (**Level I** [PRISMA]).
5. Vitamin C reduces postoperative opioid requirements (**N**) (**Level I** [PRISMA] and postoperative pain compared to placebo (**N**) (**Level IV SR** [PRISMA]).
6. Aromatherapy (**N**) (**Level I**), homeopathic preparations of arnica (*Arnica montana*) (**U**) (**Level I** [PRISMA]) and St John's wort (*Hypericum perforatum*) are not effective in treating acute postoperative pain (**U**) (**Level I** [QUOROM]).
7. St John's wort (*Hypericum perforatum*) induces metabolism of oxycodone reducing its plasma concentrations and efficacy (**U**) (**Level II**).

The following tick box represents conclusions based on clinical experience and expert opinion:

☑ There is some evidence that some complementary and alternative medicines may be effective in some acute pain states. Adverse effects and interactions with medications have been described with complementary and alternative medicines and must be considered before their use (**U**).

☑ The evidence on complementary and alternative medicines is characterised by small sample sizes and study designs prone to bias and caution is urged in interpreting results. Additionally, the safety and potential drug interactions of many complementary and alternative medicines have not been adequately assessed **(N).**

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5

Administration of analgesic medicines

Section Editor:
Prof Stephan A Schug

5.0 | Administration of analgesic medicines

Analgesic medicines can be administered by a number of different routes, either relying on a systemic or local effect or a combination of both. The choice of route may be determined by various factors, including the aetiology, severity, location and type of pain, the patient's overall condition and the characteristics of the chosen administration technique. Additional factors to consider with any route of administration are ease of use, accessibility, speed of analgesic onset, reliability of effect, duration of action, patient acceptability and cost.

The principles of individualisation of dose and dosing intervals apply to the administration of all analgesic agents, particularly opioids, by any route. A lack of flexibility in dose schedules has often meant that intermittent and prn (as needed) methods of pain relief have been ineffective when the routes of administration discussed below have been used (Bandolier 2003 **NR**). Frequent assessment of the patient's pain and their response to treatment (including the occurrence of any adverse effects) rather than strict adherence to a given dosing regimen is required if adequate analgesia is to be obtained.

Sections 5.1 to 5.5 below relate to opioids, paracetamol, nsNSAIDs and coxibs. For information relating to oral, parenteral and regional routes of administration of adjuvant medicines, refer to Sections 4.6 to 4.12.

Sections 5.6 to 5.9 below relate to routes of administration involving techniques of regional and local analgesia.

5.1 | Oral and sublingual route

Oral administration of analgesic agents is simple, non-invasive, has good efficacy in most settings and has high patient acceptability. Other than in the treatment of severe acute pain and providing there are no contraindications to its use, it is the route of choice for the administration of most analgesic medicines (Chou 2016 **GL**).

Limitations to the oral route include vomiting or delayed gastric emptying, when absorption is likely to be impaired. If multiple doses of an oral analgesic medicine are given before return of normal gastric motility, accumulated doses may enter the small intestine at the same time once emptying resumes ("*dumping effect*"). This could result in an unexpectedly large systemic uptake of the medicine and an increased risk of adverse effects.

Rates of absorption will vary according to the formulation of the oral analgesic agent (eg tablet, suspension, slow release [SR] preparation). Bioavailability will also vary between medications because of the effects of first-pass hepatic metabolism following uptake into the portal circulation. Titration of pain relief with oral analgesic medicines is slower compared with some of the other routes of administration discussed below.

Direct comparisons between oral opioid and nonopioid analgesics, or between oral and other routes of administration, are limited. Indirect comparisons, where the individual medications have been compared with a placebo, have been used to generate a "*league table*" of analgesic efficacy (see Table 5.1). This table is based on randomised, double-blind, single-dose studies or meta-analyses of such studies in patients with moderate to severe pain and shows the number of patients that need to be given the active medication to achieve at least 50% pain relief in one patient compared with a placebo ($NNT_{50\%}$) over a 4 to 6 h treatment period (Moore 2015 **Level I** [Cochrane], ≈460 RCTs, n≈50,000; Moore 2011 **Level I** [Cochrane], ≈350 RCTs, n≈45,000; Moore 2003 **Level I**, unspecified number of RCTs, n unspecified).

The validity of this approach as a true method of comparison of medicines may be questioned as there is no standardisation of the acute pain model or patient and only single doses of the analgesic agents are used. The effects of the analgesics may vary with different pain models (Gray 2005 reanalysing Barden 2004 **Level I**, 43 RCTs [paracetamol], n unspecified). However, it may be reasonable, in some circumstances, to extrapolate estimates of analgesic efficacy from one pain model to another (Barden 2004 **Level I**, 43 RCTs [paracetamol], n unspecified). Note for example that Ketoprofen 25 mg has a better $NNT_{50\%}$ of 2.0 (95% CI 1.8 to 2.3) than Ketoprofen 50mg $NNT_{50\%}$ 3.3 (95% CI 2.7 to 4.3) suggesting that significant caution should be undertaken comparing data in this way.

Table 5.1 | Table of analgesic efficacy (in all types of surgery)

Analgesic medication* and dose (mg)	Number of patients in comparison	$NNT_{50\%}$	Lower 95% confidence interval	Higher 95% confidence interval
Paracetamol + Ibuprofen 1000/400	543	1.5	1.4	1.7
Paracetamol + Ibuprofen 500/200	508	1.6	1.5	1.8
Dipyrone 1,000	113	1.6	1.3	2.2
Etoricoxib 120	798	1.8	1.7	2.0
Ketorolac 20	69	1.8	1.4	2.5
Ketorolac 60 (IM)	116	1.8	1.5	2.3
Oxycodone IR 10 + Paracetamol 1,000	289	1.8	1.6	2.2
Piroxicam 40	30	1.9	1.2	4.3
Ketoprofen 25	535	2.0	1.8	2.3
Diclofenac *potassium* 50	757	2.1	1.9	2.5
Diflunisal 1,000	357	2.1	1.8	2.6
Ibuprofen + caffeine 200/100	334	2.1	1.9	3.1
Ibuprofen *fast acting* 200	828	2.1	1.9	2.4
Ibuprofen *fast acting* 400	1364	2.1	1.9	2.3
Ketoprofen 100	321	2.1	1.7	2.6
Ibuprofen + codeine 400/26-60	443	2.2	1.8	2.6
Paracetamol 800/1,000 + Codeine 60	192	2.2	1.8	2.9

Analgesic medication* and dose (mg)	Number of patients in comparison	$NNT_{50\%}$	Lower 95% confidence interval	Higher 95% confidence interval
Oxycodone IR 5 + Paracetamol 500	150	2.2	1.7	3.2
Diclofenac *potassium* 100	787	2.3	2.0	2.5
Dipyrone 500	288	2.3	1.9	3.1
Ibuprofen + Oxycodone 400/5	603	2.3	2.0	2.8
Aspirin 1,200	249	2.4	1.9	3.2
Diclofenac *fast acting* 100	486	2.4	2.0	3.0
Ibuprofen + Caffeine 100/100	200	2.4	1.9	3.1
Ketoprofen 12.5	274	2.4	1.9	3.1
Flurbiprofen 100	416	2.5	2.0	3.1
Ibuprofen 400	6,475	2.5	2.4	2.6
Diclofenac *potassium* 25	502	2.6	2.2	3.3
Diflunisal 500	391	2.6	2.1	3.3
Celecoxib 400	722	2.6	2.3	3.0
Ketorolac 10	790	2.6	2.3	3.1
Tramadol 75 + Paracetamol 650	679	2.6	2.3	3.0
Flurbiprofen 50	692	2.7	2.3	3.3
Ibuprofen 600	203	2.7	2.0	4.2
Paracetamol 650 + Oxycodone IR 10	1,043	2.7	2.4	3.1
Naproxen 500/550	784	2.7	2.3	3.3
Naproxen 400/440	334	2.7	2.2	3.5
Piroxicam 20	280	2.7	2.1	3.8
Paracetamol 650 + Tramadol 112	201	2.8	2.1	4.4
Etodolac 400	222	2.9	2.3	4.0
Ibuprofen 200	2103	2.9	2.7	3.2
Lornoxicam 8	273	2.9	2.3	4.0

Analgesic medication* and dose (mg)	Number of patients in comparison	$NNT_{50\%}$	Lower 95% confidence interval	Higher 95% confidence interval
Morphine 10 (IM)	946	2.9	2.6	3.6
Pethidine 100 (IM)	364	2.9	2.3	3.9
Tramadol 150	561	2.9	2.4	3.6
Dexketoprophen 20/25	523	3.2	2.6	4.1
Diflunisal 250	195	3.3	2.3	5.5
Etodolac 200	670	3.3	2.7	4.2
Flurbiprofen 25	208	3.3	2.5	4.9
Ketoprofen 50	624	3.3	2.7	4.3
Ketorolac 30 (IM)	359	3.4	2.5	4.9
Naproxen 200/220	202	3.4	2.4	5.8
Paracetamol 500	561	3.5	2.2	13.3
Dexketoprofen 10/12.5	452	3.6	2.8	5.0
Paracetamol 975/1,000	3,232	3.6	3.2	4.1
Paracetamol 1,500	138	3.7	2.3	9.5
Paracetamol 1,000 + Oxycodone IR 5	78	3.8	2.1	20.0
Paracetamol 600/650 + Codeine 60	1,413	3.9	3.3	4.7
Mefenamic acid 500	256	4.0	2.7	7.1
Aspirin 600/650	4,965	4.2	3.8	4.6
Celecoxib 200	705	4.2	3.4	5.6
Ibuprofen 100	396	4.3	3.2	6.4
Lornoxicam 4	151	4.3	2.7	11.0
Oxycodone IR 15	228	4.6	2.9	11.0
Paracetamol 600/650	1,886	4.6	3.9	5.5
Ibuprofen 50	316	4.7	3.3	8.0
Etodolac 100	498	4.8	3.5	7.8
Tramadol 100	882	4.8	3.8	6.1
Aspirin 650 + Codeine 60	598	5.3	4.1	7.4

Analgesic medication* and dose (mg)	Number of patients in comparison	$NNT_{50\%}$	Lower 95% confidence interval	Higher 95% confidence interval
Tramadol 75	563	5.3	3.9	8.2
Paracetamol 325 + Oxycodone IR 5	388	5.4	3.9	8.8
Ketorolac 10 (IM)	142	5.7	3.0	53.0
Diclofenac *sodium* 50mg	284	6.6	4.2	17
Paracetamol 300 + Codeine 30	690	6.9	4.8	12.0
Dihydrocodeine 30	194	8.1	4.1	540
Etodolac 50 (dental only)	360	8.3	4.8	30
Tramadol 50	770	8.3	6.0	13.0
Gabapentin 250	327	11.0	6.4	35.0
Codeine 60	2,411	12.0	8.4	18.0

**oral route unless otherwise specified*

*Source: Compiled with data from Moore 2003 (**Level I**, unspecified number of RCTs, n unspecified), Moore 2011 (**Level I** [Cochrane], ≈350 RCTs, n≈45,000) and Moore 2015 (**Level I** [Cochrane], ≈460 RCTs, n≈50,000). Formulations and doses not approved for use in Australia, New Zealand, Europe, USA or Canada have been removed from the table.*

5.1.1 | Paracetamol

Single doses of paracetamol are effective in the treatment of postoperative pain. The NNTs for a variety of doses, as well as combinations of paracetamol with other analgesic medicines such as ibuprofen, oxycodone, tramadol and codeine, are listed in Table 5.1.

There is no good evidence for a dose-dependent analgesic effect of oral paracetamol; the effects of 500 mg ($NNT_{50\%}$ 3.5; 95%CI 2.7 to 4.8), 600/650 mg ($NNT_{50\%}$ 4.6; 95%CI 3.9 to 5.5) and 1,000 mg ($NNT_{50\%}$ 3.6; 95%CI 3.2 to 4.1) show no statistically significant difference (Moore 2015 **Level I** [Cochrane], 53 RCTs, n=5,679).

The oral bioavailability of paracetamol is good at between 63 and 89% (Oscier 2009 **NR**). However, rate of absorption and peak concentrations are reduced by factors such as recent food intake (Moore 2015 **SR**), pregnancy (Raffa 2014 **NR**), opioid administration (Raffa 2018 **BS**) and high altitude (Idkaidek 2019 **EH**). Early postoperative oral administration can result in plasma concentrations that can vary enormously after the same dose and may remain subtherapeutic in some patients (Holmer Pettersson 2004 **PK**), however there does not appear to be a clinical difference of oral vs IV paracetamol in total hip arthroplasty (THA) and total knee arthroplasty (TKA) (Sun 2018 **Level I** [PRISMA], 2 RCTs, n=236; Westrich 2019 **Level II**, n=154, JS 5), Caesarean section (Wilson 2019 **Level II,** n=141, JS 3) or laparoscopic cholecystectomy (Plunkett 2017 **Level II**, n=60, JS 4).

Paracetamol effervescent tablets are absorbed significantly faster than ordinary paracetamol (Rygnestad 2000 **PK**).

5.1.2 | Nonselective NSAIDs and coxibs

A number of nsNSAIDs and coxibs have been shown to be effective as sole therapy in a variety of acute surgical pain settings. The NNTs of each of these medicines is listed in Table 5.1.

In general, there is no good evidence that NSAIDs given parenterally or rectally are more effective, or result in fewer adverse effects, than the same NSAID given orally for the treatment of postoperative pain (Tramer 1998 **Level I**, 26 RCTs, n=2,225). Only in the treatment of renal colic do IV NSAIDs result in more rapid analgesia. Only rectal NSAIDs are effective for reducing post ERCP pancreatitis (Serrano 2019 **Level I** [PRISMA], 21 RCTs, n=6,854).

The formulation of oral NSAIDs such as diclofenac seems to significantly impact their efficacy (Derry 2015b **Level I** [Cochrane], 18 RCTs, n=3,714). For the same 50 mg dose, diclofenac sodium has an $NNT_{50\%}$ of 6.6 (95%CI 4.1 to 17) vs diclofenac potassium an $NNT_{50\%}$ of 2.1 (95%CI 1.9 to 2.5) and diclofenac fast acting (dispersible products, solutions, and softgel formulations) an $NNT_{50\%}$ of 2.4 (95%CI 2.0 to 3.0).

5.1.3 | Conventional and atypical opioids

Oral opioids can be as effective in the treatment of acute pain as opioids given by other more invasive routes, if equianalgesic doses are administered (Cheung 2017 **NR**; Chou 2016 **GL**; Macintyre 2015 **NR**). Both IR and SR formulations have been used. In a number of postoperative settings combinations of SR and IR opioids have been used successfully without any parenteral opioids to treat acute pain after ENT surgery (Pogatzki-Zahn 2013 **Level IV**, n=275), spine surgery (Rajpal 2010 **Level IV**, n=200), cardiac surgery (Ruetzler 2014 **Level II**, n=51, JS 2) and orthopaedic surgery (Lamplot 2014, **Level II**, n=36, JS 2}).

When opioids are prescribed for the treatment of acute pain, consideration should be given to duration of therapy. In most cases short-term use only of these medicines is warranted. Discharge planning must consider the duration of use of opioids prescribed for the short-term management of acute pain and the weaning of those medicines and, in a small minority of patients, the potential for prescribed opioids to be abused or misused (see Section 8.13).

5.1.3.1 | Immediate-release formulations

The NNTs for various IR opioids are listed in Table 5.1.

PO doses of morphine and oxycodone IR have an onset of analgesic effect at around 30 min with a peak at 1 to 2 h (Hoeben 2012 **EH**).

The effectiveness of the different PO conventional and atypical opioids may change with the addition of paracetamol and NSAIDs:

- PO codeine in a single dose of 60 mg is not an effective analgesic agent after a variety of operations ($NNT_{50\%}$ 12) (Moore 2015 **Level I** [Cochrane], 33 RCTs, n=2,411). The effect was even smaller in the subgroup after dental surgery ($NNT_{50\%}$ 21) (Derry 2010 **Level I** [Cochrane], 15 RCTs, n=1,146). Combined with PO paracetamol, a significant dose response was seen with $NNT_{50\%}$ of 2.2 for paracetamol 800−1,000 mg/codeine 60 mg, 3.9 for paracetamol 600−650 mg/codeine 60mg, and 6.9 for paracetamol 300 mg/codeine 30 mg, and the combination extended the duration of analgesia by 1 h compared with paracetamol alone (Toms 2009 **Level I** [Cochrane] 26 RCTs, n=2,295). There are no data on combinations of PO paracetamol with low codeine doses <30 mg. A PO combination of paracetamol 500 mg/hydrocodone 5 mg did not provide superior analgesia to paracetamol 300 mg/codeine 30 m for extremity pain after ED discharge (Chang 2014 **Level II**, n=240, JS 5).

However, codeine 25.6 to 60 mg barely improves the analgesic efficacy of 400 mg ibuprofen in a number of combinations (Derry 2015a **Level I** [Cochrane], 6 RCTs, n=1,342).

- PO oxycodone IR in a single dose of 5 mg shows no benefit over placebo for the treatment of moderate to severe acute pain (Gaskell 2009 **Level I** [Cochrane], 3 RCTs [oxycodone 5 mg], n=317); doses of 15 mg ($NNT_{50\%}$ 4.6) (2 RCTs [oxycodone 15 mg], n=228) and in combination 5 mg oxycodone/325 mg paracetamol ($NNT_{50\%}$ 5.4) (3 RCTs [combination], n=388), 10 mg oxycodone/650 mg paracetamol ($NNT_{50\%}$ 2.7) (10 RCTs [combination], n=1,043) and 10 mg oxycodone/1,000 mg paracetamol ($NNT_{50\%}$ 1.8) (2 RCTs [combination], n=289) are more effective than placebo. Similar benefits are achieved by combining 5 mg oral oxycodone with 400 mg ibuprofen ($NNT_{50\%}$ 2.3) (Derry 2013 **Level I** [Cochrane], 3 RCTs, n=1,303).
- PO tramadol IR is an effective analgesic agent for postoperative pain with $NNT_{50\%}$ of 7.1 for 50 mg, 4.8 for 100 mg and 2.4 for 150 mg (Moore 1997 **Level I**, 18 RCTs, n=3,453). The combination of tramadol 75 mg or 112.5 mg with paracetamol 560 mg or 975 mg is more effective than either of its two components administered alone (McQuay 2003 **Level I**, 7 RCTs, n>1,400).
- After 3rd molar surgery, a meta-analysis of predominantly PO tramadol showed it is less effective and associated with more adverse events (MD 21.8%; 95%CI 13.8 to 29.9) than predominantly PO NSAIDs (Isiordia-Espinoza 2014 **Level I**, 4 RCTs, n=426 [oral] & n=51 [IM]).
- In women undergoing Caesarean section under single shot spinal anaesthesia with IT fentanyl, the regular administration of oral paracetamol, ibuprofen and tramadol resulted in lower pain scores (2.8 ± 0.84 vs 4.1 ± 0.48), higher satisfaction rate (9.1 ± 1.2 vs 8.3 ± 1.5), and more breastfeeds (23.7 ± 6.5 vs 19.2 ± 6.2) vs prn administration (Yefet 2017 **Level II**, n=200, JS 3).
- PO morphine IR is effective in the treatment of acute pain. Following preloading with IV morphine, oral morphine liquid 20 mg (initial dose 20 mg; subsequent doses increased by 5 mg if breakthrough doses needed) every 4 h with additional 10 mg doses prn provided better pain relief after hip surgery than IM morphine 5 to 10 mg prn (McCormack 1993 **Level II**, n=47, JS 5).
- In comparison with IV PCA morphine alone, administration every 4 h of 20 mg but not 10 mg of PO morphine reduced PCA morphine consumption; however, there were no differences in pain relief or adverse effects (Manoir 2006 **Level II**, n=63, JS 5).
- PO tapentadol and PO oxycodone have been compared mostly postoperatively using total pain relief over 48 h. Tapentadol IR 50 mg (MD -2.83/100; 95% CI-11.8 to 6.14) (3 RCTs, n=1,003) and 75 mg (MD -0.92/100; 95% CI -9.15 to 7.32) (2 RCTs, n=885) have efficacy similar to oxycodone IR 10 mg, while 100 mg is superior (MD 9.4/100; 95% CI 2.56 to 16.24) (1 RCT, n=175) (Xiao 2017 **Level I** [PRISMA], 9 RCTs, n =3,961). Regarding adverse events, there was less constipation with 50 mg (RR 0.44; 95%CI 0.21 to 0.93) and 75 mg (RR0.37; 95% CI 0.24 to 0.59), less nausea with 50 mg (RR 0.64; 95%CI 0.48 to 0.85) and 75 mg (0.61; 95%CI 0.41 to 0.93), but more somnolence with 100 mg (RR 1.67; 95%CI 1.08 to 2.58). Overall side effects were only lower in the 75 mg group (RR 0.88; 95%CI 0.83 to 0.94) although the 50 mg group had less discontinuations due to side effects (RR 0.52; 95%CI 0.35 to 0.77).
- SL (11 RCTs, n=1,111) and IV or IM buprenorphine show similar analgesic efficacy overall (pain scores 1–48 h) (23 RCTs) and side effects including respiratory depression (OR 2.07; 95% CI 0.78 to 5.51) (10 RCTs [respiratory rate <8-12 bpm]), sedation (10 RCTs), nausea (21 RCTs) and vomiting (13 RCTs) to morphine (IV, IV-PCA, IM, PO), but with less pruritus (6 RCTs) (White 2018 **Level I**, 28 RCTs, n=2,210). See Section 4.3.1.3 for detail.

IR oral opioids such as oxycodone, morphine and tramadol have also been used as 'step-down' analgesia after PCA, with doses based on prior PCA requirements (Macintyre 2015 **NR**) and after epidural analgesia (Lim 2001 **Level II**, n=101, JS 5).

5.1.3.2 | Slow-release formulations

The role of slow release (SR) formulations (also referred to as controlled-release, extended-release or prolonged-release) in acute pain is controversial. ANZCA has published a position statement indicating their use should be avoided except on a short-term basis for post-operative and post-traumatic analgesia where pain is prolonged (ANZCA 2018 **GL**), which has been discussed extensively in the literature (Stevens 2020 **NR**; Levy 2019 **NR**). This recommendation is also in line with multiple international guidelines (FDA 2012 **GL**; Webster 2015 **GL**; Chou 2016 **GL**; Dowell 2016 **GL**; Clarke 2020 **GL**; Levy 2020 **GL**). When SR formulations are used, consideration should then be given to opioids with the least sedative (and therefore respiratory depressant) effect such as the atypical opioids tramadol, tapentadol and transdermal buprenorphine (ANZCA 2018 **GL**).

Concerns regarding the use of SR formulations include:

- SR formulations are not registered for acute pain by most regulatory authorities including the TGA, the FDA and the EMA.
- SR formulations vary widely in time to peak plasma concentrations with many being in the 3 to 6 h range. In contrast and in most cases, the analgesic effect of the IR opioid preparations will be seen within about 40 to 60 min. Rapid titration to effect is therefore easier and more appropriate with IR formulations.
- There is an increased risk of OIVI with use of SR formulations in an acute setting (Levy 2019 **NR**). This has been shown specifically for SR oxycodone >10 mg after TKA (Weingarten 2015 **Level IV**, n=11,970). There is also an increased risk of unintentional overdose with all SR opioid use (not differentiating conventional from atypical opioids) in chronic pain (Miller 2015 **Level III-2**, n= 840,606). This risk was particularly high during the first 2 weeks after initiation of treatment (HR 5.25; 95%CI 1.88 to 14.72), relevant to the acute setting. An analogy is the increased OIVI incidence with continuous infusions of opioids (Schug 1993 **Level IV**, n=3,016) and with PCA use with a continuous background infusion (George 2010 **Level I**, 12 RCTs [adults], n=674) (see also Section 6.4.3). It is of note here that regularly (instead of prn) administered IR opioids would raise similar concerns.
- Where patients are taking SR formulations at home for acute pain there is concern about the ability of the patient to down titrate medications if their pain resolves faster than expected by the prescriber, which given the variability of pain is not an unlikely event (Stevens 2020 **NR**; ANZCA 2018 **GL**; Macintyre 2015 **NR**). A retrospective analysis of US healthcare data found high rates of continued use at 1 y (27.3%) and 3 y (20.5%) in opioid naïve patients when the initial opioid prescribed was a SR opioid (Shah 2017 **Level IV**, n=1,294,247). However, it is unclear how many of these prescriptions were intentional initiations of medication for chronic pain.

Possible benefits with use of SR formulations (ideally atypical opioids) may exist in certain settings of acute pain by providing more regular analgesia ie:

- Regular analgesia may be more effective than prn only analgesia in some circumstances. Post LSCS under spinal anaesthesia, patients randomised to receive regular paracetamol, diclofenac and IR tramadol (note: an atypical opioid with reduced risk of OIVI [see Section 4.3.1.3]) had lower pain, better satisfaction, more breast feeding and less infant formula use than patients prescribed the same medications as prn (Yefet 2017 **Level II**, n=214, JS3).

- Some SR formulations may have a better tolerability profile. For example, SR tramadol formulations have lower adverse events vs IR tramadol in the treatment of chronic pain due to osteoarthritis (Langley 2010 **Level III-II SR**, 15 studies, n unspecified).
- Where opioids are being regularly administered due to the severity of the pain caused by surgery or trauma, SR opioids may have a limited role. Using SR oxycodone in titrated doses during rehabilitation after TKA improved pain control and functional rehabilitation and reduced LOS at the rehabilitation hospital. However, it is of concern that SR oxycodone use in this setting was associated with 4 times higher overall opioid use (total daily consumption of oxycodone [SR and IR] 54.4 vs 12.9 mg) (Cheville 2001 **Level** II, n=59, JS 5). The latter finding highlights reasons for caution with SR opioid use in such a setting, even where possibly indicated (Stevens 2020 **NR**).

SR opioid preparations should only be used at set time intervals and IR opioids should be used prn for acute pain exacerbations, and for titration of SR opioids. In this context it is of note, that the position paper by ANZCA regards methadone and transdermal fentanyl, due to their long half-life, as behaving similarly to SR opioids (ANZCA 2018 **GL**).

SR oxycodone is an effective component in the immediate management of acute pain (Kampe 2004 **Level II**, n=40, JS 5; Sunshine 1996 **Level II**, n=182, JS 5). However, IR oxycodone and paracetamol 325 mg given every 6 h led to better pain relief than 10 mg SR oxycodone given every 12 h (Kogan 2007 **Level II**, n=120, JS 5). In comparison with IV morphine PCA alone, SR oxycodone in addition to morphine PCA resulted in improved pain relief and patient satisfaction after lumbar discectomy and a lower incidence of nausea and vomiting, as well as earlier return of bowel function (Blumenthal 2007 **Level II**, n=40, JS 5). SR oxycodone was found to be effective as 'step-down' analgesia after 12–24 h of PCA morphine (Ginsberg 2003 **Level IV**, n=189). However after TKA/THA, the addition of SR morphine 30 mg twice daily to usual care resulted in only minimally improved analgesia but increased adverse effects (Musclow 2012 **Level II**, n=200, JS 5). Similarly, addition of preoperative SR oxycodone to a multimodal analgesia regimen increased pain intensity and opioid requirements and impaired early mobilisation on POD 1 (Cooper 2019 **Level III-3**, n=550).

The addition of oral naloxone to oral opioids results in less constipation in the setting of chronic pain (Nee 2018 **Level I** [PRISMA], 5 RCTs, n=838). While it was suggested that these benefits were transferable to acute pain settings (Kuusniemi 2012 **NR**), a difference was not found after laparoscopic hysterectomy (Comelon 2013 **Level II**, n=85, JS 5) or TKA (Oppermann 2016 **Level III-2**, n=80) but time to first bowel motion was improved after colorectal surgery (Creamer 2017 **Level II**, n=82, JS 3).

Comparing PO SR tapentadol 50 mg with SR oxycodone 10 mg/naloxone 5mg after orthopaedic trauma surgery found similar quality of analgesia (3.8 ± 1.9 vs 3.8 ± 2.1) and minor adverse effects (51% vs 49%; 95%CI for difference −8 to 14%) (Haeseler 2017 **Level II,** n=266, JS 2). In non-breastfeeding women undergoing Caesarean section with IT morphine, SR tapentadol 50 mg was inferior to SR oxycodone 10 mg in terms of summed pain intensity difference (SPID) at 36 h (MD -13.77; 95%CI -26.1 to -1.42) but not at 48 h, and with no difference in other analgesic outcomes or patient satisfaction at 36 or 48 h (Ffrench-O'Carroll 2019 **Level II**, n=68, JS 3). There was an increased time to rescue medication with SR oxycodone. Side effects were common and similar in quantity between SR tapentadol and SR oxycodone (70 vs 71%), although more oxycodone recipients received intraoperative antiemetic prophylaxis vs tapentadol recipients (71 vs 42%) including dexamethasone (43% vs 24%).

KEY MESSAGES

1. Oral combinations of paracetamol/ibuprofen provide superior analgesia to paracetamol/codeine; both combinations are more effective than the individual medicines and have a dose-response effect (**S**) (**Level I** [Cochrane Review]).
2. Oral combinations of paracetamol/tramadol are more effective than the individual medications and have a dose-response effect (**U**) (**Level I**).
3. NSAIDs given parenterally or rectally are not more effective and do not result in fewer adverse effects than the same medicines given orally (**U**) (**Level I**).
4. The formulation of oral NSAIDs (eg fast acting [dispersible, solution or gel], sodium versus potassium salt) can greatly affect their efficacy (**N**) (**Level I**).
5. Early postoperative oral administration of paracetamol results in highly variable plasma concentrations that may remain subtherapeutic in some patients (**U**) (**Level II**). However, no difference in clinical efficacy to intravenous administration is seen in hip and knee arthroplasty (**N**) (**Level I**), Caesarean section (**N**) (**Level II**) or laparoscopic cholecystectomy (**N**) (**Level II**).

The following tick boxes represent conclusions based on clinical experience and expert opinion:

☑ Other than in the treatment of severe acute pain, and providing there are no contraindications to its use, the oral route is the route of choice for the administration of most analgesic medicines (**U**).

☑ Slow-release opioid preparations (particularly conventional opioids including transdermal fentanyl and methadone) are not recommended in general for the management of acute pain in opioid-naïve patients due to difficulties in short-term dose adjustments needed for titration, an increased risk of opioid-induced ventilatory impairment and risk of initiating long-term use (**S**). In some patients with prolonged postoperative and post-traumatic acute pain states, the use of slow-release opioid preparations may be appropriate on a short-term basis with preference for use of atypical opioids (**N**).

☑ Slow-release oral opioid preparations should only be given at set time intervals (**U**).

5.2 | Intravenous route

Analgesic medicines given by the IV route have a more rapid onset of action compared with most other routes of administration.

5.2.1 | Paracetamol

IV paracetamol 1,000 mg is an effective analgesic after surgery with an $NNT_{50\%}$ of 4.0 (95%CI 3.5 to 4.8) over 4 h and an $NNT_{50\%}$ of 5.3 (95%CI 4.2 to 6.7) over 6 h (Tzortzopoulou 2011 **Level I** [Cochrane], 36 RCTs, n=3,896). As an adjunct to opioid analgesia, opioid requirements are reduced by 30% over 4 h after a single IV dose. For orthopaedic surgery specifically, IV paracetamol has similar benefits (Jebaraj 2013 **Level I** [PRISMA], 8 RCTs, n unspecified). After Caesarean section, IV paracetamol reduces opioid consumption (SMD -0.46; 95%CI -0.83 to -0.09) and pain (SMD -0.72; 95%CI -1.31 to -0.13) (Ng 2019 **Level I** [PRISMA], 7 RCTs, n=467).

IV paracetamol perioperatively reduces PONV when administered before incision and to a lesser extent before recovery from anaesthesia (Apfel 2013 **Level I** [PRISMA], 30 RCTs, n=2,364). This effect is correlated to pain relief achieved but not to reduced opioid consumption. IV paracetamol given within 1 h prior to incision is more effective than post incision in reducing pain at 1 h (MD -0.50; 95%CI -0.98 to -0.02) and 2 h (MD -0.34; 95%CI - 0.67 to -0.01), 24 h opioid consumption (SMD of -0.52; 95% CI -0.98 to -0.06) and PONV (RR 0.50; 95%CI 0.31 to 0.83) (Doleman 2015 **Level I** [PRISMA], 7 RCTs, n=544).

Dosing of IV paracetamol in bariatric patients remains undefined; in a study of adolescents and young adults undergoing bariatric surgery (mean BMI 46) plasma concentrations of paracetamol were undetectable 2 h after 1,000 mg dosing (Hakim 2019 **Level IV PK**).

The use of IV propacetamol and IV paracetamol has been associated with hypotension (with variable definitions: systolic vs MAP change – absolute value or 15-20% decrease) in mostly critically ill (often cardiac) patients (14/19 studies) (Maxwell 2019 **Level IV SR**, 5 RCTs & 14 studies, n=3,470). Hypotension may be more prevalent with IV vs NG paracetamol in critically ill patients (Kelly 2016 **Level II**, n=50, JS 3). Clinically significant hypotension appears to be an issue when patients have cardiovascular compromise prior to administration; importantly regular qid dosing with IV paracetamol exposes the patient to ≈0.23 mg/kg/d mannitol (with its diuretic and secondary hypotensive effect) (Chiam 2015 **NR**). Within the above SR, IV paracetamol (with mannitol excipient) vs mannitol vs placebo reduced MAP by only 1.8 mmHg in healthy adult volunteers (Chiam 2016 **Level II**, n=24, JS 5).

Due to the good bioavailability and tolerability of oral paracetamol, the use of the IV form should be limited to clinical circumstances where use of the enteral route is not appropriate.

There does not appear to be a clinically significant difference in efficacy between IV and oral paracetamol (see Section 5.1.1 above).

5.2.2 | Nonselective NSAIDs and coxibs

Compared with PO NSAIDs, there are only a relatively limited number of nsNSAIDs or coxibs available for IV injection at present, although this number is growing.

IV/IM Ketorolac is an effective adjuvant of multimodal analgesia with more beneficial effect of 60 mg than 30 mg and a greater opioid-sparing effect with IM than IV administration (MD -2.13 mg; 95%CI -4.1 to -0.21 mg) (De Oliveira 2012 **Level I** [PRISMA] 13 RCTs, n=782).

IV Ibuprofen in doses of 400 and 800 mg every 6 h postoperatively as an adjuvant to IV PCA morphine resulted in improved analgesia, but only the 800 mg dose showed an opioid-sparing

effect (Southworth 2009 **Level II**, n=406, JS 3). IV Ibuprofen 800 mg has also shown efficacy after orthopaedic surgery (Singla 2010a **Level II**, n=185, JS 3), abdominal hysterectomy (Kroll 2011 **Level II**, n=319, JS 3) and laparoscopic cholecystectomy (Ekinci 2019, **Level II**, n=90, JS 4). IV ibuprofen at 800 mg was more effective at relieving renal colic pain at 15, 30 and 60 min than IV ketorolac 30 mg (Forouzanfar 2019 **Level II**, n=240, JS 4).

In single doses as the sole analgesic agent, the COX-2 selective IV/IM parecoxib has been shown to be effective in a dose-dependent way (Lloyd 2009 **Level I** [Cochrane] 7 RCTs, n=1,446); $NNT_{50\%}$ vs placebo are for 10 mg 3.1 (95%CI 2.4 to 4.5), 20 mg 2.4 (95%CI 2.1 to 2.8) and 40 mg 1.8 (95%CI 1.5 to 2.3).

A single dose of IV diclofenac is effective for postoperative pain after a variety of surgeries (McNicol 2018 **Level I** [Cochrane], 8 studies, n=1,756).

IV dexketoprofen 50 mg vs IV diclofenac 75 mg resulted in less IV PCA morphine usage after laparoscopic cholecystectomy over 24 h (18 vs 46mg) (Anil 2016, **Level II**, n=60, JS 2).

IV meloxicam used as a rescue for moderate-severe pain after bunionectomy reduced pain intensity and need for further rescue opioids vs placebo (Pollak 2018, **Level II**, n=201, JS=5). IV meloxicam 15, 30 and 60 mg had faster onset of and then longer-lasting analgesia vs a single dose of PO ibuprofen 400 mg after dental impaction surgery but IV meloxicam 15mg did not provide superior analgesia to PO ibuprofen 400 mg from 2 to 8 h post administration (Christensen 2018 **Level II**, n=230, JS 5).

Both IV and IM administration of lornoxicam were similarly effective for the treatment of acute renal colic pain (with no placebo comparator) (Soylu 2019, **Level II**, n=51, JS 2).

IV flurbiprofen (given 15 min before mastectomy and 6 h post) reduced pain at 2 h but not at later points of time, nor did it reduce overall opioid consumption. The number of patients with chronic postsurgical pain at 6 mth was reduced vs placebo (3.3 vs 26.7%) (Sun 2013, **Level II**, n=60, JS 5).

IV indomethacin is only approved for use in closure of a patent ductus arteriosus in neonates and there are no recent trials in humans for acute pain.

In most cases, the route of administration does not seem to alter efficacy. IV NSAIDs or COX-2 selective inhibitors are more expensive than oral or rectal NSAIDs, although their efficacy and likelihood of adverse effects is similar (Tramer 1998 **Level I**, 26 RCTs, n=2,225). For renal colic, the onset of action of NSAIDs is faster when administered IV vs IM, PO or PR. A comparison of rectal diclofenac and IV parecoxib showed no difference in pain relief, adverse effects or rescue analgesic requirements after laparoscopic sterilisation (Ng 2008 **Level II**, n=55, JS 5). Efficacy and times to onset of analgesia are similar with IV and IM parecoxib after oral surgery (Daniels 2001 **Level II**, n=304, JS 5).

5.2.3 | Conventional and atypical opioids

5.2.3.1 | Intermittent intravenous bolus doses

Titration of opioids for severe acute pain is best achieved using intermittent IV bolus doses as it allows more rapid titration of effect and avoids the uncertainty of medicine absorption by other routes. The optimal doses and dose intervals for this technique have not yet been established.

In a postoperative care unit, bolus doses of morphine 2 mg or 3 mg, given at 5 min intervals prn and with no limitation on the number of bolus doses administered, was more effective and resulted in no greater incidence of adverse effects than the same doses given at 10 min intervals or when a maximum of five doses only was allowed (Aubrun 2001 **Level III-3**, n=1,600; Aubrun 2012 **NR**).

In prehospital care, an initial dose of IV morphine 0.1 mg/kg was more effective than 0.05 mg/kg followed by half the initial dose at 5 min prn (VAS ≤30/100: 40% vs 17% at 10 min) (Bounes 2008 **Level II**, n=106, JS 5). In a comparison of IV fentanyl and morphine bolus doses every 5 min as needed for prehospital analgesia over a period of just 30 min, no difference was found in pain relief or incidence of adverse effects (Galinski 2005 **Level II**, n=54, JS 5).

A single dose of IV morphine 10 mg vs IV paracetamol 1,000 mg in moderate to severe traumatic limb pain had a similar analgesic effect with significantly more adverse effects in the morphine arm; approximately one-third of patients in each group required rescue analgesia of titrated IV morphine (Craig 2012 **Level II**, n=55, JS 4).

Titration of IV bolus doses of an opioid is frequently accomplished using a treatment algorithm to guide management, which includes age-based bolus doses of opioid given at 3- or 5-min intervals prn (Macintyre 2015 **NR**).

Approximately one-third of patients given a 1 mg single bolus dose of hydromorphone (followed by another dose at 15 min if needed) desaturated below 95% (Chang 2009 **Level IV**, n=269). As a standardised therapy, a single 2 mg dose of IV hydromorphone in adults <65 y old resulted in more patients (11.6%; 95%CI 1.8% to 21.1%) not requiring further pain relief after 30 min vs standard care (any IV opioid in any dose) (Chang 2013 **Level II**, n=350, JS 4). Adverse effects of pruritus and nausea were more common in the hydromorphone group, who received double the morphine equivalent dose; however, all patients received oxygen via nasal prongs to prevent desaturation. Comparing the 2 mg hydromorphone bolus to a "*1+1*" titration protocol, both showed similar efficacy and safety with an opioid-sparing effect noted in the titration group, where 42.3% required only the first bolus (Chang 2013 **Level II**, n=350, JS 4).

For acute traumatic pain in an ED setting, sufentanil given as an IV bolus of 0.15 mcg/kg followed by 0.075 mcg/kg every 3 min was not more effective than IV morphine 0.15 mg/kg followed by 0.075 mg/kg and less effective at 6 h (Bounes 2010 **Level II**, n=108, JS 5).

IV tramadol was found to be more effective than the same dose given PO after dental surgery, however it was recognised that the difference in bioavailability of a single dose of tramadol may be up to 30% (Ong 2005 **Level II**, n=72, JS 5). Large IV bolus doses of tramadol can result in a high incidence of nausea and vomiting. This effect can be reduced by slowing delivery of the medicine or, in the surgical setting, by giving it before the patient emerges from general anaesthesia (Pang 2000 **Level II**, n=60, JS 5).

Comparing intermittent oxycodone with other opioids reveals oxycodone is more effective than fentanyl (5 of 6 RCTs) and sufentanil (1 of 3 RCTs) and equivalent to morphine (Raff 2019 **Level I**, 6 RCTs, n=466 [vs fentanyl]; 3 RCTs, n=287 [vs sufentanil]; 2 RCTs, n=135 [vs morphine]). There was more nausea (3 of 6 RCTs) and vomiting (1 of 6 RCTs) reported in individual RCTs with oxycodone vs fentanyl.

5.2.3.2 | Continuous infusions

A continuous infusion of opioids results in constant blood levels after approximately four to five half-lives of the opioid used. The aim of an infusion is to avoid the problems associated with the peaks and troughs of intermittent administration techniques. However, the variation in patient response, the changing intensity of acute pain with time and the delay between any alteration of the infusion rate and its subsequent effect, may result in inadequate treatment of incident pain or delayed onset of adverse effects, such as respiratory depression. Very close monitoring is therefore essential with continuous infusions of opioids.

Compared with PCA, continuous IV opioid infusions alone in a general ward setting resulted in a five-fold increase in the incidence of respiratory depression (Schug 1993 **Level IV**, n=3,016).

Furthermore, morphine infusion 0.5 mg/h vs PCA alone after abdominal hysterectomy resulted in higher opioid requirements, pain intensity and adverse effects including POV and dizziness (Chen 2011 **Level II**, n=60, JS 4).

PCA with a continuous background infusion increases the risk of respiratory events in comparison to PCA alone in adults only (OR 10.2; 95%CI 3 to 35) (George 2010 **Level I**, 12 RCTs [adults], n=674). Despite these safety concerns, PCA with a continuous background infusion of low-dose oxycodone (0.01 mg/kg/h) vs PCA alone reduced VAS at 1, 6 and 24 h after laparoscopic radical cervical surgery without altering satisfaction, PONV or FAS (Zhu 2019 **Level II,** n=90. JS 4).

KEY MESSAGES

1. Intravenous paracetamol is more effective in reducing pain, opioid consumption and PONV when given prior to versus after surgical incision (**U**) (**Level I** [PRISMA]).
2. The onset of analgesia is faster when NSAIDs are given intravenously for the treatment of renal colic (**U**) (**Level I**).
3. Continuous intravenous infusion of opioids in the general-ward setting is associated with an increased risk of respiratory depression compared with other methods of parenteral opioid administration (**U**) (**Level IV**).

The following tick box represents conclusions based on clinical experience and expert opinion:

☑ Titration of opioids for severe acute pain is best achieved using intermittent intravenous bolus doses as it allows more rapid titration of effect and avoids the uncertainty of medicine absorption by other routes (**U**).

5.3 | Intramuscular and subcutaneous routes

IM and SC injections of analgesic agents (usually opioids) are still commonly employed for the treatment of moderate or severe pain. Absorption may be impaired in conditions of poor perfusion (eg in hypovolaemia, shock, hypothermia or immobility), leading to inadequate early analgesia and late absorption of the medication depot when perfusion is restored.

5.3.1 | Nonselective NSAIDs and coxibs

Compared to oral NSAIDs there are only a relatively limited number of NSAIDs or COX-2 selective inhibitors available for IM injection at present and fewer still where Level I evidence for individual efficacy is available; IM ketorolac (Lloyd 2009 **Level I** [Cochrane], 7 RCTs, n=1,446) and IM parecoxib are effective analgesic agents (De Oliveira 2012 **Level I** [PRISMA], 13 RCTs, n=782).

IM diclofenac administration has been associated with rare soft tissue necrosis, particularly in obese patients where the needle may not be long enough to reach the muscle (Dadaci 2015 **Level IV**, n=17 [mean BMI 42]).

5.3.2 | Conventional and atypical opioids

5.3.2.1 | Intramuscular

IM injection of opioids has been the traditional mainstay of postoperative pain management despite the fact that surveys have repeatedly shown that pain relief with prn IM opioids is frequently inadequate. Although IM opioids are often perceived to be safer than opioids given by other parenteral routes, the incidence of respiratory depression reported in a review ranged from 0.8% (0.2 to 2.5) to 37.0% (22.6 to 45.9) using respiratory rate and oxygen saturation, respectively, as indicators (Cashman 2004 **Level IV SR**, 165 studies, n≈20,000). For comparisons with PCA and epidural analgesia see Chapter 6; for comments on respiratory rate as an unreliable indicator of respiratory depression see Section 4.3.1.5.

Single doses of IM morphine 10 mg (McQuay 1999 **Level I**, 15 RCTs, n=1,046) and IM pethidine (meperidine) 100 mg (Smith 2000 **Level I**, 8 RCTs, n=364) have been shown to be effective in the initial treatment of moderate to severe postoperative pain.

The use of an algorithm allowing administration of IM morphine or pethidine hourly prn and requiring frequent assessments of pain and sedation, led to significant improvements in pain relief vs longer dose interval prn regimens (Gould 1992, **Level III-3**, n=235).

The quality of pain relief is lower with intermittent IM regimens vs IV PCA (McNicol 2015 **Level I** [Cochrane], 49 RCTs, n=3,412).

5.3.2.2 | Subcutaneous

The placement of SC plastic cannulae or 'butterfly' needles allows the use of intermittent injections without repeated skin punctures. In healthy volunteers, median time to reach maximum serum concentration (T_{max}) after SC injection of morphine was 15 min (Stuart-Harris 2000 **PK**). In elderly adults, mean T_{max} after a single SC injection of morphine was 15.9 min and the rate of absorption and the variability in the rate of absorption were similar to those reported after IM injection (Semple 1997 **Level IV PK**, n=22). In patients given a second and same dose of SC morphine 5 h after the first, it was shown that there can also be significant within-patient variations in absorption (Upton 2006 **PK**). The absorption rate of SC fentanyl was found to be similar to that of SC morphine with a significantly longer terminal half-life for fentanyl (10 h vs

2.1 h) (Capper 2010 **Level IV PK**). For SC oxycodone, peak venous concentrations were seen after 22.10 min (±18.0) in healthy controls however, despite similar onset, peak plasma concentrations were markedly reduced in critically ill ICU patients vs these healthy volunteers (Krishnamurthy 2012 **Level IV EH PK**). Similarly, SC tramadol in healthy volunteers had a time to peak venous concentration of 20.6 min (±18.8), however, unlike oxycodone, plasma concentrations were not reduced in critically ill patients vs healthy controls (Dooney 2014 **Level IV EH PK**).

In children, there was no difference in rate of onset, analgesic effect and adverse effects with use of morphine SC vs morphine IM and there was a significantly higher patient preference for the SC route (Cooper 1996 **Level II**, n=55, JS 4; Lamacraft 1997 **Level IV**, n=220 [paediatric]). Also, IM and IV administration of morphine (along with IN fentanyl) were found to be equally effective with no significant differences in FLACC scores for postoperative pain in children (Hippard 2012 **Level II**, n=171, JS 5). A comparison of IM and SC morphine in patients after Caesarean section reported no significant differences in adverse effects, patient satisfaction or pain relief at rest, but lower pain scores after SC administration at 12, 16 and 20 h after surgery (Safavi 2007 **Level II**, n=60, JS 3).

A comparison of the same dose of morphine given as either a single SC or IV injection, showed that use of the IV route resulted in more rapid onset of analgesia (5 min IV vs 20 min SC) and better pain relief between 5 and 25 min after injection but also led to higher sedation scores up to 30 min after injection and higher $PaCO_2$ (Tveita 2008 **Level II**, n=40, JS 5). However, a comparison of intermittent IV and SC doses of hydromorphone (the doses adjusted in a similar manner according to the patients' pain scores and given at intervals of no less than 3 h) showed no differences in pain relief or adverse effects over a 48 h period after surgery; pain relief was the same but the incidence of pruritus lower vs PCA hydromorphone (Bell 2007 **Level II**, n=130, JS 3).

Continuous infusions of opioids via the SC route were as effective as continuous IV infusions (Semple 1996 **Level II**, n=30, JS 2).

Treatment algorithms for intermittent SC morphine, oxycodone and fentanyl using age-based dosing are published (Macintyre 2015 **GL**).

KEY MESSAGE

1. Intermittent subcutaneous morphine injections are as effective as intramuscular injections and have better patient acceptance (**U**) (**Level II**).

5.4 | Transdermal route

Not all medications applied topically have a local, peripheral action. The term 'transdermal' will be used to describe medications that, while applied to the skin, have predominantly central effects that are the result of systemic absorption of the medicine. The term 'topical' will be used in the discussion of medications – primarily NSAIDs – that are applied topically (including to skin) but have a predominantly peripheral effect. See Sections 5.4.2 and 5.5 below.

5.4.1 | Opioids

The stratum corneum of the epidermis forms a major barrier to the entry of medications. However, medications such fentanyl (Sathyan 2005 **PK**) and buprenorphine (Skaer 2006 **NR**) are available as TD preparations. The analgesic effects are a result of systemic effects rather than local peripheral opioid analgesia (Worrich 2007 **Level IV EH**, n=12).

5.4.1.1 | Transdermal fentanyl

TD fentanyl is commonly used in the management of cancer and chronic pain. Due to the formation of a significant intradermal reservoir, onset and offset times of this preparation are slow and this makes short-term titration impossible. The time to first analgesic effect is generally between 12 and 24 h after initial patch application and after the patch is removed, serum fentanyl concentrations decline with a mean terminal half-life of 17 h (Lotsch 2013 **NR**).

TD fentanyl patches are currently specifically contraindicated for the management of acute or postoperative pain in many countries and for use in opioid naïve patients (FDA 2019a **GL**; MIMS 2019 **GL**; emc 2014 **GL**).

Nevertheless, TD fentanyl patches have been trialled in the management of postoperative pain. For example after THA (Minville 2008 **Level II**, n=30, JS 2), TKA (Sathitkarnmanee 2014 **Level II**, n=40, JS 5; Abrisham 2014 **Level II**, n=40, JS 5), foot surgery (Merivirta 2015 **Level II**, n = 60, JS 5) and hysterectomy (Sandler 1994 **Level II**, n=120, JS 4), preoperative use reduced postoperative pain scores and supplementary opioid or other analgesic requirements. However, the wide variability of clinical effect (Peng 1999 **NR**) and the high incidence of respiratory depression that can occur in the postoperative setting (Bulow 1995 **Level II**, n=24 [then terminated for safety concerns], JS 4; Sandler 1994 **Level II**, n=120 [9 patients withdrawn due to severe respiratory compromise], JS 4) make TD fentanyl preparations unsuitable for acute pain management. In line with these concerns and reported fatal outcomes with perioperative use, guidelines advise against the use of transdermal fentanyl in acute pain management (ANZCA 2018 **GL**). There are concerns that studies in this indication are still undertaken and published (Nair 2017 **NR**).

Transdermal fentanyl by an iontophoretic PCA device for the management of acute pain is also available. See Section 6.5.5.

5.4.1.2 | Transdermal buprenorphine

TD buprenorphine patches are available for the management of chronic and cancer pain (Plosker 2011 **NR**). After application of the patch, steady state is achieved by 3 d; after removal of the patch, buprenorphine concentrations decrease with a terminal half-life of 12 h (range 10 to 24 h). High doses of buprenorphine patch (above 40 mcg/hr) may cause QT wave prolongation that is reversible with mu-opioid antagonists; clinical significance of this is unclear (Merivirta 2015 **Level III-1**, n=110). As with other chronic preoperative opioid use, patients on TD buprenorphine

preoperatively and continued through the perioperative period show higher opioid requirements and report worse pain than opioid-naïve controls (Martin 2019 **Level-III 2**, n=19).

TD buprenorphine showed a dose-dependent analgesic effect with no serious adverse effects in gynaecological postoperative patients (Setti 2012 **Level II**, n=47, JS 4). Use of TD buprenorphine for acute pain management in spinal surgery was noninferior to oral tramadol (Kim 2017 **Level II**, n=48, JS 3) and superior to placebo (Niyogi 2017 **Level II**, n=70, JS 5). TD buprenorphine in abdominal surgery was associated with superior analgesia but comparable adverse effect profile to placebo (Kumar 2016 **Level II**, n=90, JS 5). After surgical repair of hip fractures, TD buprenorphine 10 mcg/h vs PO tramadol 50 mg tds provided better analgesia from 24 h to POD 7 with lower rescue requirements and less PONV and higher patient satisfaction (Desai 2017 **Level II**, n=5, JS 3). After hallux valgus repair, TD buprenorphine 10 mcg/h provided superior analgesia vs celecoxib 400 mg/d and comparable analgesia to IV flurbiprofen 50 mg twice daily with highest patient satisfaction (Xu 2018 **Level II**, n=90, JS 3).

Inherent difficulty in titrating the dose according to changing analgesic requirement should be considered when using TD buprenorphine for acute pain management.

5.4.2 | Other medicines

There is no basis to recommend routine use of TD nicotine patches for acute pain management in view of no demonstrable effect on analgesia (Matthews 2016 **Level I** [Cochrane], 9 RCTs, n=666).

TD administration of ketamine as a patch delivering 25 mg over 24 h reduced rescue analgesic consumption after gynaecological surgery (Azevedo 2000 **Level II**, n=52, JS 4).

TD melatonin 7 mg patch for perioperative pain management in lumbar laminectomy was superior to placebo in analgesia and reduced supplementary analgesia consumption, but was associated with significant sedation (Esmat 2016 **Level II**, n = 75, JS 5).

TD diclofenac patches have been applied in nonsurgical settings for systemic (non-topical) analgesia. They have been trialled for acute pain management after dental surgery and 75 mg and 200 mg patches were comparable in effect to oral diclofenac 75 mg and 100 mg twice daily (Krishnan 2015 **Level II**, n = 40, JS 2; Diwan 2019 **Level III-1**, n=20, JS 2). Another study found TD diclofenac patch 100 mg applied preoperatively to be noninferior to IM diclofenac 75 mg at surgical cessation but with a longer duration of action (Perepa 2017 **Level III-1**, n=60, JS 2).

KEY MESSAGES

1. Transdermal buprenorphine reduces postoperative pain with a low rate of adverse effects (**N**) (**Level II**).
2. Transdermal fentanyl (except for iontophoretic patient-controlled transdermal devices) should not be used in the management of acute pain because of safety concerns and difficulties in short-term dose adjustments needed for titration (**S**) (**Level IV**).

The following tick box represents conclusions based on clinical experience and expert opinion:

☑ Transdermal fentanyl preparations should not be used in opioid-naïve patients or in acute pain settings because of safety concerns and, in most countries, the lack of regulatory approval for use in other than chronic pain in opioid-tolerant patients (**S**).

5.5 | Transmucosal routes

Medications administered by transmucosal routes (rectal, IN, SL, buccal and pulmonary) are rapidly absorbed directly into the systemic circulation, thus bypassing hepatic first-pass metabolism. The medications most commonly administered by transmucosal routes in acute pain management are the more lipid-soluble opioids.

5.5.1 | Rectal route

Rectal administration (PR) of medications is useful when other routes are unavailable. It results in uptake into the submucosal venous plexus of the rectum, which drains into the inferior, middle and superior rectal veins. Medication absorbed from the lower half of the rectum will pass into the inferior and middle rectal veins and then the inferior vena cava, bypassing the portal system. Any portion of the medicine absorbed into the superior rectal vein enters the portal system, subjecting it to hepatic first-pass metabolism.

Potential problems with the administration of medication by the rectal route relate to the variability of absorption, possible rectal irritation and cultural factors. Some suppositories should not be divided as the medicine may not be evenly distributed in the preparation. Contraindications to the use of this route include pre-existing rectal lesions, recent colorectal surgery, severe thrombocytopaenia and immune suppression. Whether the medication is administered to a patient who is awake or under anaesthesia, it is important to obtain prior consent from the patient or guardian.

5.5.1.1 | Paracetamol

Paracetamol is effective when given by the rectal route (Romsing 2002 **Level I**, 8 RCTs, n=640), although absorption is slower and less predictable than after oral administration with bioavailability between 24 and 98% (Oscier 2009 **NR**). In children, it is also less effective than the same dose administered by the oral route (Anderson 1996 **Level II**, n=100, JS 4; Anderson 1999 **Level IV**, n=120). However, in children aged 3 to 36 mth, there were no differences in T_{max}, C_{max} and total medicine exposure between rectal and oral administration, possibly due to slower gastric emptying in this age group (Walson 2013 **Level II**, n=30, JS 2).

Doses of 1 g PR after cardiac surgery (Holmer Pettersson 2006 **Level II**, n=48, JS 2), hysterectomy (Kvalsvik 2003 **Level II**, n=60, JS 4) and 2 g PR for laparoscopic gynaecological surgery (Hahn 2000 **Level IV**, n=23) resulted in subtherapeutic plasma concentrations, although these may increase to within the therapeutic range after repeat administration (Holmer Pettersson 2006 **Level II**, n=48, JS 2). When available, the oral route is therefore preferable.

Higher doses may be more effective. Plasma concentrations in the therapeutic range have been reported in adults after PR doses of 40 mg/kg but not 20 mg/kg (Beck 2000 **Level IV**, n=65) and sustained therapeutic levels followed the PR use of 35 mg/kg and 45 mg/kg, but not 15 mg/kg and 25 mg/kg (Stocker 2001 **Level IV PK**, n=10).

In children, initial PR doses of 40 mg/kg followed by 20 mg/kg also provided therapeutic plasma concentrations without evidence of accumulation (Birmingham 2001 **Level IV PK**, n=16). In children after ophthalmic surgery, 20 and 40 mg/kg PR were equally effective and superior to placebo (Gandhi 2012 **Level II**, n=135, JS 4). PR paracetamol 30 mg/kg provided equivalent analgesia postoperatively vs peritonsillar infiltration of bupivacaine (Dahi-Taleghani 2011 **Level III-1**, n=110). For inguinal herniorrhaphy in children, administration of PR paracetamol appeared to be as effective as IV paracetamol, both in postoperative analgesia and reduction in nausea and

vomiting (Khalili 2016 **Level II**, n=120, JS 3). However, addition of PR paracetamol to caudal epidural block did not result in a meaningful improvement vs caudal block alone for the same procedure (Nnaji 2017 **Level II**, n=87, JS 4).

5.5.1.2 | NSAIDs

Rectal administration of nsNSAIDs provides effective analgesia after a variety of surgical procedures (Tramer 1998 **Level I**, 26 RCTs, n=2,225). This continues to be supported by a number of subsequent studies (Karaman 2016 **Level II**, n=82, JS 5; Nadeem 2016 **Level II**, n=60, JS 3; Pazouki 2015 **Level III-1**, n=130). A study comparing PR diclofenac vs PR indomethacin for postepisiotomy pain found both to be similarly effective but diclofenac appeared to have a shorter duration of action (Rezaei 2014 **Level II**, n=90, JS 3).

Local effects such as rectal irritation and diarrhoea have been reported following use of the rectal route but other commonly reported adverse effects such as nausea, vomiting, dizziness and indigestion are independent of the route of administration (Tramer 1998 **Level I**, 26 RCTs, n=2,225). Rectal NSAIDs may be particularly useful as a part of multimodal analgesia in cases where an enteral route cannot be established, such as immediately after upper GI surgery (Bameshki 2015 **Level II**, n=90, JS 2).

In comparison to PR paracetamol, PR NSAIDs were more efficacious (Nikooseresht 2016 **Level II**, n=102, JS 1; Ubale 2016 **Level II**, n=60, JS 2). The synergistic benefit of combining paracetamol with an NSAID was also confirmed for the rectal route. After abdominal hysterectomy, PR paracetamol/PR diclofenac vs PR diclofenac only or vs placebo resulted in superior analgesia and significantly reduced rescue opioid requirements (Samimi Sede 2014 **Level II**, n=90, JS 4). PR NSAIDs showed superior analgesic effect when combined with paracetamol in adults (Bakhsha 2016 **Level III-1**, n=90) and children (Yallapragada 2016 **Level II**, n=60, JS 2), and also with other analgesics such as pentazocine (Olateju 2016 **Level II**, n=116, JS 5).

To provide analgesia after gynaecological procedures, PR indomethacin was superior to placebo, but inferior to intrauterine lignocaine for hysteroscopy (Senturk 2016 **Level II**, n=206, JS 4), and conferred no advantage over placebo after endometrial biopsies (Kaya 2015 **Level II**, n=90, JS 2; Telli 2014 **Level II**, n=151, JS 4).

For inguinal herniorrhaphy in children, addition of PR diclofenac to caudal epidural block did not result in improved analgesia vs caudal block alone (Nnaji 2017, **Level II**, n=87, JS 4).

For periprocedural analgesia in US-guided prostate biopsy, PR diclofenac is superior to placebo (3 RCTs), but inferior to the gold standard of periprostatic nerve block (2 RCTs) (Lee 2014a **Level I**, 106 RCTs, n unspecified). Administration 45 to 60 min prior to procedure is recommended. While the same systematic review found some benefit in combining PR diclofenac with periprostatic block (2 RCTs), a subsequent RCT failed to find additional benefit with this approach vs periprostatic block alone (Ooi 2014 **Level II**, n=96, JS 4).

For acute renal colic in the Emergency Department (ED), PR indomethacin 100 mg provided analgesia slightly inferior to PR morphine 10 mg at 20 min but was equivalent afterwards (Zamanian 2016 **Level II**, n=158, JS 5) and was inferior to IM tramadol 50 mg, with significantly higher need for rescue analgesia (Shirazi 2015 **Level II**, n=120, JS 3).

5.5.1.3 | Opioids

In most instances, similar doses of rectal and oral opioids are administered, although there may be differences in bioavailability and the time to peak analgesic effect for the reasons outlined above; rectal opioids play primarily a role in cancer-pain management (Kestenbaum 2014 **NR**). Here, no differences in either pain relief or adverse effects were found in a comparison of oral and rectally administered tramadol (Mercadante 2005 **Level II**, n=60, JS 5). Analgesic effects of rectal

opioids in acute procedural pain settings have been demonstrated (Imani 2018 **Level II**, n=90, JS 2; Rahimi 2016 **Level II**, n=70, JS 4); advantages of this approach are unclear if oral or parenteral routes are available.

5.5.1.4 | Ketamine

Rectal ketamine is advantageous for the paediatric population, when parenteral access may not be feasible and a degree of sedation in addition to analgesia is desirable. PR ketamine 2 mg/kg provided comparable analgesia to IV ketamine 0.5 mg/kg when delivered intraoperatively during tonsillectomy in children (Yenigun 2015 **Level II**, n=120, JS 1). Higher doses of PR ketamine (4 mg/kg, 6 mg/kg and 8 mg/kg) were trialled in addition to 0.5 mg/kg midazolam for analgo-sedation for outpatient burns dressing changes in children, and it was noted that the higher dose of 8 mg/kg was associated with prolonged recovery time and adverse events (Grossmann 2019 **Level II**, n=90, JS 5); a dose of ketamine 6 mg/kg with midazolam 0.5 mg/kg appeared to provide the best balance between the degree of analgo-sedation and adverse effects.

5.5.2 | Intranasal route

A variety of different medications can be administered by the IN route, including analgesics. The human nasal mucosa contains medication-metabolising enzymes but the extent and clinical significance of human nasal first-pass metabolism is unknown (Dale 2002 **NR**). It is suggested that the volume of a dose of any medication given IN should not exceed 150 microL in order to avoid run-off into the pharynx (Dale 2002 **NR**). Absorption through the nasal mucosa depends on both the lipid solubility and degree of ionisation of the medication (Shelley 2008 **NR**).

5.5.2.1 | NSAIDs

IN ketorolac has also been shown to be effective vs placebo. After major surgery, ketorolac IN 31.5 mg (Singla 2010b **Level II**, n=321, JS 5) but not 10 mg IN resulted in significant opioid-sparing and better pain relief (Moodie 2008 **Level II**, n=127, JS 5). This was also found for IN 31.5 mg after oral surgery (Grant 2010 **Level II**, n=80, JS 5). For acute migraine, IN ketorolac 31.5mg was superior to placebo and at least as effective as IN sumatriptan 20 mg (Rao 2016 **Level II**, n=72, JS 5).

5.5.2.2 | Opioids

Single-dose pharmacokinetic data in healthy volunteers for a number of opioids administered by the IN route have been published (Dale 2002 **NR**; Grassin-Delyle 2012 **NR**). The mean bioavailabilities and T_{max} reported were fentanyl 71% and 5 min; sufentanil 78% and 10 min; alfentanil 65% and 9 min; butorphanol 71% and 49 min; oxycodone 46% and 25 min; and buprenorphine 48% and 30 min. An analysis of multiple trials for IN fentanyl showed a bioavailability of 89% with an onset of analgesia at 2–5 min (Lotsch 2013 **NR**). Hydromorphone, when given to volunteers in doses of 1 mg or 2 mg IN vs 2 mg IV, had median T_{max} after the 1 mg and 2 mg IN doses of 20 min and 25 min respectively and an overall bioavailability of only 55% (Coda 2003 **PK**).

Clinical data exist for the effectiveness of several opioids administered via the IN route. IN fentanyl must be provided in a sufficient concentration to deliver an analgesic dose in a volume that does not exceed the nasal capacity. It is an effective treatment for breakthrough pain in cancer patients (Zeppetella 2013 **Level I** [Cochrane] 15 RCTs [4 INF], n=1,699) and has similar analgesic efficacy to IV administration in the ED and prehospital settings (Hansen 2012 **Level I** [PRISMA], 3 RCTs, n=301). IN fentanyl spray vs oral transmucosal fentanyl, fentanyl buccal tablet and oral morphine for the treatment of breakthrough cancer pain provides the greatest and fastest

improvement (Vissers 2010 **Level I**, 6 RCTs, n=594) (see also Section 8.9.3.2). It provides also similar or better analgesia than other opioids or routes of administration in children without compromising safety (Mudd 2011 **Level IV SR**, 12 studies, n=1,743). Effectiveness of IN fentanyl for paediatric acute pain management is confirmed by two systematic reviews (Murphy 2014 **Level I** [Cochrane], 3 RCTs, n=313; Setlur 2018 **Level I** [PRISMA], 10 RCTs, n=5,945) (2 RCTs overlap) (see also Section 10.9.1.2). When IN fentanyl was used in the prehospital setting, there was no difference in effectiveness vs IV morphine (Rickard 2007 **Level II**, n=258, JS 3) and it was also effective for burns dressing changes (Nederveld 2017 **Level III-2**, n=64) (see Section 8.5.3.1). In paediatric sickle cell crisis, it was superior to placebo at 20 min, but not earlier or later (Fein 2017 **Level II**, n=49, JS 5). Adding IN fentanyl to nitrous oxide 70% for paediatric procedural sedation does not confer any advantage for short duration procedures (Seiler 2019 **Level II**, n=399, JS 5).

Two studies have examined the role of IN fentanyl delivered via postoperative nasal packing foam soaked in fentanyl solution after nasal passage operation (Kim 2018b **Level II**, n=152, JS 5) and nasal fracture repair (Kim 2019c **Level II**, n=65, JS 5). In both cases superior analgesia vs placebo lasting for up to 24 h was achieved without an increase in adverse events. The authors postulate a significant local analgesic effect in addition to systemic absorption.

Analgesic efficacy has also been shown for IN butorphanol (Wermeling 2005 **Level II**, n=60, JS 4; Abboud 1991 **Level II**, n=186, JS 5), IN pethidine (Striebel 1995 **Level II**, n=44, JS 2; Striebel 1993 **Level II**, n=60, JS 5), IN morphine (Stoker 2008 **Level II**, n=187, JS 5), IN hydromorphone (Wermeling 2010 **Level IV**, n=99) and IN sufentanil (Mathieu 2006 **Level II**, n=40, JS 4; Stephen 2012 **Level IV**, n=15; Steenblik 2012 **Level IV**, n=40).

Butorphanol (Abboud 1991 **Level II**, n=186, JS 5) and morphine (Christensen 2008 **Level II**, n=225, JS 5) had similar efficacy when given by IN or IV routes. IN butorphanol was similarly effective to IV butorphanol, and provided advantages of reduced postoperative cognitive decline vs IV fentanyl, when given to patients aged over 65 y for palate-pharyngoplasty (Yang 2015 **Level II**, n=260, JS 2). IN pethidine was more effective than SC injections of pethidine (Striebel 1995 **Level II**, n=44, JS 2). IN sufentanil has been trialled in the ED setting and was superior to placebo at 0.4 mcg/kg (Lemoel 2019 **Level II**, n=144, JS 5) and superior to IV morphine 0.1 mg/kg at 0.7 mcg/kg (Sin 2019 **Level II**, n=60, JS 5). In both studies adverse event profiles were minor and transient.

Patient-controlled IN analgesia (PCINA) using diamorphine (bolus doses of 0.5 mg) was less effective than PCA IV morphine (1 mg bolus doses) after joint replacement surgery (Ward 2002 **Level II**, n=52, JS 2) but provided better pain relief in doses of 0.1 mg/kg than 0.2 mg/kg IM morphine in children with fractures (Kendall 2001 **Level II**, n=404, JS 3). PCINA fentanyl (54 mcg 4 min lockout) provided better postoperative analgesia vs regular IM pethidine in women after Caesarean section (Fleet 2015 **Level II**, n=156, JS 3).

Adverse effects can be related to the medication itself or to the route of administration. Systemic effects appear to be no higher for IN administration than for other routes with equivalent efficacy; nasal irritation, congestion and bad taste have been reported (Grassin-Delyle 2012 **NR**; Dale 2002 **NR**).

Technical problems with pumps have been reported in up to 10% of cases and dispensing issues for techniques such as PCINA, which could allow ready and unauthorised access to the medications, have not been addressed (Dale 2002 **NR**).

5.5.2.3 | Ketamine

IN ketamine has been shown to provide relatively rapid onset of effective pain relief within 15 min (peak effect 30 min) with estimated bioavailability of 45% (Farnia 2017 **Level II**, n=53, JS 4); any adverse effects were mild and transient (Andolfatto 2019 **Level II**, n=120, JS 5; Christensen 2007 **Level II**, n=40, JS 4). Its use in the adult ED setting has been validated for orthopaedic trauma (Mohammadshahi 2018 **Level II**, n=91, JS 5), general trauma (Shimonovich 2016 **Level III-1**, n=90) and in the prehospital setting with demonstrated efficacy over placebo and analgesia comparable to IN/parenteral opioid (Andolfatto 2019 **Level II**, n=120, JS 5).

IN ketamine for acute headache was not found to be superior to metoclopramide/diphenhydramine (Benish 2019 **Level II**, n=53, JS 4). In adult renal colic, IV fentanyl was superior in both analgesic and adverse effect profiles to IN ketamine (Mozafari 2019 **Level II**, n=130, JS 5).

As well as a premedication in paediatric patients, IN ketamine has been studied for paediatric ED pain management and was similarly effective to the usual treatment of IN fentanyl, although associated with higher rate of mild transient adverse events (Frey 2019 **Level II**, n=90, JS 5; Reynolds 2017 **Level II**, n=82, JS 5; Graudins 2015 **Level II**, n=73, JS 5). See also Section 10.4.7.1.

IN ketamine for postoperative analgesia in paediatric tonsillectomy was similarly effective to IN fentanyl (Yenigun 2018 **Level III-1**, n=63). IN S(+)-ketamine combined with midazolam delivered on demand provided analgesia comparable to IV morphine PCA for patients who underwent spinal surgery (Riediger 2015 **Level II**, n=22, JS 4).

5.5.2.4 | Alpha-2 agonists

There is no data for use of clonidine via this route for analgesia in adults or children. The analgesic effect of IN dexmedetomidine has been shown in adult populations such as after hysterectomy (Wu 2016 **Level II**, n=120, JS 3) and endoscopic sinus surgery (Tang 2015 **Level II**, n=60, JS 5). IN dexmedetomidine is used in children for preoperative sedation, and may also confer additional analgesic benefits. IN dexmedetomidine 2 mcg/kg, but not 1 mcg/kg, was associated with clinically significant postoperative analgesia vs placebo (Li 2018b **Level II**, n=90, JS 5). IN dexmedetomidine had a similar analgesic effect to IN fentanyl after myringotomy when administered intraoperatively (Dewhirst 2014 **Level II**, n=100, JS 2). IN dexmedetomidine provided persistently better analgosedation for IV cannulation (as evidenced by FLACC score) when given through a mucosal atomization device (MAD) vs IN administration of drops of solution (Xie 2017 **Level II**, n=106, JS 3). See also Section 10.4.8.

5.5.2.5 | Others

IN lignocaine has shown poor efficacy in the treatment of acute headaches with significant adverse effects vs placebo (Dagenais 2018 **Level I**, 6 RCTs, n unspecified).

While IN nicotine may have a small analgesic effect, this has been inconsistently demonstrated and is associated with significant increase in PONV (Matthews 2016 **Level I** [Cochrane], 9 RCTs, n=666).

IN desmopressin relieved subacute pain after orthopaedic surgery for up to 24 h (Yang 2019 **Level II**, n=653, JS 3).

5.5.3 | Sublingual and buccal routes

When analgesic medicines are administered by the SL or buccal routes, their efficacy will in part depend on the proportion of medication swallowed.

5.5.3.1 | Opioids

A number of different SL fentanyl preparations are currently on the market world-wide; these include oral transmucosal fentanyl citrate (OTFC), fentanyl buccal tablets (FBT), SL fentanyl citrate orally disintegrating tablet (ODT) and fentanyl buccal soluble film (FBSF); in addition, buccal or SL sprays and a wafer are under development (Schug 2017 **NR**; Paech 2012 **NR**).

The only registered indication of these preparations (commonly called 'Transmucosal Immediate-Release Fentanyl (TIRF) medicines') in all countries is the treatment of break-through pain in opioid-tolerant cancer patients. SL and buccal fentanyl are effective treatments for breakthrough pain in cancer patients vs placebo, oral or IV opioid (Zeppetella 2013 **Level I** [Cochrane], 15 RCTs, n=1,699). In this indication, OTFC, FBT and ODT provide more efficacious analgesia than oral morphine (Jandhyala 2013 **Level I**, 5 RCTs, n=415) (5 RCTs overlap). However, as outlined above, IN fentanyl was superior to OTFC and FBT here (Vissers 2010 **Level I**, 6 RCTs, n=594) (5 & 6 RCTs overlap). See also Section 8.9.4.

In many countries, regulatory authorities have specifically noted that SL preparations must not be used in opioid-naïve patients or in the management of acute and postoperative pain: OTFC has been the suspected primary cause of death in 226 USA fatalities between 2004 and 2011 (Paech 2012 **NR**). As a consequence, warnings regarding the use of all TIRF formulations have been issued (FDA 2019b **GL**) and specifically for OTFC (MIMS 2019 **GL**; emc 2014 **GL**).

Oral transmucosal fentanyl citrate

OTFC incorporates fentanyl into a flavoured solid lozenge on a stick and is available in a range of doses from 200 to 1,600 mcg. Overall, the bioavailability of OTFC is about 50% vs IV fentanyl, with C_{max} achieved in 23 min (Lotsch 2013 **NR**); the time to onset of analgesia is about 4.2 min. The relative potency vs IV morphine is 1:8 to 1:14 (200 mcg OTFC≈2 mg IV morphine) (Lichtor 1999 **Level II**, n=133, JS 5).

Only a few studies have investigated the postoperative use of OTFC. It was found to be an effective analgesic after orthopaedic surgery vs placebo (Ashburn 1993 **Level II**, n=38, JS 5), abdominal surgery vs IV morphine (Lichtor 1999 **Level II**, n=133, JS 5), retinal photocoagulation vs placebo (Hillier 2009 **Level II**, n=35, JS 5) and during burns wound care in paediatric patients vs PO opioids (Sharar 2002 **Level II**, n=22, JS 3; Sharar 1998 **Level II**, n=14, JS 3). Pain relief at 15 min in children with lower extremity injuries was the same with IV bolus doses of morphine and OTFC, but lower with OTFC after that until the end of the 75-min study period (Mahar 2007 **Level II**, n=87, JS 3). However, because of the risk of achieving high peak plasma levels with unsupervised administration, the limited data available, and the specific lack of approval for use in opioid-naïve patients, OTFC cannot be recommended for the management of acute pain.

Fentanyl buccal tablets

FBTs use an effervescent medicine delivery technology that enables more rapid absorption and delivers a larger proportion of the fentanyl dose vs OTFC (Grape 2010 **NR**); bioavailability is 65% with time to onset of effect 10 min (Lotsch 2013 **NR**). FBTs are effective in opioid-tolerant cancer patients for breakthrough pain (Zeppetella 2013 **Level I** [Cochrane] 15 RCTs [2 FBT], n=1,699; Jandhyala 2013 **Level I**, 5 RCTs, n=415; Vissers 2010 **Level I**, 6 RCTs, n=594) (full overlap between all three SRs). Although only indicated for this usage, FBTs have been studied in the ED. Here, a 100 mcg FBT had faster onset of analgesia (10 vs 35 min) than an oxycodone 5 mg/paracetamol 325 mg

combination tablet, with no other advantages (Shear 2010 **Level II**, n=60, JS 4). FBT 200 mcg was noninferior to oxycodone 10 mg/paracetamol 650 mg in an ED setting, but again without obvious advantage in terms of onset, efficacy or adverse effect profile (Arthur 2015 **Level II**, n=50, JS 2). FBT was also trialled for treatment of sickle cell crisis (De Franceschi 2016 **Level III-2**). Use of FBT for non-cancer pain in opioid-naïve patients cannot be recommend given significant safety concerns.

Sublingual fentanyl citrate orally disintegrating tablets

SL fentanyl citrate ODTs consist of a mixture of carrier particles coated with fentanyl and a mucoadhesive agent and are left under the tongue to dissolve, leading to rapid fentanyl absorption (Paech 2012 **NR**). This leads to a bioavailability of around 70% and a time to onset of effect of 15 min (Lotsch 2013 **NR**). They are effective in opioid-tolerant cancer patients for breakthrough pain (Zeppetella 2013 **Level I** [Cochrane] 15 RCTs [2 ODT], n=1,699) and one subsequent RCT (Shimoyama 2015 **Level II**, n=37, JS 3). They have also been used with effect in breakthrough noncancer pain (Guitart 2013 **Level IV**, n=182).

Fentanyl buccal soluble film

FBSF consists of a small soluble disc-shaped film containing fentanyl in doses of 200–1,200 mcg, proportional to the film surface area (Grape 2010 **NR**); bioavailability is 71% and time to onset of effect 15 min (Lotsch 2013 **NR**). FBSF is effective in opioid-tolerant cancer patients for breakthrough pain (Zeppetella 2013 **Level I** [Cochrane] 15 RCTs [1 FBSF], n=1,699).

Other transmucosal fentanyl preparations

Fentanyl buccal spray has a bioavailability of 76% and a time to onset of effect of 5 min (Lotsch 2013 **NR**). It is effective in opioid-tolerant cancer patients for breakthrough pain (Zeppetella 2013 **Level I** [Cochrane], 15 RCTs [1 SL spray], n=1,699). Fentanyl SL wafers showed a bioavailability of 79% (Lim 2012 **PK**).

Sublingual buprenorphine

SL buprenorphine, given as a tablet, has an overall bioavailability of 30–50% and a long duration of action (mean half-life 28 h) (Mendelson 1997 **NR**; Kuhlman 1996 **NR**). SL buprenorphine 0.4 mg was found to be as effective as 10 mg morphine IM after abdominal surgery (Cuschieri 1984 **Level II**, n=89, JS 2) and 75 mg pethidine IM after gynaecological surgery (Moa 1990 **Level II**, n=96, JS 4). For adults with acute fractures in the ED, SL buprenorphine 0.4mg is as effective and safe as IV morphine 5 mg (Jalili 2012 **Level II**, n=49, JS 4). A much higher dose of SL buprenorphine 2 mg for renal colic achieved comparable analgesia and adverse event to IV morphine 0.1 mg/kg (Payandemehr 2014 **Level II**, n=69, JS 5).

First pass metabolism of buprenorphine is dependent on cytochrome P450-3A4. Concurrent administration of enzyme inhibitors such as voriconazole more than posaconazole significantly elevated plasma concentrations after SL buprenorphine in healthy volunteers (Fihlman 2016 **Level II PK**, n=12, JS 3). Similarly, co-administration of rifampicin, an enzyme inducer, reduced plasma concentration of buprenorphine after SL administration by up to 25%, but had no effect when buprenorphine was given IV (Hagelberg 2016 **Level III-2 PK**, n=12).

SL buprenorphine is at least as effective as parenteral morphine for treatment of acute pain with a comparable safety profile (Vlok 2019 **Level I** [PRISMA], 9 RCTs, n=826).

Sublingual sufentanil

Sufentanil is a lipophilic drug which rapidly crosses the blood-brain barrier ($t_{1/2keo}$ 6 min), resulting in a faster onset of action than morphine (Melson 2014 **NR**). Bioavailability of SL sufentanil is estimated at 60%; and vs IV administration, SL sufentanil has a blunted peak and prolonged plasma half-life (Ringold 2015 **NR**). A sublingual sufentanil tablet system (SSTS) has been developed commercially and incorporates a hand-held computerised dispenser which is activated by a

radiofrequency ID tag linked to an individual patient, and dispenses SL sufentanil 15 to 30 mcg tablets in a patient-controlled manner with a 20 min lockout (Frampton 2016 **NR**). See Section 6.5.3.

SSTS has been trialled in both postsurgical and other acute pain settings. Compared to IV morphine PCA for analgesia after major abdominal or TKA/THA surgeries, SSTS 15 mcg provided analgesia that was noninferior with similar rate of adverse effects and superior satisfaction ratings from patients and nursing staff (Melson 2014 **Level II**, n=357, JS 2). Specifically post TKA/THA, SSTS 15 mcg was superior to placebo but associated with a higher rate of nausea and vomiting (Jove 2015 **Level II**, n=419, JS 5). While for open abdominal surgery, the analgesia from SSTS was superior to placebo, with similar adverse events profiles for SSTS 15 mcg (Ringold 2015 **Level II**, n=172, JS 5) and SSTS 30 mcg, and rapid onset of reported analgesic effect within 15 min of administration (Minkowitz 2017 **Level II**, n=161, JS 5). SSTS 30 mcg was also trialled for acute pain management in the ED setting (Miner 2018 **Level III-3**, n=76).

5.5.3.2 | Ketamine

A pharmacokinetic study in healthy volunteers calculated the bioavailability of oral ketamine as 20%, SL 30% and IN 45%: the pharmacodynamic effects of the active metabolite norketamine were thought to be of potential significance (Yanagihara 2003 **PK**). The bioavailability of a 25 mg ketamine lozenge was 24% when given by both SL and oral routes; peak plasma levels were seen at 30 min and 120 min respectively and terminal half-lives were similar at around 5 h (Chong 2009 **PK**). For both routes, norketamine concentrations exceeded the concentrations of ketamine and, given its pharmacological activity profile, norketamine is therefore likely to be a major contributor to the overall analgesic effect. A wafer preparation of ketamine showed an oral bioavailability of 29% (Rolan 2014 **PK**).

5.5.3.3 | Others

Sublingual nsNSAIDs have been used in a variety of acute pain settings. One study found SL piroxicam to be noninferior to IM diclofenac for renal colic (KandaSwamy 2015 **Level II**, n=100, JS 5), and another found SL ketoprofen to have similar efficacy to oral naproxen for acute lower back pain (Plapler 2016 **Level II**, n=83, JS 3). A novel formulation of buccal paracetamol 125 mg was noted to provide analgesia similar to IV paracetamol 1 g for limb trauma in ED (Pickering 2015 **Level II**, n=40, JS 5). Advantages of above formulations over their oral equivalents are not clear.

Sublingual desmopressin vs IM ketorolac for renal colic was found to be similarly effective (Pricop 2016 **Level II**, n=249, JS 2).

5.5.4 | Pulmonary

5.5.4.1 | Opioids

Opioids are rapidly absorbed after nebulised inhalation, reflecting the high blood flow, surface area and permeability of the lungs.

Clinical data exist for the effectiveness of several opioids administered via the pulmonary route including morphine (Thipphawong 2003 **Level II**, n=89, JS 5; Dershwitz 2000 **Level IV PK**, n=15) and fentanyl (Miner 2007 **Level II**, n=41, JS 3; Worsley 1990 **Level II**, n=30, JS 3).

For post-traumatic thoracic pain, there was no difference in the pain relief obtained from nebulised morphine and PCA morphine (Fulda 2005 **Level II**, n=44, JS 4). Nebulised morphine 20 mg every 10 min vs nebulised morphine 10 mg or IV morphine 2 mg every 5 min for ED trauma pain provided superior analgesia while being associated with a lower rate of adverse events than the IV group (Grissa 2015 **Level II**, n=300, JS 5). C_{max} following administration of morphine via a standard

nebuliser occurred within 10 min but bioavailability was low with a mean of only 5% (Masood 1996 **PK**). Bioavailability may be improved (up to 59–100%) with C_{max} occurring at 2 min using specific pulmonary-medication delivery systems (Dershwitz 2000 **PK**; Ward 1997 **PK**).

Bioavailability of inhaled fentanyl is significantly higher and may approach 100% (Mather 1998 **PK**). The pharmacokinetic profiles of inhaled and IV fentanyl showed similar peak arterial concentrations and areas under the curve (Macleod 2012 **Level II**, n=10, JS 5). The time to C_{max} was slightly shorter for inhaled vs IV fentanyl (20.5 vs 31.5 s). As is with other nebulised medications, mode of delivery and specifically achieving a particle size small enough to reach the pulmonary alveoli, but large enough to not be expired, is important for absorption (Thompson 2016 **Level I** [PRISMA], 7 RCTs, n=583). Use of breath actuated atomisers may reduce the leak of drug to the general environment while allowing the clinician to establish total dose delivered.

Nebulised fentanyl provides analgesia comparable to IV morphine for acute pain management in a variety of settings with the advantages of lower adverse effect profile, noninvasive delivery and rapid onset (Thompson 2016 **Level I** [PRISMA], 7 RCTs, n=583). Nebulised fentanyl in the ED setting for adults provided analgesia for acute limb trauma that was noninferior to IV morphine (Farahmand 2014 **Level II**, n=90, JS 5). Using a breath actuated inhaler delivering atomised fentanyl provided faster onset of and superior analgesia to IV morphine for acute abdominal pain (Deaton 2015 **Level II**, n=40, JS 5). For renal colic, IV fentanyl provided better analgesia than nebulised fentanyl (Imamoglu 2017 **Level II**, n=117, JS 5).

In children requiring pain relief in an ED, nebulised fentanyl was as effective as IV fentanyl (Miner 2007 **Level II**, n=41, JS 3). See also Section 10.4.4.4.

5.5.4.2 | Other analgesic medications

Nebulised ketamine and dexmedetomidine have been trialled for paediatric pre-medication and may contribute to improved postoperative analgesia (Zanaty 2015 **Level II**, n=60, JS 5).

See Section 4.5 for inhaled N_2O and methoxyflurane.

KEY MESSAGES

1. Intranasal, sublingual and buccal fentanyl preparations are effective treatments for breakthrough pain in cancer patients (**U**) (**Level I** [Cochrane Review]) with similar efficacy to IV administration (**U**) (**Level I** [PRISMA]) and superiority to oral morphine (**U**) (**Level I**).
2. Intranasal fentanyl is an effective treatment for paediatric acute pain management, with an acceptable adverse effect profile and ease of delivery (**N**) (**Level I**).
3. Intranasal fentanyl provides faster and better analgesia for breakthrough pain in cancer patients than oral transmucosal fentanyl and fentanyl buccal tablets (**U**) (**Level I**).
4. Sublingual sufentanil delivered by a PCA device provided analgesia comparable to IV PCA opioids in a number of acute pain settings (**N**) (**Level II**).

The following tick box represents conclusions based on clinical experience and expert opinion:

☑ Neither transmucosal immediate-release nor transdermal fentanyl preparations should be used in the management of acute pain in opioid-naïve patients because of safety concerns and, in most countries, the lack of regulatory approval for use in other than opioid-tolerant patients (**U**).

5.6 | Epidural analgesia

Epidural analgesia (ie the provision of pain relief by continuous administration of pharmacological agents into the epidural space via an indwelling catheter) is an important technique for the management of acute pain in adults and children, particularly after surgery (Weiss 2018 **NR**) and in women in labour (see Section 9.1.3.3). For epidural and caudal analgesia in children see Sections 10.6.3.1 and 10.6.3.2.

5.6.1 | Efficacy

The difficulty with interpretation of available data is that epidural analgesia is not a single entity but can be provided by a number of pharmacological agents administered into different levels of the epidural space for a wide variety of operations.

5.6.1.1 | Efficacy and outcomes in general

The universal efficacy of epidural analgesia has been well demonstrated. Regardless of analgesic agent used, location of catheter, type of surgery and type or time of pain assessment, epidural analgesia provides better pain relief than parenteral opioid administration (Guay 2019 **Level I** [Cochrane], 69 RCTs, n=4,680; Salicath 2018 **Level I** [Cochrane], 32 RCTs, n=1,716; Guay 2016a **Level I** [Cochrane], 15 RCTs [8 TEA, 2 LEA, 4 mixed, 1 unspecified], n=1,498; Popping 2014 **Level I** [PRISMA], 125 RCTs, n=9,044) (significant overlap of multiple RCTs).

One meta-analysis of epidural analgesia vs systemic opioids via PCA concludes that epidural analgesia provides better pain relief at rest and with movement after all types of surgery; with the exception of epidural analgesia using hydrophilic opioids only (Wu 2005 **Level I**, 50 RCTs, n=3,208). The epidural group has a lower incidence of nausea/vomiting and sedation but a higher incidence of pruritus, urinary retention and motor block than IV PCA. A meta-analysis of epidural analgesia provided with local anaesthetics for at least 24 h vs systemic analgesia after surgery (performed under general anaesthesia) shows reduced mortality with epidural analgesia (3.1 vs 4.9%) (OR 0.60; 95%CI 0.39 to 0.93) (Popping 2014 **Level I** [PRISMA], 125 RCTs, n=9,044), as did a large matched-cohort retrospective audit of administrative data (30-d mortality: 1.7 vs 2.0%) (RR 0.89; 95%CI 0.81 to 0.98) (Wijeysundera 2008 **Level III-2**, n=144,744). The meta-analysis also reports benefits of epidural analgesia on perioperative morbidity with decreased risk of atrial fibrillation, supraventricular tachycardia, deep vein thrombosis, respiratory depression, atelectasis, pneumonia, ileus, PONV, and time to return to normal bowel function. A preceding meta-analysis reported similar results (Guay 2006 **Level I**, 70 RCTs, n unspecified). However, adverse effects of epidural analgesia include hypotension, pruritus, urinary retention and motor block (Popping 2014 **Level I** [PRISMA], 125 RCTs, n=9,044).

With regard to pulmonary outcomes specifically, epidural analgesia vs systemic analgesia reduced rate of pneumonia (OR 0.54; 95%CI 0.43 to 0.68), but also the need for prolonged ventilation or reintubation, improved lung function and blood oxygenation (Popping 2008 **Level I**, 58 RCTs, n=5,904); however, notably a decrease of relative benefit has occurred over time where from 1971 to 2006 the baseline risk of pneumonia in the opioid group has decreased from 34 to 12%, but remained 8% in the epidural group.

5.6.1.2 | Cancer surgery outcomes

Current data do not support a benefit for cancer recurrence or survival through addition of epidural anaesthesia/analgesia to general anaesthesia/systemic analgesia following cancer

surgery; neither overall survival (HR 1.03; 95%CI 0.86 to 1.24) nor progression-free survival (HR 0.88; 95%CI 0.56 to 1.38) are improved (Cakmakkaya 2014 **Level I** [Cochrane], 4 RCTs, n=746). Evidence was graded low to very low and all four studies are secondary data analyses of previously conducted RCTs. In a much larger systematic review including not only RCTs, overall survival was improved by epidural anaesthesia (HR 0.84; 95%CI 0.74 to 0.96), in particular after surgery for colorectal cancer (HR 0.65; 95%CI 0.43 to 0.99) (Chen 2013 **Level III-3 SR**, 14 studies, n≈47,000). However, epidural anaesthesia did not improve recurrence-free survival (HR 0.88; 95%CI 0.64 to 1.22). For gastroesophageal cancer surgery, there is no evidence in favour or against an effect of epidural anaesthesia or analgesia on cancer outcomes (Perez-Gonzalez 2018 **Level I**, 6 RCTs, n=263).

5.6.1.3 | Procedure-specific efficacy

Open abdominal surgery

For intra-abdominal surgery of any kind (including hysterectomies, radical prostatectomies, Caesarean section, colorectal and upper gastrointestinal procedures), epidural analgesia (by continuous infusion [16 RCTs, n=418] or PCEA [16 RCTs, n=451]) vs IV PCA opioids improves pain relief at rest to 6 h by 5.7/100 (95%CI 1.9 to 9.5) (7 RCTs, n=384), 7 to 24 h by 9.0/100 (95%CI 4.6 to 13.4) (11 RCTs, n=558) and beyond 24 h by 5.1/100 (95%CI 0.9 to 9.4) (7 RCTs, n=393) (Salicath 2018 **Level I** [Cochrane], 32 RCTs, n=1,716). There is limited evidence for improvement of pain on movement and coughing based on few RCTs, but no evidence for differences in other outcomes such as mortality, venous thromboembolism, sedation, nausea and vomiting, and respiratory parameters. However, in the epidural group, risk of failure of the analgesic technique is increased (RR 2.48; 95%CI 1.13 to 5.45) (10 RCTs, n=678) as is hypotension requiring intervention (RR 7.13; 95%CI 2.87 to 17.75) (6 RCTs, n=479) and pruritus (RR 2.36; 95%CI 1.67 to 3.35) (8 RCTs, n=492).

Epidural local anaesthetics vs systemic or epidural opioids after abdominal surgery reduce pain on movement (SMD -0.89; 95%CI -1.08 to -0.70; equivalent to 2.5/10) (35 RCTs, n=2,731) (Guay 2016b **Level I** [Cochrane], 128 RCTs, n=8,754). Outcomes with regard to gastrointestinal transit time are improved: time to first flatus (SMD -1.28; 95%CI -1.71 to -0.86; equivalent to 17.5 h) (22 RCTs, n=1,138) and to first stool (SMD -0.67; 95%CI -0.86 to -0.47; equivalent to 22 h) (28 RCTs, n=1,559). There is no effect on vomiting within 24 h (22 RCTs, n=1,154) and gastrointestinal anastomotic leakage (17 RCTs, n=848), but very low-quality evidence on reduced LOS for open (not laparoscopic) surgery (SMD -0.20; 95%CI -0.35 to -0.04; equivalent to 1 d) (30 RCTs, n=2,598).

For a wide range of open and laparoscopic abdominal surgery in adults (6 RCTs, n=310) and children (4 RCTs, n=195), epidural analgesia vs TAPB provides similar analgesia (MD 0.3/10; 95%CI -0.1 to 0.6), but TAPB reduces the risk of hypotension (RR 0.13; 95%CI 0.04 to 0.38) (4 RCTs) and LOS (MD -0.6 d; 95%CI -0.9 to -0.3) (3 RCTs) (Baeriswyl 2018 **Level I** [PRISMA], 10 RCTs, n=505).

After open abdominal surgery in the setting of enhanced-recovery programs (ERAS), TEA vs other analgesic approaches results in no more complications (OR 1.14; 95%CI 0.49 to 2.64) but better analgesia (7 RCTs) and earlier recovery of bowel function (4 RCTs[flatus]; 6 RCTs [stool]) without reducing LOS (7 RCTs) (Hughes 2014 **Level I** [PRISMA], 7 RCTs, n=378).

A large retrospective cohort study after elective colectomy reported that postoperative epidural analgesia significantly reduced mortality at 7 d (OR 0.35; 95%CI 0.21 to 0.59) and 30 d (OR 0.54; 95%CI 0.42 to 0.70) (Wu 2006a **Level III-2**, n=12,817). In patients with COPD undergoing major abdominal surgery, TEA added to general anaesthesia vs general anaesthesia alone did not reduce the incidence of postoperative pneumonia (11 vs 16%), but was associated with decreased 30 d mortality (5 vs 9%) and with improved outcome for postoperative pneumonia (OR 0.5; 95%CI 0.3 to 0.9) (van Lier 2011 **Level III-2**, n=541 [324 epidural]). The beneficial effect of TEA increased with increasing COPD severity.

After major upper abdominal surgery, TEA in combination with NSAIDs and IV nutritional support prevented protein loss vs epidural analgesia alone or PCA with and without nutritional support (Barratt 2002 **Level II**, n=57, JS 3). Similarly, after colonic surgery, epidural analgesia increased the anabolic effect of amino acid infusions in diabetic patients (Lugli 2008 **Level II**, n=12, JS 3) and reduced whole body protein breakdown (Lattermann 2007 **Level II**, n=20, JS 2). Epidural anaesthesia/analgesia vs general anaesthesia/systemic analgesia reduced insulin-resistance only in patients who were insulin-resistant preoperatively (Donatelli 2007 **Level II**, n=60, JS 2).

After abdominal cancer surgery, continuous TEA vs continuous IT thoracic analgesia resulted in similar efficacy and adverse effects (Mercadante 2008 **Level II**, n=60, JS 3). After open gastrectomy, TEA (PCEA) was superior to IT morphine combined with IV PCA opioids for all relevant outcomes including analgesia, mobilisation, bowel recovery and pulmonary complications (Lee 2014b **Level II**, n=64, JS 3) and was superior to IV PCA morphine with regard to pain control, gastrointestinal recovery and hospital LOS (Zhu 2013 **Level II**, n=67, JS 2). Compared to continuous wound infiltration with local anaesthetics in fast-track open colectomy, epidural analgesia reduced pain scores on mobilisation until hospital discharge, reduced time to return of bowel function and tolerance of a complete diet, improved sleep quality and reduced hospital LOS (4 vs 5.5 d) (Jouve 2013 **Level II**, n=50, JS 5). These benefits were not demonstrated in another, similar RCT (Bertoglio 2012 **Level II**, n=106, JS 3).

Laparoscopic colectomy

After laparoscopic colectomy, TEA is rarely used in the USA (2.14%) (Halabi 2014 **Level III-2**, n=191,576). After laparoscopic colectomy, TEA vs IV PCA opioids improves pain at rest (2 RCTs, n=110) and on walking at POD 1 and 2 (2 RCTs, n=110) and time to first bowel opening (4 RCTs, n=190), but increases LOS (WMD 0.73 d; 95%CI 0.24 to 1.23) (8 RCTs) and total complication rate (OR 1.57; 95%CI 1.07 to 2.29) (8 RCTs) (Perivoliotis 2019 **Level I** [PRISMA], 8 RCTs, n=492).

Similarly, in a large case-matched analysis, TEA increased LOS by 0.6 d, hospital charges by USA$ 3,732.71 and higher rates of urinary tract infection without any clinical benefits (Halabi 2014 **Level III-2**, n=191,576). Outcomes were inferior with epidural vs IT analgesia or IV PCA (Levy 2011 **Level II**, n=99, JS 3). TEA also did not improve long-term survival in this setting, but increased LOS (median length 5 d vs 3 d with IV PCA) (Day 2012 **Level III-2**, n=424).

Hepatic surgery

For hepatic surgery, there is ongoing debate on the value of epidural analgesia. A large USA survey showed the technique is infrequently used in 5.9% of cases (Rosero 2014 **Level IV**, n=68,028).

Epidural analgesia vs IV PCA after open hepatectomy improves pain control at rest at 24 h (MD 0.59/10; 95%CI 0.30 to 0.88) (3 RCTs, n= 243) and with movement at 48 h (MD 0.95/10; 95%CI 0.31 to 1.60) (2 RCTs, n=98) with no difference in LOS (2 RCTs), complications (overall and analgesia-related) (2 RCTs) nor effect on transfusion (2 RCTs) (Li 2019 **Level I** [PRISMA], 4 RCTs, n=278).

However, wound catheters vs epidural analgesia for open hepatectomy result in similar pain intensity on POD 1 and only slightly worse on POD 2 (WMD 0.29; 95%CI 0.09 to 0.49) (3 RCTs) with less opioid requirements (WMD -6.29; 95%CI -7.92 to -4.65) (2 RCTs, n=176) and faster functional recovery (WMD −0.73; 95%CI −1.13 to −0.32) (3 RCTs) and no other differences in complications (Gavriilidis 2019 **Level I** [PRISMA], 3 RCTs, n=240).

Applying propensity-score matching techniques to a cohort of patients after hepatectomy, there was an association of epidural anaesthesia/analgesia with higher need for blood transfusion and slightly longer hospital LOS (Rosero 2014 **Level III-2**, n=1,604).

Compared to IT morphine with subsequent IV PCA fentanyl, TEA was not superior with the exception of pain at 12 h postoperatively and reduced blood loss (Kasivisvanathan 2014 **Level III-2**, n=73). However, an RCT found significantly improved analgesia and a 50% opioid-sparing effect

(Mondor 2010 **Level II**, n=44, JS 5). Similarly, after live liver donation, TEA vs IV PCA opioids improved analgesia but no other outcomes (Clarke 2011 **Level III-2**, n=228).

Abdominal aortic surgery

After open abdominal aortic surgery in comparison with systemic opioid administration (Guay 2016a **Level I** [Cochrane], 15 RCTs [8 TEA, 2 LEA, 4 mixed, 1 unspecified], n=1,498), epidural analgesia reduces:

- Pain scores on movement POD 1 (MD -1.78/10; 95%CI -2.32 to -1.25) (3 RCTs, n=162), POD 2 (3 RCTs, n=155) and POD 3 (2 RCTs, n=105);
- Time to tracheal extubation (SMD -0.42; 95%CI -0.70 to -0.15; equivalent to 36 h mean reduction) (8 RCTs, n=975);
- Time spent in the ICU (SMD -0.23 (95% CI -0.41 to -0.06); equivalent to 6 h mean reduction) (3 RCTs, n=523);
- Acute respiratory failure (RR 0.69; 95%CI 0.56 to 0.85); NNT 8 [95%CI 6 to 16]) (6 RCTs, n=861);
- Myocardial infarction (RR 0.54; 95%CI 0.30 to 0.97; NNT 28 [95%CI 19 to 1423]) (3 RCTs, n=503);
- Gastrointestinal bleeding (OR 0.20; 95% CI 0.06 to 0.65); NNT 32 [95%CI 27 to 74]) (4 RCTs, n=487).

However, the reduced morbidity does not translate to a difference in mortality between epidural vs systemic opioids use (RR 1.06; 95%CI 0.60 to 1.86) (14 RCTs, n=1,383).

Studies not included in this meta-analysis support these results: TEA vs systemic opioids improved pain, mobility and time to oral intake (Salman 2013 **Level III-1**, n=80) and pain and postoperative respiratory function in COPD patients (Panaretou 2012 **Level III-2**, n=30). After endoluminal aortic aneurysm repair, TEA provided better analgesia than IV opioids (Sen 2014 **Level III-2**, n=32). However, in a fast-track setting for abdominal aortic aneurysm repair, TEA was similarly effective vs continuous local anaesthetic wound infiltration with no effects on overall outcome (Renghi 2013 **Level II**, n=60, JS 3).

Gynaecological surgery

In gynaecological surgery, epidural ropivacaine infusion provided only slightly better analgesia in the first 8 h postoperatively vs wound infiltration/infusion of ropivacaine with no other clinically relevant improvements (Ammianickal 2018 **Level II**, n=102, JS 3; Fassoulaki 2014 **Level II**, n=80, JS 3). After abdominal hysterectomy (midline incision), epidural analgesia increased duration of postoperative analgesic use, nonserious postoperative complications and LOS vs parenteral opioids (Belavy 2013 **Level III-2**, n=257). Similarly, after uterine artery embolisation for uterine fibroids, epidural analgesia increased complications but reduced pain scores at high costs (179 Euro for 1/10 pain score reduction) (van der Kooij 2013 **NR**). After abdominal hysterectomy, TAPB (bupivacaine 0.25% 15 mL bilaterally)/placebo/placebo provided the best pain relief and the lowest rescue morphine requirements vs placebo/epidural analgesia/placebo (bolus injections of 8 mL bupivacaine 0.125% every 6 h) and vs placebo/placebo/parenteral (alternating diclofenac, tramadol) analgesia (Mathew 2019 **Level II**, n=60, JS 4). In contrast, single bolus TAPB was inferior to single bolus epidural analgesia in the same setting with higher pain intensity 6 to 24 h and higher rescue tramadol requirements (68.8 mg [SD 25.5] vs. 5.3 mg [SD 11.6]) (Raghvendra 2016 **Level II**, n=60, JS 3).

After abdominal hysterectomy, epidural analgesia and IT morphine 200 mcg provided acceptable analgesia over 24 h, but IT morphine resulted initially (0 to 16 h) in better pain relief and lower opioid requirements (Hassan 2017 **Level II**, n=32, JS 3).

Urologic surgery

After radical retropubic prostatectomy, TEA vs patient-controlled local anaesthetic wound infusion reduced pain scores upon coughing and opioid requirements, with better preservation of expiratory muscle strength (Fant 2011 **Level II**, n=50, JS 5). However, a cohort study found an increased median hospital LOS with use of epidural analgesia for this operation (6 vs 7 d), which remained significant after adjusting for complications (Mir 2013 **Level III-2**, n=239). Malignancy recurrence based upon prostate-specific antigen change was more common in the epidural group (14.8 vs 4.8%). TEA had no effect on blood loss or transfusion rates (Baumunk 2014 **Level II**, n=235, JS 2).

Thoracic surgery

Following thoracotomy, there is moderate-quality evidence that shows comparable analgesic efficacy at rest and after coughing over 24 (6 RCTs, n=365) and 48 h (5 RCTs, n=346) with TEA vs PVB (Yeung 2016 **Level I** [Cochrane], 14 RCTs, n=698). There is low to very low-quality evidence that shows no significant difference in mortality and major complications. There is moderate-quality evidence that PVB has a superior minor complication risk vs TEA including hypotension (RR 0.16; 95%CI 0.07 to 0.38) (8 RCTs, n=445), nausea and vomiting (RR 0.48; 95%CI 0.30 to 0.75) (6 RCTs, n=345), pruritus (RR 0.29; 95%CI 0.14 to 0.59) (5 RCTs, n=249) and urinary retention (RR 0.22; 95%CI 0.11 to 0.46) (5 RCTs, n=258). These results are consistent with a parallel meta-analysis showing that continuous PVB reduces the incidence of nausea, vomiting, hypotension and urinary retention vs thoracic epidural analgesia, wound infiltration or IV opioids with comparable post-cardiothoracic surgery analgesia (Scarfe 2016 **Level I** [PRISMA], 23 RCTs, n= 1,120) (10 RCTs overlap with Yeung 2016).

For oesophagectomy, TEA vs systemic analgesia does not improve pain relief at 24 h (MD 0.89; 95%CI −0.47 to 2.24) (2 RCTs & 2 studies) or 48 h (MD 0.15; 95%CI −0.60 to 0.91) (2 RCTs & 2 studies) nor does it reduce the rate of pulmonary complications (RR 1.69; 95%CI 0.86 to 3.29) (2 RCTs & 2 studies) (Visser 2017 **Level III-2 SR**, 5 RCTs & 5 studies, n=891). Technical failure with TEA occurs in 17 to 22%. These findings are supported by a subsequent systematic review (Hughes 2018 **Level I** [PRISMA], 3 RCTs [oesophagectomy], n=93) (2 RCTs overlap).

After lung resection, postoperative TEA reduced mortality at 7 d (OR 0.39; 95%CI 0.19 to 0.80) and 30 d (OR 0.53; 95%CI 0.35 to 0.78) in a retrospective cohort study (Wu 2006b **Level III-2**, n=3,501). TEA in patients after lobectomy resulted in better pain relief and pulmonary function vs IV morphine (Bauer 2007 **Level II**, n=93, JS 5).

After video-assisted thoracic surgery (VATS), PCEA achieved similar pain control as IV fentanyl PCA/low-dose ketamine with no difference in analgesia-related adverse effects (Tseng 2019 **Level II**, n=74, JS 3).

Following open thoracotomy, epidural anaesthesia reduces the incidence of CPSP three to 18 mth following surgery vs systemic analgesia (OR 0.52; 95%CI 0.32 to 0.84; NNT 7) (7 RCTs, n=499) (Weinstein 2018 **Level I** (Cochrane), 63 RCTs, n=3,027).

Cardiac surgery

A meta-analysis of epidural analgesia vs multiple comparators for cardiac surgery with or without cardiopulmonary bypass finds insufficient evidence to show an effect of epidural analgesia vs peripheral nerve blocks (4 RCTs), interpleural analgesia (1 RCT) or wound infiltration (1 RCT) (Guay 2019 **Level I** [Cochrane], 69 RCTs, n=4,680). In comparison to systemic analgesia, there is a reduction of pain at rest and on movement for the first 72 h eg from 6 to 8 h (SMD -1.35/10; 95%CI -1.98 to -0.72) (10 RCTs, n=502) and an increase in hypotension (RD 0.21; 95%CI 0.09 to 0.33) (17 RCTs, n=870) not leading to increased need for inotropes or vasopressors (RD 0.00; 95%CI -0.06 to 0.07) (23 RCTs, n=1,821). With regard to other outcomes, there is no difference in mortality, cerebrovascular accidents or pneumonia, there may be a reduction in myocardial infarction at

0 to 30 d, respiratory depression (RD -0.03; 95%CI -0.05 to -0.01) (21 RCTs, n=1,736) and risk of atrial fibrillation or atrial flutter at 0 to 2 wk (RD -0.06; 95%CI -0.10 to -0.01) (18 RCTs, n=2,431). A difference in mortality is reported in a meta-analysis including RCTs and case-matched studies; here epidural anaesthesia/analgesia reduces mortality (59/3123 [1.9%] vs 108/3260 [3.3%]) (RR 0.65; 95%CI 0.48 to 0.86; NNT 70) and rate of myocardial infarction (67/2785 [2.4%] vs 108/2933 [3.7%]) (RR 0.68; 95% CI 0.51 to 0.90]; NNT 78) (Landoni 2015 **Level III-2 SR**, 57 studies, n=6,383) (40 RCTs overlap).

In smaller studies, high TEA improved left ventricular function (Schmidt 2005 **Level III-3**, n=37) and increased stroke volume index and central venous oxygenation in elderly cardiac surgery patients, without an increase in heart rate or mean arterial pressure (Jakobsen 2012 **Level II**, n=60, JS 3). Prior to CABG surgery, high TEA improved myocardial oxygen availability in patients with ischaemic heart disease (Lagunilla 2006 **Level II**, n=52, JS 4) and partly normalised myocardial blood flow in response to sympathetic stimulation (Nygard 2005 **Level III-3**, n=20). After CABG surgery, high TEA postoperatively reduced insulin requirements and hyperglycaemia (Greisen 2013 **Level II**, n=42, JS 3) (included in Guay 2019). However, TEA did not reduce the ICU LOS or improve the quality of recovery in the ICU (Nielsen 2012 **Level II**, n=60, JS 3). The discussion on the overall value of epidural analgesia after cardiac surgery continues, with concerns regarding anticoagulation risk being a key factor (Ziyaeifard 2014 **NR**).

Rib fractures

Compared to thoracic epidural analgesia, systemic IV analgesia provides inferior analgesia for rib fractures (2 RCTs & 2 studies, n=205) (Peek 2019 **Level III-2 SR** [PRISMA], 8 RCTs & 11 studies, n=2,081). There was no significant difference in secondary outcomes such as duration of mechanical ventilation (3 RCTs & 1 study), ICU LOS (4 RCTs & 4 studies), hospital LOS (4 RCTs & 4 studies) and pulmonary complications (4 RCTs & 6 studies). Thoracic epidural analgesia provides similar analgesia to continuous intercostal (1 RCT & 1 study) and paravertebral blocks (1 RCT & 1 study) with no significant difference in duration of mechanical ventilation, ICU LOS, hospital LOS and pulmonary complications (2 to 3 studies per outcome).

In patients with multiple traumatic rib fractures, provision of TEA with local anaesthetic reduces the duration of ventilation vs other forms of analgesia (including LEA) (Carrier 2009 **Level I**, 8 RCTs, n=232) (2 RCTs overlap with Peek 2019); however, mortality and ICU LOS is not different in pooled analysis of all routes of epidural administration vs parenteral opioids and hypotension was more frequent in the epidural groups when TEA with local anaesthetic was used.

After blunt chest trauma with three or more rib fractures, the use of TEA was more common in USA trauma centres than in nontrauma centres; the use of TEA vs other methods of analgesia reduced adjusted mortality at 30 d (OR 0.08; 95%CI 0.01 to 0.43), 90 d (OR 0.09; 95%CI 0.02 to 0.42) and 365 d (OR 0.12; 95%CI 0.04 to 0.42) (n=100 [TEA]) (Gage 2014 **Level III-2**, n=836). See also Section 8.3.

Orthopaedic surgery

Spinal fusion

After spinal fusion, patient controlled epidural analgesia (PCEA) vs IV PCA opioids provides better analgesia on POD 1 (MD −0.47/10; 95%CI −0.74 to −0.20) and POD 2 (MD −0.66; 95%CI −1.14 to −0.19), but not on POD 3 (Tian 2015 **Level I**, 8 RCTs, n=482). There are no differences in PONV rates, but PCEA increases rates of pruritus (RR 1.53; 95%CI 1.08 to 2.6) and paraesthesia (RR 3.34; 95%CI 1.12 to 9.98). A parallel meta-analysis not differentiating results as detailed as the previous one finds similar results for analgesia overall, and no differences in all pooled adverse effects (Lu 2015 **Level I**, 9 RCTs, n=436) (7 RCTs overlap).

In RCTs not included in these meta-analyses, epidural analgesia with levobupivacaine reduced pain scores, opioid consumption, nausea, blood loss and time to first stool vs IV opioid

analgesia (Servicl-Kuchler 2014 **Level II**, n=81, JS 5). Similarly, after major spinal surgery, epidural analgesia (levobupivacaine/fentanyl/ adrenaline) vs systemic opioids reduced pain and nausea, permitted earlier mobilisation and increased satisfaction with less intraoperative and postoperative blood loss and reduced stress response markers (glucose, cortisol, IL-1beta, IL-6, and IL-10) (Ezhevskaya 2013 **Level II**, n=85, JS 2). However, when added to systemic multimodal analgesia, TEA did not provide a significant opioid-sparing effect (Choi 2014 **Level II**, n=39, JS 5).

Lower limb arthroplasty (TKA and THA)

After THA and TKA, lumbar epidural analgesia (LEA) provides better pain relief than parenteral opioids, in particular with movement (Choi 2003 **Level I** [Cochrane], 13 RCTs, n unspecified). A subsequent study showed that epidural analgesia vs systemic opioids reduced inflammatory response measured by a number of parameters after TKA (Chloropoulou 2013 **Level II**, n=56, JS 3).

However, in comparison to peripheral nerve blocks (FNB and ACB by single-injection or catheter), LEA does not improve pain following TKA for 0 to 48 h (7 & 8 RCTs), but is associated with increased PONV (RR 1.65; 95 %CI 1.20 to 2.28) (9 RCTs, n=433), hypotension (RR 1.76; 95 %CI 1.26 to 2.45) (9 RCTs, n=551) and urinary retention (RR 4.51; 95%CI 2.27 to 8.96) (7 RCTs, n=331) (Gerrard 2017 **Level I** [PRISMA], 12 RCTs, n=670). In comparison to local infiltration analgesia (LIA) by single-injection or via catheter for TKA and THA, LEA has similar analgesic effects at rest for <24 h (9 RCTs), but LIA achieves better analgesia at 48 h (MD −1.08/10; 95%CI −1.86 to −0.29)) and 72 h (MD −0.82/10; 95%CI −1.24 to −0.4) more so in TKA (6 RCTs, n=446) (Yan 2016 **Level I**, 9 RCTs [6 TKA & 3 THA], n=537) (0 RCT overlap). Pain on movement was similar overall at <24 h (4 RCTs), but better controlled by LIA at 48 h for TKA with better range of knee movement at all time points (3 RCTs).

For comparisons with other regional analgesic techniques, see also Section 5.8.

Vascular surgery of the lower limbs

Used in vascular surgery of the lower limbs, LEA improved outcome by reducing incidence of graft occlusion (Christopherson 1993 **Level II**, n=100, JS 3; Tuman 1991 **Level II**, n=80, JS 1). However, these findings have not been confirmed by other investigators in retrospective reviews (Schunn 1998 **Level III-2**, n=294; Pierce 1997 **Level III-1**, n=423), although a subsequent data base analysis of the USA National Surgical Quality Improvement Program (NSQIP) showed a number of outcome advantages (re graft failure, cardiac events, postoperative pneumonia) with epidural (and spinal) over general anaesthesia (Singh 2006 **Level III-2**, n=14,788).

For effects of epidural analgesia on pain after amputation, see Section 8.1.5.1.

5.6.1.4 | Level of administration

TEA is widely used for the treatment of pain after major abdominal and thoracic surgery. Administration of local anaesthetics into the thoracic epidural space resulted in improved bowel recovery after abdominal surgery, while these benefits are not consistent with lumbar administration (Jorgensen 2000 **Level I** [Cochrane], 22 RCTs, n=1,023). In a direct comparison between TEA and LEA for thoracotomy, TEA vs LEA reduced pain scores and opioid requirements as well as hypotension, bradycardia, atelectasis and need for ICU treatment (Sagiroglu 2014 **Level II**, n=134, JS 4). Benefits of epidural analgesia after abdominal aortic surgery were found with impact on nonanalgesic outcomes significant for TEA, but not LEA (see above) (Nishimori 2012 **Level I** [Cochrane], 15 RCTs, n=1,297). In patients with multiple traumatic rib fractures, provision of TEA with local anaesthetic reduced the duration of ventilation vs other forms of analgesia including LEA (Carrier 2009 **Level I**, 8 RCTs, n=232). In gynaecological surgery, TEA provided better pain relief vs LEA only when the incision extended above the umbilicus; TEA led to less motor block but more pruritus (Richman 2007 **Level II**, n=103, JS 5). Motor block with epidural analgesia (mainly by

infusion of bupivacaine 0.1%/fentanyl 2 mcg/mL) occurred in 36.5% of patients with the highest incidence when the catheter was placed at levels L2/3 and L 3/L4 (Ahmed 2016 **Level IV**, n=123).

TEA permits early removal of urinary catheters in many patients vs LEA; rates of urinary retention are variably reported as 6.6% (Tripepi-Bova 2013 **Level IV**, n=61), 11.9% (vs 2.2% after TEA was discontinued) (Stubbs 2013 **Level III-2**, n=118) and 26.7% (vs 12.4% in historic controls) (Hu 2014 **Level III-3**, n=101). Post removal of the urinary catheter, effective bladder emptying took hours to normalise (defined as post-void volumes <200 mL) in patients who received TEA, however without need for recatheterisation; this effect was prolonged when the urinary catheter was removed early on the morning after surgery rather than remaining *in situ* for the duration of TEA therapy (345 min ± 169 vs 207 min ± 122) (Zaouter 2012 **Level II**, n=205, JS 2). TEA for thoracotomy did not change the post-void volume from the preoperative findings in men and women (Wuethrich 2011b **Level III-3**, n=26); only three men >50 y with prostrate hypertrophy had post-void volumes >100 mL. However, in women undergoing nephrectomy, early removal of the urinary catheter under TEA led to an increase in post-void residual volume (median 5 vs 220 mL) and negatively affected other parameters of bladder emptying (detrusor pressure, maximum flow rate, voided volume) (Wuethrich 2011a **Level III-3**, n=13); the authors suggest that this necessitates indwelling or intermittent catheterisation or monitoring.

5.6.1.5 | Patterns of administration

Routinely, epidural analgesia is maintained by continuous infusion. More recently, programmed intermittent epidural bolus (PIEB) has been suggested as a superior technique, based on data in labour analgesia (see Section 9.1.3.3). After TKA, PIEB vs continuous infusion (both delivering 3 mL/h of 0.125% bupivacaine/0.005% morphine) reduced pain scores and rescue analgesia requirements (Kang 2013 **Level II**, n=53, JS 2). After major abdominal or gynaecological surgery, PIEB TEA vs continuous TEA infusion (both techniques delivering 6 mL/h ropivacaine 0.2%) resulted in reduced PCEA requirements in the first 48 h postoperatively (median 10 mL [IQR 2 to 28] vs 28 mL [12 to 64]) without any other clinically relevant benefits (Wiesmann 2018 **Level II**, n=110, JS 5). In a similar RCT following open gynaecological surgery, PIEB TEA vs continuous TEA infusion (both delivering 4 mL/h ropivacaine 0.2%/fentanyl 2 mcg/mL) resulted in slightly reduced PCEA requirements, but also improved pain control from 3 to 48 h (Satomi 2018 **Level II**, n=57, JS 5).

5.6.2 | Medicines used for epidural analgesia

Differences in analgesic effect, duration and adverse effects depend upon the various local anaesthetic, opioid and adjuvant medicines used in epidural analgesia.

5.6.2.1 | Local anaesthetics

For epidural infusions, dose-ranging studies established that 0.2% ropivacaine was a suitable concentration (Scott 1995 **Level II**, n=40, JS 3; Schug 1996 **Level II**, n=50, JS 4). Therefore, most investigators compare infusions of bupivacaine or levobupivacaine at 0.1 or 0.125% with ropivacaine 0.2%, which removes any imbalance in comparative potency. For more information on differences in efficacy and adverse effects between the local anaesthetics used for epidural analgesia see Section 4.4.

5.6.2.2 | Opioids

Opioids alone via the epidural route appear to be of limited benefit. In particular, when administered via TEA, opioids fail to demonstrate any advantage over parenteral opioids except for a slight reduction in the rate of atelectasis (Ballantyne 1998 **Level I**, 48 RCTs, n unspecified) with no benefit with regard to bowel recovery (Jorgensen 2000 **Level I** [Cochrane], 22 RCTs, n=1,023). On the basis of the available studies, the benefits of administering lipophilic opioids alone by the epidural route appear to be marginal, or unproven in the case of upper abdominal surgery, and in many situations will not outweigh the risks of the more invasive route of administration. For a detailed discussion see (Wheatley 2001 **NR**) and Section 4.3.2.

For information on the epidural use of morphine, ER morphine, pethidine, fentanyl, alfentanil, sufentanil, diamorphine and hydromorphone see also Section 4.3.2.

5.6.2.3 | Local anaesthetic-opioid combinations

Combinations of low concentrations of local anaesthetic agents and opioids provide consistently superior pain relief vs either of the medications alone (Curatolo 1998 **Level I**, 18 RCTs [fentanyl], n unspecified). Addition of fentanyl to a continuous epidural infusion of ropivacaine reduced the rate of regression of sensory block after orthopaedic (n=80) and abdominal gynaecological surgery (n=39) (Kanai 2007 **Level II**, n=119, JS 3) and decreased the discontinuation of postoperative epidural infusion due to lack of efficacy (Scott 1999 **Level II**, n=244, JS 4).

Addition of 4 mcg/mL of fentanyl to levobupivacaine 0.125% improved quality of analgesia and reduced the stress response (ACTH, cortisol and prolactin levels) after TKA vs plain levobupivacaine (Bayazit 2013 **Level II**, n=40, JS 4). Addition of 0.5 mcg/mL sufentanil to 0.1% ropivacaine vs higher sufentanil concentrations and 4 mcg/mL fentanyl resulted in no difference in quality of analgesia after arthroplasty and had the lowest rate of pruritus (Jeon 2011 **Level II**, n=80, JS 3). The MLAC of epidural lidocaine of 0.785% (95%CI 0.738 to 0.864) was reduced by 2 mcg/mL fentanyl to 0.596% (95%CI 0.537 to 0.660) and by 3 mcg/mL to 0.387% (95%CI 0.329 to 0.446) (up-down sequential titration) (Zhang 2012 **Level III-1**, n=120).

5.6.2.4 | Adjuvant medicines

The efficacy of adding of adjuvant medicines such as adrenaline (epinephrine), clonidine, dexmedetomidine, ketamine, midazolam, neostigmine and magnesium to solutions used for epidural analgesia has also been investigated (see Chapter 4).

5.6.3 | Patient-controlled epidural analgesia

The use of PCEA is based on similar concepts as for other patient-controlled techniques. It has been shown to be safe and effective in standard ward settings (Golster 2014 **Level IV**, n=4,663; Kim 2013 **Level IV**, n=2,276; Tan 2011 **Level IV**, n=928; Liu 2010 **Level IV**, n=3,736).

5.6.3.1 | Comparison with continuous epidural infusions

A systematic review comparing PCEA, continuous epidural infusions and IV PCA opioids after surgery showed that both forms of epidural analgesia (with the exception of hydrophilic opioid-only epidural regimens) provide better pain relief with rest and with activity than PCA opioids (Wu 2005 **Level I**, 50 RCTs, n=3,208). However, analgesia with a continuous epidural infusion is superior to PCEA, countered by higher incidence of nausea, vomiting and motor block.

For specific procedures, results of PCEA vs continuous infusion are conflicting. After colonic resection, PCEA was superior to continuous epidural infusion with regard to pain control, requirements for top-ups and systemic analgesia as well as patient satisfaction (Nightingale 2007 **Level II**, n=205, JS 5). In contrast, comparisons of PCEA and continuous epidural infusions for pain relief after thoracotomy using both high (0.5%) and low (0.15%) concentrations of levobupivacaine showed no differences in quality of analgesia, morphine consumption or satisfaction; more patients in the high concentration continuous epidural infusion group had significant motor block (Dernedde 2008 **Level II**, n=82, JS 3).

5.6.3.2 | Concurrent background (continuous) infusions

The addition of a continuous background infusion to PCEA using bupivacaine and fentanyl following gastrectomy resulted in better dynamic pain scores, with higher total doses and a greater incidence of pruritus than PCEA-bolus dose only (Komatsu 1998 **Level II**, n=40, JS 2). The use of a night-time-only background infusion with PCEA bupivacaine-fentanyl, also post gastrectomy, resulted in better sleep, but total cumulative doses were similar and pain scores were only better in the morning of postoperative d 2 (Komatsu 2001 **Level II**, n=40, JS 2). A Swedish case series over 7 y (Golster 2014 **Level IV**, n=4,663) and a USA case series (Liu 2010 **Level IV**, n=3,736) describe successful and safe use of PCEA with a background infusion.

Other studies have found no improvement in pain relief with background infusions. After lower abdominal surgery there was no difference in pain scores but higher total cumulative doses and incidence of adverse effects when a background infusion was added to PCEA with ropivacaine and fentanyl (Wong 2000 **Level II**, n=42, JS 2). The addition of a background infusion to bupivacaine-fentanyl PCEA did not improve pain relief after pelvic reconstruction (Nolan 1992 **Level II**, n=23, JS 5).

5.6.3.3 | Medications used in postoperative patient-controlled epidural analgesia

The medications used for PCEA are typically the same as those used for continuous epidural infusions. Conclusions about the efficacy of different medications and medication combinations administered via PCEA are difficult to make because of the wide variety of analgesic agents and concentrations used in the various studies.

5.6.4 | Adverse effects

5.6.4.1 | Neurological injury

Permanent neurological damage is the most feared complication of epidural analgesia.

A systematic review identified 647 cases of epidural haematoma (n=387) and abscess (n=260) after neuraxial anaesthesia (Bos 2018 **Level IV SR**, n=409 [reports]). Epidural anaesthesia was related to 58% of haematomas and 83% of abscesses. After epidural haematoma, 28% had partial and 25% no recovery. After epidural abscess, 21% had partial and 11% no recovery. Persistent neurological deficits were correlated with the severity of the initially presenting neurology.

A retrospective survey from Sweden put the risk of a severe neurological complication after obstetric epidural analgesia at 1 per 25,000 and for all other patients at 1 per 3,600; 67% of events resulted in permanent neurological deficit (Moen 2004 **Level IV**, n=450,000). It also identified osteoporosis as a previously neglected risk factor. A review of data from publications reporting adverse effects after obstetric epidural analgesia reported a risk estimate of 1 per 240,000 for persistent neurological injury and 1 per 6,700 for transient (resolution within 12 mth) neurological symptoms (Ruppen 2006a **Level IV SR**, 27 studies, n≈1.37 million).

A review of data from published studies of the risk of neurological injury associated with epidural and other regional anaesthesia and analgesia techniques differentiated between the risk of permanent neurological injury (deficit lasting >12 mth) and transient neuropathy (Brull 2007 **Level IV SR**, 32 studies, n unspecified). This review focussed on adverse neurological sequelae associated with the various regional techniques and did not address the overall risk of epidural haematoma or abscess. The incidence of transient neuropathy (radiculopathy) after epidural anaesthesia was estimated to be 2.19 per 10,000 (95%CI 0.88 to 5.44) (Brull 2007 **Level IV SR**, 4 studies [epidural], n unspecified). The risk of permanent neurological injury was lower and the incidences reported in the studies included in this review ranged from 0 to 7.6 per 10,000. The rates of paraplegia and cauda equina syndrome associated with epidural anaesthesia were estimated to be 0.09 per 10,000 (95%CI 0.04 to 0.22) and 0.23 per 10,000 (95%CI 0.14 to 0.39) respectively.

A project in the UK (NAP3) assessed the incidence of neurological complications in an estimated 97,925 adult patients with perioperative epidural catheters (Cook 2009 **Level IV**). Depending on the inclusion or exclusion of cases with unlikely causation, pessimistic and optimistic assessments were published. The incidence of permanent injury was pessimistically assessed as 17.4 per 100,000 (95%CI 7.2 to 27.8; 1 in 5,800) and optimistically as 8.2 per 100,000 (95%CI 3.5 to 16.1; 1 in 12,200). Laminectomy was performed with an incidence of 12.3 per 100,000 cases (95%CI 6.3 to 21.4; 1 in 8,100). Paraplegia was caused in 6.1 per 100,000 (95%CI 2.2 to 13.3; 1 in 16,400) in the pessimistic vs 1.0 per 100,000 (95%CI 1.0 to 5.7) in the optimistic model.

Audit data from a single (nonobstetric) tertiary institution of epidural catheters inserted over a 16 y period for postoperative pain relief found two spinal haematomas and six epidural abscesses; only one patient (with an epidural abscess) required surgical decompression and no patient suffered any long-term neurological deficit (Cameron 2007 **Level IV**, n=8,210 [epidural catheters]). The largest published audit of patients undergoing arthroplasty with epidural analgesia at one institution described no persistent neurologic deficit despite four patients developing epidural haematoma and two requiring surgical compression (Pumberger 2013 **Level IV**, n=62,856). Another audit at a single institution reported 1 epidural haematoma, but 57 postoperative neurologic deficits, which resolved within 3 mth except for one being permanent (unilateral lower limb paraesthesia) (Kang 2014 **Level IV**, n=5,083).

The incidence of transient neuropathy after epidural analgesia in large case series was in the range of 0.013 to 0.023% (Auroy 1997 **Level IV**, n=30,413; Tanaka 1993 **Level IV**, n=40,010; Xie 1991 **Level IV**, n=1,304,214).

5.6.4.2 | Epidural haematoma

A major concern is the development of an epidural haematoma with subsequent, potentially permanent, SCI. A review including case series involving over 1,335,000 patients with epidural analgesia reported seven cases of haematoma (1 per 191,000) (Wulf 1996 **Level IV**). On the basis of this case series, the possible incidence is in the order of 1 per 100,000 at the upper limit of the 95%CI. The Swedish case series quoted above puts the overall risk of epidural haematoma after epidural blockade at 1 per 10,300 (Moen 2004 **Level IV,** n=450,000). A Finnish closed-claims study calculated a risk of 1 per 26,400 (Pitkanen 2013) **Level IV**, n=216 [claims]). An even higher incidence of epidural haematoma (1 per 3,100) has been estimated for epidural analgesia in association with inappropriate low molecular weight heparin (LMWH) dose regimens (Horlocker 2003 **GL**) (see Section 5.9).

A systematic review of the risks of epidural haematoma and neurological injury associated with epidural anaesthesia/analgesia in cardiac, vascular and thoracic surgery patients concluded

that the maximum risks of epidural haematoma were 1 per 1,700, 1 per 1,700 and 1 per 1,400 respectively (Ruppen 2006b **Level IV SR**, 12 studies, n=14,105). However, this was a calculated risk only; there were actually no cases of epidural haematoma reported in the studies used in this analysis and the maximal calculated expected rate of permanent neurological injury associated with epidural haematoma was 1 per 4,600.

In a large USA case series of patients having epidural analgesia perioperatively, seven patients developed haematoma requiring surgical evacuation (1 per 8,921; 95%CI 1/4,330 to 1/22,189) (Bateman 2013 **Level IV**, n=62,450)). In four of the seven patients, management of anticoagulation was not in line with the guidelines of American Society of Regional Anesthesia and Pain Medicine (ASRA) discussed later (see Section 5.9). In a similarly large case series of patients having arthroplasty with an indwelling epidural catheter at one institution, four epidural haematomas occurred (1 per 15,714), of which two required emergency decompression and none resulted in persisting neurological deficits (complete recovery at 6 wk) (Pumberger 2013 **Level IV**, n=62,856). It is of note that all four patients had combined spinal and epidural anaesthesia, took at least one medication affecting coagulation (aspirin, TCA, NSAIDs, clopidogrel) and had preoperative hypertension. Additional risk factors were clopidogrel only discontinued for 4 d in one, thrombocytopenia (70,000/microL) at day of insertion and removal in one and excessive alcohol consumption in two.

In a case series after cardiac surgery, the risk of epidural haematoma was calculated at 1 per 12,000 (95%CI 1 per 2,100 to 1 per 68,000); comparable to an obstetric population (Bracco 2007 **Level IV**, n=1,293). It was described as being in the same risk range as receiving a wrong blood product (or the yearly risk of having a fatal traffic accident in a Western country). A subsequent study including a survey in cardiac surgery identified a risk of epidural haematoma of 1 per 3,552 (95%CI 1 per 2552 to 1 per 5841) (Landoni 2015 **Level IV**, n=88,820 [estimated epidural catheters]).

A review of data from publications reporting adverse effects after obstetric epidural analgesia reported a risk estimate of 1 per 168,000 for epidural haematoma (Ruppen 2006a **Level IV SR**, 27 studies, n≈1.37 million). In a large USA series of obstetric epidural analgesia, no epidural haematoma was found (Bateman 2013 **Level IV**, n=79,837); the haematoma rate in this setting was significantly lower than in the perioperative data from the same series.

Case reports of epidural haematoma after neuraxial blockade (spinal and epidural) have increased from 1994 to 2015, primarily due to increased rates in elderly women (Lagerkranser 2017a **Level IV SR**, n=166). Anticoagulants, in particular heparins, remain an important risk factor, but epidural haematomas occur also in patients with no risk factors and despite following guidelines. 80% present with paresis or paralysis, early MRI scan is the best diagnostic measure and over the period studied, outcomes have improved (Lagerkranser 2017b **Level IV SR**, n=166).

Early diagnosis and, if indicated, immediate decompression (<8 h after the onset of neurological signs) increases the likelihood of partial or good neurological recovery (Horlocker 2003 **GL**). This is confirmed by a case series of epidural haematomas (n=163), which showed worse outcome with decompression delayed >12 h vs earlier decompression (OR 4.5; 95% CI 2.1 to 9.9) (Bos 2018 **Level IV SR**, n=409 [reports]). This is confirmed by a further case series, although some patients operated >24 h regained full motor function (Lagerkranser 2017b **Level IV SR**, n=166).

5.6.4.3 | Infectious complications (including epidural abscess)

Serious neuraxial infections following epidural anaesthesia have previously been reported as rare. However, prospective studies have found rates in the range of 0.015 to 0.05% (Wang 1999 **Level IV**, n=9,232; Rygnestad 1997 **Level IV**, n=2,000; Kindler 1996 **Level IV**, n>13,000). It is of note that in the studies with these high incidences, patients had long durations of epidural catheterisation; the mean duration in patients with an epidural space infection was 11 d, no infection occurred

in any patient whose catheter was *in situ* for <2 d and the majority of patients were immunocompromised (Wang 1999 **Level IV**, n=9,232).

Only 5.5% of 915 cases of epidural abscess published between 1954 and 1997 developed following epidural anaesthesia and analgesia; 71% of all patients had back pain as the initial presenting symptom and only 66% were febrile (Reihsaus 2000 **Level IV**, n=915). The classic triad of symptoms (back pain, fever and neurological changes) was present in only 13% of patients with an epidural abscess (in a study unrelated to epidural catheterisation); diagnostic delays occurred in 75% of these patients and such delays led to a significantly higher incidence of residual motor weakness (Davis 2004 **Level IV**, n=63 [epidural abscesses]).

Audit data showed that of 8,210 patients with epidural catheters over a period of 16 y, six developed epidural abscesses (Cameron 2007 **Level IV**). Only one of these required surgical decompression and they did not suffer any long-term neurological loss. The authors stress the importance of appropriate patient monitoring and early diagnosis using MRI. In five of the six patients diagnosed with an epidural abscess, both fever and epidural insertion site infection were present. They therefore suggested that MRI investigation may be warranted if this combination is present and that urgent investigation is especially indicated if there is a third sign that could indicate an abscess, such as back pain or neurological change (Cameron 2007 **Level IV**, n=8,210). If the diagnosis of epidural abscess can be made before the onset of any neurological deficit, conservative treatment (antibiotics only) may be effective. The presence of severe or increasing back pain, even in the absence of a fever, may indicate epidural space infection and should be investigated promptly.

Thoracic epidural abscesses have been analysed; most common presentations were neurological deficits (68%) (paraparesis 48% and paraplegia 20%), back pain (64%), fever (24%) and loss of bowel or bladder control (16%) (Howie 2018 **Level IV SR** [PRISMA], 25 studies, n=25 [thoracic epidural abscesses]). Recommended diagnostic measures are early MRI scans, laboratory tests (ESR, CRP, blood count and sedimentation rate/C-reactive protein, complete blood count), empiric antibiotics (until abscess culture) and immediate surgical decompression in neurological deficits as immediate surgical compression achieves better recovery than a failed antibiotic course before surgical decompression.

A review of data from publications reporting adverse effects after obstetric epidural analgesia reported a risk estimate of 1 per 145,000 for epidural space infection (Ruppen 2006a **Level IV SR**, 27 studies, n≈1.37 million).

Septic meningitis has also been associated with neuraxial anaesthesia and analgesia, although most cases were associated with spinal or combined techniques; only 25 of 234 cases identified were linked to epidural techniques (Zorrilla-Vaca 2018 **Level IV SR**, n=234). Not using surgical masks was the most common association and *staphylococcus aureus* the most common bacterium. Time to onset of meningitis was longer with epidural than spinal techniques (96 h; IQR 84 to 240 vs 24 h; IQR 8 to 72) and mortality rate 13.3%.

5.6.4.4 | Diagnosis and prevention of Infectious complications

Bacterial colonisation of epidural catheter tips is reported to occur in 0 to 28% of patients (Yuan 2008 **Level IV**, n=205; Mishra 2006 **Level IV**, n=466; Steffen 2004 **Level IV**, n=502; Simpson 2000 **Level IV**, n=1,442). The most common organism cultured from the catheter tips was coagulase-negative staphylococcus.

Experimental data suggest that after accidental epidural catheter disconnection, cutting the catheter 2 cm distal to the level of contamination left all such treated catheters sterile, while spray-wipe disinfection or employing ropivacaine 0.75% as flushing solution or a combination of

these measures were not as effective (Scholle 2014 **BS**). The authors suggest spray-wipe disinfection and cutting as the safest strategy.

An *in vitro* comparison of the antibacterial activity of medications used in epidural solutions showed that the minimal inhibitory concentration of bupivacaine for *Staphylococcus aureus*, *Enterococcus faecalis* and *Escherichia coli* was between 0.125% and 0.25% (growth of *Pseudomonas aeruginosa* was not affected at any of the concentrations investigated) (Coghlan 2009 **Level III-2 BS**). Levobupivacaine and ropivacaine showed no activity against *S aureus*, *E faecalis* and *P aeruginosa*, even at the highest concentrations tested, and minimal activity against *E coli* (minimum inhibitory concentrations 0.5 and 1% respectively). The addition of fentanyl, clonidine and adrenaline did not improve antibacterial activity

Chlorhexidine-impregnated dressings of epidural catheters in comparison to placebo or povidone-iodine-impregnated dressings reduced the incidence of catheter colonisation (Ho 2006 **Level I**, 8 RCTs, n=2,588). Chlorhexidine was also the superior skin disinfectant prior to regional catheter insertion with a positive skin culture immediately after skin disinfection of 10% vs 35% of povidone-iodine treated (NNT 4) (Krobbuaban 2011 **Level II**, n=100, JS 4). Chlorhexidine is therefore the recommended skin disinfectant before insertion of regional catheters (Campbell 2014 **GL**). However, chlorhexidine is neurotoxic and skin preparation solutions must be allowed to dry before instrumentation of the epidural space. For this reason, chlorhexidine must also be kept clearly identified and separate from all solutions used for injection. As 2% chlorhexidine is not superior to 0.5% for skin disinfection, UK guidelines recommend the use of 0.5% to reduce neurotoxicity (Campbell 2014 **GL**).

Comprehensive reviews of infectious complications associated with central neuraxial and PNB, including epidemiology, factors affecting bacterial colonisation of the epidural catheter as well as use in febrile, infected and immunocompromised patients are published (Hebl 2011 **NR**; Horlocker 2008 **NR**).

Guidelines for skin antisepsis prior to neuraxial block (Association of Anaesthetists of Great Britain and Ireland, Obstetric Anaesthetists' Association, Regional Anaesthesia UK, Association of Paediatric Anaesthetists of Great Britain and Ireland) recommend thorough handwashing with surgical scrub solution, the use of barrier precautions, including the wearing of a cap, mask, sterile gown and gloves, and of a large sterile drape (Campbell 2014 **GL**). Chlorhexidine in alcohol (0.5%) should be used for skin preparation, but meticulous care must be taken to avoid this reaching epidural space or CSF.

5.6.4.5 | Respiratory depression

The incidence of respiratory depression with epidural opioid analgesia depends on the criteria used to define respiratory depression. In a review of published case series and audit data, the reported incidence of respiratory depression ranged from 1.1% (95% CI 0.6 to 1.9) using respiratory rate to 15.1% (95%CI 5.6 to 34.8) using oxygen saturation (see Section 4.3.1.5 for comments on respiratory rate as an unreliable indicator of respiratory depression); this was very similar to the incidence reported for PCA (Cashman 2004 **Level IV SR**, 165 studies, n≈20,000).

5.6.4.6 | Hypotension

The incidence of hypotension depends on the dose of local anaesthetic and criteria used to define hypotension. In the same review as above, the reported incidence of hypotension was 5.6% (95% CI 3.0 to 10.2) (Cashman 2004 **Level IV SR**, 165 studies, n≈20,000). In the large meta-analysis quoted above, incidence of hypotension is increased by epidural analgesia (OR 4.92; 95%CI 3.11 to 7.78) (Popping 2014 **Level I** [PRISMA], 125 RCTs, n=9,044). Hypotension requiring intervention is increased in another meta-analysis after abdominal surgery (RR 7.13, 95%CI 2.87

to 17.75) (6 RCTs, n=479) (Salicath 2018 **Level I** [Cochrane], 32 RCTs, n=1,716); a subsequent meta-analysis shows an increase in hypotension (RD 0.21; 95% CI 0.09 to 0.33) (17 RCTs, n=870) not leading to increased need for inotropes or vasopressors (RD 0.00; 95%CI -0.06 to 0.07) (23 RCTs, n=1,821) (Guay 2019 **Level I** [Cochrane], 69 RCTs, n=4,680) (significant overlap between all three SRs).

But while TEA was associated with arterial hypotension after thoracic or abdominal surgery, this did not predict inability to walk (Gramigni 2013 **Level IV**, n=161); early mobilisation may be carefully attempted despite hypotension or orthostatic changes.

5.6.4.7 | Treatment failure with epidural analgesia

Epidural analgesia may not always be successful due to a number of factors including catheter malposition or displacement, or technical and patient factors resulting in an inability to achieve effective analgesia (Hermanides 2012 **NR**). Intolerable adverse effects may also be an indication for premature discontinuation. In a large prospective audit, 22% of patients had premature termination of postoperative epidural infusions (Ballantyne 2003 **Level IV**, n=5,628): the most common causes were dislodgement (10%), inadequate analgesia (3.5%) and sensory or motor deficit (2.2%). Most of these failures occurred on or after POD 2. The rate of technical failures in a meta-analysis of epidural analgesia is 6.1% (Popping 2014 **Level I** [PRISMA], 125 RCTs, n=9,044) and risk of failure of the analgesic technique is increased in another meta-analysis (epidural vs IV PCA) (RR 2.48; 95%CI 1.13 to 5.45) (10 RCTs, n=678) (Salicath 2018 **Level I** [Cochrane], 32 RCTs, n=1,716) (siginificant overlap of RCTs). After oesophagectomy, technical failure with TEA occurred in 17 to 22% (Hughes 2018 **Level I** [PRISMA], 3 RCTs, n=93) (0 RCT overlap).

Tunnelling and then suturing the epidural catheter subcutaneously vs fixation with adhesive tape without tunnelling reduced incidence of clinically relevant dislocation of epidural catheters (>20 mm; 1/60 vs 9/61) (Sellmann 2014 **Level II**, n=121, JS 3). Bacterial contamination rates did not differ (8/59 vs 14/54). Length of the catheter in the epidural space may also influence rate of dislocation; in an RCT of 3 vs 5 vs 7 cm insertion, one patient in the 7 cm group had unilateral sensory block and four patients in the 3 cm group had epidural catheter dislodgement (Afshan 2011 **Level II**, n=102, JS 5). The authors suggest that 5 cm is the ideal depth of insertion.

5.6.4.8 | Anastomotic leakage

There has been concern among surgeons about increased risk of anastomotic leakage after bowel surgery due to the stimulating effects of epidural administration of local anaesthetics; so far there is no evidence to support these claims in colorectal surgery. This is supported by a large meta-analysis which shows no difference in the incidence of gastrointestinal anastomotic leakage (RR 0.74, 95%CI 0.41 to 1.32) (17 RCTs, n=848) (Guay 2016b **Level I** [Cochrane], 128 RCTs, n=8,754). An audit of patients undergoing surgery for colorectal cancer in one centre showed that epidural analgesia had no influence on occurrence of anastomotic leakage (Lai 2013 **Level III-2**, n=1,312). After oesophagectomy, TEA reduced the risk of anastomotic leakage (OR 0.13; 95%CI 0.02 to 0.71) (Michelet 2005 **Level III-2**, n=207).

KEY MESSAGES

1. For all types of surgery, epidural analgesia provides better postoperative pain relief compared with parenteral (including PCA) opioid administration (**S**) (**Level I** [Cochrane Review]); except epidural analgesia using a hydrophilic opioid only (**U**) (**Level I**).
2. Thoracic epidural analgesia for open abdominal aortic surgery reduces pain intensity, time to tracheal extubation, time spent in the intensive care unit, rate of acute respiratory failure, myocardial infarction and gastrointestinal bleeding when compared with intravenous opioids (**S**) (**Level I** [Cochrane Review]).
3. High thoracic epidural analgesia used for coronary artery bypass graft surgery reduces postoperative pain, risk of dysrhythmias, pulmonary complications and time to extubation when compared with intravenous opioid analgesia (**Q**) (**Level I** [Cochrane Review]).
4. Thoracic epidural analgesia for thoracotomy reduces the risk of chronic postsurgical pain (**S**) (**Level I** [Cochrane Review]).
5. Thoracic epidural analgesia improves bowel recovery after abdominal surgery (including colorectal surgery) (**S**) (**Level I** [Cochrane Review]).
6. Epidural analgesia is not associated with increased risk of anastomotic leakage after bowel surgery (**S**) (**Level I** [Cochrane Review]).
7. Epidural analgesia provided with local anaesthetics for at least 24 hours compared to systemic opioid analgesia reduces perioperative mortality and multiple morbidities (including ileus, pneumonia, respiratory depression and arrhythmias) but increases hypotension (**U**) (**Level I** [PRISMA]).
8. After laparoscopic colectomy, thoracic epidural analgesia compared to intravenous PCA reduces initial pain scores and time to first bowel opening, but length of hospital stay, total rate of complications (**S**) (**Level I** [PRISMA]), urinary tract infection rates and hospital costs are increased (**U**) (**Level III-2**).
9. Combinations of low concentrations of local anaesthetic agents and opioids for epidural analgesia provide consistently superior pain relief compared with either of the medications alone; epidural opioids alone have no advantage over parenteral opioids (**U**) (**Level I**).
10. Epidural local anaesthetic administration improves oxygenation and reduces pulmonary infections and other pulmonary complications compared with parenteral opioids (**U**) (**Level I**).
11. Chlorhexidine-impregnated dressings of epidural catheters in comparison to placebo- or povidone-iodine-impregnated dressings reduce the incidence of catheter colonisation (**U**) (**Level I**).
12. In patients with multiple rib fractures, thoracic epidural analgesia improves pain relief versus parenteral opioids (**N**) (**Level III-2 SR**), but does not reduce incidence of pneumonia and mortality (**U**) (**Level I**) and may not reduce need for ventilation (**Q**) (**Level III-2 SR**).

13. The combination of thoracic epidural analgesia with local anaesthetics and nutritional support leads to preservation of total body protein after upper abdominal surgery (**U**) (**Level II**).
14. The incidence of permanent neurological damage in association with epidural analgesia is extremely low, especially in the obstetric population, but increases with various comorbidities and risk factors; the incidence is higher where there have been delays in diagnosing an epidural haematoma or abscess (**S**) (**Level IV SR**).
15. Immediate decompression of an epidural haematoma (within 8 hours of the onset of neurological signs) increases the likelihood of partial or good neurological recovery (**S**) (**Level IV SR**).
16. Epidural abscesses present mainly with neurological deficits and back pain; they are best diagnosed with early MRI and best treated with empiric antibiotics (until abscess culture) and immediate surgical decompression when neurological deficits are present (**S**) (**Level IV SR).**

The following tick boxes represent conclusions based on clinical experience and expert opinion:

☑ The provision of epidural analgesia by continuous infusion, programmed intermittent bolus or patient-controlled administration of local anaesthetic-opioid mixtures is safe on general hospital wards, as long as supervised by an anaesthesia-based pain service with 24-hour medical staff cover and monitored by well-trained nursing staff (**U**).

☑ Prior to insertion of an epidural catheter, thorough handwashing with surgical scrub solution, the use of barrier precautions including the wearing of a cap, mask, sterile gown and gloves and use of chlorhexidine in alcohol for skin preparation are recommended; but meticulous care must be taken to avoid the chlorhexidine solution from reaching epidural space or cerebrospinal fluid (**U**).

5.7 | Intrathecal analgesia

5.7.1 | Medicines used for intrathecal analgesia

5.7.1.1 | Local anaesthetics

IT local anaesthetics provide short-term postoperative analgesia. The use of spinal microcatheters (<24 G) for postoperative infusions of local anaesthetics became controversial when multiple cases of cauda equina syndrome were reported (Bevacqua 2003 **NR**). See also Section 5.7.1.1. above.

5.7.1.2 | Opioids

Morphine is the most frequently studied IT opioid followed by fentanyl (Popping 2012 **Level I** [PRISMA], 65 RCTs, n=3,338; Meylan 2009 **Level I**, 27 RCTs, n=1,205) (0 RCT overlap). Reported IT use of other opioids includes pethidine (meperidine), hydromorphone, diamorphine, pentazocine, sufentanil, tramadol and buprenorphine (Staikou 2014 **Level I**, 105 RCTs, n unspecified). Some clinical studies used very high IT morphine doses (ie 500 mcg or more) without additional benefit. Lower doses (<300 mcg) should be used as there is no clear dose-response relationship with IT morphine for duration of analgesia nor for adverse effects (Popping 2012 **Level I** [PRISMA], 65 RCTs, n=3,338; Meylan 2009 **Level I**, 27 RCTs, n=1,205)

For patients having procedures amenable to spinal anaesthesia alone (orthopaedic, urologic, gynaecologic), the addition of IT morphine (50 mcg to 2 mg) consistently provides an increase in duration of analgesia (as time to first requirement of additional opioid analgesia) (WMD 503 min; 95%CI 315 to 641) vs IT local anaesthetic alone (13 RCTs) (Popping 2012 **Level I** [PRISMA], 65 RCTs, n=3,338). IT fentanyl (10 to 50 mcg) prolongs the duration of analgesia (WMD 114 min; 95%CI 60 to 168). When IT morphine is used, cumulative morphine consumption is reduced (WMD -12 mg; 95%CI -18 to -5) (7 RCTs). There is considerable heterogeneity in the study data and no dose-responsiveness could be identified.

For major abdominal or thoracic surgery, IT opioids are typically combined with a general anaesthetic technique. In patients having abdominal, cardiothoracic or spinal surgery, IT morphine (100 to 500 mcg, without local anaesthetic) reduces pain scores at rest and with movement by 1/10 and 2/10 respectively at both 12 h (7 RCTs, n=353) and 24 h time points (8 RCTs, n=393) (Meylan 2009 **Level I**, 27 RCTs, n=1,205). Morphine-sparing is evident for up to 48 h postoperatively (11 RCTs, n=482), being more pronounced at 24 h after abdominal (5 RCTs, n=272) than cardiothoracic surgery (6 RCTs, n=210).

IT fentanyl is inferior to IT dexmedetomidine which prolongs the pain free period (SMD 2.98; 95%CI 1.69 to 4.27) (7 RCTs, n=491) without increasing the incidence of adverse events including hypotension and bradycardia (8 RCTs each) (Sun 2017 **Level I**, 9 RCTs, n=639).

Lower limb arthroplasty (TKA and THA)

In comparison to IT morphine 100–200 mcg for THA and TKA, local infiltration analgesia (LIA: local anaesthetic, ketorolac 30 mg and adrenaline) results in a small reduction of pain scores at rest and at mobilisation at 24 h, but not at 48 h (Jia 2017 **Level I**, 4 RCTs, n=242). There is no difference in the rescue opioid consumption (4 RCTs) or LOS (3 RCTs). Nausea, vomiting and pruritus are increased in the IT morphine group (4 RCTs).

IT morphine 100–300 mcg vs FNB for TKA shows similar pain scores at 6 h (SMD -0.09; 95%CI -1.62 to 1.43) as well as at 12 h and 24 h, with no difference in morphine consumption for the same time points or PONV (Li 2016 **Level I**, 4 RCTs, n=185). The risk of postoperative pruritus is

reduced with FNB (RD 0.41; 95%CI 0.29 to 0.54). Another overlapping meta-analysis of the same issues shows significant inconsistencies in representing trial results, which makes it difficult to be confident of the conclusions drawn (Tang 2017 **Level I** [PRISMA], 5 RCTs, n=225) (4 RCTs overlap). Thus only the results of the previous meta-analysis are considered (Li 2016 **Level I**, 4 RCTs, n=185).

Several RCTs and studies have shown that the use of low-dose IT morphine has analgesic benefit. One RCT included in both meta-analyses had a third group combining continuous FNB with IT morphine 175 mcg, with no advantage of the combination over the continuous FNB, which was superior to IT morphine alone (Olive 2015 **Level II**, n=81, JS 4). In contrast, a small IT morphine 35 mcg dose improved pain scores when added to a continuous FNB, although the authors noted a higher rate of severe pain in both groups than in comparable studies of FNB (Sundarathiti 2016 **Level II**, n=70, JS 4). For TKA under spinal anaesthesia, where all patients had LIA, addition of IT morphine 100 mcg to adductor canal block [ACB] achieved the lowest pain scores and morphine requirements vs ACB alone and sham ACB (Biswas 2018 **Level II**, n=201, JS 5). However, there was no difference in the primary outcome 'Timed Up and Go (TUG)' test on POD 2 and any other short- or long-term functional outcomes. IT morphine >100–200 mcg in addition to systemic multimodal analgesia for THA and TKA (and a continuous femoral nerve block (FNB) or adductor canal block (ACB) for TKA until POD 1) achieved better analgesia, reduced opioid consumption, better mobilisation and less nausea (Cheah 2018 **Level III-2**, n=598 [467 ITM]). When compared to an US-guided fascia iliaca block for THA under spinal anaesthesia, IT morphine 100 mcg reduced the cumulative morphine consumption at 48 h and time to mobilisation (by 2 h) without a significant difference in adverse side effects (Kearns 2016 **Level II**, n=108, JS 5). Compared to a continuous lumbar plexus catheter technique for THA, IT morphine 100 mcg added to spinal anaesthesia resulted in similar pain scores and opioid supplementation rates, but higher rates of pruritus (Fredrickson 2015 **Level II**, n=50, JS 2).

Caesarean section

IT opioids have been used as a component of the spinal anaesthetic for Caesarean section for many years. The addition of IT morphine 50–250 mcg increases the median time to first analgesia from 2 h (range 1 to 4 h) to 27 h (range 11 to 29 h) (Dahl 1999 **Level I**, 15 RCTs, n=535). Higher doses of IT morphine (>100–250 mcg) vs lower doses (50–100 mcg) for analgesia after Caesarean section lead to a longer time to first analgesic request (MD 4.49 h; 95%CI 1.85 to 7.13), but with no significant difference in pain scores or morphine consumption (Sultan 2016 **Level I**, 11 RCTs, n=480) (3 RCTs overlap). The high-dose IT morphine group has higher incidence of PONV and pruritus (NNH 5.9; 95%CI 3.4 to 20.0) with no effect on Apgar scores.

IT morphine in a dose of 50 mcg had similar analgesic effects to 100 and 150 mcg when used with a spinal block and ketorolac with a similar side effect profile (with the lowest dose having a slightly reduced incidence of pruritus) (Berger 2016 **Level II**, n=144, JS 5). IT morphine 50 mcg had similar analgesic effects to 100 mcg, but the higher dose resulted in a significantly higher rate of pruritus (64 vs 40%) (Mikuni 2010 **Level II**, n=75, JS 3). Using an up–down sequential allocation the ED_{90} was determined to be 75 mcg (95%CI 46 to 93) for IT hydromorphone and 150 mcg (95%CI 145 to 185) for IT morphine with no difference between both for analgesia, side effects and patient satisfaction (Sviggum 2016 **Level II**, n=80, JS 5).

IT fentanyl 12.5 to 50 mcg added to spinal anaesthesia leads to a longer time to first analgesic request (MD 91 min; 95%CI 69 to 113) (12 RCTs, n=574) and reduces the incidence of nausea/vomiting (RR 0.41; 95%CI 0.24 to 0.70) (NNT 6.5) (12 RCTs, n=580), but increases the incidence of intraoperative pruritus (RR 5.89; 95%CI 2.07 to 16.79) (NNH 13.5) (13 RCTs, n=604) (Uppal 2020 **Level I** [PRISMA], 17 RCTs, n=1,064).

IT fentanyl 25 mcg/morphine 100 mcg combination vs morphine alone improved intraoperative analgesia and did not affect 24 h postop opioid requirements, but increased 12 h opioid requirements and PONV rates (Weigl 2017 **Level II**, n=60, JS 5).

Compared to a transversus abdominus plane (TAP) block, IT morphine 100 mcg resulted in lower pain scores, but only at 10 h, while causing more PONV and pruritus (Loane 2012 **Level II**, n=66, JS 5). This study failed to achieve full recruitment. IT morphine 100 mcg vs ropivacaine 0.2% via wound catheter had the same efficacy with no difference in median time to first morphine request (Lalmand 2017 **Level II**, n=192, JS 5). Both techniques were superior to the control group with spinal anaesthesia by bupivacaine/sufentanil only.

Labour

Adding IT morphine 50 to 250 mcg to single-injection IT bupivacaine/fentanyl 12.5 or 25 mcg or bupivacaine/sufentanil 5 or 10 mcg prolongs pain relief during labour by 61 min (range 3 to 155 min) with no effect on SMD of pain intensity (Al-Kazwini 2016 **Level I** [PRISMA], 5 RCTs, n=286).

Spinal surgery

IT morphine (100 mcg to 1 mg; 3.5–20 mcg/kg) vs placebo (6 RCTs) or control after spinal surgery results in reduced pain scores (7 RCTs) and postoperative opioid consumption (8 RCTs) during the first 24 h postoperatively with a higher rate of pruritus; respiratory depression only occurred in the IT morphine group (6/231) (8 RCTs) (Pendi 2017 **Level I**, 8 RCTs, n=393). This review includes abstract data for a later peer reviewed publication (Yen 2015 **Level II**, n=32, JS 4).

Cardiothoracic surgery

IT morphine 7 mcg/kg prior to surgical aortic valve surgery had a better analgesic effect postoperatively vs titrated systemic fentanyl, with reduced parenteral opioid requirements and increased time to first opioid rescue (Elgendy 2017 **Level II**, n=44, JS 5). In addition, the IT morphine group had a slightly earlier extubation and shorter ICU LOS. There were no reports of increased side effects. In minimally invasive cardiac surgery, IT morphine 1.5 mcg/kg reduced PCA-opioid requirements and pain scores (Mukherjee 2012 **Level II**, n=62, JS 3). For open thoracotomy procedures, the combination of IT morphine 4 to 5 mcg/kg (max 500 mcg) and sufentanil 0.2−0.3 mcg/kg (max 25 mcg) with a continuous PVB offered slightly higher but acceptable pain scores vs epidural analgesia (Dango 2013 **Level II**, n=84, JS 4).

Hepatic surgery

After liver resection, IT morphine 500 mcg/fentanyl 150 mcg resulted in better analgesia and lower opioid requirements than morphine PCA up to 18 h postoperatively (Roy 2006 **Level II**, n=20, JS 3). IT morphine 200 mcg vs epidural analgesia in liver resections showed comparable pain scores, although epidural recipients had lower opioid consumption and intubation duration (De Pietri 2006 **Level II**, n=50, JS 2). Similarly, in patients for liver resections, IT morphine 500 mcg and fentanyl 15 mcg was inferior to epidural bupivacaine infusion, with twice as much morphine consumption (123 mg vs 59 mg) and more pain (Mondor 2010 **Level II**, n=44, JS 5).

Urological surgery

IT morphine 50 to 200 mcg (± clonidine) after prostatic surgery resulted in better analgesia and lower opioid requirements vs morphine PCA up to 18 h postoperatively (Brown 2004 **Level II**, n=99, JS 5). For transurethral resection of the prostate under spinal anaesthesia, low-dose IT morphine 25 and 50 mcg resulted in similar pain scores for up to 24 h, but the higher-dose group had more pruritus (15 vs 0%) (Duman 2010 **Level II**, n=70, JS 4).

Other surgery

IT hydromorphone 5 or 10 mcg in addition to spinal anaesthesia for knee arthroscopic surgery reduced pain scores for up to 12 h vs 2.5 mcg dose or placebo (Lee 2012 **Level II**, n=60, JS 3). Nausea was more frequent (46%) in the 10 mcg group.

After open nephrectomy, IT morphine 330 mcg plus IV PCA versus IV PCA alone resulted in better analgesia and reduced systemic opioid requirements with similar adverse effects except for increased pruritus (77 vs 26%) (Kim 2016 **Level II**, n=45, JS 4).

IT morphine at three different doses (100, 200 and 300 mcg) for abdominal hysterectomy was superior to placebo for analgesia up to 24 h, with the 200 mcg dose equivalent to 300 mcg and superior to 100 mcg in rescue analgesia requirements (Hein 2012 **Level II**, n=144, JS 5). For inguinal hernia repair, IT morphine 100 mcg had similar analgesia to 400 mcg with increased PONV in the higher dose group (Meco 2016 **Level II**, n=48, JS 4).

For endovenous laser ablation in lower extremity venous insufficiency/varicose vein disease, the addition of IT morphine 100 mcg versus IT fentanyl 25 mcg to bupivacaine spinal anaesthesia reduced shivering vs placebo control as well as increased time to first analgesia use similarly (Onk 2016 **Level II**, n=90, JS 4).

5.7.1.3 | Adverse effects

Typical adverse effects of IT opioids include nausea and vomiting, pruritus and delayed respiratory depression (Popping 2012 **Level I** [PRISMA], 65 RCTs, n=3,338; Meylan 2009 **Level I**, 27 RCTs, n=1,205) (0 RCT overlap).

Opioid-induced ventilatory impairment

The definition of respiratory depression in different investigations often lacks uniformity, with many studies using respiratory rate as the primary marker and others using desaturation to different levels and a few others using the need for opioid antagonists. This significantly compromises interpretation of reported event rates. OIVI is a more appropriate term (Macintyre 2011 **NR**). Patients may be hypoxic or hypercapnic with a normal respiratory rate (Bailey 1993 **Level IV EH**, n=20), while others may be able to maintain normocarbia with a lower respiratory rate (Boezaart 1999 **Level II**, n=60, JS 5). In a volunteer study, clinical signs or symptoms including respiratory rate, sedation and pupil size did not reliably indicate hypoventilation or hypoxaemia, unlike peripheral pulse oximetry (Bailey 1993 **Level IV EH**, n=20); although desaturation itself is a late indicator when supplemental oxygen is being administered (Shapiro 2005 **Level IV**, n=1,524). Very large numbers of patient exposures are needed to adequately quantify risk of infrequent events (eg OIVI), thus most studies and meta-analyses will have a limited capacity to report meaningfully on such adverse effects (see also Section 4.3.1.4).

When measured in opioid-naïve volunteers, respiratory depression peaked at 3.5 to 7.5 h following IT morphine at 200 to 600 mcg doses (Bailey 1993 **Level IV EH**, n=20). Volunteers given 600 mcg had significant depression of the ventilatory response to CO_2 up to 19.5 h later.

In patients following major surgery, a 7.6% incidence of respiratory depression was reported for IT morphine >300 mcg vs IV PCA morphine (OR 7.86; 95%CI 1.54 to 40.3) (3 RCTs, n=172) (Meylan 2009 **Level I**, 27 RCTs, n=1,205). In patients having spinal surgery, IT morphine only resulted in respiratory depression (6/231) vs placebo (0/162) (RR 3.48; 95%CI 0.41 to 29.32) (Pendi 2017 **Level I**, 8 RCTs, n=393). In patients having minor surgery, major respiratory depression (endpoint "*SpO2 85 to 90%*" in addition to respiratory rate <12) occurred in 3 of 290 (1.0%) patients receiving IT bupivacaine alone and 15 of 410 (3.7%) receiving IT bupivacaine/morphine (OR 3.49; 95%CI 1.25 to 9.73) (Popping 2012 **Level I** [PRISMA], 65 RCTs, n=3,338). In the same analysis, the incidence of OIVI in patients receiving IT fentanyl (0.4%) was no different to control (0%). Thus,

indirect comparisons suggest that the risk of OIVI is more pronounced with IT morphine than with IT fentanyl.

A meta-analysis for a range of procedures, comparing IT morphine doses of <300 mcg, ≥300 mcg and placebo reported a greater risk of respiratory depression (respiratory rate <8 to 12) with the higher doses (9%) with no increased risk with lower morphine dose (1%) vs systemic opioids (2%) (Gehling 2009a **Level I**, 28 RCTs, n=1,414). This difference was not statistically significant but this may reflect the relatively small number of patients in the higher dose group (n=87). The incidence of pruritus was increased for all doses (low dose RR 1.8; 95%CI 1.4 to 2.2 vs high dose RR 5.0; 95%CI 2.9 to 8.6); the risk of nausea and vomiting was increased only in those patients given <300 mcg morphine.

For Caesarean section, when IT opioids (all types of opioids and all doses) were combined with local anaesthetic for analgesia, the rate of respiratory depression was low and not significantly different from controls (Dahl 1999 **Level I**, 15 RCTs, n=535). In a large case series, clinically detected respiratory depression in the 24 h following IT morphine 150 mcg was noted in 0.26% of patients (Kato 2008 **Level IV**, n=1,915). In a closed claims study from the USA, a maternal death from IT opioid overdose is reported (Clayton 2018 **CR**).

A prospective audit of IT morphine 200–800 mcg for pain relief following a range of surgical procedures reported a high degree of patient satisfaction and effective analgesia in the first 24 h (Gwirtz 1999 **Level IV**, n=5,969). The incidence of pruritus was 37%, nausea and vomiting 25% and respiratory depression 3% ($PaCO_2$ >50 mmHg and/or respiratory rate <8).

Overall, considering the increased risk of OIVI with IT morphine, the lowest effective dose of IT opioid should be used and surveillance for OIVI should continue for at least 18 to 24 h following a single dose (Bailey 1993 **Level IV**; Bujedo 2012 **NR**). A current ASA guideline recommends a minimum monitoring period of 24 h after administration of single-injection IT morphine, with monitoring of at least once per hour for the first 12 h and then at least once every 2 h for the next 12 h (ASA 2016 **GL**). The monitoring should consist of level of consciousness, adequacy of ventilation (rate and depth of respiration) and pulse oximetry. Higher risk patients may require additional monitoring and for a longer period of time. This document also discusses in further detail identification of at-risk patients and strategies for prevention, detection and management of OIVI in patients with neuraxial opioids.

A similar guideline has been published by the Society for Obstetric Anesthesia and Perinatology (SOAP) for the use of neuraxial opioids in Caesarean section patients (Bauchat 2019 **GL**).

Pruritus

Pruritus is a frequent adverse effect of opioids by all routes. The rate following IT morphine is higher than that for patients receiving IV PCA morphine (OR 3.85; 95%CI 2.40 to 6.15) (Meylan 2009 **Level I**, 27 RCTs, n=1,205) and is dose-dependent (Sultan 2016 **Level I**, 11 RCTs, n=480). The itch is thought to be caused by stimulation of spinal and supraspinal mu-opioid receptors which includes the trigeminal nucleus and explains the frequency of facial itch (Kumar 2013 **NR**). The incidence of pruritus with IT morphine 50 mcg to 1 mg was 29.2% vs 4.4% with bupivacaine alone (OR 6.92; 95%CI 4.51 to 10.6; NNH 4) (17 RCTs) (Popping 2012 **Level I** [PRISMA], 65 RCTs, n=3,338). IT fentanyl 10–40 mcg had an incidence of pruritus of 27.3% vs 0% with bupivacaine alone (13 RCTs).

Incidence following IT opioids for Caesarean section

Pregnant women report greater rates of pruritus of 60 to 100%, which may be due to an interaction of oestrogen with opioid receptors (Kumar 2013 **NR**). While the incidence of pruritus is consistently high, the number requiring treatment is lower; in post-Caesarean section patients receiving 100 mcg IT morphine, 64% of patients reported pruritus with the proportion requiring treatment being 18% (Mikuni 2010 **Level II**, n=75, JS 3). In patients having Caesarean section under spinal anaesthesia, IT morphine 100 mcg was vs oral opioid (oxycodone CR), the IT morphine

group had similar overall pain scores but reported better satisfaction at 24 h and fewer high pain scores but experienced more pruritus (87 vs 56%) (McDonnell 2010 **Level II**, n=111, JS 5).

5HT$_3$-receptor antagonists

There may be a connection between serotonin (5-HT) levels and pruritus, as IT morphine increases serotonin plasma concentrations in a dose-dependent fashion by 283% (10 mcg) vs 556% (200 mcg), with pruritus rates of 55% and 75% respectively (Aly 2018 **Level II**, n=40, JS 5). 5HT$_3$-receptor antagonists decrease the incidence of pruritus related to IT opioids with an NNT of 6 (OR 0.44; 95%CI 0.29 to 0.68) (Bonnet 2008 **Level I**, 15 RCTs, n=1,337). This analysis included a high number of Caesarean section patients, who reported higher rates of pruritus. In a subgroup analysis, the antipruritic effect is seen in the morphine (9 RCTs) but not fentanyl/sufentanil recipients (5 & 1 RCTs). A similar analysis based purely on Caesarean section patients receiving IT morphine does not identify a decrease in incidence in pruritus overall with prophylactic 5HT$_3$ antagonists, but use does reduce the incidence of severe pruritus with an NNT of 3 for established pruritus (George 2009 **Level I** [PRISMA], 9 RCTs, n=1,152) (6 RCTs overlap with Bonnet 2008). Ondansetron 4 to 8 mg reduces pruritus after IT morphine in non-obstetric cases (RR 0.63; 95%CI 0.45 to 0.89) (7 RCTs [1 RCT epidural morphine], n=576) (Wang 2017 **Level I** (PRISMA), 10 RCTs, n=811). However, the result for Caesarean section was not significant with a high degree of heterogeneity (3 RCTs, n=253). Reasons for an inconclusive result in the obstetric group highlighted by the authors include the co-administration of a lipid soluble opioid fentanyl, the delay in administration of ondansetron until after IT morphine because of concerns of placental transfer and altered pharmacokinetic handling of ondansetron in parturient women. Specifically, in pruritus caused by IT fentanyl 10 to 25 mcg and IT sufentanil 10 mcg, IV ondansetron 8 mg does not reduce the incidence of pruritus, but does reduce the need for rescue medication (RR 0.57; 95%CI 0.35 to 0.91) (Prin 2016 **Level I**, 6 RCTs, n=555).

Opioid antagonists

There is limited data and conflicting results regarding the use of opioid antagonists in treating pruritus following IT opioids. However, with parenteral opioids, overall IV naloxone reduces the incidence of pruritus (OR 0.40; 95%CI 0.21 to 0.79) and nausea (OR 0.62; 95%CI 0.43 to 0.89) but not vomiting (Murphy 2011 **Level I**, 8 RCTs, n=800). Other methods that have been described for prevention include nalbuphine (Tubog 2019 **Level I** [PRISMA}, 17 RCTs, n=1,052), mirtazapine (a noradrenergic and specific serotonergic antidepressant [NaSSA]) and dopamine antagonists such as droperidol (Kumar 2013 **NR**). SC methylnaltrexone 12 mg (a mu-opioid receptor antagonist that works peripherally and does not cross the blood brain barrier) reduced nausea, but had no effect on pruritus or urinary retention (Zand 2015 **Level II**, n=72, JS 5). Similarly, SC methylnaltrexone 12 mg versus placebo did not reduce pruritus from IT morphine 100 mcg after Caesarean section (84% vs 88%) (Paech 2015 **Level II**, n=37, JS 5).

Other treatments

Other treatments for established pruritus include pentazocine (a mixed opioid agonist-antagonist with kappa receptor effects) which was more effective in treating pruritus post Caesarean section than ondansetron 4 mg (Tamdee 2009 **Level II**, n=208, JS 5). IV pentazocine 15 mg had a prophylactic effect on pruritus after IT opioids for Caesarean section vs placebo (RR 0.69; 95%CI 0.52 to 0.90) (Hirabayashi 2017 **Level II**, n=122, JS 5). Diphenhydramine 25 mg has also been reported to be as effective as ondansetron 4 mg (Siddik-Sayyid 2010 **Level II**, n=113, JS 5).

Preoperative acupuncture vs sham acupuncture maintained for 48 h postoperatively was ineffective in reducing pruritus caused by IT morphine for Caesarean section (Mazda 2018 **Level II**, n=30, JS 5).

Nausea and vomiting

Postoperative nausea is common after IT morphine, especially in obstetrics. Consensus guidelines exist for PONV management; however, these do not address IT opioids specifically (Gan 2014 **GL**). Following minor surgical procedures, the addition of IT morphine significantly increased the risk of nausea from 29.4% to 39.4% (OR 1.66; 95%CI 1.05 to 2.64) (NNH 9.8) (10 RCTs, n=361) and vomiting from 16.6% to 26.2% (OR 1.88; 95%CI 1.20 to 2.94) (NNH 10) (14 RCTs, n=505) vs IT local anaesthetic with systemic analgesics (Popping 2012 **Level I** [PRISMA], 65 RCTs, n=3,338). Following major surgery, comparing IT opioids to systemic opioids there was a nonsignificant increase in the incidence of nausea (30.5 vs 24.2%; OR 1.22; 95%CI 0.77 to 1.95) and no difference in the incidence of vomiting (23.8 vs 22.6%; OR 1.05; 95%CI 0.63 to 1.73) (Meylan 2009 **Level I**, 27 RCTs, n=1,205). A low dose of IT morphine 100 mcg caused no vomiting vs 400 mcg (23%) for inguinal hernia repair (Meco 2016 **Level II**, n=48, JS 4).

Following Caesarean section with IT morphine and fentanyl, ondansetron and transdermal scopolamine were equally effective in reducing emesis from 59.3% (control) to 41.8% (ondansetron) and 40% (scopolamine), although scopolamine use was associated with more anticholinergic adverse effects (Harnett 2007 **Level II**, n=240, JS 4). The combination of ondansetron with either dexamethasone or droperidol had a better antiemetic effect after gynaecological surgery with IT morphine vs droperidol/dexamethasone (Sanchez-Ledesma 2002 **Level II,** n=90, JS 4), although this latter combination was superior vs either alone (Wu 2007 **Level II**, n=120, JS 5).

Urinary retention

The incidence of urinary retention is not increased in patients receiving IT morphine for major surgery (Gehling 2009b **Level I**, 28 RCTs, n=1,414; Meylan 2009 **Level I**, 27 RCTs, n=1,205); however, in patients having spinal anaesthesia for minor surgery, IT morphine increases the risk of urinary retention (OR 3.9; 95%CI 1.94 to 7.86) (NNH 6.5) (7 RCTs, n=225) (Popping 2012 **Level I** [PRISMA], 65 RCTs, n=3,338).

Other adverse effects

In women in labour, reactivation of oral herpes simplex labialis was more frequent following IT morphine for labour analgesia than IV PCA morphine (38 vs 16.6%) (Davies 2005 **Level II**, n=98, JS 4).

Cardiovascular effects of IT opioids have generally not been reported. In a retrospective cohort study, IT hydromorphone 50 to 80mcg used in patients having elective colorectal resection with restricted fluid therapy found a higher rate of hypotension (mean arterial blood pressure <60 mmHg or systolic blood pressure <110 mmHg) in those receiving hydromorphone (4.3%) vs the control group up to 12 h (Hubner 2013 **Level III-2**, n=163). This normalised by 24 h and was not associated with any identified adverse outcomes. IT morphine 7 mcg/kg in surgical aortic valve replacement decreased mean arterial pressure and heart rate while preserving cardiac output, pulmonary capillary wedge pressure and central venous pressure (Elgendy 2017 **Level II**, n=44, JS 5).

Caution has been advised regarding the use of IT opioids in patients who are at risk of spinal cord ischaemia (eg thoracic aortic stenting/surgery) (Fedorow 2010 **NR**), although its use has been described (Chaney 1996 **Level IV**). Such caution is based primarily on laboratory data, although a case report is published (Kakinohana 2003 **CR**).

5.7.1.4 | Adjuvant medicines

A variety of adjuvant medicines have been used with IT analgesia, including clonidine, dexmedetomidine, ketamine, neostigmine and midazolam. Many medicines are not licensed for use as spinal analgesic agents; however adequate evidence from the literature may make their use acceptable (for more detail see Chapter 4).

Clonidine and Dexmedetomidine

The addition of clonidine 30 to 150 mcg to IT morphine 100 to 500 mcg causes a small increase in analgesia duration (1.63 h; 95%CI 0.93 to 2.33) (5 RCTs, n=464) and reduces the amount of systemic morphine consumption over 24 h (4.45 mg; 95%CI 1.40 to 7.49) (7 RCTs, n=629) (Engelman 2013 **Level I** [PRISMA], 7 RCTs, n=503). Incidence of hypotension was also increased (OR 1.78; 95%CI 1.02 to 3.12).

For major abdominal cancer surgery, IT dexmedetomidine 5 mcg added to IT morphine 500 mcg and bupivacaine did not improve analgesia vs the IT morphine/bupivacaine group (Abdel-Ghaffar 2016 **Level II**, n=90, JS 5). Both groups with adjuvants experienced better analgesia than bupivacaine alone.

Magnesium

Magnesium most likely contributes to analgesia by acting as a noncompetitive NMDA-receptor antagonist in the spinal cord. There was no benefit with IT versus intraperitoneal magnesium in animal experiments (Messeha 2016 **BS**). Magnesium 1.67–50% with opioid with or without local anaesthetic prolongs the time to first analgesia requirement in non-obstetric populations (SMD 1.38; 95%CI 0.6 to 2.11) but not obstetric patients (Morrison 2013 **Level I**, 15 RCTs, n=980). This may be an effect of fewer studies in the obstetric group. There is no increase in incidence of hypotension. There was a high degree of heterogeneity making any firm conclusion difficult.

KEY MESSAGES

1. Intrathecal morphine improves analgesia and is opioid-sparing for up to 24 hours after major surgery including abdominal (**S**), orthopaedic (**N**), spinal (**N**) (**Level I** [PRISMA]) and cardiothoracic surgery (**N**) (**Level II**).
2. Adding intrathecal morphine to intrathecal bupivacaine/fentanyl or intrathecal bupivacaine/sufentanil prolongs pain relief after labour (**N**) (**Level I** [PRISMA]).
3. The addition of intrathecal fentanyl (**N**) (**Level I** [PRISMA]) and morphine to spinal anaesthesia prolongs time to first analgesic request after Caesarean section (**N**) (**Level I**).
4. Intrathecal morphine in comparison to peripheral regional analgesia techniques offers similar analgesic benefits, but increases adverse effects (nausea, vomiting, pruritus) after lower limb arthroplasty (**N**) (**Level I**).
5. The incidence of opioid-induced ventilatory impairment, pruritus and postoperative nausea and vomiting is higher with intrathecal morphine compared with intravenous PCA opioids (**S**) (**Level I**).
6. Pruritus with intrathecal opioids is dose-dependent (**N**) (**Level I**) and can be effectively prevented and treated with $5HT_3$ antagonists in non-obstetric patients, but only treated but not prevented in obstetric patients (**Q**) (**Level I**)
7. The addition of intrathecal magnesium to opioids and/or local anaesthetics results in slightly longer analgesia in non-obstetric patients (**U**) (**Level I**).
8. The addition of intrathecal clonidine to intrathecal morphine results in slightly longer analgesia and reduced opioid requirements (**U**) (**Level I**).
9. Pruritus with intrathecal opioids cannot be treated with methylnaltrexone (**N**) (**Level II**).

The following tick boxes represent conclusions based on clinical experience and expert opinion:

☑ The absence of consistent dose-responsiveness to the efficacy of intrathecal opioids and the increase in adverse effects with higher doses suggests that the lowest effective dose (typically 50-200 mcg morphine) should be used (**Q**).

☑ Patients receiving intrathecal opioids should be monitored for opioid-induced ventilatory impairment for the anticipated duration of opioid effects, eg 18 to 24 hours after intrathecal morphine (**S**).

☑ Clinical experience with morphine, fentanyl and sufentanil has shown no neurotoxicity or behavioural changes at normal clinical intrathecal doses (**U**), however caution is recommended in patients who are at risk of spinal cord ischaemia (**U**).

5.8 | Other regional and local analgesic techniques

Regional and local analgesic techniques have evolved recently, with a large number of new ultrasound-guided blocks. There have been developments in our understanding of anatomy and proof-of-concept studies on neuromodulation for acute pain management. Regional and local analgesic techniques should be used in conjunction with oral multimodal analgesic techniques.

Adjuvant agents to local anaesthetics are considered in other sections: eg alpha-2-agonists in Section 4.9.2 and corticosteroids in Section 4.12.2 and opioids in Section 4.2.3.

5.8.1 | Needle and catheter localising techniques

Techniques used to precisely identify correct needle location and hence local anaesthetic and catheter placement include anatomic landmarks, peripheral nerve stimulation (PNS) and ultrasound (US) guidance. Radiologic imaging and direct vision during surgery have also been used. In comparison with PNS, blocks performed using US-guidance are more likely to be successful (RR 0.41 [for block failure]; 95%CI 0.26 to 0.66) (9 RCTs), faster to perform (WMD -1.1 min less to perform with US; 95%CI -1.7 to -0.4) (7 RCTs), have faster onset (29% shorter onset time; 95%CI 45 to 12%) (8 RCTs), longer duration (SMD 25%; 95%CI 12 to 38) (5 RCTs) and reduced vascular puncture (RR 0.16; 95%CI 0.05 to 0.47) (4 RCTs) (Abrahams 2009 **Level I**, 13 RCTs, n=941). US-guidance is associated with an increase in success rate of nerve blocks vs all non-US techniques (RR 1.11; 95%CI 1.06 to 1.17) and vs PNS alone (RR 1.11; 95%CI 1.05 to 1.17) (Gelfand 2011 **Level I**, 16 RCTs, n=1,264) (8 RCTs overlap with Abrahams 2009). US-guided techniques vs PNS (17 RCTs) and other needle-localisation techniques (2 RCTs) are associated with higher success rates, faster onset of block and lower vascular puncture rate (McCartney 2010 **Level I**, 25 RCTs, n=2,187) (8 RCTs overlap with Abrahams 2009 & 9 RCTs overlap with Gelfand 2011).

These findings are also confirmed for placement of catheters, where US- vs PNS-guidance results in a higher success rate (9 RCTs, n=530) and a lower rate of accidental vascular puncture (RR 0.13; 95% CI: 0.04 to 0.38) (15 RCTs) vs PNS guidance (Schnabel 2013 **Level I** [PRISMA], 15 RCTs, n=977). Stimulating catheters have been compared with nonstimulating catheter techniques in establishing continuous FNBs for postoperative analgesia following TKA. There was no difference in quality of postoperative analgesia between these two insertion techniques (Barrington 2008 **Level II**, n=82, JS 5; Morin 2005 **Level II**, n=141, JS 3). Stimulating catheters have also been compared with nonstimulating catheter techniques at other anatomical locations with inconclusive results (Stevens 2007 **Level II**, n=43, JS 4; Dauri 2007 **Level II**, n=70, JS 3; Rodriguez 2006 **Level II**, n=48, JS 3).

US-guidance has been compared with stimulating and non-stimulating techniques for continuous infraclavicular brachial plexus block. The combination of US- and PNS-guidance (with stimulating catheters) resulted in the highest primary success and reduced secondary catheter failure (McCartney 2010 **Level I**, 1 RCT: Dhir 2008 **Level II**, n=66, JS 3). In the placement of popliteal sciatic nerve catheters, US-guidance alone resulted in similar analgesic outcomes for up to 48 h vs US- and PNS-(stimulating catheter) guidance (Robards 2013 **Level II**, n=21, JS 3). In patients having TKA, the combination of US-guidance and PNS (needle and/or stimulating catheter) was not different to US-guidance alone in analgesic efficacy over 48 h (Farag 2014 **Level II**, n=437, JS 4); stimulating catheter use was associated with a longer procedural time.

An analysis of the German Network of Regional Anaesthesia database between 2007 and 2012 reveals the effects of being awake (n=25,004), sedated (n=15.121) or anaesthetised (n=2,529) on complications of regional anaesthesia (Kubulus 2016 **Level III-2**, n=42,654). There are no differences in the rates of LAST or pneumothorax. For peripheral nerve blocks, both sedation (aOR 1.82; 95%CI 1.50 to 2.21) and general anaesthesia (aOR 1.33; 95%CI 1.01 to 1.78) are

associated with an increased risk of a bloody tap. The risk for multiple skin puncture is lower in sedated (aOR 0.78; 95%CI 0.71 to 0.85) and higher in anaesthetised patients (aOR 1.28; 95%CI 1.12 to 1.46).

5.8.2 | Continuous and single-injection peripheral nerve blocks

Percutaneous perineural catheter placement enables an infusion of local anaesthetic increasing the duration of analgesia and associated benefits. Continuous peripheral nerve blockade (CPNB) is indicated for treatment of acute postoperative pain, vascular insufficiency, chronic pain conditions and cancer-related pain. CPNB is used in hospital, ambulatory and in trauma settings (Ilfeld 2017a **NR**; Ilfeld 2011a **NR**).

5.8.2.1 | Continuous peripheral nerve block compared to single-injection techniques

Compared with single-injection techniques, CPNB improve pain control, decrease opioid requirements, reduce nausea and improve patient satisfaction postoperatively (Bingham 2012 **Level I**, 21 RCTs, n=702). CPNBs after ambulatory upper and lower limb surgery vs single-injection blocks reduce pain at rest (5 RCTs) and during movement (in 4 of 5 RCTs) and opioid requirements for the first 24 h (1 RCT), but not consistently sustained beyond this time frame (Saporito 2017 **Level I** [PRISMA], 5 RCTs, n=160); the quality and size of the RCTs included limits these statements. These findings are consistent with some but not all recent studies.

Following TKA, various analgesic modalities have been compared:

- There were no differences between continuous FNB, single-injection FNB and LIA by surgeon in pain scores on the morning of POD 2 (primary outcome) or 48 h opioid consumption (Choi 2016 **Level II**, n=120, JS 5). However, both continuous FNB and LIA resulted in superior pain control vs the single-injection group on POD 1;
- There were no differences between continuous FNB infusion of ropivacaine 0.2%, ropivacaine 0.1% vs placebo (sodium chloride 0.9 %) for the primary outcome 'time to discharge readiness' (Albrecht 2014 **Level II**, n=99, JS 5). This RCT was terminated early because of changes in institutional pathways;
- Continuous FNB was not superior (pain scores at 48 h) to single-injection FNB with no difference in opioid consumption and functional recovery (Dixit 2018 **Level II**, n=85, JS 4).
- Single-injection ACB (combined with sciatic nerve block and posterior capsule LIA by surgeon) provided comparable early analgesia for 32 h vs continuous ACB, but continuous ACB improved pain scores beyond 42 h (Turner 2018 **Level II**, n=60, JS 5). The local anaesthetic adjuvants included clonidine 33.4 mcg, buprenorphine 150 mcg, dexamethasone 2 mg, and adrenaline;
- Single-injection ACB ropivacaine 0.5% 20 mL vs ropivacaine/IV dexamethasone 8 mg similarly reduced 24 h opioid consumption vs continuous ACB (ropivacaine 0.5% 20 mL then 0.2% 5 mL/h for 48 h) where all patients received periarticular infiltration with ropivacaine 0.5% 30 mL at surgery (Lee 2018, **Level II**, n=180, JS 3). Possible reasons for superiority over catheter technique include catheter migration or poor placement and superior injectate spread of the single-injection technique.

5.8.3 | Upper limb blocks

5.8.3.1 | Interscalene and suprascapular nerve block

Compared with a single-injection interscalene block, continuous interscalene block with ropivacaine 0.2% following shoulder surgery (rotator cuff surgery, arthroplasty) improved pain outcomes, sleep, patient satisfaction, time to discharge readiness and achieved a greater degree of shoulder movement (Salviz 2013 **Level II**, n=71, JS 3; Yang 2013 **Level II**, n=56, JS 4; Mariano 2009

Level II, n=32, JS 5; Ilfeld 2006 **Level II**, n=32, JS 3). Because of close proximity to the neuraxis, a test dose of local anaesthetic through an interscalene catheter should precede a continuous infusion. Performing interscalene blockade in adults under general anaesthesia is controversial with case reports of block-related mechanical injury to the spinal cord (Benumof 2000 **CR**). Phrenic nerve block is the most common adverse effect of interscalene block. Strategies to reduce the likelihood or magnitude of phrenic nerve block include reducing local anaesthetic dose, using US-guidance, injecting at the C7 vertebral level and use of suprascapular or axillary block (Verelst 2013 **NR**). Suprascapular block resulted in reduced pain vs placebo or subacromial local anaesthetic infusion (Jeske 2011 **Level II**, n=45, JS 4). For shoulder arthroscopy, interscalene block vs combined suprascapular and axillary block resulted in superior analgesia in PACU, but inferior analgesia at 24 h (Dhir 2016 **Level II,** n=60, JS 5). Suprascapular nerve block (anterior approach deep to omohyoid muscle) was compared with interscalene block for shoulder arthroscopy using a composite outcome of pain and grip strength (Wiegel 2017 **Level II,** n=336, JS 5). Different ropivacaine dose used in the two study groups (interscalene 150 mg vs suprascapular 100 mg) resulted in reduced motor block with the suprascapular block and non-inferiority for pain outcomes. Following shoulder arthroplasty, vital capacity at 24 h (primary outcome) was reduced more with continuous interscalene (by 991 mL) vs supraclavicular (by 803 mL) block (Auyong 2017 **Level II,** n=75, JS 5). However, anterior suprascapular block had the least effect on vital capacity (reduced by 464 mL) indicating a potential advantage in using this approach in patients with pulmonary disease, while there were no differences in analgesic outcomes.

5.8.3.2 | Other brachial plexus blocks

For surgery in the area of the forearm, infraclavicular block offers advantages due to a lower likelihood of tourniquet pain during surgery, more reliable blockade of the musculocutaneous nerve when compared to a single-injection axillary block, and a significantly shorter block performance time compared to multi-injection axillary and mid-humeral blocks (Chin 2013 **Level I** [Cochrane], 22 RCTs, n=1,732). The incidence of insensate limb with continuous infraclavicular brachial plexus block was higher when the same total dosage of 0.4% ropivacaine was compared with 0.2% ropivacaine (Ilfeld 2009 **Level II**, n=50, JS 3). There was no difference in analgesia but satisfaction scores were higher in patients who received the 0.2% infusion. Following hand surgery, continuous brachial plexus block (axillary approach) (0.1 or 0.2% ropivacaine) did not improve pain outcomes vs single-injection technique with a long-acting local anaesthetic (Salonen 2000 **Level II**, n=60, JS 4). This was also true in comparison with continuous infraclavicular blocks (Mariano 2011 **Level II**, n=20, JS 3).

5.8.4 | Lower limb blocks

Patient falls following major surgery is a key concern. After TKA, inpatient falls occurred in 1.6% and this event was associated with increasing age and higher comorbidity burden, whereas PNB did not increase the risk (OR 0.85; 95%CI 0.71 to 1.03) (Memtsoudis 2014 **Level IV**, n=191,570). Following TKA, continuous lumbar plexus block was associated with an increased risk of inpatient falls vs single-injection block or no block (OR 3.85; 95%CI 1.52 to 9.72) (NNH 59) (5 RCTs, n=1,595) (Johnson 2013 **Level III-3 SR**, 10 studies, n=4,014). The risk of falls with FNB was not different from ACB following total knee arthroplasty, but patients receiving ACB had significantly increased quadriceps motor strength (Elkassabany 2016 **Level II**, n=62, JS 5).

5.8.4.1 | Femoral nerve block

Femoral nerve block (FNB) either as a continuous (7 RCTs) or single-injection (6 RCTs [FNB alone] & 2 RCTs [FNB and sciatic PNB]) technique vs IV PCA analgesia alone is associated with improved analgesia on movement, reduced morphine consumption and decreased incidence of nausea following TKA (Paul 2010 **Level I**, 23 RCTs, n=1,016). Compared with periarticular infiltration of local anaesthetic (LIA), continuous FNB for TKA reduced opioid consumption and improved functional indicators at 6 wk (Carli 2010 **Level II**, n=40, JS 4). A similar study (infiltration vs continuous FNB) reported no significant difference in opioid consumption; however, 37% of patients who received the FNB experienced quadriceps weakness vs 0% in the infiltration group (Chaumeron 2013 **Level II**, n=60, JS 5). Continuous FNB combined with single-injection sciatic block resulted in better pain relief vs IT morphine (Alvarez 2017 **Level II**, n=40, JS 2). For more information on any differences between the local anaesthetics used for FNBs see Section 4.4.2.

5.8.4.2 | Fascia iliaca compartment and lateral femoral cutaneous nerve block

Single-injection fascia iliaca compartment block (FICB) provided similar postoperative analgesia to FNB following anterior cruciate ligament repair (Farid 2010 **Level II**, n=23, JS 3); and to '3-in-1' nerve block following knee joint arthroscopy and meniscal repair (Wallace 2012 **Level II**, n=60, JS 3). Suprainguinal FICB was opioid-sparing following THA vs no block (Desmet 2017 **Level II**, n=88, JS 5). However, effect on mobilisation was not recorded, which is relevant because FICB may have resulted in motor block delaying early mobilisation. Following a posterior approach to THA under spinal anaesthesia, US-guided lateral FNB with ropivacaine 0.75% 8 mL had no effect on analgesic outcomes at 4 h vs placebo (Thybo 2016 **Level II**, n=100, JS 5). All patients received paracetamol and ibuprofen.

Continuous FICB provided similar postoperative analgesia to continuous FNB over 48 h following TKA (Brisbane 2010 **Level II**, n=98, JS 2).

5.8.4.3 | Adductor canal and distal femoral triangle block

Recent anatomical studies point to the importance of the nerve to vastus medialis innervating the anteromedial knee capsule (Burckett-St Laurant 2016 **BS**). Research into the anatomy of the adductor canal and femoral triangle has supported the development of US-guided motor-sparing techniques. Since 2014, there has been a vast literature published on adductor canal block (ACB) compared to different combination therapies. However, interpreting the results of RCTs with ACB as an intervention is confounded by lack of consistency in how the block is implemented. It is likely in many RCTs that the ACBs were performed in the femoral triangle and not in the adductor canal. There has been extensive dialogue on this topic with one group describing how the apex of the femoral triangle (and hence the adductor canal which is located between the femoral triangle apex and the adductor hiatus) can be defined using US (Wong 2017 **BS**). The apex of the femoral triangle can be identified using US as where the medial borders of the adductor longus and sartorius intersect. This knowledge permits block placement at a consistent location where the nerve to vastus medialis and saphenous nerve are closely located. In contrast, but also to maintain consistency, other investigators perform ACB exactly halfway 'mid-thigh' between the anterior iliac spine and the cephalad border of the patella (Jaeger 2012 **Level II**, n=42, JS 5). Subsequent studies have defined the optimal anatomical location further. 'Mid-thigh' placement has been compared to the more distal true adductor canal catheter location, where the superficial femoral artery descends towards the adductor hiatus in 2 RCTs with contrasting results post TKA. One found the median pain score on POD 1 was reduced with the proximal vs the distal catheter placement (0.5/10 vs 3.0/10); however the worst pain scores were not different (Sztain 2018 **Level II**, n=50, JS 4).

While the second concluded continuous distal ACB provided noninferior analgesia to mid-thigh positioning (Meier 2018 **Level II**, n=73, JS 5). Combined distal femoral triangle/obturator blockade was superior to LIA in patients having TKA (Runge 2018 **Level II**, n=74, JS 5). The median 20-h morphine consumption was 6 mg (IQR 2 to 18) vs 20 mg (12 to 28) respectively with no difference in LOS.

Adductor canal block compared to placebo

ACB reduced opioid consumption and pain scores vs placebo after TKA (Hanson 2014 **Level II**, n=80, JS 5; Grevstad 2014 **Level II**, n=50, JS 5; Jenstrup 2012 **Level II**, n=75, JS 4; Jaeger 2012 **Level II**, n=42, JS 5). Single-injection ACB with bupivacaine 0.25% 10 mL vs 0.9% saline in addition to LIA with ropivacaine 0.2% 100 mL resulted in clinically relevant improvements in analgesia outcomes (opioid consumption, pain scores) at 36 h (Nader 2016 **Level II**, n=40, JS 5).

Adductor canal compared to femoral nerve blockade

In volunteer studies, ACB produced less loss of quadriceps strength vs FNB (8 vs 49%) (Jaeger 2013 **Level II EH**, n=12, JS 5); with minimal impact on balance (Kwofie 2013 **Level II EH**, n=16, JS 5).

Following TKA, ACB vs FNB results in similar control of postoperative pain (no differences in pain at rest and with mobilisation, rescue opioid requirements and patient satisfaction) with reduced likelihood of quadriceps weakness and improved mobilisation leading to better functional recovery (Kuang 2017 **Level I** [PRISMA], 9 RCTs, n=609; Hussain 2016 **Level I**, 6 RCTs, n=447) (6 RCTs overlap).

Studies published subsequent to the meta-analyses or not included confirm these findings. Pre-block maximum voluntary isometric contraction (MVIC) of the quadriceps increased at 60 min in patients who received ACB 24 h after TKA with ropivacaine 0.75% 30 mL vs placebo (median 170% vs 93%) (Sorensen 2016 **Level II**, n=64, JS 5). Despite overall better motor function associated with ACB, decrease in MVIC (defined as MVIC <75% of pre-block values) occurred in 5/64 patients and 4 of these were unable to perform the 'Timed Up and Go' test. This underscores the importance of a thorough functional assessment and falls prevention program. Continuous FNB vs continuous ACB showed no difference in analgesic outcomes and early recovery, although quadriceps motor strength with ACB was increased (Seo 2017 **Level III-1**, n=43). Time to discharge did not differ with continuous ACB vs continuous FNB following unicompartmental knee arthroplasty despite more patients satisfying discharge criteria on POD 2 in the ACB group (Sztain 2015 **Level II**, n=30, JS 3). More ACB recipients, despite significantly worse dynamic pain scores on day of surgery and POD 1, ambulated >30 m than FNB recipients.

Adductor canal block compared to LIA

There was no difference in the 'Timed Up and Go' test (46, 45 and 52 s) on POD 2 (primary outcome) with LIA/placebo blocks vs LIA/ACB vs LIA/ACB/IT morphine (Biswas 2018 **Level II**, n=201, JS 5). However, pain control was improved in patients randomised to LIA/ACB/IT morphine. Combined ACB/LIA reduced pain on walking on POD 1 vs ACB block alone or LIA alone (Sawhney 2016 **Level II,** n=151, JS 5). ACB vs LIA following TKA reduced opioid consumption at 24 h (6 vs 13 mg) and at 48 h (10 vs 25 mg) and pain scores at 6 to 16 h (by 1.2 to 1.5/10) (Kampitak 2018 **Level II**, n=60, JS 5). See also Section 5.8.2.1 below.

Adductor canal block compared to other peripheral nerve block combinations

Patients received continuous ACB and LIA for TKA and were randomised to receive in addition: obturator, tibial or both nerve blocks (Kampitak 2019 **Level II**, n=90, JS 4). Patients who received all three blocks had superior analgesia and mobilisation outcomes, and reduced opioid use (2 mg vs 4 mg and 6 mg morphine at 24 h). Continuous ACB vs sham catheter inserted on POD 1 decreased opioid consumption and pain scores at 0–20 h following insertion (ie on POD 2) and improved function at 3 wk (Leung 2018 **Level II**, n=165, JS 4). Epidural analgesia was used as the analgesic technique in the first 24 h and multimodal analgesia (eg NSAID or Cox II inhibitors) was

not used. Due to withdrawals only 70 patients completed the study which may have introduced bias.

Adductor canal block – single-injection dose and infusion considerations

There was no meaningful difference in quadriceps strength to 4 h with 10 mL vs 30 mL ropivacaine 0.1% for ACB (Jaeger 2015b **Level II EH**, n=26, JS 5). Both volumes produced meaningfully reduced tonic heat pain response indicating successful saphenous block. The ED_{95} (minimum effective anaesthetic volume in 95% of the subjects) to fill the distal adductor canal estimated on MRI was 20 mL (Jaeger 2015a **Level III-2 EH**, n=40). The ED_{50} (minimum effective anaesthetic volume in 50% of the subjects) needed for a 30% decrease in quadriceps strength was determined used the Dixon-Massey up-and-down method in patients having arthroscopic knee surgery as being 46.5 mL (95% confidence interval, 45.01-50.43 mL) (Johnston 2017 **Level III-2**, n=26). This volume is significantly higher than standard doses used in clinical practice.

Bilateral continuous ACB was established in volunteers with one limb of each subject randomly assigned to a continuous infusion of 8 mL/h or automated hourly boluses of 8 mL (Monahan 2016 **Level II EH**, n=24, JS 5). Tolerance to transcutaneous electrical stimulation in the territory of the anterior branch of the medial femoral cutaneous nerve was evaluated at 8 h with equivalent cutaneous analgesia (non-inferiority). There were no differences in secondary endpoints such as cutaneous analgesia at later time points or motor blockade. Continuous infusion 7 mL/h was compared to intermittent boluses (23 mL/3 h) with no difference in opioid consumption and other analgesic outcomes following TKA (Jaeger 2018 **Level II**, n=110, JS 5).

5.8.4.4 | Sciatic nerve block

After lower extremity surgery (Ilfeld 2002 **Level II**, n=30, JS 4) and foot surgery (White 2003 **Level II**, n=24, JS 5), continuous popliteal sciatic nerve analgesia resulted in better pain relief, lower opioid requirements and fewer adverse effects compared with opioids alone. The benefit of sciatic nerve block in addition to single-injection and continuous FNB for analgesia following TKA remains unclear (8 RCTs [various comparators]) (Paul 2010 **Level I**, 23 RCTs, n=1,016).

Interspace between the Popliteal Artery and the Capsule of the Posterior Knee (iPACK) block

iPACK block is a motor sparing block following TKA. It is likely iPACK results in blockade of a plexus formed by the posterior division of the obturator nerve and the tibial nerve that innervates the posterior knee capsule (Tran 2019 **BS**). ACB and iPACK block when added to periarticular injection had lower pain scores on ambulation on POD 1 (Kim 2019a **Level II**, n=86, JS 5). ACB/iPACK block vs ACB resulted in improved pain scores from 8 h to POD 2 (Sankineani 2018 **Level III-2**, n=120).

5.8.4.5 | Lumbar plexus

Following THA, there was no difference for continuous posterior lumbar plexus block vs continuous FNB in postoperative pain scores, however FNB recipients had more motor block impairing ambulatory function (Ilfeld 2011b **Level II**, n=50, JS 3). Lumbar plexus block resulted in a modest improvement in pain in the early postoperative period following hip arthroscopy (YaDeau 2012 **Level II**, n=84, JS 5). Lumbar plexus block vs ACB provided similar analgesia following unicondylar knee arthroplasty at 6 h (Henshaw 2016 **Level II**, n=150, JS 5). There were also no other differences in analgesia outcomes at other time points to 24 h. Quadriceps motor strength was better in the ACB group.

5.8.5 | Truncal blocks

Truncal blocks are increasingly used to provide analgesia after surgery; the number of techniques for these blocks is continuously increasing and most are performed with US-guidance; a detailed systematic review on the current developments of these techniques with regard to anatomy (10 studies [cadaver], 6 [volunteer/imaging], 2-4 technical descriptions), clinical outcomes and complications has been published (3 SRs, 4 RCTs, 12 studies, 4 CR) (Abrahams 2016 **Level IV SR**, 42 manuscripts, n unspecified).

5.8.5.1 | Paravertebral blocks

Paravertebral block (PVB) is a technique that is likely to benefit from US-guidance because the landmark technique has been associated with a high proportion of misplaced catheters (Luyet 2012 **Level IV**, n=31), and US-guidance can improve the needle trajectory (Abdallah 2014a **NR**). All forms of PVB combined (single-injection, multi-level injection and continuous infusion) demonstrate superior analgesia for up to 48 h following breast surgery vs systemic analgesia, with a lower incidence of PONV (RR 0.26; 95%CI 0.13 to 0.5) and few specific adverse effects (Schnabel 2010 **Level I** [PRISMA], 15 RCTs, n=877). PVBs with general anaesthesia or propofol sedation reduce pain scores at rest and movement (22 RCTs, n=1,714) and reduce opioid consumption (16 RCTs, n=1,406) up to 72 h after breast surgery (Terkawi 2015 **Level I** [PRISMA], 24 RCTs, n=1,822) (14 RCTs overlap). Addition of fentanyl (11 RCTs) and multilevel injection (5 RCTs) improve quality of analgesia. Reduced nausea (OR 0.44; 95%CI 0.31 to 0.61) (12 RCTs) and vomiting (OR 0.42; 95%CI 0.25 to 0.71) (9 RCTs) and small decrease in hospital LOS (SMD -0.60; -1.13 to -0.06) (6 RCTs) are also observed. A further study confirmed an improved quality of recovery (Abdallah 2014b **Level II**, n=64, JS 5).

For breast cancer surgery, PVB (6 RCTs, n=419) reduces CPSP (OR 0.61; 95%CI 0.39 to 0.97) (NNT 11) (Weinstein 2018 **Level I** (Cochrane), 63 RCTs, n=3,027). See also Section 1.4.6.1.

For thoracotomy, paravertebral or epidural techniques provide superior analgesia vs IT, interpleural, IC and systemic opioid techniques; PVBs cause less hypotension than epidural analgesia and reduce the incidence of pulmonary complications vs systemic analgesia (Joshi 2008 **Level I**, 74 RCTs, n unspecified). Following thoracotomy, there is moderate-quality evidence that shows comparable analgesic efficacy at rest and after coughing with PVB vs epidural analgesia (3 to 6 RCTs [2-6, 24 & 48 h]) (Yeung 2016 **Level I** [Cochrane], 14 RCTs, n=698). There is low to very low-quality evidence that showed no significant difference in mortality and major complications. There is moderate-quality evidence that PVB has a superior minor complication risk vs thoracic epidural analgesia including hypotension (RR 0.16; 95%CI 0.07 to 0.38) (8 RCTs, n=445), nausea and vomiting (RR 0.48; 95%CI 0.30 to 0.75) (6 RCTs, n=345), pruritus (RR 0.29; 95%CI 0.14 to 0.59) (5 RCTs, n=249) and urinary retention (RR 0.22; 95%CI 0.11 to 0.46) (5 RCTs, n=258). These results are consistent with a parallel meta-analysis showing that continuous PVB reduces the incidence of nausea, vomiting, hypotension and urinary retention vs thoracic epidural analgesia, wound infiltration or IV opioids while providing comparable post-cardiothoracic surgery analgesia (Scarfe 2016 **Level I** [PRISMA], 23 RCTs, n= 1,120) (12 RCTs overlap).

Paravertebral block for sternotomy and open liver resection

Most of the evidence for PVB is following breast surgery or thoracotomy, but there are a limited number of studies following sternotomy for cardiac surgery (eg 2 of 18 RCTs comparing PVB and TEA in Scarfe 2016 **Level I**, 23 RCTs, n=1,120). A comparison of continuous bilateral thoracic PVB with bilateral continuous SC lidocaine infusions in patients undergoing cardiac surgery found no difference in postoperative morphine requirements (Lockwood 2017 **Level II**, n=50, JS 5). Appropriately, the authors highlight the risk of local anaesthetic systemic toxicity (LAST) with

continuous bilateral PVBs in patients with ischaemic heart disease and extensive medical comorbidities. The risk of LAST is confirmed in patients having coronary artery bypass surgery (CABG) with continuous bilateral thoracic PVB, where plasma ropivacaine concentrations consistent with toxicity and one case of toxicity occurred with dosages in the range recommended by manufacturers (Ho 2016 **Level IV PK**, n=8).

Following elective open liver resection, patients were randomised to receive either TEA or bilateral T7 or T8 PVB with ropivacaine 0.2% infused for 3 d (Schreiber 2016 **Level II**, n=87, JS 3). There was a statistically significant, but clinically modest reduction in pain score in the epidural group.

Paravertebral block for breast cancer surgery

For mastectomy, PVB reduces the risk of CPSP at 12 mth postoperatively (OR 0.43; 95% CI 0.28 to 0.68) (18 RCTs, n=1,297) (Weinstein 2018 **Level I** (Cochrane), 63 RCTs, n=3,027).

5.8.5.2 | Intercostal and interpleural block

Following a single intercostal block (ICB) using 0.5% bupivacaine, segmental analgesia can last up to 20 h (Perttunen 1995 **Level II**, n=45, JS 2). Multilevel ICBs improve analgesia vs systemic opioids alone, particularly during POD 1 (Detterbeck 2005 **Level I**, 12 RCTs [ICB vs systemic opioids], n=477); pulmonary function tests are better preserved, although pulmonary complications are not consistently reduced. There are no consistent differences in analgesia outcomes for multilevel ICBs in comparison with epidural analgesia (Detterbeck 2005 **Level I**, 5 RCTs [ICB vs epidural], n=140), although duration of follow-up was not specified and individual studies were small. Following thoracotomy, surgically delivered ICBs with liposomal bupivacaine provided improved analgesia on POD 1 and 3 vs TEA (technique unspecified) with hydromorphone PCA used as rescue in both groups (Khalil 2015, **Level III-2,** n=85).

Analgesia can be achieved using a subpleural catheter placed in the space posterior to the parietal pleura alongside the paravertebral area, or more laterally in the IC region. Following posterolateral thoracotomy, patients receiving TEA had superior pain control vs continuous subpleural analgesia (Kanazi 2012 **Level II**, n=42, JS 4; Debreceni 2003 **Level II**, n=50, JS 5). However, similar analgesia was achieved for up to 5 d with epidural vs IC catheter local anaesthetic infusions (Luketich 2005 **Level II**, n=91, JS 3).

Multilevel US-guided IC nerve blocks provided superior pain relief for 24 h vs systemic analgesics alone after percutaneous nephrolithotomy (Ozkan 2013 **Level II**, n=40, JS 5).

The incidence of pneumothorax following multilevel ICBs has been estimated at 0.07% based on data from approximately 100,000 injections (Moore 1975 **Level IV**, n=10,941 [patients]).

Interpleural local anaesthetic infusion has not been found to be superior to systemic opioid analgesia in thoracotomy patients (Detterbeck 2005 **Level I**, 11 RCTs [interpleural], n=287). Interpleural analgesia (intermittent bolus injection technique) was compared to continuous TEA following minimally invasive thoracoscopic surgery (Ishikawa 2012 **Level II**, n=40, JS 1); pain scores were not different between the groups. Interpleural analgesia is superior to systemic analgesia following open cholecystectomy but not following laparoscopic cholecystectomy or nephrectomy (Dravid 2007 **NR**).

5.8.5.3 | Erector spinae plane block and retrolaminar block

The erector spinae plane block (ESPB), an US-guided technique with plane of injection between the thoracic vertebral transverse process (often mid-thoracic) and the erector spinae muscle was described in 2016 for a chronic pain indication (Forero 2016 **CR**). The premise of erector spinae plane block and retrolaminar blocks are that spinal ventral and posterior rami are accessed with

local anaesthetic injected posterior to, instead of injection anterior to the costotransverse ligament. For retrolaminar blocks, the local anaesthetic is injected between erector spinae muscle and the thoracic lamina. It is debated whether the ESPB is a paravertebral variant involving nerve roots (Tsui 2019a **Level IV**, n=242) vs a myofascial plane block. Paravertebral spread of 15 mL radiocontrast was demonstrated during fluoroscopic study through continuous ESPB (Ueshima 2018 **Level IV**, n=3). In unembalmed cadavers, US-guided 20 mL injectate into ESP at T5 involved dorsal rami in 80%, ventral rami in 20%, but dorsal ganglion in only 10% (Ivanusic 2018 **Level IV BS**, n=10 [cadavers]). A second cadaver study assessed an injection on opposite sides into ESP and retrolaminar space with 20 mL injectate at T5; spread to the epidural and neural foraminal spaces over 2 to 5 levels was demonstrated with MRI and anatomical dissection (Adhikary 2019 **Level IV BS**, n=3 [cadavers]).

For ESPB studies, single-injection techniques are used in 80.2%, intermittent boluses in 12% and continuous infusions in 7.9% (Tsui 2019a **Level IV SR**, 85 studies, n=242). Multimodal analgesia is used in 91% of cases. Sensory changes are reported in 35% of cases; 35% report reduced opioid use. ESPB versus systemic analgesia after breast (1 RCT: Gurkan 2018 **Level II**, n=50, JS 2), cardiac surgery (1 RCT: Krishna 2019 **Level II**, n=106, JS 4) and laparoscopic cholecystectomy (1 RCT: Tulgar 2018 **Level II**, n=30, JS 1) improves analgesia and/or reduces rescue requirements (De Cassai 2019 **Level I** [PRISMA], 4 RCTs, n=242) (2 of 4 RCT overlap with Tsui 2019a). Following sternotomy (for midline cardiac surgery), continuous bilateral ESPB vs TEA resulted in similar pain scores for the first 12 h and improved pain scores between 24 h and 48 h (1 RCT: Nagaraja 2018 **Level II**, n=50, JS 3).

Subsequent RCTs not included in these SRs are in line with these results. For modified radical mastectomy, similar results were demonstrated for ESPB vs routine pain management (Singh 2019 **Level II**, n=40, JS 4). Following open epigastric hernia repair, ESPB vs sham block reduced pain scores and decreased perioperative analgesic requirements (Abu Elyazed 2019 **Level II**, n=60, JS 3). Following abdominal hysterectomy, bilateral ESPB vs sham block did not result in a clinically significant reduction in postoperative fentanyl consumption, but achieved clinically significant pain reduction for 12 h (Hamed 2019 **Level II**, n=60, JS 4).

ESPB vs TAP block following laparoscopic cholecystectomy leads to reduction of opioid requirements and pain intensity (Ciftci 2020 **Level II**, n=60, JS 3; Altiparmak 2019a **Level II**, n=68, JS 4).

For video-assisted thoracoscopic surgery (VATS), EPSB vs serratus plane block reduced pain intensity from 4 to 6 h and increased time to rescue analgesia (Gaballah 2019 **Level II**, n=60, JS 4).

5.8.5.4 | Pectoralis nerves and serratus plane blocks

US-guided pectoralis nerves (PECS) blocks and serratus anterior plane (SAP) blocks are regional analgesia techniques of the thorax (Battista 2020 **NR**). PECS and SAP blocks were developed as a less invasive alternative to PVB for breast surgery. In PECS I blocks the injectate is injected between pectoralis major and minor only. PECS II blocks refer to an US-guided block of the medial and lateral pectoral nerves (target plane between pectoralis major and minor muscles) combined with lateral cutaneous branch of the intercostal nerves (target plane between the pectoralis minor and serratus anterior muscles).

PECS I blocks vs placebo in the setting of multimodal analgesia did not reduce pain scores in PACU following tissue preserving breast cancer surgery (Cros 2018 **Level II**, n=128, JS 5).

Combined PECS I and PECS II blocks vs control reduced postoperative pain scores for 24 h and decreased morphine consumption for 12 h following modified radical mastectomy surgery (Bashandy 2015 **Level II**, n=120, JS 3). After mastectomy, PECS II block vs placebo resulted in less pain and reduced opioid requirements during PACU stay (Versyck 2017 **Level II**, n=140, JS 5). Similarly, for breast cancer surgery, PECS II blocks vs control had an opioid-sparing effect and resulted in better mobilisation of the shoulder and patient satisfaction (Neethu 2018, **Level II**, n=60,

JS 2). Following radical mastectomy, PECS II block provided superior analgesia to ESPB (tramadol requirements as primary outcome) (Altiparmak 2019b **Level II**, n=38, JS 3).

Postoperative insertion of combined bilateral PECS II blocks and drain site infiltration (35 mL bupivacaine 0.25%) vs no block (all participants received paracetamol/tramadol) following sternotomy for cardiac surgery reduced pain scores and requirement for intensive care resources (Kumar 2018, **Level II**, n=40, JS 3). After paediatric cardiac surgery via thoracotomy, PECS II and SAP blocks vs IC blocks resulted in statistically significant, but clinically modest, improvement in analgesia (Kaushal 2019 **Level II**, n=108, JS 3).

SAP block was superior (opioid consumption and first request for analgesia) to no block for mastectomy (Rahimzadeh 2018 **Level II**, n=60, JS 2). SAP block vs PVB for modified radical mastectomy was inferior with regard to time to commence PCA use (245 min vs 346 min) and opioid requirements, but with similar pain scores (Gupta 2017 **Level II**, n=50, JS 5). Similarly, following modified radical mastectomy, PVB vs SAP block prolonged analgesia (11 vs 6 h) (Hetta 2016 **Level II**, n=64, JS 3).

Following VATS, SAP block vs placebo improved 40-item Quality of Recovery (QoR-40) score at 24 h after surgery (Kim 2018a **Level II**, n=90, JS 5). SAP block vs systemic multimodal analgesia reduced pain scores following thoracoscopic surgery for 8 h (Semyonov 2019 **Level II**, n=104, JS 1). SAP block vs TEA had reduced effects on blood pressure (primary outcome) following thoracotomy (Khalil 2017 **Level II**, n=60, JS 3).

5.8.5.5 | Sternal bed blocks

PECS blocks will not block the anterior cutaneous branch of the intercostal nerves. However, transversus thoracis block, a sternal bed block with local anaesthetic injected into the neurovascular plane superficial to the transversus thoracis muscle, will result in anterior cutaneous branch block. Injections of ropivacaine 0.5% (total dose <5 mg/kg) into the 2nd to 6th parasternal intercostal spaces were superior vs placebo (same volume of sodium chloride 0.9 %) for treatment of postoperative pain in pediatric patients undergoing midline cardiac surgery (Chaudhary 2012 **Level II**, n=30, JS 4). PECS block combined with transversus thoracis block vs PECS block alone reduced pain intensity following mastectomy (Ueshima 2017a **Level II**, n=70, JS 3).

Surgeon administered sternal bed blocks combined with systemic analgesia vs systemic analgesia alone resulted in clinically relevant reduced pain scores for 24 h following CABG (Dogan Baki 2016 **Level II**, n=81, JS 4). This study included a 6 mth follow-up, where there was no difference in the incidence of chronic pain

5.8.5.6 | Transversus abdominus plane block

Transversus abdominis plane block (TAPB) is used to provide analgesia following abdominal surgery. TAPB by US-guidance has generally replaced use of landmark technique. Independent of the type of surgery (abdominal laparotomy, abdominal laparoscopy, and Caesarean section) US-guided TAPB vs sham or no block reduce IV morphine consumption at 6 h (MD -6 mg; 95%CI −7 to −4) and 24 h (MD −11 mg; 95%CI −14 to −8) vs control or placebo (Baeriswyl 2015 **Level I** [PRISMA], 31 RCTs, n=1,611). In addition, pain scores are reduced at rest (MD −10/100; 95%CI −15 to −5) and on movement (MD −9/100; 95%CI −14 to −5) at 6 h, but not PONV or pruritus. These effects are not seen in patients receiving long-acting spinal opioid, and were independent of timing of injection, approach used or the use of systemic multimodal analgesia. A parallel systematic review in all types of surgery describes similar effects; TAPB vs placebo reduces pain intensity at 6 h (SMD -1.4/10; 95%CI -1.9 to -0.8) (23 RCTs, n=1,092), at 12 h (SMD -2.0/10; 95%CI -2.7 to -1.4) (18 RCTs, n=930), at 24 h (SMD -1.2/10; 95%CI -1.6 to -0.8) (33 RCTs) and opioid requirements at 24 h (MED -14.7 mg; 95%CI -18.4 to -11.0) (28 RCTs) (Brogi 2016 **Level I** [PRISMA],

51 RCTs, n unspecified) (significant RCT overlap). These results remain consistent across surgical types, but analgesic efficacy of TAPB is inferior to IT morphine. These results are also in line with two preceding meta-analyses specifically looking at effects of TAPB in Caesarean section (Mishriky 2012 **Level I**, 9 RCTs, n=524) (4 RCTs overlap with Baeriswyl 2015) and in laparoscopic surgery (De Oliveira 2014 **Level I**, 10 RCTs, n=633) (all 10 RCTs overlap with Baeriswyl 2015). RCTs not included in these meta-analyses have shown contradictory results (Soltani Mohammadi 2014 **Level II**, n=67, JS 5; Rao Kadam 2013 **Level II**, n=42, JS 3).

For a wide range of open and laparoscopic abdominal surgery in adults and children, epidural analgesia vs TAPB provides similar analgesia (MD 0.5/10; 95%CI -0.1 to 1.0) (6 RCTs [adult], n=310), but TAPB reduces the risk of hypotension (RR 0.13; 95%CI 0.04 to 0.38) (4 RCTs, n=191) and LOS (MD: -0.6 d; 95%CI: -0.9 to -0.3) (3 RCTs, n=146) (Baeriswyl 2018 **Level I** [PRISMA], 10 RCTs, n=505).

After abdominal hysterectomy, TAPB vs sham block or no block reduce 24 h opioid consumption (3 RCTs, n=126), pain scores at 2 h (6 RCTs, n=274) and 24 h (5 RCTs, n=228), PONV (6 RCTs, n=345) and prolong time to analgesic request (4 RCTs, n=238) (Zhou 2018 **Level I** [PRISMA], 13 RCTs, n=841) (3 RCTs overlap with Baeriswyl 2015). After abdominal hysterectomy, TAPB provided the best pain relief and the lowest opioid rescue requirements vs epidural analgesia and vs parenteral analgesia (Mathew 2019 **Level II**, n=60, JS 4).

In adults undergoing lower abdominal surgery, TAPB vs local anaesthetic infiltration provided superior analgesia at 24 h, although pain scores at 2 and 4 h postoperatively were similar (Yu 2014 **Level I**, 4 RCTs, n=196) (3 RCTs overlap with Baeriswyl 2015). TAPB vs local anaesthetic infiltration reduces 24 h morphine consumption (MD -3.85 mg; 95%CI -7.47 to -0.22) (Guo 2015 **Level I**, 5 RCTs, n=127) (3 RCTs overlap with Baeriswyl 2015).

Both landmark and US-guided TAPB have been complicated by liver trauma (Lancaster 2010 **CR**; Farooq 2008 **CR**). For paediatric use, see Section 10.6.2.3.

5.8.5.7 | Quadratus lumborum block

Quadratus lumborum block (QLB) has been proposed as a superior alternative to US-guided TAPB (Elsharkawy 2019 **NR**; Ueshima 2017b **NR**). With QLB, local anaesthetic is injected anterior, posterior or lateral to the posterior abdominal wall muscle quadratus lumborum. Posterior QLB vs placebo or control reduced morphine requirements and pain intensity after Caesarean section (Krohg 2018 **Level II,** n=40, JS 5; Mieszkowski 2018 **Level II,** n=58, JS 3; Blanco 2015 **Level II,** n=50, JS 5). Posterior QLB vs TAP block reduced morphine requirements while providing comparable analgesia after Caesarean section (Blanco 2016 **Level II,** n=75, JS 4).

Following laparoscopic gynaecological surgery posterior QLB vs control improved pain relief at rest and on movement (Ishio 2017 **Level II,** n=70, JS 2). QLB was not superior to systemic IV lidocaine for the reduction of morphine requirements 24 h after laparoscopic colorectal surgery (Dewinter 2018 **Level II**, n=125, JS 5).

For paediatric use see Section 10.6.2.3.

5.8.5.8| Other abdominal wall blocks

Ilioinguinal and iliohypogastric nerves innervate the lower abdominal wall and groin region (Chin 2017 **NR**). These nerves can be blocked using landmark or ultrasound-guided techniques in the immediate vicinity of the anterior superior iliac spine. Anatomical variability likely contributes to the variable success rate of the Ilioinguinal-iliohypogastric nerve blocks. This variability together with the heterogeneity of published trials, means that there are no specific evidenced-based recommendations for this procedure. The clinical efficacy of rectus sheath blocks in the general surgical (open and laparoscopic) and obstetric populations is unclear. Transversalis fascia plane has been described in case reports.

5.8.6 | Head and Neck Blocks

5.8.6.1 | Sphenopalatine ganglion block

After endoscopic sinus surgery, sphenopalatine ganglion block vs placebo or control improved pain intensity and PONV (Kim 2019b **Level I** [PRISMA], 8 RCTs, n=441). Topical sphenopalatine ganglion block was associated with improved results for treatment of postdural puncture headache (PDPH) vs epidural blood patch (Cohen 2018 **Level IV**, n=81).

5.8.7 | Periarticular and intra-articular analgesia

The use of intra-articular (IA) infusions of bupivacaine with adrenaline has been cautioned against because of reports of glenohumoral chondrolysis following shoulder arthroscopy (Hansen 2007 **Level III-3**, n=189 [shoulders operated on]; Bailie 2009 **Level IV**, n=23). Chondrotoxic effects have been shown for all local anaesthetics in in-vitro studies of human knee cartilage (Jayaram 2019 **Level III-2 BS** [PRISMA], 16 studies, n unspecified). Chondrotoxicity is worsened by coadministration of corticosteroids; ropivacaine at concentrations ≤0.5 % was the least chondrotoxic LA. See also Section 4.4.3.1.

IA NSAIDs have demonstrated analgesic efficacy over systemic administration in some studies but the overall benefit is less clear (see Section 4.2.3.1). An analgesic effect for IA morphine following arthroscopy vs placebo cannot be shown (Rosseland 2005 **Level I**, 46 RCTs, n=3,166).

5.8.7.1 | Local infiltration analgesia

LIA refers to the systematic intraoperative injection of local anaesthetics in the periarticular and IA regions; LIA may also be referred to as periarticular infiltration. There have been methodology issues in LIA studies: lack of blinding, lack of placebo, lack of supplemental agents in controls (eg ketorolac), variable use of 'top-up' catheters, inferior results with established techniques (peripheral nerve or epidural block) compared to the literature, the use of traditional recovery programs with low activity (limiting the assessment of therapies on early functional recovery) and inadequate pain assessment (Andersen 2014 **Level I**, 27 RCTs, n=1,644). Other limitations of LIA studies have included non-uniform use of both non-opioid and opioid analgesia across treatment groups, poorly defined multimodal analgesia therapies and mobilisation pathways (Kehlet 2011 **NR**). The role of NSAIDs introduced via LIA vs systemic administration is also unclear (see Section 4.2.3.3). Similarly, there seems to be little benefit of adding opioids such as morphine; morphine 0.1 mg/kg as a component of LIA with ropivacaine/ketoprofen/methylprednisolone/adrenaline in one side vs no morphine in patients having bilateral TKA had no effect on pain, swelling or ROM (Iwakiri 2017 **Level II**, n=53, JS 4).

Total knee arthroplasty: LIA compared to placebo or no injection

Compared to placebo or no injection in TKA, LIA (with local anaesthetics in various combinations with NSAID, steroids, opioids and adrenaline) was associated with reduced pain scores and reduced opioid consumption for up to 32 h (Andersen 2014 **Level I**, 7 RCTs [LIA in TKA vs placebo/no injection], n=328); there was a high risk of bias with unbalanced systemic analgesic regimens between groups. In patients having bilateral TKA, LIA improved pain outcomes vs periarticular placebo on the opposite side (Fajardo 2011 **Level II**, n=30, JS 2; Mullaji 2010 **Level II**, n=40, JS 5; Andersen 2008 **Level II**, n=12, JS 4). Reviews comparing LIA with placebo or no injection report that following

TKA LIA achieves superior analgesia and reduced opioid consumption, however the source RCTs were at high risk of bias because of lack of blinding (Xu 2014 **Level I**, 18 RCTs, n=1,858).

Total knee arthroplasty: LIA compared to epidural analgesia

In comparison to LIA in TKA, LEA has similar analgesic effects at rest for <24 h, but LIA achieves better analgesia at 48 h (MD −1.08/10; 95%CI −1.86 to −0.29) and 72 h (MD −0.82/10; 95%CI −1.24 to −0.4) (Yan 2016 **Level I**, 9 RCTs [TKA], n=537). Similarly, pain on movement was similar at <24 h, but better controlled by LIA at 48 h and LIA enabled a better range of movement at all time points.

Total knee arthroplasty: LIA compared to peripheral nerve blockade

When comparing FNB to LIA in TKA, most RCTs report either equal analgesic efficacy or a short-term benefit of LIA (Andersen 2014 **Level I**, 5 RCTs [LIA vs FNB in TKA], n=307; Fan 2016 **Level II**, n=157, JS 2; Ashraf 2013 **Level II**, n=50, JS 3; Ng 2012 **Level II**, n=16, JS 4). Interpretation of results is hindered by the multitude of techniques, leaving the analgesic benefit of LIA *per se* unclear.

LIA achieved similar time to readiness for discharge from hospital (mean 3.2 d) vs combined PCEA/FNB (Yadeau 2013 **Level II**, n=90, JS 3). A single-injection FNB when combined with epidural analgesia resulted in reduced pain vs LIA during the first 24 h (Reinhardt 2014 **Level II**, n=94, JS 5). LIA has superior analgesic outcomes vs epidural analgesia (Andersen 2014 **Level I**, 3 RCTs [LIA vs epidural in TKA], n=204); these trials had high risk of bias because of incomplete blinding and high heterogeneity due to different systemic analgesic regimens between groups. In patients receiving epidural analgesia, there was no added analgesic or functional benefit from LIA vs placebo in the contralateral side for up to 14 d (Joo 2011 **Level II**, n=572, JS 5). When LIA was added to combined FNB and sciatic block (with spinal anaesthesia for the surgery), improved pain relief was only found at one time point postoperatively (0.6/10 ± 1.5 vs 1.7/10 ± 2.3) (Hinarejos 2016 **Level II**, n=50, JS 5). As there were no other differences in analgesic outcomes, the authors concluded that adding LIA to their regimen was not necessary.

Total hip arthroplasty

In THA, no additional analgesic benefit of LIA vs placebo LIA (5 RCTs) or no injection (2 RCTs) (added to systemic multimodal analgesia) is identified (Andersen 2014 **Level I**, 10 RCTs [THA], n=756). Compared with IT morphine (1 RCT) and epidural analgesia (1 RCT), LIA was reported to have similar or improved analgesic effects.

5.8.8 | Wound catheter infusion, instillation and wound infiltration

5.8.8.1 | Wound catheter local anaesthetic infusions and intermittent injection

Wound catheter local anaesthetic continuous infusion (21 RCTs) or intermittent injections (9 RCTs) provide minor analgesic benefits up to 48 h in obstetric and gynaecological surgery (6 RCTs), but do not improve analgesic outcomes following abdominal (7 RCTs) or other non-orthopaedic (urological, reconstructive or thoracic) surgery (Gupta 2011 **Level I**, 32 RCTs, n=1,999). LOS is not reduced (pooled for all surgery) (17 RCTs). Continuous wound infiltration with ropivacaine vs placebo leads to a reduction in pain scores and opioid consumption (Raines 2014 **Level I**, 14 RCTs, n=756) (4 RCTs overlap with Gupta 2011). Following Caesarean section, local anaesthetic wound infiltration (by infusion) reduces opioid consumption (MD −10.29 MME; 95%CI −18.36 to −2.21) (8 RCTs, n=441), but has limited effects on pain scores with movement at 24 h (MD −0.83/10; 95%CI −1.90 to −0.23) (7 RCTs, n=434) (Adesope 2016 **Level I**, 21 RCTs, n=1,435) (5 RCTs overlap with Gupta 2011). Local anaesthetic infusions (6 RCTs [continuous]), 2 RCTS [intermittent], 1 RCT [PCA]) via abdominal wound catheter vs epidural analgesia have equal analgesic efficacy for up to 48 h (7

RCTs, n=425) with a lower incidence of urinary retention (3 RCTs, n=160) (Ventham 2013 **Level I** [PRISMA], 9 RCTs, n=505); there was however considerable heterogeneity with variability in analgesic regimens, especially in the epidural arms. Epidural analgesia provided better pain relief than continuous wound infiltration at rest at 72 h (4 RCTs, n=289) (Li 2018a **Level** I, 16 RCTs, n=1,345) (8 RCTs overlap with Ventham 2013). There were no differences in pain score at rest or on mobilisation at 2 h, 12 h, 24 h and 48 h. Hypotension is more common in epidural vs wound infusion recipients (14 RCTs, n=1,350).

Continuous preperitoneal local anaesthetic infiltration is superior vs continuous subcutaneous infiltration (1 RCT, n=60) and vs placebo (9 RCTs, n=537), with similar analgesia vs active control (epidural analgesia or PCA) (13 RCTs, n =887) (Mungroop 2019 **Level I** [PRISMA], 29 RCTs, n=2,059). Preperitoneal wound catheter infusion of ropivacaine following colorectal surgery resulted in improved pain relief, opioid-sparing and earlier recovery of bowel function (Beaussier 2007 **Level II**, n=49, JS 5).

5.8.8.2 | Intraperitoneal instillation

Early postoperative abdominal pain is improved after laparoscopic cholecystectomy by the use of intraperitoneal local anaesthetic; the effect is better when given at the start of surgery vs instillation at the end of surgery (Boddy 2006 **Level I**, 24 RCTs, n=1,256). In laparoscopic gastric surgery, intraperitoneal local anaesthetic reduces postoperative abdominal pain intensity, the incidence of shoulder pain and opioid consumption (Kahokehr 2011 **Level I** [PRISMA], 5 RCTs, n=273).

5.8.8.3 |Local anaesthetic infiltration

Local anaesthetic infiltration vs a variety of controls for mastectomy did not improve analgesic outcomes (Tam 2015 **Level I** [PRISMA] 13 RCTs, n=1,150).

Infiltration of local anaesthetic into the scalp is used to treat postoperative pain following craniotomy. Preoperative scalp infiltration provides improved pain scores for up to 8 h postoperatively, with postprocedural infiltration improving analgesia for up to 12 h (Guilfoyle 2013 **Level I** [PRISMA], 7 RCTs, n=325).

5.8.9 | Topical application of local anaesthetics

Topical EMLA® cream (eutectic mixture of lignocaine and prilocaine) is effective in reducing the pain associated with venous ulcer debridement (Briggs 2012 **Level I** [Cochrane], 6 RCTs, n=343). When compared with EMLA® cream, topical amethocaine provides superior analgesia for superficial procedures in children, especially IV cannulation (Lander 2006 **Level I**, 6 RCTs, n=534). Topical tetracaine, liposome-encapsulated tetracaine and liposome-encapsulated lignocaine are as effective as EMLA® cream for dermal instrumentation analgesia in the ED (Eidelman 2005 **Level I**, 25 RCTs, n=2,096). See Sections 10.6.3.5 and 10.6.6 for use in penile surgery, 10.7.1 to 10.7.3 and 10.8.2 for procedures involving skin puncture use in children and Section 8.11.2 for use in the ED.

Topical local anaesthetic provides no analgesic benefit when performing flexible diagnostic nasoendoscopy, either alone or in combination with a vasoconstrictor (Conlin 2008 **Level I**, 8 RCTs, n=818; Nankivell 2008 **Level I**, 18 RCTs, n=1,356). Intraurethral instillation of lidocaine gel provides superior analgesia to lubricating gel during flexible cystoscopy (Aaronson 2009 **Level I**, 4 RCTs, n=411). Following tonsillectomy, local anaesthetics provide a modest reduction in post-tonsillectomy pain; administering the local anaesthetic on swabs appeared to provide a similar level of analgesia to that of infiltration (Grainger 2008 **Level I**, 13 RCTs [6 adult & 7 paediatric], n unspecified). Topical local anaesthetic gel and/or nebulised local anaesthesia of the nose and

pharynx reduced pain associated with nasogastric tube insertion in adults (OR 0.42; 95%CI 0.20 to 0.88) (Kuo 2010 **Level I**, 5 RCTs, n=212). See also paediatric Section 10.7.2.6.

The lignocaine 5% patch may reduce acute pain intensity following herpes zoster once lesions have healed (McCarberg 2013 **NR**).

5.8.10 | Neuromodulation

There is some emerging evidence that percutaneous peripheral nerve stimulation may be a promising alternative to infusions of local anaesthetics through a perineural catheter (Gabriel 2019 **NR**). In this technique, small gauge insulated electrical leads are placed percutaneously through needle that is placed remotely 0.5 to 3.0 cm from a peripheral nerve using US-guidance. The lead is connected to an external stimulator and narrow pulse duration electrical stimulation is applied to selectively activate pain-relieving fibres in a peripheral nerve trunk. This technique does not activate fibres that would result in muscle contractions, loss of strength or loss of proprioception. US-guided percutaneous peripheral nerve stimulation has been used successfully for analgesia following pain refractory to standard therapy following knee arthroplasty (Ilfeld 2017b **Level IV**, n=5). Following ambulatory rotator cuff repair, although initial pain control was inadequate, the later postoperative quality of analgesia (POD 1 to 14) was considered excellent (Ilfeld 2019a **Level II**, n=11, JS 5). Proof of concept studies have used percutaneous femoral nerve stimulation for ambulatory anterior cruciate ligament reconstruction (Ilfeld 2019b **Level II**, n=10, JS 5) and percutaneous sciatic nerve stimulation for ambulatory foot surgery (Ilfeld 2018 **Level II**, n=10, JS 5). Development issues with this technique include optimal lead location and insertion technique, the stimulating protocol and prevention of lead fracture/dislodgement.

5.8.11 | Safety

Regional anaesthesia techniques when performed with vigilance and professionalism are associated with a high degree of safety (Barrington 2013 **Level IV**, n=25,336 [PNBs in 20,021 patients]; Orebaugh 2012 **Level IV**, n=14,498 [PNBs]; Barrington 2009 **Level IV**, n=8,189 [PNBs in 6,950 patients]). Simple strategies such as preprocedural checklists, including a pre-block "*time-out*" ('Stop Before You Block') and a "*pause*", may help reduce the incidence of events such as wrong-site blockade (Barrington 2015 **GL;** ANZCA 2015 **GL**).

For paediatric data see Sections 10.6.1.3, 10.6.3.5 and Table 10.10.

5.8.11.1 | Anticoagulation

Caution should be used when considering and performing some peripheral nerve or plexus blocks in patients with impaired coagulation (see Section 5.9.2). This particularly applies to where the PNB is performed at a deep location that prevents external compression, should bleeding occur.

5.8.11.2 | Nerve injury and postoperative neurologic symptoms

A new onset postoperative nerve injury regardless of severity is of concern to patients and healthcare providers. Methods used to capture, define and report neurologic outcomes vary considerably. A multicentre registry using systematic postoperative contact with all patients reported the incidence of block-related nerve injury as 4/10,000 blocks (95%CI 0.8 to 11) (Barrington 2009 **Level IV**, n=8,189 [PNBs in 6,950 patients]). A large single-institution database identified four cases of peripheral nerve injuries with sensory loss persisting for 6 to 12 mth, which were not able to be attributed to nonblock causes (≈3/10,000) (Orebaugh 2012 **Level IV**, n=14,498 [PNBs]). A single-centre study reported the incidence of postoperative neurologic symptoms

(PONS) >6 mth duration as 9/10,000 (95%CI 5 to 17) (Sites 2012 **Level IV**, n=12,668). Nerve injury may follow surgery independently of nerve block procedures. The baseline risk of nerve injury risk inherent to common elective orthopaedic surgical procedures is now better understood (Neal 2015 **GL**). Awareness of the mechanism, location, and frequency of nerve injuries associated with elective orthopedic surgery may facilitate diagnosis and treatment of peripheral nerve injury. After TKA, the all-cause incidence of perioperative nerve injury was 0.79%; however, this outcome was not associated with PNB (Jacob 2011b **Level III-3**, n=12,329). Similarly, PNB following THA (Jacob 2011a **Level III-3**, n=12,998) and shoulder arthroplasty (Sviggum 2012 **Level III-3**, n=1,569) was not associated with perioperative nerve injury. Observational studies consistently report that PONS or postoperative neurologic dysfunction may be related to patient and surgical factors and that the incidence of neuropathy directly related to peripheral regional anaesthesia is infrequent or rare (Sviggum 2012 **Level III-3**, n=1,569; Jacob 2011a **Level III-3**, n=12,998; Jacob 2011b **Level III-3**, n=12,329; Sites 2012 **Level IV**, n=12,668; Orebaugh 2012 **Level IV**, n=14,498; Barrington 2009 **Level IV**, n=8,189 [PNBs in 6,950 patients]). However, distinguishing between contributing surgical, anaesthetic, and patient factors is often difficult. Differential diagnosis should include use of a pneumatic tourniquet (>120 min), which has been associated with nerve injury. These injuries often present as diffuse sensorimotor deficits. Delaying placement of regional blocks if assessment of postoperative nerve function is important for the surgeon is a consideration. Mechanical, ischaemic or neurotoxic injury of the neuraxis or peripheral nervous system associated with regional anaesthesia and pain medicine interventions has been summarised into a practice advisory (Neal 2015 **GL**).

5.8.11.3 | Local Anaesthetic Systemic Toxicity

US-guidance has been associated with a reduced incidence of local anaesthetic systemic toxicity (LAST) following PNB, with an incidence of 8.7/10,000 PNBs and no related deaths (Barrington 2013 **Level IV**, n=25,336 [PNBs in 20,021 patients]). This result is consistent with an analysis of block outcomes over 10 y period, which revealed higher LAST incidence with landmark vs US-guided technique: 7 of 5,932 vs 0 of 16,858 respectively (Melnyk 2018 **Level IV**, n=22,790 [PNBs]). A review of case reports and registries estimates LAST incidence to be 2.7/10,000 PNBs (95%CI 2.1 to 3.5) (Gitman 2018 **Level IV** n=251,325). Seizure was the most common presenting feature (53% [CRs] and 61% [registries]). It is important to note that presenting features of LAST may not comply with classic descriptions and be overlooked or disguised by perioperative processes and interventions. There is a trend toward delayed presentation, which may mirror the increased use of US-guidance (fewer intravascular injections), local infiltration techniques (slower systemic uptake), and continuous local anaesthetic infusions. Small patient size, sarcopenia and patient co-morbidities potentially increase the risk of LAST. An increasing number of reported events occur outside of the traditional hospital setting and involve non-anaesthetists. Caution must be exercised with all regional techniques as case reports of adverse outcomes, including death, continue to occur (Vadi 2014 **CR** & **NR**), even with local anaesthetic infusion catheters placed under direct vision (Calenda 2014 **CR**). This caution also applies to fascial plane techniques such as TAPB that tend to involve large doses (Hessian 2013 **Level IV PK**, n=20; Griffiths 2013 **Level IV PK**, n=8) (see also Section 4.4.3.2). Of note, an analysis from the Pediatric Regional Anesthesia Network database indicates that TAPB has a low risk of local anaesthetic systemic toxicity in this patient population (Long 2014 **Level IV**, n=19,994).

Treatment of LAST should be directed towards importance of the airway and oxygenation (avoiding hypercarbia and acidosis), seizure control and lipid emulsion therapy (100 mL lipid emulsion 20% for patient 70 kg or over; 1.5 mL/kg for patient less than 70 kg). Mechanisms of lipid emulsion reversal of LAST include rapid partitioning, direct inotropy, and post ischaemic conditioning (Neal 2018a **GL**). The American Society of Regional Anesthesia and Pain Medicine (ASRA) has updated its

checklist for the management of LAST (Neal 2018b **GL**). Exact volume and flow rate of lipid emulsion are not essential; however recommendations include avoiding administration of >10 to 12 mL/kg of lipid emulsion, calling for help early, and use of electronic decision support tools. The pharmacological treatment of LAST is different to other cardiac arrest scenarios. It is recommended to reduce individual doses of adrenaline to less than 100 mcg, avoiding vasopressin, calcium channel blockers, beta-blockers and use of other local anaesthetics. A guideline for management of severe LAST has been developed by the AAGBI and is endorsed by ANZCA (AAGBI 2010 **GL**).

5.8.11.4 | Infection

The strongest recommendations for infection-prevention are effective hand hygiene and skin preparation with alcohol-based chlorhexidine solution; as per the UK epic2 National Guidelines (Pratt 2007 **GL**). These guidelines recommend full barrier precautions for central venous catheter placement (cap, mask, sterile gown and gloves; and large drape). Although specific data for aseptic technique in CPNB is lacking, advisories have been developed which advocate similar practices (Hebl 2011 **NR**). In a review of infections associated with CPNB, the use of full surgical-type aseptic technique for CPNB procedures was supported (Capdevila 2009 **NR**). Identified risk factors for local CPNB catheter inflammation include ICU stay, duration of catheter use >48 h, lack of antibiotic prophylaxis, axillary or femoral location and frequent dressing changes (Capdevila 2009 **NR**). The use of a chlorhexidine-impregnated patch designed to inhibit bacterial growth for days as a dressing after femoral nerve catheter insertion did not reduce the low rate of bacterial colonisation, nor reduce local skin inflammation (2.1 vs 10.6%) in an underpowered RCT (Schroeder 2012 **Level 2**, n=100, JS 3). Chlorhexidine was also the superior skin disinfectant prior to regional catheter insertion vs povidone iodine (Krobbuaban 2011 **Level II**, n=100, JS 4); a positive skin culture immediately after skin disinfection occurred in 10 vs 35% (NNT 4).

The implications of catheter-related sepsis in patients with implanted prosthetic devices (eg joint arthroplasty) are significant and therefore all reasonable measures should be taken to minimise the risk of infection. The widespread use of US-guidance has introduced a potential risk related to contamination. The use of a sterile disposable sheath reduces the risk of contamination of the aseptic field by the transducer. Decontaminating US transducers with 70% isopropyl alcohol was effective at removing pathogenic organisms (Chuan 2013 **Level IV**, n=120 [swabs]).

KEY MESSAGES

1. Topical EMLA® cream (eutectic mixture of lignocaine [lidocaine] and prilocaine) is effective in reducing the pain associated with venous ulcer debridement (**U**) (**Level I** [Cochrane Review]).
2. Transversus abdominis plane blocks provide pain relief superior to local anaesthetic infiltration for a range of abdominal surgeries (**N**) (**Level I** [PRISMA]).
3. Intraperitoneal local anaesthetic instillation after laparoscopic gastric surgery (**N**) (**Level I** [PRISMA]) and laparoscopic cholecystectomy (**U**) (**Level I**) improves postoperative pain outcomes.
4. Adductor canal block results in similar postoperative pain outcomes following total knee arthroplasty versus femoral nerve block with less quadriceps weakness, earlier mobilisation and better functional recovery (**S**) (**Level I** [PRISMA]).
5. Following thoracotomy, thoracic paravertebral block provides comparable analgesia to thoracic epidural analgesia (**U**) (**Level I**).
6. Continuous peripheral nerve block, compared with single-injection peripheral nerve block, results in improved pain control, decreased need for opioid analgesics, reduced nausea and improved patient satisfaction in some settings, in particular in the first 24 hours postoperatively (**W**) (**Level I**).
7. Femoral nerve block, either single-injection or continuous, provides better analgesia and decreased nausea compared with parenteral opioid-based techniques after total knee arthroplasty (**U**) (**Level I**).
8. Compared with opioid analgesia, continuous peripheral nerve block (regardless of catheter location) provides better postoperative analgesia and leads to reductions in opioid use as well as nausea, vomiting, pruritus and sedation (**U**) (**Level I**).
9. Blocks performed using ultrasound guidance are more likely to be successful, faster to perform, with faster onset and longer duration compared with localisation using a peripheral nerve stimulator (**U**) (**Level I**).
10. Morphine injected into the intra-articular space following knee arthroscopy does not improve analgesia compared with placebo (**U**) (**Level I**).
11. Following total knee arthroplasty, local infiltration analgesia reduces postoperative pain for up to 32 hours when compared to systemic analgesics alone; however, there is limited benefit in comparison to femoral nerve block (**U**) (**Level I**).
12. Following total hip arthroplasty, there is no additional analgesic benefit for local infiltration analgesia over conventional multimodal analgesia (**S**) (**Level I**) and peripheral nerve blocks have limited or no effect on postoperative pain (**Q**) (**Level II**).
13. Following either knee or hip arthroplasty, there is insufficient evidence to support postoperative administration of local infiltration analgesia via catheter (**U**) (**Level I**).
14. Local anaesthetic infusions or intermittent injections through wound catheters provide analgesic benefits following gynaecological and obstetric surgery, but not other abdominal or nonorthopaedic surgery (**Q**) (**Level I**).

15. Intraurethral instillation of lignocaine gel provides analgesia during flexible cystoscopy (**U**) (**Level I**).
16. The benefit of routine sciatic nerve block in addition to femoral nerve block for analgesia following total knee joint arthroplasty remains unclear (**U**) (**Level I**).
17. Continuous interscalene analgesia provides better analgesia, reduced opioid-related adverse effects and improved patient satisfaction compared with intravenous PCA or single-injection interscalene block after open shoulder surgery (**U**) (**Level II**).
18. Erector spinae plane blocks provide postoperative analgesia superior to systemic analgesia after cardiac surgery (**N**) (**Level II**) and to transverse abdominus blocks after laparoscopic cholecystectomy (**N**) (**Level II**).
19. Quadratus lumborum block reduces pain scores and opioid requirements following Caesarean section compared to placebo or control (**N**) (**Level II**).
20. Intra-articular bupivacaine infusions have been associated with chondrolysis and their use has been cautioned against (**U**) (**Level IV**).
21. Postoperative neurologic symptoms or dysfunction is often related to patient and surgical factors and the incidence of neuropathy directly related to peripheral regional anaesthesia is rare (**S**) (**Level III-3**).
22. Ultrasound guidance of regional blocks is associated with a reduced risk of local anaesthetic systemic toxicity in adults (**N**) (**Level IV**).

The following tick boxes represent conclusions based on clinical experience and expert opinion:

☑ Continuous peripheral nerve blocks carry a risk of infection; skin preparation with alcohol-based chlorhexidine and full barrier precautions (including face masks) are recommended for insertion of peripheral nerve catheters (**U**).

☑ Ultrasound-guided techniques should be practiced with a high degree of skill and care, including aseptic techniques, as they do not eliminate the risks of injury to tissues and structures, local anaesthetic systemic toxicity or site contamination (**U**).

☑ Caution should be used when considering and performing some peripheral nerve or plexus blocks in patients with impaired coagulation, in particular where the PNB is performed at a deep location that prevents external compression, should bleeding occur (**N**).

5.9 | Regional analgesia and concurrent anticoagulant medications

5.9.1 | Neuraxial block and anticoagulant medication

The low event rate of epidural haematoma means that evidence cannot be based on RCTs but must rely on data from case reports, case series and large audits. An American Society of Regional Anesthesia and Pain Medicine (ASRA) Practice Advisory publication provides a good overview of and guidance on neurological complications of regional anaesthesia (Neal 2008 **GL**).

The population incidence of epidural haematoma following neuraxial block is possibly smaller than that of spontaneous epidural haematoma, however the rate in patients exposed to epidural anaesthesia is more appropriate for comparison. Between 1962 and 1992, 326 case reports of spontaneous epidural haematoma were published (Schmidt 1992 **Level IV**), while between 1906 and 1996 only 51 cases of epidural haematoma following epidural anaesthesia or analgesia were reported (Wulf 1996 **Level IV**).

Anticoagulation (present in 48% of cases) was the most important risk factor for epidural haematoma following insertion of an epidural needle/catheter, followed by coagulopathy (present in 38% of cases) (Wulf 1996 **Level IV**, n=51). This was confirmed by the series of epidural haematomas that followed epidural anaesthesia/analgesia in combination with inappropriate LMWH regimens in the USA, where the incidence was reported to be 1 in 3,000 (Horlocker 2003 **Level IV**).

In view of the increased risk with anticoagulation, ASRA (Horlocker 2010 **GL**) and the European Society of Anaesthesiology (ESA) (Gogarten 2010 **GL**) published a number of consensus statements and recommendations on regional anaesthesia in patients receiving antithrombotic or thrombolytic therapy. Such statements should be viewed as "*a panel of experts*" best faith efforts to offer reasonable pathways to provide safe and quality patient care while allowing for clinical differences based on individual situations (Bergqvist 2003 **NR**). It is recognised that variances from recommendations outlined in the ASRA guidelines "*may be acceptable based on the judgement of the responsible anesthesiologist*" (Horlocker 2010 **GL**). That is, these guidelines will not substitute for an individual risk/benefit assessment of every patient by the individual anaesthetist.

The ASRA guideline was updated in 2018 (Horlocker 2018 **GL**), but the ESA (Gogarten 2010 **GL**) recommendations have not been updated since 2010, despite the fact that new information on both established and newly introduced anticoagulants has become available. Subsequent guidelines developed for interventional spine and pain procedures jointly by ASRA, European Society of Regional Anaesthesia and Pain Therapy (ESRA), the American Academy of Pain Medicine (AAPM), the International Neuromodulation Society (IMS), the North American Neuromodulation Society and the World Institute of Pain (WIP) in 2015 (Narouze 2015 **GL**) were updated in 2018 (Narouze 2018 **GL**). These guidelines classify pain procedures according to potential risk of serious bleeding and emphasise the importance of assessing both procedure and patient-specific risk factors, such that concurrent use of anticoagulant or antiplatelet agents increases the potential procedural risk.

The Society for Obstetric Anesthesia and Perinatalogy (SOAP) published a consensus statement in 2018 also (Leffert 2018 **GL**), in the context of increased use of thromboprophylaxis in obstetrics and differences in pharmacokinetics of anticoagulants in the obstetric population, as well as the competing risks to the fetus and from general anaesthesia, which were issues not directly addressed in the aforementioned guidelines.

Table 5.2 summarises recommendations from these guidelines for timing of antithrombotic or antifibrinolytic administration in relation to neuraxial blockade including epidural catheter insertion and removal.

Recommendations aim to minimise anticoagulant presence during both insertion and removal of an epidural catheter due to associated risk of spinal haematoma formation. Time intervals between discontinuation of therapeutic anticoagulation and neuraxial block are predominantly pharmacologically based. After 5 half-lives (adjusted for renal impairment, if the anticoagulant is renally excreted), the residual anticoagulant activity will be 3%. Prophylactic doses of parenteral anticoagulants are interrupted for 2 half-lives due to lower levels of anticoagulation, although this may not be the case for non-vitamin K oral anticoagulants (NOACs) as discussed below.

Time intervals for subsequent dosing are based on the time to reach peak effect for each anticoagulant which is subtracted from the 8 h required for platelet plug stabilisation (Rosencher 2007 **GL**; Bouma 2006 **NR BS**).

Pregnancy-related physiological changes may impact unfractionated heparin (UFH) and/or LMWH pharmacokinetics. Increased maternal plasma volume may increase their volume of distribution with decreased peak and steady-state concentrations, more rapid renal clearance due to increased blood flow and glomerular filtration rate (GFR) and the free fraction of highly protein bound drugs may be increased due to lower serum albumin concentration in pregnancy (Leffert 2018 **GL**). Consequently, recommendations for the range of drug doses, including intermediate and high doses have been included in the SOAP guideline and Table 5.2.

For some anticoagulants there is a role for coagulation studies and use of anticoagulant reversal agents may be relevant if urgent neuraxial block is required.

- *Unfractionated heparin SC or IV*— Thromboprophylaxis with SC UFH given twice-daily is not a contraindication to neuraxial block after an appropriate time interval (see Table 5.2). IV UFH administration results in immediate anticoagulant activity. SC administration has lower bioavailability than IV UFH administration with a 1 to 2 h delay in onset of anticoagulant activity. Offset of action is also slower when higher SC doses are used. To identify heparin-induced thrombocytopenia (HIT), a platelet count should be checked during therapy continued for more than 5 d and specifically prior to removal of an epidural catheter in patients who have had more than 4 d of heparin therapy. In patients with prior heparin exposure, pre-formed heparin-platelet factor 4 antibodies may exist and the onset of HIT may occur by 2 d. The anticoagulant activity of unfractionated heparin, administered IV or SC can be fully reversed with protamine (1 mg per 100 IU heparin, max dose 50 mg).
- *Low molecular weight heparin* — Routine use of anti-Xa monitoring is not recommended and a safe level of residual anti-Xa activity for neuraxial block has not been determined. Concurrent administration of other medicines that may affect haemostasis (eg antiplatelet medicines) should be avoided. Renal impairment prolongs the effect of LMWH (for dosing recommendations in renal impairment see Table 5.3), although only one of the guidelines suggests determination of antifactor Xa activity in patients with renal insufficiency (Narouze 2015 **GL**). Protamine reverses approximately 60% of LMWH activity.
- *Fondaparinux* – This parenteral synthetic pentasaccharide with antiXa activity has a plasma half-life of 21 h and is not reversed by protamine. Neuraxial anaesthesia is not recommended outside of the context of clinical trials and an alternative VTE prophylactic agent should be utilised (Horlocker 2018 **GL**).
- *Oral warfarin* — Established warfarin therapy should be discontinued 5 d prior to neuraxial block and the INR normalised. Preoperative initiation of warfarin therapy requires an INR check prior to neuraxial block if a single dose of warfarin 5 mg was given >24 h preoperatively or a second dose was given. The INR should also be checked prior to

removal of indwelling epidural catheters if warfarin was administered >36 h before. An INR <1.5 is estimated to be a safe level for removal, while an INR >3 requires withholding warfarin and waiting for normalisation or actively reversing warfarin to allow earlier catheter removal. Specific advice on warfarin reversal is available in an updated Australian and New Zealand guideline (Tran 2013 **GL**).

Non-vitamin K oral anticoagulants (NOACs)

Neuraxial techniques should be avoided whilst patients are anticoagulated with NOACs.

- *Rivaroxaban* and *apixaban* are oral direct factor Xa inhibitors with partial renal excretion. They require cessation at least 3 d prior to neuraxial blockade (see Table 5.2 for details) and may be recommenced 6 h post epidural catheter removal or at least 24 h post-surgery. Andexanet alpha partly reversed the anti-Xa activity of these agents in patients with major bleeding but is not currently available for use in Australia or New Zealand and has not been trialled in a surgical or procedural setting (Connolly 2019 **Level IV**, n=352).
- *Dabigatran* is an oral direct thrombin inhibitor with 80% renal clearance. It also requires cessation at least 3 d prior to neuraxial anaesthesia and longer periods of interruption for various degrees of renal impairment and it may be recommenced 6 h post epidural catheter removal or at least 24 h post-surgery. Idarucizumab is a direct specific reversal agent for dabigatran and is widely available in Australia and New Zealand. A 5 g dose rapidly and completely reverses dabigatran in patients with major bleeding and 92% patients requiring urgent surgery or procedures had normal haemostasis post administration of idarucizumab including some patients requiring urgent neuraxial anaesthesia (Pollack 2017 **Level III-1**, n=503). A dilute thrombin time assay can quantify the dabigatran concentration in plasma and should be tested 24 h after administration of idarucizumab as a minority of patients may show rising dabigatran concentrations potentially requiring a further dose of idarucizumab.
- The timing of NOAC interruption was standardised for the particular anticoagulant, renal function and surgical bleeding risk (Douketis 2019 **Level III-2**, n=3,007). Patients did not receive bridging anticoagulation. Rates of major bleeding (2%) and arterial thromboembolism (<1%) were low. A subgroup of 230 patients received neuraxial anaesthesia and were managed according to the 'high-bleeding risk' protocol in which patients received their last NOAC dose 3 d prior to surgery or 5 d prior for patients on dabigatran with creatinine clearance less than 50 mL/min. Almost all patients (98.8%) had a residual anticoagulant level less than 50 ng/mL. The proportion of these patients with residual anticoagulant level less than 30 ng/mL was 93.1% in the apixaban cohort, 98.9% in the dabigatran cohort and 85.4% in the rivaroxaban cohort. The optimal preoperative anticoagulant level has not been established and some assays show increased result variability below 50 ng/mL. No spinal haematomas were reported in this study. The same NOAC interruption protocol was used for different doses of each NOAC and there was no significant difference in drug levels preoperatively. NOACs have a wide therapeutic index and consequently shorter periods of interruption are not currently recommended for the lower drug doses.

Antiplatelet medications

NsNSAIDs and other antiplatelet therapies

NsNSAIDs including aspirin alone do not significantly increase the risk of spinal haematoma but should be regarded as a risk factor if combined with other classes of anticoagulants. In such situations, coxibs should be preferred. Recommended time intervals between discontinuation or recommencement of nsNSAIDs and other antiplatelet medications (eg prasugrel) and neuraxial

block are given in Table 5.2. There are significant changes in the updated guidelines with wide variation in recommendations for different agents. For some agents, the post-operative time interval to recommencement is longer than the recommendation for neuraxial procedures without surgery.

Herbal therapy

Although garlic (*Allium sativum*), ginkgo (*Ginkgo biloba*), ginseng (*Panax* spp), dong quai (*Angelica sinensis*) and danshen (*Salvia miltiorrhiza*) have effects on haemostasis, there are currently no specific concerns about their use alone with neuraxial block. However, their combination with other anticoagulants or antithrombotics increases the risks. Patients taking dong quai and danshen combined with warfarin require an INR check.

Fibrinolytics and thrombolytics

Patients receiving fibrinolytic or thrombolytic medicines should not undergo neuraxial block except in exceptional circumstances; no data are available on a safe time interval after use of such medicines but at least 48 h and normalisation of fibrinogen level are recommended. No definite recommendations are given for the removal of neuraxial catheters after initiation of such therapy, although fibrinogen level might be a useful guide in such situations.

5.9.2 | Plexus and other peripheral regional block and anticoagulant medication

Significant blood loss or haematoma formation, rather than neurological deficit, seems to be the main risk when plexus or other regional blocks are performed in patients taking anticoagulant medications (Horlocker 2010 **GL**). Technical and anatomical considerations are different for pain interventions with both patient-specific and procedure-specific risk factors requiring assessment (Narouze 2018 **GL**).

In a series of peripheral nerve blocks for joint replacement (continuous lumbar plexus, continuous femoral and continuous or single sciatic block), with removal of the catheters at POD 2 or 3, no perineural haematoma was found despite use of warfarin (50.0%), fondaparinux (12.8%), dalteparin (11.6%), enoxaparin (1.8%) and aspirin (23.8%) (Chelly 2008a **Level IV**, n=6,935). A case series of patients receiving rivaroxaban 10 mg with a femoral catheter for TKA replacement *in situ* and removal 20 h after intake reported no cases of haematoma formation (Idestrup 2014 **Level IV**, n=504). However, a case series of bleeding complications after removal of femoral and sciatic catheters under LMWH suggests that caution is appropriate (Bickler 2006 **Level IV**, n=3; Horlocker 2010 **GL**).

For obvious reasons, deep blocks may be more at risk of bleeding complications than superficial blocks, where external compression is possible. Case reports of retroperitoneal haematoma after lumbar plexus block in conjunction with anticoagulation are published with either no neurological sequelae (Weller 2003 **CR**) or plexopathy (Klein 1997 **CR**). However, in a case series where lumbar plexus catheters were removed in warfarinised patients (36.2% with an INR >1.4 [range 1.5–3.9]), only one superficial bleeding event occurred (in a patient with INR 3.0) (Chelly 2008b **Level IV**, n=670).

The updated guidelines developed for interventional spine and pain procedures classify procedure–related risks, then upgrade the risk for patients on anticoagulants such that preoperative recommendations are similar to other guidelines but the post-operative resumption of anticoagulants is aligned with postsurgical recommendations of at least 24 h delay (Narouze 2018 **GL**). An expert panel of the Regional Anesthesia and Acute Pain Section of the Canadian Anesthesiologists Society (CAS) published a practice advisory on the bleeding risks for peripheral nerve and interfascial plane blockade, which categorises blocks into low, moderate and high risk (Tsui 2019b **GL**).

KEY MESSAGES

1. Anticoagulation and coagulopathy are the two most important risk factors for the development of epidural haematoma after neuraxial block (**U**) (**Level IV**).

The following tick box represents conclusions based on clinical experience and expert opinion:

☑ Consensus statements of experts guide the timing and choice of regional anaesthesia and analgesia in the context of anticoagulation but do not represent a standard of care and will not substitute the risk/benefit assessment of the individual patient by the individual anaesthetist (**S**).

☑ Caution should be used when considering and performing some peripheral nerve or plexus blocks in patients with impaired coagulation, in particular where the peripheral nerve block is performed at a deep location that prevents external compression, should bleeding occur (**S**).

TABLE 5.2 | Recommendations for timing of antithrombotic or antifibrinolytic administration in relation to neuraxial blockade

Medication	Dosing	Before epidural insertion	Whilst epidural catheter in place	Prior to epidural catheter removal	After epidural catheter removal
		Minimum time after last anticoagulant or thrombotic/thrombolytic dose until insertion	Delay from epidural insertion until next anticoagulant or thrombotic/ thrombolytic dose	**Minimum** time after last anticoagulant or thrombotic/thrombolytic dose until removal of epidural catheter	**Minimum** time after epidural catheter removal and next dose of anticoagulant or thrombotic/thrombolytic dose
Unfractionated heparin subcutaneous	prophylactic, up to 15000 IU/d	4-6 h or ensure normal APTT	1 h	4-6 h	1 h
Unfractionated heparin subcutaneous	intermediate, >15000 IU/d up to 20000 IU/d	12 h* AND ensure APTT normal	Safety of higher doses not established. Assess individual risks and benefits	12 h* AND ensure APTT normal	1 h
Unfractionated heparin subcutaneous	therapeutic (full dose), > 20000 IU/d s/c	24 h* AND ensure APTT normal	Safety of higher doses not established. Assess individual risks and benefits	24 h* AND ensure APTT normal	1 h
Unfractionated heparin intravenous (IV) infusion	therapeutic (full dose), IV	Discontinue infusion for 4-6 h AND ensure normal APTT	1 h (Wait 24 h if bloody tap)	4-6 h	1-2 h
LMWH (Low molecular weight heparin) Eg: enoxaparin (Clexane®), dalteparin (Fragmin®) subcutaneous	prophylactic (dosing adjusted to renal function see Table 5.3)	12 h	12 h	12 h	4 h
LMWH	therapeutic (full dose)	24 h	12 h	24 h	4 h**
Fondaparinux (Arixtra®) subcutaneous	prophylactic	2 d (longer if higher doses used)	CONTRAINDICATED	CONTRAINDICATED	6 h
Warfarin	therapeutic (full dose)	5 d AND ensure INR < 1.5	CONTRAINDICATED	INR < 1.5	4 h
Apixaban (Eliquis®)	2.5mg BD or 5mg BD				
CrCl > 50 ml/min		3 d	CONTRAINDICATED	CONTRAINDICATED	At least 6 h
CrCl 25-50 ml/min		3 d	CONTRAINDICATED	CONTRAINDICATED	At least 6 h
CrCl < 25 ml/min		Seek specialist advice with haematologist. Drug levels can be measured to assist in decision making.	CONTRAINDICATED	CONTRAINDICATED	CONTRAINDICATED
Rivaroxaban (Xarelto®)	15 or 20mg daily				
CrCl > 50 ml/min		3 d	CONTRAINDICATED	CONTRAINDICATED	At least 6 h
CrCl 30-50 ml/min		3 d	CONTRAINDICATED	CONTRAINDICATED	At least 6 h
CrCl < 30 ml/min		Seek specialist advice with haematologist. Drug levels can be measured to assist in decision making.	CONTRAINDICATED	CONTRAINDICATED	CONTRAINDICATED
Dabigatran (Pradaxa®)					
CrCl > 80 ml/min		3 d	CONTRAINDICATED	CONTRAINDICATED	At least 6 h
CrCl 50-80 ml/min		4 d	CONTRAINDICATED	CONTRAINDICATED	At least 6 h
CrCl 30-49 ml/min		5 d	CONTRAINDICATED	CONTRAINDICATED	At least 6 h
CrCl < 30 ml/min		Seek specialist advice with haematologist. Drug levels can be measured to assist in decision making.	CONTRAINDICATED	CONTRAINDICATED	CONTRAINDICATED
Thrombolytic therapy eg: tissue plasminogen activator tpA		At least 48 h and ensure normal coagulation studies	CONTRAINDICATED	CONTRAINDICATED	If thrombolytics required, check that no lumbar puncture, epidural or spinal anaesthesia in the preceding 10 d

Medication	Dosing	Before epidural insertion	Whilst epidural catheter in place	Prior to epidural catheter removal	After epidural catheter removal
Non-steroidal anti-inflammatory drugs (NSAIDS)	Interruption not required unless combined with other antithrombotics	COX-2 agents have minimal effect on platelet function			
Aspirin (COX inhibitor)	Interruption not required unless combined with other antithrombotics				
Thienopyridines (Inhibition of ADP-induced platelet aggregation)					
Ticlopidine		10 d	May be used without loading dose		6 h if loading dose given, or post-operatively 24 h
Clopidogrel		5-7 d	May be used without loading dose		6 h if loading dose given, or post-operatively 24 h
Prasugrel		7-10 d	CONTRAINDICATED due to rapid onset of action	CONTRAINDICATED	6 h if loading dose given, or post-operatively 24 h
Direct and reversible P2Y12 receptor inhibitors: Ticagrelor		5-7 d	CONTRAINDICATED due to rapid onset of action	CONTRAINDICATED	6 h if loading dose given, or post-operatively 24 h
Direct and reversible P2Y12 receptor inhibitors: Cangrelor		3 h	CONTRAINDICATED due to rapid onset of action	CONTRAINDICATED	8 h
Glycoprotein IIb/IIIa Inhibitors: Abciximab		24-48 h	CONTRAINDICATED due to rapid onset of action	CONTRAINDICATED	4 weeks post-surgery, if emergent use required minimise sensory and motor block to facilitate assessment of neurological function
Eptifibatide, Tirofiban		4-8 h	CONTRAINDICATED due to rapid onset of action	CONTRAINDICATED	4 weeks post-surgery, if emergent use required minimise sensory and motor block to facilitate assessment of neurological function
Selective inhibition of PDE IIIA: Cilostazol		2 d	CONTRAINDICATED	CONTRAINDICATED	6 h post catheter removal or post-operatively 24 h
Dipyridamole	Potential risk in combination with aspirin	24 h (for extended release formulations)			
Selective serotonin re-uptake inhibitors (SSRIs) - antidepressants with inhibition of serotonin-mediated plateletr aggregation	Low risk unless associated with other patient specific risk factors or combined with other antithrombotics	Consider discontinuation or switch to alternative agent			

** SC UFH - delayed excretion with higher doses administered by this route*
*** For post-operative therapeutic LMWH dosing, commencement should be at least 24 h post-surgery with low bleeding risk and 48-72 h post-surgery with high-bleeding risk*

References:
Horlocker 2018, Narouze 2018, Gogarten 2010, Leffert 2018, Douketis 2019

Table 5.3 | Dosing of prophylactic LMWH in renal impairment

Normal dosing (CrCl greater than 30 mL / min)	Renal impairment (CrCl =10 to 30 mL / min)	Renal impairment (CrCl less than 10 mL / min)
TWICE a day regimen: Enoxaparin (Clexane®): 1 mg / kg TWICE a day (max. 150 mg TWICE a day Dalteparin (Fragmin®): 100 units / kg / TWICE a day (max. 15,000 units TWICE a day)	Enoxaparin (Clexane®)*: 1 mg / kg ONCE daily Dalteparin (Fragmin®)*: 100 units / kg ONCEdaily	Use unfractionated heparin
ONCE daily regimen: Enoxaparin (Clexane®): 1.5 mg / kg ONCE daily (max. 180 mg ONCE daily) Dalteparin (Fragmin®): 200 units / kg ONCE daily (max. 25,000 units ONCE daily)		

*The determination of an tiXa levels is recommended for optimal dosing
(*adapted from Sanofi-Aventis Australia 2018; Pfizer Australia 2019*)

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6

Patient-controlled analgesia

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6.0 | Patient-controlled analgesia

Patient-controlled analgesia (PCA) refers to all methods of pain relief that allow a patient to self-administer small doses of an analgesic agent as required. Most often, the term PCA refers to programmable infusion pumps that deliver opioid medications IV. However, many other methods and routes of delivery using opioids as well as other analgesic agents have been described (SC, epidural, IT, SL, IN, oral, pulmonary, and TD). In addition to treating postoperative pain, PCA is used for pain following trauma and with cancer.

For epidural PCA see Section 5.6.3; for PCA use in labour see Section 9.1.3.1 and in children see Sections 10.5.2 to 10.5.4.

6.1 | Efficacy of intravenous PCA

6.1.1 | Analgesia, patient preference and outcomes

An updated Cochrane review is published (McNicol 2015 **Level I** [Cochrane], 49 RCTs, n=3,412); this includes only four RCTs since 2005, which may reflect the adoption of PCA into usual clinical practice. The meta-analysis compares IV PCA using full mu-opioids with intermittent full mu-opioids (usually IM morphine), and also includes the use of supplemental NSAIDs or paracetamol. The most frequently used opioid is morphine (33/49 RCTs); the most common bolus size is 1 mg and the most common lockout intervals are 5 to 10 min. There was a lack of head-to-head trials comparing different opioids via PCA so no comparison of opioids could be made. IV opioid by PCA for treatment of postoperative pain provides better analgesia than conventional (IM, SC) opioid regimens, although the magnitude of the difference in analgesia is small (MD 9.7/100; 95%CI 12.5 to 7 [0 to 48 h]). PCA use increases opioid consumption at 0 to 24 h (7 MME; 95%CI 1.4 to 13) and 25 to 48 h (5 MME; 95%CI 3 to 8). PCA improves number of patients satisfied (80% vs 61) (RR 1.32; 95%CI 1.12 to 1.53) (11 RCTs, n= 547) and satisfaction scores (SMD 0.55; 95%CI 0.13 to 0.97) (7 RCTs, n=427). This benefit may relate to the increased autonomy that PCA confers. None of the studies measured 'readiness for discharge'. LOS does not differ (10 RCTs), but this outcome may have been dependent on other factors. Serious adverse event rates (including death, wound infections, atelectasis and adhesions) do not differ between the two groups (19 RCTs, n=1,284). However, as death is a rare event, larger patient numbers are required to reliably evaluate this outcome. Other adverse events occur similarly: sedation (15 vs 16%), respiratory depression (Sa02 ≤ 90% or RR <10/min or need for naloxone) (2.3 vs 2%) and nausea and/or vomiting (30 vs 32%), while pruritus was more frequent in the PCA group (15 vs 8%) (RR 1.8; 95%CI 1.1 to 2.8).

In an ED setting, IV PCA was as effective as nurse-administered IV bolus doses of opioid (Evans 2005 **Level II**, n=86, JS 3). In two other RCTs in the ED setting, PCA morphine provided more effective analgesia with more rapid onset and higher patient satisfaction than nurse-administered IV morphine (Rahman 2012 **Level II**, n=96, JS 3; Birnbaum 2012 **Level II**, n=211, JS 3).

Other information obtained from published RCTs as well as cohort studies, case-controlled studies and audit reports suggests that IV PCA may be appreciably more effective than intermittent IM opioid analgesia in a "real world" clinical setting; patients given IM opioid analgesia were more than twice as likely to experience moderate to severe pain and severe pain than those given PCA (Dolin 2002 **Level IV SR**, 165 studies, n≈20,000).

In settings where there are high nurse:patient ratios and where it might be easier to provide analgesia truly on-demand, conventional forms of opioid administration may be as effective as IV PCA. A comparison of PCA vs nurse-administered analgesia following cardiac surgery found no difference in analgesia at 24 h (a period when nursing attention is likely to be higher) but significantly better pain relief with PCA at 48 h (Bainbridge 2006 **Level I**, 10 RCTs, n=666).

The enormous variability in PCA parameters (bolus doses, lockout intervals and maximum permitted cumulative doses) used in many studies indicates uncertainty as to the ideal PCA program and may limit the flexibility, and thus the efficacy, of the technique. Individual PCA prescriptions may need to be adjusted if patients are to receive the maximal benefit (Macintyre 2015 **NR**; Macintyre 2008 **NR**; Macintyre 2005 **NR**).

A number of studies have shown that PCA provides less effective pain relief vs epidural analgesia. See Section 5.6.1.1 .

6.2 | Cost of PCA

The use of any analgesic technique, even if it is known to provide more effective pain relief, requires consideration of the cost involved. There is limited data on the economic assessment of PCA vs conventional opioid analgesic techniques; information that is available often does not include the full scope of costs (eg cost of adverse effects or failure of an analgesic technique, as well as the more obvious costs of pumps, disposables and nursing time). However, in general, PCA comes at a higher cost because of the equipment, consumables and medicine preparation; nursing time needed is much less (Chang 2004 **Level II**, n=125, JS 3; Choiniere 1998 **Level II**, n=126, JS 3; Rittenhouse 1999 **Level III-2**; Jacox 1997 **NR**). PCA was more cost-effective than epidural analgesia after major abdominal surgery (LOS and morbidity excluded) (Bartha 2006 **Level III-2**, n=644). In a subsequent assessment, PCA costs were estimated by analysis of a large administrative database covering 500 USA hospitals (Palmer 2014 **Level III-3**, n=11,805,513). The direct and indirect cost estimates (US$ in 2012) were assessed for the first 48 h after major surgery (TKA, THA and open abdominal procedures). The cost estimates range from US$196 to 243 per patient. Further estimates, adding in the costs of adverse effects of PCA programming errors, phlebitis and bacteraemia due to IV access, increased the costs to US$342 to 389 per patient. See also Section 3.3.

6.3 | Medicines used for parenteral PCA

6.3.1 | Opioids

In general, there is little evidence, on a population basis, to suggest that there are any major differences in efficacy or the incidence of adverse effects between morphine and other opioids commonly used in PCA, although the results of individual studies are inconsistent (for more details see 6.3.1.10 below). Most studies are not powered adequately to make conclusions about comparative safety, especially for respiratory depression.

On an individual patient basis, one opioid may be better tolerated than another and a change to an alternative opioid may be beneficial if the patient is experiencing intolerable adverse effects (Woodhouse 1999 **Level II**, n=82 [cross over], JS 4).

6.3.1.1 | Morphine

Morphine is still a commonly used opioid for IV PCA (Palmer 2014 **Level III-2**, n=11,805,513). Compared with other opioids, morphine has a long equilibration half-life between plasma and the CNS effect site (2 to 3 h) (Aubrun 2012 **NR**; Lötsch 2005 **NR**). Furthermore, morphine has an active metabolite, M6G, which has opioid effects, with an equilibration half-life of 7 h and a long elimination half-life (Lötsch 2005 **NR**). Simulated peak effect-site concentration for morphine occurs 8 to 24 h after the commencement of PCA (Sam 2011 **Level III-3 PK**, n=10). These pharmacokinetic features may make morphine less suitable for IV PCA use than other opioids. Limited clinical data suggest that morphine may have a higher incidence of sedation and respiratory depression than fentanyl (Hutchison 2006 **Level III-2**, n=241).

6.3.1.2 | Fentanyl

In general, there is limited evidence to show a difference between morphine and fentanyl in terms of pain relief or the incidence of most adverse effects (Woodhouse 1996 **Level II**, n=50, JS 5; Howell 1995 **Level II**, n=37, JS 3); pruritus was more common with morphine (Woodhouse 1996 **Level II**, n=50, JS 5). A retrospective cohort study of patients having hip or knee surgery found those receiving PCA fentanyl, when compared with morphine or hydromorphone, had lower pain scores and fewer opioid-related adverse effects (PONV, sedation, pruritus or urinary retention) (Hutchison 2006 **Level III-2**, n=241). Fentanyl PCA vs morphine PCA after cardiac surgery had a lower incidence of nausea (32 vs 52%) (Gurbet 2004 **Level II**, n=75, JS 3).

6.3.1.3 | Tramadol

Tramadol by IV PCA has similar analgesic efficacy vs other opioids by IV PCA, mainly vs morphine (7 RCTs) (Murphy 2010 **Level I**, 12 RCTs, n=782). However, the adverse-effect profile is different with the tramadol group experiencing more PONV (OR 1.52; 95%CI 1.07 to 2.14) but less pruritus (OR 0.43; 95%CI 0.19 to 0.98). There was no difference in sedation or fatigue. Data were insufficient to assess safety**.** Tramadol also has a lower risk of respiratory depression and less effect on gastrointestinal motor function compared with other opioids. See also Section 4.1.1.2.

6.3.1.4 | Hydromorphone

There is limited data examining the use of hydromorphone when delivered by IV PCA. A survey of a large USA inpatient database found that hydromorphone was the second most commonly used opioid for PCA after morphine (Palmer 2014 **Level IV**, n=11,805,513). When compared with morphine in patients having general surgery, there was no difference in adverse effects, pain relief or satisfaction (Hong 2008 **Level II**, n=50, JS 4). Hydromorphone and morphine IV PCA had similar rates of opioid-induced adverse effects, with fentanyl having the lowest in a retrospective comparison of patients after hip or knee surgery (Hutchison 2006 **Level III-2**, n=254). In a comparison of IV PCA morphine with hydromorphone in patients having open abdominal surgery, analgesia was equivalent and there were similar adverse effects (Rapp 1996 **Level II**, n=61, JS 3). The morphine group had less cognitive impairment and the hydromorphone group had better mood. A study of patients having IV PCA for oral mucositis pain after bone marrow transplantation found that hydromorphone vs morphine was equally effective for analgesia but hydromorphone had more frequent adverse effects (Coda 1997 **Level II**, n=119, JS 4). Comparing PCA hydromorphone with PCA sufentanil in patients having surgery for colorectal cancer found that postoperative mood assessment differed, with ‘anger’ being lower in the hydromorphone

group (Yang 2018 **Level II**, n=80, JS 5). This may be due to differences in opioid receptor type affinity.

Safety issues have occurred due to confusion about the name of the medicine and its high potency (5 times that of morphine) (NSW Health 2011 **GL**). See also Section 9.5.5.

6.3.1.5 | Oxycodone

Oxycodone, unlike morphine, has a rapid equilibration with the CNS which might make it more suited to PCA use (Sadiq 2013 **BS** & **PK** [rodent]). Oxycodone IV PCA vs morphine IV PCA resulted in similar pain relief and adverse effects during the first 24 h after surgery (breast or spinal) (Silvasti 1998 **Level II,** n=50, JS 3). The dose requirements were similar. After laparoscopic hysterectomy, IV PCA oxycodone dose requirements were lower than with morphine (Lenz 2009 **Level II**, n=91, JS 4) with less sedation in the oxycodone group; pain scores were lower but only in the first h after surgery and thereafter were similar. After maxillofacial surgery, IV PCA oxycodone vs IV PCA tramadol provided equivalent analgesia (Silvasti 1999 **Level II**, n=54, JS 3).

In patients having laparoscopic gynaecological surgery, IV PCA oxycodone and PCA fentanyl produced equivalent analgesia and satisfaction. Dizziness was more common in the oxycodone group, whilst nausea and vomiting were the same (Park 2015 **Level II**, n=74, JS 4). In laparoscopic hysterectomy patients (who received ketorolac and ramosetron), IV PCA oxycodone improved pain relief vs PCA fentanyl, but increased adverse effects of PONV, dizziness, and drowsiness (Kim 2017 **Level II**, n=130, JS 5).

Trials to date are not adequate in sample size to assess if IV PCA oxycodone confers superiority over other opioids.

6.3.1.6 | Pethidine

Compared with morphine, IV PCA pethidine (meperidine) may lead to less effective pain relief on movement (Plummer 1997 **Level II**, n=102, JS 4; Sinatra 1989b **Level II**, n=75, JS 4; Bahar 1985 **Level II**, n=48, JS 1), no difference in nausea and vomiting (Plummer 1997 **Level II**, n=102, JS 4; Woodhouse 1996 **Level II**, n=50, JS 5; Stanley 1996 **Level II**, n=40, JS 5; Bahar 1985 **Level II**, n=48, JS 1) and less sedation (Sinatra 1989a **Level II**, n=75, JS 4) and pruritus (Woodhouse 1996 **Level II**, n=50, JS 5; Sinatra 1989b **Level II**, n=75, JS 4). IV PCA pethidine may cause more cognitive impairment than morphine (Plummer 1997 **Level II**, n=102, JS 4). Pethidine has a neurotoxic metabolite (norpethidine) that can accumulate during PCA administration and can cause adverse effects (Simopoulos 2002 **Level IV**, n=355; Stone 1993 **Level IV**, n=3; McHugh 1999 **NR**).

6.3.1.7 | Methadone

Methadone by IV PCA, in comparison to morphine, provided more effective pain relief at rest and during movement for the first 24 h after surgery, with no difference in adverse effects (Neto 2014 **Level II,** n=34 [trial discontinued prematurely], JS 4). It should be noted, that the pharmacokinetics of methadone are complex (and are not suited to IV PCA use in acute pain management) (Weschules 2008 **NR**). (See also Section 4.3.1.2)

6.3.1.8 | Other opioids

Remifentanil IV PCA provided at least equivalent analgesia vs morphine or fentanyl PCA and may be associated with less nausea and vomiting (Kucukemre 2005 **Level II**, n=69, JS 4; Gurbet 2004 **Level II**, n=75, JS 3). See also Section 9.1.3.1 for discussion of use of IV PCA remifentanil during labour.

6.3.1.9 | Opioid combinations

The combination of two opioids in the PCA syringe has been investigated.

There was no difference in pain scores and adverse effects between fentanyl/morphine and fentanyl by PCA, apart from slightly less nausea with the combination (Friedman 2008 **Level II**, n=64, JS 5).

Beneficial effects on pain relief and the incidence of pruritus in a comparison of morphine, nalbuphine and varying combinations of the two medicines were dependent on the ratio of medicines used (Yeh 2007 **Level II**, n=311, JS 5). The combination, when compared to morphine alone, provided improved analgesia and reduced nausea.

The combination of alfentanil/morphine IV PCA resulted in no differences in pain relief or adverse effects vs morphine alone, although patients who received alfentanil/morphine rated speed of onset and adequacy of analgesia as better (Ngan Kee 1999 **Level II**, n=80, JS 5). There was no improvement in pain-related sleep disturbance with this combination vs fentanyl alone but analgesia, both at rest and movement, was better in the first 24 h after surgery (Lee 2013 **Level II**, n=212, JS 5).

Compared with IV PCA tramadol alone, remifentanil added to tramadol improved pain relief but increased total opioid doses used (Unlugenc 2008 **Level II**, n=62, JS 4).

6.3.2 | Adverse effects of PCA opioids

As noted in Section 6.1.1 above, meta-analyses and individual studies have shown that, in general, the risk of adverse effects is similar for all opioids administered by PCA, regardless of the opioid used. However, individual patients may be intolerant of specific opioids but tolerant of others (Woodhouse 1999 **Level II**, n=82 [cross over], JS 4). In a network meta-analysis, adverse effects occur at differing frequencies for the various opioids at equianalgesic doses (Dinges 2019 **Level I** [NMA], 63 RCTs, n unspecified). Results are reported as a relative risk (with morphine as the comparator):

- Nausea and vomiting are most frequent with buprenorphine (RR 1.37; 95%CI 1.05 to 1.8) and least with fentanyl (RR 0.82; 95%CI 0.67 to 1.0). Other opioids are not different to morphine (39 RCTs, n=4,614);
- Pruritus is the most frequent with morphine, and the least frequent with methadone (RR 0.17; 95%CI 0.03 to 0.90) and pethidine (RR 0.47; 95%CI 0.25 to 0.87). Other opioids (including oxycodone, tramadol, fentanyl, hydromorphone and remifentanil) are not significantly different to morphine (39 RCTs, n=3,480);
- Sedation is least frequent with fentanyl, oxymorphone and pethidine. Other opioids are not different to morphine (31 RCTs, n=1,528);
- Satisfaction is highest with oxycodone, alfentanil, remifentanil, fentanyl, and pethidine. Tramadol has the least satisfaction. Other opioids are not different to morphine (17 RCTs, n=1,476).

OIVI is rare with 22 cases reported (n=2,452); sufentanil, alfentanil, remifentanil and morphine have the highest reported rates here.

Two reviews of published RCTs, cohort studies, case-controlled studies and audits reported the following incidences associated with IV PCA use: respiratory depression 1.2 to 11.5% (depending on whether respiratory rate or oxygen saturation were used as indicators), nausea 32%, vomiting 20.7% and pruritus 13.8% (Dolin 2005 **Level IV SR**, 183 studies [PONV] & 89 studies [sedation] & 166 studies [pruritus], n≈100,000; Cashman 2004 **Level IV SR**, 165 studies, n≈20,000). Excessive sedation was not used as an indicator of respiratory depression in any of the studies included in these reviews (see importance of sedation score in Section 4.3.1.4).

The incidence of respiratory depression (<10 breaths/min) with PCA morphine was 0.06% and no patient required naloxone (Cheung 2009 **Level IV**, n=5,137). The incidence of nausea was 47.4% and vomiting was 18.5%; these were most common in female patients and those having gynaecological surgery. The incidence of pruritus was 8%.

In 1.86% of patients who received PCA for postoperative pain relief, respiratory depression (defined as a respiratory rate of <10 breaths/min and/or a sedation score of 2; defined as "asleep but easily roused") was identified; of these 13 patients all had respiratory rates of <10 breaths/min and 11 also had sedation scores of 2 (Shapiro 2005 **Level IV**, n=700).

Impact of adjuvants on IV PCA adverse effects

The combination of NSAIDs with IV PCA morphine reduces adverse effects vs IV PCA morphine alone:

- PONV is reduced by 30% (OR 0.70; 95%CI 0.53 to 0.88) (Maund 2011 **Level I**, 60 RCTs, n unspecified);
- Sedation is reduced by 29%, while respiratory depression, pruritus and urinary retention are not reduced (Marret 2005 **Level I**, 22 RCTs, n=2,307).

These benefits are most likely due to the opioid-sparing effect of concurrent NSAIDs, rather than a direct effect of NSAIDs themselves. Similar beneficial effects have also been found for the addition of IV ketamine via various regimens (Assouline 2016 **Level I** [PRISMA], 19 RCTS, n=1,453; Wang 2016 **Level I** [PRISMA], 36 RCTs, n=2,502) (12 RCTs overlap), gabapentin (Fabritius 2016 **Level I** [PRISMA], 132 RCTs, n=9,498), pregabalin (Fabritius 2017 **Level I** [PRISMA], 97 RCT, n=7,201), IV lidocaine (Weibel 2018 **Level I** [Cochrane], 68 RCTs, n=4,525) and the alpha-2 agonists clonidine (Sanchez Munoz 2017 **Level I** [PRISMA], 57 RCTs, n=14,790) and dexmedetomidine by various administration regimens (Wang 2018 **Level I** [PRISMA], 40 RCTs, n=2,401).

6.3.3 | Adjuvant medicines

Discussion of adjuvant medicines in this section will be confined to those added to the PCA opioid solution. For additional information see Chapter 4.

6.3.3.1 | Antiemetics

Droperidol added to the PCA morphine solution is effective in preventing nausea (NNT 2.7; 95%CI 1.8 to 5.2) and vomiting (NNT 3.1; 95%CI 2.3 to 4.8) with no apparent dose-responsiveness (Tramer 1999 **Level I**, 6 RCTs [droperidol], n=642). Adverse effects were not increased when the dose of droperidol was <4 mg/d. However, in a subsequent comparison of 0.5 mg, 1.5 mg and 5 mg droperidol added to 100 mg PCA morphine, the smallest dose had no significant antiemetic effect and the 1.5 mg dose was effective against nausea (NNT 6.3; 95%CI 3.3 to 100) but not vomiting (Culebras 2003 **Level II**, n=340, JS 4). The 5 mg dose significantly reduced both nausea and vomiting but at the cost of unacceptable sedation (NNH 6.4; 95%CI 4.1 to 15), which was not seen at the other doses. The 1.5 mg and 5 mg doses also reduced pruritus. There was no difference in dysphoric effects. In another RCT, droperidol 5 mg added to morphine 100 mg by PCA resulted in morphine-sparing and, in the first 24 h after surgery, reduced the frequency of PONV (Lo 2005 **Level II**, n=179, JS 5). While, droperidol given as a single dose at the end of surgery was as effective as adding droperidol to PCA morphine (Gan 1995 **Level II**, n=82, JS 3). The cost-benefit and risk-benefit of the routine addition of droperidol to PCA opioids must therefore be considered, because all patients receive the medication when not all will need it and some patients might receive inappropriately high doses of droperidol.

Evidence of benefit from the addition of $5HT_3$ antagonists to IV PCA is unclear. Ondansetron, given both as a bolus at the end of surgery and mixed with morphine in the PCA solution, reduced the incidence of nausea and the need for additional antiemetics but not the patients' perception of their overall satisfaction with care (Cherian 2001 **Level II**, n=81, JS 4). Adding ondansetron to PCA opioids reduces nausea and/or vomiting (NNT 2.9; 95%CI 2.1 to 4.7) (Tramer 1999 **Level I**, 2 RCTs [ondansetron], n=184). A later study showed that ondansetron given as an initial dose of 4 mg followed by 0.2 mg/1 mg morphine PCA morphine could reduce nausea and vomiting; although pain scores were higher (Boonmak 2007 **Level II**, n=160, JS4). The combination of ondansetron plus prochlorperazine to IV PCA morphine was more effective than ondansetron alone (Jellish 2009 **Level II**, n=150, JS 4).

Dexamethasone 8 mg given at the start of surgery reduced the incidence of severe nausea and vomiting only vs ondansetron at the end of surgery in patients receiving PCA fentanyl with added ondansetron (12 mg added to 2 mg fentanyl) (Song 2011 **Level II**, n=130, JS 4). The addition of midazolam to PCA morphine had a similar antiemetic effect to that of ondansetron but was associated with an increase in mild sedation (Huh 2010 **Level II**, n=90, JS 3).

6.3.3.2 | Ketamine

Two systematic reviews evaluated the effect of peri- and postoperative ketamine (sub-anaesthetic doses) coadministered as an adjuvant to PCA (morphine 15 RCTs and 1 RCT each in adults for tramadol & fentanyl and in adolescents for fentanyl & hydromorphone) (Assouline 2016 **Level I** [PRISMA], 19 RCTs, n=1,453) and to PCA morphine (33 RCTs, n=2,374) or PCA hydromorphone (3 RCTs, n= 128) (Wang 2016 **Level I** [PRISMA], 36 RCTs, n=2,502) (12 RCTs overlap).

Adding ketamine to an opioid in the PCA pump in various ratios has benefits to pain scores at rest at 24 h (WMD 21.1/100; 98%CI 21.8 to 20.39) (9 RCTs, n=595) and opioid consumption (-28%) (7 RCTs, n=495) and PONV (-44%) (7 RCTs, n=435) (Assouline 2016 **Level I** [PRISMA], 19 RCTs, n=1,453). Respiratory depression (RR 0.31; 98%CI 0.06 to 1.51) (9 RCTs, n=871) and hallucinations (OR 1.16; 98%CI 0.47 to 2.79) (7 RCTs, n=690) are not increased. A parallel meta-analysis on ketamine added to morphine or hydromorphone PCA confirms these results (Wang 2016 **Level I** [PRISMA], 36 RCTs, n=2,502) (12 RCTs overlap). There was no dose-response effect found and the optimum analgesic/sub-anaesthetic dose is uncertain.

IV ketamine PCA vs hydromorphone PCA reduced supplemental analgesia and need for supplemental oxygenation, but was associated with more hallucinations (Takieddine 2018 **Level II**, n=20, JS 5).

The stability and compatibility of mixtures of tramadol with ketamine in polyolefin bags were satisfactory over a test period of 14 d at 4° and 25°C (Gu 2015 **BS**).

For more details see also Section 4.6.

6.3.3.3 | Naloxone

There was no analgesic benefit of adding naloxone to the PCA morphine solution (Cepeda 2004 **Level II**, n=265, JS 5; Sartain 2003 **Level II**, n=96, JS 5; Cepeda 2002 **Level II**, n=166, JS 5); with "ultra-low doses" only (naloxone 0.6 mcg per morphine 1 mg), the incidence of nausea and pruritus was decreased (Cepeda 2004 **Level II**, n=265, JS 5).

6.3.3.4 | Other adjuvants

Ketorolac added to morphine (Chen 2009 **Level II**, n=102, JS 5; Chen 2005b **Level II**, n=79, JS 5) or tramadol (Lepri 2006 **Level II**, n=60, JS 3) by PCA did not improve pain relief or alter the incidence

of adverse effects; however, it was opioid-sparing and led to an earlier return of bowel function after colorectal surgery (Chen 2009 **Level II**, n=102, JS 5).

The addition of lidocaine to morphine conferred no benefit in terms of pain relief or adverse effects (Cepeda 1996 **Level II**, n=195, JS 5).

The addition of clonidine to IV PCA morphine resulted in significantly better pain relief for the first 12 h only, and less nausea and vomiting vs morphine alone; there was no reduction in morphine requirements (Jeffs 2002 **Level II**, n=60, JS 5).

Dexmedetomidine/morphine by IV PCA resulted in better pain relief (at rest and movement), significant opioid-sparing (29%) and a lower incidence of nausea vs IV PCA morphine alone (Lin 2009 **Level II,** n=100, JS 5). Adverse cardiovascular effects, sedation or respiratory depression were not increased in the dexmedetomidine/morphine group. Dexmedetomidine/sufentanil IV PCA sufentanil IV PCA alone in patients having elective abdominal surgery (laparoscopic and open) improved pain relief at rest and with movement, nausea (25% vs 12.5%) and vomiting (18.2% vs 6.25%) (Gao 2018 **Level II**, n=210, JS 4).

Magnesium added to morphine was opioid-sparing and led to better pain relief (Unlugenc 2003 **Level II**, n=90, JS 3); added to tramadol, it was opioid-sparing but only provided better pain relief for the first 2 h (Unlugenc 2002 **Level II**, n=66, JS 4).

Midazolam/morphine IV PCA after spinal surgery reduced anxiety and provided a small reduction in the pattern of morphine consumption over time vs IV PCA morphine (Day 2014 **Level II,** n=29, JS 4). Sedation scores were not reported.

The addition of nalbuphine to PCA morphine resulted in reduced pruritus without affecting pain relief (Yeh 2008 **Level II**, n=311, JS 5).

6.4 | Program parameters for IV PCA

6.4.1 | Bolus dose

While the optimally sized bolus dose should provide good pain relief with minimal adverse effects, there are only limited data available concerning the effects of various dose sizes. In patients prescribed 0.5 mg, 1 mg and 2 mg bolus doses of morphine, most of those who were prescribed 0.5 mg were unable to achieve adequate analgesia, while a high incidence of respiratory depression was reported in those who received 2 mg (Owen 1989a **Level II**, n=21, JS 3). It was concluded that the optimal PCA bolus dose for morphine was therefore 1 mg.

Similarly, in patients prescribed 20, 40 or 60 mcg bolus doses of fentanyl, the larger dose was associated with an increased risk of respiratory depression and a conclusion was made that the optimal dose of fentanyl for use in PCA was 40 mcg (Camu 1998 **Level II**, n=150, JS 4). However in this study, each dose was infused over 10 min, which could alter the effect of that dose.

Four different demand doses of fentanyl (10, 20, 30 and 40 mcg) were assessed for the management of pain during changes of burns dressings. Pain relief was significantly better with the 30 mcg and 40 mcg doses; no patient became sedated or experienced nausea and vomiting (Prakash 2004 **Level II**, n=60, JS 2).

Rigid adherence to an "optimal" dose may not, however, lead to the best pain relief for all patients. If the prescribed dose is not "optimal" and not too small, the patient will be able to compensate to some degree by changing their demand rate. However, they will only compensate to a certain degree. Even if uncomfortable, patients may only average four demands/h, even though they could press the PCA button more frequently (Owen 1989a **Level II**, n=21, JS 3).

Initial orders for bolus doses should take into account factors such as a history of prior opioid use (see Section 9.7) and patient age (Macintyre 2015 **NR**; Macintyre 2008 **NR**). PCA morphine requirements are known to decrease as patient age increases (Gagliese 2008 **Level IV**, n=246; Macintyre 1996 **Level IV**, n=1,010) (see also Section 9.2.4.2). Subsequent bolus doses may require adjustment according to patient pain reports or the onset of any adverse effects.

The number of demands a patient makes, including the number of "unsuccessful" demands, is often used as an indication that the patient is in pain and as a guide to adjusting the size of the bolus dose. However, there may be a number of reasons for a high demand rate other than pain. For example, excessive PCA demands may correlate with anxiety, poor perioperative adaptation to surgery involving avoidance behaviour and intrusive thoughts, as well as high pain scores (Katz 2008 **Level IV**, n=117). See also Section 1.2.2 for additional information on the relationship between pain relief and psychological factors in PCA.

6.4.2 | Lockout interval

The lockout interval is a safety mechanism that limits the frequency of doses delivered to the patient. For maximum safety, it should be long enough to allow the patient to feel the full effect of one opioid dose before another dose can be delivered. However, if it is too long the effectiveness of PCA could be reduced. There were no differences in pain relief, adverse effects or anxiety when lockout intervals of 7 or 11 min for morphine and 5 or 8 min for fentanyl were used (Ginsberg 1995 **Level II**, n=78, JS 4).

6.4.3 | Concurrent background (continuous) infusions

When a background infusion is used, opioid will continue to be delivered regardless of the patient's sedation level or respiratory status. The addition of a continuous background infusion significantly increases the risk of respiratory depression (OR 4.68; 95%CI 1.20 to 18.21) (George 2010 **Level I** [Cochrane], 14 RCTs, n=769); in 12 of the 14 RCTs, morphine was used. The risk was increased in adults in comparison to children (OR 10.2; 95%CI 3 to 35) (11 adult, 1 mixed, 2 paediatric). The definition of respiratory depression in this meta-analysis was either respiratory rate ≤10, saturation ≤90% or $PaCO_2$ ≥50.

There is no good evidence to show that the addition of a background infusion to IV PCA improves pain relief or sleep or reduces the number of demands (Dal 2003 **Level II**, n=35, JS 3; Parker 1992 **Level II**, n=156, JS 2; Parker 1991 **Level II**, n=230, JS 3; Owen 1989b **Level II**, n=22, JS 2). In adults, the routine use of a background infusion is therefore cautioned against, although it may be useful in opioid-tolerant patients (see Section 9.7).

Limited data found that the use of time-scheduled decremental continuous infusion of opioid added to the PCA program provided better pain relief than bolus only PCA in women having laparoscopic gynaecological surgery (Zhu 2019 **Level II**, n=90, JS 5; Kim 2013 **Level II**, n=99, JS 4). The use of PCA with a variable rate feedback background infusion in patients having spinal fusion surgery showed equivalent analgesia, and less total opioid dose than PCA with a constant rate background infusion (Lee 2019 **Level II**, n=78, JS 5). Estimating the risk of respiratory depression with these techniques from small studies is not possible.

6.4.4 | Dose limits

Limits to the maximum amount of opioid that can be delivered over a certain period (commonly 1 or 4 h) can be programmed into most PCA machines. There is no good evidence of any benefit that can be attributed to these limits (Macintyre 2015 **NR**).

6.4.5 | Loading dose

There is enormous variation in the amount of opioid a patient may need as a "loading dose", and there is no good evidence of any benefit that can be attributed to the use of the loading dose feature that can be programmed into PCA machines. PCA is essentially a maintenance therapy; therefore adequate pain relief should be established before PCA is started by administration of individually titrated loading doses (Macintyre 2015 **NR**; Macintyre 2008 **NR**). IV opioid loading improved the analgesic efficacy of subsequent oral and PCA opioid therapy in the treatment of acute sickle cell pain (Rees 2003 **GL**).

When administering IV loading doses of opioids, lipophilic medicines such as fentanyl are more appropriate than morphine for titrating analgesia because they equilibrate more quickly with the brain. While plasma and CNS fentanyl levels equilibrate within minutes, morphine takes many hours, which can lead to OIVI occurring well after a patient has been deemed "comfortable" and discharged from a high acuity area to a lower level area (eg PACU or ED to the ward) (Aubrun 2012 **NR**; Lötsch 2005 **NR**).

6.5 | Efficacy of PCA using other systemic routes of administration

6.5.1 | Subcutaneous PCA

Data on the effectiveness of SC PCA vs IV PCA are variable and inconsistent. Both similar (Bell 2007 **Level II**, n=130, JS 3; Munro 1998 **Level II**, n=80, JS 3; White 1990 **Level II**, n=24, JS 5; Urquhart 1988 **Level II**, n=30, JS 1) and significantly better (Keita 2003 **Level II**, n=40, JS 3; Dawson 1999 **Level II**, n=100, JS 2) pain relief has been reported, as well as the same (Keita 2003 **Level II**, n=40, JS 3; Dawson 1999 **Level II**, n=100, JS 2; Munro 1998 **Level II**, n=80, JS 3; Urquhart 1988 **Level II**, n=30, JS 1) or higher incidence of nausea and vomiting (White 1990 **Level II**, n=24, JS 5) or pruritus (Bell 2007 **Level II**, n=130, JS 3). SC PCA vs IV PCA may result in higher opioid use (Bell 2007 **Level II**, n=130, JS 3; Dawson 1999 **Level II**, n=100, JS 2; White 1990 **Level II**, n=24, JS 5; Urquhart 1988 **Level II**, n=30, JS 1) or may not (Munro 1998 **Level II**, n=80, JS 3).

6.5.2 | Oral PCA

Oral PCA, using a modified IV PCA system, is as effective as IV PCA (Striebel 1998 **Level II**, n=64, JS 2). An oral PCA device has been developed that uses radiofrequency identification (RFID) technology to allow patients in an oncology ward access (subject to a lockout interval) to a medication-dispensing system at the bedside (Rosati 2007 **Level IV**, n=20).

The use of a computer-controlled oral PCA dispensing device (the PCoA® Acute Device) was compared to conventional nurse-administered on-request oral opioid analgesia in patients having a variety of elective surgical procedures (Wirz 2017 **Level II**, n=70, JS 3). This device allowed secure patient access to bedside oral opioid analgesia (oxycodone or morphine) via RFID technology with higher use of opioid analgesia.

6.5.3 | Sublingual PCA

A sublingual sufentanil tablet system (SSTS) has been trialled in both postsurgical and other acute pain settings. When compared to IV morphine PCA for analgesia after major abdominal or arthroplasty surgeries, SSTS 15 mcg provided analgesia that was noninferior to IV PCA with a similar rate of adverse effects and superior satisfaction ratings from patients and nursing staff (Melson 2014 **Level II**, n=357, JS 2). Specifically for postarthroplasty pain management, SSTS 15 mcg was found to be superior to placebo but with a higher rate of nausea and vomiting (Jove 2015 **Level II**, n=419, JS 5). For abdominal surgeries, the analgesia from SSTS was superior to placebo with similar adverse events profiles for 15 mcg (Ringold 2015 **Level II**, n=172, JS 5) and 30 mcg, with rapid onset of reported analgesic effect within 15 min of administration (Minkowitz 2017 **Level II**, n=161, JS 5). SSTS 30 mcg was also trialled for acute pain management in the ED setting (Miner 2018 **Level III-3**, n=76). See also Section 6.7.2.2 below.

6.5.4 | Intranasal PCA

IN PCA fentanyl can be as effective as IV PCA (Paech 2003 **Level II**, n=24, JS 3; Manjushree 2002 **Level II**, n=40, JS 4; Toussaint 2000 **Level II**, n=57, JS 3; Striebel 1996 **Level II**, n=50, JS 2), as is IN PCA butorphanol (Abboud 1991 **Level II**, n=186, JS 2). As would be expected from the data on IN bioavailability of opioids (see Section 5.5.2), higher doses are needed via the IN route (Manjushree 2002 **Level II**, n=40, JS 4; Striebel 1996 **Level II**, n=50, JS 2). IN PCA pethidine is as effective as IV PCA pethidine, although larger doses are needed (Striebel 1993 **Level II**, n=112, JS 3), and more effective than SC injections of pethidine (Striebel 1995 **Level II**, n=44, JS 2).

Diamorphine IN PCA (bolus doses of 0.5 mg) is less effective than IV PCA morphine (non-equivalent higher bolus doses of 1 mg were used) after joint arthroplasty surgery (Ward 2002 **Level II**, n=52, JS 2). It provided better pain relief in doses of 0.1 mg/kg vs 0.2 mg/kg IM morphine in children with fractures (Kendall 2003 **NR**). See also Section 6.7.2.3 below.

6.5.5 | Transdermal PCA

Iontophoretic TD fentanyl PCA provided analgesia superior to placebo but significantly more patients in the TD group withdrew because of inadequate analgesia vs IV PCA morphine (Poon 2009 **Level I** [QUOROM], 6 RCTs, n=2,866). There was no difference in patient global assessment.

Maximum blood concentrations of fentanyl were the same if the fentanyl patient-controlled TD patch was placed on the chest or upper outer arm, but less if placed on the lower inner arm; the pharmacokinetics were not affected by gender, ethnicity, age or weight (Gupta 2005 **Level IV PK**). See also Section 6.7.2.4 below.

6.6 | Safety and complications related to PCA

Complications related to the use of PCA can be divided into operator or patient-related errors, and problems due to the equipment, practice environment or opioid used.

A large case series of PCA use (by IV, epidural and regional routes) including various device types (elastomeric, CO2 driven, semiprogammable disposable and programmable electronic) reported an incidence of adverse events related to with human error (0.74%), and device-related errors (0.19%) (Son 2019 **Level IV**, n=82,685). Human error in this study included the process of PCA solutions prepared by clinical staff rather than prepared commercially. The highest device error-rates occurred in the programmable electronic device group. Adverse events were associated with 63% of the errors and two patients had severe respiratory depression requiring ICU admission; there was no PCA-related death.

An early prospective study of patients given PCA postoperatively found nine cases of respiratory depression (Looi-Lyons 1996 **Level IV**, n=4,000). These were associated with drug interactions, continuous (background) infusions, nurse- or physician-controlled analgesia, and inappropriate use of PCA by patients. A similar sized prospective study showed that use of PCA was associated with 14 critical events: 8 programming errors (all associated with the setting of a continuous infusion); 3 family members activating PCA; 1 patient tampering; and 3 errors in clinical judgment (Ashburn 1994 **Level IV**, n=3,785).

Analysis of data from the USA FDA's Manufacturer and User Facility Device Experience (MAUDE) database shows that 76.4% of adverse effects related to IV PCA were attributed to technical problems with devices (eg frayed wires or cracks in syringes/ cartridges) and 6.5% were caused by operator error (Schein 2009 **Level** IV, n=2,009 [events]). Of these operator errors (n=131 events), most (81%) related to pump misprogramming and 48% were associated with patient harm. In contrast, only 0.5% of technical device problems resulted in patient harm.

A later retrospective analysis (from July 2000 to June 2005) reported to a national voluntary medication error-reporting database (MEDMARX), showed that PCA-related medication errors continue where 9,571 (1%) were related to PCA use (Hicks 2008 **Level IV**, n= 919,241 [errors]). Of these, 624 (6.5%) were associated with patient harm. By comparison, only 1.5% of medication error reports in general led to harm. The majority of PCA errors occurred during the administration of the medication. Of these, 38% were errors in dose or quantity, 17.4% involved an omission and 17.3% were related to an unauthorised or wrong medicine; human

factors were the main cause of errors; distractions (37.8%) and inexperienced staff (26.3%) were the leading contributing factors. Overall, human factors were the leading cause of PCA errors. A postmarketing surveillance program (2011 to 2016) by the FDA identified 1,430 events with use of IV PCA, of which 11% were associated with an unfavorable clinical outcome; device related issues, which were mostly identified as preventable, occurred in 87% of these (Lawal 2018 **Level IV**, n=1,430 [events]). The authors suggest that education, training and development of improved safety features for PCA devices are needed to improve the overall safety of PCA use.

The implementation of "smart pump" technologies may reduce the incidence and severity of PCA pump programming errors (Ohashi 2014 **Level IV SR** [PRISMA], 22 studies, n unspecified; Mai 2012 **Level III-3**). These technologies include the adoption of standardised and preselected medicine concentrations and dosages. Additionally, the extent of dose sizes is limited to safe ranges through the use of "soft" and "hard" limits.

The safety of PCA can be improved by the use of a hospital-wide safety improvement program (Paul 2010 **Level III-3**, n=25,198). A large prospective survey initially found that the incidence of errors with the use of PCA was 0.25%. Following the introduction of a safety improvement initiative, the incidence of PCA errors was reduced to 0.09% (OR 0.28; 95%CI 0.14 to 0.53).

The costs and rates of errors due to the use of IV PCA were estimated from two large safety-reporting databases in the USA (Meissner 2009 **Level IV**). The datasets included medication errors and device errors. The estimated average cost of a PCA adverse effect in the medication error dataset was US$733, whereas the cost related to a pump error was US$552. An error which lead to patient harm cost 120–250 times more than a non-harmful error. The estimated annual error rates per 10,000 patients in the USA using PCA were 407 for PCA drug errors and 17 for PCA device errors.

The safety of PCA prescribing and patient observation may be improved by the adoption of a common and standardised form and process that incorporates human factors and safety triggers (Agency for Clinical Innovation 2014 **GL**).

PCA safety can be addressed through a variety of strategies including the adoption of new and emerging technologies such as bar-code scanning of prefilled syringes, computer provider order entry (electronic medication management), and feedback using continuous capnography in combination with pulse oximetry (Ocay 2018 **NR**).

For more detail on adverse effects due to the opioid administered, equipment used or operator and patient-related factors, see Sections 6.3, 6.7 and 6.8 respectively.

6.7 | Equipment

Both programmable PCA pumps and disposable PCA devices are available.

6.7.1 | Programmable PCA pumps

These types of pumps allow significant flexibility of use. Adjustments can be made to the dose delivered and lockout intervals, background infusions can be added and accurate assessments can be made of the total dose of medicine delivered. In addition, access to the syringe (or other medicine reservoir) and the microprocessor program is only possible using a key or access code.

All require disposable items eg generic or dedicated syringes or cartridges, antisiphon valves (to prevent siphoning of medicine from the medicine reservoir) and anti-reflux valves (to prevent backflow of medicine into the IV infusion line). See Section 6.7.3 below.

6.7.2 | Disposable PCA devices

6.7.2.1 | Parenteral PCA devices

Disposable PCA devices are often based on the same physical principle; the volume of pressurised fluid delivered (dependent upon spring or elastomer technology) is determined by mechanical restrictions within the flow path and the speed of filling of the bolus dose reservoir determines the lockout interval (Skryabina 2006 **NR**). Advantages include small size and weight, freedom from an external power source, elimination of programming errors and simplicity of use. Disadvantages include an inability to alter the volume of the bolus dose delivered or add a background infusion, difficulties accurately determining the amount of medicine the patient has received, the possibility of inaccurate flow rates, and long-term costs (Skryabina 2006 **NR**). There may also be security issues as the medicine reservoirs for these devices are more readily accessible.

6.7.2.2 | Sublingual PCA devices

A sublingual sufentanil tablet system (SSTS) has been developed commercially and incorporates a hand-held computerised dispenser which is activated by an RFID tag linked to an individual patient, and dispenses SL sufentanil 15 mcg tablets in a patient-controlled manner with a 20 min lockout (Frampton 2016 **NR**).

6.7.2.3 | Intranasal PCA devices

Metered-dose PCINA devices are available. The medicines must be administered in small volumes to avoid significant run-off into the pharynx.

Initial PCINA devices delivered sprays of a reasonable dose but a large volume (eg 25 mcg fentanyl/0.5 mL) (Striebel 1996 **Level II**, n=50, JS 2; Striebel 1993 **Level II**, n=112, JS 3) or smaller volume but with smaller doses than commonly used with IV PCA (eg 9 mcg fentanyl/0.180 mL) (O'Neil 1997 **Level IV**, n=10). A specially formulated solution of 300 mcg/mL fentanyl has been used in a device that enables fentanyl doses of 54 mcg to be delivered in just 0.18 mL (Paech 2003 **Level III-1**, n=21).

6.7.2.4 | Transdermal PCA devices

The iontophoretic TD PCA fentanyl system uses a low-intensity electric current to drive the medicine from the reservoir through the skin and into the systemic circulation (Scott 2016 **NR**). The IONSYS™ device, which is applied to the chest or upper outer arm, delivers a fixed dose of 40 mcg fentanyl over a 10-min period following a patient demand and allows delivery of up to 6 doses/h, up to a maximum of 80 doses in 24 h (Power 2008 **NR**). This device must be replaced every 24 h and is designed for in-hospital use only.

After initial technical difficulties related to corrosion, the device was reapproved by the FDA for short-term use in hospitalised patients in 2015; however, the manufacturer discontinued sale and distribution for business reasons in June 2017 (The Medicines Company 2017).

6.7.3 | Equipment-related complications

In general, modern PCA pumps have a high degree of reliability. However, problems continue to be reported as well as problems related to the disposable items required. Information regarding complications due to equipment problems is mainly case-series or report-based.

While the number of reports of "run-away" pumps, where the PCA pump unexpectedly delivers an unprescribed dose of medication (Notcutt 1990 **Level IV**, n=1,000), has decreased following changes made to pump design, they continue to occur, including a report of spontaneous triggering (Christie 1998 **CR**) and of a frayed wire in the demand apparatus leading to triggering as a result of an electrical short circuit (Doyle 2001 **CR**).

Uncontrolled siphoning of syringe contents when the PCA machine was above patient level has been reported following cracked glass PCA syringes (ECRI 1996 **CR**; Thomas 1988 **CR**), failure of a damaged drive mechanism to retain the syringe plunger (Kwan 1995 **CR**), improperly secured PCA cassettes (ECRI 1995 **CR**) and broken medication cartridge syringe (Doyle 2008 **CR**). To minimise the risk of siphoning, the use of antisiphon valves is recommended (ECRI 1996 **CR**).

Antireflux valves are essential if the PCA infusion is not connected to a dedicated IV line. The non-PCA infusion tubing should have an antireflux (one-way) valve upstream from the connection with the PCA line to prevent back-flow up the non-PCA line should distal obstruction occur; otherwise, inappropriate dosing can occur (Rutherford 2004 **CR**; Paterson 1998 **CR**)

In response to concern about problems with infusion pumps, including PCA pumps, in 2010 the FDA commenced the Infusion Pump Improvement Initiative. Areas for improvement included software, design of user interface, and mechanical and electrical defects (FDA 2010 **GL**). Device-related errors occurred in 0.19% of patients in a large series (Son 2019 **Level IV**, n=82,685). The highest device error-rates occurred in the programmable electronic device group. See also Section 6.6 above.

6.8 | Patient and staff factors

6.8.1 | Patient factors

Patient factors play a role in the effectiveness of PCA as well as complications that can arise from its use; as for equipment issues, much of the information regarding complications due to patient factors is case-based. Psychological factors that may affect PCA use and efficacy are discussed in Section 1.2.2.

6.8.1.1 | Education

Few controlled studies have evaluated the influence of information provision on PCA use. Of patients surveyed who used PCA, approximately 20% were worried that they may become addicted, 20% felt that the machine could give them too much medicine and 30% that they could self-administer too much opioid (Chumbley 1998 **Level IV**, n=200). In a follow-up study, the same group conducted focus groups with previous PCA users, developed a new information leaflet and then undertook a randomised study comparing the old and new leaflet. They found that patients wanted more information on the medication in the PCA, the possible adverse effects and assurance that they would not become addicted (Chumbley 2002 **Level IV**, n=100).

Comparisons have been made between different forms of education given to patients about PCA and results are inconsistent. In an assessment of patient information delivered using structured preoperative interviews or leaflets vs routine preoperative education, patients given leaflets were better informed and less confused about PCA and became familiar with using PCA more quickly but there were no effects on pain relief, worries about addiction and safety or knowledge of adverse effects; the structured preoperative interview resulted in no benefits (Chumbley 2004 **Level III-2**, n=225). Another comparison of structured education vs routine information showed that overall analgesic efficacy, adverse effects and recovery times were not affected by the education program (Lam 2001 **Level II**, n=60, JS 2). Patients who were shown a video on PCA prior to surgery had better knowledge about the technique and reported better pain control after surgery (Chen 2005a **Level III-2**, n=60; Knoerl 1999 **Level III-2**).

6.8.1.2 | Inappropriate use of PCA

The safety of PCA depends on an adequate understanding of the technique by the patient and the fact that unauthorised persons do not press the demand button.

Oversedation with PCA has followed the patient mistaking the PCA handset for the nurse-call button, and family or unauthorised nurse-activated demands ("*PCA by proxy*") (Tsui 1997 **Level IV**, n=2,509; Sidebotham 1997 **Level IV**, n=6,035; Ashburn 1994 **Level IV**, n=3,785; Fleming 1992 **Level IV**, n=1,122; Chisakuta 1993 **CR**; Wakerlin 1990 **CR**).

There have been case reports expressing concerns that patients can use PCA to treat increasing pain and therefore mask problems such as compartment syndrome (Richards 2004 **Level IV**, n=4; Harrington 2000 **CR**), urinary retention (Hodsman 1988 **CR**), pulmonary embolism (Meyer 1992 **CR**) and myocardial infarction (Finger 1995 **CR**). However, appropriate routine patient monitoring should detect changes in pain scores and analgesic consumption enabling identification of such complications.

6.8.2 | Nursing and medical staff

The information regarding complications due to nursing and medical staff factors is also case-based.

Of 9,571 PCA-related adverse effects, 69.8% were related to human factors (Schein 2009 **Level IV**). Improper dose and quantity was the most common factor in 38.9%.

As noted above, operator error is a common safety problem related to PCA use (Looi-Lyons 1996 **Level IV**, n=4,000; Ashburn 1994 **Level IV**, n=3,785). Misprogramming of PCA pumps is thought to account for around 30% of PCA errors, be twice as likely to result in injury or death than errors involving general-purpose infusion pumps and lead to more harm than errors in other types of medication administration (ECRI 2006 **NR**). Mortality from programming errors has been estimated to range from 1 in 33,000 to 1 in 338,800 patients prescribed PCA (Vicente 2003 **NR**).

A number of reports involve the programming of medication concentrations that were lower than the concentration used, with the resultant delivery of an excessive amount of opioid leading to respiratory depression and sometimes death (ECRI 2002 **Level IV**; ECRI 1997 **Level IV**). The use of an incorrect prefilled "standard syringe" for PCA (morphine 5 mg/mL instead of the prescribed 1 mg/mL) also had a fatal outcome (Vicente 2003 **CR**). It has been suggested that medicine concentrations should be standardised within institutions to reduce the chance of administration and programming errors (ECRI 2002 **Level IV**).

PCA pumps using "smart pump" technology now incorporate dose error reduction systems described in Section 6.2 above.

Inappropriate prescriptions of supplementary opioids (by other routes) and sedative medicines (including some antihistamines) can lead to oversedation and respiratory depression (Tsui 1997 **Level IV**, n=2,509; Ashburn 1994 **Level IV**, n=3,785; Lotsch 2002 **NR**).

Human error occurred in 0.74% of patients in a large series, including mistakes with the preparation of PCA solutions by clinical staff rather than prepared commercially (Son 2019 **Level IV**, n=82,685). Documentation of the management of patient care during PCA use can be significantly improved with the PCA smart pump transmitting data directly into the electronic medical record. This automated integration resulted in an increased rate of fully completed PCA charts from 38% to 91% (Suess 2019 **Level III-3**, n=113).

6.9 | PCA in specific patient groups

For PCA use in the paediatric patient see Section 10.5.2, the obstetric patient Section 9.1.3.1,, the elderly patient Section 9.2, the patient with sleep disordered breathing Section 9.4, and the opioid-tolerant patient Section 9.7 respectively.

KEY MESSAGES

1. Intravenous opioid PCA provides better analgesia than conventional parenteral opioid regimens (**S**) (**Level I** [Cochrane Review]).
2. Opioid administration by IV PCA leads to higher opioid consumption, a higher incidence of pruritus, but no difference in other opioid-related adverse effects, or hospital stay compared with traditional methods of intermittent parenteral opioid administration (**S**) (**Level I** [Cochrane Review]).
3. Patient satisfaction with intravenous PCA is higher when compared with conventional regimens (**S**) (**Level I** [Cochrane Review]).
4. The adjuvant use of ketamine with PCA opioid (in varying ratios) improves pain relief and reduces opioid consumption along with nausea and vomiting, with no increase in neurocognitive effects including hallucinations (**N**) (**Level I** [PRISMA]).
5. Iontophoretic transdermal fentanyl PCA is not as effective as intravenous morphine PCA, with more patients withdrawing from studies because of inadequate pain relief (**U**) (**Level I** [QUOROM]).
6. In settings where there are high nurse to patient ratios, there may be no difference in the effectiveness of PCA and conventional parenteral opioid regimens (**U**) (**Level I**).
7. Tramadol via intravenous PCA provides effective analgesia comparable to morphine by intravenous PCA (**U**) (**Level I**).
8. The addition of a background infusion to intravenous PCA morphine in adults increases the incidence of respiratory depression (**U**) (**Level I**) and does not improve pain relief or sleep, or reduce the number of PCA demands (**U**) (**Level II**).
9. Different opioids by intravenous PCA show different rates of adverse effects; fentanyl PCA has the least rates of sedation, nausea and vomiting while pruritus is most frequent with morphine PCA (**N**) (**Level I** [NMA]). Furthermore, on an individual patient basis, one opioid may be better tolerated than another (**U**) (**Level II**).
10. There is no analgesic benefit in adding naloxone to the PCA morphine solution; however, the incidence of nausea and pruritus may be decreased (**U**) (**Level II**).
11. Subcutaneous PCA opioids can be as effective as intravenous PCA (**U**) (**Level II**).
12. Intranasal PCA opioids can be as effective as intravenous PCA (**U**) (**Level II**).
13. In the emergency department, PCA morphine compared with IV morphine administered by nursing staff, provides more effective analgesia with more rapid onset and with higher patient satisfaction (**U**) (**Level II**).
14. The safety of PCA use can be significantly improved by hospital-wide safety initiatives (equipment, guidelines, education, monitoring) (**U**) (**Level III-3**).
15. The adoption of “smart pump” technologies in PCA design can improve documentation of patient care (**N**) (**Level III-3**), reduce programming errors and improve safety (**N**) (**Level IV SR**).
16. Operator-error, in particular programming error, remains a common safety problem with PCA useoften leading to patient harm (**S**) (**Level IV**).

The following tick boxes represent conclusions based on clinical experience and expert opinion:

- ☑ There is insufficient data to compare the risk of rare but serious adverse events with PCA opioid use to conventionally administered opioid analgesia (**N**).
- ☑ Adequate analgesia needs to be attained prior to commencement of PCA. Initial orders for bolus doses should consider individual patient factors such as a history of prior opioid use and patient age. Individual PCA prescriptions may need to be adjusted (**U**).
- ☑ The routine addition of antiemetics to PCA opioids is not encouraged, as it is of no benefit compared with selective administration (**U**).
- ☑ PCA infusion systems must incorporate anti-siphon valves and, in non-dedicated lines, antireflux valves (**U**).
- ☑ Drug concentrations, prescription and observation forms should be standardised to improve patient safety (**U**).
- ☑ The pharmacokinetics of morphine (long equilibration half-time and active metabolites) may make it less suitable for PCA use than other opioids (**U**).
- ☑ Pethidine, when used in PCA, may cause central nervous system toxicity due to the accumulation of norpethidine (**U**).
- ☑ Improved methods of patient monitoring (eg continuous pulse oximetry, continuous capnography) may offer opportunities to improve safety in at-risk patient groups (**N**).

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7

Nonpharmacological techniques

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7.0 | Nonpharmacological techniques

7.1 | Psychological interventions

The role of psychological interventions in the management of acute pain is usually as adjunctive therapies to traditional pharmacological and physical treatment modalities; there is increasing evidence for their role in pre-emptive and multimodal acute pain therapy as well as in reducing the risk of chronic postsurgical pain (CPSP) (Horn 2020 **NR**).

By their very nature, psychological interventions share several common features. Some of these features may also apply to effective pharmacological and physical interventions. Typically, the treatment provider is encouraged to firstly establish a degree of rapport or acceptance with the patient as well as give some information about the purpose and nature of the intervention and reasonable expectations the patient should hold for their outcome. These aspects may be seen as necessary to gain both the informed consent of the patient for treatment, as well as their active cooperation.

Psychological interventions may be divided into four broad categories:

- Information provision (procedural information, description of expected sensory experience or behavioural instructions) (see also Section 3.1.1);
- Stress or tension reduction (relaxation and hypnotic strategies);
- Attentional strategies;
- Cognitive-behavioural interventions.

It should be emphasised that these are rarely 'stand-alone' interventions and elements of each may form a single intervention package.

Similar to physical therapies, a lack of clinician blinding and questions as to what constitutes an adequate psychology placebo arm in an RCT, as well as heterogeneous interventions, limit the strength of conclusions (Guidi 2018 **NR**). In the Cochrane meta-analysis presented below, almost all RCTs were ranked at high risk of performance bias due to lack of clinician blinding (Powell 2016 **Level I** [Cochrane], 105 RCTs, n=10,302).

When pooled for all pre-procedural psychological interventions in a range of surgery types (including cardiothoracic 10 RCTs and coronary artery bypass surgery [CABG] 17 RCTs) and procedures, there is a small reduction in postoperative pain scores (SMD -0.2; 95%CI -0.35 to -0.06) (38 RCTs, n=2,713), length of stay (LOS) (MD -0.52 d; 95%CI -0.82 to -0.22) (36 RCTs, n=3,313) and reduction in negative affect (SMD -0.35; 95%CI -0.54 to -0.16) (31 RCTs, n=2,496) (Powell 2016 **Level I** [Cochrane], 105 RCTs, n=10,302). However, multiple pooled psychological interventions for acute pain after open heart surgery do not reduce postoperative pain intensity or PCA usage but do slightly reduce postoperative mental distress over the short and longer term in RCTs of low quality (Ziehm 2017 **Level I** [Cochrane], 23 RCTs, n=2,669) (5 RCTs overlap).

For paediatric specific information, see Sections 10.7.5 and 10.11.1.

7.1.1 | Provision of information

7.1.1.1 | Procedural information

Procedural information is information given to a patient before any treatment that summarises what will happen during that treatment. Here, four information factors were each associated with global evaluations of care by patients: surgical information, recovery information, general

information and sensory information (Krupat 2000 **Level IV**, n=3,602). Procedural information (often combined with behavioural instructions, like exercises or body positions) effectively reduces reported pain in 3 of 7 RCTs and pain medications in 7 of 12 RCTs (Johnston 1993 **Level I**, 38 RCTs, n=1,734).

In orthopaedic surgery, patient education regarding the procedure or recovery provided a small improvement in post-operative pain (SMD -0.21; 95%CI -0.02 to -0.39) (12 RCTs, n=1,242), pre-operative anxiety (SMD -0.27; 95%CI -0.10 to -0.44) (12 RCTs, n=1,260) and post-operative anxiety (SMD -0.26; 95%CI -0.08 to -0.43) (11 RCTs, n=921), but had no impact on analgesic use (10 RCTs, n=860) (Szeverenyi 2018 L**evel I** [PRISMA], 62 RCTs, n=4,908).

7.1.1.2 | Sensory information

Sensory information is information that describes the sensory experiences the patient may expect during treatment. Sensory information given alone has some positive, albeit inconsistent, effects vs no instruction (Suls 1989 **Level III-3 SR**, 21 studies, n unspecified). With all but two studies involving adults, sensory information reduced self-rated pain more than procedural information; however, the effect sizes were variable. In contrast, a subsequent meta-analysis shows a beneficial effect on pain in three RCTs and shows a reduction in the use of pain medication in two of five RCTs (Johnston 1993 **Level I**, 38 RCTs [7 RCTs sensory information], n=1,734). A subsequent RCT found sensory only information had no significant effect on postoperative pain perception (Campbell 1999 **Level II**, n=63, JS 2).

7.1.1.3 | Combined sensory-procedural preparatory information

Combined sensory-procedural preparatory information, when compared to procedural information and sensory information given alone, yielded the strongest and most consistent benefits in reducing negative affect, pain reports and other related distress (Suls 1989 **Level III-3 SR**, 21 studies, n unspecified). However, many studies relate to medical procedures such as pelvic examination or to experimental pain. Subsequent systematic reviews are consistent with these findings (Johnston 1993 **Level I**, 38 RCTs, n=1,734; Devine 1992 **Level IV SR**, 191 studies, n unspecified). Interventions investigated include the provision of information about medical procedures and associated emotional responses and sensations before, during and after surgery, and instructions about how to adhere to medical advice to support the recovery, with teaching or instructing patients in different relaxation techniques or helping patients to understand their thoughts and feelings that influence their behaviour.

In some patients, especially those with an avoidant coping style, giving too much information or asking them to make too many decisions may exacerbate anxiety and pain (Wilson 1981 **Level II**, n=70, JS 2). However, later evidence suggested that this may not be a strong effect (Miro 1999 **Level II**, n=92, JS 3). Nevertheless, it may be useful to assess a patient's normal approach to managing stress to identify the best option for that patient. This concept is supported by the finding in patients undergoing colposcopy where stress related to the procedure was reduced when information was tailored to individual coping styles (Kola 2013 **Level II**, n=117, JS 2).

See also Section 3.1.1 on patient education.

7.1.2 | Relaxation techniques

Relaxation training usually involves teaching a patient ways to reduce their feelings of stress and/or arousal. Techniques used may be taught by audio recording or written or spoken instructions. The use of audio recording often includes the use of calming music or suitable

imagery (mental pictures of relaxing scenes). Typically, all methods require the patient to practise the technique regularly, especially when feeling stressed. Some methods focus on altering muscle tension, often sequentially, while others focus on altering breathing patterns (eg emphasising releasing tension with exhalation). Relaxation techniques are closely related to, and often indistinguishable from, forms of meditation and self-hypnosis.

A systematic review of relaxation techniques, when used alone for the management of pain after surgery and during procedures, concluded that there was weak evidence to support the use of relaxation in these settings; three of the 7 RCTs reported significant reductions in pain and distress (Seers 1998 **Level I**, 7 RCTs, n=362). Methodological shortcomings of the included RCTs meant that a meta-analysis was not possible, limiting the strength of the findings. Similar conclusions were made in another systematic review, which found that 8 of 15 RCTs (again, most had weaknesses in methodology) demonstrated reductions in pain (Kwekkeboom 2006 **Level I**, 15 RCTs, n=1,269); the most supported methods were progressive muscle relaxation for arthritis pain and a systematic relaxation technique for postoperative pain. Little evidence was found for autogenic training (another relaxation technique), and no support for rhythmic breathing or other relaxation techniques. Another review of studies using relaxation techniques for burns pain also found insufficient high-quality evidence to draw any conclusions but did recommend further research into the use of a technique that combined focusing on breathing and jaw muscle relaxation (de Jong 2006, **Level III-3 SR**, 11 studies, n=1,541) (1 RCT overlap). The most recent meta-analysis found a reduction in post-operative pain (SMD -0.45; 95%CI -0.11 to -0.79) (9 RCTs, n=473) but no effect on analgesic consumption (SMD -0.36; 95%CI 0.25 to -0.98) (7 RCTs, n=183) (Szeverenyi 2018 **Level I** [PRISMA], 62 RCTs, n=4,908) (0 to 1 RCT overlap).

In patients with acute whiplash associated disorder, physiotherapy directed exercises and education combined with stress inoculation training (comprising relaxation training, guidance on problem solving strategies, and their application to stressful situations) reduced pain-related disability vs exercise alone at 6 wk, 6 mth and 12 mth (Sterling 2019 **Level II**, n=108, JS 3).

Studies of relaxation techniques with cancer patients (in acute pain) provide moderately strong support for its effectiveness in improving pain, but also nausea, pulse rate and blood pressure, as well as emotional adjustment variables (depression, anxiety and hostility) (Luebbert 2001 **Level I**, 15 RCTs, n=742).

7.1.3 | Mindfulness-based interventions (MBI)

Mindfulness meditation is a type of attentional technique that includes attending to pain sensations. It has much in common with breathing-based relaxation techniques. This approach encourages the patient to deliberately experience their pain in a calm manner just like any nonpainful sensation (ie without judging it as good or bad), often while engaging in slowed breathing styles (Kabat-Zinn 2003 **NR**). This approach derives from ancient Buddhist methods. Mindfulness-based approaches have been used to promote adjustment in people experiencing chronic pain, often in conjunction with a form of cognitive-behavioural therapy (CBT) called acceptance and commitment therapy (ACT) (McCracken 2007 **Level IV**, n=105).

MBI/ACT for experimental pain vs other emotion-regulation techniques are superior for pain tolerance (except for distraction) but not for pain intensity (Kohl 2012 **Level I EH** [PRISMA], 30 RCTs, n=2,085). Two subsequent RCTs have provided slightly conflicting findings. In healthy participants undergoing experimental pain (electric shock), both acceptance methods and suppression were equally effective, and both were superior to a control condition in reducing pain and anxiety (Braams 2012 **Level II EH**, n=123, JS 3). In contrast, in healthy students,

mindfulness was as ineffective as relaxation training in reducing experimental pain (with the cold-pressor test) (Sharpe 2013 **Level II EH**, n=140, JS 1).

Brief MBI in mostly healthy volunteers (including adult, some children & adolescent groups) or patients with chronic pain delivered by either audio/video recorder instruction or provider delivered instruction is of unclear effectiveness (McClintock 2019 **Level IV SR**, 18 RCTs & 2 studies, n=1,740). However, brief MBI delivered by a clinician and lasting more than 5 min may be more useful than shorter durations and virtual delivery. The single clinical RCT in acute pain included in this review compared brief MBI vs hypnotic suggestions vs psychosocial education in patients with pre-existing "*intolerable pain*" or "*inadequate pain control*" and found both brief MBI and suggestion were superior to education for pain relief, anxiety and desire for opioids (Garland 2017 **Level II**, n=244, JS 3).

A pilot RCT in veterans after major orthopaedic surgery at high risk of CPSP (severe preoperative pain, moderate postoperative pain, depression or anxiety), found a 1 d ACT workshop vs standard care did not reduce time to cessation of pain (HR 1.42; 95%CI 0.68 to 2.95) or cessation of opioids (HR 1.62; 95% CI 0.82 to 3.21) (Dindo 2018, **Level II**, n=88, JS 3).

7.1.4 | Hypnosis

Hypnosis shares many features of relaxation with imagery and has a long history of use in acute pain conditions. Techniques vary but they have the common feature of one person responding to suggestions made by another regarding experiences involving changes in perception, memory and voluntary actions (Kihlstrom 1985 **NR**). The variable nature of hypnotic procedures has made it difficult to compare studies or draw general conclusions (Ellis 1994 **NR**) although some more standardised (according to a manual) procedures have been reported (Liossi 2003 **Level II**, n=80, JS 2).

Preoperative hypnosis was investigated as one of several methods to reduce postoperative pain in surgical patients; there is no effect on postoperative pain but partial support for improvements in psychological wellbeing measures (Nelson 2013 **Level III-1 SR**, 4 studies [hypnosis], n=144). Another meta-analysis looking at women having breast cancer surgery found preoperative hypnosis does not reduce postoperative pain but reduces perioperative distress (Holger 2012 **Level I**, 4 RCTs, n=550). However, a subsequent meta-analysis found that live and recorded hypnosis both reduce anxiety and live hypnosis reduces pain scores (SMD -0.51; 95%CI -0.06 to -0.96) (8 RCTs, n=669) but both have no effect on analgesic use; while therapeutic suggestion has no effect on anxiety, pain scores or analgesic use (Kekecs 2014 **Level I**, 26 RCTs, n=1,890) (2 RCTs overlap).

Note: reversal of conclusion
This reverses the Level I key message in the previous edition of this document; a preceding meta-analysis had described no effect of hypnosis on postoperative pain scores.

For labour, hypnosis (eight antenatal and one intrapartum intervention) may reduce pharmacological analgesic use (RR 0.73; 95% CI 0.57 to 0.94) (8 RCTs, n=2,916) but has no effect on rate of spontaneous vaginal birth (6 RCTs, n=2,361), sense of coping with labour (1 RCT, n=420) or satisfaction with pain relief when combined with either pethidine (1 RCT, n=72) or epidural analgesia (1 RCT, n=127) (Madden 2016 **Level I** [Cochrane], 9 RCTs, n=2,954).

Note: reversal of conclusion
This reverses the Level I key message in the previous edition of this document; a preceding meta-analysis had described no effect of hypnosis in the management of labour pain.

A reduction is seen with hypnosis in a small majority of study measurements during procedural pain in paediatric and adult patients vs standard care, attention control or other active treatments (Kendrick 2016 **Level I** [PRISMA], 29 RCTs, n=2,202).

Hypnosis vs control for needle-related procedural pain in children reduces pain scores (SMD -1.4; 95%CI -2.32 to -0.48) (5 RCTs n=176), distress scores (SMD -2.53; 95%CI -3.93 to -1.12) (5 RCTs, n=176) and behavioural measures of distress (SMD -1.15; 95%CI -1.76 to -0.53) (6 RCTs, n=193) (Birnie 2018 **Level I** [Cochrane], 59 RCTs, n=5,550) (6 RCT overlap). Analgesic benefits of hypnosis are confirmed in children undergoing cancer-related procedures (Tome-Pires 2012 **Level I**, 10 RCTs [procedural pain], n=394) (5 RCTs overlap). See also Section 10.7.5.

7.1.5 | Attentional techniques

A range of attention-based strategies have been reported, from those involving distraction from the pain through shifting attention to cognitive tasks, imagined stimuli or external stimuli (such as audio, video, tactile sensations, smells or a combination) (Bascour-Sandoval 2019 **NR**). Use of distraction (video, toys, music or stories) is effective in infants, young children and adolescents across a range of procedures eg needle-related pain (Birnie 2018 **Level I** [Cochrane], 59 RCTs, n=5,550; Birnie 2015 **Level III-1 SR**, 22 studies, n=1,717 [10 RCTs overlap]; Pillai Riddell 2015 **Level III-1 SR**, 10 studies, n=1,259 [0 RCT overlap]). See also paediatric sections for vaccine injection (10.7.3.4) and other procedural pain (10.7.5) including that related to paediatric cancer (10.8.2) and burns (10.9.2).

Some techniques also involve deliberately attending to the pain (or pain site) but in ways intended to modify the threat value of pain rather than to divert attention from pain. There is some evidence that this method can alter pain perception but possibly mainly among subgroups of patients (Haythornthwaite 2001 **Level II**, n=42, JS 1; Logan 1995 **Level III-2**; Baron 1993 **NR**).

Attempting to alter the patient's emotional state, from distress or fear to relative comfort or peace, is also a common feature of many of these techniques. Commonly, these techniques are used in conjunction with relaxation methods and at times may be inseparable (Williams 1996 **NR**).

Patients may exhibit pre-existing attention bias which prioritises painful sensations or pain-related experiences over other sensory experiences which may be amenable to attention bias modification); however, results are equivocal, especially when used in isolation (Van Ryckeghem 2019 **Level IV SR EH**, 52 studies, n=4,466).

7.1.5.1 | Music

Music therapy may be either active or passive: active therapy is when the patient participates in creating sounds; in passive music therapy, the patient listens to recorded or live music. When played by medical staff or with music therapists, music reduces acute or procedural pain (MD -1.11/10; 95%CI -1.45 to -0.77) (67 RCTs, n=5,679) with other beneficial effects in terms of emotional distress, anaesthetic use, opioid use, non-opioid use, heart rate, blood pressure and respiratory rate (Lee 2016 **Level I**, 97 RCTs, n=9,184). Patient, rather than clinician or researcher selected music, may be most effective (Lunde 2019 **NR**). In two subsequent RCTs, patient selected music was of benefit during shockwave lithotripsy (Cakmak 2017 **Level II**, n=200, JS 3), but Mozart's Symphony No. 40 played during colposcopy provided no benefit (Hilal 2018, **Level II**, n=215, JS 3).

Similarly, music reduces pain in cancer patients (SMD -0.59; 95%CI -0.92 to -0.27) (Bradt 2011 **Level I** [Cochrane], 30 RCTs, n=1,891). In burns patients, music interventions are helpful for pain alleviation, anxiety relief and heart rate reduction (Li 2017c **Level I** [PRISMA], 17 RCTs, n=804).

In children, music is effective during dental procedures (see 10.7.2.7), heel lance (see 10.7.1.1), burns dressing changes (see 10.7.2.9), vaccination (see 10.7.5) and general procedural pain (see 10.7.3.4).

7.1.5.2 | Virtual reality

Virtual reality (VR) has led to reductions in pain unpleasantness and pain-related brain activity in volunteers using thermal pain stimulation and measuring pain-related brain activity with functional magnetic resonance imaging (fMRI): where both opioids and immersive VR reduced pain and the combination was more effective than opioid alone (Honzel 2019 **NR)**.

VR may be effective at reducing procedural pain eg for needles and burns dressing changes vs usual care (SMD -0.49; 95%CI -0.83 to -0.41) (Chan 2018 **Level III-2 SR** [PRISMA], 9 RCTs & 7 crossover studies, n=656). However, studies were heterogeneous and inherently unblinded.

In burns patients, VR reduces pain intensity, time spent thinking about pain and unpleasantness (Luo 2019b **Level I** [PRISMA], 13 RCTs, n=362; Scheffler 2018 **Level I** [PRISMA], 21 RCTs, n=660) (4 RCTs overlap).

See 8.5.5 for more information on VR use in burns pain and 10.7.5 on VR use in the paediatric population.

7.1.5.3 | Smell

Olfaction can induce analgesia and emotional changes in both humans and animals and may play a role in pain therapy (Lotsch 2016 **NR**).

See Sections 4.14.3 and 8.5.5 for effects of aromatherapy in adults and 10.11.1 in paediatric patients.

7.1.5.4 | Tactile sensations

See 10.7.3.4 for information on use of vibration in paediatric vaccine injection pain.

7.1.6 | Cognitive-behavioural interventions

Typically, cognitive-behavioural interventions involve the application of a range of behaviour-change principles, such as differential positive reinforcement of desired behaviours, identification and modification of unhelpful thoughts and goal setting, in order to achieve change in targeted behaviours. In the context of acute pain this would include encouraging the use of the techniques outlined above to modify the pain experience, reduce distress, and to provide alternative, more helpful responses.

Cognitive-behavioural methods focus on both overt behaviours and cognitions (thought processes) in patients, but interactions with environmental factors are also often addressed. This means that interactions between patients and others, especially medical and nursing staff as well as families, may need to be addressed to support the desired responses in the patient. The latter may entail displaying a calm and reassuring manner and encouragement to persevere with a given task or procedure. Specific training in skills (eg relaxation and other coping strategies), other behavioural techniques (eg modelling and systematic desensitisation), information provision and reconceptualisation of the experiences of the patient may also be provided as part of this approach (as outlined above).

Cognitive-behavioural interventions are usually aimed at reducing the distressing or threat value of pain and enhancing a patient's sense of his or her ability to cope with pain (pain self-efficacy). Effective coping with pain may be reflected in minimal pain-related distress (eg reduced catastrophising) or disability (interference in normal activities). If patients are able to perceive their pain as less threatening, they might also evaluate their pain as less severe. However, in this context, reduced severity would be seen more as a by-product than as the primary goal.

Critically, in using cognitive-behavioural methods, the patient must be an active participant in the process, rather than a passive recipient, as he or she must apply the methods taught as needed.

7.1.6.1 | Applying pain coping strategies within a cognitive-behavioural intervention

Generally, while some responses by patients to their pain may be helpful, others may not. For example, those who respond with overly alarmist (or catastrophic) thoughts tend to experience more pain and distress, vs those who do not respond in this way (eg Haythornthwaite 2001 **Level II**, n=42, JS 1; Sullivan 2001 **NR;** Jensen 1991 **NR**). Identifying unhelpful responses, whether they are cognitive or behavioural, and changing these responses is a common feature of many cognitive-behavioural interventions.

Catastrophic thinking has been associated with increased postsurgical acute pain, opioid use and reduced function (Darnall 2016 **NR**) as well as being a risk factor for development of persistent postsurgical pain (OR 1.55-2.10) (15 RCTs) (Theunissen 2012 **Level IV SR**, 29 studies, n=6,628). Thus, identifying and reducing catastrophic thoughts about pain has become a common intervention within this approach, whether the pain is acute or persistent. A single preoperative 130 min lecture session was effective at reducing pain catastrophisation (Darnall 2014 **Level III-2**, n=76). Before breast cancer surgery, delivery of virtual psychoeducation vs general health education reduced time to opioid cessation (5 d vs 13) (Darnall 2019 **Level II**, n=68, JS 3). However, attrition rates were higher in the psychoeducation group vs general education (44% vs 18%). For breast cancer surgery, patients who received stress management training (mainly relaxation and coping skills) had less depression and fatigue up to 3 mth post-surgery, but there were no differences for anxiety, pain and sleep problems vs a usual care control group (Garssen 2013 **Level II**, n=70, JS 3).

Perioperative CBT may improve pain and functional outcomes; however, heterogeneity of interventions (only in 1 of 6 RCTs delivered by psychologist), outcome measures and time frames limits firm conclusions (Nicholls 2018 **Level I** [PRISMA], 6 RCTs, n=578). A previous meta-analysis found that during preparation for surgery or painful medical procedures, training in cognitive coping methods and behavioural instructions in addition to relaxation training and procedural information, improves patients' pain measures and reduces postoperative use of analgesics (Johnston 1993 **Level I**, 38 RCTs, n=1,734). These interventions effectively improve measures of negative affect, LOS, and recovery.

It has also been recognised that a given coping strategy may not always be useful and that this may depend upon circumstances and timing (Turk 2002 **NR**). For example, ignoring or denying the presence of pain may be useful when first injured (to reduce distress) but, if it means that appropriate help is not sought, it could place the person in danger or at risk of treatment for complications being delayed.

Details on the psychological management of post-operative pain have been incorporated into guidelines (Chou 2016 **GL**).

For information on paediatric cognitive behavioural interventions for procedural pain see 10.7.5.

7.1.6.2 | Complex psychosocial interventions

Increasingly, researchers are reporting the application of psychologically-based interventions in complex acute pain settings, especially in relation to work-related injuries and their management. Instead of employing a single technique (like relaxation), the researchers may employ strategies aimed at the patient's responses (eg distress and avoidance) as well as the responses of key environmental factors, such as in the workplace and in the family.

Injured workers identified within 5 to 15 d of injury as at risk for delayed recovery offered a comprehensive management plan (that included medical/physical treatments, brief CBT-based intervention by a psychologist, and workplace accommodations) had half the time off work (32 d vs 67 d) in the following 2 y vs the usual care recipients (Nicholas 2020 **Level III-2**, n=113). These results are consistent with those reported by a systematic review of interventions for return to work (Cullen 2018 **Level III-2 SR,** 36 studies**,** n≈195,722).

KEY MESSAGES

1. Preoperative psychological interventions may be effective at reducing pain, length of stay and negative affect after various procedures (**N**) (**Level I** [Cochrane Review]) but may not be effective after cardiac surgery (**N**) (**Level I** [Cochrane Review]).
2. Distraction (including with video, toys, music or stories) and hypnosis reduces needle related pain (**S**) and distress (**N**) in children and adolescents (**Level I** [Cochrane Review])
3. Hypnosis may reduce procedural pain and anxiety (**N**) (**Level I** [Cochrane Review]), postoperative pain (**R**) (**Level I**), postoperative anxiety (**N**) and analgesia consumption in labour (**R**) (**Level I** [Cochrane Review]).
4. Listening to music produces a small reduction in postoperative or procedural pain, analgesic requirements and emotional distress (**S**) (**Level I**); patient selected music may be more effective than clinician selected music (**N**) (**Level II**).
5. Patient education regarding the procedure or recovery may reduce postoperative pain (**Q**), preoperative anxiety (**N**) and postoperative anxiety (**N**) but does not affect analgesia use (**U**) (**Level I** [PRISMA]).
6. Training in coping methods or behavioural instruction prior to surgery reduces pain, negative affect and analgesic use (**U**) (**Level I**).
7. Relaxation techniques may reduce postoperative pain but do not reduce analgesic consumption (**S**) (**Level I**).
8. Immersive virtual reality distraction is effective in reducing pain (**S**) and anxiety (**N**) in some clinical situations (**Level III-2 SR** [PRISMA]).
9. In work injury-related acute pain, psychologically informed and workplace-oriented interventions may reduce time lost from work (**N**) (**Level III-2 SR**).

The following tick boxes represent conclusions based on clinical experience and expert opinion:

☑ Pain catastrophisation and anxiety negatively impact the postoperative experience and are risk factors for the development of chronic postsurgical pain and prolonged opioid use. Interventions aimed at reducing catastrophisation may be useful in improving patient outcomes, but retaining patient engagement with perioperative psychoeducation may also prove challenging (**N**).

☑ Preoperative psychoeducation may be cost effective from the perspective of reducing length of stay (**N**).

☑ The evidence that sensory and combined sensory-procedural information is effective in reducing procedure-related pain is equivocal and not sufficient to make recommendations (**U**).

☑ There is insufficient evidence to make a recommendation about the role of brief mindfulness-based interventions in acute pain (**N**).

7.2 | Transcutaneous electrical nerve stimulation

Transcutaneous electrical nerve stimulation (TENS) is the application of pulses of electrical current between two or more transcutaneous electrodes in order to stimulate cutaneous nerves. Unlike medications which only have dosage and route of administration as variables, TENS varies by anatomical location of electrodes, duration of usage, pulse amplitude, pulse frequency, pulse duration and pattern (eg burst, continuous or modulated). The variable ways in which TENS can be applied and lack of uniform reporting in studies makes pooling of results and interpretation of conflicting studies challenging. Furthermore, the blinding of such a physical intervention is difficult. Sham TENS varies in studies between a passive deactivated box connected to the patient where no stimulus is felt and devices which provide a short duration of therapeutic TENS. In a trial of inactive sham TENS vs 45 s transient sham TENS vs real TENS the investigators and patients were blinded 0% and 21% for inactive sham TENS, and 100% and 40% for transient sham TENS (Rakel 2010 **EH**). Thus, for the purposes of applying the Jadad score to studies we have not considered inactive TENS to be an adequate placebo.

TENS reduces acute pain (procedural and nonprocedural) vs no treatment (MD -19/100; 95%CI -27.3 to -10.8) (6 RCTs, n=413) and sham TENS (MD -24.6/100; 95%CI -31.79 to -17.46) (6 RCTs, n=376), with more participants achieving ≥50% reduction in pain vs sham TENS (RR 3.91; 95%CI 2.42 to 6.32) (4 RCTs, n=157) (Johnson 2015b **Level I** [Cochrane], 19 RCTs, n=1,346). These results are limited by a high risk of bias due to inadequate sample sizes in the trials and unsuccessful blinding including the use of non-TENS-naïve patients. Minor adverse effects reported were mild erythema, itching and participants disliking the TENS sensation (7 RCTs).

7.2.1 | Orthopaedic surgery

TENS vs placebo TENS reduces pain after total knee arthroplasty (TKA) at 12 h (SMD -0.26; 95%CI -0.44 to -0.08), 24 h (SMD -0.24; 95%CI -0.43 to -0.06) and 48 h (SMD -0.21; 95%CI -0.40 to -0.03) and opioid consumption at 12, 24, and 48 h (Li 2017b **Level I** [PRISMA], 5 RCTs, n=472). TENS also reduces the incidence of postoperative nausea by 9.8% and vomiting by 9.4%, but not the hospital LOS. The results are limited by small sample sizes in the trials; however, the quality of evidence is high. Repeated TENS provides long term pain reduction up to 6 mth postoperatively vs placebo TENS (2 RCTs, n=189) (Tedesco 2017 **Level I** [PRISMA], 39 RCTs, n=5,509). However, after anterior cruciate ligament repair, adding high-frequency transcutaneous TENS to exercise vs exercise alone did not improve pain and function in early rehabilitation (Forogh 2019 **Level II**, n=70, JS 4).

After rotator cuff repair TENS for four 45 min sessions/d for the first postoperative wk reduced pain at 12 h (3.1/10 ± 3.6 vs. 5.8/10 ± 4.4) and 1 wk (3.6/10 ± 2.1 vs. 5.8/10 ± 1.2) with less oxycodone 5 mg/paracetamol 325 mg requirements at 48 h (12.8 tablets ± 4.7 vs. 17.2 ± 6.3) and 7 d (25.2 tablets ± 10.0 vs. 33.8 ± 14.3) vs placebo TENS (Mahure 2017 **Level II**, n=37, JS 5).

Postoperative TENS applied to the surgical site for 15 min/d consecutively for 5 d after surgery did not reduce pain or analgesic use after Colles' Fracture vs placebo TENS (Lee 2015b **Level II**, n=36, JS 3).

7.2.2 | General and thoracic surgery

After thoracic surgery (thoracotomy or sternotomy), TENS reduces pain intensity vs sham TENS (thoracotomy -1.3/10; 95%CI -1.9 to -0.7; sternotomy -1.3/10; 95%CI -1.9 to -0.8) (Sbruzzi 2012

Level I [PRISMA], 11 RCTs, n=570). Subsequent RCT findings are consistent with these results (Sezen 2017 **Level II**, n=96, JS 1; Engen 2016 **Level II**, n=40, JS 3; Erden 2015 **Level II**, n=40, JS 1; Esteban Gonzalez 2015 **Level II**, n=50, JS 3). Although TENS was not more effective than a paravertebral (PVB) in relieving pain or reducing PCA usage following thoracotomy procedures, it had fewer adverse effects (Baki 2015 **Level II,** n=40, JS 1).

After liposuction, TENS vs placebo TENS reduced pain intensity (0/10 vs 4/10) and need for rescue analgesia at 6 h (95.2% vs. 47.6%) (da Silva 2015 **Level II**, n=42, JS 3).

After cessation of epidural analgesia following open colon resection, TENS reduced pain at 24 h post cessation (10/100 vs 23/100) vs placebo TENS, but no differences in quality of recovery or opioid use were found (Bjersa 2015 **Level II,** n=28, JS 5).

TENS (starting 1 h pre-operatively for inguinal hernia repair and ceased on induction) reduced pain at 2 h (3.5/10 ±1.5 vs 5.1/10 ±1.4) and 4 h (4.0/10 ±1.5 vs 4.8/10 ±1.4) and diclofenac use at 12 h (15.2% vs 39.4%), with no difference in other time points or anti-emetic use (Eidy 2016 **Level II**, n=66, JS 3).

7.2.3 | Procedural pain and prehospital analgesia

TENS reduced procedural pain (MD -2.7/10; 95%CI -1.6 to – 4.0) during carboxytherapy in patients with cellulite in the gluteal region vs placebo TENS (Sadala 2018 **Level II**, n=84, JS 1).

TENS used in the prehospital setting reduces pain intensity vs scores before TENS use (MD 38/100; 95%CI 28 to 44) and vs sham TENS (MD 33/100; 95%CI 21 to 44), as well as acute anxiety secondary to pain (Simpson 2014 **Level I** [PRISMA], 4 RCTs, n=261).

7.2.4 | Gynaecological surgery and obstetrics

In labour, TENS has no effect on pain, interventions or outcomes vs sham TENS (10 RCTs) or routine care (7 RCTs), when applied to the back (13 RCTs, n=1,150) or cranium (2 RCTs, n=140), with the exception of a reduction in reports of severe pain when applied to acupuncture points (2 RCTs, n=190) (Dowswell 2009 **Level I** [Cochrane], 17 RCTs, n=1,466). These findings of no analgesic effect are confirmed by two subsequent meta-analyses (Bedwell 2011 **Level I**, 14 RCTs, n=1,456 (14 RCTs overlap); Mello 2011 **Level I**, 9 RCTs, n=1,076 (3 RCTs overlap)).

Three subsequent RCTs not included in the above meta-analyses showed benefit from TENS in labour. A 30 min session of TENS over thoracic and sacrum area reduced immediate pain during the active phases of labour vs non-TENS control (Santana 2016 **Level II**, n =46, JS 3) or placebo TENS box (Baez-Suarez 2018 **Level II**, n =63, JS 3). TENS with varying high-frequency (80 to 100 Hz) was more effective than TENS of constant frequency (100 Hz) (Baez-Suarez 2018 **Level II**, n =63, JS 3). TENS produced sustained pain relief 4 h after the intervention and had shortened first-stage labour vs placebo or no TENS controls (Shahoei 2017 **Level II**, n=90, JS 1).

High-frequency TENS is effective in primary dysmenorrhoea (Proctor 2002 **Level I** [Cochrane], 7 RCTs, n=164). A subsequent systematic review did not add new information except for highlighting that quality of life is not reported in any RCT (Igwea 2016 **Level I**, 6 RCTs [TENS], n=247) (2 RCTs overlap). Subsequent RCTs reported similar results of daily TENS during menstrual bleeding; pain intensity, hours in pain and use of pain medications were reduced with inconsistent results on quality of life improvement vs placebo (Bai 2017 **Level II**, n=134, JS 3; Lauretti 2015 **Level II**, n=40, JS 3). TENS plus thermotherapy reduced period pain and duration in pain vs placebo TENS, without impact on analgesic use or quality of life (Lee 2015a **Level II**, n=115, JS 3).

7.2.5 | Migraine

TENS use in migraine reduces affected days/mth (SMD -0.5; 95%CI -0.7 to - 0.2) and pharmacological treatment intake (SMD -0.8; 95%CI -1.1 to - 0.4) (Tao 2018 **Level I** [PRISMA], 4 RCTs, n=161). Similarly, TENS over the supraorbital nerve (for 12 wk) reduced days in migraine and days using rescue medications among patients with refractory migraine and not responding to topiramate (Vikelis 2017 **Level IV**, n=35).

One 60 min TENS session reduced pain intensity of acute migraine attacks at one and 24 h after treatment by 50%, and two-thirds of the patients did not require rescue pain medication at 24 h (Chou 2017 **Level IV**, n=30).

7.2.6 | Musculoskeletal pain

One 30 min TENS session reduces acute low back pain in an emergency setting (MD – 28.0/100; 95%CI – 32.7 to −23.3) (1 RCT, n=63), whereas a course of TENS for 4-5 wk does not reduce sub-acute low back pain (MD −2.8/100; 95%CI −11.6 to 6.1) (2 RCTs, n=132) (Binny 2019 **Level I**, 3 RCTs, n=192). The evidence is limited by low quality and insufficient sample size.

One TENS session over shoulder myofascial trigger points increased pressure pain threshold and improved range of motion vs sham intervention (Takla 2018 **Level II**, n=70, JS 3). Burst-TENS was superior to medium-frequency, low intensity amplitude modulated frequency treatment.

7.2.7 | Neuropathic and phantom limb pain

In patients with herpes zoster, 10 to 15 TENS sessions reduced pain and incidence of PHN vs anti-viral agent alone and TENS/anti-viral agents (Stepanovic 2015 **Level II**, n=222, JS 1). However, the trial reporting quality is very low.

A systematic review of TENS in the treatment of phantom limb pain found no studies (Johnson 2015a **Level I** [Cochrane], 0 RCTs, n=0). However, a subsequent RCT found TENS vs mirror therapy equally effective at reducing pain scores from baseline (Barbin 2016 **Level I** [PRISMA], 1 RCT: Tilak 2016 **Level II**, n=25, JS 3).

KEY MESSAGES

1. Transcutaneous electrical nerve stimulation compared to sham reduces acute pain (procedural and nonprocedural) (**U**) (**Level I** [Cochrane Review]), including pain after thoracic surgery (**U**) (**Level I** [PRISMA), after total knee replacement (**N**) and in the prehospital setting (**N**) (**Level I** [PRISMA]).
2. High-frequency transcutaneous electrical nerve stimulation is effective in primary dysmenorrhoea (**U**) (**Level I** [Cochrane Review]).
3. Transcutaneous electrical nerve stimulation has no effect on pain, interventions or outcomes in labour with the exception of a reduction of reports of severe pain when applied to acupuncture points (**U**) (**Level I** [Cochrane Review]).
4. Transcutaneous electrical nerve stimulation used preventatively in migraine reduces attack frequency and medication use (**N**) (**Level I** [PRISMA])

7.3 | Acupuncture and acupressure

Acupuncture, originally a Chinese practice, involves inserting fine needles through the skin at specific points (acupoints) to cure disease or relieve pain. However, the term acupuncture is often interpreted broadly in many meta-analyses to incorporate all forms of acupoint stimulation including by electroacupuncture (EA: where a small electric current is passed between pairs of acupuncture needles), laser (laser acupuncture), pressure (acupressure), transcutaneous electrical acupoint stimulation (TEAS), chemical (capsicum plaster) or heat (moxibustion). Acupuncture needling or acupressure can be applied to the specific points on the ears and this form of technique is called auricular acupuncture (AA) or auriculotherapy. Even for traditional needle-based acupuncture angle, depth, location, rotation, duration and temperature of needles can all vary between studies.

A significant amount of the literature is published in the Chinese language; these references were excluded from this assessment in line with the agreed methodology, although many quoted meta-analyses incorporate Chinese language papers.

Similar to other physical therapies, blinding in acupuncture studies is difficult to achieve. Options such as non-penetrative needles (eg toothpicks) or using real acupuncture needles in non-acupoint locations might blind the patient, but do not blind the proceduralist and may be unintentionally therapeutic (Langevin 2011 **NR**). Furthermore, both experienced proceduralists and patients may expect to feel *De qi* (the Chinese expression for the sensation of tingling, heaviness and numbness associated with the needle application and rotation). Placebo acupuncture needles which look identical but retract to a short needle on use may also not fool proceduralists and, similar to using acupuncture in non-acupoint locations, might also be unintentionally therapeutic (Langevin 2011 **NR**). In one RCT, 68% of patients and 83% of proceduralists correctly guessed their allocation (vs an expected 50% if blinding was appropriate) (Vase 2015 **Level II**, n=67, JS 5). These blinding issues combined with extremely heterogeneous methods for heterogeneous conditions and often small sample sizes weaken the strength of recommendations from pooled results of these meta-analyses.

For paediatric specific acupuncture information see 10.11.2.

7.3.1 | Postoperative pain

The effect of acupuncture on postoperative pain has been examined in different surgical procedures, such as cardiac, abdominal, orthopaedic, gynaecological and obstetric surgery.

Overall, acupuncture (excluding AA), compared with sham controls reduces postoperative pain at 24 h (WMD -1.27/10; 95%CI -1.83 to -0.71) and opioid consumption at 24 h (SMD -0.72; 95%CI -1.21 to -0.22) (Wu 2016 **Level I**, 11 RCTs, n=682). A subgroup analysis found TEAS (5 RCTs, n=305) reduces both pain and opioid consumption, needle acupuncture (2 RCTs, n=165) reduces pain, but EA has no effect (4 RCTs, n=212).

In a prior meta-analysis (9 RCTs overlap), all forms of acupuncture (body or auricular points) reduce postoperative pain (at 24 h) vs both sham controls (SMD -0.72; 95% CI -1.03 to -0.41) (23 RCTs, n=1,284) and standard treatment (SMD -1.05; 95% CI -1.44 to -0.67) (20 RCTs, n=1,227) (Liu 2015a **Level I**, 59 RCTS, n=4,578). Opioid analgesia use decreases (ME −4.99mg; 95%CI −7.51 to −2.47) (6 RCTs, n=399) over an unspecified time period.

Similar findings were reported for a number of specific postoperative settings as outlined below.

7.3.1.1 | Abdominal and general surgery

After open abdominal surgeries (including Caesarean section, gynaecological and general surgical), acupuncture vs sham or no treatment reduces postoperative pain at rest (≈-7 to -13/100) (18 RCTs, n=1,088), and with movement (≈-4 to -26/100) (6 RCTs, n=436) at 4 to 48 h, and reduces opioid consumption at 24 h (WMD -9.17 mg; 95%CI -12.47 to - 5.87) (13 RCTs, n=806) (Zhu 2019 **Level I** [PRISMA], 35 RCTs, n=2,015). Pain scores are less at 4 h in patients who receive distal acupuncture vs peri-incisional acupuncture. However, reduction of opioids at 24 h is four times more in the peri-incisional acupuncture group than that in distal acupuncture group. Distal acupuncture reduces the incidence of post-operative nausea and dizziness; however, this data was not reported in the studies of peri-incisional acupuncture.

Haemorrhoidectomy

After haemorrhoidectomy, 30 min EA around the surgical site vs sham reduced pain intensity at 6 h, 24 h and during defecation, with no difference in eating, sleeping and anxiety (Wu 2018 **Level II**, n=72, JS 3).

Hernia repair

Combined pre-emptive acupuncture on body points and intraoperative acupuncture at the incision site for open inguinal hernia repair reduced postoperative pain intensity at 0.5 to 6 h postoperatively as well as PCA requirements and dizziness (Taghavi 2013 **Level II**, n=90, JS 1). Pre- and intraoperative EA resulted in a late reduction in pain scores at POD 4 and 7 only (Dias 2010 **Level II**, n=33, JS 5). For inguinal herniorrhaphy under spinal anaesthesia, preoperative acupuncture on body points enhanced intraoperative sedation and reduced postoperative pain intensity and opioid requirements (Parthasarathy 2009 **Level II**, n=50, JS 3). Preoperative and intra-operative EA had similar pain reduction and opioid sparing effect in inguinal hernia (mesh) repair under general anaesthesia (Dalamagka 2015, **Level II**, n=54, JS 2).

Laparoscopic Surgery

Intraoperative EA for laparoscopic cholecystectomy had no impact on pain, PCA use or PONV vs no acupuncture (El-Rakshy 2009 **Level II**, n=107, JS 5). However, one to two sessions of postoperative acupuncture reduced shoulder pain in patients with established shoulder pain after laparoscopic abdominal surgery (mostly cholecystectomy) (mean reduction 6.4/10 [SD 2.3]) (Kreindler 2014 **Level IV**, n=25).

Appendicectomy

Sustained acupressure with an 'acuband' after open appendicectomy was better than sham control in relieving postoperative pain (Adib-Hajbaghery 2013 **Level II**, n=70, JS 3).

7.3.1.2 | Orthopaedic surgery

Lumbar spinal surgery

Needle acupuncture after lumbar spinal surgery reduces pain at 24 h (SMD -0.67; 95%CI -1.04 to -0.31) (Cho 2015 **Level I** [PRISMA], 5 RCTs, n=480). In addition to PCA, postoperative AA and TEAS improved pain scores vs sham only, and reduced opioid use vs both sham and control groups (Chung 2014 **Level II**, n=135, JS 3). During the rehabilitation phase, EA in addition to standard medical and physiotherapy care, reduced disability at 2 mth postoperatively, but did not reduce pain or improve quality of life (Heo 2018 **Level II**, n=39, JS 3).

Total Knee Arthroplasty

Perioperative acupuncture for TKA reduces pain at POD 2 (WM -1.14/10; 95%CI −1.90 to −0.38) and delayed time to first PCA use (WMD 46 min; 95%CI 20.8 to 71.5) (Tedesco 2017 **Level I** [PRISMA], 3 RCTs, n=230), with no effect on opioid consumption within the first 48 h. Acupressure may improve range of motion vs sham controls (He 2013 **Level II**, n=90, JS 5; Chang 2012 **Level II**, n=68, JS 5). During the rehabilitation phase, acupuncture in addition to exercise was not better than exercise alone either in reducing pain or improving function at 3 mth post TKA (Petersen 2018 **Level II**, n=172, JS 3).

Total Hip Arthroplasty

Perioperative AA or acupressure continuing into the postoperative period reduces pain after THA at 12 h, 24 h, 48 h, 72 h, POD 5, POD 7 (1 to 6 RCTs) and intraoperative fentanyl use (SMD -0.73; 95%CI -1.09 to -0.36) (3 RCTs, n=250) (Ye 2019 **Level I**, 9 RCTs, n=605). There were no differences in the time to first analgesic request or PONV.

Shoulder Surgery

One session of postoperative acupuncture performed in PACU reduced pain after arthroscopic shoulder surgery on POD1 and improved sleep quality vs non-acupuncture control (Ward 2013 **Level III-1**, n=22).

7.3.1.3 | Cardiac & thoracic surgery

Cardiac surgery

For cardiac surgery, EA started 20 to 30 min prior to induction of GA may improve some perioperative outcomes, but has no impact on opioid requirements (Asmussen 2019 **Level I** [PRISMA], 7 RCTs, n=321).

Preoperative EA administered 12–18 h before cardiac surgery (including myocardial revascularisation and valve replacement) reduced postoperative pain intensity (2.5/10 ± 1.1 vs 4.0/10 ± 2.0) and PCA fentanyl use by 41% vs placebo (Coura 2011 **Level II**, n=22, JS 5). Postoperative acupressure reduced pain intensity after cardiac surgery via median sternotomy and improved lung function vs acupressure to nonspecific points or no acupressure control (Maimer 2013 **Level II**, n=100, JS 5). When acupuncture was repeated daily for 7 d, the benefit for pain and lung function accumulated and improved over time (Colak 2010 **Level II**, n=30, JS 3).

Thoracic surgery

Repeated postoperative EA (delivered distant to the surgery site over three days) reduced post-thoracic pain at 2, 24, 48 and 72 h and breakthrough pethidine consumption (9.2 mg ± 2.8 vs 11.5 mg ± 1.8) (Chen 2016 **Level II**, n=92, JS 3). EA also reduced nausea (21.7% vs 47.8%) but not vomiting. There was shortened time to first flatus (24.3 h ± 8.2 vs 35.7 h ± 7.76) and defaecation (42.7 h ± 13.9 vs 59.2 h ± 11.3) n=).

7.3.1.4 | Gynaecological and obstetric surgery

Hysterectomy

After open hysterectomy, EA improved postoperative analgesia over 24 h vs control and sham acupuncture (Lee 2011 **Level II**, n=47, JS 3). Postoperative auricular EA applied ≈24 h after open hysterectomy reduced pain at rest and on movement vs control and sham stimulation (Tsang 2011 **Level II**, n=48, JS 5).

EA during surgery under general anaesthesia provided no benefit vs no acupuncture for pain, PCA opioid use or PONV after open hysterectomy and laparoscopic cholecystectomy (El-Rakshy 2009 **Level II**, n=107, JS 5).

Oncological surgery

After open gynaecological surgery for malignancy, EA was superior to traditional acupuncture in relieving pain initially but not at 48 h (Gavronsky 2012 **Level II**, n=20, JS 1).

Laparoscopic gynaecological surgery

Auricular EA did not affect pain or opioid requirements after laparoscopic gynaecological surgery (Holzer 2011 **Level II**, n=40, JS 5); whereas EA to body points delivered 24 h prior to surgery or during surgery reduced pain and PONV (Li 2017d **Level II**, n=40, JS 3; Praveena Seevaunnamtum 2016 **Level II**, n=64, JS 3).

Oocyte retrieval

For oocyte retrieval, conscious sedation plus EA reduces procedural and postoperative pain more than sedation plus placebo, or sedation alone (Kwan 2018 **Level I** [Cochrane], 6 RCTs, n=1,159). However, a paracervical block achieves lower procedural pain scores than EA (4 RCTs, n=781).

Caesarean section

After Caesarean section, postoperative EA and acupuncture reduced pain scores and PCA requirements for up to 2 h (Wu 2009 **Level II**, n=60, JS 3).

7.3.1.5 | Ear, nose and throat surgery

For tonsillectomy, perioperative acupuncture vs sham or no therapy reduces pain for the first 48 h, postoperative analgesia requirements and PONV (Cho 2016 **Level I** [PRISMA], 12 RCTs, n=1,025 [11 RCTs in children & adolescents, 1 in adults]).

Battlefield auricular acupressure vs usual care reduces post-tonsillectomy pain in adults at discharge, with no effect on pain or opioid use at POD 10 (Plunkett 2018 **Level II**, n=95, JS 3).

7.3.1.6 | Neurosurgery

TEAS vs placebo reduces post craniotomy pain, PCA fentanyl use from 0 to 6 h and reduces dizziness and feelings of "a full head" up to 24 h (Tsaousi 2017 **Level I** [PRISMA], 2 RCTs [TEAS], n=176).

7.3.2 | Other acute pain states

7.3.2.1 | Emergency department and acute trauma setting

AA including acupressure improves pain relief vs control treatment for pain due to acute hip fracture (1 RCT), acute biliary colic (1 RCT) and acute burn and acute emergency conditions (SMD 1.35; 95%CI 0.08 to 2.64) (2 RCTs, n=111) (Asher 2010 **Level I** [PRISMA], 4 RCTs [acute pain], n=197). These findings were confirmed in a later meta-analysis which found AA vs sham or standard care reduces pain (WMD -2.6/10; 95%CI -2.00 to -3.22) but had a variable effect on analgesic use with only 1 of 3 studies reporting a difference (Jan 2017a **Level I** [PRISMA], 4 RCTs, n=281) (3 RCTs overlap). Adverse effects of AA were documented in only 2 studies in which minor pain was experienced in 2 patients. It takes about 2 to 10 min to apply the treatment at the cost of AU$7.50 per patient (Jan 2017b **Level I** [PRISMA], 4 RCTs, n=281).

Needle acupuncture on the body was faster (16 ± 8 min vs 28 ± 14 min) and more successful (92% vs 78%) at reducing pain by 50% with less nausea and vomiting vs IV morphine control (mean dose 0.17 mg/kg ± 0.08) (Grissa 2016 **Level II**, n=300 [46% abdominal pain, 54% musculoskeletal or other pain], JS 3). Similarly, for renal colic a 30 min acupuncture session vs

titrated IV morphine achieved a 50% pain reduction faster (14 min vs 28), with far fewer patients experiencing side effects (acupuncture 3/54 vs morphine 42/61) (Beltaief 2018, **Level II**, n=115, JS 3). An RCT of acupuncture vs acupuncture/pharmacotherapy vs pharmacotherapy alone for back pain, ankle sprain and migraine found no difference between pain scores at 1 h or satisfaction at 1 h or 24 h (Cohen 2017 **Level II**, n=528, JS 3). The acupuncture alone group required more rescue analgesia vs the pharmacology alone and combination groups, with lower hospital admission rate in the combination group.

Acupuncture reduced pain (by 2.3/10) and nausea (by 1.2/6) in patients with acute pain vs retrospectively matched controls, with a high satisfaction rate (98%) (Zhang 2014 **Level III-3**, n=400 [59% musculoskeletal, 25% abdominal pain]). Acupuncture treatment provided before medical consultation reduced the staff time spent managing the patient vs acupuncture given after medical consultation.

Acupuncture vs sham reduced pain on movement in bed and cough after rib fracture but not pain on deep breathing (Ho 2014 **Level II**, n=58, JS 5). Acupressure reduced acute musculoskeletal pain due to sports injuries vs sham or no acupressure (Macznik 2017 **Level II**, n=79, JS 3).

In acute pain due to sports injury, athletes had significant pain reduction (4 to 8/10) after auricular acupuncture treatment (deWeber 2011 **Level IV**, n=8).

Acupressure performed during prehospital transport led to better pain relief vs sham acupressure after hip fracture (auricular) (Barker 2006 **Level II**, n=38, JS 5) and radial fracture (Lang 2007 **Level II**, n=32, JS 5), and after minor trauma vs sham and no acupressure (Kober 2002 **Level II**, n=60, JS 5).

7.3.2.2 | Acute back pain

Compared to sham acupuncture, one session of acupuncture reduces pain intensity (MD -9.38/100; 95%CI -17.00 to -1.76) (2 RCTs, n=100) but not function or disability in acute back pain (3 RCTs, n=148) (Lee 2013 **Level I** [PRISMA], 11 RCTs, n=1,139). Slightly more patients improved with acupuncture than NSAIDs (RR 1.11; 95%CI 1.06 to 1.16) (5 RCTs, n=662).

In a large well-designed RCT, five sessions of acupuncture over 14 d were added to conventional treatment for acute low-back pain (Vas 2012 **Level II**, n=275, JS 5). Acupuncture was more effective in reducing pain and analgesic use and improving work readiness vs conventional treatment alone; but there was little difference between real acupuncture, sham acupuncture (penetrating) and placebo acupuncture (nonpenetrating). One session of acupuncture with concurrent gentle exercise produced better analgesia for severely disabling acute low-back pain (Oswestry Disability Index [ODI] value ≥60%) than diclofenac (75 mg IM) (Shin 2013 **Level II**, n=58, JS 3). Patients in the acupuncture group had less pain at 30 min after treatment (MD 3.12/10; 95%CI 2.26 to 3.98), much improved function (decreased ODI by 33%; 95%CI 27 to 39) and fewer hospital admissions (66 vs 93%). The pain reduction was maintained at 2 wk and 4 wk follow-up.

Battlefield AA plus standard therapy has better pain reduction for acute low back pain in ED over standard care alone with no differences in functional recovery (Fox 2018 **Level II**, n=30, JS 3). Acupuncture with concurrent lumbar exercise has better sustained pain reduction in acute lumbar sprain than conventional acupuncture, sham intervention or TENS at 24 h (Lin 2016 **Level II**, n=60, JS 3). Similar results are shown in a cohort study (Liu 2015c **Level III-2**, n=74).

Acupuncture plus spinal manipulation has similar pain reduction in sub-acute low back pain vs acupuncture alone or spinal manipulation alone (Kizhakkeveettil 2017 **Level II**, n=101, JS 3).

7.3.2.3 | Labour and post-partum pain

With regard to use of acupuncture in labour (Smith 2020 **Level I** [Cochrane], 28 RCTs, n=3,960):

- Acupuncture vs sham does not reduce pain scores (2 RCTs, n=325), but does increase satisfaction with pain relief (RR 2.38; 95%CI 1.78 to 3.19) (1 RCT, n=150) and decrease use of pharmacological analgesia (RR 0.75; 95%CI 0.63 to 0.89);
- Acupuncture vs usual care reduces pain scores (4 RCTs, n=495) and use of pharmacological analgesia (6 RCTs, n=1,059) but does not improve satisfaction (2 RCTs, n=343).
- Acupuncture vs no treatment reduces pain scores (1 RCT, n=163);
- Acupuncture vs water injection did not reduce use of pharmacological analgesia (1 RCT, n=128);
- Acupressure vs sham lowered VAS (MD -1.93/10; 95%CI -3.31 to -0.55) but had no effect on use of pharmacological analgesia (6 RCTs, n=472);
- Acupressure vs usual care reduced VAS (SD -1.07; 95%CI -1.45 to -0.69) (8 RCTs, n=620) and improved satisfaction (1 RCT, n=105);
- Acupressure vs both placebo and usual care reduced VAS (-0.42 SD; 95%CI -0.65 to -0.18) (2 RCTs, n=322) and marginally increased satisfaction with analgesia (1 RCT, n=212).

There was no effect on Caesarean section rate for all interventions. No study was at a low risk of bias on all domains.

Note: reversal of conclusion
This reverses the Level I key message in the previous edition of this document; a preceding meta-analysis had described a reduction of Caesarean section rate by use of acupuncture.

A critical review (Levett 2014 **NR**) of the previous iteration of this and another meta-analysis (Cho 2010 **Level I**, [PRISMA], 10 RCTs, n=2,038) suggests that these meta-analyses may compare very different approaches in very different settings, in particular by comparing trials of efficacy with trials of effectiveness.

TEAS provided inferior analgesia in labour vs epidural (SMD -53.00/100; 95%CI -58 to -48) or tramadol/ondansetron PCA but was superior to placebo (Anim-Somuah 2018 **Level I** [Cochrane], 1 RCT: Liu 2015b **Level II**, n=120, JS 3).

Patients with mastitis are less likely to have severe symptoms 5 d after acupuncture in 1 of 2 RCTs (Mangesi 2016 **Level I** [Cochrane], 2 RCTs, n=293).

Auricular acupressure (by taping seeds to the ear) did not reduce acute postpartum perineal pain in women with 1st or 2nd degree tears or episiotomies (Kwan 2014 **Level II**, n=266, JS 3) contrasting with a previous study where wrist-ankle needle acupuncture for perineal pain after episiotomy reduced requirements for rescue analgesia vs controls (Marra 2011 **Level III-1**, n=42) (See also section 9.1.3.5).

7.3.2.4 | Dysmenorrhoea

Acupuncture may reduce pain in primary dysmenorrhoea vs NSAIDs (14 RCTs, n=850) or no-acupuncture controls (6 RCTs, n=384), but not vs sham or placebo controls (6 RCTs, n=477); whereas acupressure reduces pain vs sham or placebo control (5 RCTs, n=538), but not vs NSAIDs (1 RCT, n=136) or no treatment (2 RCTs, n=140) (Smith 2016 **Level I** [Cochrane], 42 RCTs, n=4,640). Only one of the 42 RCTs was considered of low risk of bias in all domains and generally data was unsuitable for pooling due to heterogeneity.

A subsequent network meta-analysis found acupuncture may be more effective than NSAIDs in reducing the risk of pain episodes of primary dysmenorrhoea, with EA being the most effective (Luo 2019a **Level I** [NMA]**,** 17 RCTs, n=1,511). Another systematic review found EA more effective than needle acupuncture or NSAIDs (Woo 2018 **Level I** [PRISMA], 60 RCTs, n=5,901) (6 RCT overlap). While, another meta-analysis found acupuncture (pooled all types) reduces symptom severity scores (6 RCTs, n=621) but not pain scores (2 RCTs, n=168) (Xu 2017 **Level I** [PRISMA], 19 RCTs, n=1,690) (5 RCTs overlap with Smith 2016).

Acupressure to SP6 (a lower leg acupoint) delivered by trained therapists reduces pain in primary dysmenorrhoea vs controls and the effect lasts for 3 h (5 RCTs), whereas patient self-administered acupressure does not reduce pain immediately, and takes 3 mth to be effective (3 RCTs) (Abaraogu 2016 **Level III-1 SR** [PRISMA], 5 RCTS & 1 study, n=461).

7.3.2.5 | Dental pain

Acupuncture may be useful for pain during dental procedures (Ernst 1998 **Level I**, 16 RCTs, n=941). Acupuncture reduced dental pain from 6.6/10 to ≈1.0/10 in an ED case series, with 119/120 patients responding (Grillo 2014 **Level IV**, n=120).

7.3.2.6 | Acute neuropathic pain

In severe pain due to acute herpes zoster (NRS >7/10), acupuncture was as effective as standard pharmacological treatment (pregabalin, local anaesthetics and TD buprenorphine or oral oxycodone) at 4 wk (Ursini 2011 **Level II**, n=102, JS 3).

7.3.2.7 | Headache

Acupuncture (at least 6 sessions) provides clinically relevant improvement in pain for tension type headache (TTH) over 3 mth vs standard care (2 RCTs, n=1,472), but only minimal clinical improvement vs sham treatment (5 RCTs, n=703) (Linde 2016a **Level I** [Cochrane], 12 RCTs, n=2,349).

Similarly, acupuncture reduces migraine frequency at 3 mth vs no treatment or routine care (4 RCTs, n=2,199), but only minor improvements were seen vs sham treatments (14 RCTs, n=1,825) (Linde 2016b **Level I** [Cochrane], 22 RCTs, n=4,985). Acupuncture reported fewer adverse effects (5 RCTs, n=931) vs pharmacological prophylaxis and acupuncture was slightly superior at 3 mth but not at 6 mth (3 RCTs, n=739). A subsequent RCT also found a prophylactic effect of EA (5 sessions per wk for 12 wk) on migraine (Li 2017a, **Level II**, n=61, JS 3).

In the guidelines for headache by the National Clinical Guideline Centre of the UK, 10 sessions of acupuncture are recommended for TTH treatment and as a prophylaxis, and for migraine when prophylactic medications are ineffective (NICE 2012 **GL**).

Acupuncture vs sham as a treatment for acute migraine attacks reduced pain intensity, but had no impact on pain freedom at or beyond 24 h or risk of recurrence (Wang 2012 **Level II**, n=150, JS 5).

AA was marginally better than sham acupuncture at 15, 30, 45 and 60 min in reducing migraine pain and recurrent analgesia usage within 24 h occurred in 1/30 of AA vs 13/30 of sham patients (Farahmand 2018 **Level II**, n=60, JS 3).

7.3.2.8 | Other painful conditions

Battlefield AA reduced sore throat vs standard therapy (Moss 2015, **Level II**, n=54, JS 3). Acupressure also reduced procedure pain and anxiety related to venepuncture over sham or standard care (Hosseinabadi 2015, **Level II**, n=187, JS 2).

Acupuncture may reduce post-stroke pain (MD −1.59/10; 95%CI −1.86 to −1.32]) when added to routine rehabilitation (25 RCTs), however with low certainty due to poor study quality (Liu 2019 **Level I** [PRISMA], 38 RCTs, n=3,184).

KEY MESSAGES

1. Acupuncture and acupressure for labour pain may reduce pain, use of pharmacological pain relief and increase satisfaction with pain management versus standard care or placebo (**Q**) (**Level I** [Cochrane Review]); Caesarean section rates are unchanged (**R**) (**Level I** [Cochrane Review]).
2. For oocyte retrieval, electroacupuncture plus sedation reduced procedural and postoperative pain compared with sedation plus placebo or sedation alone (**U**), but may be inferior to paracervical block plus sedation (**Q**) (**Level I** [Cochrane Review]).
3. Acupuncture or acupressure may be effective in the treatment of primary dysmenorrhoea (**S**) (**Level I** [Cochrane Review]).
4. Acupuncture may reduce the frequency of tension-type headaches and migraine (**U**) (**Level I** [Cochrane Review]); in migraine, it may be better tolerated than pharmacological prophylaxis (**N**) (**Level I** [Cochrane Review]).
5. Acupuncture may be effective in a variety of acute pain conditions in the emergency department setting (**S**) (**Level I** [PRISMA]) including back pain (**N**) (**Level I** [PRISMA])
6. Acupuncture by a variety of techniques may reduce postoperative pain and opioid consumption for a variety of surgical types (**S**) (**Level I**); specifically, the benefit may occur after lumbar spinal surgery (**U**) (**Level I** [PRISMA]), total knee arthroplasty (**U**) (**Level I** [PRISMA]), total hip arthroplasty (**N**) (**Level I**) and craniotomy (**N**) (**Level I** [PRISMA]).
7. There is no difference between distant acupuncture and acupuncture at the incisional site for open abdominal surgery (**S**) (**Level I** [PRISMA]).
8. Acupuncture may reduce post-stroke pain (**N**) (**Level I** [PRISMA]).

7.4 | Photobiomodulation

Photobiomodulation (PBM), previously called low-level laser therapy (LLLT), is the application of non-thermal laser in the red and near-infrared light wave lengths (600 to 1,000 nm) to tissue in order to produce biological effects. Light-matter interactions are well appreciated to occur where the encounter between a photon (or series of photons) causes the biology to enter an altered energetic state which causes an altered function. Sometimes this is destructive (eg UV and DNA), other times the effects are transient. PBM has multiple potential mechanisms of action including the displacement of inhibitory nitric oxide from cytochrome c oxidase increasing mitochondrial ATP production as well as interaction with light-sensitive ion channels, ultimately resulting in reversible inhibition of peripheral nerve conduction (Chow 2011 **SR EH BS**, 44 studies [18 human, 26 animal]) and reduced levels of prostaglandin E2 and inflammatory mediators (de Freitas 2016 **NR**). Studies vary in both total energy (J), energy density (J/cm^2) and wavelength of light used.

7.4.1 | Mucositis and stomatitis

A systematic review of PBM for recurrent aphthous stomatitis could not carry out a meta-analysis, but reports pain relief in 5 of 6 RCTs immediately after treatment, and 7 of 9 RCTs in the days following treatment (Suter 2017 **Level I**, 10 RCTs, n=512).

PBM may be effective in reducing pain intensity, severity and duration of mucositis based on moderate evidence (Anschau 2019 **Level I** [PRISMA], 5 RCTs, n=315). This is in line with findings of two small low-quality RCTs not included in the meta-analysis (Abramoff 2008 **Level II**, n=11, JS 2; Arora 2008 **Level II**, n=28, JS 2).

PBM used prophylactically reduces the risk of severe mucositis and pain in patients with cancer or undergoing hematopoietic stem cell transplantation (Oberoi 2014 **Level I** [PRISMA], 18 RCTs, n=1,144). This approach is recommended in a specific clinical practice guideline (Zadik 2019 **GL**).

For more details see also Section 8.9.8.2 and for paediatric mucositis see Section 10.8.3.1.

7.4.2 | Maxillofacial, ENT and dental surgery

After surgical removal of third molars, PBM reduces postoperative pain on POD 2 (WMD -1.42/10; 95%CI -2.18 to -0.67) (11 studies, n=434) and less on POD 7 (WMD -0.59/10; 95%CI -0.96 to -0.22) (10 studies, n=350) (Dawdy 2017 **Level III-2 SR [**PRISMA], 11 studies, n=434). However, studies were assessed as high risk of bias in multiple domains and had high heterogeneity. Similarly, an earlier meta-analysis finds reductions in pain from POD 1 to POD 3 after 3rd molar surgery (He 2015 **Level III-2** [PRISMA], 4 RCTs, n=150) (3 RCTs overlap). A subsequent study also showed reductions in postprocedural pain (Singh 2019 **Level III-2**, n=25).

After Le Fort I osteotomy in patients acting as their own controls, PBM vs no treatment reduced pain on the irradiated side of the face at 24 and 72 h after surgery, but not during the immediate post-operative assessment and there was no pain on either side by POD 7 (Bittencourt 2017 **Level III-2 SR** [PRISMA], 1 study: Gasperini 2014 **Level III-2**, n=10).

After orthodontic treatment with fixed appliances in children and young adults, 11 of 13 studies reported a reduction in acute pain, however, no meta-analysis was performed and studies were broadly of low quality (Sonesson 2016 **Level III-1 SR** [PRISMA], 13 studies, n=333).

Paracetamol usage in children undergoing secondary palatal surgery was reduced by PBM (970 nm, 2 W, 35 J/cm^2) vs undescribed placebo on POD 2 and POD 3 (Ezzat 2016 **Level II**, n=20, JS 2).

See also orofacial pain in Section 8.6.7.

7.4.2.1 | Tonsillectomy

Immediately after tonsillectomy in 5 to 15 y old children, intraoperative PBM (685 nm, 4 J/cm^2) vs no treatment reduced pain scores on POD 1, POD 2, POD 4 and POD 5 as well as the need for breakthrough non-opioid analgesic on POD 1 (45% vs 100%) (Neiva 2010, **Level II**, n=18, JS 1).

Intraoperative PBM (980 nm, 4 J/cm^2) applied immediately after tonsillectomy in adults vs unpowered probe application reduced mean pain scores in the first 24 h (1.43/4 vs 2.11/4) and need for rescue opioids (6.6% vs 33.3%) (Aghamohammadi 2013 **Level II**, n=60, JS 1).

7.4.2.2 | Vascular access

PBM reduces the incidence of needle pain during arteriovenous fistulas access vs placebo (RR 0.08; 95%CI 0.06 to 0.10) (Wan 2017 **Level I**, 3 RCTs, n=186), however, heterogeneity was reported as high.

7.4.2.3 | Cardiothoracic surgery

PBM (660 nm, 6 J/cm^2, 2.4 J) reduced sternotomy pain after CABG surgery on POD 6 and POD 8 vs both placebo and usual care groups, but all groups had negligible pain 1 mth after surgery (Fernandes 2017 **Level II**, n=90, JS 4).

After off-pump CABG surgery, pain was reduced post PBM (980 nm, 10 J/cm^2, 150 J; commenced 30 min post-extubation) at 1 h and 24 h vs pre-PBM levels (Karlekar 2015 **Level IV**, n=100).

7.4.2.4 | Musculoskeletal pain and orthopaedic surgery

After the first presentation with acute ankle sprain, two sessions of PBM (635 nm, 4.5 and 9 J/cm^2), in addition to standard care of rest, icing, compression and elevation, did not reduce pain at 10 d or 6 wk vs standard care (Calin 2019, **Level II**, n=19, JS 2).

After tibial fracture surgery, PBM (808 nm, 6 J/cm^2 and 650 nm, 3 J/cm^2) reduced pain scores from 2 h to 24 h and IV pethidine administration over 24 h (51.6 mg ± 29.5 vs 89.3 ± 35.5) (Nesioonpour 2014b **Level II**, n=54, JS 1).

In patients undergoing radius fracture fixation under intravenous regional anaesthesia (IVRA) the addition of cervical and affected extremity PBM (808 nm) reduced procedural and post procedural pain and opioid consumption (Nesioonpour 2014a **Level II**, n=48, JS 3).

After total hip arthroplasty, PBM (905 nm, 875 nm and 640 nm, total 201.5 J) reduced pain scores from baseline more vs placebo, as well as IL-8 and TNF-α concentrations (Langella 2018 **Level II**, n=18, JS 5). However, pain scores were higher in the PBM group initially and absolute pain scores were not reported in the study.

7.4.2.5 | Labour, puerperium and Caesarean section

After episiotomy, PBM (780 nm or 660 nm, 8.8 J/cm^2, 1.05 J) did not reduce pain immediately or at 30 min (Santos Jde 2012 **Level II**, n=114, JS 5). A subsequent RCT had similar findings with PBM (780 nm, 5 J/cm^2, 5.4 J) applied 6-10 h postpartum for episiotomy being ineffective for pain (Alvarenga 2017 **Level II**, n=54, JS 5).

PBM (650 nm and 804 nm, total 21 to 30 J) after Caesarean section under spinal reduced pain at 1 h to 24 h and pethidine consumption (57.83 mg ± 29.57 vs 107.78 mg ± 34.28) and prolonged time to first analgesia request (226.5 min ± 14.56 vs 88.5 min ± 15.78) (Poursalehan 2018 **Level II**, n=80, JS 2).

7.4.2.6 | Other surgery

After breast augmentation, application of pre-incision PBM (630 to 640 nm) reduced pain scores at 24 h (21.4/100 vs 36.8) but not at 7 d to 28 d (Jackson 2009 **Level II**, n=104, JS 2).

Post open inguinal herniorrhaphy, PBM (830 nm, 13 J/cm^2, 10.4 J) on POD 1 , POD 3 and POD 7 did not reduce pain scores at 6 mth (Carvalho 2010, **Level II**, n=28, JS 3).

KEY MESSAGES

1. Photobiomodulation may be effective for both prophylaxis and treatment of mucositis in oncology patients (**S**) (**Level I** [PRISMA]).
2. Photobiomodulation may reduce pain after 3rd molar extraction (**N**) (**Level I** [PRISMA]).
3. Needle related pain after arteriovenous fistula access may be reduced by photobiomodulation (**N**) (**Level I**)
4. After episiotomy, photobiomodulation may not reduce pain (**N**) (**Level II**).

The following tick box represents conclusions based on clinical experience and expert opinion:

☑ Photobiomodulation may have a role in acute postsurgical pain management, however evidence is currently insufficient to make any furrher recommendations (**N**).

7.5 | Physical therapies

Physical therapies for acute pain management are typically adjunctive to the psychological and pharmacological treatments discussed elsewhere in this book. The physical therapies covered in this section include the active therapies of exercise, prehabilitation and rehabilitation as well as the passive therapies of massage and other manual therapies, warming and cooling. Other passive physical therapies discussed elsewhere include TENS (see Section 7.2), acupuncture (see Section 7.3) and PBM (low-level laser therapy [LLLT]) (see Section 7.4). Specific conditions addressed elsewhere include acute back pain (see Section 8.7) and acute musculoskeletal pain (see Section 8.8). Some therapies such as aromatherapy which are not considered core physical therapies for acute pain are not covered in this chapter, but in complementary and alternative medicine (see Section 4.14.3).

Evidence for the benefits and harm of physical therapies in acute pain management is variable. The use of physical therapies for acute pain management should reflect contemporary practice guidelines promoting the use of active self-management (including exercise) rather than a sole focus on passive therapies. Physical therapies typically incorporate contemporary education on pain, including the provision of clear and meaningful information and advice about the management of acute pain and this component is covered under education (see Section 3.1).

The evidence for physical therapies is currently limited by wide heterogeneity of multimodal interventions and conditions, limited studies with small sample sizes and difficulties with consistent blinding leading to a risk of bias.

This section focuses on the effect of physical therapies on pain outcomes; other benefits may be present but have not been thoroughly reviewed.

7.5.1 | Active exercise-based therapies

7.5.1.1 | Exercise

Total joint arthroplasty

Exercises carried out preoperatively before total knee arthroplasty (TKA) do not improve postoperative pain at 4 wk (2 RCTs, n=224) or 8 wk (3 RCTs, n=242) vs standard interventions (Umehara 2018 **Level I**, 27 RCTs**,** n=2,432). An exercise intervention in addition to standard postoperative interventions for 8 wk after discharge, reduces pain relative to standard postoperative interventions alone (SMD −0.65; 95%CI −1.22 to −0.08) and improvement in function (eg stiffness, extension strength, knee flexion range and gait speed). No differences are found for implementation of early vs late postoperative exercise for pain outcomes at 4 wk (2 RCTs, n=573) or 8 wk (2 RCTs, n=318) (Umehara 2018 **Level I**, 27 RCTs**,** n=2,432).

After total hip replacement (THA), adding supervised exercise (two 30 to 40 min sessions/wk for 10 wk) did not further increase leg extension, but improved walking speed and stair climbing speed vs non-supervised exercise alone (Hansen 2019 **Level I** [PRISMA], 1 RCT: Mikkelsen 2014, **Level II**, n=60, JS 3).

Meniscal lesions

There is no significant difference in knee pain between exercise therapy and meniscectomy for patients with a degenerative meniscal lesion in the short term (2 studies, n=125) (Swart 2016, **Level III-1 SR**, 12 studies, n=594). Even at two to three mth follow-up, exercise or an exercise-

based physical therapy program vs arthroscopic partial meniscectomy results in no difference in pain (3 RCTs, n=344) (van de Graaf 2016, **Level I** [PRISMA], 6 RCTs, n=773).

The outcomes of exercise therapy versus no exercise therapy after meniscectomy at <3 mth are conflicting (2 RCTs, n=125), with one study finding a significant benefit of exercise on knee pain, while the other did not; however, data could not be pooled due to the measurement of pain at different time points (Swart 2016 **Level I**, **Level III-1 SR**, 12 studies, n=594).

Anterior cruciate ligament (ACL) reconstruction

Immediate postoperative weight bearing significantly decreased the proportion of patients reporting pain symptoms 2 wk after anterior cruciate ligament (ACL) reconstruction and did not increase joint laxity vs patients who had 2 wk delayed weight bearing (Secrist 2016 **Level I** [PRISMA] 1 RCT: Tyler 1998 **Level II**, n=45, JS 2).

Ankle sprains

Compared with home exercise programs, physiotherapy supervised rehabilitation resulted in less pain and subjective instability at 8 wk after ankle sprain (Feger 2015 **Level I,** 1 RCT: van Rijn 2009, **Level II**, n=102, JS 3).

Dysmenorrhoea

Physical activity (single or co-intervention) in any setting or via any mode for the treatment of primary dysmenorrhea (non-athlete females with regular menstruation not using hormonal contraception) reduces pain intensity (MD -1.89/10; 95%CI -2.96 to -1.09) and pain duration (MD -3.92 h; 95%CI -4.86 to -2.97) (Matthewman 2018 **Level I** [PRISMA], 11 RCTs, n=817 [intensity] & n=469 [duration]). Yoga (20 min/day for 14 d/cycle) vs no treatment improved pain intensity from dysmenorrhea at 1 mth (MD -3.2/10; 95%CI -2.2 to -4.2) (Kannan 2014 **Level I**, 1 RCT: Rakhshaee 2011, **Level II**, n=92, JS 1). Overall quality of this evidence was rated as low due to high risk of bias.

Labour pain

The use of birth ball exercises for labour pain relief improves pain (MD -0.9/10; 95% CI -1.3 to -0.6) (Makvandi 2015, **Level I**, 3 RCTs, n=205). Overall, the quality of the studies was mixed, with most providing little information on the exact methods they used**.**

KEY MESSAGES

1. Following total knee arthroplasty, an exercise intervention in addition to standard post-operative interventions for 8 weeks after discharge may reduce pain and improve function (**N**) (**Level I**).
2. In primary dysmenorrhoea, exercise may reduce acute pain intensity and pain duration (**N**) (**Level I**).
3. Use of a birth ball may improve labour pain (**N**) (**Level I**).

The following tick boxes represent conclusions based on clinical experience and expert opinion:

☑ Clear recommendations on the components of exercise interventions (including time point of application, frequency, mode, dose and duration) for acute postoperative pain management cannot be made; different surgical procedures may require different exercise-based interventions (**N**).

☑ Immediate post-operative weight bearing post anterior cruciate ligament reconstruction may reduce pain and does not appear to result in increased joint laxity (**N**).

Total joint arthroplasty

Following TKA, despite improvements in function and quadriceps strength, there was no effect of prehabilitation on postoperative pain pooled across heterogeneous time points and scales nor were significant differences were found at ≤6 wk (3 RCTs) or 3 mth (9 RCTs) (Moyer 2017 **Level I** [PRISMA], 16 RCTs, n=1,178). Multiple systematic reviews and meta-analyses with significant study overlap come to the same conclusion, with no significant effects demonstrated for:

- Pain intensity at 1 mth (2 RCTs, n=297) or WOMAC scores at 3 mth (3 RCTs, n=252) (Cabilan 2016 **Level I**, 5 RCTs, n=549);
- Pain measured variously by WOMAC (5 RCTs), SF-36 (4 RCTs) or VAS (2 RCTs) (Kwok 2015, **Level III-1 SR**, 8 studies, n=619);
- WOMAC pain intensity between 1.5 and 3 mth (Chen 2018 **Level I**, 7 RCTs, n=424);
- Pain at 6 or 12 wk (Tedesco 2017, **Level I** [PRISMA], 3 RCTs, n=110).

For THA, in addition to improving function, prehabilitation reduces postoperative pain scores vs usual care when pooled across heterogeneous time points (SMD 0.15; 95% CI 0.03 to 0.27) (Moyer 2017, **Level I** [PRISMA], 13 RCTs, n=905). When analysed at specific time periods, pain scores are reduced at 3 mth vs usual care (3 RCTs) (SMD 0.34; 95%CI 0.07 to 0.62), but not at ≤6 wk (7 RCTs) or 6 mth (3 RCTs).

When any joint replacement surgery was considered, prehabilitation reduces pain at 4 wk or less (assessed by multiple scales: WOMAC, VAS, Knee injury and Osteoarthritis Outcome Score (KOOS) and 10 graded scale, subsequently converted to WOMAC 0-100 subscales) (WMD -6.1/100; 95%CI -10.6 to -1.6) (Wang 2016 **Level I** [PRISMA]**,** 2 RCTs, n=105 [THA] & 2 RCTs, n=114 [TKA]). The authors noted a low overall quality of evidence in these trials. No significant difference between prehabilitation and usual care groups for pain is seen at 6 to 8 wk (5 RCTs, n=488) or 12 wk (10 RCTs, n=806) post-operation.

Anterior cruciate ligament (ACL) reconstruction

For ACL reconstruction, despite improving function and strength, prehabilitation does not significantly improve patient reported pain vs controls (Alshewaier 2015 **Level I** [PRISMA], 3 RCTS, n=291).

Spinal Surgery

For spinal surgery, in spite of earlier discharge times and reduced time to functional milestones, prehabilitation did not improve pain at one or 3 mth (Cabilan 2016 **Level I**, 1 RCT: Nielsen 2010, **Level II**, n=60, JS 3).

Dosing of prehabilitation

A systematic review looking at prehabilitation duration in TKA, THA and spinal surgery patients shows no effects of quantity on WOMAC pain scores (Cabilan 2015 **Level I** [PRISMA], 2 RCTs [<500 min], 3 RCTs [500-999 min], 2 RCTs [1,000-1,499 min], 2 RCTs [>= 1,500 min]). A single RCT (n=23) in the 1,000 to 1,499 min range reported an improvement in pain intensity (5.5/10 ± 2.2 vs 7.3/10 ± 2.0), but not WOMAC scores.

KEY MESSAGES

1. Prior to total hip arthroplasty, prehabilitation may reduce postoperative hip pain at 3 months (**N**) (**Level I** [PRISMA]).

The following tick box represents conclusions based on clinical experience and expert opinion:

☑ A recommendation for the specific type of prehabilitation and dosing parameters cannot be made at this time (**N**).

7.5.1.3 | Rehabilitation

Spinal Surgery and Injuries

After spinal surgery, physiotherapy commenced within the first 4 wk reduces pain at 12 wk (SMD -0.38; 95%CI -0.66 to -0.10) and 12 to 18 mth (SMD -0.30; 95%CI -0.59 to -0.02) vs no or sham physiotherapy (Snowdon 2016 **Level I** [PRISMA], 4 RCTs, n=250). Early comprehensive physiotherapy (active rehabilitation, education on the performance of daily functional tasks, functional weight-bearing exercise, cardiovascular endurance exercise, lower limb strengthening and dynamic proximal stabilisation) does not increase the risk of adverse events (3 RCTs, n=196).

For osteoporotic vertebral compression fractures, spinal orthoses reduce pain (SMD -1.47; 95%CI -1.82 to -1.13) vs no intervention over the medium term (Rzewuska 2015 **Level I**, 2 RCTs, n=170). However, there was no difference in pain between a proprietary spinal orthosis (SpinoMed®) and a soft lumbar orthosis at short-term follow up (Li 2015 **Level II**, n=51, JS 1).

Total knee arthroplasty (TKA)

After TKA, accelerated physiotherapy (starting within 24 h) versus standard physiotherapy (after bed rest for 24 h) reduced time to discharge by 2.1 days (± 1.45) and pain at the time of discharge (MD −0.96/10; 95%CI −1.21 to −0.71) (Henderson 2018, **Level I** [PRISMA], 1 RCT: Labraca 2011, **Level II**, n=273, JS 3). Twice daily vs once daily physiotherapy did not significantly reduce pain (Henderson 2018, **Level I** [PRISMA], 1 RCT: Lenssen 2006 **Level II**, n=43, JS 3).

After TKA, continuous passive motion (CPM) does not improve pain vs standard care over the short term (< 6 wk) (Tedesco 2017 **Level I** [PRISMA], 9 RCTs, n=1,025; Harvey 2014, **Level I** [Cochrane], 8 RCTs, n=414) (7 RCTs overlap). No difference was found for adverse events.

Anterior cruciate ligament (ACL) reconstruction

After outpatient ACL reconstruction, the role of mobilisation strategies was investigated (Secrist 2016 **Level I** [PRISMA], 3 RCTs, n unspecified). Individual trials showed that CPM use for 16 h/d immediately after surgery did not decrease pain vs controls, but did decrease PCA usage (41 mg ± 18.9 vs 65 mg ± 21.4) (Secrist 2016 **Level I** [PRISMA], 1 RCT: McCarthy 1993 **Level II**, n=35, JS 1). A continuous active motion device, in which the patient used the contralateral leg to pedal the injured leg, did not decrease VAS scores vs a CPM device (Secrist 2016 **Level I** [PRISMA], 1 RCT: Friemert 2006 **Level II**, n=60, JS 1). There was no difference in pain between an unhinged immobilising brace for 2 wk postoperatively and no immobilisation (Secrist 2016 **Level I** [PRISMA], 1 RCT: Hiemstra 2009 **Level II**, n=82, JS 2).

Movement representation

Movement representation (mirror therapy, motor imagery, action observation combined with standard physiotherapy or rehabilitation) techniques reduced limb pain acutely

(SMD -0.7; 95%CI -1.24 to -0.15) (Thieme 2016, **Level I** [PRISMA], 6 RCTs, n=140). A sub-analysis of both acute and chronic pain by type found reductions in pain for Complex Regional Pain Syndrome (CRPS) (SMD -2.23; 95%CI -3.88 to -0.57) (4 RCTs, n=108) and nociceptive pain conditions (ankle sprain, ACL reconstruction, TKA and rotator cuff injury) (SMD -1.26; 95%CI -1.92 to -0.61) (4 RCTs, n=64), but not phantom limb pain (3 RCTs, n=41) or post stroke pain (3 RCTs, n=116).

See also Section 8.1.5.2.

KEY MESSAGES

1. Early comprehensive active physiotherapy in the first 4 weeks post spinal surgery may reduce pain and does not appear to increase adverse events (**N**) (**Level I** [PRISMA]).
2. Movement representation interventions (mirror therapy/motor imagery) may reduce acute pain after trauma and surgery (**N**) (**Level I** [PRISMA]).

The following tick box represents conclusions based on clinical experience and expert opinion:

☑ Accelerated rehabilitation, started within 24 hours post total knee arthroplasty, may reduce pain at the time of discharge (**N**).

7.5.2 | Manual and massage therapies

Postoperative pain in general

Massage improves postoperative pain vs routine care (SMD -0.58; 95%CI -0.93 to -0.53) (Kukimoto 2017, **Level I** [PRISMA], 9 RCTs, n=1,105). Reductions in pain are seen in both single dose (SMD -0.49; 95%CI -0.64 to -0.34) (6 RCTs, n=757) and multiple doses of massage (SMD -0.53; 95%CI -0.91 to -0.14) (7 RCTs, n=1,031). When analysed for incision type, the beneficial effects of massage on postsurgical pain persists for both sternal (SMD -0.68; 95%CI -0.91 to -0.46) (4 RCTs, n=333) and abdominal incisions (SMD -0.57; 95%CI -1.04 to -0.11) (2 RCTs, n=193).

Cardiac and thoracic surgery

In addition to reducing anxiety, massage reduces pain intensity after cardiac surgery (MD −1.52/10; 95%CI −2.2 to −0.84) (Miozzo 2016 **Level I** [PRISMA], 10 RCTs, n=409). Different forms of massage have also been found to have significant beneficial effects on pain post cardiac surgery: Integrative massage (n=113 [2 sessions]), Swedish massage (n=152 [2 sessions]), Thai massage (n=74 [one session]) and general massage (n=40 [3 sessions]; n=65 [one session]) (Ramesh 2015**, Level I** [PRISMA], 7 RCTS, n=764). One included RCT showed no effect for general massage (n=252 [2 sessions]).

20 to 30 min of healing coach (health care professionals with special training in massage or touch therapy or massage therapist-administered massage) added to standard analgesia reduces pain vs standard care alone (MD -0.85/10; 95%CI -1.28 to -0.42) (Boitor 2017 **Level I** [PRISMA], 7 RCTs, n=1,087); similar results are found in the early period after ICU discharge (MD -0.89/10; 95%CI -1.45 to -0.33) (6 RCTs, n=684). Additionally, 10 to 20 min of massage in conjunction with analgesia administered by a nurse or massage therapist significantly reduces pain in ICU (MD -0.80/10; 95%CI -1.25 to -0.35) (3 RCTs, n=462), while massage without analgesia also reduces pain (MD-2.47/10; 95%CI -4.88 to -0.06) (2 RCTs, n=150).

Labour

Massage reduces pain intensity in first stage labour vs standard care (SMD −0.81; 95%CI −1.06 to −0.56) (6 RCTs, n=362), but not at the second (SMD −0.98; 95%CI −2.23 to 0.26) (2 RCTs, n=124) or third stage (SMD −1.03/10; 95%CI −2.17 to 0.11) (2 RCTs, n=122) vs standard care (Smith 2018, **Level I** [Cochrane], 6 RCTs, n=362). Massage vs a music intervention reduced severe labour pain (RR 0.40; 95% CI 0.18 to 0.89) (1 RCT, n=101).

An earlier systematic review (including only studies from Iran) found that in labour, massage reduces labour pain across all phases including: latent (SMD −1.23; 95%CI −1.73 to −0.74) (9 RCTs, n=642), active (SMD −1.59; 95%CI −2.06 to −1.12) (7 RCTs, n=422) and transitional (SMD −1.90; 95%CI −3.09 to −0.71) (6 RCTs, n=362) as well as having an overall effect (SMD −1.52; 95%CI −1.90 to −1.14) (Ranjbaran 2017 **Level I** [PRISMA], 10 RCTs, n=702) (1 RCT overlap).

Primary dysmenorrhea

In primary dysmenorrhea, manipulative therapy may reduce pain vs sham (WMD -0.94/10; 95%CI -0.66 to -1.2) (Abaraogu 2017 **Level I**, 3 RCTs, n=217); however, these studies were methodologically heterogeneous.

Acute back pain

Manual therapy is also considered with respect to Acute Back Pain in the NICE guidelines NICE 2018 and the older Australian Acute Musculoskeletal Pain Guidelines (Australian Acute Musculoskeletal Pain Guidelines Group 2003 **GL**). See also Section 8.7. and 8.8.

KEY MESSAGES

1. Single and multiple doses of massage in the early postoperative period may reduce pain after surgical procedures, including cardiac surgery (**N**) (**Level I [**PRISMA])
2. Massage may decrease pain in the first stage of labour pain compared to standard care (**N**) (**Level I** [Cochrane Review])

The following tick box represents conclusions based on clinical experience and expert opinion:

☑ The role of manipulative therapy in primary dysmenorrhea is currently unclear (**N**).

7.5.3 | Warming and cooling interventions

7.5.3.1 | Warming interventions

Dysmenorrhea

In a 4-arm RCT, treatment with heat pads reduced pain vs placebo (unheated pads) (MD 1.8/10; 95%CI 0.9 to 2.7), but ibuprofen plus heat pad was no more effective than ibuprofen with placebo heat pad (Kannan 2014 **Level I** 1 RCT: Akin 2001, **Level II**, n=81, JS 3). Time to noticeable pain relief was reduced from 2.8 h to 1.5 h with ibuprofen plus heat pad vs ibuprofen with placebo heat pad.

A subsequent review identified three further studies. Heat therapy interventions including heat patches (1 study, n=147), hot water (1 study, n=44) and heated red bean pillows (1 study, n=51), improves pain from dysmenorrhoea, however high heterogeneity and a lack of placebo controls prevent firm conclusions (Igwea 2016 **Level III-1 SR**, 3 studies, n=242).

Labour pain

Warm packs vs usual care reduce pain intensity in the first stage of labour (SMD −0.59; 95%CI −1.18 to −0.00) (3 RCTs, n=191) and second stage of labour (SMD -1.49; 95%CI −2.85 to −0.13) (2 RCTs, n=128) (Smith 2018 **Level I** [Cochrane], 14 RCTs, n=1,172). Thermal manual methods resulted in a reduction in pain intensity vs usual care (MD −1.44/10; 95%CI −2.24 to −0.65) (1 RCT, n=96) and intermittent hot and cold packs reduced pain in the first phase of labour vs usual care (MD −1.46/10; 95% CI −2.59 to −0.33) (1 RCT, n=48).

Periocular surgery

Warming the local anaesthetic agent so it is close to body temperature when injected decreased pain in one of two small RCTs (Gostimir 2019, **Level I** [PRISMA], 2 RCTs, n=100).

7.5.3.2 | Cooling interventions

All knee surgery

Compression cryotherapy vs cryotherapy alone after any knee surgery improves pain on POD 1 (MD -0.94/10; 95%CI -1.63 to -0.26) (7 RCTs, n=420), POD 2 (MD -0.55/10; 95%CI -0.78 to -0.32) (7 RCTs, n=420) and POD 3 (MD -0.46/10; 95%CI -0.87 to -0.05) (2 RCTs, n=100) (Song 2016 **Level I** [PRISMA], 10 RCTs [2 TKA, 3 arthroscopy, 5 ACL reconstruction], n=662).

Knee Arthroplasty

Cryotherapies reduces pain after TKA (MD -0.51/10; 95%CI -1.00 to -0.02) (8 RCTs, n=1,382) (Tedesco 2017 **Level I** [PRISMA], 12 RCTs [cryotherapy], n=1,382; Ni 2015 **Level I**, 13 RCTs [9 TKA, 2 THA, 1 mixed], n=782) (9 RCT overlap). However, when data for POD 1 (7 RCTs, n=529), POD 2 (5 RCTs, n=422) and POD 3 were considered separately, no effect is seen. Cryotherapy is also not better than compression therapy (5 RCTs, n=407).

Anterior cruciate ligament (ACL) reconstruction

Cold compress devices improve pain 48 h after ACL surgery vs no therapy (MD -1.41/10; 95%CI -1.66 to -1.17) (2 studies, n=71) (Martimbianco 2014 **Level III-1 SR** [PRISMA], 10 studies, n=573) (2 RCTs overlap with Song 2016). There is no effect from cold therapy (3 studies) or cold compression therapy with cold water vs room temperature water (placebo) (3 studies). Cold compression therapy vs ice packs reduces pain at 1 wk (1 RCT, n=44) and 6 wk (1 RCT, n=36). Cold compression devices vs ice packs or no cold therapy reduce the amount of medication taken by patients (6 studies).

A subsequent systematic review of cryotherapy following outpatient ACL surgery shows superior pain relief in 4 of 8 studies vs no cryotherapy or water at room temperature (Secrist 2016, **Level III-1 SR** [PRISMA]**,** 10 studies, n unspecified) (8 studies overlap with Martimbianco 2014).

Haemarthrosis of haemophilia

Cryotherapy has been recommended for treatment of pain and swelling in haemarthrosis due to haemophilia (Rodriguez-Merchan 2018 **NR**).

Venipuncture

Vapocoolants for pain during IV cannulation vs pooled no or placebo treatments reduce pain when assessed as a continuous measure (SMD -0.53; 95%CI -0.83 to -0.23) (8 RCTs, n=682) or dichotomised (OR 4.62; 95%CI 1.84 to 11.63) (4 RCTs, n=681) (Zhu 2018 **Level I**, 11 RCTs, n=1,410). However, in the paediatric subgroup analysis (2 RCTs, n=172), no effect is seen. A prior meta-analysis also concluded that vapocoolants are superior to pooled no or placebo treatment; however, with increased discomfort at the time of application (Griffith 2016 **Level I** [Cochrane], 9 RCTs, n=1,070) (8 RCTs overlap). In contrast, an earlier systematic review including non-RCTs

does not confirm all these findings (Hogan 2014 **Level III-I SR** [PRISMA]**,** 12 studies, n unspecified) (8 RCTs overlap).

See also Section 10.7.2 for paediatric specific information.

Periocular Surgery

Application of ice for 2 min before injection of local anaesthesia reduced pain (Gostimir 2019 **Level I** 1 RCT**:** Goel 2006 **Level II**, n=39, JS 2). In a crossover trial, patients received two injections, one where treatment with ice (for 2 min) occurred prior to unbuffered lidocaine injection vs another where buffered lidocaine was injected without ice pretreatment; with less pain at the site of the ice-treated unbuffered injection (Huang 2015 **Level III-2**, n=60).

Tonsillectomy

Cryotherapy (ice lollipop) over 4 h reduced pain post-tonsillectomy in children (2 to 12 y) at 30 min and 1 h (Keefe 2018 **Level I** [PRISMA] 1 RCT**:** Sylvester 2011 **Level II**, n=87, JS 3). Intraoperative cryotherapy with a cryotherapy probe (-56°C) (1 RCT) and ice-water cooling (4°C to 10°C) (2 RCTs) reduces post-tonsillectomy pain scores consistently vs no treatment by 21 to 32% (0.9/10 to 1.8/10) (Raggio 2018 **Level I** [PRISMA], 3 RCTs, n=153).

Dental Surgery

After 3rd molar extraction, cryotherapy is effective at reducing oedema, but mixed results were found with regard to effect on pain where 5 of 11 studies were positive (Fernandes 2019 **Level IV SR**, 11 studies, n=721).

Maxillofacial surgery

Hilotherapy (the application of cold compression at a regulated temperature through a face mask) reduces pain on POD 2 after facial skeletal surgery vs cold compression (MD -2.37/10; 95%CI -3.24 to -1.50) (n=146) and reduces swelling on POD 2 and POD 3, but not POD 28 (Glass 2016 **Level I** [PRISMA], 6 RCTs, n=286).

Mucositis

Cryotherapy during chemotherapy may have a preventive effect on mucositis see Section 8.9.8.2.

Labour

Cold packs reduce pain intensity in the first stage of labour (MD −1.43/10; 95%CI −2.56 to −0.30) (Smith 2018 **Level I** [Cochrane] 1 RCT: Shirvani 2014 **Level II**, n=64, JS 3).

Puerperium perineal pain

There is only limited evidence to support the effectiveness of local cooling treatments (ice packs, cold gel pads, cold/iced baths) for relieving perineal trauma pain vs various alternatives or no interventions (East 2012 **Level I** [Cochrane], 10 RCTs, n=1,825). Ice packs provided superior analgesia vs no treatment for 24 to 72 h postpartum (RR 0.61; 95%CI 0.41 to 0.91) (1 RCT, n=208).

KEY MESSAGES

1. Heat packs may reduce labour pain during the first and second stages (**N**) (**Level I** [Cochrane Review]).
2. Vapocoolants may reduce the pain of intravenous cannulation in adults but its application is associated with discomfort (**N**) (**Level I** [Cochrane Review]).
3. Cryotherapy may reduce pain after total knee arthroplasty but is not superior to compression (**N**) (**Level I** [PRISMA]).
4. Compression cryotherapy may reduce acute pain and analgesia requirements post anterior cruciate ligament reconstruction and pain on day one to three post knee surgery (**N**) (**Level I** [PRISMA]).
5. Intraoperative cryotherapy may reduce post-tonsillectomy pain (**N**) (**Level I** [PRISMA]).
6. Hilotherapy (the application of cold compression at a regulated temperature through a face mask) may reduce pain and swelling after facial skeletal surgery vs cold compression (**N**) (**Level I** [PRISMA]).

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8

Specific clinical situations

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8.1.1 to 1.6 | Postoperative pain
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8.1.7 | Ambulatory or short-stay surgery
Contributor: Dr Myles Conroy

8.1.8 | Cranial neurosurgery
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Contributors: Dr Charles Kim, Dr Andrew Zacest

8.2 | Acute pain following spinal cord injury
Contributor: Prof Philip Siddall

8.3 | Acute pain following chest injury
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8.4 | Acute pain following hip (neck of femur) fracture
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8.10 | Acute pain management in intensive care
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8.1 | Postoperative pain

One of the most common sources of acute pain is postoperative pain. A large amount of the evidence presented so far in this document is based on studies of pain relief in the postoperative setting. However, many of the management principles derived from these studies can be applied to the management of acute pain in general, as outlined in this and other sections that follow.

The treatment of postoperative pain in specific settings such as day-stay surgery will be discussed later in this chapter.

8.1.1 | Multimodal postoperative pain management

The concept of multimodal (or "balanced") analgesia has been advocated as being beneficial for the management of postoperative pain (Kehlet 1993 **NR**). This concept suggests that combinations of analgesics with different modes or sites of action can improve analgesia, reduce opioid requirements *("opioid-sparing effect"*) and thereby reduce adverse effects of opioids in the postoperative period (Gritsenko 2014 **NR**). This approach, by reducing the reliance on opioids in the postoperative setting, also offers opportunities to overcome current concerns about opioid use in pain management (Savarese 2017 **NR**). See also Sections 8.13. and 9.7. and for paediatric information Section 10.4.5.4.

As outlined in previous chapters, there is Level I evidence to support a large number of nonopioid analgesics, adjuvants and regional anaesthetic techniques as potential components of multimodal analgesia by fulfilling the above criteria: paracetamol, nsNSAIDs and coxibs, local anaesthetic techniques (local anaesthetic infiltration, peripheral nerve blocks and neuraxial blocks), systemic local anaesthetics, steroids, ketamine, alpha-2 agonists and alpha-2-delta ligands (Gabriel 2019 **NR**; Pitchon 2018 **NR**; Wick 2017 **NR**; Rosero 2014 **NR**).

In this context, depth of general anaesthesia (BIS 30–40 vs 45–60) had no effect on postoperative pain or opioid requirements (Law 2014 **Level II**, n=135, JS 4).

Comparative studies of solely opioid-based analgesia with multimodal approaches show benefits not only with regard to analgesia and patient satisfaction but also for other postoperative outcomes:

- After total knee joint arthroplasty (TKA), multimodal analgesia (including local anaesthetic infiltration, nsNSAIDs, tramadol and oxycodone) vs IV PCA hydromorphone alone resulted in lower pain scores, opioid-sparing, fewer adverse effects, higher satisfaction scores and earlier achievement of physical therapy milestones (Lamplot 2014 **Level II**, n=36, JS 3). For total hip and knee arthroplasty (THA/TKA), adding IV paracetamol to other techniques of analgesia reduces pain scores and opioid consumption (Yang 2017 **Level I** [PRISMA], 4 RCTs, n=865). After THA/TKA, 85.6% of patients received multimodal analgesia (Memtsoudis 2018 **Level III-2**, n=1,318,165). Addition of more modes of analgesia was associated with positive effects in a stepwise fashion; for THA patients, more than 2 modes of analgesia vs opioids only was associated with reduction of respiratory (OR 0.81; 95%CI 0.70 to 0.94) and gastrointestinal complications (OR 0.74; 95%CI 0.65 to 0.84), decreased opioid prescriptions (-18.5%; 95%CI -19.7% to -17.2%) and reduced LOS from median 3 to 2 d (-12.1%; 95%CI -12.8% to -11.5%). NSAIDS and coxibs had the most effect here. Multimodal analgesia has also been examined in adult OSA patients undergoing elective THA/TKA (Cozowicz 2019 **Level III-2**, n=181,182). Assessment of this higher perioperative risk population demonstrated a step-wise reduction in opioid dose, prescription and PCA use (26.6% in opioid only vs 19.2%, 13.7%, and 7.7%) with increasing modes of multimodal analgesia over 10 y (2006—2016). With regards to postoperative complications, there were significantly reduced odds for

postoperative mechanical ventilation (OR 0.23; 95%CI 0.16 to 0.32) and critical care admission (OR 0.60; 95%CI 0.48 to 0.75) with the addition of two or more non-opioid analgesic modes. Of note, the most commonly used components of multimodal analgesia included paracetamol, coxibs, nsNSAIDs, gabapentin or pregabalin, regional analgesia, ketamine and corticosteroids.

- After spinal surgery, the use of multimodal analgesia (paracetamol, NSAIDs, gabapentin, S-ketamine, dexamethasone, ondansetron and epidural local anaesthetic infusion or IV PCA morphine) vs historical controls, reduced opioid consumption, nausea, sedation and dizziness and improved postoperative mobilisation (Mathiesen 2013 **Level III-3**, n=85). This was confirmed by a subsequent RCT in a similar setting (lumbar fusion), where pre- and postoperative multimodal analgesia (celecoxib, pregabalin, oxycodone CR and paracetamol) with IV PCA morphine vs IV PCA morphine alone reduced pain and disability (Oswestry Disability Index) without any difference in adverse effects (Kim 2016 **Level II**, n=80, JS 3).
- After upper extremity orthopaedic surgery, multimodal analgesia (including NSAID and alpha-2-delta ligand) vs IV PCA opioid alone provided similar quality of analgesia with reduced incidence of opioid-related complications and greater patient satisfaction (Lee 2013b **Level II**, n=61, JS 3).
- Introduction of a multimodal protocol for analgesia in laparoscopic sleeve gastrectomy (preoperative etoricoxib, intraoperative and postoperative paracetamol with optional postoperative tramadol) vs historic control (previous standard care) resulted in reduced opioid requirements, reduced adverse effects of opioids (8.8% vs 33%) with similar analgesic efficacy (Ng 2017 **Level III-3**, n=158). Similarly, adding paracetamol to PCEA (thoracic) for open gastrectomy in cancer patients improved pain control on coughing and reduced PCEA requirements (Kinoshita 2019 **Level II**, n=120, JS 3).
- After cardiac surgery, multimodal analgesia (paracetamol, nsNSAID, dexamethasone, alpha-2-delta ligand and rescue morphine) vs paracetamol and morphine resulted in lower pain scores for the first 3 d, reduced PONV and a trend towards reduced complications (Rafiq 2014 **Level II**, n=180, JS 3).
- In reconstructive pelvic surgery, a multimodal analgesic regimen (preoperative and postoperative celecoxib, gabapentin, intraoperative and postoperative IV and oral paracetamol and opioids prn) vs usual care (postoperative ibuprofen and opioids prn) resulted in reduced opioid requirements in hospital and after discharge (overall 195.5 MME [± 147.2] vs 304.0 MME [± 162.1]; 34.8% vs 10.6% no opioid use after discharge) with comparable pain relief and no difference in other outcomes (Reagan 2017 **Level II**, n=138, JS 2).. A multimodal bundle of standardised use of preoperative paracetamol, postoperative comfort education, simethicone, postoperative gum chewing, and abdominal binders reduced morphine requirements after Caesarean section by 61% (Burgess 2019 **Level III-1**, n=9,313). Furthermore, more women received less than 20 tablets of oxycodone at discharge (96.7% vs 26.3%).
- After rhinoplasty, multimodal analgesia (pregabalin alone and combined with dexamethasone added to IV tramadol and diclofenac IM) vs IV PCA tramadol alone reduced pain scores, tramadol consumption, rescue opioid use and nausea (Demirhan 2013 **Level II**, n=60, JS 5).

An additional benefit of a multimodal approach to pain relief after THA/TKA (paracetamol, pregabalin and celecoxib or ketorolac) was a reduction in postoperative fever incidence (5 vs 25%) resulting in fewer patients undergoing tests (1.8 vs 9.8%) (Karam 2014 **Level III-3**, n=3,901).

A meta-analysis could not identify any RCTs comparing three non-opioids in the setting of postoperative analgesia after major surgery (Martinez 2017 **Level I** [NMA], 135 RCTs, n=13,287). Double combinations with the highest opioid sparing effects over 24 h were paracetamol/nefopam (-23.9 mg; 95%CI -40 to -7.7), paracetamol/NSAIDs (-22.8 mg; 95%CI -31.5

to -14) and an atypical opioid combined with a non-opioid tramadol/metamizole (tramadol being classified by the authors as a non-opioid) (-19.8 mg; 95%CI -35.4 to -4.2). In abdominal hysterectomy, an RCT comparing a triple combination of paracetamol, meloxicam and gabapentin vs the three double combinations was prematurely discontinued for futility, as interim analysis showed only a minimal chance of showing advantages (Gilron 2015 **Level II**, n=87 [terminated], JS 5). In the 8 armed OCTOPUS study, a triple combination of paracetamol, nefopam and ketoprofen (PCA morphine rescue in all groups) was compared to placebo, the non-opioids singly and as double combinations (Beloeil 2019 **Level II**, n=237 [of 1,000 required], JS 5). The study was discontinued early for logistical and ethical reasons, but showed superiority of the triple combination over some arms with reduced opioid requirements and pain intensity.

Preemptive or preventive pain psychoeducation is an underutilised component of multimodal analgesia despite data showing reduced pain intensity, analgesic use, LOS, return to ED, patient anxiety and possibly chronic postsurgical pain (Horn 2020 **Level IV SR**, 33 studies, n unspecified).

On the basis of the available evidence, multimodal analgesia regimens are therefore recommended in the management of postoperative pain, including in the setting of enhanced recovery after surgery (ERAS) (Dunkman 2018 **NR**; Beverly 2017a **NR**) and ambulatory surgery (Kaye 2019 **NR**; Prabhakar 2017 **NR**). A novel approach to introduce multimodal analgesia into routine clinical practice are Standardised Clinical Assessment and Management Plans (SCAMPs), providing an algorithmic approach to standardisation of postoperative analgesic care with the aim of increasing compliance with existing guidelines (Beverly 2017b **NR**).

Multimodal analgesia is the recommended approach in guidelines for the management of postoperative pain (Savoia 2010 **GL**; ANZCA 2013 **GL**; Chou 2016 **GL**) including guidelines specifically targeted at reduction of perioperative opioid use (Wu 2019 **GL**).

KEY MESSAGES

1. Multimodal analgesia compared to mainly opioid-based analgesia improves pain control and reduces opioid consumption ("opioid-sparing") and adverse effects (**S**) (**Level I** [NMA]).

The following tick box represents conclusions based on clinical experience and expert opinion:

☑ The concept of multimodal (or "balanced") analgesia suggests the use of combinations of analgesics with different mode or site of action (**S**).

8.1.2 | Procedure-specific postoperative pain management

In addition to the overall assessment of the efficacy of acute pain management, there is also a need for information on postoperative pain management that relates to the site of surgery and specific surgical procedures (Singla 2014 **NR**; Ward 2014 **NR**; Kehlet 2005 **NR**; Rowlingson 2003 **NR**).

This becomes obvious when considering that even a simple analgesic, like paracetamol, has different efficacy in different surgical settings; it is significantly less effective after orthopaedic surgery (RR [of achieving >50% maximal pain relief] 1.87; 95%CI 1.36 to 2.57) than after dental extraction (RR 3.77; 95%CI 2.80 to 5.07) (Gray 2005 reanalysing Barden 2004b **Level I**, 43 RCTs [paracetamol], n unspecified). Although calculation of NNTs requires the pooling of data from at least 500 patients to be credible (McQuay 2002 **NR**), pooling of data from different postoperative pain states may ignore the specific effects of a specific analgesic in a specific postoperative pain state (Joshi 2013 **NR**).

Furthermore, different surgical procedures cause different pain states (eg musculoskeletal vs visceral) of different severity in different locations. On POD 4 after ambulatory surgery, moderate (16.3%) to severe (12.1%) postoperative pain presented with procedure-specific variation; shoulder, anal and dental surgery was associated with the most intense pain (Vrancken 2018 **Level III-2**, n=1,123); preoperative pain intensity predicted postoperative pain intensity, but again related to the procedure performed. Similarly in another study, in addition to preoperative pain and patient derived expected pain, different types of surgery were the strongest predictor of moderate to severe pain 4 d after ambulatory surgery (Stessel 2017 **Level III-3**, n=1,118). Different surgical procedures influenced the wide range of IV PCA opioid requirements; open pancreatectomy had the highest (77 mg) and open hysterectomy the lowest requirements (34 mg) (Lin 2019a **Level III-2**, n=3,284). The paper presents a table/graph of all procedures and the respective IV PCA requirements. However, a large cohort study of postoperative patients reported those with worst pain (NRS > 6/10) on POD 1 included orthopaedic/trauma procedures on the extremities, while very high pain scores were also associated with so called "*minor*" surgery (eg appendectomy, cholecystectomy, hemorrhoidectomy and tonsillectomy) suggesting insufficient access to analgesia in this group (Gerbershagen 2013 **Level III-2**, n=50,523).

On the basis of these finding, postoperative pain requires a procedure-specific approach. The recognition of this need has led to the development of the PROSPECT (PROcedure-SPECific postoperative pain managemenT) initiative, which aims to provide procedure-specific evidence-based recommendations for the treatment of pain after a wide range of operations (Kehlet 2007 **NR**; Lee 2018 **NR**). Their guidelines can be found at the website of the European Society of Regional Anaesthesia & Pain Therapy (ESRA) which is supporting the PROSPECT initiative: https://esraeurope.org/prospect/. The revised methodology underlying this approach is accessible on the website and has been published (Joshi 2019b **NR**); it uses an evidence-based approach including meta-analysis of available procedure-specific data. Surgical factors contributing to postoperative pain are also considered (eg trocar size in laparoscopic cholecystectomy) (McCloy 2008 **Level I**, 13 RCTs, n=968).

Procedure-specific evidence for the following operations is currently available at the website with most of the underlying meta-analyses also published in the peer-reviewed literature; translated PDFs of the recommendations are available in severallanguages (Chinese, French, German, Japanese, Portuguese and Spanish):

- Abdominal hysterectomy;
- Caesarean section;
- Haemorrhoidectomy (Sammour 2017 **Level I** [QUOROM], 48 RCTs, n unspecified);
- Hernia repair (Joshi 2012 **Level I** [PRISMA], 79 RCTs, n unspecified);

- Laparoscopic cholecystectomy (Barazanchi 2018 **Level I** [PRISMA], 258 RCTs, n unspecified);
- Laparoscopic hysterectomy (Lirk 2019 **Level I** [PRISMA], 56 RCTs, n unspecified);
- Laparoscopic sleeve gastrectomy (Macfater 2019 **Level I** [PRISMA], 18 RCTs, n unspecified);
- Oncological breast surgery (Jacobs 2020 **Level I** [PRISMA], 9 SRs & 53 RCTs, n unspecified);
- Open colorectal surgery;
- Radical prostatectomy (Joshi 2015 **Level I** [PRISMA], 38 RCTs, n unspecified);
- Rotator cuff repair surgery (Toma 2019 **Level I** [PRISMA], 1 SR & 59 RCTs, n unspecified);
- Thoracotomy (Joshi 2008 **Level I**, 74 RCTs, n unspecified);
- Total hip arthroplasty (Fischer 2005 **Level I**, 55 RCTs, n unspecified);
- Total knee arthroplasty (Fischer 2008 **Level I**, 112 RCTs, n unspecified).

KEY MESSAGES

1. An analgesic may have different efficacy in different surgical settings (**U**) (**Level I**).
2. Different surgical procedures cause different pain states (eg musculoskeletal vs visceral) of different severity in different locations, thereby requiring a procedure-specific approach (**S**) (**Level III-2**).

The following tick box represents conclusions based on clinical experience and expert opinion:

☑ Pooling of data from different postoperative pain states may ignore the specific effects of a specific analgesic in a specific postoperative pain state (**U**).

8.1.3 | Acute rehabilitation after surgery, "fast-track" surgery and enhanced recovery after surgery (ERAS)

The concept of fast-track surgery is underpinned by a multimodal approach to the perioperative care of the patient (Nanavati 2014 **NR**; Kehlet 2008 **NR**; Wilmore 2001 **NR**). The approach uses combinations of perioperative interventions to facilitate the postoperative recovery involving a multidisciplinary team approach of surgeons, anaesthetists, nutritionists, physiotherapists, nurses and pharmacists. Management of the surgical stress response, perioperative fluids and pain are key factors of this approach (Kehlet 2011 **NR**).

Evidence-based approaches following these principles have resulted in a significantly reduced hospital stay for many operations without increasing, and often reducing, complications and readmissions. Evidence-based detailed protocols for enhanced recovery after surgery (ERAS) are published for multiple operations on the ERAS© Society's website: https://erassociety.org.

For example, application of an ERAS protocol to colorectal surgery results in reduced LOS (WMD -2.55 d; 95%CI -3.24 to -1.85) and complication rates (RR 0.53; 95%CI 0.44 to 0.64) (Varadhan 2010 **Level I**, 6 RCTs, n=452). However, it is of note that the number of individual ERAS elements employed ranged from 4 to 12, with a mean of 9 elements targeting perioperative care. The use of multiple components in enhanced recovery confirms previous findings that provision of good analgesia alone may have only minimal effects on speed and quality of postoperative recovery (Kehlet 1997 **NR**). This is not surprising given the numerous triggers of the injury response, of which acute pain is only one. This is confirmed in a systematic review of the role of pain management in recovery from colorectal surgery following ERAS protocols (Chemali 2017 **Level I** [PRISMA], 21 RCTs, n=1,261). It suggests that the modality for postoperative analgesia has no impact on the hospital LOS, pain, the time to the first bowel motion or nausea, although data are of limited quality. The authors suggest that as long as pain is reasonably well controlled, choice of the technique of pain management is of minor relevance.

Even thoracic epidural analgesia (TEA) use, with its superior analgesic effect and faster return of bowel function, does not shorten LOS or improve morbidity and mortality vs alternative analgesic techniques when used within an ERAS protocol for open abdominal surgery (Hughes 2014 **Level I** [PRISMA], 7 RCTs, n=378). This finding highlights the importance of other elements of these protocols. Similarly after laparoscopic colectomy, TEA significantly improves time to first bowel motion (WMD -0.62 d; 95%CI -1.11 to -0.12) and pain scores (WMD -1.23/10; 95%CI -2.4 to -0.07) but does not reduce LOS (WMD -0.47 d; 95%CI; -1.55 to 0.61) (Khan 2013 **Level I** [PRISMA], 6 RCTs, n=340).

The importance of the various elements of enhanced recovery protocols is well demonstrated in an analysis of the ERAS register for elective primary colorectal cancer resection (ERAS Compliance Group 2015 **Level IV**, n=2,352). Elements associated with shorter LOS were laparoscopic surgery (OR 0.83), increasing ERAS protocol compliance (OR 0.88), preoperative carbohydrate and fluid loading (OR 0.89) and total IV anaesthesia (OR 0.86). Here, epidural analgesia increased LOS (OR 1.07). While, risk of complications was reduced with restrictive perioperative IV fluids (OR 0.35), laparoscopic surgery (OR 0.68) and increasing ERAS protocol compliance (OR 0.69).

Other analgesic factors that reduced LOS after elective colorectal surgery including avoidance of oral opioids in the postoperative period (OR 0.39; 95%CI 0.18 to 0.84) and the use of shorter duration of epidural analgesia (OR 0.44; 95%CI 0.12 to 0.94) (Ahmed 2010 **Level IV**, n=231). Opioid-sparing analgesic techniques reduced postoperative ileus (Barletta 2011 **Level IV**, n=279; Barletta 2012 **NR**).

Overall, independent predictors of early recovery after open and laparoscopic colorectal surgery were enforced advancement of oral intake (normal diet at POD 1 to 3) and early

mobilisation (Vlug 2012 **Level III-2**, n=400). Effective analgesia facilitates these elements of ERAS protocols enabling early enteral feeding and mobilisation/ambulation. It follows that provision of analgesia by appropriate techniques remains an important component of these protocols (Kehlet 2011 **NR**; White 2007 **NR**; Kehlet 2003 **NR**). Therefore evidence-based and procedure-specific guidelines for pain management need to be incorporated in ERAS protocols for various operations; goals are not specifically low pain scores, but improved functionality and improved ambulation (Joshi 2019a **NR**).

In comparison to conventional care after breast reconstruction, following an ERAS pathway does not only reduce LOS, but also pain severity and reliance on opioid analgesia as measured by shortened IV PCA usage and reduced IV, oral and total opioid requirements (Tan 2019 **Level III-2 SR**, 10 studies, n=1,838). In an ambulatory setting, implementation of an ERAS protocol for mastectomy and breast reconstruction included multimodal analgesia (preoperative paracetamol, gabapentin; regional anaesthesia [PECS type 1 and 2 or PVB] and intraoperative dexamethasone and ondansetron) (Simpson 2019a **Level III-3**, n=437). Compared to historical controls prior to implementation of the ERAS protocol, patients in the ERAS group had lower highest pain scores (median 4/10 [IQR 2,6] vs 6/10 [IQR 4,7]), lower total opioid consumption in oral morphine equivalents (mean 111.4 mg [SD 46.0) vs 163.8 mg [SD 73.2]) and reduced PONV incidence (28% vs 50%).

KEY MESSAGES

1. Adherence to multimodal enhanced recovery protocols after surgery protocols reduces hospital length of stay, complication rates (**S**) (**Level I**), postoperative pain severity and opioid requirements (**N**) (**Level III-2 SR**)**.**

The following tick boxes represent conclusions based on clinical experience and expert opinion:

☑ Provision of appropriate analgesia is only one of several elements of enhanced recovery after surgery protocols (**S**).

☑ Analgesic techniques, which permit early mobilisation and early enteral feeding, in particular those that are opioid-sparing, may contribute to early recovery after surgery protocols (**S**).

8.1.4 | Risks of acute postoperative neuropathic pain

Neuropathic pain has been redefined as "*pain caused by a lesion or disease of the somatosensory nervous system*" (Jensen 2011 **NR**). Although neuropathic pain is often considered a chronic pain state, it can occur acutely. Acute causes of neuropathic pain can be iatrogenic, traumatic, inflammatory or infective (Gray 2008a **NR**). Nerve injury is a risk in many surgical procedures and may present as acute neuropathic pain postoperatively.

Screening questionnaires for neuropathic pain such as DN4, LANSS or painDETECT are widely used in the acute setting, but are only validated for chronic neuropathic pain (Schnabel 2018 **NR**). Therefore there is no diagnostic standard for acute neuropathic pain and an attempt has been made to develop diagnostic criteria in a three-step Delphi process among pain specialists (Searle 2012 **GL**). Besides the usual descriptors of neuropathic pain, the items "*difficult to manage pain*", "*poor response to opioids*" and "*good response to anti-neuropathics*" were suggested.

The incidence of acute neuropathic pain has been reported as 1 to 3%, based on patients referred to an APS, primarily after surgery or trauma (Hayes 2002 **Level IV**, n=4,888). The majority of these patients had persistent pain at 12 mth, suggesting that acute neuropathic pain is a risk factor for chronic pain. These qualitative results were confirmed subsequently (Beloeil 2017 **Level III-2**, n=593). Using a screening tool (DN-4), 5.6% (95% CI 3.6 to 8.3) screened positive on the day of surgery and 12.9% (95%CI 9.7 to 16.7) on POD 1. At phone follow-up 2 mth postsurgery, 33.3% of patients screened positively; acute positive screening was a risk factor for later positive screening (OR 4.2; 95%CI 2.2 to 8.1). Similarly, immediately after thoracotomy or video assisted thoracic surgery, 8% of patients scored positively on another screening tool for neuropathic pain (LANSS) and 22% 3 mth later; again acute positive was a risk factor for chronic positive results (RR 3.5; 95%CI 1.7 to 7.2) (Searle 2009 **Level III-2**, n=100).

The role of acute neuropathic pain as a component of postoperative pain is possibly underestimated; after sternotomy, 50% of patients had dysaesthesia in the early postoperative period, which was closely associated with severity of postoperative pain (Alston 2005 **Level IV**, n=50). After cancer surgery, a prospective study using the painDETECT screening tool identified acute neuropathic pain in 10% of cases in the first week postoperatively (Jain 2014 **Level IV**, n=300). In a general surgical population, the incidence was 3 to 4.2% (Sadler 2013 **Level IV**, n=165). Similarly, a high incidence of acute neuropathic pain in the lower limbs with lumbosacral plexus injury after pelvic trauma has been reported (Chiodo 2007 **Level IV**, n=78). In cohort studies, 6 to 13% of postoperative patients screened positive for acute neuropathic pain (Searle 2009 **Level III-2**, n=100).

Management of acute neuropathic pain is primarily based on extrapolation of data from the chronic neuropathic pain setting (see Sections 4.6 to 4.10). However, selection of a preferred treatment in the acute setting may be based on a faster onset of effect; tramadol, opioids and alpha-2-delta ligands are suggested (Macintyre 2015 **NR**; Dworkin 2010 **GL**). In two small series of acute neuropathic pain due to SCI, all patients responded positively to IV ketamine followed by oral ketamine (Kim 2013a **Level IV**, n=13) and salmon calcitonin (Humble 2011 **Level IV**, n=3).

There is some evidence that specific early analgesic interventions may reduce the development of chronic pain (often neuropathic pain) after some operations (eg thoracotomy, amputation). For more details, see Sections 1.4, 1.5, 8.1.5 and 8.1.6.

KEY MESSAGES

1. Positive screening for acute postoperative neuropathic pain is a risk factor for positive screening of chronic postsurgical neuropathic pain (**N**) (**Level III-2**).
2. Acute neuropathic pain occurs after trauma and surgery (**S**) (**Level IV**).

The following tick boxes represent conclusions based on clinical experience and expert opinion:

☑ Treatment of acute neuropathic pain should follow guidelines for chronic neuropathic pain; ketamine, opioids (including tramadol and tapentadol in particular) and alpha-2-delta ligands may offer faster onset of effect than other treatment options (**U**).

8.1.5 | Acute postamputation pain syndromes

Following amputation of a limb, and also breast, tongue, teeth, genitalia, the eye and even inner organs such as the rectum, or a deafferentation injury such as brachial plexus avulsion (Ahmed 2014 **Level IV**, n=80; Boas 1993 **Level IV**, n=33; Bates 1991 **Level IV**, n=30; Andreotti 2014 **NR**), a number of phenomena can develop which require differentiation:

- *Residual limb pain (stump pain)* is pain localised to the site of amputation. It can be acute (usually nociceptive) or chronic (usually neuropathic) and is most common in the immediate postoperative period (Jensen 1985 **Level IV**, n=58; Nikolajsen 2001 **NR**). The overall incidence of residual limb pain is uncertain but the risk of early stump pain is increased by the presence of severe preamputation pain (Nikolajsen 1997 **Level IV**, n=56).
- *Phantom sensation* is defined as any sensory perception of the missing body part with the exclusion of pain. Almost all patients who have undergone amputation experience phantom sensations (Jensen 1983 **Level IV**, n=58). These sensations range from a vague awareness of the presence of the missing body part via associated paraesthesia, to complete sensation including size, shape, position, temperature and movement.
- *Phantom limb pain* is defined as any noxious sensory phenomenon in the missing body part. The estimated incidence of phantom limb pain is 30–85% after limb amputation and usually occurs in the distal portion of the missing limb (Jensen 1985 **Level IV**, n=58; Nikolajsen 2001 **NR**; Perkins 2000 **NR**). Pain may be early, 75% of patients will report phantom pain within the first few days after amputation (Nikolajsen 1997 **Level IV**, n=56), or delayed in onset. The pain is typically intermittent and diminishes with time after amputation. Factors that may be predictive of postamputation phantom pain are the severity of preamputation pain, the degree of postoperative stump pain, and chemotherapy or radiotherapy (see also Sections 1.4. and 1.5.). If preamputation pain was present, phantom pain might resemble that pain in character and localisation (Katz 1990 **Level IV**, n=68). The intensity of preamputation pain and acute postoperative pain were strong predictors of the intensity of chronic pain after amputation (Hanley 2007 **Level III-3**, n=57). Preoperative passive coping strategies, in particular catastrophising, were other strong predictors of phantom limb pain 6 mth later (Richardson 2007 **Level III-3**, n=59). Reduction of chronic phantom limb pain intensity by peripheral nerve blocks suggests that afferent input from the periphery plays a role in maintaining phantom limb pain (Buch 2019 **Level II EH**, n=12 [crossover], JS 5).

There is a strong correlation between phantom limb and residual limb or site pain, and they may be inter-related (Kooijman 2000 **Level IV**, n=124; Jensen 1983 **Level IV**, n=58). All three of the above phenomena can coexist (Nikolajsen 1997 **Level IV**, n=56).

A survey identified the high incidence of these pain syndromes after amputation; only 14.8% were pain-free, 74.5% had phantom limb pain, 45.2% residual limb pain and 35.5% a combination of both (Kern 2009 **Level IV**, n=537).

Phantom breast pain has also been described; however, the incidence was low in the range of 7% at 6 wk and 1% at 2 y (Dijkstra 2007 **Level III-3**, n=82). Phantom sensations are more common; reported in 19% of patients more than 5 y after surgery (Peuckmann 2009 **Level IV**, n=2,000).

Predictive factors of phantom limb pain were longstanding preoperative chronic pain, subacute postoperative pain as well as psychological factors (depression and anxiety) (Larbig 2019 **Level IV**, n=52). Preoperative state anxiety is a risk factor for acute residual and phantom limb pain (Raichle 2015 **Level IV**, n=69).

8.1.5.1 | Prevention of phantom limb pain

Evidence for the benefit of epidural analgesia in the prevention of all phantom limb pain is inconclusive (Halbert 2002 **Level III-2 SR**, 3 studies [epidural], n=106). However, perioperative (pre, intra and postoperative) epidural analgesia reduced the incidence of severe phantom limb pain (NNT 5.8; 95%CI 3.2 to 28.6) (Gehling 2003 **Level III-2 SR**, 9 studies, n=836). In a subsequent systematic review, chronic pain is reduced by epidural analgesia at 6 mth in 3 of 7 studies, however with poor study quality (von Plato 2018 **Level IV SR** [PRISMA], 9 RCTs & 10 studies, n=949).

Epidurally administered calcitonin reduced the incidence of chronic phantom limb pain, allodynia and hyperalgesia at 6 and 12 mth in diabetic patients undergoing lower limb amputation (Yousef 2017 **Level II**, n=60, JS 5).

In a small observational study, the overall incidence of long term phantom limb pain was similar in regional analgesia recipients given IV ketamine (bolus dose followed by an infusion, started prior to skin incision and continued for 72 h) vs no ketamine; however the incidence of severe phantom limb pain was reduced in the ketamine group (Dertwinkel 2002 **Level III-3**, n=28). An RCT was inadequately powered to show a difference with IV ketamine vs controls in the incidence of phantom limb pain at 6 mth after amputation (47% vs 71%; p=0.28) (Hayes 2004 **Level II**, n=45, JS 4). Perioperative ketamine/bupivacaine given by the epidural route showed no preventive effect vs epidural saline/bupivacaine (Wilson 2008 **Level II**, n=53, JS 5).

Perioperative gabapentin was ineffective in reducing incidence and severity of phantom limb pain vs placebo (Nikolajsen 2006 **Level II**, n=46, JS 5). Valproic acid for the duration of the hospital stay after amputation had no preventive effect on phantom limb pain vs placebo (Buchheit 2019b **Level II**, n=128, JS 5).

Infusions of local anaesthetics via peripheral nerve sheath catheters, usually inserted by the surgeon at the time of amputation, show no benefit in preventing phantom pain or residual limb pain (McCormick 2014 **Level I**, 2 RCTs [perineural], n=151; Bosanquet 2015 **Level III-2 SR** [PRISMA], 2 RCTs & 5 studies, n=416; von Plato 2018 **Level IV SR** [PRISMA], 2 RCTs & 8 studies [CPNB], n=949) (2 RCTs overlap [between all 3 SR] & 5 studies overlap Bosanquet 2015 with von Plato 2018). In the latter systematic review, acute postoperative opioid requirements are reduced (SMD -0.59; 95%CI -1.10 to -0.07) without any other positive outcomes.

Common peroneal nerve to tibial nerve coaptation and collagen nerve wrapping vs traction neurectomy only for transfemoral amputation resulted in less neuroma formation and phantom limb pain respectively at 2 mth (0% vs 36.3% and 0% vs 54.5%) and at 6 mth (0% vs 54.5% and 0% vs 63.6%) (Economides 2016 **Level III-2**, n=17). Furthermore, pain scores at 6 mth were lower (0.75/10 vs 5.6/10) and more patients were walking with a prosthesis (67% vs 9%).

8.1.5.2 | Therapy for phantom limb pain

A survey in 1980 identified over 50 different therapies used for the treatment of phantom limb pain (Sherman 1980 **NR**), suggesting limited evidence for effective treatments. Not a lot of progress has been made since then (Urits 2019 **NR**; Collins 2018 **NR**).

Pharmacological treatment

With regard to pharmacological treatment, most conclusions are based on studies limited by their small sample size (Alviar 2016 **Level III-1 SR** [Cochrane], 14 studies, n=269). Oral and IV morphine are effective in the short term (2 RCTs, n=43) as are the NMDA-antagonists ketamine (2 RCTs) and dextromethorphan (1 RCT). Gabapentin also has an analgesic effect (MD -1.16/10; 95%CI -1.94 to -0.38) (2 RCTs, n=43). An earlier meta-analysis of gabapentin specifically in this setting included a third RCT that showed no benefit (Nikolajsen 2006 **Level II**, n=46, JS 5) which therefore weakens this conclusion (Abbass 2012 **Level I**, 3 RCTs, n=89).

Amitriptyline may be ineffective in acute phantom limb pain management (1 RCT, n=39) as well as botulinum toxin A (1 RCT, n=14) (Alviar 2016 **Level III-1 SR** [Cochrane], 14 studies, n=269).

For memantine no effect is shown in the overarching systematic review (4 RCTs and 2 studies, n=81) (Alviar 2016 **Level III-1 SR** [Cochrane], 14 studies, n=269). Although an overlapping memantine specific systematic review reports use immediately after amputation reduces phantom limb pain (1 RCT, n=19; 3 studies, n=5), but lacks efficacy in established chronic phantom limb pain (4 RCTs, n=75) (Loy 2016 **Level IV SR** [PRISMA], 5 RCTs & 3 studies, n=99) (4 RCTs overlap).

In acute phantom limb pain, IV (and likely SC) salmon calcitonin (within 7 d of amputation) was more effective than placebo (Alviar 2016 **Level III-1 SR** [Cochrane], 1 RCT: Jaeger 1992 **Level II**, n=21 [cross over], JS 3; Bornemann-Cimenti 2017 **CR**; Turek 2012 **CR**). However, it was not effective for chronic phantom limb pain (Alviar 2016 **Level III-1 SR** [Cochrane], 1 RCT: Eichenberger 2008 **Level II**, n=20 [cross over], JS 5).

Systemic lignocaine (1 RCT, n=31) may be ineffective, while contralateral myofascial injection of bupivacaine (administered once) may reduced phantom limb pain in a very small study (1 RCT, n=8 [cross-over]) (Alviar 2016 **Level III-1 SR** [Cochrane], 14 studies, n=269).

A subsequent systematic review reports similar results in a less thorough way (McCormick 2014 **Level III-1 SR**, 27 RCTs & 1 study, n=807 [& multiple CRs]). With regard to morphine an additional RCT (n=12) confirms long term benefits (with a slow-release preparation). An RCT excluded from the Cochrane review above due to its complex study design is incorrectly interpreted by this systematic review; the RCT shows that amitriptyline as well as tramadol provided good control of phantom limb pain (Wilder-Smith 2005 **Level II**, n=94 [cross-over], JS 4).

Neurostimulation

Neurostimulation has some effect in case series for the treatment of phantom limb pain in the form of spinal cord (McAuley 2013 **Level IV**, n=12) and peripheral nerve stimulation (Rauck 2014 **Level IV**, n=16). Percutaneous peripheral nerve stimulation resulted in more patients achieving ≥50% reduction in neuropathic postamputation pain after 4 weeks vs placebo (58% vs 14%) (Gilmore 2019 **Level II**, n=28, JS 5). Transcranial magnetic stimulation is also reviewed for treatment of phantom limb pain and non-painful phantom sensations (Nardone 2019 **Level IV SR**, 18 studies, n unspecified). However, a systematic review concludes that there /are currently no robust and reliable data on efficacy and safety of any neurostimulation in the setting of postamputation pain (Corbett 2018 **Level IV SR**, 7 RCTs & 69 studies, n unspecified); spinal cord stimulation specifically shows mixed results with some weak evidence for benefit (Aiyer 2017 **Level III-3** [PRISMA], 12 studies, n=115)..

Surgery

Targeted muscle reinnervation, originally developed to improve prosthetic tolerance and bioprosthetic outcomes, has been used for the treatment of residual and phantom limb pain (Bowen 2017 **NR**). It may even have preventive effects on both types of pain if performed at the time of amputation (Valerio 2019 **Level III-2**, n=489).

Nonpharmacological treatment

A systematic review of RCTs excluded low quality RCTs (Batsford 2017 **Level I** [PRISMA], 12 RCTs, n=135). The 5 high to moderate quality RCTs show:

- Inconclusive evidence for an effect on phantom limb pain by electromagnetically shielding limb liner (2 RCTs, n=91);
- Graded motor imagery to reduce phantom limb pain and improve function at 6 mth (1 RCT, n=9);
- A single session of mirror therapy to be ineffective (1 RCT, n=15);
- Hypnosis to reduce phantom limb pain in the short-term vs waitlist control (1 RCT, n=20).

However, nonpharmacological treatment options for phantom limb pain based on concepts of cortical reorganisation are widely discussed (Aternali 2019 **NR**; Andoh 2018 **NR**). All studies of mirror therapy, motor imagery, and virtual feedback show an effect on intensity of phantom limb pain in amputees; however the evidence is weak, as the studies included are of limited quality (Herrador Colmenero 2018 **Level III-3 SR** [PRISMA], 6 RCTs & 6 studies, n in range of 5 to 41) (2 RCTs overlap with Batsford 2017). Mirror therapy specifically shows a short-term beneficial effect in 3/4 RCTs vs controls and similar effects to TENS in 1 RCT and the authors regard the evidence as weak and insufficient to support its current use as a *"first-intention"* treatment for phantom limb (Barbin 2016 **Level IV SR** [PRISMA], 5 RCTS & 15 studies, n=258). An RCT published subsequent to the systematic review showed that graded motor imagery for 6 wk was superior to routine physiotherapy in reducing intensity of phantom limb pain and interference with function (Limakatso 2019 **Level II**, n=21, JS 3).

These findings are supported by even weaker evidence in the form of case reports excluded from the systematic review above. Maladaptive changes in cortical organisation were reversed during mirror treatment, which over 4 wk resulted in an average decrease of phantom limb pain intensity of 27% (Foell 2014 **Level IV**, n=13); mirror therapy was also effective if self-administered at the home of patients (Darnall 2012 **Level IV**, n=40). Use of a hand prosthesis with somatosensory feedback on grip strength reduced phantom limb pain (Dietrich 2012 **Level IV**, n=8). Illusory touch was another effective approach in this context (Schmalzl 2013 **Level IV**, n=6).

A technique not included in the systematic review is sensory discrimination training, which was associated with reduced phantom limb pain and cortical reorganisation (Flor 2001 **Level II**, n=10, JS 2).

There are only case series and reports describing a beneficial effect on phantom limb pain by use of virtual or augmented reality treatments (Dunn 2017a **Level IV SR**, 8 studies, n=45).

A systematic review of TENS in the treatment of phantom limb pain found no studies (Johnson 2015 **Level I** [Cochrane], 0 RCTs, n=0). However, a subsequent RCT of TENS vs mirror therapy found both were equally effective at reducing pain scores from baseline (Barbin 2016 **Level I** [PRISMA], 1 RCT: Tilak 2016 **Level II**, n=25, JS 3).

KEY MESSAGES

1. Morphine, gabapentin, ketamine and dextromethorphan reduce phantom limb pain compared to placebo (**U**) (**Level I** [Cochrane Review]).
2. Calcitonin reduces phantom limb pain in the acute (<7 days post amputation) but not the chronic setting (**U**) (**Level I** [Cochrane Review]).
3. Continuous regional block via nerve sheath catheters provides postoperative analgesia after amputation but has no preventive effect on phantom limb pain (**U**) (**Level I**).
4. Treatments aiming at cortical reorganisation such as mirror therapy (**W**) (**Level IV SR**), sensory discrimination training and motor imagery may reduce chronic phantom limb pain (**W**) (**Level III-2 SR**).
5. Perioperative epidural analgesia reduces the incidence of severe phantom limb pain (**U**) (**Level III-2 SR**).
6. Anxiety may be a predictor of phantom limb pain (**N**) (**Level IV**).

The following tick box represents conclusions based on clinical experience and expert opinion:

☑ Perioperative ketamine may prevent severe phantom limb pain (**U**).

8.1.6 | Other postoperative pain syndromes

Increasing evidence for the development of postoperative chronic pain syndromes has led to the more detailed study of some of them. In the latest revised version of the International Classification of Diseases (ICD-11), accepted by the WHO, "chronic postsurgical and posttraumatic pain" is a new classification (Schug 2019 **GL**); a range of postsurgical pain syndromes are listed (eg chronic pain after thoracotomy, breast surgery, herniotomy, hysterectomy).

The progression from acute to chronic pain and specific early analgesic interventions to reduce the incidence of chronic pain after some operations are discussed in Sections 1.4 and 1.5.

8.1.6.1 | Post-thoracotomy pain syndrome

Post-thoracotomy pain syndrome is one of the most common chronic pain states. The incidence of chronic pain after thoracotomy was 57% at 3 mth (95%CI 51 to 64) (17 studies, n=1,439) and 47% at 6 mth (95%CI 39 to 56) (15 studies, n=1,354) (Bayman 2014 **Level IV SR**, 17 studies, n=1,439). The average severity of pain at these time points was respectively 30/100 (95%CI 26 to 35) and 32/100 (95%CI 17 to 46). Quality of life (QoL) was reduced in the SF-36 domains of physical functioning, bodily pain and vitality (Kinney 2012 **Level IV**, n=110).

Pathophysiology

Post-thoracotomy pain syndrome is thought to be caused primarily by trauma to intercostal nerves and most patients relate their pain directly to the site of surgery (Karmakar 2004 **NR**). Neurophysiological assessments (QST) have revealed that patients with post-thoracotomy pain, but also pain-free patients after thoracotomy, show increased thresholds suggesting nerve injury in both groups (Wildgaard 2009 **NR**). However, only the patients in pain show increased sensitivity to heat and cold and hyperaesthesia; this suggests that nerve injury by itself is not a predictor for post-thoractomy pain syndrome and other factors need to be present. Increased or decreased sensitivity and allodynia were reported more by patients with chronic post-thoracotomy pain at 6 and 12 mth; between the 6 and 12 mth assessments, pain resolved in some patients but developed in others (Hetmann 2017 **Level IV**, n=170). Furthermore, sensory dysfunction on the nonoperated side was found in patients with post-thoracotomy pain, while such "*mirror-image sensory dysfunction*" was not accompanied by mirror pain (Werner 2013 **Level IV**, n=28). However, myofascial pain syndromes as a consequence of thoracotomy have also been described (Hamada 2000 **Level IV**, n=27).

Predictive factors

As with other postsurgical pain syndromes, poorly controlled acute postoperative pain was a strong predictor of chronic post-thoracotomy pain (Niraj 2017 **Level IV**, n=504). Other risk factors were diagnosis of cancer and preceding chronic pain (Shanthanna 2016 **Level III-3**, n=106). Similar findings of chronic preoperative and severe acute postoperative pain were confirmed in other studies (Kampe 2017 **Level III-2**, n=174; Wang 2017a **Level III-2**, n=298). A further study identified preoperative pain as the major predictor of chronic pain (OR 6.97; 95%CI 2.40 to 20.21) while finding dispositional optimism was a protective factor (OR 0.36; 95%CI 0.14 to 0.96) (Hetmann 2015 **Level IV**, n=170). Surgical approach is relevant where video-assisted thoracoscopic surgery (VATS) vs open thoracic surgery has reduced risk of post-thoracotomy pain (adjusted OR 0.33; 95%CI 0.13 to 0.86) and neuropathic pain (adjusted OR 0.18; 95%CI 0.04 to 0.85), but VATS still carries a significant risk (35% incidence) (Shanthanna 2016 **Level III-3**, n=106); this was confirmed in another study (VATS 13.3% vs thoracotomy 32.2%) (Wang 2017a **Level III-2**, n=298).

Preventive strategies

Following open thoracotomy (7 RCTs, n=499), epidural anaesthesia reduces the incidence of CPSP three to 18 mth following surgery vs systemic analgesia (OR 0.52; 95%CI 0.32 to 0.84) (NNT 7) (Weinstein 2018 **Level I** [Cochrane], 63 RCTs, n=3,027). A subsequent RCT is in line with these results (Khoronenko 2018 **Level II**, n=300, JS 3), while a single bolus perioperative PVB had no protective effect (Li 2018b **Level II**, n=56, JS 5).

Cryoanalgesia provides pain relief superior to other techniques only in 6 of 12 RCTs in the immediate postoperative period but increased the incidence of post-thoracotomy pain in 4 of 4 RCTs evaluating this outcome (Khanbhai 2014 **Level I**, 12 RCTs, n unspecified).

Magnesium (IV bolus and 24 h postoperative infusion) may have a preventive effect on chronic neuropathic pain after thoracotomy (Ghezel-Ahmadi 2019 **Level III-2**, n=100).

Treatment

Detailed reviews of treatments for acute and chronic pain after thoracotomy have been published (Doan 2014 **NR**; Romero 2013 **NR**).

8.1.6.2 | Post-mastectomy pain syndrome

Chronic pain after mastectomy is common (Kokosis 2019 **NR**). A consensus document on suggested diagnostic criteria has been published suggesting the following: *"Postmastectomy pain syndrome is pain that occurs after any breast surgery; is of at least moderate severity; possesses neuropathic qualities; is located in the ipsilateral breast/chest wall, axilla, and/or arm; lasts at least 6 months; occurs at least 50% of the time; and may be exacerbated by movements of the shoulder girdle."* (Waltho 2016 **NR**).

In epidemiological studies, an overall prevalence of 29.8% has been found (Wang 2018c **Level IV SR**, 30 studies [postmastectomy], n=3,746). In this context, it is of interest that the same systematic review found an incidence of chronic pain after radiotherapy of 27.3% (Wang 2018c **Level IV SR**, 41 studies, n=15,019).

Phantom breast pain has also been described; however, the incidence was low in the range of 7% at 6 wk and 1% at 2 y (Dijkstra 2007 **Level III-3**, n=82). Phantom sensations are more common; reported in 19% of patients >5 y after surgery (Peuckmann 2009 **Level IV**, n=2,000). Postmastectomy pain syndrome has a negative effect on many domains of quality of life (Meijuan 2013 **Level IV**, n=225).

Pathophysiology

Sensory testing (thermal thresholds, cold allodynia and temporal summation of repetitive stimulation) showed that postmastectomy pain is often a neuropathic pain condition (Vilholm 2009 **Level III-2**, n=82); in line with this, 64% of patients after mastectomy describe sensory disturbances with an increased risk of chronic pain (Meijuan 2013 **Level IV**, n=225).

Predictive factors

Significant predictors for the development of postmastectomy chronic pain were younger age (Meijuan 2013 **Level IV**, n=225) and radiotherapy (Henderson 2014 **Level III-2**, n=272; Peuckmann 2009 **Level IV**, n=2,000). Other risk factors were higher postoperative pain scores and inclusion of major reconstructive surgery (Chang 2009 **Level IV**). Psychosocial factors including catastrophising, somatisation, anxiety (OR 1.63; 95% CI 1.23 to 2.40) (Nishimura 2017 **Level IV**, n=64) and sleep disturbance were significant predictors (Belfer 2013 **Level IV**, n=611). Type of surgery, axillary node dissection, surgical complication, recurrence, tumour size and, contrary to above findings, radiation and chemotherapy were not significantly associated with postmastectomy chronic pain. Immediate breast reconstruction (implant or pedicled flap) does not increase

postmastectomy pain vs mastectomy alone (Henderson 2014 **Level III-2**, n=272). In contrast, a subsequent study (prevalence of postmastectomy pain 57.3%) identified the risk factors of postdischarge chemotherapy (OR 2.52; 95%CI 1.13 to 5.82) and postdischarge radiation (OR 3.39; 95%CI 1.24 to 10.41), while reconfirming the importance of severe acute pain (OR 5.39; 95%CI 2.03 to 15.54) and even moderate acute pain (OR 5.31; 95%CI 1.99 to 15.30) (Habib 2019 **Level IV**, n=124).

Preventive strategies

PVB reduces postmastectomy pain syndrome at 3 to 12 mth vs systemic analgesia (OR 0.43; 95%CI 0.28 to 0.68) (NNT 5) (Weinstein 2018 **Level I** [Cochrane], 18 RCTs [breast surgery], n=1,297). A subsequent RCT has confirmed these findings of reduced chronic postmastectomy pain with PVB use at 3 mth (OR 0.51; 95%CI 0.28 to 0.94) and at 6 mth (OR 0.48; 95%CI 0.25 to 0.94) (Qian 2019 **Level II**, n=184, JS 5).

Lidocaine IV infusion vs placebo reduces the risk of chronic postmastectomy pain (OR 0.29; 95%CI 0.18 to 0.48) (Bailey 2018 **Level I** [PRISMA], 6 RCTs, n=420).

Following mastectomy, 10 d treatment with venlafaxine commencing preoperatively was associated with significantly lower burning and stabbing pain after 6 mth (Amr 2010 **Level II**, n=150, JS=3). A 4 wk course of memantine (5-20 mg/d;started 2 wk before surgery) reduced pain intensity,neuropathic analgesia requirements and improved emotional state at 3 mth vs placebo (Morel 2016 **Level II**, n=43, JS 5).

Perioperative use of gabapentin or mexiletine after mastectomy reduced the incidence of neuropathic pain at 6 mth postoperatively, from 25% in the placebo to 5% in both treatment groups (Fassoulaki 2002 **Level II**, n=75, JS 4). Similar protective results were reported by the same group by the use of a eutectic mixture of local anaesthetics alone (Fassoulaki 2000 **Level II**, n=46, JS 4) or in combination with gabapentin (Fassoulaki 2005 **Level II**, n=50, JS 5).

Treatment

For treatment of chronic postmastectomy pain, amitriptyline (1 RCT, n=15 [crossover]), venlafaxine (1 RCT, n=13 [crossover]), topical capsaicin (0.075%) (1 RCT, n=23) and autologous fat grafting into the scar area (2 studies [Level III-2], n=209) are effective, while levetiracetam (1 RCT, n=27) is ineffective (Larsson 2017 **Level III-2 SR**, 4 RCTs & 2 studies, n=277).

8.1.6.3 | Post-herniotomy pain syndrome

At 6 mth after herniotomy, 12.4% had “moderate/severe” pain (Aasvang 2010 **Level IV**, n=442) and 16.0% had substantial pain-related functional impairment (Bischoff 2012 **Level III-3**, n=244).

Pathophysiology

This syndrome is thought to be mainly neuropathic pain as a result of nerve injury. This assumption was confirmed in a study that showed that all patients with chronic postherniotomy pain had features of neuropathic pain (Aasvang 2008 **Level IV**, n=46). Ejaculatory pain is a feature of this syndrome and occurs in around 2.5% of patients after herniotomy (Aasvang 2007b **Level IV**, n=10).

Predictive factors

The following risk factors were identified: preoperative Activity Assessment Scale score, preoperative pain to tonic heat stimulation, 30-d postoperative pain intensity and sensory dysfunction in the groin at 6 mth (nerve damage). An attempt to predict risk also identified open vs laparoscopic herniotomy as an additional intraoperative risk factor (OR 0.45; 95%CI 0.23 to 0.87). Furthermore, a genetic risk factor may exist as a homozygous single nucleotide polymorphism in the TNF-α gene was associated with an increased risk of neuropathic pain after

herniotomy (Kalliomaki 2016 **Level III-2**, n=200). Another study suggests that functional variations in COMT and GCH1 may predict to some extent impairment due to chronic pain after herniotomy (Belfer 2015 **Level III-2**, n=429).

Very young age may be a protective factor as hernia repair in children <3 mth age did not lead to chronic pain in adulthood (Aasvang 2007a **Level IV**, n=651).

Preventive strategies

Deliberate neurectomy (of the ilioinguinal nerve) for inguinal hernia repair reduced the incidence of CPSP (from 21–6%) in one RCT (Malekpour 2008 **Level II**, n=100, JS 4) and in another study (Smeds 2010 **Level III-2**, n=525), while an earlier nonrandomised multicentre prospective study found this increased CPSP risk (Alfieri 2006 **Level III-2**, n=973). Intraoperative nerve identification of the iliohypogastric, ilioinguinal and genitofemoral nerves did not reduce the risk of development of sensory loss or postherniotomy pain syndrome vs nonidentification (Bischoff 2012 **Level III-3**, n=244).

Mesh removal and selective neurectomy of macroscopically injured nerves reduced impairment in patients with postherniorrhaphy pain syndrome (Aasvang 2009 **Level III-3**, n=21).

Treatment

Evidence-based consensus guidelines for prevention and management of postoperative chronic pain following inguinal hernia surgery have been published (Alfieri 2011 **GL**). Recommended approaches include to identify and preserve all three inguinal nerves and to perform elective resection of a suspected injured nerve. Patients with a postherniotomy pain syndrome not responding to other pain management treatment should be offered surgical treatment (including all three nerves) after at least 1 y from the previous hernia repair.

8.1.6.4 | Post-hysterectomy pain syndrome

The incidence of chronic post-hysterectomy pain was 27.7% at 3 mth (Han 2017 **Level IV**, n=870), 32% at 4 mth and 15.7% at 6 mths (Sng 2018 **Level IV**, n=216), in line with previous data (Brandsborg 2012 **NR**). Incidence at 5 y was 17.1% in another study (Pinto 2018 **Level III-2**, n=170).

Predictive factors

In most women pain was present preoperatively; at a 1 to 2 y follow-up, pain was reported as a new symptom in 1 to 15% of patients (Brandsborg 2008 **NR**). In an initial small prospective survey postoperative pain intensity, as well as preoperative nonpelvic pain, were associated with the presence of pain 4 mth after surgery (Brandsborg 2009 **Level III-3**, n=90). For pain reported 1 y after surgery, risk factors were preoperative pelvic and nonpelvic pain and previous Caesarean section; there was no difference found between vaginal or abdominal hysterectomy or the type of incision for abdominal hysterectomy (Brandsborg 2007 **Level IV**, n=1,299). Preoperative pain sensitisation (cutaneous and vaginal hypersensitivity) is associated with acute pain after hysterectomy; but only preoperative brush-evoked allodynia was associated with chronic pain at 4 mth postoperatively (Brandsborg 2011 **Level IV**, n=90). Subsequent more detailed analyses confirmed most of these risk factors for pain at 4 mth: preoperative lower abdominal pain (OR 8.55), postoperative itching at 24 h (OR 3.33) and severe pain in PACU (OR 1.39) (Sng 2018 **Level IV**, n=216); presurgical anxiety (OR 1.18), emotional representation of the surgical disease (OR 1.21), pain catastrophising (OR 1.143), acute postsurgical pain intensity (OR 1.21) and frequency (OR 3.00) and postsurgical anxiety (OR 1.182), as well as preoperative depression, pre-existing pelvic pain and sexual dissatisfaction (Han 2017 **Level IV**, n=870).

Preventive strategies

Patients given perioperative gabapentin and a postoperative ropivacaine wound catheter infusion had lower opioid requirements after surgery and less pain 1 mth later vs placebo, although there was no difference in pain scores for the first 7 d postoperatively (Fassoulaki 2007 **Level II**, n=60, JS 5). Perioperative pregabalin (150 mg 3 times/d for 5 d) reduced postoperative opioid requirements, but had no effect on any pain outcome at 3 mth (Fassoulaki 2012 **Level II**, n=80, JS 5).

Spinal anaesthesia in comparison with general anaesthesia reduced the risk of chronic postsurgical pain after hysterectomy (OR 0.42; 95%CI 0.21 to 0.85) (Brandsborg 2007 **Level IV**, n=1,299). Propofol-based general anaesthesia vs sevoflurane-based anaesthesia reduced the incidence (17.5 vs 52.5%; p<0.01) and severity of posthysterectomy pain (0.78/10 ±0.55 vs 2.23/10 ±0.73; p<0.01) at 3 mth postoperatively (Ogurlu 2014 **Level II**, n=80, JS 5).

KEY MESSAGES

1. Following thoracotomy, epidural analgesia reduces the incidence of chronic postsurgical pain (**S**) (**Level I** [Cochrane Review]).
2. Following breast cancer surgery, paravertebral block (**S**) (**Level I** [Cochrane Review]) and lidocaine IV infusions reduce the incidence of chronic postsurgical pain (**N**) (**Level I** PRISMA]).
3. Cryoanalgesia of the intercostal nerves at the time of thoracotomy results in no improvement in acute pain, but an increase in chronic pain (**U**) (**Level I**).
4. Video-assisted thoracoscopic surgery versus open thoracic surgery resulted in a reduced rate of chronic post-thoracotomy pain (**N**) (**Level III-3**).
5. Post-thoracotomy, post-mastectomy, post-herniotomy and post-hysterectomy pain syndromes occur frequently (**S**) (**Level IV**) and psychological factors (eg anxiety, catastrophising), chronic preoperative pain and severe acute postoperative pain are consistently reported risk factors for these pain syndromes (**N**) (**Level IV**).

8.1.7 | Ambulatory or short-stay surgery

Ever increasing numbers of surgical procedure are now performed on an ambulatory or short-stay basis, here defined as hospital LOS <24 h. Adequate postoperative pain management is often the limiting factor when determining whether a patient can have surgery performed as a day-stay procedure.

Provision of effective analgesia after ambulatory surgery remains poor. In two Swedish nationwide surveys of ambulatory surgery, pain was the most common problem at follow-up after discharge in a mixed (Segerdahl 2008b **Level IV**, n=92 [hospitals]) and a paediatric population (Segerdahl 2008a **Level IV**). Another survey from a single institution found that at 3 and 4 d after day-stay surgery, 10 and 9% of patients respectively reported moderate to severe pain (Greengrass 2005 **Level IV**). Even after cataract surgery in an ambulatory setting, ocular pain was reported by 10% of patients at 24 h, 9% at 7 d and 7% at 6 wk (Porela-Tiihonen 2013 **Level IV**, n=201). Similarly, a French survey identified variable quality and a lack of standardisation of postoperative analgesia provision after ambulatory surgery across 221 randomly selected health care facilities (Aubrun 2019 **Level IV**, n=7,382).

After paediatric adenotonsillectomy, 52% patients had pain >5/10 at POD 3 (33% had nausea) and 30% at 7 d (Stanko 2013 **Level IV**, n=100). Pain scores during the first 24 h were slightly increased for day-stay tonsillectomy vs overnight inpatient stay, although maximal pain scores at 24 h and 7 d were unchanged (Norrington 2013 **Level III-2**, n=60). Differences in parental attitudes, understanding and access to medications, nausea or fear of adverse effects may explain some of these differences. Barriers have been summarised as parental, child, medication and system factors (Dorkham 2014 **NR**). Neither supplying a discharge medication package (Hegarty 2013 **Level II**, n=200, JS 2) nor nurse telephone follow-up improved pain relief after ambulatory tonsillectomy (Paquette 2013 **Level II**, n=45, JS 2). An audit of children found that pain reports were significantly higher at home than in hospital (Shum 2012 **Level IV**, n=200). Pain scores, functional limitation and analgesic use are greater after tonsillectomy than after inguinal hernia repair or orchidopexy in children discharged from ambulatory surgery, with the majority requiring at least one analgesic medication for 7 d after surgery and more than half of the patients requiring visits to a general practitioner (Stewart 2012 **Level IV**, n=105).

The best predictive factor of postoperative pain after ambulatory surgery is the presence of preoperative pain; other factors include high expectations of postoperative pain, anticipation of pain by clinicians, younger age, and surgery type (particularly orthopaedic, dental, inguinal hernia, anal, scrotal, and tendon/fascia surgeries) (Gramke 2009 **Level IV**, n=648). Not all of these factors could be confirmed in a subsequent modelling attempt, which identified preoperative pain, patient derived expected pain, and different types of surgery as the strongest predictors of moderate to severe pain 4 d after ambulatory surgery (Stessel 2017 **Level III-3**, n=1,118). Younger age and orthopaedic surgery were risk factors for severe postoperative pain in wk 1 after ambulatory surgery and high pain scores predicted more severe nausea for POD 1 to 5 (Odom-Forren 2015 **Level IV**, n=248). On POD 4 after ambulatory surgery, moderate (16.3%) to severe (12.1%) postoperative pain presented with procedure-specific variation; shoulder, anal and dental surgery was associated with the most intense pain (Vrancken 2018 **Level III-2**, n=1,123); preoperative pain intensity predicted postoperative pain intensity, but again related to procedure performed.

8.1.7.1 | Adverse effects of pain and principles of management

Inadequate analgesia delays patient discharge; pain was the most common cause of delayed recovery affecting 24% of patients (Pavlin 2002 **Level IV**, n=150). Uncontrolled pain is also associated with nausea and vomiting, extending the patient's stay in the recovery room (Eriksson 1996 **Level III-1**, n=90; Michaloliakou 1996 **Level III-1**, n=49) and is likely to continue after hospital discharge (Odom-Forren 2015 **Level IV**, n=248). The most common reason for unplanned hospital admission across 14 day-stay surgical units in Finland was unrelieved pain (Mattila 2009 **Level III-2**, n=7,915). The readmission rate was 5.4% in ambulatory surgery cases with nearly half related to inadequate pain management and half of these potentially avoidable with appropriate management (Herbst 2017 **Level IV**, n=28,674). Inadequate pain management may cause sleep disturbance and limit early mobilisation, which may be crucial for early return to normal function and work (Strassels 2002 **Level IV**, n=30).

More complex surgery continues to be performed on an ambulatory or short-stay basis and therefore the analgesic drugs and techniques required are similar to those used for inpatient pain relief. Multimodal analgesia is recommended in this setting (Schug 2015 **NR**; Elvir-Lazo 2010 **NR**) and seen as an essential part of enhanced recovery in ambulatory surgery settings (Kaye 2019 **NR**). Preoperative implementation of multimodal analgesia (various regimens including paracetamol, gabapentin and celecoxib) for ambulatory breast surgery reduced pain scores and opioid requirements vs no preoperative use and to IV paracetamol alone (Barker 2018 **Level III-3**, n=560).

See also relevant sections of this document:

- Systemically administered analgesic drugs (Chapter 4);
- Regionally and locally administered analgesics drugs (Chapter 4);
- Regional and other local analgesia techniques (Chapter 5);
- Postoperative pain (Chapter 8);
- Paediatric issues (Chapter 10).

8.1.7.2 | Systemic analgesia

Paracetamol, nonselective NSAIDs and coxibs

Following outpatient surgery, ibuprofen (1,200 mg/d) or celecoxib (400 mg/d) for 4 d vs placebo reduced the need for breakthrough analgesia in the early postdischarge period leading to improved patient satisfaction and quality of recovery (White 2011 **Level II**, n=180, JS 4). A study in minor oral surgery demonstrated equivalent benefit of celecoxib 400 mg to diclofenac 50mg over placebo for VAS scores and opioid consumption, and while acetaminophen had a similar effect it was not manifest until 5 and 6 h post administration (Hanzawa 2018 **Level II**, n=128, JS 4).

For ambulatory laparoscopic cholecystectomy, parecoxib preoperatively (30 min prior to surgery) vs postoperatively or placebo was associated with less pain and analgesic requirements for up to 24 h leading to shorter times to attain PACU and hospital discharge criteria (Shuying 2014 **Level II**, n=120, JS 4). However, for minor day-stay gynaecological surgery, paracetamol or parecoxib, either alone or in combination, did not produce a clinically significant impact on pain in the first 24 h after surgery vs placebo (Mohamad 2014 **Level II**, n=240, JS 4).

In children undergoing ambulatory inguinal hernia repair under general anaesthesia with caudal bupivacaine, rectal diclofenac provided longer duration of analgesia vs rectal paracetamol or placebo (Nnaji 2017 **Level II**, n=90, JS 4).

After ambulatory surgery, the combination of paracetamol/metamizole vs paracetamol/ibuprofen provided similar acute postoperative pain control at home including comparable patient satisfaction levels (Stessel 2019 **Level II**, n=200, JS 5).

Conventional and atypical opioids (alone or in combination)

Paracetamol/tramadol provided similar analgesia to tramadol alone after ambulatory hand surgery and resulted in a reduced rate of adverse effects (Rawal 2011 **Level II**, n=80, JS 5). Paracetamol/tramadol was also superior to combination paracetamol/codeine with better analgesia, fewer adverse effects and higher patient satisfaction in a mixed day-stay surgical population (Alfano 2011 **Level II**, n=122, JS 2). Paracetamol/codeine provided similar analgesia but with more discontination due to adverse effects vs paracetamol/ibuprofen after day-stay breast surgery (Mitchell 2012 **Level II**, n=145, JS 5).

Morphine vs hydromorphone in patients having ambulatory (including laparoscopic) surgery showed no difference in analgesic efficacy or side effects (Shanthanna 2019 **Level II**, n=402, JS 5). Similarly after pregnancy termination, intraoperative administration of IV oxycodone (0.06 mg/kg and 0.08 mg/kg) vs IV fentanyl (2 mcg/kg) resulted in no clinically relevant difference in pain score at 30 min (Xie 2017 **Level II**, n=120, JS 2); statistically the higher dose oxycodone group had the lowest pain scores.

For ambulatory surgery, the use of intraoperative methadone (0.15 mg/kg IBW) resulted in similar pain control and adverse effects vs conventional prn dosing of short acting opioids (eg fentanyl, hydromorphone) (Komen 2019 **Level II**, n=66, JS 3). Although the authors report reduced postoperative requirements for other opioids, the potential risks of methadone administration (OIVI, QT prolongation), particularly in an ambulatory setting, were not discussed (Dunn 2018a **Level IV**, n=1,478).

Systemic adjuvant medications

IV dexamethasone 0.1 mg/kg in an ambulatory gynaecological surgery population improved Quality of Recovery score (QoR-40) and reduced opioid consumption in the first 24 h postoperatively vs dexamethasone 0.05 mg/kg or placebo (De Oliveira 2011 **Level II**, n=120, JS 5). Similarly in a paediatric setting, the addition of systemic dexamethasone (0.5 mg/kg; 10 mg maximum) to caudal blocks for day-stay orchidopexy improved and extended postoperative analgesia (Hong 2010 **Level II**, n=77, JS 5). After ambulatory knee arthroscopy, IV betamethasone (8 mg) vs placebo increased the number of patients with no or minor pain at POD 2 (67 vs 44%) (Segelman 2016 **Level II**, n=74, JS 5).

IV dexmedetomidine (0.5 mcg/kg) intraoperatively vs placebo after ambulatory ureteroscopy and ureteric stenting improved pain control at 1 h and on POD 1 to 3 (at rest and on movement) and return to daily activities (Shariffuddin 2018 **Level II**, n=60, JS 5). For outpatient gynaecological diagnostic laparoscopy, dexmedetomidine (0.5 mcg/kg) vs fentanyl (0.5 mcg/kg) on induction reduced postoperative pain severity, rescue analgesic requirements and PONV (Techanivate 2012 **Level II**, n=40, JS 4).

Nebulised dexmedetomidine/ketamine (1 mcg/kg and 1 mg/kg) preoperatively in the setting of outpatient dental surgery was superior to either ketamine (2 mg/kg) or dexmedetomidine (2 mcg/kg) alone with regard to preoperative sedation and recovery and superior to ketamine alone for postoperative analgesia (Zanaty 2015 **Level II**, n=60, JS 4).

IV lidocaine infusion intraoperatively until 30 min after arrival in PACU vs placebo for ambulatory laparoscopic sterilisation had no effect on postoperative pain and opioid requirements, increased requirement of PONV rescue, but resulted in earlier readiness for discharge (Dewinter 2016 **Level II**, n=80, JS 5).

8.1.7.3 | Local anaesthesia techniques

Certain local and regional techniques offer specific benefits to patients after day-stay or short-stay surgery. There has been increasing interest in the use of single dose ("single injection") as

well as continuous peripheral nerve block (CPNB) in patients discharged home (Ardon 2019 **NR**; Schug 2015 **NR**). See also Section 5.8.

Local and peritoneal infiltration

After day-stay hernia repair, wound infiltration with levobupivacaine provided analgesia for 24 h (Ausems 2007 **Level II**, n=120, JS 5) and with bupivacaine reduced pain and tramadol requirements in the first 4 h (Qureshi 2016 **Level II**, n=80, JS 3). However, after day-stay laparoscopic gynaecological surgery, wound infiltration did not significantly reduce pain or opioid requirements (Fong 2001 **Level II**, n=100, JS 5).

After ambulatory hallux valgus repair, mid foot infiltration vs sciatic nerve block provided similar analgesia, but infiltration permitted earlier ambulation (Adam 2012 **Level II**, n=40, JS 3).

Three systematic reviews of local anaesthetic interventions for day-stay laparoscopic cholecystectomy have been performed with significant overlap of included RCTs; the two Cochrane reviews highlight the very low quality of the included RCTs. Local anaesthetic infiltration provides superior analgesic benefit vs placebo in 6 of 8 RCTs, with preincisional infiltration being superior to postincisional administration (Ahn 2011 **Level I**, 8 RCTs [local infiltration], n unspecified). Pain intensity is lower with local anaesthetic infiltration vs placebo at 4 to 8 h (MD -1.33/10; 95%CI -1.54 to -1.12) (13 RCTs, n=806) and 9 to 24 h (MD -0.36/10; 95%CI -0.53 to -0.20) (12 RCTs, n=756) (Loizides 2014 **Level I** [Cochrane], 19 RCTs, n=1,263). Intraperitoneal local anaesthetic is beneficial in 7 of 9 RCTs, with one of the two negative RCTs using local anaesthesia at the end of the procedure (Ahn 2011 **Level I**, 9 RCTs [intraperitoneal], n unspecified). Local anaesthetic is more effective when applied before the commencement of pneumoperitoneum and use of aerosolised local anaesthetic is more effective than simple instillation. Two RCTs showed the combination of incisional and intraperitoneal local anaesthesia is more effective than either intervention alone. Intraperitoneal local anaesthetic vs placebo lowers pain intensity at 4 to 8 h (MD -0.99/10; 95%CI -1.10 to -0.88) (32 RCTs, n=2,020) and at 9 to 24 h (MD -0.53/10; 95%CI -0.62 to -0.44) (29 RCTs, n=1,787) (Gurusamy 2014 **Level I** [Cochrane], 48 RCTs, n=2,849).

After laparoscopic cholecystectomy, same day discharge readiness criteria were achieved after intraincisional ropivacaine in 31% patients, intraperitoneal ropivacaine in 48%, and after combined intraincisional and intraperitoneal ropivacaine in 89% patients (Kaushal-Deep 2019 **Level II**, n=191, JS 5).

Intraperitoneal instillation of local anaesthetic at gynaecological laparoscopy reduced pain scores for up to 6 h postoperatively (Marks 2012 **Level I**, 7 RCTs, n=478). Intraperitoneal local anaesthetic also reduces shoulder tip pain within 24 h of ambulatory gynaecological laparoscopy (OR 0.23; 95%CI 0.06 to 0.93) (2 RCTs, n=157) (Kaloo 2019 **Level I** [Cochrane], 32 RCTs, n=3,284).

Single injection peripheral nerve block

PNBs are useful in ambulatory surgery as they provide site-specific anaesthesia with prolonged analgesia and minimal haemodynamic changes (Salinas 2014 **NR**).

The decision to discharge ambulatory patients following PNB with long-acting local anaesthesia is controversial due to the potential risk of harm to an insensate limb. A prospective study demonstrated that long-acting PNBs were safe and that patients could be discharged with an insensate limb (Klein 2002 **Level IV**, n=1,119 [upper] & 1,263 [lower extremity blocks]). Therefore, provided patients are given verbal and written information regarding the risks as well as appropriate follow-up, it would seem reasonable to discharge these patients with the benefit of prolonged analgesia. Patients may suffer intense pain following resolution of a PNB, although it maximises pain relief in the first 12 to 24 h (Chung 1997 **Level IV**, n=10,008). After outpatient shoulder arthroscopy with single injection interscalene block, 15% of

patients experienced severe pain at home in the first 3 d and 5% contacted their general practitioner for analgesia issues (Trompeter 2010 **Level IV**, n=109). After wrist fracture surgery, patients who received a single injection brachial plexus block were 3 times more likely to require medical attention for pain management within 48 h vs GA (Sunderland 2016 **Level IV**, n=419). These studies illustrate a major concern with the use of single injection PNBs, in particular in the ambulatory setting, of 'rebound' pain after the regional block wears off (Lavand'homme 2018 **NR**).

Ilioinguinal and iliohypogastric block

Ambulatory herniorrhaphy performed under ilioinguinal and iliohypogastric nerve block led to superior pain relief, less morbidity, less urinary retention and cost advantages (Ding 1995 **Level II**, n=30, JS 4). The analgesic benefit with bupivacaine lasted around 6 h (Toivonen 2001 **Level II**, n=100, JS 3). For open inguinal hernia surgery, US-guided ilioinguinal and iliohypogastric blocks with bupivacaine vs saline reduced pain scores at rest and on movement in the PACU, although opioid consumption and time to discharge did not differ (Baerentzen 2012 **Level II**, n=60, JS 5).

For paediatric information, see Section 10.6.2.3.

Transversus abdominis plane blocks (TAPB)

After day-stay laparoscopic cholecystectomy, TAPB with ropivacaine vs placebo reduced opioid requirements for 2 h and pain on coughing, but not at rest, for up to 4 h (Petersen 2012 **Level II**, n=80, JS 5).

After day-stay inguinal hernia repair, local infiltration and TAPB vs local infiltration for surgical anaesthesia alone reduced the need for intraoperative rescue analgesia (36 vs 8%) and improved postoperative pain scores for 12 h (Milone 2013 **Level II**, n=150, JS 3). When blind ilioinguinal/iliohypogastric nerve blocks were compared to US-guided TAPB for day-stay open inguinal hernia surgery, there was a small reduction in pain at rest (but not on movement) in the TAPB group for up to 24 h (Aveline 2011 **Level II**, n=273, JS 5). There was also a modest reduction in postoperative oral morphine requirement over the first 2 d. The primary outcome for this study was pain at 6 mth, where no difference was found.

For paediatric information, see Section 10.6.2.3.

Paravertebral block (PVB)

For inguinal herniorrhaphy, PVB vs general anaesthesia/systemic analgesia (4 RCTS, n=268) or neuraxial anaesthesia (6 RCTs, n=377) reduced PONV, although pain outcomes and hospital LOS were similar (Law 2015 **Level I** [PRISMA], 14 RCTs, n unspecified). PVBs provided better analgesia than more distal nerve blocks (2 RCTs [ilioinguinal block], n=140; 1 RCT [TAPB], n=60). Successful use after outpatient lithotripsy has also been reported (Jamieson 2007 **Level IV**, n=2).

After ambulatory breast augmentation, PVB was superior to direct surgical infiltration with ropivacaine with regard to pain scores and requirements for rescue analgesia (Gardiner 2012 **Level II**, n=40, JS 3). However, comparing PVB to general anaesthesia for minor breast surgery in a day-care setting, the benefits were small and may not justify the increased risk (Terheggen 2002 **Level II**, n=30, JS 3). After PVB performed for ambulatory breast surgery, complications included hypotension and/or bradycardia in 2.2%, LAST in 0.17%, and pneumothorax requiring only conservative management in 0.26% (Kelly 2018b **Level IV**, n=1,322).

Newer blocks, such as erector spinae plane blocks (ESPB) may prove suitable alternatives to PVB for abdominal and thoracic surgery (Hannig 2018 **Level IV**, n=3).

For paediatric information, see Section 10.6.2.3.

Upper and lower limb blocks

Adductor canal blocks (ACBs) offer potential for improved analgesia without significant motor block for ambulatory arthroscopic knee surgery. For simple arthroscopic procedures, ACBs

reduced pain scores modestly to 8 h and opioid consumption up to 24 h (4 RCTs, n=247); however, no benefit was demonstrated after anterior cruciate ligament repair from either ACB vs placebo (3 RCTs, n=135) or ACB vs FNB (3 RCTs, n=308) (Sehmbi 2019 **Level I** [PRISMA], 10 RCTs, n=716).

Interscalene (Bishop 2006 **Level IV**, n=299; Faryniarz 2006 **Level IV**, n=133) and supraclavicular (Liu 2010 **Level IV**, n=1,169) plexus blocks provided safe and effective analgesia after ambulatory shoulder surgery. For hand and wrist surgery, infraclavicular nerve blocks with propofol sedation vs general anaesthesia followed by local anaesthetic wound infiltration resulted in less postoperative pain, less nausea, earlier ambulation and earlier hospital discharge (Hadzic 2004 **Level II**, n=52, JS 3). US-guided PNBs with ropivacaine can be added to brachial plexus anaesthesia with lignocaine to prolong analgesia after hand surgery, while avoiding significant motor block (Dufeu 2014 **Level IV**, n=125). For day-stay hand surgery (trapeziectomy) performed under an axillary plexus block, distal nerve blocks (radial and median nerve) with levobupivacaine 0.125% vs systemic analgesia provided superior pain relief on POD 1 with reduced opioid requirements and PONV incidence (Rodriguez Prieto 2018 **Level II**, n=52, JS 4).

For ambulatory shoulder surgery, using 20 vs 40 mL of mepivacaine 1.5%/bupivacaine 0.5% for US-guided interscalene blocks resulted in similar analgesia and patient satisfaction, but 20 mL had lower incidence of hoarseness and provided better hand grip strength (Maalouf 2016 **Level II**, n=154, JS 4). For major day-stay arthroscopic shoulder surgery, the anterior suprascapular block was non-inferior to the interscalene block and preserved best pulmonary function (Auyong 2018 **Level II**, n=189, JS 5).

Pelvic plexus block

Pelvic plexus block provided better intra and postoperative analgesia than periprostatic nerve block for ambulatory transrectal US-guided prostate biopsy (Cantiello 2012 **Level II**, n=180, JS 3).

Gynaecological paracervical block

In awake patients, paracervical local anaesthesia for cervical dilatation and uterine intervention reduces intraoperative pain vs placebo (10 RCTs), but fails to show a benefit over sedation (6 RCTs) or other local anaesthesia techniques for postoperative pain (Tangsiriwatthana 2013 **Level I** [Cochrane], 26 RCTs, n=2,790). Overall, no recommendations regarding benefits could be made.

Specifically, for ambulatory hysteroscopy, paracervical block (SMD -1.28/10; 95%CI -2.22 to -0.35 [vs placebo]) provides superior analgesia vs intracervical injection of LA (SMD -0.36/10; 95%CI -0.61 to -0.10 [vs placebo]) (Cooper 2010 **Level I**, 20 RCTs, n unspecified); transcervical and topical application of LA has no analgesic effect.

Adjuvants to single injection peripheral nerve block

Buprenorphine

Buprenorphine added to local anaesthetic for brachial plexus and intraoral blocks increased the duration of analgesia vs local anaesthetic alone (Kumar 2013 **Level II**, n=100, JS 3; Modi 2009 **Level II**, n=50, JS 3; Candido 2001 **Level II**, n=40, JS 5). However, with infragluteal sciatic block for foot and ankle surgery, when buprenorphine was either added to bupivacaine or given IM, there was only a modest analgesic benefit, with increased vomiting in the groups receiving buprenorphine (Candido 2010 **Level II**, n=103, JS 5).

Dexamethasone

Caudal dexamethasone improved the quality and duration of caudal epidural ropivacaine analgesia in a paediatric day-stay orchidopexy population (Kim 2014a **Level II**, n=80, JS 5). In the setting of paediatric day-care hernia repair, IV dexamethasone (0.5 mg/kg) also increased duration of caudal levobupivacaine analgesia (800 vs 520 min) and improved pain control on POD 1 and 2 (Murni Sari Ahmad 2015 **Level II**, n=64, JS 5).

For arthroscopic ambulatory shoulder surgery, both systemic and perineural dexamethasone (10 mg) prolonged interscalene block with 0.5% ropivacaine, with both dexamethasone groups requiring less analgesics in the first 48 h vs placebo (Desmet 2013 **Level II**, n=150, JS 5). When dexamethasone 4 mg was added to interscalene ropivacaine for shoulder arthroscopy, median duration of analgesia was longer than systemic administration (18 h vs 14 h), which was similar to placebo (Kawanishi 2014 **Level II**, n=39, JS 3). However, a subsequent RCT found only a minor prolongation of duration of interscalene block for ambulatory arthroscopic shoulder surgery with perineural vs systemic dexamethasone, which might not be clinically relevant (Holland 2018 **Level II**, n=280, JS 5); there was no difference between doses of 4 and 8 mg.

For more details, see Section 4.12.2.

Dexmedetomidine

When added to caudal ropivacaine for paediatric day-stay patients undergoing lower abdominal and perineal surgery, dexmedetomidine (0.5 to 1.5 mcg/kg) prolongs analgesia with minor prolongation of motor block, time to void and sedation, without increased hypotension or delay in hospital discharge (Bharti 2014 **Level II**, n=80, JS 5). For paediatric day-stay orchidopexy, addition of dexmedetomidine (1 mcg/kg) to caudal ropivacaine prolonged time to first analgesic request (Cho 2015a **Level II**, n=80, JS 4).

For more details, see Section 4.9.2.2

Ketamine

A systematic review of ketamine 0.25 to 0.5 mg/kg added to caudal local anaesthetic prolongs analgesia (time to first request) by a median difference of 5.6 h, without prolonged motor block (Schnabel 2011 **Level I** [PRISMA], 13 RCTs, n=884). Of the 13 RCTs, 9 were in the ambulatory paediatric population. Although many adverse effects were more frequent in the ketamine group, there was no significant difference to placebo. However, concerns of local neurotoxicity *in vitro* continue to limit the use of neuraxial ketamine, in particular when combined with lignocaine (Werdehausen 2011 **NR**).

For more details, see Section 4.6.2.1

Continuous peripheral nerve block

Continuous peripheral nerve blocks (CPNBs) after ambulatory surgery vs single injection blocks reduce pain at rest and during movement and opioid requirements for the first 24 h, but not consistently sustained beyond this time frame (Saporito 2017 **Level I** [PRISMA], 5 RCTS, n=160); the quality and size of the RCTs limits the strength of these conclusions.

Upper and lower limb CPNB

CPNB using perineural catheters and continuous infusions of local anaesthetic led to sustained postoperative analgesia (Zaric 2004 **Level II**, n=63, JS 5; Ilfeld 2002b **Level II**, n=30, JS 5; Ilfeld 2002a **Level II**, n=30, JS 5), was opioid-sparing (Ilfeld 2003 **Level II**, n=25, JS 5; Ilfeld 2002b **Level II**, n=30, JS 5; Ilfeld 2002a **Level II**, n=30, JS 5) and resulted in less sleep disturbance (Ilfeld 2002b **Level II**, n=30, JS 5; Ilfeld 2002a **Level II**, n=30, JS 5) and improved rehabilitation (Capdevila 1999 **Level II**, n=56, JS 2).

Patients achieved discharge criteria significantly earlier in a number of settings approaching short-stay discharge times: after total shoulder arthroplasty with use of continuous interscalene blocks (21 vs 51 h) (Ilfeld 2006 **Level II**, n=29, JS 5); after hip arthroplasty with use of continuous lumbar plexus block (29 vs 52 h) (Ilfeld 2008a **Level II**, n=47, JS 5); and after total knee arthroplasty with the use of continuous FNBs (25 vs 71 h) (Ilfeld 2008b **Level II**, n=50, JS 5). Adductor canal catheters allowed discharge on POD 1 after knee arthroplasty in 12% of patients in one series (Hanson 2016 **Level IV**, n=512). These benefits have the potential to reduce hospital costs (Ilfeld 2007 **Level III-3**, n=20). Similar benefits have been observed with a range of CPNBs in a predominantly paediatric population (Gurnaney 2014 **Level IV**, n=1,285).

A 2 d interscalene infusion at home after shoulder surgery vs a single injection interscalene block, was opioid-sparing and improved pain relief, sleep and patient satisfaction (Salviz 2013 **Level II**, n=70, JS 4; Mariano 2009 **Level II**, n=32, JS 5). Furthermore at day 7, fewer patients had an NRS > 4 (26% v. 83%), suggesting a sustained analgesic benefit. Similarly, after arthroscopic rotator cuff repair, continuous (3 d of 0.125% bupivacaine at 5 mL/h plus a patient-controlled bolus of 5 mL/h) vs single injection interscalene block provided better analgesia with better sleep pattern and reduced opioid requirements (Malik 2016 **Level II**, n=92, JS 4). Patient-controlled bolus added to continuous infusion of ropivacaine improved analgesia and function more than a continuous infusion and even more so vs IV morphine PCA (Capdevila 2006 **Level II**, n=86, JS 4).

Continuous popliteal sciatic nerve block for foot and ankle surgery has a high success rate and a low rate of complications, with a catheter dislocation rate of 0.2% (Borgeat 2006 **Level IV**, n=1,001). Compared to inpatients, ambulatory sciatic popliteal catheters were not associated with increased pain, complications or healthcare interventions in outpatients, allowing a significant reduction in healthcare costs (Saporito 2014 **Level II**, n=120, JS 4). For day-case hallux valgus surgery, placing the tip under US-guidance of the sciatic nerve catheter medial to the tibial nerve vs between the tibial and peroneal components provides equivalent analgesia with reduced insensate limb and foot drop and was therefore advantageous in an ambulatory setting (Ambrosoli 2016 **Level II**, n=84, JS 3).

Paravertebral CPNB

Continuous PVB after short-stay mastectomy with 0.4% ropivacaine vs saline at 5 mL/h for 3 d demonstrated improved pain scores and less pain-induced physical and emotional dysfunction for the infusion duration (Ilfeld 2014 **Level II**, n=60, JS 5). Adding a continuous infusion to maintain the PVB after a single injection block for outpatient breast cancer surgery did not add further benefits (Buckenmaier 2010 **Level II**, n=94, JS 5).

Safety and management of CPNB in an ambulatory setting

The safety and efficacy of CPNBs in an ambulatory setting has been confirmed in adult (Nye 2013 **Level IV**, n=281; Fredrickson 2008 **Level IV**, n=300; Swenson 2006 **Level IV**, n=620) and paediatric patients (Gurnaney 2014 **Level IV**, n=1,285; Ludot 2008 **Level IV**, n=47; Ganesh 2007 **Level IV**, n=226 [catheters]).

Inadvertent intravascular catheter placement needs to be excluded prior to patient discharge using a test dose of local anaesthetic and adrenaline (epinephrine) (Rawal 2002 **NR**). Patients and their carers should be given extensive oral and written instructions about management, adverse effects and care of the local anaesthetic catheter, and have 24 h telephone access to an anaesthesiologist during the postoperative period while CNPB is in use (Swenson 2006 **Level IV**, n=620) as 30% of patients make unscheduled phone calls regarding catheter infusions despite been given adequate written and verbal instructions (Ilfeld 2002a **Level IV**, n=30). A review of outpatients with CPNB (including popliteal fossa, fascia iliaca and interscalene) showed that 4.2% required assistance by the anaesthesiologist after discharge from hospital for problems relating to issues such as patient education, inadequate analgesia and equipment malfunction; only one patient was unable to remove their catheter (Swenson 2006 **Level IV**, n=620), although patients may have significant anxiety about catheter removal at home (Ilfeld 2004 **Level IV**, n=24). While patient satisfaction is high, failure of brachial plexus catheters within 72 h of insertion in the ambulatory setting may be as high as 26% for supraclavicular and 19% for infraclavicular approaches (Ahsan 2014 **Level IV**, n=207). In another series, approximately one third of patients with brachial plexus catheters (continued for an average of 4 d) experienced adverse effects or required additional healthcare intervention (King 2019 **Level IV**, n=501).

Detailed narrative reviews of the use of CPNBs for ambulatory surgery have been published (Jones 2019b **NR**; Salinas 2014 **NR**; Ilfeld 2011 **NR**).

8.1.7.4 | Nonpharmacological techniques

Nonpharmacological techniques such as TENS, acupuncture, hypnosis, US, laser and cryoanalgesia have also been used in the treatment of acute pain management after ambulatory surgery. Pressure on acupoints decreased pain following knee arthroscopy (Felhendler 1996 **Level II**, n=44, JS 3). TENS resulted in a significant, but clinically trivial reduction of pain after endometrial biopsy vs placebo TENS (Yilmazer 2012 **Level II**, n=65, JS 1). Continuous-flow cold therapy has been shown to be effective following outpatient anterior cruciate ligament reconstruction, also reducing analgesic requirements (Barber 1998 **Level II**, n=100, JS 1).

An educational intervention (individualised education using written and verbal information as well as two telephone support calls before and after surgery) vs usual care improves multiple measures of pain intensity and function on POD 2 (Sawhney 2017 **Level II**, n=82, JS 5). An empathic patient-centered interview vs standard care prior to ambulatory general surgery resulted in lower levels of pain, preoperative anxiety and higher levels of daily activity and satisfaction with the information received (Pereira 2016 **Level II**, n=104, JS 1).

8.1.7.5 | Procedure-specific pain management after ambulatory surgery

Ambulatory arthroscopic anterior cruciate ligament reconstruction

A systematic review finds that arthroscopic anterior cruciate ligament (ACL) reconstruction preformed as an outpatient vs an inpatient procedure resulted in similar or better outcomes with regard to pain, satisfaction, knee function, strength and complications (Ferrari 2017 **Level III-3 SR** [PRISMA], 2 RCTs & 5 studies, n=407); included studies were of low methodological quality. In the same setting, there was no more postoperative discomfort in outpatients vs inpatients and outpatients had less difficulty sleeping, were less often woken by pain during the first postoperative night and more often walked regularly on POD 1 (Lefevre 2015 **Level III-1**, n=133).

A systematic review of analgesic approaches to ambulatory arthroscopic ACL reconstruction finds regional nerve blocks and intra-articular LA injections equally effective analgesic techniques (Secrist 2016 **Level III-2** [PRISMA], 77 studies, n unspecified). Gabapentin, zolpidem, ketorolac, and ibuprofen have opioid sparing effects and cryotherapy-compression (10 studies) as well as early mobilisation are effective non-pharmacological approaches. There is no support for the routine use of FNBs in this setting (Vorobeichik 2019 **Level I** [PRISMA], 8 RCTs, n=716) and ACB is not superior to FNB (Sehmbi 2019 **Level I** [PRISMA], 10 RCTs, n=714), while use of LIA reduces pain intensity and opioid requirements with minimal complications (Yung 2019 **Level I** [PRISMA], 11 RCTs, n=515).

Procedure-specific guidelines for pain management after ambulatory arthroscopic ACL reconstruction have been published (Abdallah 2019 **GL**).

Ambulatory shoulder arthroscopy

After ambulatory shoulder arthroscopy, interscalene nerve blocks (ISBs) are the most effective approach to pain management (Warrender 2017 **Level I** [PRISMA], 40 RCTs, n unspecified); increasing LA concentrations, continuous infusions, and patient-controlled methods are effective strategies to improve analgesia. Duration of the analgesic effect can be extended by adding dexamethasone, clonidine, intrabursal oxycodone, and magnesium. Preoperative oral pregabalin and coxibs improve analgesia and patient satisfaction.

8.1.7.6 | Discharge analgesia

A survey of day-surgery practices in 100 hospitals in 8 European countries reported take-home analgesics were provided as a "*tablet-package*" by 69% or as prescription by 80% of hospitals (Stomberg 2013 **Level IV**). Strong opioids on discharge were given or prescribed by 59% of units. Written instructions about management of pain were provided by 69% of units.

Early discharge after day-stay surgery with a prescription of opioids or NSAIDs carries an increased risk of subsequent long term use of these analgesics. In a population of 391,139 opioid-naïve patients aged >65 y having short-stay surgery, patients receiving an opioid prescription within the 7 d after surgery were more likely to become long term opioid users within 1 y in comparison to those without a prescription (OR 1.44; 95%CI 1.39 to 1.50) (Alam 2012 **Level III-2**, n=391,139). Discharge NSAID prescriptions were also more likely to be associated with persistent use (OR 3.74; 95%CI 3.27 to 4.28).

Implementation of multimodal analgesia pathways for same-day thyroid, parathyroid, and parotid surgery (adherence increased from 0% to 87% from 2015 to 2017) resulted in a dramatic reduction of opioid prescription on discharge (OR 0.13; 95%CI 0.04 to 0.44) (Militsakh 2018 **Level III-3**, n=528). After ambulatory surgical procedures, there was a wide range of amounts of opioids prescribed; only 28% of prescribed opioids were taken and suggestions for more appropriate prescribing are made (Hill 2017 **Level IV**, n=642). An educational intervention based on estimated opioid requirements for specific outpatient procedures resulted in decreased prescribing rates without increasing patients' refill requirements (Hill 2018b **Level IV**, n=224).

The importance of opioid stewardship specifically in the ambulatory surgery setting has been emphasised (Roth 2018 **NR**).

For more details, see Section 8.13 and for paediatric information, see Section 10.4.5.

KEY MESSAGES

1. Wound infiltration and intraperitoneal instillation with local anaesthetics for short-stay laparoscopic cholecystectomy has good analgesic efficacy, in particular when combined and administered prior to trocar insertion and at commencement of pneumoperitoneum respectively (**S**) (**Level I** [Cochrane Review]).
2. Intraperitoneal instillation with local anaesthetic provides good analgesia for up to 6 hours after short-stay gynaecological laparoscopy (**U**) (**Level I**) and reduces shoulder tip pain for 24 h (**N**) (**Level I** [Cochrane Review]).
3. Ketamine added to caudal local anaesthetic for paediatric day-stay surgery prolongs analgesia, but not motor block (**U**) (**Level I** [PRISMA]); however, concerns regarding neurotoxicity remain.
4. Continuous peripheral nerve blocks after short-stay surgery provide extended analgesia for at least 24 h, leading to reduced opioid requirements (**S**) (**Level I** [PRISMA]), earlier achievement of discharge criteria, less sleep disturbance and improved early rehabilitation (**S**) (**Level II**).
5. Paravertebral block improves pain-related outcomes after short-stay hernia repair (**S**) (**Level I** [PRISMA]) and major breast surgery (**U**) (**Level II**).
6. After ambulatory anterior cruciate ligament repair, analgesia is superior with local infiltration anaesthesia versus femoral nerve blocks and adductor canal blocks; multimodal systemic analgesia, early mobilisation and cooling/compression are also supported (**N**) (**Level I** [PRISMA]).
7. After ambulatory shoulder arthroscopy, interscalene nerve block is superior to other peripheral nerve blocks; adjuvants to increase block duration and systemic multimodal analgesia are also supported (**N**) (**Level I** [PRISMA]).
8. Gynaecological paracervical block provides superior analgesia to intracervical and transcervical block and topical local anaesthetic administration (the latter both without analgesic effect) for ambulatory hysteroscopy (**N**) (**Level I**).
9. Dexamethasone added to local anaesthetics in peripheral nerve blocks and for caudal analgesia or given systemically prolongs duration of analgesia after short-stay surgery (**S**) (**Level I**).
10. Single injection peripheral nerve blocks with long-acting local anaesthetics provide long-lasting postoperative analgesia after short-stay surgery (**S**) (**Level II**).
11. Infiltration of the wound with local anaesthetic provides effective and long-lasting analgesia after many short-stay procedures (**U**) (**Level II**).
12. In the short-stay surgery setting, anti-inflammatories (nonselective NSAIDs, coxibs and dexamethasone) and paracetamol contribute to reduced pain and improved recovery (**U**) (**Level II**).
13. Buprenorphine or dexmedetomidine added to local anaesthetics for peripheral nerve blocks prolong duration of analgesia after short-stay surgery (**U**) (**Level II**).

14. Anterior cruciate ligament repair performed as a short-stay procedure in comparison to an inpatient setting achieves comparable quality of pain relief and better outcomes (**N**) (**Level III-3 SR**).
15. Pain relief after short-stay surgery remains poor (**U**) (**Level IV**) and is a common cause of unplanned re-presentation (**U**) (**Level III-3**).
16. Continuous peripheral nerve blocks have been shown to be safe at home after short stay surgery, if adequate resources and patient education are provided (**U**) (**Level IV**).
17. Predictive factors of severe pain after short-stay surgery are preoperative pain, high expectation of postoperative pain, younger age and certain types of surgery (in particular orthopaedic surgery) (**N**) (**Level IV**).

The following tick box represents conclusions based on clinical experience and expert opinion.

☑ Preoperative patient-centered education (verbal and written) and telephone follow-ups may improve anxiety, pain and functional outcomes and patient satisfaction after ambulatory surgery (**N**).

8.1.8 | Cranial neurosurgery

There is a widespread belief that intracranial surgery does not result in much patient discomfort and pain. However, surveys have shown that patients have significant pain in the early phase after intracranial surgery; the incidence of acute post craniotomy pain varies from 27% (de Oliveira Ribeiro Mdo 2013 **Level IV**, n=91) to 80% of patients (Gottschalk 2007 **Level IV**, n=187; Nemergut 2007 **NR**). These findings are in line with other studies that found incidences of 56% moderate and 25% severe pain (Thibault 2007 **Level IV**, n=299) and of 87% pain overall in the first 24 h (NRS 1 to 3, 32%; 4 to 7, 44%; 8 to 10, 11%) despite conventional pain management (Mordhorst 2010 **Level IV**, n=256). In a paediatric population, 35% of patients had moderate to severe pain in the immediate postoperative setting but this reduced to 8% at POD 1 (Bronco 2014 **Level IV**, n=206). Similarly, 42% of children had at least one episode of pain ≥3/10 in the first 72 h after craniotomy (Teo 2011 **Level IV**, n=52).

However, the pain is not as severe as after other surgical procedures such as extracranial maxillary/mandibular surgery or lumbar surgery (Klimek 2006 **Level III-2**, n=649; Dunbar 1999 **Level III-2**, n=99). The findings that the pain is more severe after an infratentorial rather than a supratentorial approach (Gottschalk 2007 **Level IV**, n=187) are disputed by another study (Irefin 2003 **Level III-2**, n=128). Noncraniotomy neurosurgery, for example trans-sphenoidal surgery, seems to be associated with very limited pain and minimal morphine requirements (Flynn 2006 **Level IV**, n=877).

It is noteworthy that craniotomy can lead to significant chronic headache, defined as postcraniotomy headache by the International Headache Society (Headache Classification Committee 2018 **GL**). At 6 mth after supratentorial craniotomy for aneurysm repair, 40% of patients reported headache, of whom 10.7% had acute and 29.3% chronic headache (Rocha-Filho 2008 **Level IV**, n=79). A review of the issues related to postcraniotomy headache has been published (Molnar 2014 **NR**).

The management of postoperative pain after intracranial surgery is often poor. The problems of postcraniotomy analgesia were analysed in a survey of UK neurosurgical centres (Roberts 2005 **Level IV**, n=23 [centres]); the principal analgesic was IM codeine, only 3 of 23 centres used morphine and only one used PCA. Pain was only assessed in 57% of cases. Similar data are reported in a survey of Canadian neurosurgeons, with 59% describing codeine as their first-line opioid (Hassouneh 2011 **Level IV**, n=103 [neurosurgeons responding]). This practice has changed little since 1995, when IM codeine was the primary analgesic used by 97% of centres (Stoneham 1995 **Level IV**, n=110 [neuroanaesthetists responding]).

Concerns about the adverse effects of opioids and their ability to interfere with recovery and neurological assessment contribute to this, as well as the concern that opioid-induced respiratory depression will lead to hypercarbia and increased intracranial pressure (Nemergut 2007 **NR**). Similarly, there is a concern that NSAIDs could interfere with haemostasis and increase intracranial bleeding. Furthermore, there is poor evidence on which to base protocols for the assessment and treatment of pain after cranial surgery (Nemergut 2007 **NR**); the limited number of trials are heterogeneous and have many weaknesses in study design and methodology. The question remains as to whether all craniotomies are the same with regard to analgesic requirements.

8.1.8.1 | Treatment of acute postoperative pain after cranial neurosurgery

A systematic review of pain treatments after craniotomy identified scalp infiltration/block, opioids and diclofenac as some evidence-based approaches, but could not make firm

recommendations due to limited data (Tsaousi 2017 **Level I** [PRISMA], 19 RCTs, n=1,805 [limited search period January 2011 to April 2016]).

Paracetamol

A trial comparing paracetamol alone with paracetamol/tramadol or paracetamol/nalbuphine was stopped early as paracetamol alone gave ineffective pain relief in most patients (Verchere 2002 **Level II**, n=64, JS 5). Another case series found that oral paracetamol only reduced pain effectively in 27% of patients post supratentorial craniotomy (Nair 2011 **Level IV**, n=43).

Nonselective NSAIDs

Ketoprofen was more effective than paracetamol in reducing PCA opioid requirements after craniotomy, but with minimal benefits in regard to pain scores and no change in adverse effects (Tanskanen 1999 **Level II**, n=45, JS 4). Similarly, diclofenac was superior to placebo and comparable to another nonopioid analgesic, flupirtine, for pain post craniotomy (Yadav 2014 **Level II**, n=390, JS 2). Preoperative single dose PO diclofenac 100 mg resulted in improved analgesia and reduced opioid requirement up to 5 d postoperatively (Molnar 2015 **Level II**, n=200, JS 4). A single-centre, retrospective cohort study over 5 y identified an association between the development of postoperative haematoma and the use of aspirin or nsNSAIDs (Palmer 1994 **Level IV**, n=71 [haematomas] in n=6,668 [neurosurgical operations]).

Coxibs

There was no benefit with a single dose of IV parecoxib (40 mg given at the end of the case) over the first 24 h postoperatively with regard to pain scores, morphine use and analgesia-related adverse effects in one study (Williams 2011 **Level II,** n=100, JS 5), although another study showed limited benefit over the first 6 h postoperatively (Jones 2009 **Level II**, n=82, JS 5).

Opioids

IV PCA morphine (with or without ondansetron) was superior to placebo after infratentorial craniotomy (Jellish 2006 **Level II**, n=120, JS 5). Morphine was also more effective than codeine following craniotomy; this was found for IM prn administration of both compounds (Goldsack 1996 **Level II**, n=40, JS 3), but also in a comparison of PCA morphine with IM codeine (Sudheer 2007 **Level II**, n=60, JS 3). PCA morphine provided better analgesia than PCA tramadol (Sudheer 2007 **Level II**, n=60, JS 3). PCA fentanyl was more effective than IV fentanyl prn and did not increase the risk of adverse effects after craniotomy, although more fentanyl was used in the PCA group (Jalili 2012 **Level II**, n=80, JS 5; Morad 2009 **Level II**, n=79, JS 2).

IM codeine 60 mg was more effective than IM tramadol 50 mg or 75 mg (Jeffrey 1999 **Level II**, n=75, JS 5). However, the addition of tramadol 100 mg twice daily to a paracetamol and morphine or oxycodone analgesic regimen improved analgesia and reduced opioid requirements vs placebo (Rahimi 2010 **Level II**, n=50, JS 2).

The intraoperative use of remifentanil may result in increased pain and/or increased analgesia requirements postoperatively (see Section 4.3.1.5). This was found vs both fentanyl (Gelb 2003 **Level II**, n=91, JS 4) and sufentanil (Gerlach 2003 **Level II**, n=36, JS 3).

Local anaesthetic scalp block

A meta-analysis found that regional scalp block improved pain scores up to 12 h postoperatively and reduced opioid requirements until 24 h postoperatively vs placebo block (Guilfoyle 2013 **Level I** [PRISMA], 7 studies, n=325). An RCT performed after this meta-analysis confirmed not only better analgesia after aneurysm clipping, but also improved outcome (reduced PCA consumption, requirement for a postoperative antihypertensive agent and PONV incidence) with scalp block (0.75% levobupivacaine) vs placebo (Hwang 2015 **Level II**, n=52, JS 5). Preemptive scalp block vs block at the end of surgery provided improved analgesia up to 6 h postoperatively and

reduced number of patients requiring opioid and median opioid consumption up to 24 h postoperatively (Song 2015 **Level II**, n=52, JS 3). Scalp blocks have also been used in children following craniosynostosis repair (Pardey Bracho 2014 **Level IV**, n=32).

Systemic adjuvant medications

Dexmedetomidine given intraoperatively for craniotomy provides superior analgesia in PACU and up to 12 h postoperatively vs placebo (2 RCTs, n=128) and remifentanil (1 RCT, n=139) (Tsaousi 2017 **Level I** [PRISMA], 19 RCTs, n=1,805). It also reduces opioid requirements up to 24 h postoperatively, with inconclusive evidence on effects on PONV and increased risk of delayed recovery. Clonidine did not improve analgesia after supratentorial craniotomy (Stapelfeldt 2005 **Level II**, n=34, JS 3).

Gabapentin improved postoperative analgesia and reduced opioid consumption, but increased sedation and delayed extubation (by 12 min) vs phenytoin perioperatively for supratentorial craniotomy (Ture 2009 **Level II**, n=80, JS 2). This was contradicted by a later study, which was however inadequately powered with pain relief only as a secondary outcome (Misra 2013 **Level II**, n=79, JS 4). Pregabalin showed marginal benefit for postoperative analgesia and reduced number of patients requiring opioids for up to 48 h (Shimony 2016 **Level II**, n=100, JS 4).

Non-pharmacological techniques

Transcutaneous electric acupuncture stimulation (TEAS) may improve postoperative analgesia and reduce opioid requirements; however, studies were of poor quality with a high risk of bias (2 RCTs, n=176) (Tsaousi 2017 **Level I** [PRISMA], 19 RCTs, n=1,805).

Cryotherapy (cold bags and ice gel packs) improved pain control along with eyelid oedema and facial ecchymosis after craniotomy (Shin 2009 **Level II**, n=97, JS 3).

KEY MESSAGES

1. Local anaesthetic infiltration of the scalp provides early analgesia after craniotomy and reduces opioid requirements (**S**) (**Level I** [PRISMA]).
2. Intraoperative dexmedetomidine provides early analgesia after craniotomy and reduces opioid requirements compared to placebo or remifentanil (**S**) (**Level I** [PRISMA]).
3. Morphine is more effective than codeine and tramadol for pain relief after craniotomy (**U**) (**Level II**).
4. Craniotomy leads to significant pain in the early postoperative period (**U**) (**Level IV**), which is however not as severe as pain from other surgical interventions (**U**) (**Level III-2**).
5. Craniotomy can lead to significant chronic headache (**U**) (**Level IV**).

The following tick box represents conclusions based on clinical experience and expert opinion:

☑ Acute pain following craniotomy is underestimated and often poorly treated (**U**).

8.1.9 | Spinal surgery

A considerable number of patients presenting for surgery on the spine have pre-existing persistent and/or acute pain and some may be on long term analgesic medications. Therefore, managing acute postoperative pain can be more difficult with an increased risk of persistent postoperative pain.

8.1.9.1 | Type of Anaesthesia

Propofol/fentanyl TIVA versus desflurane/fentanyl anaesthesia resulted in a minor not clinically meaningful reduction of postoperative pain, but also reduces opioid requirement up to 48 h post spinal surgery (Lin 2019b **Level II**, n=60, JS 4).

8.1.9.2 | Systemic anlgesics

Use of IV paracetamol vs placebo is associated with better analgesia postoperatively, although an opioid-sparing effect was not demonstrated (Cakan 2008 **Level II**, n=40, JS 4).

NSAIDs

Consistent with general postoperative data, nsNSAIDs have demonstrated analgesic benefit and are opioid-sparing in spinal surgery (Zhang 2017 **Level I** [PRISMA], 8 RCTs, n=408).

A meta-analysis of retrospective studies of spinal fusion concluded that the use of normal doses of nsNSAIDs or coxibs for <14 d postoperatively was not associated with increased non-union (Li 2011 **Level III-3 SR**, 5 studies, n=1,403). However, high-dose ketorolac (>120 mg/d) was associated with increased rates of nonunion (RR 2.9; 95%CI 1.5 to 5.4).

Opioids

Single IV doses of methadone given at the start of spine surgery provided improved pain control and reduced analgesic requirements up to 72 h postoperatively (Murphy 2017b **Level II**, n=150, JS 5; Gottschalk 2011 **Level II**, n=29, JS 5). Although no significant adverse effects were noted in these RCTs, caution is advised re potential OIVI (37%), hypoxaemia (80%) and QTc prolongation (59%) in a case series of spinal surgery patients, of whom 72% were taking opioids preoperatively (Dunn 2018a **Level IV**, n=1,478).

8.1.9.3 | Systemic adjuvant medications

Alpha-2-delta ligands (gabapentin and pregabalin)

Both gabapentin and pregabalin given preoperatively reduced postoperative pain and opioid requirements up to 48 h post spinal surgery vs placebo (Liu 2017a **Level I** [PRISMA], 16 RCTs, n=1,112). Although heterogenous in dosing and timing, in all of the RCTs gabapentin or pregabalin was given 1 to 2 h preoperatively as a single dose and then continued in some up to POD 3. Two RCTs examined variable doses suggesting that the maximal benefit of gabapentin is achieved with 600 mg (Liu 2017a **Level I** [PRISMA] 1 RCT: Pandey 2005 **Level II**, n=100, JS 5) to 900 mg (Liu 2017a **Level I** [PRISMA], 1 RCT: Khan 2011 **Level II**, n=175, JS 5) with no further benefit in larger doses.

Long term benefits of perioperative gabapentin or pregabalin use beyond the acute postoperative period after lumbar spine surgery were found in three RCTs. After lumbar discectomy, pain intensity was reduced and functional outcome improved at 3 mth with perioperative pregabalin administration (Khurana 2014 **Level II**, n=90, JS 4; Burke 2010 **Level II**, n=40, JS 5) and quality of life was improved at 3 mth, but not at 1 y (Gianesello 2012 **Level II**, n=60, JS 5). In one of these studies, 75 mg pregabalin every 8 h for 7 d was more effective than 300 mg gabapentin administered in the same way (Khurana 2014 **Level II**, n=90, JS 4).

Alpha-2 agonists

IV dexmedetomidine used intraoperatively (14 RCTs) and intra- and postoperatively for 24 h (1 RCT) in spinal surgery reduces postoperative pain at 2 h (3 RCTs, n=237) and analgesic requirements at 12 h (2 RCTs,n=149) and 48 h, but not 24 h (3 RCTs, n=380) (Tsaousi 2018 **Level I** [PRISMA], 15 RCTs, n=913).

Antidepressants

Use of duloxetine 60 mg given preoperatively for spinal surgery and 24 h postoperatively had contradictory effects on pain scores in 2 RCTs, but reduced opioid requirements up to 48 h postoperatively (Attia 2017 **Level II**, n=60, JS 5; Bedin 2017 **Level II**, n=57, JS 3).

Corticosteroids

IV corticosteroids given intraoperatively for spinal surgery reduce pain up to 48 h postoperatively, as well as nausea and length of stay (Wang 2018b **Level I** [PRISMA], 8 RCTs, n=918).

Epidural corticosteroids (triamcinolone, methylprednisolone or dexamethasone) applied by the surgeons intraoperatively for microdiscectomy or laminectomy reduce pain at 24 h and 1 mth postoperatively as well as opioid requirements and hospital LOS vs placebo (Wilson-Smith 2018 **Level I** [PRISMA], 17 RCTs, n=1,727; Arirachakaran 2018 **Level I** [PRISMA], 12 RCTs, n=1,006) (10 RCTs overlap). The effects on opioid requirements are more pronounced after open laminectomy vs microdiscectomy (Arirachakaran 2018 **Level I** [PRISMA], 12 RCTs, n=1,006). There is no difference in complications in these two systematic reviews and a further meta-analysis looking specifically for complications also found no increase in overall complication (RR 1.94; 95%CI 0.72 to 5.26) or infectious complication rates (RR 4.6; 95%CI 0.8 to 28.0) (Akinduro 2015 **Level III-2 SR**, 16 RCTs & 1 study, n=1,933).

Systemic lidocaine

A perioperative IV lidocaine infusion reduced pain scores and postoperative opioid requirements after complex spinal surgery (Farag 2013 **Level II**, n=116, JS 5), microdiscectomy (Kim 2014c **Level II**, n=51, JS 5) and spinal fusion (Ibrahim 2018 **Level II**, n=44, JS 4). The latter study showed a clinically insignificant pain reduction even at 3 mth; in this RCT, one participant had a convulsion after the loading dose of lignocaine (2mg/kg). However, a more recent RCT in spinal fusion showed none of these benefits (Dewinter 2017 **Level II**, n=70, JS 5).

Ketamine

Ketamine as an adjuvant to PCA fentanyl after lumbar spinal surgery decreased fentanyl requirements, but increased nausea with no other benefits (Song 2013 **Level II**, n=50, JS 5). In children undergoing spinal fusion, there was no benefit of perioperative ketamine continued until POD 3 (Pestieau 2014 **Level II**, n=50, JS 5).

Ketamine may have a special role in patients who are opioid tolerant prior to back surgery (Boenigk 2019 **Level II**, n=122, JS 5; Nielsen 2017 **Level II**, n=147, JS 5; Loftus 2010 **Level II**, n=101, JS 4). Here perioperative ketamine resulted in significantly reduced opioid requirements up to 6 wk postoperatively with limited benefit on pain intensity in the immediate postoperative period. However, there was pain reduction as well as functional benefit seen at 6 wk (Loftus 2010 **Level II**, n=101, JS 4) and 6 mth follow-up (Nielsen 2017 **Level II**, n=147, JS 5).

Magnesium

A perioperative magnesium infusion reduced pain scores and analgesic requirements and improved patient satisfaction (Levaux 2003 **Level II**, n=24, JS 5). However, this might be due to reduction of OIH associated with perioperative remifentanil infusion rather than an additional analgesic benefit.

Muscle Relaxants

Chlorzoxazone, a centrally acting muscles relaxant, used after spine surgery did not improve rest or movement pain (Nielsen 2016 **Level II**, n=110, JS 5).

8.1.9.4 | Neuraxial analgesia

IT morphine vs systemic opioids after spinal surgery results in reduced pain scores and postoperative opioid consumption during the first 24 h in the IT morphine group; however, with a higher rate of pruritus and respiratory depression only occurring in the IT morphine group (Pendi 2017 **Level I**, 8 RCTs, n=393).

Patient-controlled epidural analgesia with opioid and/or local anaesthetic vs IV PCA results in clinically irrelevant improvements of analgesia in the first 2 postoperative days with a higher incidence of pruritus and paraesthesia (Tian 2015 **Level I**, 8 RCT, n=405). A subsequent RCT in posterior spinal fusion showed analgesic benefits with reduced opioid requirement for up to 3 days and increased patient satisfaction (Park 2016 **Level II**, n=94, JS 3). Similarly, in children undergoing thoraco-lumbar spinal surgery, epidural analgesia reduced pain for up to 72 h postoperatively vs systemic analgesia (Guay 2019 **Level I** [Cochrane], 7 RCTs, n=249).

8.1.9.5 | Peripheral regional analgesia

Local infiltration analgesia (LIA) reduces pain at 1 h (but not at 12 and 24 h) postoperatively and analgesic requirement vs placebo infiltration (Perera 2017 **Level I** [PRISMA], 11 RCTs, n=438). Preemptive infiltration with local anaesthetic provided additional benefits vs infiltration at wound closure; addition of steroid did not improve analgesic efficacy (Gurbet 2008 **Level II**, n=100, JS 1; Ersayli 2006 **Level II**, n=75, JS 3).

Continuous infusion of local anaesthetics (ropivacaine) after posterior spinal fusion surgery through wound catheters did not show any further benefit when added to systemic multimodal analgesia (Greze 2017 **Level II**, n=39, JS 5).

8.1.9.6. | Non-pharmacological techniques

Acupuncture used postoperatively after spinal surgery reduces pain without reduction of opioid requirement in the first 24 h postoperatively (Cho 2015b **Level I** [PRISMA], 5 RCTs, n=480).

Cognitive Behavioural Therapy (CBT) preoperatively (total 9 h group sessions) improved mobilisation in the early postoperative period after lumbar fusion and reduced analgesic requirements without changing pain scores suggesting improved coping skills (Rolving 2016 **Level II**, n=96, JS 3); however, there was no longer a benefit at 1 y follow-up (Rolving 2015 **Level II**, n=90, JS 3).

KEY MESSAGES

1. Epidural analgesia compared to systemic analgesia after spinal surgery in children improves pain up to 72 hours postoperatively (**N**) (**Level I**[Cochrane Review]).
2. Perioperative use of gabapentin or pregabalin improves analgesia and reduces opioid requirements after spinal surgery (**S**) (**Level I** [PRISMA]).
3. NSAIDs provide analgesic benefits as well as opioid-sparing effects after spinal surgery (**S**) (**Level I** [PRISMA]).
4. Intravenous dexmedetomidine improves early postoperative analgesia and reduces analgesic requirement up to 48 hours after spinal surgery (**N**) (**Level I** [PRISMA]).
5. Intravenous corticosteroids improve analgesia and reduce nausea and length of stay after spinal surgery (**N**) (**Level I** [PRISMA]).
6. Epidural steroid application intraoperatively by the surgeon provides analgesic benefit up to 24 hours and reduces length of stay after spinal surgery(**N**) (**Level I** [PRISMA]).
7. Perioperative pregabalin improves functional outcome after laminectomy at 3 months (**U**) (**Level II**).
8. Local infiltration anaesthesia improves analgesia and reduces opioid requirements after spinal surgery; this benefit is enhanced with preincision infiltration compared to infiltration at wound closure (**U**) (**Level II**).
9. Perioperative systemic lidocaine infusion improves analgesia and reduces opioid requirements after spinal surgery (**W**) (**Level II**).
10. NSAID use for less than 14 days does not increase the risk of nonunion after spinal fusion, except with high-dose ketorolac (**U**) (**Level III-3**).

The following tick box represents conclusions based on clinical experience and expert opinion:

☑ Acute pain management following spinal surgery is often complicated by preoperative chronic pain and long term medication use (**U**).

8.2 | Acute pain following spinal cord injury

Acute pain following spinal cord injury (SCI) is common, with over 90% of patients experiencing pain in the first 2 wk following injury (Siddall 1999 **Level IV**, n=100). Acute pain may also develop during the rehabilitation phase due to intercurrent disease (eg renal calculus) or exacerbation of a chronic pain syndrome.

Pain associated with SCI usually falls into two main categories: neuropathic pain, either at or below the level of the injury, and nociceptive pain, from somatic and visceral structures (Bryce 2012 **GL**). Neuropathic pain associated with a lesion or disease of the central somatosensory nervous system is termed central neuropathic pain (Jensen 2011 **GL**). Phantom pain and complex regional pain syndromes may also develop in patients with SCI.

Table 8.1 | Taxonomy of acute pain associated with spinal cord injury pain

Pain type	Pain subtype	Examples of primary pain source or pathology
Neuropathic pain	At level	Cauda equina compression, nerve root compression, spinal cord compression
	Below level	Spinal cord compression or ischaemia
	Other	Trigeminal neuralgia, diabetic neuropathy
Nociceptive pain	Somatic	Musculoskeletal pain (eg vertebral fracture, muscle spasms, overuse syndromes) Procedure-related pain (eg pressure sore dressings)
	Visceral	Renal calculus, pain due to bowel impaction
Other		Complex regional pain syndrome

*Source: Based on the International Spinal Cord Injury Pain Classification (Bryce 2012 **GL**).*

8.2.1 | Treatment of acute neuropathic pain after spinal cord injury

There are only case series specifically examining the treatment of acute neuropathic pain following SCI.

Three patients with acute neuropathic pain following SCI were administered SC calcitonin 100 IU in addition to other medications with improved pain relief in each person and reduced analgesic requirements (Humble 2011 **Level IV**).

Thirteen patients with acute neuropathic SCI pain received IV ketamine (50 mg over 2 h, twice daily for several days followed by 50 mg orally for up to 3 mth) with a mean pain reduction of 75% at the time of treatment cessation (mean 17 d) with further benefit over the subsequent months (Kim 2013a **Level IV**).

Treatment of acute neuropathic pain must therefore be based on evidence from studies of chronic central neuropathic pain and other neuropathic pain syndromes (see below). An algorithm for the treatment of pain in patients with SCI has been promulgated (Siddall 2006 **GL**).

8.2.2 | Treatment of chronic neuropathic pain after spinal cord injury

Clinical practice guidelines have been published which make a number of recommendations for the treatment of chronic neuropathic pain after SCI (Guy 2016 **GL**). These guidelines recommend:

- First line: pregabalin, gabapentin and amitriptyline;
- Second line: tramadol and lamotrigine (in incomplete SCI);
- Third line: Transcranial direct current stimulation (tDCS) alone and combined with visual illusion;
- Fourth line: TENS, oxycodone and dorsal root entry zone lesions.

Further information based on results from individual studies and other systematic reviews is described below.

8.2.2.1 | Conventional and atypical opioids

Under experimental conditions, IV alfentanil decreased central pain following SCI vs placebo or ketamine (Eide 1995 **Level II EH**, n=9, JS 5). IV morphine decreased tactile allodynia but had no effect on other neuropathic pain components in SCI and poststroke patients (Attal 2002 **Level II EH**, n=21, JS 5). Tramadol was effective for the treatment of neuropathic pain after SCI but the incidence of adverse effects was high (Norrbrink 2009 **Level II**, n=35, JS 4). A review of animal studies is concerning here as it shows that high doses of opioids in the acute (<14 d) period following SCI may be associated with impaired locomotor recovery and increased risk of the development of pain and infection (Woller 2013 **BS**). Although these findings have not been verified in clinical studies, they suggest the need for caution in administering high doses of opioids in the acute period post injury.

8.2.2.2 | Ketamine

Ketamine infusion decreased acute (see above) and chronic neuropathic pain in SCI patients. IV Ketamine is superior to placebo and comparable to IV lignocaine and IV alfentanil in the treatment of pain after SCI (Teasell 2010 **Level I**, 2 RCTs [ketamine], n=19).

8.2.2.3 | Membrane stabilisers

There is good evidence to support the effectiveness of lidocaine and mexiletine, when data from neuropathic pain studies done in a variety of conditions including neuropathic SCI pain are grouped together (Challapalli 2005 **Level I** [Cochrane], 30 RCTs, n=750). However, the effects in SCI specifically are mixed. IV lidocaine reduced neuropathic pain in SCI (Finnerup 2005a **Level II**, n=24, JS 5) and reduced spontaneous pain and brush allodynia in central pain (Challapalli 2005 **Level I** [Cochrane], 1 RCTs: Attal 2000 **Level II**, n=16, JS 4). Other trials have found that lidocaine reduced pain >50% in only one of ten SCI patients (Challapalli 2005 **Level I** [Cochrane], 1 RCT: Kvarnstrom 2004 **Level II**, n=10, JS 5) and that mexiletine was ineffective (Challapalli 2005 **Level I** [Cochrane], 1 RCT: Chiou-Tan 1996 **Level II**, n=11, JS 2). Lidocaine is most effective in the treatment of neuropathic pain due to peripheral nerve lesions (Kalso 1998 **Level I**, 17 studies, n=450).

8.2.2.4 | Antidepressants

There is lack of evidence to support the effectiveness of antidepressants (amitriptyline, duloxetine, venlafaxine and trazadone) in people with neuropathic SCI pain, except in those with

co-existing depression (Mehta 2016 **Level I**, 5 RCTs, n=295). There are no studies of SSRIs in the treatment of central neuropathic pain (Finnerup 2005b **Level I**, 0 RCTs [SSRIs], n=0). An RCT of amitriptyline vs lamotrigine found that both medications were effective in reducing neuropathic SCI pain, with no difference between the two medications (Agarwal 2017 **Level II**, n=147, JS 3).

8.2.2.5 | Anticonvulsants

Alpha-2-delta ligands (gabapentin and pregabalin) are effective for the treatment of neuropathic pain after SCI (Mehta 2016 **Level I**, 10 RCTs, n=567).

Lamotrigine reduced spontaneous and evoked pain in patients with incomplete SCI (Finnerup 2002 **Level II**, n=30, JS 5). Valproate was ineffective in the treatment of SCI pain (Drewes 1994 **Level II**, n=20, JS 3).

8.2.2.6 | Cannabinoids

The cannabinoid dronabinol did not reduce pain intensity in people with chronic neuropathic SCI pain (Rintala 2010 **Level II**, n=7, JS 5). Inhalation of vaporized cannabis (delta 9-THC) vs placebo reduced neuropathic SCI pain over an 8 h period ($NNT_{30\%}$ 4 [95%CI 2.1 to 25.3] for 2.9% and $NNT_{30\%}$ 3 [95%CI 1.6 to 4.2] for 6.7%) although with dose-dependent psychoactive side effects (Wilsey 2016 **Level II EH**, n=42 [crossover], JS 4).

8.2.2.7 | Intravenous anaesthetics

An IV bolus of low-dose propofol reduced the intensity of central neuropathic pain and allodynia for up to 1 h in approximately 50% of patients (Canavero 2004 **Level II**, n=21, JS 4).

8.2.2.8 | Botulinum toxin

SC injection of botulinum toxin type A (200 U total) into the painful area in people with neuropathic SCI pain reduced pain intensity when measured at 4 and 8 wk (VAS -18.6 $\pm$ 16.8 and -21.3 $\pm$ 26.8 respectively) following injection (Han 2016 **Level II,** n=40, JS 5).

8.2.2.9 | Baclofen

IT baclofen had an analgesic effect in patients with spinal cord lesions and reduced spasticity (Kumru 2018 **Level II**, n=13, JS 4).

8.2.2.10 | Palmitoylethanolamide (PEA)

Ultramicronised palmitoylethanolamide (PEA) for 12 wk had no analgesic or other effect on neuropathic pain after spinal cord injury (Andresen 2016 **Level II**, n=73, JS 5).

8.2.2.11 | Nonpharmacological treatments

There is currently insufficient evidence to support the effectiveness of TENS, acupuncture, self-hypnosis or cognitive behavioural therapy for chronic pain in SCI (Boldt 2014 **Level I** [Cochrane], 16 RCTs, n=616).

A systematic review found transcranial direct current stimulation (tDCS) reduces chronic neuropathic SCI pain immediately post treatment, but not at follow-up (Mehta 2015 **Level I**, 4 RCTs, n=57). A more recent RCT found that significant improvements up to 4 wk post treatment with tDCS could be demonstrated if the initial 5 d of treatment was followed by a second 10 d period of treatment 3 mth later (Thibaut 2017 **Level II,** n=9, JS 3).

Repetitive transcranial magnetic stimulation (rTMS) of the prefrontal cortex was found to result in a significant reduction in neuropathic SCI pain, but this was only maintained for one day following treatment (Nardone 2017 **Level II**, n=12, JS 2).

Virtual reality techniques to create leg illusions demonstrated a modest and non-significant reduction in pain intensity (Pozeg 2017 **Level II**, n=20, JS 2). Virtual walking resulted in a greater reduction in pain intensity than virtual wheeling, but the pre to post change was not significant (Jordan 2016 **Level IV**, n=50).

Breathing controlled electric stimulation has an immediate analgesic effect on chronic neuropathic SCI pain, with no augmentation when combined with tDCS (Li 2018a **Level III-2**, n=12).

8.2.3 | Treatment of nociceptive and visceral pain after spinal cord injury

There is no specific evidence to guide the treatment of acute nociceptive and visceral pain in SCI patients. Treatment is therefore based on evidence from other studies of nociceptive and visceral pain and is usually directed at treating the specific underlying cause of the pain.

KEY MESSAGES

1. Alpha-2-delta ligands (gabapentin/pregabalin) are effective in the treatment of neuropathic pain following spinal cord injury (**S**) (**Level I**).
2. Antidepressants (amitriptyline, duloxetine and venlafaxine) are effective in the treatment of neuropathic pain following spinal cord injury but only in those with co-morbid depression (**N**) (**Level I**).
3. Intravenous opioids, ketamine ((**U**) (**Level I**), lidocaine and tramadol are effective in the treatment of neuropathic pain following spinal cord injury (**U**) (**Level II**).

The following tick box represents conclusions based on clinical experience and expert opinion:

☑ Treatment of acute spinal cord injury pain is largely based on evidence from studies of other neuropathic and nociceptive pain syndromes (**U**).

☑ There is currently insufficient evidence to support non-pharmacological treatments (TENS, acupuncture, self-hypnosis or cognitive behavioural therapy) for spinal cord injury pain (**N**).

8.3 | Chest trauma (Rib fractures)

Rib fractures occur in approximately 10% of multi-trauma patients (Flagel 2005 **Level IV**, n=732,823; Ziegler 1994 **Level IV**, n=7,147). This is also a common injury in the elderly population, often with serious consequences (Christie 2019 **NR**). There are multiple complications associated with rib fractures such as pneumonia, aspiration, atelectasis and acute respiratory distress syndrome (Witt 2017 **NR**). The prevention of such complications relies on high quality analgesia and aggressive physical rehabilitation. General recommendations are to implement a protocolised bundled clinical pathway (Witt 2017 **GL**).

8.3.1 | Paracetamol

A single dose of IV paracetamol 1 g vs IV morphine (0.1 mg/kg) had similar analgesic effects and adverse event rates (Esmailian 2015 **Level II**, n=54, JS 5).

8.3.2 | NSAIDS

Regular IV ibuprofen reduced pain scores over the 7 d study period and IV morphine requirements on d 3 to 7 vs control (Bayouth 2013 **Level III-3**, n=42). Regular IV ketorolac reduced the incidence of rib fracture related pneumonia vs control (Yang 2011 **Level III-3**, n=619).

8.3.3 | Adjuvant medications

IV ketamine infusions (0.1-0.15 mcg/kg/hr) reduced pain scores and opioid requirements (Carver 2019 **Level II**, n=91, JS 5; Walters 2018 **Level III-3**, n=30). There were no other benefits with regard to outcome.

IV dexmedetomidine (1 mcg/kg loading followed by 0.5mcg/kg/h infusion) was inferior to thoracic epidural analgesia in terms of pain and sedation scores (Mahmoud 2016 **Level II**, n=58, JS 2).

Regular gabapentin (300mg) provided no benefit in terms of pain scores, opioid requirement and adverse events (Moskowitz 2018 **Level II**, n=40, JS 5).

Lignocaine patches (5%) showed no difference vs placebo with regard to pain scores, opioid consumption, LOS or adverse outcomes (Ingalls 2010 **Level II**, n=58, JS 5). Another study showed a reduction in pain scores, but no effect on morphine consumption or adverse events (Zink 2011 **Level III-3,** n= 58). A further study showed no benefit in the first 4 d, but then reduced pain scores from the fifth day, reduced opioid requirements and LOS (Cheng 2016 **Level II**, n=44, JS 3).

8.3.4 | Epidural analgesia

Thoracic epidural analgesia vs systemic IV analgesia (5 RCTs & 6 studies, n=1,057) improves pain scores (4 RCTs) (Peek 2019 **Level III-2 SR** [PRISMA], 8 RCTs & 11 studies, n=2,081). There was no significant difference in secondary outcomes such as hospital LOS (4 RCTs, n=130 & 4 studies, n=523), ICU LOS (4 RCTs, n=118 & 4 studies, n=501), duration of mechanical ventilation (3 RCTs, n=94 & 1 study, n=165) and pulmonary complications (widely variable rates) (4 RCTs, n=126 & 6 studies, n=907). Thoracic epidural analgesia achieves similar pain scores vs continuous intercostal (1 RCT, n=60 & 1 study n=169) and vs paravertebral blocks (1 RCT, n=30 & 2 studies, n=1,224), with no difference in hospital LOS, ICU LOS, duration of mechanical ventilation and pulmonary complications (0 to 13.3%) (2 or 3 studies each outcome: 6 studies, n=1,045). Dexmedetomidine/bupivacaine via thoracic epidural catheters improved pain scores slightly vs bupivacaine alone (Agamohammdi 2018 **Level II**, n=64, JS 2).

8.3.5 | Peripheral regional analgesia

Continuous paravertebral and intercostal blocks are effective regional analgesia techniques providing analgesia superior to IV systemic analgesia (1 study [PVB], n=54; 1 study [ICB], n=90) and equivalent to thoracic epidural analgesia (see above) (Peek 2019 **Level III-2 SR** [PRISMA], 8 RCTs & 11 studies, n=2,081).

Interpleural blocks did not provide analgesia superior to placebo blocks (Short 1996 **Level II**, n=16, JS 5) and were inferior to epidural analgesia (Luchette 1994 **Level IV**, n=19).

Serratus anterior blocks (Iotti 2019 **Level IV**, n=3; Jadon 2017 **Level IV**, n=6; Camacho 2019 **CR**; Fu 2017 **CR**) and erector spinae plane blocks (ESPB) (Luftig 2018 **Level IV**, n=3; Nandhakumar 2018 **Level IV**, n=2; Hamilton 2017 **CR**) are described as effective analgesic options after rib fractures. ESPBs reduced pre to post insertion pain scores in patients with up to seven or more rib fractures (Adhikary 2019 **Level IV**, n=79).

8.3.6 | Surgical fixation

Surgical fixation vs non-surgical treatment in patients with three or more fractured ribs reduces duration of ventilation (Level I, 3 RCTs; Level III-2 SR, 1 RCT & 4 studies), need for tracheostomy (Level I [Cochrane], 2 RCTs; Level III-2 SR, 1 RCT & 6 studies) and intensive care LOS (Level I, 3 RCTs; Level III-2 SR, 1 RCT & 2 studies), pneumonia (Level I [Cochrane], 3 RCTs; Level III-2 SR, 2 RCTs & 6 studies), hospital LOS (Level I, 2 RCTs; Level III-2 SR, 1 RCT & 6 studies) and mortality (OR 0.28; 95%CI 0.08 to 0.92) (Level III-2, 3 studies); pain and opioid requirements were not assessed (Cataneo 2015 **Level I** [Cochrane], 3 RCTs, n=123; Schuurmans 2017 **Level I**, 3 RCTs, n=123 [all 3 RCTs overlap]; Liu 2019c **Level III-2 SR** [PRISMA], 2 RCTs and 12 studies, n=839 [1 RCT overlap]). There was contradictory information on hospital costs; significant reduction (Level I, 2 RCTs) and significant increase (Level III-2, 3 studies) respectively.

8.3.7 | Non-pharmacological therapy

TENS was superior to regular naproxen (275 mg tds) in terms of pain scores for up to 3 d (Oncel 2002 **Level II**, n=100, JS 4). Acupuncture vs sham acupuncture on top of background ibuprofen reduced pain on deep breathing and coughing for up to 6 h on each of 3 d of treatment (Ho 2014 **Level II**, n=58, JS 4).

KEY MESSAGES

1. Surgical fixation in patients with 3 or more fractured ribs improves outcome with regard to incidence of pneumonia and need for tracheostomy (**N**) (**Level I** [Cochrane Review]), duration of ventilation, ICU and hospital stay (**N**) (**Level I**) and mortality (**N**) (**Level III-2 SR**).
2. Continuous thoracic epidural analgesia and continuous intercostal and paravertebral blocks provide similar analgesia and are superior to intravenous opioids for rib fracture related pain (**N**) (**Level I** [PRISMA]).
3. Systemic NSAIDs and ketamine are efficacious analgesic adjuvants for rib fracture related pain (**N**) (**Level III-3**)

The following tick boxes represent conclusions based on clinical experience and expert opinion:

☑ Emerging regional techniques such as serratus anterior and erector spinae plane blocks (single shot and continuous infusion) are supported by case series and could be considered for rib fracture analgesic management (**N**).

☑ Chest trauma with rib fractures carries a high risk of potentially life-threatening complications; excellent analgesia and aggressive physical rehabilitation, ideally provided in a protocolised clinical pathway, can improve outcome (**N**)

8.4 | Acute pain after hip (neck of femur) fractures

Hip fractures occur in 199 to 240/100 000 people per year in Australia and New Zealand (AIHW 2018b **Level IV**; HQSC 2018 **Level IV**) and cause significant morbidity and mortality largely due to patient age (mean age 84 y), cognitive impairment (39%) and pre-existing co-morbidities (majority ASA 3 or above) (ANZFHR 2018 **Level IV**, n=9,408). Three mth following a hip fracture, mortality is 10%, and although 71-76% of people have returned home, only 23-26% will have achieved pre-injury mobility.

Pain is a significant feature of a hip fracture, causing discomfort and distress to the person and family, thus satisfactory analgesia is a critical aspect of care. Risk factors for severe post-operative pain in the immediate post-operative period include level of education, cognitive function, preoperative delirium and depression (Radinovic 2014 **Level III-2**, n=344).

Delirium following hip fracture is common (24% of patients) (Yang 2017 **Level III-2 SR**, 24 studies, n=5,364) and is associated with increased 1 y mortality (Ruggiero 2017 **Level III-2**, n=514; Mitchell 2017 **Level III-2**, n=27,888). Risk factors for developing postoperative delirium are older age, pre-admission aged care facility residency, multiple co-morbidities, pre-existing cognitive impairment and morphine use (Yang 2017 **Level III-2 SR**, 24 studies, n=5,364; Smith 2017b **Level III-2 SR**, 32 studies, n=6,704) (17 studies overlap). Effective analgesia provision is an important factor to reduce the risk of delirium (ANZFHR Steering Group 2014 **GL**).

Surgical intervention is often the most effective form of analgesia and is one of the main drivers to timely access to surgery (ANZFHR Steering Group 2014 **GL**). Arthroplasty techniques are associated with less pain and opioid requirements than internal fixation, dynamic hip screw or intramedullary nail (A'Court 2017 **Level III-2**, n=357; Salpakoski 2016 **Level III-2**, n=136). Hemiarthroplasties performed with cement (Ng 2014 **Level III-2**, n=197) and minimally invasive anterior approach (Pala 2016 **Level III-2**, n=89) have less post-operative pain than non-cemented or posterolateral approach hemiarthroplasties.

Guidelines to direct care of hip fracture patients are published (ANZFHR Steering Group 2014 **GL**); integrated orthogeriatric care, utilisation of care bundles and adherence to clinical care standards improves outcomes in hip fracture patients (ACSQHC 2016 **GL**).

8.4.1 | Nerve Blocks

In 2017, on average 36% of patients in New Zealand and 66% of patients in Australia received a nerve block before hip fracture surgery, whilst overall 78% had a nerve block during admission (ANZFHR 2018 **Level IV**, n=9,408). No major complications due to peripheral nerve blocks for hip fractures have been reported in the literature (Guay 2017 **Level I** [Cochrane], 31 RCTs, n=1,760).

8.4.1.1 | Pain Relief

Peripheral nerve blocks (pooled data) decrease pain at rest and movement within 30 min of block placement (SMD -1.41; 95% CI -2.14 to -0.67 [equivalent to -3.4/10]) (8 RCTs, n=373) vs systemic analgesia (Guay 2017 **Level I** [Cochrane], 31 RCTs, n=1,760). Femoral nerve blocks (FNB) (Hartmann 2017 **Level I**, 2 RCTs, n=84) and fascia iliaca compartment blocks (FICB) (Steenberg 2018 **Level I**, 11 RCTs, n=1,062) performed before positioning lead to less pain and shorten time to performing spinal anaesthesia vs IV opioids alone.

When performed in the emergency department or on admission, FICB (Hong 2019 **Level I** [PRISMA], 11 RCTs, n=937; Steenberg 2018 **Level I**, 11 RCTs, n=1,062) (8 RCTs overlap), FNB (Riddell 2016 **Level I**, 7 RCTs, n=224) or 3-in-1 blocks (4 RCTs, n=199) (Ritcey 2016 **Level I** [PRISMA], 9 RCTs, n=547) are

superior to systemic opioids in reducing pain on movement, decrease preoperative opioid requirements and lengthen time to rescue analgesia. These findings are consistent even in patients with dementia (Unneby 2017 **Level II,** n=266, JS 2).

Nerve blocks decrease pain at rest 6 to 8 h after surgery and reduce pain at rest, opioid requirements, time to first mobilisation and lead to higher patient satisfaction up to 24 h after surgery (Guay 2017 **Level I** [Cochrane], 31 RCTs, n=1,760). There is no reduction in pain on movement 6 to 8 and 24 h after surgery, or pain on rest or movement 48 to 72 h after surgery.

Single injection PNBs and CPNBs (pooled data) are equivalent in effect 24 h after surgery (4 RCTs, n=195); CPNBs do not improve pain on movement or at rest 48 h (5 RCTs, n=335) and 72 h (2 RCTs, n=140) after surgery (Guay 2017 **Level I** [Cochrane], 31 RCTs, n=1,760). However, CPNBs vs systemic analgesia reduced postoperative pain, opioid requirements, opioid adverse effects, time to mobilisation and resulted in more frequent discharge home (Arsoy 2017a **Level III-3**, n=265; Arsoy 2017b **Level III-3**, n=29; Morrison 2016 **Level II**, n=161; JS 5).

8.4.1.2 | Prevention of other complications

Moderate quality evidence demonstrates that PNBs (pooled data) reduce the risk of pneumonia vs systemic analgesia (RR 0.41; 95%CI 0.19 to 0.89) (NNT 7) (3 RCTs, n=131) (Guay 2017 **Level I** [Cochrane], 31 RCTs, n=1,760). PNBs do not decrease the risk of acute confusional states, acute myocardial infarction/ischaemia or 6 mth mortality; although evidence was low to very low quality. FICB led to better abbreviated mental test scores following hip fracture surgery vs systemic analgesia (Odor 2017 **Level III-2**, n=959).

8.4.1.3 | Nerve Block Technique

There is no evidence for superiority of a particular nerve block or its insertion technique (Steenberg 2018 **Level I**, 11 RCTs, n=1,062; Riddell 2016 **Level I**, 7 RCTs, n=224; Ritcey 2016 **Level I**, 9 RCTs, n=547) (significant overlap of all 3 SRs). US guided 3-in-1 blocks and landmark guided FICBs are equivalent for pain reduction at 30 and 60 min after intervention (Reavley 2015 **Level II**, n=178, JS 3). Nerve stimulator guided FNB reduced pain scores and opioid requirements more than landmark guided FIC blocks, but the reduction (-0.9/10) was felt not to be clinically significant (Newman 2013 **Level II**, n=107, JS 3).

8.4.1.4 | High volume local anaesthesia infiltration

High volume, low concentration (75 mL containing 200 mg ropivacaine [0.266 %]) local anaesthetic fracture, capsular and tissue infiltration followed by post-operative boluses (20 mL containing 100 mg ropivacaine [0.5%]) via surgically placed catheter did not reduce postoperative pain or opioid consumption vs placebo (Bech 2018 **Level II**, n=74, JS 5).

Periarticular infiltration with bupivacaine (50 mL of 0.25%) followed by liposomal bupivacaine (20 mL diluted into 40 mL) did not result in significantly better pain control or less opioid requirements vs no local anaesthetic infiltration (Hutchinson 2019 **Level III-2**, n=178). However, LOS was lower by 1.1 d and patients were more likely to be ambulatory on discharge (82% vs 69%) if they had received high volume local anaesthetic infiltration.

8.4.2 | Systemic analgesia

Generally, post-operative analgesia administered on a regular time-based regime leads to less pain vs prn regimens (Di Filippo 2015 **Level III-2**, n=131). Choice and dose of analgesia should be age appropriate with close monitoring for associated side effects (ANZFHR Steering Group 2014 **GL**).

8.4.2.1 | Paracetamol

Regular paracetamol should be prescribed every 6 h unless contra-indicated (ANZFHR Steering Group 2014 **GL**); dose adjustments should be considered (older age, malnutrition, low body weight) (see Section 4.1.3.). When compared to oral paracetamol, patients administered IV paracetamol had lower pain scores, less opioid use and shorter hospital LOS (Sanzone 2016 **Level III-3 SR**, n=332). Paracetamol prescribed on discharge is not associated with increased 6 mth mortality, falls or hospital readmission (Harstedt 2016 **Level III-2**, n=272)

8.4.2.2 | NSAIDs

Development of acute kidney injury (AKI) following hip fracture surgery ranges from 11 to 24% and is associated with higher mortality. Risk factors for developing AKI include male sex, older age, number of co-morbid conditions, antihypertensives (particularly ACE-inhibitors and ATRA2-antagonists), pre-existing renal impairment, hypalbuminaemia and obesity (Shin 2018 **Level III-2**, n=481; Porter 2017 **Level III-2**, n=2,959; Hong 2017 **Level III-2**, n=450; Pedersen 2017 **Level III-2**, n=13,529; Pedersen 2016 **Level III-2**, n=13,259). NSAIDs are not an independent risk factor for developing AKI in hip fracture patients (Hong 2017 **Level III-2**, n=450; Pedersen 2016 **Level III-2**, n=13,259). In the largest population-based study, NSAIDs were prescribed to 12.3% of patients who developed AKI vs 14.2% of patients who did not (Pedersen 2016 **Level III-2**, n=13,259).

Caution should be exercised when considering NSAIDs in hip fracture patients, due to the predominantly older population with co-existent disease; however time limited use of NSAIDs may be clinically appropriate and relatively safe for short term use in patients with preserved renal function (Hong 2017 **Level III-2**, n=450; ANZFHR Steering Group 2014 **GL**). A retrospective analysis using data from 2003 to 2016 looking at transfusion risk for hip fractures found a small increase in risk of transfusion with preoperative NSAID use within 90 d of surgery (RR 1.07; 95%CI 1.04 to 1.10) (Glassou 2019 **Level III-2**, n=74,791). There is insufficient evidence to conclude whether NSAIDs are associated with other complications in hip fracture patients or to compare analgesic regimes with and without NSAIDs.

8.4.2.3 | Conventional and atypical opioids

Additional opioids should be offered if non-opioids alone do not provide sufficient pain relief (ANZFHR Steering Group 2014 **GL**). Ninety-five percent of hip fracture patients receive opioids during their admission (Lindestrand 2015 **Level IV**, n=416). Opioid analgesia is part of standard systemic analgesia in the majority of studies (Guay 2017 **Level I** [Cochrane], 31 RCTs, n=1,760). Continuous IV morphine infusion (0.01 mg/kg/h) provides similar pain scores and rescue analgesia requirements as regular paracetamol, but was associated with more complications requiring cessation (Di Filippo 2015 **Level III-2**, n=131). Compared to other patients, hip fracture patients with dementia and cognitive impairment receive less opioid analgesia (Moschinski 2017 **Level I** [PRISMA], 17 RCTs, n=4,249; Jensen-Dahm 2016 **Level III-2**, n=1,507). High prevalence of renal impairment (11-24%) and association of morphine use with increased risk of postoperative delirium in hip fracture patients (OR 3.01; 95%CI 1.30 to 6.94) would suggest that if opioids are required, those not relying on renal elimination should be used in this cohort (Yang 2017 **Level III-3 SR**, 24 studies, n=5,364).

Pre-existing chronic opioid use occurs in approximately 1 in 4 hip fracture patients (Lindestrand 2015 **Level IV**, n=416) and is associated with increased risk of hip fracture (RR 1.54; 95%CI 1.34 to 1.77) (Ping 2017 **Level I**, 10 RCTs, n=697,011).

Eighty-one percent of hip fracture patients are discharged on opioids with 30% still on prescribed opioids 6 mth later (Lindestrand 2015 **Level IV**, n=416). Pre-existing opioid use and osteoporosis were the most significant factors associated with continued use at 6 mth. Conflicting evidence exists regarding opioids and mortality in hip fracture patients. One study found that discharge opioids were associated with an increased risk (OR 2.95; 95%CI 1.19 to 7.34) of mortality within 6 mth of surgery (Harstedt 2016 **Level III-2**, n=272), whereas another study found that opioids were not associated with increased risk at 30 d, 6 mth or 1 y (Lindestrand 2015 **Level IV**, n=416).

Tramadol

Following hip fracture surgery, patients prescribed tramadol on discharge had an increased risk of hospital readmission (OR 2.84) within 6 mth due to falls (Harstedt 2016 **Level III-2**, n=272). There is insufficient evidence to compare perioperative analgesic regimes with and without tramadol.

8.4.2.4 | Acupuncture

Auricular acupressure performed during prehospital transport led to better pain relief after hip fracture (Barker 2006 **Level II**, n=38, JS 5).

KEY MESSAGES

1. Lower limb nerve blocks with local anaesthetics reduce pain, analgesia requirements and lengthen time to rescue analgesia in hip fracture patients compared to systemic analgesia; there is no advantage of a specific nerve block, insertion technique or continuous versus single injection administration (**S**) (**Level I** [Cochrane Review]).
2. Lower limb nerve blocks decrease the risk of pneumonia in hip fracture patients, but do not decrease the risk of delirium, myocardial infarction/ischaemia or mortality (**N**) (**Level I** [Cochrane Review]).
3. Morphine should be avoided due to increased risk of delirium in hip fracture patients, who have a high prevalence of renal impairment (**N**) (**Level III-3 SR**).
4. Arthroplasty techniques in hip fracture patients are associated with less pain and opioid requirements than non-arthroplasty techniques (**N**) (**Level III-2**).

The following tick box represents conclusions based on clinical experience and expert opinion:

☑ Integrated orthogeriatric care, utilisation of care bundles and adherence to clinical care standards improve outcomes in hip fracture patients (**N**).

8.5 | Acute burns injury pain

Acute pain following burns injury can be nociceptive and/or neuropathic in nature (Nelson 2019 **NR**; Gray 2008a **NR**) and may be constant (background pain), intermittent or procedure-related. Itch can also be a significant symptom (for details see Section 10.9.2.3). The multifaceted character of burns injury pain requires a broad-based assessment tool for clinical application and research, which is currently not available (Mahar 2012 **Level I**, 25 RCTs, n≈800).

Burns pain is often undertreated, particularly in the elderly (Choiniere 2001 **NR**). However, effective pain management after acute burns injury is essential, not only for humanitarian and psychological reasons but also to facilitate procedures such as dressing changes and physiotherapy and possibly to minimise the development of chronic pain, which is reported in 18–58% of burns patients (Browne 2011 **Level IV**, n=492; Dauber 2002 **Level IV**, n=358; Choiniere 1989 **NR**).

More severe acute pain following burns injury leads to a greater risk of post-traumatic stress disorder (McGhee 2011 **Level IV**, n=113; Browne 2011 **Level IV**, n=492). Increased early use of opioids in children with burns injury reduces post-traumatic stress symptoms up to 4 y after the injury (Sheridan 2014 **Level III-3**, n=147 [paediatric]).

There is limited evidence for the management of pain in burns injury, and treatment continues to be largely based on evidence from several randomised clinical trials, case reports and case series, or data extrapolated from other relevant areas of pain medicine. The use of a highly protocolised pain management flowchart may be helpful in improving the pain experience (Yang 2013 **Level III-3**, n=107).

For paediatric information, see also Section 10.9.2.

8.5.1 | Management of background nociceptive pain

Immediately after the injury, simple measures such as cooling (Davies 1982 **NR**), covering and immobilising the burn may provide analgesia (Allison 2004a **GL**; Gallagher 2000b **NR**; Kinsella 1991 **NR**). Cooling under running tap water for ≥20 min or the application of a wet towel (ANZBA 2014 **GL**) is supported by porcine data (Rajan 2009 **BS**) and is useful up to 3 h post initial burn injury. Temporary burns dressings such as thin film plastic “cling” wrap (or clean sheets if unavailable) reduce pain caused by contact and draft; they should not be applied circumferentially as swelling is inherent (ANZBA 2014 **GL**; Allison 2004a **GL**).

In the initial presentation of severe burn, analgesia is best achieved by titration of IV opioids. Absorption of IM and SC opioids may be unreliable in the presence of hypovolaemia and vasoconstriction associated with burns (Kinsella 2008 **NR**). PCA with morphine is effective for burns pain in adults (Choiniere 1992 **Level II**, n=24, JS 4; Lin 2019c **Level IV**, n=23) and children (Gaukroger 1991 **Level IV**, n=11).

The addition of dexmedetomidine to an IV PCA (0.5 mcg/kg dexmedetomidine loading 10 min before induction, then 200 mcg to 100 mcg sufentanil per IV PCA bolus) vs IV PCA sufentanil only reduced rest and dynamic pain as well as opioid consumption slightly and improved recovery scores in the first 24 h after burns surgery (Jiang 2019 **Level II**, n=60, JS 5); however, the bolus dose of sufentanil was quite low and therefore this may have biased towards a positive response in the combination group.

Conversion to oral opioids is possible once normal gastrointestinal function has returned; even severe burns injury does not affect gastric emptying or the absorption of oral paracetamol (Hu 1993 **Level III-2 PK**, n=30).

Morphine doses do not require adjustment in burns injury, as its pharmacokinetics are unchanged in burns patients (Kinsella 2008 **NR**; Perreault 2001 **PK**).

In the ICU, intrathecal (IT) infusion of morphine has been reported as a method to control burns pain and thereby avoiding the adverse effects of systemic opioids (Zuehl 2018 **CR**).

8.5.2 | Management of acute neuropathic pain and hyperalgesia

Animal and human volunteer studies in burns injury have shown that secondary hyperalgesia develops around the injured site. In addition, burns injury results in damage to cutaneous nociceptors and conducting neurons that may lead to acute neuropathic pain. There is growing evidence that the addition of antihyperalgesic agents is an important part of multimodal treatment of burn injury pain. This is also relevant in view of the development of pruritus in the context of burns injury. Evidence based guidelines for post-burn pruritus recommend cetirizine and cimetidine as first line and loratadine as second line peripherally acting agents, gabapentin as a first line centrally acting agent, and laser therapy and pressure garments as possible nonpharmacological interventions (Goutos 2010 **GL**). Combination therapy is commonly used and should be implemented in a judicious stepwise fashion that includes peripherally acting, centrally acting and nonpharmacological interventions early.

Gabapentin reduced pain and opioid consumption following acute burns injury (Cuignet 2007 **Level III-3**, n=20) and reduced neuropathic pain descriptors in a small case series (Gray 2008b **Level IV**, n=6).

Pregabalin reduced pain in outpatient burns patients (Wong 2010 **Level IV**, n=24) and reduced "hot" and "sharp" pain as well as itch and procedural pain in severe burns injury (Gray 2011 **Level II**, n=90, JS 5).

Parenteral methylprednisolone or ketorolac reduced secondary hyperalgesia surrounding an experimental burns injury in human volunteers; however further clinical research is required prior to recommending these agents (Stubhaug 2007 **Level II**, n=12, JS 5).

There is also evidence in a burns injury model in human volunteers for beneficial effects of ketamine (McGuinness 2011 **Level I EH**, 4 RCTs, n=67) and dextromethorphan (Ilkjaer 1997 **Level II EH**, n=24, JS 3). Although ketamine is effective as an analgesic and reduces secondary hyperalgesia without relevant adverse effects, the limitations of the studies (no clinical studies, heterogeneity of results, small study size) preclude any definitive recommendations on clinical use of ketamine in a burns setting (McGuinness 2011 **Level I EH**, 4 RCTs, n=67).

8.5.3 | Management of procedural pain

Treatment and rehabilitative procedures for burns patients may be associated with frequent and prolonged periods of pain. It was previously reported that up to 84% of burns patients experience extreme and intense pain during therapeutic procedures (Ashburn 1995 **NR**). Analgesic strategies have more recently improved, but managing procedural pain remains a significant and ongoing challenge that requires a balance of pharmacological and nonpharmacological approaches.

8.5.3.1 | Opioids

Opioid therapy is the mainstay of analgesia for burns procedures. However, very high doses may be required (Linneman 2000 **Level IV**, n=55) and opioid-related sedation and respiratory depression may develop when the pain stimulus decreases following the procedure.

Short-acting opioids such as fentanyl (Prakash 2004 **Level II**, n=60, JS 4) or alfentanil (Sim 1996 **Level IV**) administered via PCA or target-controlled IV infusions (Gallagher 2000a **Level IV**, n=10) successfully provide analgesia during burns dressing changes. IN fentanyl was a viable alternative

to oral morphine in children for burns dressings (Borland 2005 **Level II**, n=28, JS 4). In adults, there was no difference in pain scores or rescue analgesic requirements between IN fentanyl and oral morphine for burns dressings (total surface less than 26%) (Finn 2004 **Level II**, n=26, JS 5). Oral transmucosal fentanyl provided similar analgesia to oral oxycodone (Sharar 2002 **Level II**, n=20, JS 4) and hydromorphone (Sharar 1998 **Level II**, n=14, JS 4) with a similar adverse-effect profile in children and adolescents. See also Section 10.9.4.

8.5.3.2 | Adjuvant medications

N_2O, ketamine and IV lidocaine infusions (Jonsson 1991 **Level IV**, n=7) have also been used to provide analgesia for burns procedures (see Sections 4.5.1, 4.6.1 and 4.4.1). However, efficacy of IV lidocaine for procedural pain could not be confirmed in an RCT (Wasiak 2011 **Level II**, n=45, JS 5) and a subsequent Cochrane review found no further trials (Wasiak 2014a **Level I** [Cochrane], 1 RCT, n=45; see above).

A systematic review of ketamine in volunteers with a burns injury model has been discussed above (McGuinness 2011 **Level I EH**, 4 RCTs, n=67). PCA with a ketamine/midazolam mixture was effective and well tolerated when used for analgesia and sedation during burns dressings (MacPherson 2008 **Level IV**, n=44). In children aged 12 to 36 mth with major burns requiring deep sedation for dressings, a propofol/remifentanil infusion was as effective as a propofol/ketamine infusion, but had a faster recovery (Seol 2015 **Level II**, n=50, JS 5). Oral ketamine/midazolam may provide superior pain reduction vs an oral midazolam/paracetamol/codeine combination for burns dressing changes in children aged 1 to 5 y (Norambuena 2013 **Level III-1**, n=60). IM ketamine/tramadol/ dexmedetomidine was found to be more effective than IM ketamine/tramadol/midazolam or IM ketamine alone in adult burns patients (Zor 2010 **Level III-1**, n=24). In contrast, there was no difference in the pain experience between three groups receiving ketamine/midazolam, ketamine/dexmedetomidine or ketamine alone in the same setting (Gunduz 2011 **Level II**, n=90, JS 3). Oral ketamine was better than oral dexmedetomidine for pain reduction during dressing changes in adult burns patients (Kundra 2013 **Level II**, n=30, JS 4).

The heterogeneous nature of the studies and the lack of pain outcome data in a meta-analysis of dexmedetomidine in burns patients mean no conclusions can be drawn as to its effect on burn pain (Asmussen 2013 **Level I**, 4 studies, n=266). Only improved sedation is identified.

Sedation and anxiolysis as an adjunct to analgesia can improve pain relief. This has been shown for lorazepam combined with morphine (Patterson 1997 **Level II**, n=79, JS 5). However, a retrospective case series of patients receiving midazolam for dressing changes did not demonstrate a reduction in overall pain or opioid use during the hospital admission (Bidwell 2013 **Level III-2**, n=36). Patient-controlled sedation with propofol may also be effective (Coimbra 2003 **Level IV**, n=20). A propofol/ketamine combination resulted in less “restlessness” during burns dressing changes vs a propofol/fentanyl combination, with no difference in emergence phenomena (Tosun 2008 **Level II**, n=32, JS 5).

Inhaled methoxyflurane may be helpful for dressing changes for burns patients in an ambulatory setting but further evidence is required prior to recommending routine use (Wasiak 2014b **Level IV**, n=15).

Topical analgesic techniques, such as lidocaine as a cream (Brofeldt 1989 **Level IV**, n=30) or a spray (Desai 2014 **Level II**, n=29, JS 5) or morphine-infused silver sulfadiazine cream (Long 2001 **Level IV**, n=4) may be effective; however a topical gel dressing containing morphine was not more effective than other gel dressing in reducing burns injury pain in the ED (Welling 2007 **Level II**, n=59, JS 5). The use of biosynthetic dressings is associated with a reduction in pain during dressing changes and a decrease in time to healing (Wasiak 2013 **Level I** [Cochrane], 30 RCTs of various dressings, n unspecified). The use of a soft silicone wound contact layer on split thickness skin grafts

reduced pain on dressing changes in comparison to conventional dressings (Patton 2013 **Level II**, n=43, JS 2).

Puerarin, a Chinese herb extract, was found to be analgesic and anti-inflammatory for dressing changes; however, the control group received no analgesia (Zhang 2013b **Level II**, n=32, JS 5).

8.5.4 | Regional analgesia for donor site pain management

Traditionally, regional analgesia is often avoided in burns patients due to the high incidence of bacteraemia and bacterial colonisation. However, recent research suggests that well-selected patients may benefit from regional analgesia for donor site pain management.

US-guided local anaesthetic block of the lateral femoral cutaneous nerve in 16 consecutive patients resulted in no pain 4 h after surgery at the donor site (lateral thigh) (Shteynberg 2013 **Level IV**, n=16); however longer-term effects of this intervention are not known. Fascia iliaca compartment block reduced dynamic, but not rest pain, at the skin donor site and injection of local anaesthetic through the catheter placed in the compartment reduced pain at the first dressing change on d 3 following surgery (Cuignet 2005 **Level II**, n=81, JS 3).

8.5.5 | Nonpharmacological pain management

Numerous non-pharmacological techniques have been described to assist in reducing the pain and suffering of procedures necessary in burns management

Distraction techniques of virtual reality and hypnosis have the most beneficial effects on reducing procedural pain, however with high heterogeneity of study effects (Scheffler 2018 **Level I** [PRISMA], 21 RCT, n=660). Stratified analysis suggest that relaxation alone is insufficient to reduce procedural pain. Hypnosis provides benefit in pain and anxiety reduction but not medication use for pain of burn wound care (Provencal 2018 **Level I** [PRISMA], 6 RCTs, n=234) (4 RCTs overlap); however, the conclusion states that it may be premature to make hypnosis a general clinical recommendation in the burn injured population. Indeed, a subsequent RCT found that hypnosis had no benefit in pain reduction (Chester 2018 **Level II**, n=64, JS 5).

Virtual reality reduces pain intensity, time spent thinking about pain and unpleasantness (Luo 2019 **Level I** [PRISMA], 13 RCTs, n=362; Scheffler 2018 **Level I** [PRISMA], 21 RCT, n=660) (4 RCTs overlap). VR techniques in combination with pharmacological measures reduce the pain experience during dressing changes and physiotherapy in children (Morris 2009 **Level IV SR**, 9 studies, n=152) (6 RCTs overlap). Providing a VR service requires significant physical and staffing resources (Markus 2009 **Level IV**, n=10). Simply watching television during burns care may be as effective as VR techniques in reducing pain scores (van Twillert 2007 **Level III-3**, n=19) and use of commercially available video games may be another option (Parry 2012 **Level III-2**, n=24).

Music interventions are helpful for pain alleviation, anxiety relief and heart rate reduction (Li 2017b **Level I** [PRISMA], 17 RCTs, n=804).

Aroma therapy may reduce pain, anxiety and improve sleep quality, but the low quality of trials with regard to randomisation and bias does not permit a conclusion (Choi 2018 **Level I** [PRISMA], 4 RCTs, n=248).

Transcranial direct current stimulation (Hosseini Amiri 2016 **Level II**, n=60, JS 1) and whole body vibration reduce pain and/or anxiety (Ray 2017 **Level II**, n=31, JS 3).

KEY MESSAGES

1. The use of biosynthetic dressings is associated with a decrease in time to healing and a reduction in pain during burns dressings changes (**U**) (**Level I** [Cochrane Review]).
2. Virtual reality distraction, augmented reality techniques and multimodal distraction methods reduce pain and unpleasantness during burns dressings (**S**) (**Level I** [PRISMA]).
3. Music interventions are helpful in reducing pain, anxiety and heart rate in burns patients (**N**) (**Level I** [PRISMA])
4. Opioids, particularly via PCA, are effective in burns pain, including procedural pain (**U**) (**Level II**).
5. Pregabalin reduces pain following acute burns injury (**U**) (**Level II**).
6. Sedation and anxiolysis with lorazepam improves procedural pain relief in acute burns injury (**U**) (**Level II**).
7. Regional analgesia reduces donor site pain in selected burns patients (**U**) (**Level II**).
8. Gabapentin reduces pain and opioid consumption following acute burns injury (**U**) (**Level III-3**).
9. PCA with ketamine and midazolam mixture provides effective analgesia and sedation for burns dressings (**U**) (**Level IV**).

The following tick boxes represent conclusions based on clinical experience and expert opinion:

☑ Acute pain following burns injury can be nociceptive and/or neuropathic in nature and may be constant (background pain), intermittent or procedure-related (**U**).

☑ Acute pain following burns injury requires aggressive multimodal and multidisciplinary treatment and may benefit from protocolised management approaches (**S**). This is particularly important as severely burn injured patients require repeated procedures and frequently have persistent issues of chronic pain, pruritus, post-traumatic stress and other psychological consequences.

☑ Pruritus is a common symptom following burns injury and alpha-2-delta ligands are useful in its management (**N**).

8.6 | Acute medical pain

Acute pain in medical wards is common (Vallano 2006 **Level IV**, n=1,675) with a prevalence of 37.7% to 84% (Gregory 2016 **Level IV SR** [PRISMA], 11 studies, n=17,705). Comparative rates with surgical inpatients are variably reported as higher (and less well treated) (Korczak 2013 **Level IV SR**, 16 studies, n unspecified) or lower (30-56% vs 55-78%) (5 studies, n=5,134), with severe pain prevalence ranging from 7 to 36% (5 studies, n=7,479) (Gregory 2016 **Level IV SR** [PRISMA], 11 studies, n=17,705).

8.6.1 | Acute abdominal pain

Acute abdominal pain may originate from visceral or somatic structures or may be referred; neuropathic pain states should also be considered. Recurrent acute abdominal pain may be a manifestation of a chronic visceral pain disorder such as chronic pancreatitis, pelvic pain or irritable bowel syndrome and will require a multidisciplinary pain management approach.

8.6.1.1 | Analgesia and the diagnosis of acute abdominal pain

A common misconception is that analgesia masks the signs and symptoms of abdominal pathology and should be withheld until a diagnosis is established. Pain relief (usually in the form of opioids) does not interfere with the diagnostic process in acute abdominal pain in adults (Manterola 2011 **Level I**, 8 RCTs, n=922) or in children (Green 2005 **Level II**, n=108, JS 5; Kim 2002 **Level II**, n=60, JS 5) and does not lead to increased errors in clinical management (Ranji 2006 **Level I**, 12 RCTs, n=1,389).

8.6.1.2 | Renal and ureteral colic/stones

Nonselective NSAIDs, opioids (Holdgate 2005b **Level I** [Cochrane], 20 RCTs, n=1,613) and metamizole (dipyrone) (Edwards 2002b **Level I** [Cochrane], 11 RCTs, n=1,053) provide effective analgesia for renal colic. Nonselective NSAIDs reduce requirements for rescue analgesia and cause less vomiting than opioids (particularly pethidine [meperidine]) (Holdgate 2005b **Level I** [Cochrane], 20 RCTs, n=1,613).

Specifically NSAIDs are superior to placebo and to antispasmodics in reducing pain of renal colic and requirements for rescue analgesia; indomethacin was less effective than other NSAIDs (Afshar 2015 **Level I** [Cochrane], 50 RCTs, n=5,734) (7 RCTs overlap with Holdgate 2005b). The combination of NSAIDs with antispasmodics results in better analgesia than NSAIDs alone, but does not show higher responder rates for 50% pain reduction and does not reduce requirements for rescue analgesia further. NSAIDs show a clinically marginal advantage in early pain reduction over opioids (MD –5.58/100; 95%CI –10.22 to –0.95) (11 RCTs, n = 1,985) with reduced rescue requirements and reduced vomiting rates (Pathan 2018 **Level I** [PRISMA], 36 RCTs, n=4,887) (9 RCTs overlap). NSAIDs do not differ for early pain relief vs paracetamol, but reduce rescue requirements.

Onset of analgesia was fastest when nsNSAIDs were administered IV (Tramer 1998 **Level I**, 26 RCTs, n=2,225), although suppositories were also effective (Lee 2005a **Level II**, n=200, JS 3). IV ibuprofen 800 mg was faster and more effective than IV ketorolac 30 mg in controlling pain caused by renal colic (Forouzanfar 2019 **Level II**, n=240, JS 3). Combination IV ketorolac/morphine provided a greater reduction in pain scores, earlier onset of complete pain relief and reduced need for rescue analgesia, vs using either analgesic alone (Safdar 2006 **Level II**, n=130, JS 5).

An overarching network meta-analysis on early pain management in renal colic concludes that NSAIDs are superior to opioids, paracetamol, and combination therapy and NSAIDs with IV or IM route ranked first from efficacy and safety perspectives (Gu 2019 **Level I** [PRISMA] [NMA], 65 RCTs, n=8,633) (many RCTs overlap with previous meta-analyses).

IV paracetamol 1 g provides analgesia for renal colic which is superior to IV morphine (MD -7.5/100; 95%CI -1.99 to -13.00) and comparable to NSAIDs (MD 0.01/100; 95%CI, -0.10 to 0.13) (Sin 2017 **Level I**, 5 RCTs, n=2,020). In contradistinction to their meta-analysed results, the authors advise against paracetamol as an alternative to opioids or NSAIDs in view of the poor quality of the RCTs included (ambiguous description of study protocol, incomplete presentation of data, small sample sizes, and/or methodological flaws).

If opioids are used for renal colic in the ED, there is no difference in clinical efficacy between morphine and pethidine (O'Connor 2000 **Level II**, n=103, JS 5). SL buprenorphine had similar analgesic and adverse effects to IV morphine (Payandemehr 2014 **Level II**, n=69, JS 5). Addition of IV ketamine (0.15 mg/kg or 0.2 mg/kg) to IV morphine (0.1 mg/kg) increased the effectiveness of pain relief and also decreased the rate of nausea, vomiting and use of rescue medication (Hosseininejad 2019a **Level II**, n=22, JS 5; Abbasi 2018 **Level II**, n=106, JS 4). IN ketamine (1 mg/kg) had a slower onset of action vs IV morphine (0.1 mg/kg), but analgesia was comparable after 15 min (Farnia 2017 **Level II**, n=53, JS 4). Addition of low dose naloxone to IV morphine made no difference to analgesia (Hosseininejad 2019b **Level II**, n=150, JS 5).

The smooth muscle relaxant buscopan failed to improve analgesia when combined with nsNSAIDs (Song 2012 **Level II**, n=89, JS 5; Jones 2001 **Level II**, n=59, JS 3), opioids (Holdgate 2005a **Level II**, n=192, JS 4) or metamizole (2 RCTs) (Edwards 2002b **Level I** [Cochrane], 11 RCTs, n=1,053).

IV ketamine 0.6 mg/kg is as effective as IV ketorolac 30 mg in the management of renal colic, but with an increased rate of adverse effects (Sotoodehnia 2019 **Level II**, n=126, JS 3). IV ketamine 0.15 mg/kg combined with IV NSAID lornoxicam 8 mg achieved better pain control with less adverse effects and better functional scores than IV pethidine 50 mg (Metry 2019 **Level II,** n=120, JS 3). Combination IV morphine 0.1 mg/kg with ketamine 0.15 mg/kg vs IV morphine alone improved control of renal colic pain and reduced further opioid requirements in the first 30 min (Abbasi 2018 **Level II**, n=106, JS 4). IN ketamine 1 mg/kg vs IV morphine 0.1 mg/kg resulted in better pain relief in the first 15 min (Farnia 2017 **Level II**, n=40, JS 5).

Papaverine was as effective as IV diclofenac in the initial treatment of renal colic but required increased use of rescue analgesia (Snir 2008 **Level II**, n=90, JS 2). However, as a rescue analgesic, papaverine was of similar efficacy to pethidine and superior to hyoscine in patients who failed to respond to initial treatment with a diclofenac-hyoscine combination (Yencilek 2008 **Level II**, n=110, JS 2).

IV ondansetron produced analgesia in 42% of patients with renal colic but was less effective than IM diclofenac (Ergene 2001 **Level II**, n=64, JS 3).

Ureteral calculus expulsive therapy using alpha-blockers (mainly PO tamsulosin) vs standard therapy reduces the number of pain episodes, the need for analgesic medication and even hospitalisation (Campschroer 2014 **Level I** [Cochrane], 32 RCTs, n=5,864; Hollingsworth 2016 **Level I** [PRISMA] 55 RCTs, n=5,990; Raison 2017 **Level I**, 67 RCTs, n=6,654) (overlap by a majority of RCTs). Tamsulosin was more effective in reducing analgesic requirements than nifedipine in this setting (Ye 2011 **Level II**, n=3,189, JS 2). However, PO tadalafil, a phosphodiesterase-5 (PDE5) inhibitor, resulted in a higher stone expulsion rate than tamsulosin (Kc 2016 **Level II**, n=99, JS 3).

IV lidocaine bolus provided superior analgesia to IV morphine in renal colic (2 RCTs and 1 study) (E. Silva 2018 **Level IV SR** [PRISMA], 6 RCTs & 2 studies, n=536; Masic 2018 **Level IV SR** [PRISMA], 4 RCTs & 9 studies, n=512) (1 RCT overlap). IV lidocaine/ketorolac bolus achieved better analgesia for renal colic patients vs IV lidocaine alone, but not vs IV ketorolac alone (Motov 2019, **Level II,** n=100, JS 3).

The addition of IV magnesium to morphine/ketorolac improved pain control and reduced the need for rescue analgesics (Jokar 2017 **Level II**, n=100, JS 5). However, addition of IV magnesium to ketorolac alone did not improve renal colic pain relief (Maleki Verki 2019 **Level II,** n=87, JS 3).

IV fluid therapy has no effect on pain outcomes or stone transition in renal colic (Worster 2012 **Level I** [Cochrane], 2 RCTs, n=118).

Desmopressin is inferior to NSAIDs in reducing pain of renal colic, but may be a useful adjuvant therapy to opioids based on weak evidence (Jalili 2016 **Level III-1 SR**, 9 RCTs & 1 study, n=1,000).

Intercostal nerve block at T 12 level improved pain vs IM diclofenac from 1 to 45 min (Maldonado-Avila 2017 **Level II**, n=60, JS 2)

TENS applied over the painful flank during prehospital transport reduced pain scores, anxiety and nausea in patients with renal colic (Mora 2006 **Level II**, n=73, JS 4).

The addition of aroma therapy (lavender) to standard treatment of renal colic with parenteral diclofenac improved pain scores at 30 min, but only in female patients (Irmak Sapmaz 2015 **Level II**, n=100, JS 0).

Sexual intercourse (3-4 times/wk) added to standard NSAID therapy prn reduced stone expulsion time, number of colic episodes and need for rescue analgesia in married male patients (Abdel-Kader 2017 **Level II**, n=66, JS 3). Similarly, sexual intercourse (3 to 4 times/wk) vs tamsusoline vs standard medical therapy (control group) increased rate of and reduced time to stone expulsion (Doluoglu 2015 **Level II**, n=90, JS 3).

8.6.1.3 | Biliary colic and acute pancreatitis

In the absence of any patient-specific contraindications, a multimodal analgesic regimen is recommended for the treatment of pain due to biliary colic and acute pancreatitis, including paracetamol, NSAIDs and opioids (Greenberg 2016 **GL**).

All opioids increase sphincter of Oddi tone and bile duct pressures in animal and human experimental models (Thompson 2001 **NR**). Morphine increased sphincter of Oddi contractions more than pethidine during cholecystectomy (Thune 1990 **Level IV EH**, n=36). However, there is no difference in the risk of pancreatitis complications or clinically serious adverse effects between the use of opioids or other analgesic options when treating acute pancreatitis (Basurto Ona 2013a **Level I** [Cochrane], 5 RCTs, n=227). Similarly, a systematic review of parenteral analgesia in acute pancreatitis found mainly RCTs of low (2 RCTs overlap).

NSAIDs for treatment of biliary colic pain result in better pain relief than placebo (5 RCTs) or spasmolytics (4 RCTs) with no difference to opioids (4 RCTs) (Fraquelli 2016 **Level I** [Cochrane], 12 RCTs, n=828). NSAIDs reduce cholelithiasis-related complications (eg acute cholecystitis, acute pancreatitis, jaundice, cholangitis) vs spasmolytic drugs (2 RCTs) but not vs placebo (3 RCT), with inadequate power to confirm no difference vs opioids (1 RCT).

The perioperative use of rectal indomethacin for ERCP reduces the risk of post ERCP pancreatitis (OR 0.49; 95%CI 0.34 to 0.71) vs placebo (NNT 17) (Ahmad 2014 **Level I**, 4 RCTs, n=1,422). This was subsequently confirmed for NSAID use in general via any route of administration with a similar reduction of risk of post ERCP pancreatitis (RR 0.54; 95%CI 0.45 to 0.64) vs controls (Liu 2019a **Level I** [PRISMA], 19 RCTs, n=5,031).

IM atropine was no more effective than saline in the treatment of acute biliary colic (Rothrock 1993 **Level II**, n= 55, JS 4). There is no difference in outcomes including exacerbation of pain between nasogastric and nasojejunal feeding in patients with acute pancreatitis (Chang 2013b **Level I**, 3 RCTs, n=151).

Epidural analgesia improved pain control in severe acute pancreatitis vs IV opioid PCA (Sadowski 2015 **Level II**, n=38, JS 2)

Rhubarb combined with trypsin inhibitor vs trypsin inhibitor alone improves outcome of acute pancreatitis including abdominal pain (Hu 2018 **Level I**, 16 RCTs, n=912).

8.6.1.4 | Irritable bowel syndrome and colic

Bulking agents are not more effective than placebo for treating pain in irritable bowel syndrome (4 RCTs, n=186), while antispasmodics (cimetropium/dicyclomine), peppermint oil, pinaverium and trimebutine (13 RCTs, n=1,392) and antidepressants (TCAs, but not SSRIs) are effective here (8 RCTs, n=517) (Ruepert 2011 **Level I** [Cochrane], 56 RCTs, n=3,725) as well as psychological interventions such as CBT, hypnotherapy, multicomponent psychological therapy, and dynamic psychotherapy (Ford 2014 **Level I,** 32 RCTs, n=2,189) (0 RCT overlap for psychological interventions).

$5HT_3$ antagonists (alosetron and cilansetron) significantly improve global IBS symptoms including abdominal pain and discomfort versus placebo or mebeverine (spasmolytic) (Andresen 2008 **Level I** [QUOROM], 14 RCTS, n=3,024). There is an increased risk of constipation and possibly ischaemic colitis.

Probiotics reduce the pain and symptom severity in IBS vs placebo (Didari 2015 **Level I**, 15 RCTs, n=1,793).

8.6.1.5 | Primary dysmenorrhoea

The management of primary dysmenorrhoea embraces both biological and psychosocial aspects and frequently uses multimodal pharmacological approaches (eg paracetamol, NSAIDs and the oral contraceptive pill). However, there is no evidence base for multimodal intervention with clinical trials restricted to single agents. Women with primary dysmenorrhoea have features of elevated pain sensitivity and reduced pain tolerance vs controls (Payne 2017 **Level III-2 SR EH**, 19 studies, n=1,975 [including 110 men]).

The oral contraceptive pill has limited evidence for better pain relief vs placebo (OR 2.01; 95%CI 1.32 to 3.08) (7 RCTs, n=497), with no differences between different preparations (Wong 2009 **Level I** [Cochrane], 10 RCTs, n unspecified).

Nonselective NSAIDs are more effective analgesics in dysmenorrhoea vs placebo, however withincreased rate of adverse effects (Marjoribanks 2015 **Level I** [Cochrane], 80 RCTs, n=5,820). Nonselective NSAIDs are more effective than paracetamol, with no difference between the different nsNSAIDs with regard to efficacy and safety. Nonselective NSAIDs also reduce bleeding and pain associated with the use of an intrauterine device (Grimes 2006 **Level I** [Cochrane], 15 RCTs, n=2,702).

There is no high-quality evidence to support the effectiveness of any complementary medicine in the treatment of dysmenorrhoea, but there is low quality evidence for effectiveness of some (Pattanittum 2016 **Level I** [Cochrane], 27 RCTs, n=3,101). See also Section 4.14.3.

High-frequency TENS is effective in primary dysmenorrhoea (Proctor 2002 **Level I** [Cochrane], 7 RCTs, n=164). See also Section 7.2.

Acupuncture, acupressure (Smith 2016a **Level I** [Cochrane], 42 RCTs, n=4,640) and acupoint stimulation (Chung 2012 **Level I**, 25 RCTs, n=3,109) reduce pain in primary dysmenorrhoea (vs no treatment or NSAIDs), but the quality of studies is low to very low. See also Section 7.3.

8.6.1.6 | Acute abdominal pain in children

Children and adolescents experience all of the above listed medical causes of abdominal pain.

For discussion of the management of recurrent abdominal pain which is mainly a paediatric disorder (Brusaferro 2018 **NR**), see Section 10.9.4. For the principles of management of abdominal

pain asscociated with vaso-occlusive crises in sickle cell disorder see Section 8.6.4.1 below and for paediatric issues Section 10.9.5. For CAMT interventions for infantile colic see Section 10.11.3.

KEY MESSAGES

1. Provision of analgesia does not interfere with the diagnostic process in acute abdominal pain and does not increase the risk of errors in clinical management (**U**) (**Level I** [Cochrane Review]).
2. NSAIDs, opioids and intravenous metamizole (dipyrone) provide effective analgesia for renal colic (**S**) (**Level I** [Cochrane Review]).
3. NSAIDs given for renal colic reduce pain (**N**) (**Level I** [PRISMA]) and rescue analgesia requirements with less vomiting compared with opioids, particularly pethidine (meperidine) (**S**) (**Level I** [Cochrane Review]).
4. Alpha blockers as expulsive therapy for ureteral stones reduce the number of pain episodes and analgesic requirements (**S**) (**Level I** [Cochrane Review]).
5. Antispasmodics and tricyclic antidepressants, but not bulking agents, are effective for the treatment of acute pain in irritable bowel syndrome (**S**) (**Level I** [Cochrane Review]) as well as psychological interventions (**N**) (**Level I**).
6. NSAIDs are effective in primary dysmenorrhoea and superior to paracetamol (**S**) (**Level I** [Cochrane Review]).
7. The smooth muscle relaxant buscopan does not add further analgesic benefit when combined with metamizole (dipyrone) (**U**) (**Level I** [Cochrane Review]), opioids or NSAIDS to treat pain of renal colic (**U**) (**Level II**).

9. High-frequency TENS, possibly some dietary supplements and acupuncture/acupressure are effective in the treatment of primary dysmenorrhoea (**S**) (**Level I** [Cochrane Review]).

9. NSAIDS are superior to placebo and spasmolytics and as effective as opioids in the treatment of biliary colic (**S**) (**Level I** [Cochrane Review])
10. The perioperative use of NSAIDs for endoscopic retrograde cholangiopancreatography (ERCP) reduces the risk of post ERCP pancreatitis (**S**) (**Level I** [PRISMA]).
11. $5HT_3$ antagonists reduce some of the symptoms of irritable bowel syndrome (**S**) (**Level I** [QUOROM).
12. The onset of analgesia is faster when NSAIDs are given intravenously for the treatment of renal colic (**U**) (**Level I**).
13. Intravenous paracetamol is as effective as intravenous morphine and superior to intramuscular piroxicam for analgesia in renal colic (**U**) (**Level II**).
14. There is no difference between pethidine and morphine for analgesia in renal colic (**U**) (**Level II**).
15. Low-dose ketamine is an effective analgesic for renal colic pain (**N**) (**Level II**).
16. IV lidocaine is an effective analgesic for renal colic pain (**N**) (**Level IV SR**).

8.6.2 | Herpes zoster-associated pain

Herpes zoster (shingles) is caused by reactivation of the varicella-zoster virus (VZV), which lies dormant in dorsal root and cranial nerve ganglia following primary infection with chickenpox (varicella), usually in childhood (Le 2019 **NR**). There is a marked increase in the lifetime risk of herpes zoster with increasing age and with diseases and drugs that impair immunity estimated at 30%, with 68% of cases occurring in those aged ≥50 y.

Herpes zoster-associated pain occurs in up to 90% of those affected and may occur before onset of the characteristic rash (during the prodrome), with onset of the rash or following its resolution (Le 2019 **NR**). The pain varies in intensity and may be described as "burning", "throbbing" or "shooting"; itching, dysaesthesias, and allodynia may also be present (Dworkin 2008). In the majority of cases, herpes zoster is an acute self-limiting disease, although it may progress to postherpetic neuralgia (pain that persists for >3 mth after the onset of herpes zoster). The incidence of postherpetic neuralgia increases with age (>50 y), occurring in up to 75% of patients aged ≥70 y who had herpes zoster (Johnson 2004 **NR**). Identified risk factors for the development of postherpetic neuralgia are prodromal pain (RR 2.29; 95%CI 1.42 to 3.69), severe acute pain (RR 2.23; 95%CI 1.71 to 2.92), severe rash (RR 2.63; 95%CI 1.89 to 3.66), and ophthalmic involvement (RR2.51; 95%CI 1.29 to 4.86) (Forbes 2016 **Level III-2 SR**, 19 studies, n=40,238). As previously reported there was an increase with older age; for individual studies, relative risk estimates per 10-year increase ranged from 1.22 to 3.11.

Early, aggressive treatment of herpes zoster infection and pain may reduce the incidence of postherpetic neuralgia, although data on preventive strategies are limited.

Detailed consensus-based guidelines on the treatment of herpes zoster have been published (Werner 2017 **GL**).

8.6.2.1 | Prevention of herpes zoster

Two vaccines are licensed for the prevention of herpes zoster and post-herpetic neuralgia in older adults: Zostavax®, a live attenuated vaccine, and Shingrix®, a recombinant subunit vaccine (Le 2019 **NR**). Zostavax® is still recommended in Australia for adults aged ≥60 y (Australian Vaccines Handbook **GL**) in NZ for adults aged ≥65 y (IMAC 2019 **GL**) and in the UK for adults aged 70 to 79 y. In the US, the US Advisory Committee on Immunization Practices (ACIP) updated its guidance and now recommends Shingrix® for adults aged ≥50 y (Dooling 2018 **GL**).

Zostavax® is effective in the prevention of herpes zoster (and thereby postherpetic neuralgia) in individuals aged >60 y (Gagliardi 2012 **Level I**, 8 RCTs, n=52,269). A large, multicentre, randomised placebo-controlled trial (The Shingles Prevention Study) demonstrated the vaccine's efficacy, with the incidence of herpes zoster reduced by 51.3%, that of postherpetic neuralgia by 66.5 % and herpes zoster-associated "burden of illness" by 61.1% (Oxman 2005 **Level II**, n=38,546, JS 4). The estimated number needed to vaccinate to prevent a case was 11 (95%CI 10 to 13) for herpes zoster and 43 (95%CI 33 to 53) for postherpetic neuralgia (Brisson 2008 **Level III-3**). Zostavax is less effective with increasing age and its efficacy wanes 10 y after vaccination (Morrison 2015 **Level IV**, n=6,867).

Shingrix® is a newer vaccine with substantially higher efficacy than Zostavax® (Syed 2018 **NR**) reducing the risk of herpes zoster infection by 97% vs placebo, with mean follow-up duration of 3.2 y (Lal 2015 **Level II**, n=15,411, JS 5). Unlike Zostavax®, the efficacy of Shingrix® was higher for patients over 70 y of age and reduced the incidence of postherpetic neuralgia by 88.8% (Cunningham 2016 **Level II**, n=13,900, JS 5). Protection, however, declines slightly four y after vaccination with long term efficacy unknown (Morrison 2015 **Level IV**, n=6,867). As it is not a live vaccine, Shringrix® should be theoretically safe to administer to immunocompromised

patients, unlike Zostavax®, though no recommendations have been made for vaccinating this group (Le 2019 **NR**; Syed 2018 **NR**).

8.6.2.2 | Treatment of acute herpes zoster-associated pain

Around 95% of patients will present with acute pain; processes of neuroinflammation are in part responsible for the acute pain state (Werner 2017 **GL**).

Antiviral agents

Antiviral agents should be considered in all patients with acute herpes zoster, in particular those who have severe disease, are over 50 y of age, immunocompromised, or have evidence of trigeminal nerve involvement (Werner 2017 **GL**; Le 2019 **NR**). Acyclovir (Wood 1996 **Level I**, 4 RCTs, n=691), valaciclovir (Beutner 1995 **Level II**, n=1,141, JS 5) or famciclovir (Tyring 2000 **Level II**, n=597, JS 5), given within 72 h of rash onset, accelerated the resolution of acute herpes zoster pain. Famciclovir, in various doses and frequencies, was as effective as acyclovir for herpes zoster-related outcomes including acute pain, with fewer adverse effects (Gopal 2013 **Level II**, n=100, JS 2; Shafran 2004 **Level II**, n=559, JS 5; Shen 2004 **Level II**, n=55, JS 5). Famciclovir or valaciclovir have replaced acyclovir as the drugs of choice in the treatment of herpes zoster because of more favourable pharmacokinetics and simpler dosing profiles (Cunningham 2008 **NR**). FV-100, a prodrug for the bicyclic nucleoside analogue CF-1743 with high specificity for the VZV showed faster resolution of clinically significant pain vs valaciclovir (Tyring 2017 **Level II**, n=450, JS 5).

Systemic analgesics

For mild herpes zoster-associated pain, simple analgesics such as paracetamol and NSAIDs such as ibuprofen are regarded as sufficient (Le 2019 **NR**). Multimodal analgesia with regular non-opioids, in addition to an opioid such as oxycodone or tramadol as required, has been recommended for more severe pain (Werner 2017 **GL**; Cunningham 2008 **NR**; Dworkin 2007 **NR**; Dwyer 2002 **NR**).

Oxycodone CR, but not gabapentin, effectively reduced the average worst pain during the first 14 d of herpes zoster vs placebo, although oxycodone-treated patients had higher withdrawal rates from the trial, primarily because of constipation (Dworkin 2009 **Level II**, n=87, JS 5).

Corticosteroids

Prednisolone added to acyclovir for acute herpes zoster minimally reduced pain intensity but improved the rate of skin lesion healing for up to 14 d, with no effect on the overall recovery rate at 3 wk (Wood 1994 **Level II**, n=400, JS 4). A later trial showed prednisolone, either as monotherapy or in combination with acyclovir, increased the likelihood of being “pain-free” at 1 mth by a factor of 2.3 (95%CI 1.4 to 3.5), with no difference in the rate of skin healing vs placebo (Whitley 1996 **Level II**, n=208, JS 4).

Anticonvulsants

A single dose of gabapentin 900 mg during herpes zoster reduced acute pain intensity by 66% (33% for placebo) and also reduced the area and severity of allodynia, for up to 6 h (Berry 2005 **Level II**, n=26, JS 5). When given in divided doses between 300 to 900 mg/day within 72 h of onset of rash, gabapentin reduced pain by 26 to 38% after 4 wk (Kanodia 2012, **Level II,** n=52, JS 3). This was also found with pregabalin 150 mg (Jensen-Dahm 2011 **Level II**, n=8, JS 5). However, one study showed no analgesic benefit was found when gabapentin up to 1,800 mg daily was administered for 28 d (Dworkin 2009 **Level II**, n=87, JS 5) or with pregabalin 150 to 300 mg daily for 3 wk (Krcevski Skvarc 2010 **Level II**, n=29, JS 3).

Topical lignocaine

Topical lignocaine patches (5%) applied for 12 h twice daily (on intact skin) during acute herpes zoster reduced pain intensity and improved patients' global impression of pain relief, vs a vehicle patch: the incidence and severity of adverse effects was low (Lin 2008 **Level II**, n=46, JS 5).

Aspirin

Topical aspirin, in either moisturiser or diethyl ether, was an effective analgesic in acute herpes zoster, vs similar preparations containing indomethacin, diclofenac or placebo (De Benedittis 1996 **Level II**, n=37, JS 3) or oral aspirin (Balakrishnan 2001 **Level II**, n=45, JS 3).

Neuraxial or sympathetic block

Nerve blocks in general for acute herpes zoster vs standard treatment without nerve blocks reduce duration of acute pain (MD −13.68 d; 95%CI −18.70 to −8.66) (1 RCT [2 stellate ganglion blocks LA/dexamethasone 1 wk apart]; 1 RCT [continuous PVB]; 1 study [continuous epidural analgesia]) (Kim 2017a **Level I**, 8 RCTs & 1 study, n=1,645).

Acupuncture and moxibustion

Based on data from one RCT for each outcome, acupuncture and moxibustion reduces acute pain of herpes zoster and its duration with questionable clinical significance (Coyle 2017 **Level I**, 9 RCTs, n=945).

8.6.2.3 | Prevention of postherpetic neuralgia

Immunisation of persons aged ≥60 y with live attenuated VZV vaccine reduces the incidence of herpes zoster and thereby the incidence of postherpetic neuralgia; however there is no evidence that the immunisation prevents postherpetic neuralgia beyond this effect (Chen 2011 **Level I** [Cochrane], 1 RCT, n=38,546).

The use of acyclovir does not significantly reduce the incidence of postherpetic neuralgia at 6 mth (Chen 2014 **Level I** [Cochrane], 6 RCTs, n=1,211). There is insufficient evidence to determine the preventive effects of other antiviral agents.

Similarly, systemic corticosteroids (Han 2013 **Level I** [Cochrane], 5 RCTs, n=787) are ineffective preventive strategies in postherpetic neuralgia.

Nerve blocks in general for acute herpes zoster vs standard treatment without nerve blocks reduce the incidence of PHN at 3 mth (RR 0.43; 95%CI 0.25 to 0.7) (7 RCTs and 1 study), at 6 mth (RR 0.41; 95%CI 0.2 to 0.83) (6 RCTs) and at 12 mth (RR 0.17; 95%CI 0.1 to 0.28) (2 RCTs) (Kim 2017 **Level I,** 8 RCTs & 1 study, n=1,645). With regard to specific blocks, stellate ganglion blocks (3 RCTs) and single epidural block had no preventive effect (1 RCT), while repeated or continuous epidural (2 RCTs, 1 study) and paravertebral analgesia (2 RCTs) have a preventive effect.

During acute herpes zoster, the early administration of amitriptyline (25 mg for 90 d) significantly reduced the incidence of postherpetic neuralgia at 6 mth (Bowsher 1997 **Level II**, n=80, JS 4).

KEY MESSAGES

1. Antiviral agents started within 72 hours of onset of the herpes zoster rash accelerate the resolution of acute pain (**U**) (**Level I**) but do not reduce the incidence, severity and duration of postherpetic neuralgia (**U**) (**Level I** [Cochrane Review]).
2. Immunisation of persons aged 60 years or older reduces the incidence of herpes zoster and thereby postherpetic neuralgia with Zostavax® (**U**) (**Level I** [Cochrane Review]) and Shingrix® (**N**) (**Level II**).
3. Continuous or repeated paravertebral blocks in the acute phase of herpes zoster reduce the incidence of postherpetic neuralgia at 3, 6 and 12 months (**N**) (**Level I**).
4. Amitriptyline (used in low doses for 90 days from onset of the herpes zoster rash) reduces the incidence of postherpetic neuralgia (**U**) (**Level II**).
5. Topical aspirin, topical lignocaine patch or controlled-release oxycodone provide analgesia in acute pain due to herpes zoster (**U**) (**Level II**).
6. Nerve blocks in the acute phase of herpes zoster reduce the duration of herpes zoster-associated pain (**N**) (**Level III-I SR**).
6. Continuous epidural analgesia in the acute phase of herpes zoster reduces the incidence of postherpetic neuralgia at 3 months (**N**) (**Level III-I SR**).

The following tick box represents conclusions based on clinical experience and expert opinion:

☑ Provision of early and appropriate analgesia is an important component of the management of herpes zoster and may have benefits in reducing the incidence of postherpetic neuralgia (**U**).

8.6.3 | Acute cardiac pain

Acute coronary syndrome refers to a range of acute myocardial ischaemic states including unstable angina and myocardial infarction. Typically, myocardial ischaemia causes central chest pain, which may radiate into the arm, neck or jaw; nontypical presentations can occur, particularly in the elderly patient (see also Section 9.2). Reducing ischaemia by optimising myocardial delivery, reducing myocardial oxygen consumption and restoring coronary blood flow will reduce ischaemic pain and limit myocardial tissue damage. The mainstay of analgesia in acute coronary syndrome is the restoration of adequate myocardial oxygenation as outlined above.

Inhaled oxygen does not reduce all-cause mortality in acute myocardial infarction and also does not reduce chest pain measured directly or by surrogate outcome of opioid requirements (Cabello 2016 **Level I** [Cochrane], 5 RCTs, n=1,172). The meta-analysis could not rule out a potentially harmful effect. These findings are confirmed by a subsequent meta-analysis, which showed that oxygen therapy does not reduce the risk of in-hospital or 30-day mortality, infarct size or chest pain in patients with suspected AMI (Sepehrvand 2018 **Level I** [PRISMA], 8 RCTs, n=7,998) (5 RCTs overlap). Current guidelines by the Australian and New Zealand Cardiology Society (Chew 2016 **GL**) and by NICE (NICE 2016b **GL**) state that the use of supplemental oxygen is not recommended unless hypoxia (oxygen saturation [SaO_2] <94%) is present. In acute coronary syndrome, hyperbaric oxygen therapy reduced time to relief of ischaemic pain, although insufficient evidence exists to recommend its routine use (Bennett 2011a **Level I**, 6 studies, n=665).

Nitroglycerine (glyceryl trinitrate) was effective in relieving acute ischaemic chest pain; however, the analgesic response did not predict the diagnosis of coronary artery disease (Henrikson 2003 **Level IV**, n=459). During exercise testing, nitroglycerine caused changes in the systemic and coronary circulation that combine to reduce myocardial oxygen demand and to increase supply, thereby attenuating exercise induced ischaemia (Asrress 2017 **Level IV EH**, n=40). The Australian and New Zealand Cardiology Society (Chew 2016 **GL**) and NICE (NICE 2016b **GL**) provide recommendations to use nitrates to alleviate symptoms including pain in acute coronary syndrome.

In patients with suspected acute coronary syndrome, IV morphine significantly reduced pain within 20 min of administration (Everts 1998 **Level IV**, n=2,988); morphine doses were low (average of 7 mg over 3 d) and 52% of patients required no morphine at all. Independent predictors of increased morphine requirements included suspicion or confirmation of infarction, ST-segment changes on the admission electrocardiogram, male sex and a history of angina or cardiac failure. After an initial dose of IV metoprolol, IV morphine provided better analgesia than further IV metoprolol (Everts 1999 **Level II**, n=265, JS 4). It was associated with better cardiovascular outcomes during acute hospital admission and later follow-up, vs a fentanyl/droperidol mixture administered early in the treatment of patients with acute ischaemic chest pain (Burduk 2000 **Level II**, n=112, JS 2). IV bolus doses of morphine and alfentanil were equally effective in relieving acute ischaemic chest pain but the onset of analgesia was faster with alfentanil (Silfvast 2001 **Level II**, n=40, JS 2). Morphine was similar to buprenorphine (Weiss 1988 **Level II**, n=76, JS 3) and pethidine (Nielsen 1984 **Level II**, n=275, JS 4) in terms of analgesia and adverse effects. IN fentanyl and IV morphine were equally effective in reducing acute cardiac chest pain during prehospital transfer (Rickard 2007 **Level II**, n=258, JS 3).

However regarding impact on antiplatelet therapies, IV fentanyl lowered plasma concentrations of ticagrelor and delayed its antiplatelet function in patients undergoing PCI (McEvoy 2018 **Level II**, n=70, JS 3). Similarly, morphine decreased clopidogrel plasma concentrations and its effect (Hobl 2014 **Level II EH**, n=24, JS 5) and decreased ticagrelor (Hobl 2016a **Level II EH**, n=24, JS 5) and prasugrel plasma concentrations without affecting their antiplatelet effects (Hobl 2016b **Level II EH**, n=12, JS 5). On the other hand, morphine co-administered with metoclopramide in

patients with unstable angina resulted in significantly higher ticagrelor mean plasma concentrations within the first one and two h following loading dose (Sikora 2018 **Level II**, n=32, JS 3). Overall, morphine administration before loading with P2Y12 inhibitors (prasugrel or ticagrelor) possibly decreases their efficacy with regard to platelet inhibition and reduces ticagrelor plasma concentrations without a negative effect on a composite endpoint of in-hospital mortality, stroke and reinfarction (Vaidya 2019 **Level III-2 SR**, 8 studies, n=752).

The Australian and New Zealand Cardiology Society (Chew 2016 **GL**) and NICE (NICE 2016b **GL**) recommend IV morphine (or other IV opioids eg fentanyl) for treatment of chest pain in acute coronary syndrome. However, a subsequent meta-analysis with high risk of bias identified concerns with the use of morphine in acute coronary syndrome (Duarte 2019 **Level III-2 SR** [PRISMA], 5 RCTs, n=2,237 & 12 studies, n=63,112). The pooled results show associations between morphine administration and an increased in-hospital mortality (RR 1.45; 95%CI 1.10 to 1.91), major adverse cardiovascular events (RR 1.21; 95%CI 1.02 to 1.45) and increased platelet reactivity. However, in two cohort studies, prehospital use of morphine vs non-use was not associated with worse in-hospital complications or 1 y survival (HR 0.69; 95%CI 0.35 to 1.37) (Puymirat 2016 **Level III-3**, n=2,438+1,726).

In patients with chest pain due to cocaine-induced acute coronary syndrome, the addition of IV diazepam or lorazepam to treatment with SL nitroglycerine wasbeneficial (Honderick 2003 **Level II**, n=36, JS 3) or made no difference to chest pain resolution or cardiac performance (Baumann 2000 **Level II**, n=43, JS 5).

N_2O in oxygen was effective in relieving acute ischaemic chest pain, with a significant reduction in betaendorphin levels (O'Leary 1987 **Level II**, n=12, JS 2).

NSAIDs may be useful in the treatment of acute pain in pericarditis (Schifferdecker 2003 **NR**).

KEY MESSAGES

1. The routine use of oxygen in normoxic patients with acute myocardial infarction does not reduce pain or mortality (**S**) (**Level I** [Cochrane].
2. Morphine is an effective and appropriate analgesic for acute cardiac pain, but may interfere with pharmacokinetics and pharmacodynamics of some platelet inhibitors (**Q**) (**Level II**).
3. Nitroglycerine is an effective and appropriate agent in the treatment of acute ischaemic chest pain (**S**) (**Level IV**).

The following tick box represents conclusions based on clinical experience and expert opinion:

☑ The mainstay of analgesia in acute coronary syndrome is the restoration of adequate myocardial oxygenation, nitroglycerine, beta blockers and strategies to improve coronary vascular perfusion (**U**).

8.6.4 | Acute pain associated with haematological disorders

8.6.4.1 | Sickle cell disease

Sickle cell disease (SCD) includes a group of inherited disorders of haemoglobin production. Haemoglobin S polymerises when deoxygenated, causing rigidity of the erythrocytes, blood hyperviscosity and occlusion of the microcirculation with resultant tissue ischaemia and infarction (Niscola 2009 **NR**).

Sickle cell disease is a systemic multiorgan disease that most commonly presents with painful vaso-occlusive crises (VOC), occurring either spontaneously or due to factors such as dehydration, infection, hypothermia and low oxygen tension. There is considerable interindividual variability in the frequency and severity of crises. Pain during an acute VOC is typically severe, in multiple sites and most frequently reported in the arm, shoulder, upper back, sternum, clavicle, chest and pelvis (McClish 2009 **Level IV**, n=308). Pain may last from hours to weeks. VOCs involving abdominal organs can mimic an acute surgical abdomen. Acute chest syndrome secondary to SCD may present with chest pain, cough, dyspnoea and fever (Niscola 2009 **NR**). An evidence-based approach and detailed consensus guidelines to the management of VOC in SCD are published (NICE 2012b **GL**; Glassberg 2011 **GL**; Mousa 2010 **GL**).

Treatment of pain

Biopsychosocial assessment and multidisciplinary pain management may be required when treating patients with frequent, painful sickle cell crises. Attendance to a multidisciplinary clinic specialising in the management of patients with SCD reduced hospitalisations and improved quality of life (Terry 2018 **Level III-3**, n=30). A pain management plan in the form of a letter, card or portfolio carried by the patient is recommended (Rees 2003 **GL**). The implementation of clinical practice guidelines (Morrissey 2009 **Level III-3**, n=263 [children]) or a clinical pathway (Ender 2014 **Level III-3**, n=68) for acute pain treatment in VOC leads to more timely and effective analgesia. An individualised pain management plan results in improved pain control, a higher level of patient satisfaction and reduced hospitalisations in children (Krishnamurti 2014 **Level III-2**). Underdosing of pain medication leads to a higher rate of ED visits for pain (Morrison 2018 **Level III-3**, n=100). Early achievement of maximum analgesia improved hospitalisation outcomes (Payne 2018 **Level III-3**, n=236).

NSAIDs

Single-dose parenteral ketorolac did not reduce opioid requirements in painful VOC (Hardwick 1999 **Level II**, n=41, JS 5; Wright 1992 **Level II**, n=24, JS 5). Patients who receive ketorolac for pain may be at risk of acute kidney injury and subsequently require longer periods of hospitalisation (Baddam 2017 **Level III-3**, n=197).

Opioids

Opioids are an integral component of treatment regimens for patients suffering from debilitating acute pain from SCD (Rodday 2018 **Level III-3**, n=449). Pain from a VOC is often undertreated in the hospital setting due to perceived opioid addiction and drug seeking behaviour despite a similar incidence of opioid addiction in the general population (Pack-Mabien 2001 **Level III-3**, n=77 [nurses]). Higher initial doses of opioids in the Emergency Department (ED) along with earlier introduction of oral opioids in a VOC results in significantly shorter hospital LOS and improved outcomes (Brandow 2015 **Level II**, n=204, JS 4). However, it is important to consider opioid tolerance in these patients as a large cohort study reported 40% of patients with SCD were taking regular opioid analgesics (Han 2018 **Level III-2**, n=3,882).

In the hospital setting, IV opioids are recommended for severe pain (NICE 2012b **GL**). When treating acute pain during a sickle cell crisis, IV opioid loading improved the analgesic efficacy of subsequent oral and PCA opioid therapy (Rees 2003 **GL**). PCA only was superior to background infusions only and PCA with background infusion as it reduced total opioid dose, total time on PCA , opioid-related adverse effects and hospital LOS (van Beers 2007 **Level II**, n=19, JS 2). Although IV opioid PCA is widely accepted in the management of acute pain in sickle cell disease, oral opioids are also effective. In one paediatric RCT, oral sustained-release morphine for acute pain was just as effective as a continuous IV morphine infusion (Jacobson 1997 **Level II**, n=56, JS 5). However, in children, the incidence of acute sickle chest syndrome (a severe complication in sickle cell crisis) and plasma levels of morphine and M6G, were significantly higher with oral morphine vs IV infusion (Kopecky 2004 **Level II**, n=50, JS 4). IN fentanyl was a suitable alternative in the ED to reduce time to initiation of opioid analgesic therapy, however did not reduce the need for IV opioid analgesia (Kelly 2018a **Level III-2**).

Care must be taken when prescribing opioids for the treatment of pain in SCD. In a review of 35 patients who died in hospital following an exacerbation of SCD, 9 received excessive opioids and "overdose" directly contributed to death in 5 patients (NCEPOD 2008 **Level IV**). Inadequate observations of sedation and respiratory rates after opioid administration was noted as a contributing factor and IM pethidine administration was prevalent.

Corticosteroids

Parenteral corticosteroids reduce the duration of severe pain and analgesia requirements and hospital LOS during VOC without major adverse effects (Dunlop 2006 **Level I** [Cochrane], 9 RCTs, n unspecified). In children, a short course of high dose IV methylprednisolone decreased the duration of severe pain associated with acute sickle cell crises, but patients who received methylprednisolone had more rebound attacks after therapy was discontinued (Griffin 1994 **Level II**, n=36, JS 5).

Ketamine

Low-dose ketamine improved analgesia and reduced opioid requirements (Puri 2019 **Level III-3**, n=4; Tawfic 2014 **Level IV**, n=9; Uprety 2014 **CR**). This approach is also suggested for paediatric patients (Neri 2013a **NR**); here a single sub-dissociative dose of ketamine given IV over 10 min was a suitable alternative to morphine for acute exacerbations of pain during a VOC (Lubega 2018 **Level II**, n=240, JS 5).

Dexmedetomidine

Dexmedetomidine may have a role in the management of recalcitrant pain due to VOC as infusions for up to 6 d duration reduced opioid requirements and pain scores without adverse haemodynamic effects (Sheehy 2015 **Level IV**, n=3).

Inhaled nitric oxide

Nitric oxide deficiency or defective nitric oxide-dependent mechanisms may underlie many of the processes leading to VOC. An early paediatric study suggested inhaled nitric oxide may be of benefit in painful acute VOC (Weiner 2003 **Level II**, n=25, JS 4); however in young adults admitted with VOC, there was no difference between inhaled nitric oxide vs nitrogen placebo in time to VOC resolution or LOS (Gladwin 2011 **Level II**, n=150**,** JS 5).

Inhaled nitrous oxide

Inhaled N_2O in 50% oxygen used for limited periods may provide analgesia for VOC pain in the primary-care setting (Rees 2003 **GL**).

Oxygen

Although oxygen supplementation is often prescribed during acute sickle cell crises, there was no difference in pain duration, number of pain sites or opioid consumption in patients treated with either air or oxygen (Robieux 1992 **Level II**, n=66, JS 2; Zipursky 1992 **Level II**, n=28, JS 3). However, nocturnal oxygen desaturation was associated with a significantly higher rate of painful VOC in children (Hargrave 2003 **Level IV**, n=95). Hyperbaric oxygen therapy was effective in reducing pain of VOC rapidly (Stirnemann 2012 **Level III-3**, n=9).

Rehydration

While commonly practiced, there is no evidence to support fluid replacement therapy to reduce pain associated with sickle cell crises (Okomo 2017 **Level I** [Cochrane], 0 RCTs, n=0).

Epidural analgesia

In severe crises, where pain is unresponsive to pharmacological measures, epidural analgesia has been used effectively in nine paediatric patients (Yaster 1994 **Level IV**, n=9). Epidural analgesia has also been described in a pregnant patient with poorly responsive pain from VOC (Winder 2011 **CR**).

Intravenous lidocaine

IV lidocaine Infusions (1 mg/kg/h to 1.3 mg/kg/h) for treating pain of SCD achieved more than 20% pain reduction in 53% of patients, while opioid requirements were reduced by 32% (Nguyen 2015 **Level IV**, n=11). These findings are confirmed in a subsequent study (Puri 2019 **Level III-3**, n=4).

Magnesium Sulphate

IV magnesium or oral magnesium therapy has been shown to have no effect on reducing pain during painful crises in SCD or hospital LOS (Than 2019 **Level I** [Cochrane], 5 RCTs, n=386).

Non-pharmacological management

Yoga in children admitted with VOC has demonstrated significant reduction in pain scores (Moody 2017 **Level II,** n=73, JS 1).

Based on limited evidence, there may be an effect of CBT on pain in SCD (1 RCT, n=59) (Anie 2012 **Level I** [Cochrane], 5 RCTs, n=260). In young adults, CBT reduced the affective (not sensory) component of pain (MD -0.99; 95% CI -1.62 to -0.36) but with no benefit for coping strategies (1 RCT, n=59).

Prevention of painful sickle cell crises

Hydroxyurea acts to increase fetal haemoglobin levels. It has demonstrated efficacy in reducing the frequency of acute crises, the severity of pain during an acute crisis, the need for blood transfusions and the incidence of acute chest syndrome (Nevitt 2017 **Level I** [Cochrane], 8 RCTs, n=899). Zinc supplementation reduces the incidence of painful sickle cell crises (Nagalla 2012 **Level I** [Cochrane], 3 studies, n=524). Niprisan (an anti-sickling agent) reduces the frequency of crises with severe pain (Wambebe 2001 **Level II**, n=82, JS 4) while the evidence for piracetam is insufficient to support its use (Al Hajeri 2016 **Level I** [Cochrane], 3 RCTs, n=169).

8.6.4.2 | Haemophilia

Deficiency of Factor VIII (haemophilia A) and deficiency of Factor IX (haemophilia B) are inherited disorders of coagulation characterised by spontaneous and post-traumatic haemorrhages, the frequency and severity of which are proportional to the degree of clotting factor deficiency. Bleeding into joints and muscle is common, although other sites such as abdominal organs may also be involved. In haemophilic arthropathy, the most frequent sites of pain are the ankle joints (45%), knee joints (39%), spine (14%) and elbow joints (7%) (Wallny

2001 **Level IV**, n=71). Pain is significantly associated with age and severity of disease (Rambod 2016 **Level III-3**, n=154). Patients with haemophilia presenting with acute pain have a background of chronic pain in 29% of cases (Witkop 2017 **Level III-3**, n=764 [haemophilia]). Patients with haemophilia may also have pain syndromes associated with HIV/AIDS (see Section 8.6.8). Recurrent acute pain may have a significant adverse impact on mood, mobility and QoL in haemophilia patients; biopsychosocial assessment and treatment should be considered (Wallny 2001 **Level IV**, n=71).

The following five features should be considered in the treatment of acute pain resulting from haemarthrosis; haematologic treatment, short-term rest of the involved joint, cryotherapy, joint aspiration and analgesic medication (Rodriguez-Merchan 2018 **NR**). Many haemophilia patients use Factor VIII to decrease pain associated with a bleeding episode (Wallny 2001 **Level IV**, n=71). Higher-dose Factor VIII replacement reduced the number of patients with restricted joint movement after an acute haemarthrosis (Aronstam 1983 **Level II**, n=114, JS 4). Despite this, approximately 30% of patients experience ongoing pain after the infusion of Factors VIII or IX (Rodriguez-Merchan 2018 **NR**). Joint aspiration may reduce pain and improve joint function (Baker 1992 **NR**).

Although there is no good evidence available, simple analgesics, opioids, cryotherapy and bandaging have been used in treating acute pain associated with haemophilia. In a Europe-wide survey, the preferred first-line drug was paracetamol for children and paracetamol or NSAIDs for adults (Holstein 2012 **Level IV**, n=5,103 [adults] & n=1,678 [children]). There are no data on NSAID use in acute haemarthrosis; coxibs may be of benefit due to a lack of platelet inhibitory effects (see Section 4.2.2.2). Pregabalin and gabapentin are increasingly used as part of a multimodal analgesia approach despite lack of evidence to support their use in this clinical setting (Powell 2014 **Level IV**). IM analgesics should be avoided due to the risk of bleeding.

8.6.4.3 | The porphyrias

The acute porphyrias are a group of inherited disorders of haem biosynthesis. The most common autosomal dominant forms are acute intermittent porphyria, variegate porphyria and hereditary coproporphyria. The disorder of haem biosynthesis leads to accumulation of neurotoxic aminolaevulinic acid and porphyrin metabolites, which can result in peripheral, visceral and autonomic neuropathies (eg clinical features might include motor weakness, abdominal pain and tachycardia) as well as CNS toxicity (neuropsychiatric symptoms, seizures, brainstem and pituitary dysfunction); some patients may have a cutaneous photosensitivity (Visser 2008 **NR**).

Pain management in acute porphyria is based on treatment of the disease, including resuscitation and supportive care, ceasing "triggers", the early administration of haematin (Herrick 1989 **Level II**, n=12, JS 4) and possibly high-dose IV dextrose or cimetidine administration ("*disease modifying agents*") (Rogers 1997 **NR**).

Specific evidence for pain management in acute porphyria is limited. Analgesia is based largely on the use of IV and (later) oral opioids (Anderson 2005 **NR**; Herrick 2005 **NR**). Analgesics that lower seizure threshold such as pethidine (Deeg 1990 **CR**) or tramadol and others (such as TCAs) should be avoided in acute porphyria because of increased seizure risk.

The safety of NSAIDs or coxibs in acute porphyria has not been established; paracetamol, buscopan (for colic) or inhaled N_2O in oxygen are considered safe (Anderson 2005 **NR**; Stoelting 1993 **NR**).

There may be a place for low-dose IV ketamine or regional analgesia, although the safety of these approaches has not been established in acute porphyria. Ketamine does not induce aminolaevulinic acid synthetase in rats (Harrison 1985 **BS**) and has been used for anaesthesia in porphyria patients without apparent problems (Capouet 1987 **CR**). However, one case report

noted increased porphyrin levels in a patient after induction with ketamine (Kanbak 1997 **CR**). A combined spinal epidural technique has been described in patients with porphyria undergoing Caesarean section with epidural analgesia continued in the postoperative period minimising IV opioid requirements (Horvat 2015 **Level IV**, n=2). As metoclopramide is contraindicated and the safety of $5HT_3$ antagonists is as yet unclear, droperidol has been suggested as the antiemetic of choice in acute porphyria (Anderson 2005 **NR**).

KEY MESSAGES

1. Parenteral corticosteroids reduce the duration of severe pain, analgesia requirements and hospital length of stay, without major adverse effects, during vaso-occlusive crises in sickle cell disease (**U**) (**Level I** [Cochrane Review]).
2. There is no evidence that fluid replacement therapy (**S**) or intravenous or oral magnesium reduces pain associated with vaso-occlusive crises in sickle cell disease (**N**) (**Level I** [Cochrane Review]).
3. Hydroxyurea decreases the frequency of vaso-occlusive crises, life-threatening complications and transfusion requirements in sickle cell disease (**S**) (**Level I** [Cochrane Review]).
4. Zinc reduces the incidence of painful vaso-occlusive crises in sickle cell disease (**U**) (**Level I** [Cochrane Review]).
5. Intravenous opioid loading optimises analgesia in the early stages of a vaso-occlusive crisis in sickle cell disease; effective analgesia may be continued with intravenous opioid therapy, optimally as PCA, or as oral opioids (**S**) (**Level II**).
6. Single-dose ketorolac does not reduce opioid requirements in vaso-occlusive crisis in sickle cell disease (**N**) (**Level II**), but may increase the risk of acute kidney injury (**N**) (**Level III-3**).
7. Oxygen supplementation does not decrease pain during a vaso-occlusive crisis in sickle cell disease (**U**) (**Level II**), but hyperbaric oxygen may be effective (**U**) (**Level III-3**).
8. Intravenous ketamine and intravenous lidocaine reduced pain intensity and opioid requirements in vaso-occlusive crisis in sickle cell disease (**N**) (**Level IV**).

8.6.5 | Acute headache

Headaches are a common cause of acute pain. Headaches may be primary or secondary. There are many causes of acute headache, some of which involve structures other than the head (eg the neck). Before treating acute headache, it is vital to exclude serious cranial pathologies such as tumour, infection, cerebrovascular abnormalities, acute glaucoma and temporal arteritis (Silberstein 2000 **GL**; Steiner 2002 **NR**).

The most frequent causes of acute primary headache are episodic tension type headaches (TTH) and migraine (Headache Classification Committee 2018 **GL**). Less common primary headaches are trigeminal autonomic cephalalgias (episodic cluster headache, episodic paroxysmal hemicrania and Short lasting Unilateral Neuralgiform headache attacks with Conjunctival injection and Tearing [SUNCT]) or "secondary headaches", such as acute post-traumatic headache, postdural puncture headache (PDPH), headache attributed to substance use or its withdrawal and cervicogenic headache.

Comprehensive guidelines for the evaluation and treatment of acute headaches including migraine have been promulgated (Diener 2019 **GL**; Pringsheim 2016 **GL**; Marmura 2015 **GL**; Beithon 2013 **GL**; Worthington 2013 **GL**) including for children and adolescents (see Section 10.9.3).

8.6.5.1 | Tension-type headache

TTH may be episodic (frequent or infrequent) or chronic in nature. The lifetime prevalence of TTH in the general population is between 30 and 78%. Episodic TTH is usually bilateral and is often described as mild to moderate "pressing" or "tight" pain (sometimes with pericranial tenderness), not worsened by movement and not associated with nausea or vomiting. Photophobia or phonophobia may occasionally be present but not both (Headache Classification Committee 2018 **GL**).

The symptoms and pathogenesis of TTH may overlap with migraine and particularly with chronic daily headache, medication overuse headache and cervicogenic headache (NICE 2012a **GL**). Psychological, physical and environmental factors are important in TTH and should be addressed during assessment and treatment (Bougea 2013 **Level II**, n=35, JS 3; NICE 2012a **GL**; Bendtsen 2010 **GL**).

TTHs are frequently self-limiting with total duration under 12 h in many cases. Therefore, the efficacy of various treatments should be assessed against the background of natural history. The acute adverse effects and the propensity for analgesic medications to transform intermittent headaches to a chronic daily pattern must be considered in relation to choice of agents (Barbanti 2014 **NR**). Evidence-based guidelines for TTH treatment are published (Bendtsen 2010 **GL**).

Treatment

The NNTs for patients with TTH being pain free at 2 h vs placebo are similar for all oral analgesics in the range of 8.7 to 9.8 for paracetamol 1,000 mg (5 RCTs, n=1,387), ibuprofen 400 mg (3 RCTs, n=826) and ketoprofen 25 mg (2 RCTs, n=285) (Moore 2014 **Level I** [PRISMA], 55 RCTs, n=12,143).

In a meta-analysis of RCTs including a paracetamol arm, the NNT for 1000 mg vs placebo for being pain free at 2 h is higher at 22 (95%CI 15 to 40) (8 RCTs, n=5,890) and the NNT for less frequent rescue medication was 7.8 (95%CI 6.0 to 11) (6 RCTs, n=1,856) (Stephens 2016 **Level I** [Cochrane], 23 RCTs, n=8,079) (possible 22 RCTs overlap). Based on limited data, the efficacy of paracetamol 500 mg to 650 mg was not superior to placebo, and paracetamol 1000 mg was not different from either ketoprofen 25 mg or ibuprofen 400 mg.

A single dose of aspirin between 500 mg and 1000 mg provides some benefit in terms of less frequent use of rescue medication (NNT 6.0; 95%CI 4.1 to 12) and more participants satisfied

with treatment vs placebo (NNT 5.7; 95%CI 3.7 to 12) (Derry 2017a **Level I** [Cochrane], 5 RCTs, n=1,812) (3 RCTs overlap with Stephens 2016). The quality of the evidence is low and was downgraded because of the small number of studies and events, and because the most important measures of efficacy were not reported.

A paracetamol/aspirin/caffeine combination is superior to paracetamol alone (Diener 2014 **Level I**, 4 RCTs, n=1,900) (3 RCTs overlap with Stephens 2016).

Parenteral medications are more effective in TTH than oral ones; IV metoclopramide has an NNT of 2 and IV metamizole and IV chlorpromazine have an NNT of 4 (Weinman 2014 **Level I** [PRISMA], 8 RCTs, n=486).

IV lidocaine in refractory chronic daily headache was associated with reduced pain intensity over an 8.5 d treatment period from 7.9/10 to 3.9/10, with low incidence of adverse effects (Rosen 2009 **Level IV**, n=68).

IV magnesium was ineffective in treating acute TTH in the ED (Frank 2004 **Level II**, n=42, JS 5).

Acupuncture for TTH (at least 6 sessions) over 3 mth provides clinically relevant improvement in pain vs standard care (2 RCTs, n=1,472), but only minimal clinical improvement vs sham treatment (5 RCTs, n=703) (Linde 2016, **Level I** [Cochrane], 12 RCTs, n=2,349). See also Section 7.3.

8.6.5.2 | Migraine

Migraine is common, with a prevalence of 6 to 8% in males and 12 to 14% in females (Evers 2009 **GL**). Migraine headache is usually unilateral and is often severe, disabling and often worsened by movement. Either nausea/vomiting or photophobia/phonophobia must be present and 20% of migraineurs experience an aura.

Most migraines are successfully managed by the patient and their family doctor, with up to 57% of patients not seeking medical attention for significant attacks (Mitchell 1998 **Level IV**). However, a small number of patients fail to respond and present for treatment at EDs; approximately 80% of patients have tried their usual medications, including simple analgesics or triptans, before presentation.

Evidence-based recommendations for the treatment of migraine in ED settings are published (Orr 2015 **GL**). For treatment of migraine in the ED, see Section 8.11.2.6 below.

Treatment

The management of migraine includes avoidance of triggers such as sleep deprivation, stress, sensory stimulation such as bright lights, exercise, alcohol, foods etc. Management of associated symptoms, particularly nausea and vomiting is important, as is the prevention of acute recurrence.

Environmental modification (quiet dark room) and particularly sleep is integral to successful migraine treatment (Steiner 2007 **NR**).

Analgesia outcomes in migraine trials are usually listed as the proportion of patients who either:

- are pain free at 2 h;
- report significant pain relief at 2 h (no headache or mild headache);
- report a sustained response over 24 h (migraine stays away for at least 1 d).

Many trials fail to document associated outcomes such as improvement in nausea, vomiting or disability (Moore 2003 **NR**).

Strategies for the use of migraine medications

There are three major strategies for the use of analgesics in the treatment of acute migraine (Lipton 2000 **Level II**, n=930, JS 5):

- *Stratified care* — where for each attack, the severity and disability caused by the migraine is assessed and the patient uses simple analgesia for a mild attack and a triptan for a severe attack;
- *Step-up during an attack* — for each attack a simple analgesic is always tried first but the patient "steps up" to a triptan if there is no relief in 2 h;
- *Step-up across attacks* — a patient tries simple analgesics exclusively for the first three attacks; if there has been no benefit from simple analgesia over the trial period then a triptan is used for all further attacks.

The US Headache Consortium (Silberstein 2000 **GL**) and European Federation of Neurological Societies (Evers 2009 **GL**) have recommended a "stratified care" approach; Canadian guidelines recommend this as the most effective and cost-effective approach but also describe the two other approaches as suitable in selected patients (Worthington 2013 **GL**).

Placebo

A significant placebo effect has been observed in migraine trials, particularly if the treatment is administered by injection (Macedo 2006 **Level I** [QUOROM], 98 RCTs, n=35,481) and this may be more relevant in children and adolescents (Evers 2009 **Level I**, 27 RCTs, n unspecified). Accordingly, the beneficial effect of specific analgesic mechanisms may be underestimated by prominent placebo responses (Lund 2014 **Level II**, n=48, JS 5).

Simple analgesics

Patients who experience mild migraine-related headache and disability may be effectively treated with simple analgesics, either alone or in combination with an antiemetic. European consensus guidelines recommend the routine, early use of metoclopramide in adults (or domperidone in children) (Evers 2009 **GL**).

Paracetamol 1,000 mg is superior to placebo in the treatment of migraine but has a lower efficacy than other analgesics (NNT 12 for pain free at 2 h) (Derry 2013a **Level I** [Cochrane], 11 RCTs, n=2,942). The efficacy of the combination with 10 mg metoclopramide was comparable to oral sumatriptan 100 mg. Serious adverse effects occurred only with sumatriptan (NNH 32).

Aspirin 1,000 mg is of similar efficacy to sumatriptan 50 or 100 mg orally (NNT 8.1 for pain free at 2 h) with slightly fewer adverse effects (Kirthi 2013 **Level I** [Cochrane], 13 RCTs, n=4,222); adding 10 mg metoclopramide improves nausea and vomiting.

Ibuprofen is also effective here (NNT 7.2 for pain free at 2 h [400 mg]; NNT 9.7 [200 mg]) and soluble preparations provide faster onset of effect (Rabbie 2013 **Level I** [Cochrane], 9 RCTs, n=4,473). Adverse effects are similar to placebo.

Diclofenac has similar efficacy (NNT 6.2 for pain free at 2 h) and low rates of adverse effects for this indication (Derry 2013b **Level I** [Cochrane], 5 RCTs, n-=1,356).

Dipyrone is also effective for the treatment of migraine and episodic TTHs (Ramacciotti 2007 **Level I** [Cochrane], 4 RCTs, n=636).

Parecoxib IV was similarly effective to oral rizatriptan and SC sumatriptan in an RCT with no placebo arm (Muller 2011 **Level II**, n=57, JS 2).

In a network meta-analysis of NSAIDs and triptans for the treatment of migraine, triptans (in particular eletriptan and rizatriptan) have superior efficacy to NSAIDs; ibuprofen is slightly less effective, but has the best tolerability of all medications analysed (Xu 2016 **Level I** [NMA], 88 RCTs, n=9,372). The combination naproxen/sumatriptan in particular has increased efficacy and better

tolerability than sumatriptan on its own; this is also confirmed by another by systematic review (Law 2016 **Level I** [Cochrane], 13 RCTs, n=9,334) (4 RCTs overlap).

For paediatric information, see Section 10.9.3.1.

Triptans

All triptans are more effective in the treatment of acute migraine than placebo (Thorlund 2014 **Level I**, 74 RCTs, n unspecified), particularly in the presence of severe pain and disability where simple analgesia has failed to provide adequate relief in the past. This must be placed in the context of a high placebo response rate and interindividual differences in response to the different triptans, with recommendations for patients to trial a variety of drugs and doses until the most suitable regimen is found (Worthington 2013 **GL**; Pringsheim 2014 **NR**).

In a review of trials with an eletriptan arm, 30–40% of migraine sufferers do not respond to triptan treatments (Diener 2008 **Level I**, 10 RCTs, n=8,473). The three clinical variables that predict poor therapeutic response are: severe pain, photophobia or phonophobia, and nausea; while time of dosing following onset of headache has no effect on 2-h pain-free response.

The route of administration of a triptan may affect its efficacy, speed of onset and tolerability. For sumatriptan, a comparison of different routes of administration showed that SC administration (in comparison to oral, IN and rectal administration) has the highest efficacy and speed of onset but also the highest rate of adverse effects (Derry 2014b **Level I** [Cochrane], 4 Cochrane Reviews, n=52,236). Most effective doses for each route of administration are PO 100 mg, SC 6 mg, IN 20 mg and rectal 25 mg.

Zolmitriptan is effective in acute migraine with oral doses of 2.5 and 5 mg being comparable in efficacy to oral sumatriptan 50 mg (Bird 2014 **Level I** [Cochrane], 25 RCTs, n=20,162).

As most RCTs have compared a single triptan with placebo, it is difficult to determine the relative efficacy of different triptans. A multiple treatment comparison meta-analysis combining available head-to-head and placebo-controlled trials has been published (Thorlund 2014 **Level I** [NMA], 74 RCTs, n unspecified). It shows eletriptan followed by rizatriptan, zolmitriptan and sumatriptan having the highest efficacy at 2 h and eletriptan followed by zolmitriptan and sumatriptan at 24 h.

The combination of sumatriptan/naproxen provides a greater headache reduction in the acute treatment of migraine headaches than the same dose of either agent alone, but the difference in efficacy is small in comparison to sumatriptan alone (Law 2016 **Level I** [Cochrane], 13 RCTs, n=9,334). The combination and sumatriptan alone causes more adverse effects than naproxen (3 RCTs) or placebo (10 RCTs).

The most frequent adverse effects associated with triptans are dizziness, fatigue, sleepiness, nausea, chest tightness and paraesthesiae (Johnston 2010 **NR**). Triptans may cause an increase in light touch-evoked allodynia and thermal sensitivity (Linde 2004 **Level III-2 EH**, n=24). Concerns about an increase in cardiovascular events with the use of triptans could not be confirmed (Roberto 2015 **Level III-2 SR**, 4 studies, n≈131,000); the pooled OR of serious ischaemic events was 0.86 (95%CI 0.52 to 1.43).

Frequent use of triptans may lead to triptan-induced rebound headaches (medication-overuse headache), often described as chronic migraine (Tepper 2012 **NR**). This risk increases with increasing days of triptan use, in particular with use on more than 10 d/mth (Lipton 2013 **Level IV**, n=11,249).

Calcitonin Gene Related Peptide inhibitors

Calcitonin gene-related peptide (CGRP) inhibitors (humanised monoclonal antibodies or small molecule CGRP receptor antagonists) are useful in migraine management (Edvinsson 2018 **NR**). Currently, only two such monoclonal antibodies are registered in Australia, fremanezumab

(Silberstein 2017 **Level II**, n=1,130, JS 5) and erenumab (Jain 2018 **NR**) as preventive treatment, the latter also in New Zealand. As well, the CGRP pathway may be engaged for emergency management of acute headache utilising small molecule CGRP receptor antagonists (gepants) and serotonin 5-HT1F receptor agonists (ditans) may have a major role, but are currently only in Phase III trials and still awaiting registration (Moreno-Ajona 2019 **NR**).

Ergot derivatives

Ergotamine and dihydroergotamine preparations have been used for many years to treat migraine, although they have been superseded by the triptans, as they are less effective and have more adverse effects (Tfelt-Hansen 2008 **NR**). In particular, oral triptans are superior to oral ergotamine, because the bioavailability of oral ergotamine is extremely low (<1%).

IN dihydroergotamine (2 mg) has a NNT of 2.5 for 2 h headache response in migraine (Oldman 2002 **Level I**, 1 RCT [ergotamine], n=203). As a single agent, parenteral dihydroergotamine may not be as effective as other migraine treatments (Colman 2005 **Level I**, 3 RCTs [ergotamine alone], n=423). However, when dihydroergotamine is combined with an antiemetic such as metoclopramide, the efficacy of this combination is similar to valproate, ketorolac and opioids (Colman 2005 **Level I**, 8 RCTs [ergotamine/antiemetic], n=384).

Importantly, in contrast to the data for triptans, ergot derivatives cause an increased rate of ischaemic events (OR 2.51; 95%CI 1.10 to 5.71) (Roberto 2015 **Level III-2 SR**, 4 studies, n≈131,000).

Antiemetics and major tranquillisers

Parenteral metoclopramide, as monotherapy or in combination, is effective for the treatment of headache and nausea in acute migraine (Orr 2015 **Level I** [PRISMA], 8 RCTs [metoclopramide], n unspecified; Colman 2004 **Level I**, 13 RCTs, n=728) (2 RCTs overlap).

Parenteral droperidol is also effective in this indication; the minimum effective dose is 2.5 mg IM or IV (Thomas 2015 **Level I**, 5 RCTS, n=685).

Phenothiazines such as chlorpromazine (2 RCTs) and prochlorperazine (3 RCTs) vs placebo provide better headache relief (OR 15.02; 95%CI 7.57 to 29.82) (4 RCTs, n=303) and achieve more clinical success (OR 8.92; 95%CI 4.08 to 19.51) (5 RCTs, n=349) (Kelly 2009 **Level I**, 13 RCTs, n=917). Phenothiazines achieve also more clinical success than metoclopramide (OR 2.25; 95%CI 1.29 to 3.92) (4 RCTs, n=271) and combinations of other active compounds (OR 2.04; 95%CI 1.25 to 3.31) (10 RCTs, n=569), but not better headache relief. The overall clinical success rate of phenothiazines is high (78%; 95%CI 74 to 82). Butyrophenones achieve similar benefits in an ED setting, however with significant adverse effects (Leong 2011 **Level I**, 6 RCTs, n=574). IV prochlorperazine was more effective than IV promethazine for initial ED treatment of migraine (Callan 2008 **Level II**, n=70, JS 4). Buccal prochlorperazine was superior to an oral ergotamine/caffeine combination or placebo (Sharma 2002 **Level II**, n=45, JS 5).

A combination of indomethacin/prochlorperazine/caffeine (Di Monda 2003 **Level II**, n=112, JS 3) and a combination of prochlorperazine/diphenhydramine were more effective than SC sumatriptan (Thomas 2015 **Level II**, n=68, JS 5).

Conventional and atypical opioids

Opioids are of limited benefit in the treatment of migraine and should not be used (Casucci 2013 **NR**; Tepper 2012 **NR**). IV hydromorphone vs IV prochlorperazine/diphenhydramine was less effective for the treatment of acute migraine; the RCT was halted when the primary outcome was achieved by 60% of the prochlorperazine/diphenhydramine arm vs 31 % of the hydromorphone arm (Friedman 2017b **Level II**, n=127, JS 5).

Opioid use for migraine was associated with more severe headache-related disability, symptomology, comorbidities (depression, anxiety and cardiovascular disease and events), and

greater healthcare utilisation than no use (Buse 2012 **Level III-2**, n=5,796). Among current opioid users for migraine, 16.6% met criteria for probable dependence. Opioids induce migraine progression with a dose-dependent effect beyond approximately 8 d exposure/mth (Tepper 2012 **NR**; Bigal 2009 **NR**).

Despite these disadvantages and recommendations, opioids continue to be used in more than half of all patients attending EDs in the USA for migraine (Friedman 2014a **Level IV**). However, when other migraine treatments are contraindicated, use of opioids may have to be considered as a last resort (Dodson 2018 **NR**; Finocchi 2013 **NR**). Among patients requiring readmission for primary headache, those given opioids initially (22.8%) had significantly longer ED LOS (median 5.0 h vs. 3.9 h) and higher rates of return ED visits within 7 d (7.6% vs. 3.0%) vs those receiving non-opioids in a univariate analysis (McCarthy 2015 **Level III-3**, n=574); the association with longer length of stay remained significant in multivariable regression.

Overall, the most commonly trialled opioids in migraine (pethidine, tramadol and nalbuphine) are more effective in reducing migraine pain than placebo (Kelley 2012 **Level I**, 23 RCTs, n unspecified). Morphine without an antiemetic was no more effective than placebo (Nicolodi 1996 **Level III-1**). Butorphanol was effective when given by the IN or IM route (Hoffert 1995 **Level II**, n=157, JS 3; Elenbaas 1991 **Level III-1**). There is inadequate evidence to recommend parenteral tramadol in the treatment of acute migraine (Marmura 2015 **GL**).

Pethidine in particular is not recommended for the treatment of migraine, due to lack of evidence of efficacy, neurotoxicity of its metabolite norpethidine (epileptogenic) and the high risk of developing dependency. Pethidine is less effective than dihydroergotamine or antiemetics for the treatment of migraine; however, its efficacy is similar to ketorolac (Friedman 2008 **Level I**, 11 RCTs, n=625).

Ketamine

SC ketamine 0.08 mg/kg vs placebo was more effective in treating acute migraine pain (Nicolodi 1995 **Level II**, n=17, JS 3). In contrast, IV ketamine 0.2 mg/kg was not superior to placebo in acute migraine (Etchison 2018 **Level II**, n=34, JS 5). IV ketamine 0.3 mg/kg/IV ondansetron 4 mg vs IV prochlorperazine 10 mg/IV diphenhydramine 25 mg achieved inferior pain relief at 45 and 60 min (MD 20/100; 95%CI 2.8 to 37.2) and lower patient satisfaction at 24 h in primary headache (Zitek 2018 **Level II**, n=54, JS 5). Similarly, IN ketamine was not superior to standard treatment (metoclopramide/diphenhydramine) in the treatment of primary headache (Benish 2019 **Level II**, n=53, JS 4).

Other drug treatments

Parenteral dexamethasone reduces the rate of moderate or severe headache recurrence after 24 to 72 h (RR 0.71; 95%CI 0.59 to 0.86) (Orr 2016 **Level I**, 68 RCTs, n unspecified; Huang 2013 **Level I**, 8 RCTs, n=905) (1 RCT overlap). There are no differences in efficacy between oral and parenteral steroids. IM methylprednisolone acetate, a long-acting steroid, was not superior to IM dexamethasone in this setting (Latev 2019 **Level II**, n=220, JS 4).

The efficacy of lidocaine in the treatment of migraine is unclear. Analgesia provided by IV lidocaine was similar to dihydroergotamine but not as effective as chlorpromazine (Bell 1990 **Level II**, n=76, JS 2) and, in another trial, no better than placebo (Reutens 1991 **Level II**, n=25, JS 3). IN lidocaine was more effective than placebo (Maizels 1996 **Level II**, n=91, JS 4). IN lidocaine 10 to 20 mg repeated at variable intervals (4 RCTs using Barre method) vs placebo in primary headache (mainly acute migraine) shows some benefit only in poor quality RCTs (4 RCTs), but not in fair quality RCTs (2 RCTs); overall there is no effect on recurrence or repeat ED visits, but more adverse events and lower patient satisfaction (Dagenais 2018 **Level I** [PRISMA], 6 RCTs, n=685).

No firm conclusions can be drawn on the effect of IV magnesium in acute migraine due to the heterogeneity of the studies included in a systematic review; however, there may be some

effects on pain after >1 h, aura duration and need for rescue analgesia (Miller 2019 **Level I** [PRISMA], 7 RCTs, n=545).

IV sodium valproate is ineffective in treating acute migraine (Frazee 2008 **Level IV SR**, 3 RCTs & 4 studies, n=243). This was contradicted by a subsequent case series (Shahien 2011 **Level IV**, n=36), but confirmed in an RCT, which found sodium valproate inferior to ketorolac and metoclopramide (Friedman 2014b **Level II**, n=330, JS 5).

Propofol in 30–40 mg IV bolus doses was more effective than sumatriptan 6 mg SC at 30 min with less need for antiemetics and lower rate of recurrence (Moshtaghion 2015 **Level II**, n=91, JS 5). Propofol in 10 mg IV bolus doses (max 80 mg) was also superior to dexamethasone IV 0.15 mg/kg (max 16 mg) (Soleimanpour 2012a **Level II**, n=90, JS 5). The efficacy was also confirmed in a number of case series (Ward 2013 **Level IV**, n=15; Mosier 2013 **Level IV**, n=4; Soleimanpour 2012b **Level IV**, n=8), including one in paediatric patients (Sheridan 2012 **Level IV**). A susbequent paediatric RCT demonstrated similar pain reduction (51% vs 59) with low dose bolus IV propofol 0.25 mg/kg (1–5 doses) with IV fluid bolus vs standard IV combination therapy with less rebound headache at 24 h (7% vs 25) (Sheridan 2018 **Level II**, n=74, JS 2). Notably, guidelines give a weak recommendation against the use of propofol (Orr 2015 **GL**).

There is no evidence for use of caffeine alone in treatment of tension type headache or migraine. However, combinations of caffeine with simple analgesics improve their analgesic efficacy and tolerability in a number of painful conditions including primary headache and migraine (Derry 2014a **Level I** [Cochrane], 20 RCTs, n=7,238) (2 RCTs overlap with Stephens 2016). However, discontinuation of regular caffeine intake improves subsequent acute migraine management over the next 35 d (Lee 2016b **Level III-2**, n=108).

Pramipexole has been linked with a significant reduction in migraine, particularly the morning headaches in patients with concomitant restless legs syndrome (Suzuki 2013 **Level IV**).

SC Octreotide 100 mcg vs placebo had no analgesic effect in acute migraine (Levy 2005 **Level II**, n=51, JS 5).

Sublingual ginger (*Zingiber officinale*)/feverfew (*Tanacetum parthenium*) extract was more effective than placebo in aborting acute migraine when used in early mild headache (Cady 2011 **Level II**, n=60, JS 5).

Hyperbaric oxygen therapy

Hyperbaric oxygen therapy was effective in relieving migraine headaches vs sham therapy (RR 6.2; 95%CI 2.4 to 16) (3 RCTs, n=58), but there was no effect on nausea and vomiting, rescue analgesic requirements or migraine prevention (Bennett 2015 **Level I** [Cochrane], 11 RCTs, n=209).

Intravenous fluids

IV fluid hydration is a common component of emergency department migraine therapy (Jones 2017 **Level IV**, n=1,251). However, in a post hoc analysis of data collected from 4 ED-based migraine RCTs, IV fluids/metoclopramide vs IV metoclopramide alone did not improve acute migraine outcomes (Balbin 2016 **Level III-2**, n=570) similar to the findings of a subsequent RCT (Jones 2019a **Level II**, n=49, JS 5).

TENS

TENS use in migraine reduces monthly affected days (SMD: -0.48; 95%CI -0.73 to - 0.23) and pharmacological treatment intake (SMD -0.78; 95%CI -1.14 to - 0.42) (Tao 2018 **Level I** [PRISMA], 4 RCTs, n=161). Similarly, TENS applied to the supraorbital nerve over 12 wk reduced days with migraine and days using rescue medications among patients with refractory migraine and not responding to topiramate (Vikelis 2017 **Level IV**, n=35).

One 60-min session of TENS treatment reduced pain intensity of acute migraine attacks at one and 24 h after treatment by 50%, and two thirds of the patients did not require rescue pain medication at 24 h (Chou 2017 **Level IV**, n=30).

See also Section 7.2.

Acupuncture

Similarly, acupuncture reduces migraine frequency at 3 mth vs no treatment or routine care (4 RCTs, n=2,199), but only minor improvements were seen vs sham treatments (14 RCTs, n=1,825) (Linde 2016 **Level I** [Cochrane], 22 RCTs, n=4,985). Acupuncture reported fewer adverse (5 RCTs, n=931) vs pharmacological prophylaxis and acupuncture was slightly superior at 3 mth but not 6 mth (3 RCTs, n=739). A subsequent RCT also found a prophylactic effect of electroacupuncture (5 sessions per wk for 12 wk) on migraine (Li 2017a **Level II**, n=61, JS 3).

See also Section 7.3.

8.6.5.3 | Menstruation-related migraine

Management of acute migraine during menstruation does not differ from treatment at other phases of the menstrual cycle. Prophylaxis is based on modifying hormone fluctuations, usually by intake of oestrodiol-containing oral contraceptive preparations (MacGregor 2010 **NR**).

Sumatriptan, zolmitriptan, rizatriptan and mefenamic acid are more effective than placebo for acute treatment (Pringsheim 2008 **Level I**, 10 RCTs [acute abortive treatment], n=3,255). Eletriptan is as effective to achieve 2 h pain relief in females in and outside of the menstrual phase but with higher rate of recurrence and less sustained suppression of nausea during menstruation (Bhambri 2014 **Level I**, 5 RCTs, n=3,217).

8.8.5.4 | Migraine in pregnancy and breastfeeding

Migraine can occur for the first time during pregnancy and pre-existing migraine may worsen, particularly during the first trimester or may improve in later pregnancy with the patient becoming headache-free (MacGregor 2014 **NR**). Approximately 60–70% of migraineurs improve during pregnancy (frequency, duration) with a sharp rise in the incidence after delivery (Kvisvik 2011 **Level IV**, n=2,126). Breastfeeding is protective (David 2014 **NR**).

Migraine in pregnancy is a risk factor for gestational hypertension and preeclampsia (OR 2.3; 95%CI 2.1 to 2.5) and is also associated with ischaemic stroke (OR 30.7; 95%CI 11.1 to 22.5), myocardial infarction (OR 4.9; 95%CI 1.7 to 14.2), deep vein thrombosis (OR 2.4; 95%CI 1.3 to 4.2) and thrombophilia (OR 3.6; 95%CI 2.1 to 6.1) (Bushnell 2009 **Level III-2**, n=33,956).

The major concerns in the management of migraine in pregnancy are the effects of medication and the disease itself on the fetus. Medication use should ideally be limited. Paracetamol, metoclopramide, caffeine, codeine (or perhaps other opioids) can be used during pregnancy, while aspirin, NSAIDs or coxibs should not be used during the third trimester (David 2014 **NR**).

There is contradictory information on the safety of triptan therapy during pregnancy. While there are human data suggesting potential teratogenicity (David 2014 **NR**), a large Scandinavian population study has shown no significant risk of congenital malformation but a small risk of uterine atony and haemorrhage with use during the second and third trimesters (Nezvalová-Henriksen 2013 **Level III-2**, n=181,124).

Ergot alkaloids during pregnancy may disrupt fetoplacental blood supply and cause uterine contractions, which can result in low birth weight and preterm birth (Banhidy 2007 **Level IV**, n=33,851). Birth defects and stillbirths due to vascular spasm have been reported and it is recommended that ergotamines be avoided in pregnancy (Acs 2006 **NR**). However,

dihydroergotamine has significantly fewer vasoconstrictor and uterotonic effects vs other ergotamines: dihydroergotamine use in pregnancy did not increase risk for major malformations but increased the risk of prematurity and resulted in a risk of spontaneous abortion similar to that of triptan and NSAID use (Berard 2012 **Level III-2**, n=59,707).

Low-dose acetylsalicylic acid, ibuprofen, sumatriptan, paracetamol, caffeine and metoclopramide are considered safe for the treatment of acute migraine in breastfeeding mothers (Davanzo 2014 **Level IV SR**; David 2014 **NR**; Hutchinson 2013 **NR**). Acute migraine medications that should be avoided include high-dose acetylicsalicylic acid, dihydroergotamine, ergotamine and opioids.

See also Section 9.1 and Tables 9.1 and 9.2.

8.6.5.5 | Cluster headache and other trigeminal autonomic cephalalgias

Cluster headache is a rare primary headache disorder, presenting almost exclusively in males with recurrent, acute episodes of brief, severe, unilateral, periorbital pain associated with autonomic phenomena such as conjunctival injection and tearing.

Guidelines for the treatment of cluster headache attacks propose as first-line treatments SC sumatriptan 6 mg, IN zolmitriptan 5 mg and 10 mg, and 100% oxygen 6–12 L/min (Francis 2010 **GL**).

Oxygen

High-flow oxygen is recommended as a first-line treatment (Francis 2010 **GL**); this is supported by a meta-analysis with limited quality of evidence, which suggests that more than 75% of cluster headaches were likely to respond to non-hyperbaric oxygen therapy (3 RCTs), but possibly not superior to ergotamine (Bennett 2015 **Level I** [Cochrane], 11 RCTs, n=209). One RCT not included in this meta-analysis found high-flow oxygen (12 L/min) superior vs high-flow air in cluster headache with regard to the outcome pain free at 15 min (78%; 95%CI 71 to 85 [150 attacks] vs 20%; 95%CI 14 to 26 [148 attacks]) (Cohen 2009 **Level II**, n=109, JS 5). High-flow oxygen treatment had a superior effect to high-flow room air in all types of headaches in an ED setting (Ozkurt 2012 **Level II**, n=204, JS 5). In a survey of patients with cluster headache, oxygen was rated highly effective with few complications (Pearson 2019 **Level IV**, n=2,193). The presence of nausea/vomiting and "*restlessness*" was predictive of a poor response to oxygen (Schurks 2007 **Level IV**, n=256).

Hyperbaric oxygen is no more effective than sham hyperbaric treatment in reducing the frequency or duration of cluster headaches (1 RCT) (Bennett 2015 **Level I** [Cochrane], 11 RCTs, n=209).

Triptans

Triptans are effective to treat cluster headaches; SC sumatriptan 6 mg is superior to IN zolmitriptan 5 mg or 10 mg for rapid response at 15 min, while oral routes of administration are not appropriate for this condition (Law 2013 **Level I** [Cochrane], 6 RCTs, n=1,180).

Calcitonin Gene-Related Peptide Inhibitors

Humanised monoclonal antibodies that selectively bind to calcitonin gene-related peptide (CGRP) are effective in rapidly reducing the frequency and intensity of acute headaches in individuals with episodic cluster headache and are awaiting registration (Ashina 2017 **NR**).

Local anaesthetic blocks

Sphenopalatine ganglion local anaesthetic block has moderate evidence support for the treatment of acute cluster headaches (1 RCT, 6 studies, 2 CR) (Ho 2017 **Level IV SR**, 88 studies, n unspecified).

Occipital nerve blocks have been shown to be effective in multiple case series and two RCTs but the mechanism is uncertain and the role of additional steroids unclear (Leroux 2013a **Level IV SR**, 12 studies, n≈334).

Neuromodulation

Sphenopalatine ganglion stimulation (1 RCT, 2 studies) and radiofrequency ablation (9 studies) as well as bilateral occipital nerve stimulation has been used successfully as a prophylaxis (Ho 2017 **Level IV SR**, 88 studies, n unspecified; Blumenfeld 2013 **GL**; Pedersen 2013 **NR**).

Non-invasive vagus nerve stimulation is a well-tolerated and effective acute treatment for episodic cluster headache (1 RCT, n=112), but less effective for chronic cluster headache (1 RCT, n=113) (de Coo 2019 **Level I**, 2 RCTs, n=225).

Other treatments

The efficacy of cannabis in cluster headaches is limited and should not be recommended (Leroux 2013b **Level IV**, n=139).

In attacks of high frequency, short courses of high-dose oral corticosteroids, dihydroergotamine and occipital nerve blocks with local anaesthetic and steroids are recommended with limited evidence (Becker 2013 **NR**).

8.6.5.6 | Paroxysmal hemicrania and SUNCT

Paroxysmal hemicrania and SUNCT are rarer forms of trigeminal autonomic cephalalgia. Paroxysmal hemicrania is similar to cluster headache except that it is more common in females, episodes are shorter, but more frequent, and diagnosis requires the complete abolition of symptoms with indomethacin, which is the suggested treatment of choice (Headache Classification Committee 2018 **GL**; May 2006 **GL**).

There is no high-level evidence to guide the treatment of SUNCT (Arca 2018 **NR**). However consensus guidelines and limited data suggest that IV lidocaine for acute treatment and lamotrigine, topiramate and gabapentin may be useful prophylactics (May 2006 **GL**; Weng 2018 **NR**). Occipital nerve stimulation (Lambru 2014 **Level IV**, n=9; Young 2012 **Level IV**) and non-invasive vagal stimulation may be a potential effective treatment for SUNCT and hemicrania continua (Tso 2017 **Level IV**, n=15).

8.6.5.7 | Postdural puncture headache

Postdural puncture headache (PDPH), usually following spinal anaesthesia, inadvertent dural puncture with an epidural needle, diagnostic or therapeutic lumbar puncture or neurosurgery, occurs with an incidence of approximately 0.7 to 50% (Bezov 2010a **NR**; Bezov 2010b **NR**). Up to 85% of cases improve spontaneously within 6 wk.

Risk factors are younger age, female gender, low BMI, history of prior PDPH and history of chronic headache. Children who undergo lumbar puncture may present a special group (Janssens 2003 **NR**) (see Section 10.6.3.5).

Spinal needle size, type and lumbar puncture technique

Data in the anaesthesiology and neurology literature indicate that needle calibre, bevel type and lumbar puncture technique affects the incidence of PDPH. The incidence of DPH following spinal anaesthesia is reduced by using a smaller gauge (-g) needle (26-g or less: NNT 3) or a needle with a noncutting bevel (eg pencil point: NNT 27) (Halpern 1994 **Level I**, 16 RCTs, n=3,593).

Subsequent studies support these findings for noncutting bevel needles (Schmittner 2011 **Level II**, n=363, JS 3) but could not find a difference between 23- and 25-g needles in patients >60 y (Kim 2011b **Level II**, n=53, JS 5) or between cutting 22- and 25-g needles in children aged 4 to 15 y (Crock 2014 **Level II**, n=93 [341 punctures], JS 5).

The incidence of PDPH is also reduced by orientating the cutting bevel parallel to the spinal sagittal plane (dural fibres) (Richman 2006 **Level I**, 5 RCTs, n=521) or by replacing the stylette prior to withdrawing a noncutting needle (Strupp 1998 **Level II**, n=600, JS 3); these techniques presumably reduce CSF loss. However, a subsequent study could not confirm the benefit of replacing the stylette in a 25-g Quincke needle (Sinikoglu 2013 **Level II**, n=630, JS 4).

Similarly for diagnostic lumbar punctures, noncutting (pencil point) needles significantly reduced the incidence of PDPH vs cutting (Quincke) needles (Lavi 2006 **Level II**, n=58, JS 4; Strupp 2001 **Level II**, n=306, JS 5), leading to a recommendation to use noncutting needles routinely in neurology practice (Arendt 2009 **NR**).

During epidural catheter insertion in labour, the incidence of accidental dural puncture was not reduced when using an 18-g epidural Sprotte (pencil point) needle vs a 17-g epidural Tuohy needle (Morley-Forster 2006 **Level II**, n=1,077, JS 5). However, the incidence of PDPH was significantly lower with the epidural Sprotte needle.

Epidural blood patch

The use of an epidural blood patch (EBP) for the treatment of PDPH has been recommended as first-line therapy (Bezov 2010a **NR**), especially in obstetric patients (Thew 2008 **NR**) and following inadvertent dural puncture with an epidural needle (Gaiser 2006 **NR**). However, the risks of the intervention must be carefully weighed with the benefits (Suescun 2016 **NR**).

EBP is more effective than conservative treatment (OR 0.18; 95%CI 0.04 to 0.76) (1 RCT) and a sham procedure (OR 0.04; 95%CI 0.00 to 0.39) (1 RCT) (Boonmak 2010 **Level I** [Cochrane], 9 RCTs, n=379).

The most effective blood volume for EBP administration is not known. Data vary significantly from 7.5 to 30 mL. There was no difference in the severity of PDPH at 3 d in patients who received either a 7.5 or 15 mL EBP, except for a lower incidence of nerve-root irritation during injection with the lower volume (Chen 2007 **Level II**, n=33, JS 3). EBP volumes in the range of 10 to 20 mL were effective in relieving PDPH in 98% of patients following spinal or epidural anaesthesia (Wu 1994 **Level IV**, n=159). There was no difference in the frequency of PDPH resolution (approximately 91%) with either 10 or 15 mL blood volumes randomised according to patient height (Taivainen 1993 **Level III-1**, n=81). Significant relief of PDPH was obtained in 93% of patients, who received a mean EBP volume of 23 (± 5) mL (Safa-Tisseront 2001 **Level IV**, n=504). With use of volumes of 15, 20 and 30 mL, permanent or partial relief of headache was achieved in 61%, 73%, and 67% respectively and complete relief in 10%, 32%, and 26% without a difference in backache (Paech 2011 **Level II**, n=121, JS 5); the authors recommended 20 mL as the "optimal" target volume.

EBP is sometimes performed prophylactically to prevent PDPH after an inadvertent dural puncture (eg by an epidural needle) (Bezov 2010a **NR**). However, there is conflicting evidence of benefit with prophylactic EBP administration; there is improvement vs no treatment (OR 0.11; 95%CI 0.02 to 0.64) (1 RCT), conservative treatment (OR 0.06; 95%CI 0.03 to 0.14) (2 RCTs) and epidural saline patch (OR 0.16; 95%CI 0.04 to 0.55) (1 RCT), but not vs a sham procedure (1 RCT) (Boonmak 2010 **Level I** [Cochrane], 9 RCTs, n=379). The authors of this Cochrane Review do not recommend prophylactic EBP due to concerns about inconclusive findings in small studies. However, a subsequent RCT showed benefit with reduction of incidence of PDPH from 79.6 to 18.3% by a prophylactic blood patch (Stein 2014 **Level II**, n=60, JS 3).

The use of autologous blood patch may be contraindicated in patients with cancer, leukaemia, coagulopathy or infection, including HIV, although there is debate for some of these in the literature (Tom 1992 **Level IV**, n=252).

Bed rest and hydration

There is no evidence of benefit with bed rest or fluid supplementation in the treatment or prevention of PDPH (Arevalo-Rodriguez 2013 **Level I** [Cochrane], 23 RCTs, n=2,477). However, patients with PDPH may have difficulty in mobilising and the headache subsides with bed rest.

Other treatments

PDPH is successfully prevented with morphine, cosyntropin and aminophylline, especially in patients with high risk of PDPH, while dexamethasone increased PDPH and there were inconclusive data for fentanyl, caffeine and indomethacin (Basurto Ona 2013b **Level I** [Cochrane], 10 RCTs, n=1,611). These findings are based on studies of limited quality with small sample size.

PDPH responds to caffeine (reducing persistence and further treatment requirements) and gabapentin, hydrocortisone and theophylline (reducing pain severity), while there is insufficient evidence for sumatriptan, adrenocorticotropic hormone, pregabalin and cosyntropin (Basurto Ona 2015 **Level I** [Cochrane], 13 RCTs, n=479). These findings are based on studies of limited quality with small sample size and limited generalisability.

A number of other studies and treatments were not considered in the above Cochrane reviews:

- Gabapentin (Vahabi 2014 **Level II**, n=120, JS 3) reduced the intensity and duration of PDPH; preoperative administration before spinal anaesthesia for elective Caesarean section did not reduce PDPH incidence, but did reduce severity (Nofal 2014 **Level II**, n=88, JS 5);
- IT administration of 5 mL normal saline reduced the overall incidence of PDPH from 24 to 2% (Faridi Tazeh-Kand 2014 **Level II**, n=100, JS 4);
- Topical sphenopalatine ganglion block has been used successfully in PDPH (Kent 2016 **Level IV**, n=3) and was superior to EBP with no complications (Cohen 2018 **Level III-3**, n=81; Dubey 2018 **Level IV**, n=11).

Low CSF pressure headache may result from disruption of the dural integrity, often in cervical or thoracic levels with persisting headaches of identical character to PDPH. Management requires careful evaluation of the potential site of CSF leak. Extradural spinal fluid may be apparent on careful MRI and a clue to the site of leak may come from the clinical history. Management is similar to that of PDPH (Mokri 2013 **NR**; Mokri 2003 **NR**).

8.6.5.8 | Other headaches

There is little evidence to guide the treatment of acute cervicogenic headache, post-traumatic headache (Minen 2019 Level I, 7 RCTs, n=1,108; Larsen 2019 Level IV SR, 7 studies, n=121 [adults] & 618 [children]) or acute headache attributed to substance use or its withdrawal, although general principles of evaluation of headache and management of acute pain must apply (Silberstein 2000 GL).

Giant cell arteritis

The treatment of giant cell arteritis is with high-dose steroids but there are no evidence-based guidelines and the steroid dose and route of administration are empirical. Because of the potential devastating effect on vision in this common vasculitic disorder, high-dose steroid is recommended: IV methylprednisolone 15 mg/kg/d showed more rapid and sustained remission vs oral prednisone 40 mg/d (Mazlumzadeh 2006 **Level II**, n=27, JS 5).

Tocilizumab, a humanized anti-interleukin-6 receptor (IL-6R) monoclonal antibody has shown efficacy in the induction and maintenance of remission of giant cell arteritis (Schirmer 2018 **Level I**, 2 RCTs, n=281).

Headache attributed to substance withdrawal (severe analgesic "rebound" headache)

Patients may present with severe acute-on-chronic headache due to the overuse and/or withdrawal of antimigrainal (triptans or ergot alkaloids) or other analgesics. Inpatient treatment is often required to manage this chronic pain condition and may include cessation of analgesics, IV hydration, steroids, NSAIDs, antiemetics and benzodiazepines (Kristoffersen 2014 **NR**). Medication withdrawal is usually recommended as a first step in treatment with use of preventive medications, but current evidence does not provide definite guidance (Chiang 2016 **Level VI SR**, 68 studies, n unspecified). Limiting acute headache treatment to no more than 10 or 15 d/mth (depending on medication type) is commonly recommended to prevent headache frequency progression; analgesics including opioids may carry a higher risk of medication overuse headache than triptans and ergotamines (Thorlund 2016 **Level IV SR**, 29 studies, n=3,092).

KEY MESSAGES

Tension-type headache

1. Acupuncture may be effective in the treatment of tension-type headache (**S**) (**Level I** [Cochrane Review]).
2. Simple analgesics such as paracetamol or NSAIDs, either alone or combined, are effective in the treatment of episodic tension-type headache (**S**) (**Level I** [PRISMA]).
3. Metoclopramide, metamizole and chlorpromazine as parenteral treatments of tension-type headache have high efficacy (**U**) (**Level I** [PRISMA]).
4. The combination of caffeine/aspirin/paracetamol is superior to paracetamol in the treatment of episodic tension-type headache (**U**) (**Level I**).

Migraine

5. Paracetamol is effective in the treatment of migraine, however less than other analgesics; the efficacy is increased when combined with metoclopramide (**U**) (**Level I** [Cochrane Review]).
6. Aspirin, ibuprofen, diclofenac and dipyrone are effective in the treatment of migraine; soluble preparations of ibuprofen provide a faster onset (**U**) (**Level I** [Cochrane Review]).
7. For sumatriptan, subcutaneous administration achieves the fastest onset of effect and highest efficacy (**U**) (**Level I** [Cochrane Review]).
8. The combination naproxen/sumatriptan has increased efficacy and better tolerability than sumatriptan on its own (**N**) (**Level I** [Cochrane Review]).
9. The addition of caffeine to simple analgesics improves their analgesic efficacy and tolerability in acute migraine (**N**) (**Level I** [Cochrane Review]).
10. Hyperbaric oxygen therapy is effective in controlling pain in migraine, but no other symptoms and outcomes (**U**) (**Level I** [Cochrane Review]).

11. A significant placebo effect occurs in migraine treatment (**N**) (**Level I** [QUOROM]), leading to an underestimation of treatment effects of analgesic medications (**N**) (**Level II**).
12. Parenteral antiemetics, metoclopramide (**S**) (**Level I** [PRISMA]) and droperidol (**U**) (**Level I**) are effective in the treatment of migraine.
13. Phenothiazines and butyrophenones (at the expense of more adverse effects) are effective in the treatment of migraine, in particular in the emergency department (**S**) (**Level I**).
14. All triptans are more effective than placebo in the treatment of severe migraine (**S**) (**Level I**), however 30 to 40% of patients may not respond (**N**) (**Level I**).
15. Triptans and mefenamic acid are effective in treatment of menstruation-related migraine (**U**) (**Level I**).
16. Some opioids are more effective than placebo in the treatment of acute migraine (**U**) (**Level I**), but their use in this setting is associated with significant adverse effects and poor outcomes (**S**) (**Level III-2**).
17. Pethidine is less effective than most other migraine treatments and should not be used (**U**) (**Level I**).
18. Intravenous magnesium may have some analgesic effect compared to placebo in migraine (**Q**) (**Level I** [PRISMA]).
19. A "*stratified care strategy*" is effective in treating migraine (**U**) (**Level II**).
20. Ergotamine derivatives, but not triptans, increase the rate of severe myocardial ischaemic events (**U**) (**Level III-2 SR**).
21. Migraine in pregnancy is a risk factor for gestational hypertension, preeclampsia and cardiovascular complications (**U**) (**Level III-2**).

Cluster headache

22. Parenteral triptans (sumatriptan or zolmitriptan) or high-flow oxygen therapy are effective treatments for cluster headache attacks (**S**) (**Level I** [Cochrane Review]).
23. Sphenopalatine ganglion local anaesthetic block has moderate evidence support for the treatment of acute cluster headaches (**N**) (**Level IV SR**).

Postdural puncture headache

24. There is no evidence that bed rest or fluid supplementation are beneficial in the treatment and prevention of postdural puncture headache (**S**) (**Level I** [Cochrane Review]).
25. Epidural blood patch administration is more effective than conservative treatment or a sham procedure in the treatment of postdural puncture headache (**S**) (**Level I** [Cochrane Review]).
26. Risk of postdural puncture headache is reduced with preventive use of morphine, cosyntropin or aminophylline, especially in patients at high risk; preventive dexamethasone use increases risk of postdural puncture headache (**N**) (**Level I** [Cochrane Review]).

27. Caffeine, gabapentin, hydrocortisone or theophylline are effective treatments for postdural puncture headache (**S**) (**Level I** [Cochrane Review]).

28. The incidence of postdural puncture headache is reduced by using smaller-gauge spinal or non-cutting bevel needles or by orientating the cutting bevel parallel to the spinal sagittal plane (**U**) (**Level I**).

Medication overuse headache

29. Frequent use (>8–10 days/month) of paracetamol, NSAIDs and opioids for recurrent acute headache (more so than triptans and ergot derivatives) may lead to medication overuse headache; weaning and use of preventive medication are recommended management approaches (**S**) (**Level IV SR**).

The following tick boxes represent conclusions based on clinical experience and expert opinion:

☑ Opioids should be used with extreme caution in the treatment of headache; pethidine should not be used at all (**S**).

8.6.6 | Acute pain associated with neurological disorders

Pain associated with neurological disorders is usually neuropathic in nature, although nociceptive pain due to problems such as muscle spasms may also occur. Neuropathic pain may be acute or chronic and is due to a lesion or disease of the somatosensory system, either in the periphery or centrally (Jensen 2011 **NR**).

Treatment of acute neuropathic pain is based largely on evidence from trials for the treatment of a variety of chronic neuropathic pain disorders (see also Section 8.1.4 above). Effective treatments for neuropathic pain include TCAs, anticonvulsants, membrane stabilisers, NMDA-receptor antagonists, opioids or tramadol (see Sections 4.3, 4.4 and 4.7 to 4.9).

Associated psychosocial problems and physical disabilities must also be managed within a multidisciplinary framework.

8.6.6.1 | Multiple sclerosis

Chronic pain is experienced by 26 to 86% of patients with multiple sclerosis (Truini 2013 **NR**). These data are confirmed by a systematic review, which finds a prevalence of 63% (95%CI 55 to 70) (Foley 2013 **Level IV SR**, 17 studies, n=5,319).

A mechanism-based classification distinguishes the following types of pain related to multiple sclerosis (Truini 2013 **NR**):

- trigeminal neuralgia and Lhermitte's phenomenon (paroxysmal neuropathic pain directly related to the MS disease processes due to ectopic impulse generation along primary afferents) (Solaro 2013 **NR**);
- ongoing extremity pain (deafferentation pain secondary to lesion in the spinothalamocortical pathways);
- spasticity is the most common cause of pain in MS patients with 90% of patients with hypotonia experiencing pain: painful tonic spasms and spasticity pain (mixed pains secondary to lesions in the central motor pathways but mediated by muscle nociceptors);
- pain associated with optic neuritis (nerve trunk pain originating from Nervi nervorum);
- musculoskeletal pains (nociceptive pain arising from postural abnormalities secondary to motor disorders);
- migraine (nociceptive pain favoured by predisposing factors or secondary to midbrain lesions);
- treatment-induced pains.

The prevalence of headache (43%; 95%CI 33 to 52%), neuropathic extremity pain (26%; 95%CI 7 to 53%), back pain (20%; 95%CI 13 to 28%), painful spasms (15%; 95%CI 8.5 to 23%), Lhermitte's sign (16%; 95%CI 10 to 25%) and trigeminal neuralgia (3.8%; 95%CI 2 to 6%) is reported (Foley 2013 **Level IV SR**, 17 studies, n=5,319). Treatment approaches need to be targeted to the wide variety of different pain types occurring in multiple sclerosis balanced with adverse-effect profiles.

A systematic review of pharmacological management of pain in multiple sclerosis identified only two treatment approaches amenable to meta-analysis (anticonvulsants and cannabinoids) (Jawahar 2013 **Level I** [PRISMA], 15 RCTS, n unspecified). Various anticonvulsants have a pooled effect size (Cohen's d) of -1.88 (95%CI -3.13 to -0.64) on reducing pain intensity (Jawahar 2013 **Level I** [PRISMA], 4 RCTs [anticonvulsants], n=78). The pooled effect size (Cohen's d) for cannabinoids demonstrates no effect on pain intensity (0.08; 95%CI -0.74 to 0.89) (3 RCTs [cannabinoids], n=565). In contrast, a subsequent systematic review found moderate- to high-grade evidence supporting use of nabiximols to achieve modest reductions in pain as adjunctive therapy in MS-

related pain (Stockings 2018 **Level IV SR** [PRISMA], 3 RCTs and 13 studies [multiple sclerosis], n=9,958) (all 3 RCTs overlap). Adverse events occurred in 81.2% of cannabinoid-treated patients vs 66.2% of placebo treated patients (OR 2.33; 95%CI 1.88 to 2.89) (NNH 6; 95%CI 5 to 8) (10 RCTs, n=1,959); severe adverse events resulting in study withdrawal occurred in 15.8% vs 4.6% (OR 3.47; 95%CI 2.64 to 4.56) (NNH 40; 95%CI 35 to 49) (19 RCTs, n=3,265).

In spasticity due to multiple sclerosis, the treatment difference vs placebo is -0.32/10 (95%CI -0.61 to -0.04) for nabiximols (Sativex®; containing THC:cannabidiol = 1:1), with high numbers of subjects experiencing at least one adverse effect (Wade 2010 **Level I**, 3 RCTs, n=666). Overall, cannabinoids may be effective for pain and spasticity control in MS, but the effects may be relatively modest with issues of statistical significance versus clinical relevance and the lack of reporting of negative results in sponsored trials (Nielsen 2018 **Level III-3 SR**, 11 SRs of 10 RCTs and 22 studies, unspecified) (see also Section 4.11).

In MS patients, duloxetine (30 to 120 mg/d) vs placebo improved pain at wk 6 (-1.83/10 vs. -1.07/10) (Vollmer 2014 **Level II**, n=239, JS 5). Similarly, duloxetine (30 mg, then 60 mg) reduced average daily pain at 6 wk by 39% (± 29) vs placebo 10% (± 18.8) (Brown 2015 **Level II**, n=38, JS 4).

Microvascular decompression in MS related trigeminal neuralgia has shown limited effectiveness in comparison to non-MS trigeminal neuralgia; the relapse rate is up to 51% at 2 years and is complicated by sensory dysaesthesia in 11% of patients (Ferraro 2020 **Level III-2**, n=298).

Gamma knife radiosurgery may be effective compared with other interventions (Helis 2019 **Level IV**, n=74). The duration of pain relief has not been fully evaluated, although a 12 y follow-up indicated a clinically useful pain modification lasting up to 5 y with benefit from repeat Gamma knife treatment.

Overall, there is insufficient evidence to support medical or surgical therapy for MS related trigeminal neuralgia (Zakrzewska 2018 **Level IV SR**, 10 studies [medical management], 26 studies [surgical management], n unspecified). No study included long-term follow-up and all studies evaluated were of low quality.

Transcutaneous spinal direct current stimulation (ts-DCS) reduced MS-related central neuropathic pain in a pilot trial (Berra 2019 **Level II**, n=33, JS 3). Other techniques of neuromodulation may have a role in the management of MS-related pain (Abboud 2017 **NR**).

Exercise vs passive controls improves pain in patients with MS, however, the evidence is based on poor quality RCTs with high risk of bias (Demaneuf 2019 **Level I**, 10 RCTs, n=389). There is low level evidence from studies with no large-scale trials of yoga and other postural treatments in reducing acute MS pain (Aboud 2019 **NR**).

Mindfulness reduces fatigue, but not pain in multiple sclerosis (Simpson 2019b **Level I**, 10 RCTs, n=678).

8.6.6.2 | Parkinson's disease

Pain is a common distressing symptom in Parkinson's disease; between 30 and 50% of patients with Parkinson's disease have pain (Beiske 2009 **Level IV**, n=176; Fil 2013 **NR**). Pain may occur independently of Parkinson's disease, related to underlying musculoskeletal disorders (89%), radicular and peripheral neuropathic pain (31.5%) and dystonic pain (15.1%); however, Parkinsonian central pain resulting from disordered nociceptive processing has the lowest prevalence (4.1%), but highest severity, is poorly characterized and is difficult to describe not only by patients but also by neurologists (Chaudhuri 2015 **Level III-2**, n=261; Ozturk 2016 **Level IV**, n=113).

Optimization of dopaminergic therapies should always be the first step in the management of Parkinson's disease pain (Jost 2019 **NR**; Skogar 2016 **NR**). Medications used to treat pain include

specific Parkinson-related agents, mainly dopaminergic, as well as opioid and non-opioid analgesics, anticonvulsants, antidepressants particularly duloxetine, cannabinoids and botulinum toxin injections for dystonia related pain (Rukavina 2019 **NR**; Sophie 2012 **NR**; Ford 2010 **NR**). Currently, therapy is prescribed without necessarily considering special requirements of Parkinson patients and drug interactions. In many cases, pain is resistant to standard therapies: physiotherapy is essential in the management of Parkinson's disease related pain.

Tapentadol improved pain related to Parkinson's disease, but also anxiety, depression and quality of life (Freo 2018 **Level IV**, n=21).

Subthalamic Nucleus deep brain stimulation (DBS) is often used to improve motor function in advanced Parkinson's disease, but improvement in pain with this treatment has been observed, too. Severity of pain (from mean pain score 6.2/10 (SD 2.5) to 3.5/10 (SD 2.2) and number of body parts affected by pain (from 21 to 8) decreased over an 8 y follow-up after surgery; however, new pain developed in 75% of patients (Jung 2015 **Level IV**, n=24). In a comparison of Subthalamic Nucleus vs Globus Pallidus Internus DBS, both techniques provided similar analgesia (from 4.4/10 [± 1.67] before surgery to 1.1/10 [± 1.39] 4 mth after surgery) (Gong 2020 **Level III-3**, n=64).

8.6.6.3 | Central post-stroke pain

Central pain develops in 8 to 35% of stroke patients (Kumar 2009 **NR**). It is not only a consequence of thalamic stroke but also lateral medullar and parietal cortical stroke or ischaemic events affecting the spinothalamic or trigeminothalamic pathways (Flaster 2013 **NR**; Akyuz 2016 **NR**). The majority of the cases are intractable and unresponsive to analgesic treatment. Electrical stimulation such as deep brain stimulation and repetitive transcranial magnetic stimulation seems to be effective in certain cases: anticonvulsants, antidepressant, an opioid antagonist, acupuncture and transcutaneous magnetic stimulation all have minimal effect on pain (Mulla 2015 **Level I** [PRISMA], 8 RCTs, n=459).

IV lidocaine (Attal 2000 **Level II**, n=6 [poststroke], JS 5) and IV propofol in subhypnotic doses (Canavero 2004 **Level II**, n=44, JS 5) may provide short-term relief in central poststroke pain. Amitriptyline was more effective than placebo and carbamazepine (which were equivalent) (Leijon 1989 **Level II**, n=15, JS 4). Lamotrigine was moderately effective and well tolerated in central poststroke pain (Vestergaard 2001 **Level II**, n=30, JS 5). Pregabalin in poststroke pain did not result in significant pain relief at the endpoint of the trial but there was a profound placebo response and pain relief at other time points and secondary outcomes were in favour of pregabalin (Kim 2011a **Level II**, n=219, JS 5). The SSRI fluvoxamine showed benefit in poststroke pain (Shimodozono 2002 **Level IV**, n=31).

Non-invasive brain stimulation by two approaches (direct current stimulation [DCS] and repetitive transcranial magnetic stimulation) reduces intensity of post-stroke pain and also experimental pain sensitivity, however, based on low-quality evidence (Ramger 2019 **Level III-3 SR**, 1 RCT & 5 studies, n=111). Motor cortex stimulation specifically reduces refractory post-stroke pain by 35.2% (Mo 2019 **Level IV SR**, 12 studies, n=198).

Acupuncture may reduce post-stroke pain (MD −1.59; 95%CI −1.86 to −1.32]) (25 RCTs), however with low certainty due to poor study quality (Liu 2019b **Level I**, 38 RCTs, n=3,184).

On the basis of the limited data available, a practical guideline recommends trials of amitriptyline, lamotrigine, gabapentin or pregabalin or a combination of these to treat central poststroke pain with consideration of non-invasive brain stimulation for refractory patients (Kim 2014b **GL**). However, the available evidence suggests limited beneficial effect of any of the therapies that have been evaluated in RCTs and clinical practice guidelines are mainly empirical.

8.6.6.4 | Trigeminal neuralgia

Exacerbations of trigeminal neuralgia can present as acute neuropathic pain.

For acute exacerbations of trigeminal neuralgia, local anaesthetic (mainly lidocaine [administered ophthalmic, nasal or oral mucosal, trigger point injection, IV infusion, nerve block), anticonvulsants (phenytoin or IV fosphenytoin) and SC or IN sumatriptan reduce pain by 50% within 24 h (Moore 2019 **Level IV SR**, 4 RCTs & 14 studies, n unspecified); there is very limited evidence supporting IV magnesium sulphate and botulinum toxin by trigger point injection.

Sumatriptan, IN and IV lidocaine and botulinum toxin provide better analgesia vs placebo and ophthalmic proparacaine based on pooled estimates in a Bayesian mixed treatment comparison network meta-analysis (Sridharan 2017 **Level I** [NMA], 11 RCTs, n unspecified); the evidence is very low quality except for botulinum toxin. Pulsed and combined continuous and pulsed radiofrequency thermocoagulation may be the most effective invasive therapies.

Topiramate is as effective as carbamazepine at 1 mth after treatment commencement and slightly more effective at the 2 mth endpoint in trigeminal neuralgia (RR 1.20; 95%CI 1.04 to 1.39) (Wang 2011 **Level I**, 6 RCTs, n=354). All included RCTs were of poor methodological quality; this is also an issue for carbamazepine trials, which show probable effectiveness over placebo (Wiffen 2014 **Level I** [Cochrane], 10 RCTs, n=480). There is insufficient evidence to support or refute the use of gabapentin for trigeminal neuropathic pain (Ta 2019 **Level I** [PRISMA}, 2 RCTs, n=95). There is insufficient evidence to support the use of any nonantiepileptic medications (tizanidine, pimozide, tocainide) in trigeminal neuralgia (Zhang 2013c **Level I** [Cochrane] 3 RCTs [systemic medications], n=92). However, IV infusion of magnesium/lignocaine once/wk for 3 wk resulted in reduction of pain in patients with trigeminal neuralgia not responding to previous treatments (Arai 2013a **Level IV**, n=9). Duloxetine has been shown to have an effect in trigeminal neuralgia (Anand 2011 **Level IV**, n=15).

Topical ophthalmic anaesthesia has been studied with varying results. Proparacaine hydrochloride 0.5% was not superior to placebo (Zhang 2013c **Level I** [Cochrane] 1 RCT [proparacaine hydrochloride], n=47). Amethocaine 1% eye drops reduced paroxysms of pain in trigeminal neuralgia (Brill 2010 **Level IV**, n=40). Intraoral lignocaine 8% was also effective (Niki 2014 **Level II**, n=24, JS 4).

Motor cortex stimulation (MCS) has a positive effect on refractory pain and the total percentage improvement was 46.5% in trigeminal neuropathic pain (Mo 2019 **Level IV SR**, 12 studies, n=198).

Published guidelines mainly focus on chronic pain medications but do not identify sufficient evidence for the effectiveness of any IV medication in the acute setting (Cruccu 2008 **GL**). The same guidelines rate carbamazepine as effective and oxcarbazepine as probably effective and suggest that baclofen, oxcarbazepine, gabapentin, lamotrigine, tizanidine and pimozide may be considered, if the first-line medications are ineffective. An updated review of the evidence supports carbamazepine and oxcarbazepine with insufficient data to support baclofen, lamotrigine and gabapentin (Zakrzewska 2014 **NR**).

KEY MESSAGES

1. Various anticonvulsants (**U**) (**Level I** [PRISMA]) and duloxetine (**N**) (**Level II**) have beneficial effects in the treatment of neuropathic pain associated with multiple sclerosis
2. Cannabinoids have a clinically small effect on spasticity caused by multiple sclerosis (**U**) (**Level I**); the effect on neuropathic pain associated with multiple sclerosis is unclear and may depend on the preparation used (**W**) (**Level I** [PRISMA]).
3. With cannabinoid use in multiple sclerosis, there is a high rate of minor adverse effects and serious adverse psychopathological effects occur in nearly 1% of patients (**U**) (**Level I**).
4. Acupuncture (**N**) (**Level I**), non-invasive brain stimulation (**N**) (**Level III-3 SR**) and motor cortex stimulation (**N**) (**Level IV SR**) may reduce post-stroke pain.
5. Local anaesthetics (mainly lidocaine) by local and systemic administration, anticonvulsants (phenytoin or IV fosphenytoin) and sumatriptan reduce pain in acute exacerbations of trigeminal neuralgia (**N**) (**Level IV SR**).
6. Motor cortex stimulation may reduce acute pain in trigeminal neuralgia (**N**) (**Level IV SR**)
7. Deep brain stimulation may improve pain relief in Parkinson's disease (**N**) (**Level IV**).

The following tick box represents conclusions based on clinical experience and expert opinion:

☑ Treatment of acute pain associated with neurological disorders is based largely on evidence from trials for the treatment of a variety of chronic neuropathic pain states (**S**).

8.6.7 | Acute orofacial pain

Acute orofacial pain may be caused by infective, traumatic, neuropathic, vascular, neoplastic and other pathologies (Khawaja 2015 **NR**; Zakrzewska 2013 **NR**; Hegarty 2011 **NR**). Most commonly, acute orofacial pain is due to either dental or sinus disease. It may also be associated with flare-ups of more chronic orofacial pain syndromes eg temporomandibular disorders (TMDs; see Section 8.6.7.4 below), trigeminal neuralgia (see Section 8.6.6.4 above), migraine and other primary headaches (see Section 8.6.5 above). Pain may also be referred from adjacent structures such as the cervical spine, ear and throat.

Post-traumatic neuropathic orofacial pain (including post-traumatic trigeminal neuropathy) may be caused by nerve injury secondary to common dental surgical procedures eg extraction of teeth, root canal therapy, local anaesthetic injections or placement of dental implants. Such orofacial pain conditions may be exacerbated by repeated procedures, incorrect treatment and comorbid psychological factors.

A thorough medical/dental history and clinical examination (particularly of the mouth, jaw and cranial nerves) are essential components of the assessment of acute orofacial pain (Zakrzewska 2013 **NR**; Hegarty 2011 **NR**).

Recurrent or persistent orofacial pain may require additional biopsychosocial assessment and appropriate multidisciplinary management (de Leeuw 2018 **NR**; Vickers 2000 **NR**).

8.6.7.1 | Acute dental pain

In general, patients suffering acute oral and dental pain should be referred to a dentist for appropriate diagnosis and management. NSAIDs and emergency pulpectomy reduces pain in patients with acute apical periodontitis (Sutherland 2003 **Level I**, 8 RCTs, n=531), but there is insufficient evidence to determine if the addition of antibiotics reduces pain due to irreversible pulpitis (Agnihotry 2019 **Level I** [Cochrane], 1 RCT, n=40) or apical periodontitis or abscess (Cope 2018 **Level I** [Cochrane], 2 RCTs, n=62). Unless it has been established that infection is the cause, it is inappropriate for antibiotics to be prescribed, even though they may provide some symptomatic relief (Abbott 2007 **NR**). Pulpitis due to extension of caries into the pulp or pulp exposure may lead to pulp necrosis and acute apical periodontitis.

The use of local anaesthetics to permit dental treatment is not presented here as it is deemed beyond the scope of this document.

8.6.7.2 | Acute postoperative dental pain

Common dental surgical procedures, particularly tooth extractions and endodontic treatments, are frequently associated with acute postoperative pain, requiring pharmacological management.

Paracetamol and NSAIDs

Acute pain after third molar extraction is the most extensively studied model for testing postoperative analgesics in single-dose investigations. Nonselective NSAIDs or coxibs are recommended as “first-line” analgesics following third molar extraction (Derry 2011 **Level I**, 155 RCTs, n=16,104), however paracetamol is also safe and effective with a dose of 1,000 mg providing better pain relief than lower doses (Weil 2007 **Level I** [Cochrane], 21 RCTs, n=1,968). The best available evidence suggests the use of NSAIDs either with or without paracetamol is effective and well-tolerated (Moore 2018 **Level I**, 5 SRs, n unspecified).

Nonselective NSAIDs are more effective than paracetamol or codeine (either alone or in combination) (Ahmad 1997 **Level I**, 33 RCTs, n=5,171). Ibuprofen (200–512 mg) specifically is

superior to paracetamol (600–1,000 mg) in this setting and combining these two drugs improves analgesia further (Bailey 2014 **Level I** [Cochrane], 7 RCTs, n=2,241).

Based on a meta-analysis of limited quality, pre-emptive use of NSAIDs does not appear to be effective in reducing postoperative pain in this setting (OR 2.30; 95%CI 0.60 to 8.73) (4 RCTs, n=298) (Costa 2015 **Level I**, 6 RCTs, n=420).

For acute pain of endodontic origin, NSAIDs are the analgesic of choice (Aminoshariae 2016 **Level I** [PRISMA], 27 RCTs, n=400). When NSAIDs are not effective on their own, there is support for combining these with paracetamol, tramadol or an opioid; moderate evidence supports the use of steroids in symptomatic irreversible pulpitis.

In patients with preoperative pain, ibuprofen 600 mg and ibuprofen 600 mg/paracetamol 1,000 mg are similarly effective and provide superior analgesia after endodontic treatment vs placebo (Smith 2017a **Level I** [PRISMA], 15 RCTs, n=1,107). Ketoprofen 50 mg and naproxen 500 mg may be effective alternatives.

A number of RCTs not included in the above meta-analyses support their overall conclusions. The combination of paracetamol 1,000 mg with ketoprofen 100 mg was more effective than either drug given alone (Akural 2009 **Level II**, n=76, JS 5). IM/IV ketorolac 30 mg provided better analgesia with fewer adverse effects than IM pethidine 100 mg (Fricke 1992 **Level II**, n=145, JS 5) or IV tramadol 50 mg (Ong 2004 **Level II**, n=64, JS 3). IV meloxicam 60 mg showed faster onset of then longer-lasting analgesic effect than PO ibuprofen 400 mg (Christensen 2018 **Level II**, n=230, JS 5). PO meloxicam 15 mg provided superior analgesia to PO diclofenac 100 mg in a small RCT (Orozco-Solis 2016 **Level II**, n=36, JS 4).

In a direct comparison, PO diclofenac 50 mg provided superior analgesia to PO ibuprofen 400 mg and PO paracetamol 1,000 mg (Gazal 2017 **Level II**, n=120, JS 5).

Coxibs are of similar efficacy to nsNSAIDs in acute postoperative dental pain. Single-dose celecoxib 200 mg is less effective than ibuprofen 400 mg (Chen 2004 **Level I**, 18 RCTs, n=2,783); while celecoxib 400 mg provided similar analgesia to ibuprofen 400 mg with increased time to rescue analgesia following dental surgery (Cheung 2007 **Level II**, n=171, JS 5). In a comparison of PO celecoxib (400 mg, then 200 mg every 12 h), ibuprofen (400 mg every 8 h) and tramadol (100 mg PO every 8 h), celecoxib was the most effective analgesic (Akinbade 2018 **Level II**, n=135, JS 4). Single daily doses of etoricoxib 90 mg and 120 mg were similar in analgesic efficacy to ibuprofen 600 mg every 6 h but longer lasting, as well as superior to a paracetamol 600mg/codeine 60 mg combination (Brown 2013 **Level II**, n=588, JS 5).

A combination of oxycodone/ibuprofen (5/400 mg) was more effective than other combinations of paracetamol, ibuprofen, oxycodone or hydrocodone or placebo for analgesia following dental surgery (Litkowski 2005 **Level II**, n=249, JS 5).

A systematic review to investigate the influence of pain models revealed that the placebo response for analgesia was significantly lower post third molar extraction pain than in other acute pain models (Barden 2004a **Level I**, 160 RCTs, n=14,410).

Tramadol

Tramadol 100 mg had a similar efficacy to aspirin/weak opioid or paracetamol/weak opioid combinations in treating acute dental pain (Moore 1997 **Level I**, 18 RCTs, n=3,453). A tramadol/paracetamol combination is superior to tramadol alone with fewer adverse effects due to a reduced tramadol dose (Edwards 2002a **Level I**, 7 RCTs, n=1,376; Fricke 2004 **Level II**, n=456, JS 5) and was comparable to a codeine/acetaminophen/ibuprofen combination preparation (Jung 2004 **Level II**, n=128, JS 5).

However, tramadol provides inferior analgesia with an increased rate of adverse events vs NSAIDs in the treatment of acute dental pain (Isiordia-Espinoza 2014 **Level I**, 5 RCTs, n=200). This is confirmed by RCTs not included in this meta-analysis. PO Tramadol 100 mg was significantly less

effective than PO naproxen 500 mg (Mehrvarzfar 2012 **Level II**, n=100, JS 5). In comparison of PO tramadol (100 mg every 8 h), PO celecoxib (400 mg, then 200 mg every 12 h) and PO ibuprofen (400 mg every 8 h), tramadol was the least effective analgesic (Akinbade 2018 **Level II**, n=135, JS 4).

Steroids

Perioperative steroid administration reduced swelling and trismus, but not pain following third molar extraction (Markiewicz 2008 **Level I**, 12 RCTs, n=287). However, two subsequent studies suggested there might be an analgesic benefit from dexamethasone (Klongnoi 2012 **Level II**, n=20, JS 2), with dexamethasone 4 mg being similarly effective to 120 mg etoricoxib (Sotto-Maior 2011 **Level II**, n=50, JS 3).

A submucosal injection of dexamethasone 4 and 8 mg immediately before surgery similarly reduced postoperative facial swelling, but not pain or trismus, vs placebo at 48 h (Grossi 2007 **Level II**, n=72, JS 5). A single 40 mg injection of methylprednisolone into the masseter muscle following third molar extraction reduced pain, swelling and trismus (Vegas-Bustamante 2008 **Level II**, n=35, JS 5).

Following root canal treatment, there is an analgesic effect from steroid use, however, with marked heterogeneity of the included RCTs (Iranmanesh 2017 **Level I**, 18 RCTs, n unspecified)

Painful irreversible pulpitis may be alleviated for up to 24 h by administering dexamethasone (4 mg PO or by intraligamentary or root canal injection) (Nogueira 2018 **Level I** [PRISMA], 5 RCTs, n=292).

Ketamine (topical or infiltrated)

After mandibular molar extraction, topical administration (to the extraction sockets on resorbable gelatine sponges) of ketamine 0.5 mg/kg vs tramadol 1 mg/kg vs saline achieved the lowest pain scores and rescue analgesic use for the first 24 h after surgery (Gonul 2015 **Level II**, n=90, JS 2). In a similar setting, the addition of 0.3 mg/kg ketamine to lidocaine 2% for the local anaesthesia (inferior alveolar, lingual and buccal nerve blocks) reduced pain at 1 and 4 h and facial swelling at 1 d, while improving mouth opening up to 7 d (Kumar 2015 **Level II**, n=60, JS 1).

Pregabalin

Postoperative administration of PO pregabalin 75 mg provided better analgesic effects than administration before third molar extraction surgery (Cheung 2012 **Level II**, n=34, JS 5).

Nonpharmacological treatment

After 3rd molar extraction, cryotherapy is effective at reducing oedema (Fernandes 2019 **Level IV SR**, 11 studies, n=721). Results were mixed for an effect on pain where 5 of 11 studies found beneficial effect, but no meta-analysis was performed due to non-standardised evaluation methods. Facial compression reduced pain for up to 3 d, with no additional benefit from ice packs (Forouzanfar 2008 **Level II**, n=95, JS 5).

Acupuncture may have a beneficial effect on acute dental pain but the quality of evidence is limited (Ernst 1998 **Level III-1 SR**, 16 studies, n=941).

Low-level laser energy irradiation fails to reduce either pain or swelling after removal of third molar teeth, but reduces trismus slightly (Brignardello-Petersen 2012 **Level I**, 10 RCTs, n=581). This is contradicted by a subsequent meta-analysis which reports low-level laser therapy as effective for the treatment of pain, swelling and trismus (He 2015b **Level I** [PRISMA], 6 RCTs, n=193) (2 RCTs overlap). A subsequent RCT supports the effects on pain and swelling described in the latter meta-analysis (Eshghpour 2016 **Level II**, n=44, JS 3).

For paediatric patients, see Section 10.4 and 10.6.6

Systemic analgesics

In adults, paracetamol (2 of 2 RCTs), NSAIDs (2 of 9 RCTs: ibuprofen, ketoprofen, rofecoxib, lornoicam, celecoxib, parecoxib vs placebo or active comparator aspirin, diclofenac or ketorolac), dexamethasone (5 of 10 RCTs), gabapentinoids (3 of 3 RCTs), and dextromethorphan (2 RCTs) provide some limited analgesia on POD 1 after tonsillectomy (Tolska 2019 **Level I** [PRISMA], 29 RCTs, n=1,816). The limited efficacy of single medications suggests that multimodal analgesic strategies are required.

The risks of bleeding with the use of NSAIDs are discussed in detail in Section 4.2.1.2 in adult and in Section 10.4.2.3 in paediatric patients.

Alpha-delta-2 ligands

Preoperative gabapentin (6 RCTs) and pregabalin (3 RCTs) similarly reduce pain in the first 8 h, analgesic requirements in the first 24 h and PONV without increasing adverse effects after tonsillectomy (Hwang 2016a **Level I** [PRISMA], 8 RCTs [3 adult, 2 mixed, 3 paediatric], n=608; Tolska 2019 **Level I** [PRISMA], 4 RCTs [alpha-2-delta ligands], n=255) (2 RCTs overlap).

Steroids

Dexamethasone in doses >10 mg over 24 h given to adults undergoing tonsillectomy reduces pain by 23% at 4 h (MD -1.4/10; 95% CI -1.6 to -1.2) (Tolska 2019 **Level I [**PRISMA], 10 RCTs [dexamethasone], n=590). In tonsillectomy in adults and children, all steroids reduce pain severity at all time points up to POD 7 with a peak benefit on POD 1 (SMD -0.99/10; 95%CI -1.32 to -0.67) (41 RCTs, n=3,477) (Titirungruang 2019 **Level I** [PRISMA], 64 RCTs [22 adult], n=6,327) (8 RCTs overlap). These effects are similar for systemic vs local steroid administration. Furthermore, steroids reduce PONV (OR 0.31; 95%CI 0.24 to 0.40) (46 RCTs, n=4,784), while not increasing the risk of primary (OR 0.96; 95%CI 0.55 to 1.67) (15 RCTs, n=1,736) or secondary haemorrhage (OR 1.05; 95%CI 0.74 to 1.51) (23 RCTs, n=2,440).

Antibiotics

Perioperative antibiotics show no benefit in decreasing post-tonsillectomy pain (3 RCTs positive, 4 RCTs no difference, 1 RCT negative) and secondary haemorrhage rates (12 RCTs, n=1,397); adverse effects were more common with their use (Abdelhamid 2019 **Level I**, 12 RCTs, n=1,397). The conclusions reflected those of an earlier Cochrane review which found no difference in pain (6 RCTs), need for analgesia (6 RCTs) or secondary haemorrhage (7 RCTs) (Dhiwakar 2012 **Level I** [Cochrane], 10 RCTs, n=1,035) (5 RCT overlap).

Peritonsillar infiltration with local anaesthesia and analgesics

Peritonsillar injection or topical application of local anaesthetics produce equally modest reductions in post-tonsillectomy pain for up to 24 h (Grainger 2008 **Level I**, 13 RCTs, n=777). Ropivacaine 1.0% with adrenaline resulted in better pain relief up to 4 d after tonsillectomy than either bupivacaine 0.25% with adrenaline or placebo (Arikan 2008 **Level II**, n=58, JS 5). Peritonsillar infiltration with bupivacaine provided pain relief comparable to rectal paracetamol (Dahi-Taleghani 2011 **Level II**, n=110, JS 2).

Dexamethasone added to local anaesthetics reduces pain intensity, analgesic requirements and PONV (3 RCTs, n=361) (Vlok 2017 **Level I**, 11 RCTs, n=854). Magnesium added to local anaesthetics reduces pain intensity, analgesic requirements and incidence of laryngospasm, but not PONV (4 RCTs, n=240). There is only limited support for the addition of pethidine (1 RCT, n=80) or tramadol (1 RCT, n=60), and addition of clonidine shows no effect (2 RCTs, n=123).

Infiltration of the tonsillar bed with tramadol (Atef 2008 **Level II**, n=40, JS 5) as well as an equivalent IM tramadol dose reduced pain and analgesic requirements in the first few hours after tonsillectomy vs placebo (Ugur 2008 **Level II**, n=45, JS 5). Peritonsillar infiltration with tramadol resulted in better early pain control with preoperative infiltration (up to 2 h postop), but better late (beyond 8 h) pain control with postoperative infiltration (Maryam 2017 **Level II**, n=80, JS 3). See also Section 10.4.4.12.

Topical administration

There is poor and inconsistent evidence on the analgesic effects of oral rinses, mouthwashes and sprays after tonsillectomy, although lidocaine spray is more effective than saline spray (1 RCT) (Fedorowicz 2011 **Level I** [Cochrane], 6 RCTs, n=528 [131 adults]). While in a subsequent RCT, topical ropivacaine (swabs soaked in 1% ropivacaine packed into the tonsillar beds for 5 min) vs placebo had no effect on pain after tonsillectomy (Tolska 2017 **Level II**, n=160, JS 5).

Non-pharmacological treatment

Intraoperative cryotherapy (with a cryotherapy probe [-56°C]) (1 RCT) and ice-water cooling (4°C to 10°C) (2 RCTS) reduces post-tonsillectomy pain scores consistently by 21 to 32% (0.9/10 to 1.8/10) (Raggio 2018 **Level I** [PRISMA], 3 RCTs, n=153).

Acupuncture vs control or sham may reduce pain intensity, analgesic requirements and PONV for up to 48 h after tonsillectomy with high levels of heterogeneity (Cho 2016 **Level I**, 12 RCTs, n=1,025).

Honey in children vs placebo reduces pain and analgesic use for up to 5 to 10 d post-tonsillectomy; regimens of honey administered varied substantially in volume (4 to 15 mL), frequency (daily to hourly) and duration (1 to 10 d) (Hwang 2016b **Level I** [PRISMA], 4 RCTs n=264; Lal 2017 **Level I** [QUOROM], 8 RCTs n=545) (4 RCTs overlap). The analgesic medication regimens used in the included studies were not clear.

8.6.7.4 | Acute pain associated with temporomandibular disorders

Temporomandibular disorders (TMDs) are a group of musculoskeletal pains affecting the masticatory muscles and/or temporomandibular joints (TMJs) and are the most common cause of orofacial pain apart from the teeth (Zakrzewska 2013 **NR**; Hegarty 2011 **NR**). The common TMDs include masticatory myalgia, myofascial pain, TMJ disc interference disorders and TMJ degenerative joint disease. The primary TMD symptoms include painful limitation of mouth opening and/or deviation of the mandible on opening, TMJ tenderness, TMJ crepitus and/or clicking noise and masticatory muscle pain or tenderness. Headaches are often an associated feature. Management approaches to TMD pain include medication, physiotherapy, occlusal splints, self-management strategies, and interventions based on cognitive behavioural approaches.

There is limited evidence for the successful pharmacological management of TMD pain (Mujakperuo 2010 **Level I** [Cochrane], 11 RCTs, n=496). A subsequent systematic review and network meta-analysis identified NSAIDs as well as corticosteroid and hyaluronate injections as successful treatments for TMD joint pain (15 RCTs, n=790), while the muscle relaxant cyclobenzaprine is effective in TMD muscle pain (9 RCTs, n=375) (Haggman-Henrikson 2017 **Level I** [NMA], 41 RCTs, n=2,033). Based on transferable evidence from similar conditions, topical NSAIDs are a treatment option also as in adult patients with acute pain resulting from strains, sprains or sports injuries, topical diclofenac, ibuprofen, ketoprofen, piroxicam and indomethacin are effective vs placebo, whereas benzydamine is not (Derry 2015 **Level I** [Cochrane] 61 RCTs, n=8,386).

The evidence for IA morphine, tramadol, buprenorphine, fentanyl and NSAIDs was inconclusive due to a small number of low-quality studies for temporomandibular joint arthrocentesis (Gopalakrishnan 2018 **Level I** [PRISMA], 3 RCTs, n=91 [& 3 other studies]).

Low-level laser therapy in the treatment of TMD has no analgesic benefit vs placebo (WMD -19.4; 95%CI -40.8 to 2.0), but improves functional outcomes (Chen 2015 **Level I**, 14 RCTs, n=454).

8.6.7.5 | Acute pain associated with pharyngitis

Systemic analgesics

Paracetamol, nsNSAIDs, coxibs and opioids, administered as monotherapy or in combination, were effective in the treatment of pain associated with acute pharyngitis (Thomas 2000 **Level I**, 17 RCTs, n=3,259).

Corticosteroids

Corticosteroids provide relief of pain, in particular in patients with severe or exudative sore throat (Hayward 2012b **Level I** [Cochrane], 8 RCTs, n=743). Here, corticosteroids in combination with analgesics and antibiotics increase the likelihood of complete resolution of pain at 24 h (RR 3.2; 95%CI 2.0 to 5.1) and the time to onset of pain relief by 6.3 h (6 RCTs, n=609). In acute pharyngitis potentially caused by group A beta-haemolytic Streptococcus, corticosteroids reduce the time to clinically meaningful pain relief; however provide only a small reduction in pain scores at 24 h (Wing 2010 **Level I**, 10 RCTs, n=1,096) (8 RCTs overlap). Corticosteroids administered in a single dose (most commonly 10 mg dexamethasone orally) provide pain relief for sore throat including pharyngitis more effectively and faster than placebo (Sadeghirad 2017 **Level I**, 10 RCTs [7 RCTs in adults], n=1,426) (9 RCTs overlap). On the basis of these findings, clinical practice guidelines make a weak recommendation to treat acute sore throat with a single dose of oral corticosteroid (Aertgeerts 2017 **GL**).

Dexamethasone decreases incidence and severity of sore throat after extubation when administered IV at induction (Kuriyama 2019 **Level I** [PRISMA], 15 RCTs, n=1,849).

Following drainage and antibiotics for peritonsillar abscess, a single dose of IV corticosteroid reduces fever and with less certainty pain, trismus and hospital LOS (Hur 2018 **Level I** [PRISMA], 3 RCTs, n=153).

Antibiotics

Antibiotics for sore throat reduce pain, headache and fever by 50% on d 3; this effect was more pronounced if throat swabs were positive for Streptococcus (Spinks 2013 **Level I** [Cochrane], 27 RCTs, n=12,835). Antibiotics reduce throat soreness at 3 d vs controls (RR 0.68; 95%CI 0.59 to 0.72). Antibiotics also shortened the duration of symptoms by 16 h, although the absolute benefits are modest.

Topical analgesics

Topical analgesics such as lozenges containing amylmetacresol/2,4-dichlorobenzylalcohol (AMC/DCBA) (Weckmann 2017 **Level I** [PRISMA], 3 RCTs, n=661), flurbiprofen (Watson 2000 **Level II**, n=301, JS 5), ibuprofen (Bouroubi 2017 **Level II**, n=385, JS 5) and benzocaine (Chrubasik 2012 **Level II**, n=50, JS 3) as well as benzydamine spray (Thomas 2000 **Level I**, 17 RCTs, n=3,259) or benzydamine/chlorhexidine spray (Cingi 2010 **Level II**, n=164, JS 5) provide analgesia superior to placebo in acute sore throat with minimal adverse effects.

Ketamine gargle vs placebo or no treatment reduces the incidence of postoperative sore throat for up to 24 h (RR 0.42 to 0.52 over time points 0 to 24 h) based on high-quality evidence (Mayhood 2015 **Level I** [PRISMA] 5 RCTs, n=291); systemic absorption is an unknown factor.

Ambroxol, a mucolytic substance with local anaesthetic properties, reduces pain of pharyngitis slightly (with questionable clinical relevance) vs placebo (mint lozenges) (Chenot 2014 **Level I**, 3 RCTs, n=1,772).

Nonpharmacological treatment

A single-point acupuncture treatment at large intestine meridian for pain of acute pharyngitis and tonsillitis was not more effective than sham laser acupuncture (Fleckenstein 2009 **Level II**, n=60, JS 5).

8.6.7.6 | Acute pain associated with sinusitis and otitis media

Treatment of sinusitis and otitis media is primarily symptomatic using analgesics and antipyretics; it may be appropriate to use nsNSAIDs, coxibs, paracetamol, weak opioids or tramadol, based on evidence for treatment of dental pain. Evidence based clinical practice guidelines for the diagnosis and treatment of acute sinusitis (Chandran 2013 **GL**; Meltzer 2011 **GL**) and acute otitis media are published (Rosenfeld 2014 **GL**). Evidence for individual interventions are presented here.

Antihistamines and/or decongestants

Antihistamines and/or decongestants have no clinically relevant benefit in acute otitis media (Coleman 2008 **Level I** [Cochrane], 15 RCTs, n=2,695).

Antibiotics

Antibiotic treatment of acute otitis media vs placebo or control has no effect on acute pain after 24 h and leads to some pain reduction at 2–3 d, but with an $NNT_{50\%}$ of 20 (Venekamp 2015 **Level I** [Cochrane], 13 RCTs, n=3,401). Individual patient data meta-analysis from 959 children show no better analgesia at d 3 to 7 and from 247 children at d 7 to 14. As the effects on pain are questionable and adverse effects (such as vomiting, diarrhoea or rash) are increased (RR 1.38; 95%CI 1.19 to 1.59; NNH 14), for most children with mild disease antibiotic use might not be justified.

Steroids

Oral corticosteroids as a monotherapy are not effective and in combination with antibiotics may be modestly beneficial for symptoms of acute sinusitis (Venekamp 2014 **Level I** [Cochrane] 5 RCTs, n=1,193).

Topical treatment

For sinusitis, IN corticosteroids have consistently significant benefits for facial pain (Hayward 2012a **Level I**, 6 RCTs, n=2,495). Improvement or resolution of symptoms are more likely with IN corticosteroids than placebo or control, with higher doses being more effective (Zalmanovici Trestioreanu 2013 **Level I** [Cochrane], 4 RCTs, n=1,943) (4 RCTs overlap).

A phytotherapeutic nasal spray containing *Cyclamen europaeum* provided better facial pain relief than placebo in sinusitis (Pfaar 2012 **Level II**, n=99, JS 3).

Topical local anaesthetic drops (benzocaine/ antipyrine or lidocaine) used in acute otitis media in children, in addition to PO analgesia, are effective vs saline at 10 min (RR 2.13; 95%CI 1.19 to 3.80) and 30 min after instillation (RR 1.43; 95% CI 1.12 to 1.81) (2 RCTs, n=117) (Foxlee 2011 **Level I** [Cochrane], 5 RCTs, n=391). Superiority of local anaesthetic (amethocaine/ antipyrine) vs naturopathic drops (3–4 herbal extracts in olive oil) is not established in three RCTs (in addition to paracetamol in one RCT and amoxicillin in one RCT) (3 RCTs, n=274 [analysed]).

8.6.7.7 | Acute pain associated with oral ulceration/stomatitis

Acute oral ulceration/stomatitis due to trauma (physical, chemical, thermal), infection (eg herpes simplex), drugs, radiation or chemotherapy (mucositis) may be extremely painful and debilitating. Mucositis is a common adverse effect of high-dose chemo- and radiotherapy for

malignancies affecting the head and neck, for conditioning prior to bone marrow transplants and treatment of leukaemia. For details of chemotherapy-induced mucositis, see Section 8.9.8.2.

For recurrent aphthous stomatitis, laser treatment (Nd:YAG laser ablation, CO2 laser applied through a transparent gel [non-ablative] and diode laser in a low-level laser treatment [LLLT] mode) vs placebo, no therapy or topical corticosteroids leads to improved immediate and delayed pain control and reduced duration of healing (Suter 2017 **Level III-1 SR**, 10 RCTs & 1 study, n≈512).

In children with acute infectious mouth ulcers in the ED, viscous lidocaine solution applied did not enable increased oral intake (Hopper 2014 **Level II**, n=100, JS 5). However, 2% lignocaine gel was effective in children with mouth ulcers with a reduction of mucosal pain by 20/100 (+/- 18) (Coudert 2014 **Level II**, n=64, JS 5).

KEY MESSAGES

Acute dental pain

1. NSAIDs and emergency pulpectomy reduce pain in patients with acute apical periodontitis (**U**) (**Level I**) with insufficient evidence to support analgesic benefit from adding antibiotics (**S**) (**Level I** [Cochrane Review]).

Dental extraction

2. Paracetamol, nonselective NSAIDs and coxibs provide safe and effective analgesia with minimal adverse effects after dental extraction (**S**) (**Level I** [Cochrane Review]).
3. Combinations of paracetamol with ibuprofen (**U**) (**Level I** [Cochrane Review]) and other nonselective NSAIDs (**U**) (**Level I**) provide superior analgesia to either drug alone after dental extraction.
4. Tramadol provides equal analgesia to paracetamol/weak opioid and aspirin/weak opioid combinations (**U**) (**Level I** [Cochrane Review]) and tramadol/paracetamol combinations provide superior analgesia to tramadol alone after dental extraction (**U**) (**Level I**).
5. Nonselective NSAIDs and coxibs provide similar analgesia, which is superior to paracetamol, codeine, combinations of paracetamol/codeine (**U**) (**Level I**), tramadol (**S**) (**Level I**) and pethidine (**U**) (**Level II**) after dental extraction.
6. Perioperative corticosteroid administration reduces swelling, but not pain (**U**) (**Level I**), and reduces postoperative nausea (**U**) (**Level II**) after third molar extraction.

Tonsillectomy

7. Nonselective NSAIDs (**U**) (**Level I**), in particular aspirin and ketorolac (**U**) (**Level II**), increase the risk of reoperation for bleeding after tonsillectomy in adults, but not in children (**U**) (**Level I** [Cochrane Review]).
8. Intraoperative dexamethasone administration reduces postoperative pain, nausea and vomiting and time to resumption of oral intake after tonsillectomy (**S**) (**Level I** [Cochrane Review]), with no increase in adverse effects (**U**) (**Level I** [Cochrane Review]).
9. Paracetamol, NSAIDs (**S**) (**Level I** [PRISMA]), dexamethasone, preoperative alpha-2-delta ligands (**S**) and dextromethorphan are effective analgesics after tonsillectomy (**N**) (**Level I** [PRISMA]).
10. Intraoperative cryothgerapy may reduce post-tonsillectomy pain (**N**) (**Level I** [PRISMA]).
11. Oral administration of honey versus control reduces postoperative pain and analgesic use after tonsillectomy (**N**) (**Level I** [PRISMA]).
12. Peritonsillar infiltration or topical application of local anaesthetics are equally effective in producing a modest reduction in acute post-tonsillectomy pain (**U**) (**Level I**).
13. Dexamethasone, magnesium (and with limited support pethidine and tramadol) combined with local anaesthetics for peritonsillar infiltration improve analgesia and other outcomes after tonsillectomy (**N**) (**Level I**).
14. Perioperative antibiotics show no benefit in post-tonsillectomy pain, but increase adverse effects (**S**) (**Level I**).

15. Acupuncture may reduce post-tonsillectomy pain compared to control group or sham acupuncture (**N**) (**Level I**)

16. Peritonsillar infiltration with tramadol or ketamine may reduce post-tonsillectomy pain and analgesia requirements but was no more effective than equivalent doses administered parenterally (**U**) (**Level II**).

Pharyngitis

17. Corticosteroids (**S**) (**Level I** [Cochrane Review]) and antibiotics (**U**) (**Level I** [Cochrane Review]) improve analgesia and reduce duration of pain in pharyngitis.

18. Amylmetacresol/2,4-dichlorobenzylalcohol (AMC/DCBA) lozenges (**N**) (**Level I** [PRISMA]), ketamine gargle (**N**) (**Level I** [PRISMA]), benzydamine spray (**U**) (**Level I**) and other topical analgesics (**U**) (**Level II**) provide analgesia superior to placebo in acute sore throat with minimal adverse effects.

19. Corticosteroids reduce acute pain associated with peritonsillar abscess (following drainage and antibiotics) (**S**) (**Level I** [PRISMA]).

20. Paracetamol, NSAIDs (nonselective NSAIDs or coxibs) and opioids, administered as monotherapy or in combination, are effective analgesics in acute pharyngitis (**U**) (**Level I**).

Sinusitis and Otitis media

21. Oral corticosteroids have no analgesic effect in sinusitis (**U**) (**Level I** [Cochrane Review]), but intranasal corticosteroids reduce facial pain and improve recovery (**S**) (**Level I** [Cochrane Review]).

22. Antibiotic treatment of acute otitis media vs placebo or control has no effect on acute pain, only limited effect on later pain, but increases the risk of adverse effects (**N**) (**Level I** [Cochrane Review]).

23. In acute otitis media, topical local anaesthetic drops are effective in children compared to placebo and equivalent to naturopathic drops (**S**) (**Level I** [Cochrane Review]).

The following tick boxes represent conclusions based on clinical experience and expert opinion:

☑ Codeine should not be used in children, especially after adenoidectomy or tonsillectomy, due to an increased risk of opioid-induced ventilatory impairment and death (**U**).

☑ Recurrent or persistent orofacial pain requires biopsychosocial assessment and appropriate multidisciplinary approaches (**U**).

☑ Neuropathic orofacial pain, which is often post-traumatic (iatrogenic), may be exacerbated by repeated dental procedures, incorrect drug therapy or psychosocial factors (**U**).

8.6.8 | Acute pain in patients with HIV infection

Pain is common in people infected with HIV (Ebirim 2013 **Level IV**, n=157; Namisango 2012 **Level IV**, n=302; Simmonds 2005 **Level IV**, n=100; Frich 2000 **Level IV**, n=95; Vogl 1999 **Level IV**, n=504; Larue 1997 **Level IV**; Breitbart 1996 **NR**) and may have diverse aetiologies, including HIV itself (which is a neurotropic virus), opportunistic infections and malignancies, and unrelated comorbidities (Hewitt 1997 **Level IV**, n=274; Glare 2001 **NR**; O'Neill 1993 **NR**). In untreated HIV infection, pain becomes more common as disease progresses and is almost universal among those with advanced acquired immunodeficiency syndrome (AIDS) (Kimball 1996 **Level IV**, n=157; O'Neill 1993 **NR**). Even among relatively well individuals, pain is prevalent and associated with depression and impaired function (Vogl 1999 **Level IV**, n=504; Singer 1993 **Level IV**).

Adults diagnosed with HIV today can have a near normal life expectancy with access to antiretroviral therapy, both in well-resourced and resource-limited settings (Gueler 2017 **Level III-2**, n=16,532 [HIV-positive patients]; Mills 2011 **Level IV**, n=22,315; van Sighem 2010 **Level IV**, n=4,612). This improvement in HIV prognosis has however been associated with an ageing HIV-infected population with increasing numbers of comorbidities and an ongoing high prevalence of pain (Balderson 2013 **Level IV**, n=452). The ongoing high prevalence of chronic pain among people living with HIV today has prompted the Infectious Diseases Society of America to publish specific management guidelines (Bruce 2017 **GL**).

Pain continues to be associated with poorer quality of life and impaired function among people living with HIV (Merlin 2013 **Level IV**, n=1,903; Ebirim 2013 **Level IV**, n=157; Namisango 2012 **Level IV**, n=302; Simmonds 2005 **Level IV**, n=100). Several studies have found that pain is undertreated in those with HIV infection, with both physician and patient barriers suggested (Ebirim 2013 **Level IV**, n-157; Frich 2000 **Level IV**, n=95; Breitbart 1998 **Level IV**, n=199; Larue 1997 **Level IV**, n=174; Breitbart 1999 **NR**; Breitbart 1996 **NR**). An unmet need for analgesia is one of the commonest reasons for people with HIV to use complementary therapies (Peltzer 2008 **Level IV**, n=618; Tsao 2005 **Level IV**, n=2,466). HIV/AIDS patients with diagnosed mood/anxiety or substance-use disorders report much higher levels of pain than HIV/AIDS patients without these comorbidities or the general population (Tsao 2009 **Level III-2**). Further, preliminary data support an association between perceived HIV stigma and pain in this population (Wadley 2019 **Level IV**, n=50).

8.6.8.1 | Treatment of pain in people infected with HIV

The optimal management of pain in an individual with HIV will depend on the cause of the pain. The general principles of treating the underlying cause where possible and providing adequate analgesia are the same as for any other individual with the same injury or illness. Some special considerations (particularly drug interactions) may be important and are set out below.

HIV and its treatment are frequently complicated by a distal, small-fibre, sensory neuropathy that is typically painful (painful HIV-associated sensory neuropathy) (Cherry 2012 **NR**). Prevalence rates >50% are described in cohorts exposed to stavudine (a potentially neurotoxic antiretroviral agent) (Wadley 2011 **Level IV**, n=395). Although stavudine use has been phased out, many patients living with HIV have previously been exposed to this drug. Further, a large, USA-based prospective survey found that 15% of adults with HIV who had never used stavudine are affected by painful sensory neuropathy, with older patients at higher risk (Ellis 2010 **Level IV**, n=1,539). Further follow-up of the same cohort has demonstrated new onset of distal neuropathic pain in 27% of patients after a median of 24 mth observation, associated with factors including older age, female gender, and failure to suppress HIV replication (Malvar 2015 **Level IV**, n=493).

Neuropathic pain is particularly difficult to treat in HIV. Despite anecdotal reports of individual patients responding well to each of the pain-modifying agents typically used in other small-fibre neuropathies, only smoking of cannabis, topical capsaicin and recombinant human nerve growth factor are more effective than placebo for HIV neuropathy pain (Phillips 2010 **Level I** [PRISMA], 14 RCTs, n=1,764). Smoking cannabis has only short term effects in studies with potential bias due to difficulties in patient blinding; in one trial 92% guessed treatment allocation correctly. Furthermore, no associations were found between marijuana use and either pain intensity or opioid use (Merlin 2019 **Level IV**, n=433). A meta-analysis of data on high-dose capsaicin 8% found limited efficacy with $NNT_{50\%}$ of 11 (Derry 2013c) **Level I** [Cochrane], 2 RCTs, n=801). Those with lower baseline pain scores and females may be most likely to respond (Katz 2015b **Level I**, 6 RCTs, n=1,014).

In a pilot study of hypnosis for managing HIV-neuropathy pain, 26 of 36 patients were responders with a mean 44% reduction in pain scores at 7 wk after the intervention (Dorfman 2013 **Level IV**, n=36). These data together with the larger placebo responses seen in HIV-neuropathy analgesia trials compared with studies of neuropathic pain from other causes suggest that nonpharmacological interventions may be useful in this difficult pain syndrome and warrant further study (Cepeda 2012 **Level I**, 94 RCTs, n=5,317).

The chronic nature of HIV disease as well as the many possible causes of pain in those infected mandate a holistic approach to managing HIV-associated pain. Ideally, disease-specific therapy, psychosocial interventions and physical modalities should accompany standard analgesic treatment (Glare 2001 **NR**)

8.6.8.2 | Special considerations in treating pain in patients with HIV infection

Drug interactions

Antiretroviral agents (notably non-nucleoside reverse transcriptase inhibitors, protease inhibitors, and the "boosting" agents ritonavir and cobicistat) may cause important drug interactions by inducing and inhibiting various enzymes in the cytochrome P450 family. In addition, both cobicistat and ritonavir inhibit p-glycoprotein and can therefore increase absorption of susceptible drugs from the gastrointestinal tract. Several antiretroviral agents are also hepatically metabolised with potential for drug interactions. Predicting clinically relevant interactions is made extremely complex, both by the fact that antiretroviral drugs are used in combinations and because most interactions have not been formally studied. Updated information on likely interactions between individual antiretroviral agents (and cobicistat) and medications used to treat common comorbidities are provided by The University of Liverpool HIV Pharmacology Group at: https://www.hiv-druginteractions.org/checker (including a chart specific for interactions with a large number of analgesic medicines at https://liverpool-hiv-hep.s3.amazonaws.com/prescribing_resources/pdfs/000/000/002/original/TS_Analgesic_2019_Feb.pdf?1550073234.

The importance of routinely considering interactions with antiretroviral drugs when prescribing for individuals with HIV is highlighted by the variable interactions seen with opioids. For example, ritonavir (an HIV protease inhibitor) is a potent inhibitor of cytochrome P450 3A4. This results in clinically relevant inhibition of fentanyl metabolism (Olkkola 1999 **Level II**, n=12, JS 3), but no clinically meaningful interaction with methadone or buprenorphine (McCance-Katz 2003 **Level III-2**). Conversely, both lopinavir (another protease inhibitor) (McCance-Katz 2003 **Level III-2**) and nevirapine (a non-nucleoside reverse transcriptase inhibitor) (Arroyo 2007 **Level III-3**, n=10) significantly induce methadone metabolism and may lead to withdrawal in patients on maintenance doses. Reference to current resources such as the Liverpool site, together with involvement of a pharmacist

experienced in this area whenever possible, is strongly recommended when prescribing additional medications to patients on antiretroviral therapy.

Some medications used to treat opportunistic infections in HIV patients may also interact with analgesics. For example, both rifampicin and rifabutin may increase opioid metabolism (particularly methadone) (Finch 2002 **NR**) and fluconazole (and other azoles) may potentiate adverse effects of methadone (Tarumi 2002 **CR**). A useful online tool for checking interactions with antifungal agents and other medications, including analgesics, can be found at http://www.fungalpharmacology.org, which also offers a free app for smartphones.

HIV patients with a history of substance abuse

Pain may be more common in those with HIV and a history of injecting drugs (Martin 1999 **Level III-2**, n=211; Vogl 1999 **Level IV**, n=504) and is more likely to be inadequately treated in this group (Breitbart 1997 **Level IV**; Breitbart 1996 **Level IV**). Two cohort studies showed that that even though HIV-positive patients with a history of problematic illicit drug use/substance abuse report higher ongoing use of prescription analgesics specifically for pain, these patients continue to experience persistently higher levels of pain, relative to nonproblematic users (Tsao 2007 **Level III-2**, n=2,267; Passik 2006 **Level III-2**, n=73 [AIDS patients]). Importantly, opioid analgesia was similarly effective for treating severe pain in those with AIDS who had previously injected drugs as in those who were opioid naïve, although higher doses were required (Kaplan 2000 **Level III-2**, n=44). Similarly, patients in a methadone-maintenance program, who also suffered from HIV/AIDS-related pain, gained improved analgesia without adverse effects with use of additional methadone (Blinderman 2009 **Level IV**, n=53).

The principles of pain management in patients with a history of substance abuse are outlined in Sections 9.7 and 9.8.

KEY MESSAGES

1. High-concentration capsaicin patches have some efficacy in treating neuropathic pain in patients with HIV/AIDS (**S**) (**Level I** [Cochrane Review]).
2. Smoking cannabis has short-term efficacy in treating neuropathic pain in patients with HIV/AIDS, although potential study bias means that this is not recommended as routine treatment (**Q**) (**Level I** [PRISMA])**.**
3. HIV/AIDS patients with a history of problematic drug use report higher opioid analgesic use but also more intense pain (**U**) (**Level III-2**).
4. Pain, and notably neuropathic pain, is common in patients with HIV (**U**) (**Level IV**).

The following tick boxes represent conclusions based on clinical experience and expert opinion:

☑ HIV/AIDS has become a chronic, manageable condition; in view of limited specific evidence, the treatment of pain in patients with HIV/AIDS should be based on similar principles to those for the management of acute, cancer and chronic pain in the general population (**S**).

☑ Interactions between antiretroviral medications, antibiotics and analgesics should be considered in this population and reference to a current guide of likely drug interactions is strongly recommended (**S**).

8.7 | Acute back pain

Acute back pain in the cervical, thoracic or, in particular, lumbar and sacral regions, is a common problem affecting most adults at some stage of their lives. The causes are rarely from serious pathology (Hartvigsen 2018 **NR**). Acute back pain is most often nonspecific and the pain is usually self-limiting; however, recurrence is common and for a small percentage of people, acute back pain becomes persistent and disabling. Overuse of imaging, opioids, and surgery in back pain management remains a widespread problem (Maher 2017 **NR**).

Appropriate investigations are indicated in patients who have signs or symptoms that might indicate the presence of a more serious condition ('red flags'). Such 'red flags' include symptoms and signs of infection (eg fever), risk factors for infection (eg underlying disease processes, immunosuppression, penetrating wounds), history of trauma or minor trauma, history of osteoporosis or taking corticosteroids, past history of malignancy, age >50 y, failure to improve with treatment, unexplained weight loss, pain at multiple sites or pain at rest, and the absence of aggravating features (Oliveira 2018 **GL SR**, 10 GL [acute low back pain]). In assessment of new acute back pain, 'red flags' to predict potential cancer as a cause have been proposed, yet the only evidence-based predictor of spinal malignancy is "*previous history of cancer*" (Henschke 2013 **SR** of diagnostic studies; Downie 2013 **SR** of diagnostic studies). A full neurological examination is warranted in the presence of lower limb pain and other neurological symptoms.

Psychosocial and occupational factors ('yellow flags') appear to be associated with an increased risk of progression from acute to chronic pain. Such factors should be assessed early in order to facilitate appropriate interventions (Oliveira 2018 **GL SR**, 10 GL [acute low back pain]).

NHMRC guidelines for the evidence-based management of acute musculoskeletal pain include chapters on acute neck, thoracic spinal and low-back pain (Australian Acute Musculoskeletal Pain Guidelines Group 2003 **GL**). In view of the high quality and extensiveness of these guidelines, and the subsequent publication of more recent international guidelines, no independent assessment of these topics has been undertaken for this document even though the Australian guidelines have been rescinded by the NHMRC because of their age.

However, reviews of best practice for management of low back pain (Strudwick 2018e **GL**) and neck pain (Strudwick 2018f **GL**) in the emergency department have been published by an Australian group.

Other international guidelines include those produced by:

- the Orthopedic Section of the American Physical Therapy Association (APTA) — these also cover acute and chronic back pain (Delitto 2012 **GL**);
- the Toward Optimized Practice (TOP) Program of Canada (Canada TOP 2015 **GL**);
- the NSW Agency for Clinical Innovation (NSW Agency for Clinical Innovation 2016 **GL**);
- the American College of Physicians (ACP) – presenting a clinical practice guideline on noninvasive treatments for acute, but also subacute (and chronic) low back pain (Qaseem 2017 **GL**);
- the Institute for Clinical Systems Improvement (ICSI 2018 **GL**);
- the National Institute for Clinical Excellence (NICE 2018 **GL**).

Overviews of these guidelines have been published (Koes 2010 **GL**; Verhagen 2016 **GL**) including a particularly useful overview of all recent guidelines (Oliveira 2018 **GL SR**, 10 GL [acute low back pain]). The reader is referred to these references for the diagnosis and management of acute back pain. All these high quality guidelines for acute back pain recommend the first-line use of non-pharmacological approaches, including education that supports self-management and resumption of normal physical activity (Foster 2018 **NR**).

8.8 | Acute musculoskeletal pain

A summary of findings relating to acute musculoskeletal pain can be found in *Evidence-based Management of Acute Musculoskeletal Pain*, published by the Australian Acute Musculoskeletal Pain Guidelines Group and endorsed by the NHMRC (Australian Acute Musculoskeletal Pain Guidelines Group 2003 **GL**). In view of the high quality and extensiveness of these guidelines, no further assessment of these topics has been undertaken for this document, even though these guidelines have been rescinded by the NHMRC in view of a lack of an update.

However, reviews of best practice for management of specific musculoskeletal pain conditions in the emergency department have been published by an Australian group:

- ankle and foot injuries (Strudwick 2018b **GL**);
- closed hand and wrist (Strudwick 2018a **GL**);
- common knee injuries (Strudwick 2018c **GL**);
- common shoulder injuries and conditions (Strudwick 2018d **GL**).

The same group has also published quality outcome indicators (Strudwick 2020 **GL**) and process quality indicators (Strudwick 2019 **GL**) for musculoskeletal injuries in the emergency department.

An updated clinical practice guideline for acute musculoskeletal pain has been published by the Musculoskeletal Pain Task Force of the Orthopaedic Trauma Association in the USA (Hsu 2019 **GL**).

Guidelines for specific conditions such as acute shoulder pain by the American College of Radiology (Wise 2011 **GL**) or even more specific for acute and chronic subacromial pain by the Dutch Orthopaedic Association (Diercks 2014 **GL**) have been published.

A systematic review of clinical practice guidelines has been published, which condenses these to eleven key recommensations (Lin 2020 **SR of GLs**, 11 GLs).

Furthermore, the National Institute for Clinical Excellence (NICE) offers access to a multitude of guidelines via a website providing pathways for musculoskeletal conditions:
https://pathways.nice.org.uk/pathways/musculoskeletal-conditions

8.9 | Acute cancer pain

Acute pain in the cancer patient may signify an acute oncological event including pathological fracture or microfracture, spinal cord or nerve compression, visceral obstruction or cutaneous ulceration due to tumour. Cancer pain may become acute in the presence of infection, and during diagnostic or therapeutic interventions. Anticancer therapies, including surgery, chemotherapy, hormonal therapy and radiotherapy, may be associated with both acute and chronic pain of a nociceptive or neuropathic nature. In progressive cancer, there is increasing potential for acute clinical change.

Pain is commonly associated with cancer and is one of the most feared symptoms (Swarm 2019 **GL**). The prevalence of cancer pain in an adult population is 39.3% after curative treatment, 55.0% during anticancer treatment and 66.4% in people with advanced, metastatic or terminal disease, with 38.0% of all patients reporting moderate to severe (NRS $\geq$ 5/10) pain (van den Beuken-van Everdingen 2016 **Level III-3 SR**, 117 studies, n=63,533 [pain prevalence], 52 studies, n=32,261 [pain severity]). It is recommended that all patients with cancer are screened for pain during the initial evaluation and at each subsequent contact, and whenever new therapy is initiated, using self-reported NRS (Swarm 2019 **GL**; AACPMGWP 2019 **GL**).

An overarching systematic review of interventions to treat acute cancer-related pain rates epidural analgesia and local anaesthetic infusions as recommended for clinical practice and gabapentin, intraspinal analgesia, music and music therapy, hypnosis and hypnotherapy as likely to be effective (Sundaramurthi 2017 **Level IV SR**, 114 studies, n unspecified).

8.9.1 | Assessment of acute cancer pain

Acute pain requires urgent assessment to exclude cancer recurrence or an oncological emergency requiring rapid treatment in addition to acute pain management (Swarm 2019 **GL**).

Where malignancy is advanced, there is urgency in differentiating an acute pain crisis, which is readily reversible, from an intractable painful condition (Moryl 2008 **NR**). Standardised assessment tools for the comprehensive assessment of cancer pain are advantageous, and required for quality research trials (Caraceni 2019 **NR**). There is no consensus on the ideal multidimensional pain-assessment tool for cancer pain, with electronic tools and a standard prognostic classification system for cancer pain being considered (Arthur 2017 **Level IV**, n=386; Burton 2014 **NR**). Palliative-care physicians identified the most important dimension to assess was pain intensity with unidimensional tools (eg NRS, VRS) followed by documentation of temporal pattern, treatments, exacerbating or relieving factors, location, pain interference, pain quality, pain affect, duration, pain beliefs and previous pain history (Holen 2006 **NR**). The revised Edmonton Staging System, the MPQ and the Brief Pain Inventory are well validated in many settings (Arthur 2017 **Level IV**, n=386; Gauthier 2014 **Level IV**; Nekolaichuk 2013 **Level IV**; Wu 2010 **Level IV**; Bennett 2009 **Level IV**; Fainsinger 2005 **Level IV**; Ngamkham 2012 **NR**).

8.9.2 | Principles of management of acute cancer pain

Comprehensive consensus best-practice guidelines relating to cancer pain management have been developed by several agencies worldwide (with online access provided to most) (AACPMGWP 2019 **GL**; Swarm 2019 **GL**; Fallon 2018 **GL**; Jara 2018 **GL**; WHO 2018 **GL**; Scarborough 2018 **NR**). A person-centred, multidisplinary team approach involving allied care health professionals and primary care health professionals is a recommended approach to pain management.

The WHO Analgesic Ladder (WHO 1996 **GL**) underpins these guidelines but was determined to provide inadequate pain relief in 12% of patients (Zech 1995 **Level IV**, n=2,118). Hence the WHO ladder has undergone considerable scrutiny over the last decade with proposals to abolish the second step of the WHO analgesic ladder in favour of the early use of morphine at low doses gaining more favour (Fallon 2018 **GL**). Where pain is moderate to severe, a jump from Step I (simple analgesics) directly to Step III (strong opioids) reduces the time to pain control relative to staged progression through Step II (weak opioids) (Maltoni 2005 **Level II**, n=54 [prematurely terminated], JS 2). In adult patients with moderate cancer pain, low-dose morphine had significantly higher response rate and early onset of response vs weak opioids (Step II), with a similarly good tolerability and comparable opioid-related adverse effects (Bandieri 2016, **Level II**, n=240, JS 3).

Simple analgesics, adjuvants and specific targeted therapies, such as anticonvulsant medicines for neuropathic pain and radiotherapy and bone-modifying agents for metastatic bone pain, should be considered at every step of the ladder. Despite availability of numerous consensus guidelines, a survey of Australian palliative care physicians identified barriers to best practice, notably access to nonpharmacological interventions, patient-educational resources, and optimal care coordination (Lovell 2013 **Level IV**).

Patient education about cancer pain is a key factor in optimising pain management (Marie 2013 **Level I**, 15 RCTs, n=1,710; Martinez 2014 **Level III-2 SR** 16 RCTs & 3 studies, n=2,192; Lee 2014 **Level III-3 SR**, 12 RCTs, n=2,380 & 5 studies, n=475; Lovell 2014 **NR**). Despite this, a patient-centred approach is often overlooked in guidelines (Luckett 2013 **Level IV SR**, 70 studies, n unspecified). For all patients with pain, education should be provided about cancer-related pain and its management with verbal and written information. It is also recommended to include the person's family, carers and significant others in education process (AACPMGWP 2019 **GL**).

There is similar urgency in managing an acute pain crisis in the patient with cancer as there is when managing any other medical crisis. Acute pain, particularly in patients with terminal cancer, causes immense distress in the patient, the family and the care team (Moryl 2008 **NR**). In such a crisis, hospital admission should be considered to evaluate the patient, assess and manage the aetiology of pain and achieve patient-specific pain goals (Swarm 2019 **GL**). Treatment of the underlying cause of pain may be urgent.

For data specific to pain management in children with cancer see Section 10.8.

8.9.3 | Medicines for acute cancer pain

8.9.3.1 | Paracetamol and NSAIDs

Any addition of NSAIDs or paracetamol to strong opioids should be justified on the basis of individual improved analgesia or reduction of opioid-related adverse effects, recognising the NSAID-associated risks of gastrointestinal bleeding and relative contraindications in patients with renal, hepatic and cardiac failure.

There is no convincing evidence that addition of paracetamol to established treatment with strong opioids provides any analgesic or quality of life benefit for cancer pain in adults (Wiffen 2017b, **Level I** [Cochrane], 3 RCTs, n=122).

The efficacy of oral NSAIDs for moderate or severe cancer pain alone or combined with opioids in adults is not supported by high-quality evidence (Derry 2017b **Level I** [Cochrane], 11 RCTs, n=949). There is very low-quality evidence that NSAIDs reduce pain after 1 to 2 wk of treatment (4 RCTs). Side-effects were inconsistently reported and discontinuation occurred commonly due to lack of efficacy (24%) or adverse events (5%). This is supported by a subsequent systematic review, which found no additional high-quality evidence and was unable to draw conclusions

due to heterogeneity in outcome measures and short duration of follow-ups (Magee 2019 **Level I**, 30 RCTs, n=2,329).

Use of parecoxib by continuous SC infusion for 7 days in cancer patients in a hospice setting resulted in a reduction in pain scores and the number of rescue opioid doses required without an opioid-sparing effect (Armstrong 2018, **Level III-3**, n=80).

Metamizole (dipyrone), another non-opioid analgesic, is effective in reducing cancer pain intensity vs placebo, even at low doses (1.5 to 2 g/d), with higher doses (3 x 2 g/d) being more effective than low doses (3 x 1 g/d) (Gaertner 2017 **Level III-2 SR**, 4 studies, n=252)

8.9.3.2 | Conventional and atypical opioids

Opioid analgesics play an important role in pain management for patients with cancer (NICE 2016a **GL**; Caraceni 2012 **GL**; Ripamonti 2011 **GL**; WHO 1996 **GL**). Nineteen out of 20 people with moderate or severe pain who were given and tolerated opioids have a reduction in pain intensity to mild or no pain within 14 d, although quantity and quality of evidence for this is low (Wiffen 2016 **Level I** [Cochrane], 9 SRs [152 RCTs], n= 13,524).

If the patient persistently requires doses of "as-needed" opioids, or if the "around-the-clock" opioid regimen fails to relieve pain at peak effect or at end of dose, it is recommended to consider increasing the dose of slow-release opioids (Swarm 2019 **GL**).

There is increased likelihood of patients using higher than 200 mg of oral morphine equivalent at home being undertreated with prn opioids in emergency departments (Patel 2017 **Level III-2**, n=216).

See also Section 4.3.1.

Routes of administration

Rapid analgesic control of acute pain or persistent pain exacerbations may be achieved with a regular dose schedule of a parenteral opioid with frequent reassessment and dose adjustment, or by use of PCA techniques. A single RCT demonstrated more rapid pain control with IV than oral morphine for severe cancer pain (Harris 2003 **Level II**, n=62, JS 2). IV and SC bolus dosing and infusions have similar tolerability and efficacy but IV route provides faster relief (Radbruch 2011 **Level III-2 SR**, 18 studies, n=674; Elsner 2005 **Level II**, n=39, JS 2; Anderson 2004 **NR**). The use of IV or SC PCA in patients with cancer pain is a safe and convenient method of delivering opioid analgesia (Nijland 2019 **Level IV SR,** 6 RCTs & 44 studies, n unspecified).

Consensus clinical practical guidelines and systematic reviews are available to guide the administration of short-acting opioids including IV, SC and rectal morphine in exacerbations of pain (Swarm 2019 **GL**; WHO 2018 **GL**; Caraceni 2012 **GL**; Klepstad 2011 **GL**).

Controlled release formulations

Once acute pain control is achieved, analgesia should be maintained with CR preparations of opioids. There is a lack of good evidence in the patient with cancer pain for differences in efficacy or safety between various CR opioids (Mesgarpour 2014 **Level III-2 SR**, 5 RCTs & 4 studies, n=2,626).

Combination opioid therapy

Combination opioid therapy for poorly controlled cancer pain has little evidence to support the practice despite encouraging preclinical scientific studies, and well-designed studies are needed (Fallon 2011 **Level III-2 SR**, 2 studies, n=36).

Opioid rotation/switching

Opioid rotation, due to preference, uncontrolled pain or intolerable adverse effects, may improve opioid response and reduce adverse effects (Mercadante 2011 **Level III-2 SR**, 31 studies, n=1,885). Opioid conversion should be carefully individualised, as conversion ratios may be

influenced by multiple factors including relative potency, prior doses, tolerance and reason for switch (Webster 2012 **NR**). Conversion ratios are less predictable at higher opioid doses and conversion tools of which there are many should be used with caution as opioid rotations undertaken based on such tables alone without consideration of clinical factors carry a significant risk of toxicity and even fatality.

When health care professionals (physicians, pharmacists, and nurse practitioners/physician assistants) were surveyed, there was a large variation in mean opioid conversions (Rennick 2016 **Level IV**, n=319). A detailed analysis of equianalgesic doses and suggestions for opioid rotations based on these calculations has been published (Treillet 2018 **Level IV SR**, 20 studies, n=949). FPMANZCA provides an opioid calculator including references and background material on a website (FPMANZCA 2019 **GL**), which is also available as an app ("Opioid Calculator") for smartphones.

Scientific evidence for opioid rotation remains poor because of a lack of controlled studies (Jara 2018 **NR**), although a parallel systemic review concluded that opioid rotation can improve analgesia and patient satisfaction (Schuster 2018 **Level IV SR** [PRISMA], 3 SRs, 4 RCTs & 5 studies, n=3,021).

Opioids in patients with renal dysfunction

Fentanyl, alfentanil and sufentanil are recommended in patients with renal impairment based on pharmacokinetics and clinical experience although there is very little clinical evidence for this (Sande 2017 **Level IV SR**, 18 studies, n=2,422). Morphine, hydrocodone and pethidine are not recommended in patients receiving dialysis treatment. Hydromorphone and fentanyl are advocated as safe opioids in patients receiving dialysis due to their favourable pharmacokinetic profile. Based on inconclusive evidence, morphine and oxycodone should be used with caution in patients with renal failure.

See also Section 9.6.

Side effects

As opioid-naïve patients are more vulnerable to opioid adverse effects, pre-emptive plans for aggressive management of adverse effects need to be clearly documented, including for prophylaxis against constipation from the onset of opioid therapy (for more details see also Section 4.3.1.4).

There is no evidence that opioids used for pain control in terminal cancer have any adverse impact on patient survival (Lopez-Saca 2013 **Level III-3 SR**, 10 studies, n=2,964). Optimising patient comfort, function and safety should be the goal of care. All management options should be fully discussed with the treating and palliative care teams, to meet the physical, psychosocial and existential needs of the patient and family, with consideration of an end-of-life care pathway when cancer is advanced.

Opioids have immunoregulatory actions that vary with mode and timing of administration. Concern regarding the potential impact of opioids on immune tumour surveillance is increasing. Overall, there is currently inadequate evidence to guide opioid selection in cancer patients, based on immune function, as no studies have measured any clinical endpoints or outcomes, including cancer progression or disease-free survival (Boland 2014 **Level III-3 SR**, 5 studies, n=106).

Conventional Opioids

Morphine

Oral morphine remains an effective analgesic for cancer pain (Wiffen 2016 **Level I** [Cochrane], 62 RCTs, n=4,241). Pain relief did not differ between CR and IR formulations. CR preparations of morphine were effective for 12- or 24-hrly dosing depending on the formulation. Adverse events were common and predictable; approximately 6% of participants discontinued treatment with

morphine because of intolerable adverse events. Morphine's efficacy and toxicity are related to morphine and morphine-metabolite concentrations (Gretton 2013 **Level III-2**, n=212). Higher morphine and metabolite concentrations are associated with severe central adverse effects, including drowsiness, confusion or hallucinations, particularly with higher metabolite:morphine ratios in plasma. Myoclonus occurs unpredictably at morphine doses >400 mg/d, with higher morphine and metabolite concentrations in adults with moderate to severe cancer pain.

Codeine

Despite shortcomings in the evidence available (small study size, other risk of bias, clinical and methodological heterogeneity), available evidence indicates that codeine is more effective in cancer pain treatment than placebo (Straube 2014 **Level I** [Cochrane], 15 RCTs, n=721).

Fentanyl

The TD route of administration is inappropriate for unstable acute pain due to its slow titratability. In cancer patients, TD fentanyl shows similar effectiveness for pain control as TD buprenorphine (Ahn 2019 **Level III-2 SR** [NMA], 15 studies & 2 SRs, n= 6,368) and oral morphine (RR 1.00; 95%CI 0.97 to 1.03) (29 RCTs, n=2,769), but lower rates of constipation (35 RCTs), nausea and vomiting (31 RCTs), drowsiness (28 RCTs), and urinary retention (24 RCTs) (Wang 2018a **Level I** [PRISMA], 35 RCTs, n=3,406). Studies of TD fentanyl for chemoradiation-induced mucositis indicated only gradual reduction in pain intensity over several days (Xing 2014 **Level III-3**, n=46).

Hydromorphone

Hydromorphone provides similar pain relief as oxycodone or morphine with a consistent analgesic effect, although overall quality of the evidence was very low (Bao 2016 **Level I** [Cochrane] 4 RCTs, n=604). Hydromorphone effectively reduced pain that was inadequately controlled by other analgesics, although pain relief was not associated with improved quality of life (Han 2014 **Level III-3**, n=432). Once-daily hydromorphone CR vs oxycodone CR BD (Yu 2014 **Level II**, n=137, JS 5) and hydromorphone IR QID vs oxycodone IR QID (Inoue 2018 **Level II**, n=183, JS 5) were non-inferior for relieving moderate to severe cancer pain.

Methadone

Appropriately titrated methadone, although more difficult to manage than morphine, has similar efficacy and tolerability and has a role in treating cancer pain (Nicholson 2017 **Level I** [Cochrane], 6 RCTs, n=388). Methadone requires considerable care in dose estimation, titration and monitoring, due to complex pharmacokinetics/pharmacodynamics and marked variability in response (Good 2014 **Level I**, 4 RCTs, n=272). Guidelines outline starting doses and recommended monitoring for drug accumulation and adverse effects, particularly over the first 4 to 7 days, with the caution that a steady state may not be reached for several days to 2 wk (McPherson 2019 **GL**; Swarm 2019 **GL**). Low-dose methadone may improve pain control when used as a co-analgesic in patients with cancer-related pain that were receiving another regularly scheduled opioid analgesic (Courtemanche 2016 **Level III-3**, n=146)

Oxycodone

Oxycodone provides similar analgesia and has a similar adverse effect profile to morphine; these agents can be interchangeable as first-line oral opioids for treatment of cancer-related pain (Schmidt-Hansen 2017 **Level I** [Cochrane], 23 RCTs, n=2,648); oxycodone CR provides similar analgesia to oxycodone IR with no significant differences in adverse events. Oxycodone/naloxone CR preparations are an effective treatment for moderate to severe cancer-related pain and provide relief from opioid-induced constipation (Morlion 2018 **Level III-3 SR**, 7 studies, n=981).

Atypical opioids in cancer pain

Buprenorphine

There is insufficient evidence to recommend buprenorphine as a first-line choice for cancer-related pain vs standard opioids like morphine, oxycodone and fentanyl (Schmidt-Hansen 2015 **Level I** [Cochrane], 19 RCTs, n=1,421). However, its various routes of administration, in particular TD (Ahn 2019 **Level III-2 SR** [NMA], 15 studies & 2 SRs [10 TD buprenorphine], n= 6,368) and SL, make it a practical option in some patients and in some clinical settings.

Tapentadol

There are limited data to support tapentadol use in cancer pain with insufficient numbers to pool RCTs; efficacy and safety were comparable to morphine and oxycodone (Wiffen 2015 **Level I** [Cochrane], 4 RCTs, n=1,029; Mercadante 2017 **Level IV SR**, 2 RCTs & 6 studies, n=791) (2 RCTs overlap). It may be a suitable alternative in patients who suffer considerable nausea, vomiting or constipation with use of conventional opioids (Mercadante 2017 **Level IV SR**, 2 RCTs & 6 studies, n=791; Kress 2019 **NR**). Opioid-tolerant cancer patients taking the equivalent of at least 60 mg oral morphine daily could be rotated to tapentadol (oral conversion ratio morphine:tapentadol 1:3.3) with significant improvement in pain control within the first week and few withdrawals due to uncontrolled pain (5/30), adverse effects (2/30) or other reasons (3/30) (Mercadante 2014 **Level III-3**, n=30). An analgesic benefit of controlled-release tapentadol for moderate to severe bone pain in opioid-naïve myeloma patients was found (Coluzzi 2015 **Level III-3**, n=25). Patients with haematological malignancies treated with slowly titrated doses of tapentadol (to a final dose of 244 mg ±106) for 1 mth showed reduction in neuropathic pain from 54% to 14%, and improvement in sleep quality to "good" or "refreshing" from 20% to 95% of patients (Brunetti 2016 **Level III-3**, n=36).

Tramadol

Tramadol (with or without paracetamol) has only limited, very low-quality evidence supporting its use for treatment of cancer pain; tramadol is not as effective as morphine in this setting (1 RCT, n=227) (Wiffen 2017a **Level I** [Cochrane], 10 RCTs, n=958). As a non-controlled substance, it plays an important role in the treatment of cancer pain in countries where it may be the only opioid treatment option eg in parts of South-East Asia (Vijayan 2018 **NR**).

8.9.3.3 | NMDA receptor antagonists

Ketamine

Despite extensive evidence to support the use of ketamine for acute perioperative pain and procedural analgesia, very limited evidence guides its use in cancer-related pain (Bell 2017 **Level I** [Cochrane] 3 RCTs, n=215; Bredlau 2013 **Level IV SR**, 5 RCTs & 6 studies, n=483). The largest multicentre RCT included in these systematic reviews concluded that ketamine had no therapeutic benefit with an adverse safety profile in cancer patients (Hardy 2012 **Level II**, n=187, JS 5). Despite relating to chronic moderate to severe pain in a palliative setting and a broad patient population, this trial has negatively influenced the use of ketamine for all cancer-related pain, including acute exacerbations, with resultant debate and calls for further controlled studies targeting more specific cancer pain populations (Hardy 2014 **Level IV**, n=123 [clinicians]; MacKintosh 2012 **Level IV**; Jackson 2013 **NR**; Leppert 2013 **NR**). Certain types of cancer pain, including mucositis, bone and neuropathic pain, may be "good responders" to ketamine and merit more focussed, higher quality, controlled studies (Jackson 2005 **NR**).

Larger case series and individual reports have highlighted the wide range of clinical situations, routes of administration and dose schedules for ketamine in the cancer setting. Ketamine has been used successfully for morphine-resistant pain (Mercadante 2000 **Level II**, n=10 [cross over], JS 3), acute incident pain (Mercadante 2009 **Level IV**, n=2) and for cancer patients in the perioperative

period, where ketamine can be morphine-sparing, lower pain scores and promote earlier return of function (Nesher 2009 **Level II**, n=44, JS 3; Kollender 2008 **Level II**, n=60, JS 5). Oral and topical use of ketamine resulting in effective analgesia has been described in case series (Okamoto 2013 **Level IV**, n=46; Uzaraga 2012 **Level IV**, n=16; Soto 2012 **NR & CR**; Amin 2014 **CR**). Analgesia was successfully maintained when continuous ketamine infusion was converted to oral ketamine (Benitez-Rosario 2011 **Level III-2**, n=29). Topical ketamine-amitriptyline did not reduce chemotherapy-induced peripheral neuropathic pain (Gewandter 2014 **Level II**, n=462, JS 5).

Magnesium

Elemental magnesium (65 mg BD) added to morphine in patients with cancer did not improve analgesia, functional performance or quality of life nor reduce side effects (Baaklini 2017 **Level II**, n=43, JS 4).

8.9.3.4 | Glucocorticoids

Common indications for glucocorticoids in cancer include spinal cord compression, superior vena cava compression, raised intracranial pressure, bowel obstruction, anorexia and pain related to inflammation, bone tumour or neuropathy. Despite good evidence for many of these clinical scenarios, only weak evidence supports glucocorticoids for cancer pain (Paulsen 2013 **Level I** [PRISMA], 4 RCTs, n=667; Leppert 2012 **NR**). Methylprednisolone provided no significant analgesic benefit but improved fatigue, appetite and patient satisfaction (Paulsen 2014 **Level II**, n=50, JS 5). A meta-analysis of studies comparing corticosteroids, notably dexamethasone, to standard therapy did suggest a statistically significant, but clinically limited, reduction in cancer pain at 1 wk (MD -0.84/10; 95%CI -1.38 to -0.30); however, data were flawed by attrition, potential bias, small sample size and infrequent indication of adverse effect rates (Haywood 2015 **Level III-2 SR** [Cochrane], 15 studies, n=1,926). Once-daily dexamethasone (average dose of 13 mg [SD 10]) recommended by a specialty palliative care team in patients with cancer pain receiving opioids resulted in an opioid-sparing (-23% MEDD) and analgesic effect (-19% pain scores); in 61% the pain was primarily acute cancer pain (Barghi 2018 **Level III-3**, n=59).

Consequently, no recommendation can be made regarding selection of glucocorticoid, dose, route or duration of administration, and adverse-effect profile. Dexamethasone is often preferred due to high potency, long duration of action and minimal mineralocorticoid effect. Immediate adverse effects include immunosuppression, hyperglycaemia and psychiatric disorders, whereas longer-term use increases risk of proximal myopathy, peptic ulceration, osteoporosis and Cushing's syndrome (Leppert 2012 **NR**). Steroid/nsNSAID combination therapy in a large population of general hospitalised patients resulted in a 15-fold increase in gastrointestinal bleeding, reinforcing the need for gastroprotective therapy (Piper 1991 **Level III-2**, n=7,478). If glucocorticoids are used in the acute setting for >3 wk, a schedule of dose reduction must precede cessation.

8.9.3.5 | Anticonvulsants and antidepressants

Combining opioid analgesia with alpha-2-delta ligands does not improve pain relief in patients with cancer pain vs opioid monotherapy, although benefit in patients with neuropathic cancer pain could not be excluded due to heterogeneity of patient samples (Kane 2018 **Level I SR** [PRISMA], 7 RCTs, n=605); data on amitriptyline, fluvoxamine, and phenytoin were inconclusive. However, RCTs not included in the systemic review above support use of gabapentin with opioids in severe cancer pain (VAS≥7) (Chen 2016 **Level II**, n=60, JS 5) and pregabalin with opioids in cancer patients with severe neuropathic pain (Dou 2017 **Level II**, n=40, JS 4). Pregabalin was more effective in relieving neuropathic cancer-related pain vs TD fentanyl (Raptis 2014 **Level II**, n=120, JS 3).

8.9.3.6 | Cannabinoids

In cancer pain, very low-quality evidence shows no benefit of nabiximols or THC (the only cannabinoids in the included RCTs) on any outcome including pain, sleep problems and opioid consumption, with increased adverse events (GI and nervous system) (Hauser 2019 **Level I** [PRISMA], 5 RCTs, n=1,534). There is no convincing, unbiased, high quality evidence for an effect of cannabinoids on anorexia or cachexia in a palliative care setting (Mucke 2018 **Level I** [PRISMA], 9 RCTs, n=1,561).

8.9.4 | Breakthrough pain

The term "breakthrough pain" typically refers to a transitory acute flare-up of pain in the setting of chronic cancer pain managed with a fixed opioid drug schedule. On the basis of two Delphi surveys, breakthrough pain has been defined as *"a transient pain exacerbation that can occur in patients with stable and adequately controlled background pain not necessarily treated with opioids"* (Lohre 2016 **GL**). There are specific tools that have been recommended to assess the prevalence and severity of breakthrough pain in patients with cancer (Webber 2014 **GL**). Despite stable therapy, breakthrough pain is common, heterogeneous, frequently severe or excruciating, often paroxysmal, and may occur several times daily for seconds to hours in duration (Deandrea 2014 **Level IV SR**, 33 studies, n unspecified; Portenoy 1990 **Level IV**, n=63). Some episodes of breakthrough pain may be an end-of-dose failure of maintenance opioids. In contrast, incident pain is predictably precipitated by some movement or action. Assessment should elucidate the severity, duration, pattern and cause of breakthrough pain.

Conventional management guidelines dictated that the opioid breakthrough dose should be a proportion (one-sixth to one-tenth) of the daily dose; for example, an oral breakthrough dose of morphine would be equivalent to a 4-hourly dose, or one-sixth the oral morphine equivalent daily dose. However, there is little evidence to support the standard practice of utilising the same opioid for breakthrough pain as for maintenance analgesia, and most recent studies indicate a poor relationship between rescue and maintenance doses (Zeppetella 2011). Rescue medication used for breakthrough pain should ideally have a pharmacokinetic profile that mirrors the time-course of that pain and ideally have high potency, rapid onset and fast offset. Meta-analyses of emerging evidence support the rapid efficacy and safety of several transmucosal immediate-release fentanyl (TIRF) preparations for breakthrough pain (Zeppetella 2013 **Level I** [Cochrane] 15 RCTs, n=1,699; Rogriguez 2015 **Level I**, 11 RCTs, n unspecified; Jandhyala 2013 **Level I**, 5 RCTs, n=415; Brant 2017 **NR**) (significant overlap between all 3 SRs) (see also Section 5.5.3.1). These TIRF are superior to placebo at 15 min and require individual titration to effect. The titrated rescue dose is largely independent of background opioid dosing (Portenoy 1999 **Level IV**). The slower onset of oral morphine (45 min) limits its suitability to more gradual-onset pain or for pre-emptive anticipation of incident pain (1 RCT, n=89) (Zeppetella 2014 **Level I** [NMA], 10 RCTs [various transbuccal fentanyl formulations], n=892). Notably, not all breakthrough pain may be opioid responsive. A large observational study identified 23% of patients who found nothing to relieve their breakthrough pain, indicating further investigations are required in this area (Davies 2013 **Level IV**, n=1,000).

8.9.5 | Acute neuropathic cancer pain

8.9.5.1 | Incidence and diagnosis of neuropathic cancer pain

Neuropathic pain or mixed nociceptive-neuropathic pain has an estimated frequency of 31 to 40% in patients with cancer (Roberto 2016 **Level IV SR**, 40 studies (29 general cancer & 17 palliative settings), n=18,136; Bennett 2012 **Level IV SR**, 22 studies, n=13,683). Diagnosis was largely based on

clinical judgement rather than objective criteria, and most studies predated the updated IASP definition of neuropathic pain as pain due to a disease or lesion in the somatosensory system. Peripheral or central neuropathic pain may result from disease progression, cancer treatment, a comorbid condition or be multifactorial. No clear standardised approach or taxonomy has been used to assess neuropathic pain in cancer or to guide treatment. Improvements in the classification, assessment and diagnosis of neuropathic cancer-pain conditions are required to address gaps in understanding of this diverse condition (Lema 2010 **NR**). The neuropathic grading scale of the Neuropathic Pain Special Interest Group of the IASP is recommended for use in cancer patients to facilitate recognition, management and study of neuropathic cancer pain (Mulvey 2014 **GL**). Screening tools recommended for neuropathic pain such as Leeds Assessment of Neuropathic Symptoms and Signs (LANSS), Douleur Neuropathique en 4 (DN4) or painDETECT (PDQ) show concordance with clinicians' diagnosis of neuropathic pain in cancer patients (Mulvey 2017 **Level IV SR**, 6 studies, n=2,301).

8.9.5.2 | Treatment of neuropathic cancer pain

Adjuvant medications may be needed for acute or persistent neuropathic cancer pain that is poorly responsive to opioids, or where opioid intolerance limits further dose escalation. Acute neuropathic cancer pain may also be associated with inflammation and require specific targeted therapy. A systematic review of European clinical practice guidelines for management of cancer-associated neuropathic pain highlighted a lack of evidence (Piano 2014 **SR**, 9 GLs). Extrapolation of data from individuals without cancer to a population with neuropathic cancer pain may not provide optimal care. Only 11% of references supporting European clinical practice guidelines came from patients with cancer.

All of the guidelines include recommendations for TCAs as first-line treatment, despite the lack of high-level evidence. Imipramine (to 75 mg; 1 RCT) and amitriptyline (to 50 mg; 1 RCT) in small RCTs in patients with advanced cancer or chemotherapy-induced painful neuropathy has resulted in only a small analgesic benefit, with increased adverse effects including sedation, confusion and dry mouth (Bennett 2011b **Level I**, 2 RCTs [TCAs], n=85). A further systematic review included two additional amitriptyline RCTs (to 100 mg), one venlafaxine and one trazodone RCT and calculated the weighted mean absolute risk benefit for antidepressants overall as 0.55 (95%CI 0.40 to 0.69) (Jongen 2013 **Level III-2 SR**, 6 RCTs [antidepressants], n=189 [analysed]); this is comparable to the effect of anticonvulsants here.

Anticonvulsant medications added to opioids for control of neuropathic pain caused by cancer have also only a small effect (Bennett 2011b **Level III-2 SR**, 3 RCTs and 3 studies [anticonvulsants], n=380). Anticonvulsants (gabapentin 2 RCTs and 2 studies; sodium valproate 1 study; phenytoin 1 RCT) provide limited improved analgesia within 4 to 8 d, after which benefits do not further increase. The addition of an adjuvant to a stable opioid dose results in only modest pain reduction at the expense of increased adverse effects, whereas when opioid dose is lowered after the introduction of the adjuvant, pain intensity is maintained or reduced, and adverse effects decreased. A further systematic review calculated a mean absolute relative benefit of 0.57 (95%CI 0.43 to 0.70) for anticonvulsants (Jongen 2013 **Level III-2 SR**, 14 RCTs & 16 studies, n=2,267) (2 RCTs & 3 studies overlap); gabapentin was the most studied anticonvulsant. A systematic review of pregabalin for neuropathic pain in cancer was unable to make any clear recommendations due to limitations in the study methodology and data (Bennett 2013 **Level IV SR**, 1 RCT, 3 studies & 1 CR, n= 761). A single RCT (included in both systematic reviews) compared the efficacy of amitriptyline, pregabalin and gabapentin for severe neuropathic cancer pain and reported efficacy of all treatments but superiority of pregabalin (Mishra 2012 **Level II**, n=120, JS 4).

Beneficial effects of antidepressants and anticonvulsants are found overall to outweigh harms in neuropathic cancer pain (Jongen 2013 **Level III-2 SR**, 14 RCTs & 16 studies, n=2,267). Benefits did not differ for neuropathic and mixed nociceptive-neuropathic pain states. Use of anticonvulsants or antidepressants in combination pharmacotherapy vs controls reduces global pain (MD -0.41/10; 95%CI -0.70 to -0.12) (Guan 2016 **Level I**, 8 RCTs, n=1,359).

Lack of data precluded conclusions regarding opioids alone, however oral methadone vs TD fentanyl in treating neuropathic pain in patients with head-and-neck cancer resulted in better analgesia at 1 and 3 wk (Haumann 2016 **Level II**, n=52, JS 3). In cancer pain in general, combining opioids with gabapentin or pregabalin does not improve pain relief and data on amitriptyline, fluvoxamine and phenytoin are inconclusive (Kane 2018 **Level I** [PRISMA], 7 RCTS, n=605). See also Section 8.1.4.

8.9.5.3 | Painful chemotherapy-induced peripheral neuropathy

Chemotherapy-induced peripheral neuropathy (CIPN) is resistant to treatment and remains poorly understood although multiple risk factors have been identified including cumulative chemotherapy dose, genetics, age, history of diabetes, history of neuropathy and low levels of physical activity (Kim 2017b **NR**). Approximately 68% of patients developed CIPN within 30 d of any chemotherapy and by 6 mth 30% of patients are still affected by CIPN (Seretny 2014 **Level III-3 SR** [PRISMA], 31 studies, n=4,179).

Acute severe CIPN may adversely limit cancer treatment and hence survival, while chronic CIPN is a major cause of pain and poor QoL in survivors. Chemotherapies causing painful CIPN include vinca alkaloids (vincristine), platins (cisplatin, oxaliplatin), taxanes (paclitaxel, docetaxel), the proteasome inhibitor bortezomib and immunomodulatory agent thalidomide. Each class of agent has a distinct neuropathology, site of toxicity in the peripheral nerves and risk profile (Park 2013 **NR**). CIPN is dependent on dose and duration of treatment. CIPN is a predominantly sensory neuropathy, with many agents at higher doses also causing myalgia and myopathy (taxanes), muscle cramps (oxaliplatin, vincristine, thalidomide) and autonomic neuropathy (vincristine, bortezomib). Paclitaxel and oxaliplatin have distinct acute and chronic CIPN syndromes. Significant acute neurotoxicity complicates oxaliplatin infusion in 90% of patients for up to 1 wk and is exacerbated by exposure to cold. Acute pain (1 wk) is caused by oxaliplatin in 55.6% and chronic peripheral neuropathic pain in 49.2% of patients (Brozou 2018 **Level IV SR** [PRISMA], 96 studies, n unspecified).

Paclitaxel-induced acute pain syndrome with painful paraesthesias and numbness, poor motor skills, myalgias and arthralgias may persist up for up to 4 d. Bortezomib-induced CIPN is a common small-fibre neuropathy characterised by severe, sharp, burning pain in the feet that resolves by 3 mth in most affected patients. The severity of acute neuropathy and pain (paclitaxel, oxaliplatin) and the use of combination chemotherapies promoting neurotoxicity may be predictors of chronic CIPN.

There is a lack of evidence to support any agent for prevention of CIPN. Current protective strategies include dose modification or cessation of the causative chemotherapy. Risk stratification should include identification of individuals with pre-existing conditions predisposing to peripheral neuropathy. Multiple natural products and complementary therapies have been evaluated as possible preventive measures with some evidence that vitamin E and glutamine may prevent development of CIPN (Brami 2016 **Level I**, 13 RCTs, n=1,341).

There is limited specific evidence to guide treatment of established CIPN. Duloxetine (30 mg titrated to 60 mg/d over 5 wk) resulted in a modest reduction in pain severity vs placebo (MD -1.06/10; 95%CI 0.72 to 1.40); additional benefits included improved QoL and reduced numbness

and tingling of the feet (Smith 2013 **Level II**, n=231, JS 5). The analgesic benefit of duloxetine was greater in patients with oxaliplatin-induced CIPN.

Venlafaxine may be effective in acute oxaliplatin-induced CIPN but additional supportive evidence is recommended prior to any routine use in clinical practice (Hershman 2014 **GL**). Trials of amitriptyline (to 50 mg/d) and nortriptyline (to 100 mg/d), and gabapentin (2,700 mg/d) were inconclusive, while lamotrigine (300 mg/d) provided no benefit for CIPN. Tapentadol use in patients with moderate-to-severe neuropathic pain from CIPN that was unresponsive to maximum doses of antidepressants and anticonvulsants resulted in a reduction of overall and neuropathic pain scores in 86% of patients (Galie 2017 **Level III-3**, n=31). Nerve conduction values were unchanged from baseline to 3 mth suggesting that tapentadol relieved neuropathic pain without affecting or reversing peripheral nerve damage. There is insufficient evidence to support acupuncture for the treatment of CIPN (Li 2019b **Level I** [PRISMA], 3 RCTs, n=203) (1 RCT overlap with Brami 2016).

Taxane acute pain syndrome (TAPS) is characterised by acute onset of muscle and joint pain within a couple of days of receiving taxane chemotherapy. The pain is self-limiting and resolves within one week. Much like CIPN, TAPS can greatly affect patients' quality of life and can lead to dose decreases and chemotherapy discontinuation (Chiu 2017 **NR**). Multiple pharmacologic agents have been evaluated in the treatment of TAPS, including corticosteroids, gabapentin, glutamine and glutathione, with no studies showing benefit (Fernandes 2016 **Level III-3 SR**, 5 studies, n=311).

Guidelines for the management of CIPN concede that "*there are no agents recommended for the prevention of CIPN*" and support only duloxetine with the recommendation to try tricyclic antidepressants, gabapentin, and a compounded topical gel containing baclofen, amitriptyline HCL and ketamine despite lack of evidence (Hershman 2014 **GL**). These statements are supported by an overarching systematic review, which could only support use of duloxetine in the setting of CIPN (Hou 2018 **Level III-3 SR** [PRISMA], 13 RCTs & 22 studies, n=2,401).

8.9.6 | Procedural pain in cancer patients

Both adults and children with cancer may undergo multiple painful diagnostic and therapeutic procedures. Few trials have evaluated procedural pain in adults with cancer. Attention to adequate analgesia and anxiolysis is imperative to reduce anticipatory stress with repeat interventions. Simple techniques include premedication, administration of prophylactic breakthrough analgesia, application of topical local anaesthetic, inhalational analgesia including methoxyflurane via the Penthrox® inhaler and N_2O-oxygen as Entonox® (see Section 4.5), and sedation (midazolam, ketamine, propofol) by appropriately trained personnel (see respective sections of Chapter 4).

For pleurodesis in patients with malignant pleural effusion, NSAIDs provided comparable analgesia to opioids except for higher rescue analgesia requirements (Rahman 2015b **Level II**, n=206, JS 5); rates of pleurodesis efficacy at 3 mth were not inferior. Placement of 12 Fr vs 24 Fr chest tubes resulted in a modest pain reduction (MD −6.0/100; 95%CI −11.7 to −0.2), but was associated with higher pleurodesis failure (30% vs 24%).

Few interventions decrease acute pain during mammography, including provision of prior information about the procedure, some degree of self-control over the extent of breast compression and the use of breast cushions; in contrast, pre-emptive paracetamol was of no benefit (Miller 2008 **Level I**, 7 RCTs, n=1,671).

For paediatric information, see Sections 10.7.2 and 10.8.2.

8.9.7 | Acute pain due to bone cancer

Refractory severe pain with acute incident pain is commonly caused by primary and metastatic bone cancers, notably prostate, breast, lung, bladder, renal and thyroid cancers, and multiple myeloma. Bone pain may also be precipitated during some cancer treatments eg granulocyte-colony stimulating factor (G-CSF) for febrile neutropenia prophylaxis. Malignant bone pain often has mixed nociceptive, inflammatory and neuropathic components. Preclinical studies have highlighted the pathophysiology of malignant bone pain (Mantyh 2014b **BS**; Mantyh 2014a **BS**; Falk 2014 **BS**; Currie 2013 **BS**).

8.9.7.1 | Diagnosis of bone cancer pain

In the setting of known or potential bone primary or metastatic cancer, any new onset constant aching, gnawing pain over bone, or acute incident pain precipitated by movement or weight-bearing, requires prompt evaluation to pre-empt or exclude critical bone-related events, with assessment for pathological fracture, neurological deficit or hypercalcaemia. Many studies and reviews have informed guidelines to predict, expedite diagnosis and appropriately treat bone metastases. A systematic approach to assessment of spinal metastases is imperative. For detection of bone metastases, MRI and fludeoxyglucose F 18 PET offer advantages of sensitivity and/or specificity over bone scintigraphy and computed tomography (CT), although tumour type may influence diagnostic performance (Yang 2011 **SR** of diagnostic studies; Liu 2011 **SR** of diagnostic studies; Cheng 2011 **SR** of diagnostic studies). In assessment of new, acute back pain, 'red flags' to predict potential cancer have been proposed, yet the only evidence-based predictor of spinal malignancy is "*previous history of cancer*" (Henschke 2013 **SR** of diagnostic studies; Downie 2013 **SR** of diagnostic studies). "*History of cancer*" increased the probability of malignancy to between 7% (95%CI 3 to 16) and 33% (95%CI 22 to 46); "*older age*", "*unexplained weight loss*", and "*failure to improve after 1 mth*" increased probability by <3% (Downie 2013 **SR** of diagnostic studies). Diagnostic imaging pathways that advocate larger lists of red flags and promote imaging for a single red flag may lead to "*substantial and arguably unwarranted*" referrals for imaging. However, there is no data on the diagnostic accuracy of combinations of proposed red flags.

8.9.7.2 | Spinal cord compression

Risk of spinal cord compression is between 5 and 20% of patients with spinal bone metastases, yet diagnosis and treatment are often delayed until neurological dysfunction is irreversible. Early suspicion and referral improve outcome. Spinal cord compression risk relates to many factors including the type and characteristics of malignancy, extent of vertebral invasion, thoracic metastases, the number and duration of spinal metastases (Sutcliffe 2013 **Level III-3 SR**, 33 studies, n=5,782). Localised back pain is the most common presenting feature and neurological deficit is a late presentation; MRI is the investigation of choice (Cheng 2011 **SR** of diagnostic studies; Samphao 2010 **SR** of diagnostic studies).

Early referral for surgical assessment is required within 24 h of MRI. In addition to analgesic medications and adjuvants for pain, treatment options include corticosteroids, radiotherapy and decompressive surgery (Loblaw 2012 **GL**; Ivanishvili 2014 **NR**; Samphao 2010 **NR**). The Neurologic, Oncologic, Mechanical and Systemic (NOMS) framework is a recognised decision tree to optimise local tumour control, pain relief, neurological preservation and functional restoration (Laufer 2013 **NR**). A Canadian scoring system (LMNOP) also incorporates a spinal instability neoplastic score into a similar decision framework (Ivanishvili 2014 **NR**).

8.9.7.3 | Treatment strategies for bone cancer pain including spinal cord compression

Treatment strategies for bone cancer pain, including pain of spinal cord compression, should focus on analgesia, preservation of function and prevention of complications (WHO 2018 **GL**; Kane 2015 **NR**). Rapid analgesia should be provided and advice given regarding nonpharmacological strategies such as rest, avoidance of strenuous activity of painful areas and use of general mobility aids. For acute bone pain, an accepted approach includes omission of Step II of the WHO ladder when simple analgesics are inadequate, with progression directly to strong opioids (Maltoni 2005 **Level II**, n=54 [prematurely terminated], JS 2). For predictable incident pain, pre-emptive treatment with rapid-onset opioids should be prescribed. Preclinical data indicates a role for NSAIDs for bone pain but there is a lack of clinical evidence to support this. In a systematic review of NSAIDs (7 studies) and paracetamol (5 studies) added to strong opioids for cancer pain, no subgroup analysis of the combination for bone cancer pain was undertaken (Nabal 2012 **Level III-2 SR**, 12 studies, n=396). Using two NSAIDs (diclofenac 100 mg BD and celecoxib 400 mg/d) along with an opioid resulted in reduced pain scores, lower incidence of breakthrough pain as well as decreased opioid requirements vs using each NSAID in the same dose alone (Liu 2017b **Level II**, n=342, JS 3). Guidelines recommend topical diclofenac, including as gel or patch, to provide relief for pain due to bone metastases with minimal systemic adverse effects (Swarm 2019 **GL**)

Management of bone pain, in addition to complications of bone cancers, also includes targeted strategies that may be local (external beam radiotherapy, surgery) or systemic (chemotherapy, bisphosphonates, denosumab, hormonal therapy) (Kane 2015 **NR**; Poon 2013 **NR**; Samphao 2010 **NR**).

Tanezumab is a monoclonal antibody against neurotrophin nerve growth factor (NGF). In an RCT of painful bone metastases assessing tanezumab vs placebo, the primary endpoint of a difference in change from baseline in daily average pain was not achieved (Sopata 2015 **Level II**, n=59, JS 5). However, the data suggest improved analgesia and a Phase-3 trial is currently ongoing (Jara 2018 **NR**).

Electrochemotherapy, the combination of chemotherapy and local delivery of electric pulses to the tumour nodule (through electrodes surgically drilled into healthy bones surrounding metastases), was shown to be safe and feasible with improved pain scores >50% in 84% of patients and reduced opioid consumption (Bianchi 2016 **Level III-3**, n=24)

Generalised bone pain secondary to G-CSF treatment (eg pegfilgrastim) can result from a number of proposed mechanisms including bone marrow expansion, neuromodulation and alterations in bone metabolism (Lambertini 2014 **NR**). The most commonly utilised pain relief method for refractory severe pegfilgrastim-induced bone pain was use of the antihistamine loratadine (Pawloski 2016 **Level IV**, n=69).

8.9.7.4 | Surgery

In the case of imminent or actual pathological fracture of long bones and pelvis, surgical intervention with stabilisation may be of considerable benefit to reduce acute pain but has attendant risks. The incidences following surgical management of metastases in the humerus, femur and pelvis/acetabulum are 89 to 94% for pain relief, 91 to 93% for maintained or improved function, 17% for morbidity and 4% mortality (Wood 2014 **Level IV SR**, 47 studies, n=807). Placement of catheters for regional nerve or plexus block may eliminate acute incident pain leading up to orthopaedic surgery and during the perioperative period. The high infection rates (10%) after limb salvage surgery for primary bone cancer should be considered when evaluating and managing acute pain in the postoperative period (Racano 2013 **Level IV SR**, 48 studies, n=4,838). A

systematic review of treatment for metastatic spinal cord compression (1970 to 2007) that compared surgical stabilisation with or without radiotherapy and radiotherapy alone, concluded that tumour excision and instrumented stabilisation may improve clinical outcomes, with regard to both pain and neurological function (Kim 2012 **Level IV SR**, 33 studies, n=2,495). Periacetabular metastatic lesions treated by curettage and cemented reconstruction resulted in improved pain relief and functional status postoperatively, despite high rates of major complications (23%) and large mean surgical blood loss (3,150 mL) (Charles 2017 **Level IV**, n=35).

Radical surgical treatments should be considered where spinal metastases have a favourable prognosis, such as thyroid metastases (Zhang 2013a **Level IV**, n=22). Surgery to correct craniocervical instability also may alleviate acute pain, improve QoL and reduce hospitalisations (Kirchner 2014 **Level IV SR**, 9 studies, n=48). Prognosis should be re-evaluated, to ascertain the primary goals of treatment and to undertake risk-benefit assessment of potential treatment (Sutcliffe 2013 **Level III-3 SR**, 33 studies, n=5,782).

Out of 24 patients with cervical spine metastases who underwent palliative surgical treatment, 21 patients experienced complete or almost complete pain relief, and 7 patients experienced complete neurological recovery (Vazifehdan 2017 **Level IV**, n=24).

Resection of intradural extramedullary spine tumours appears to significantly improve patient QoL by decreasing patient disability and pain with improvement in each of the EQ-5D domains (Viereck 2016 **Level IV**, n=44).

8.9.7.5 | Radiation therapy

Radiotherapy effectively reduces malignant bone pain and may reduce complications of bone cancer. It is recommended as the first-line treatment for the majority of patients with spinal metastases causing spinal cord compression as it provides back pain relief in 50% to 58% of cases (Fallon 2018 **GL**; WHO 2018 **GL**).

At 1 mth after radiation therapy, around 25% patients experience complete pain relief (NNT 4.2; 95%CI 3.7 to 4.9) and 41% experience 50% pain relief (McQuay 2000 **Level I** [Cochrane] 43 RCTs, n=1,933). A later meta-analysis of palliative radiotherapy treatment for uncomplicated bone metastases indicates similar response rates following single-fraction (60%) and multiple-fraction (61%) radiation, including 23% and 24% complete response rates respectively (Chow 2012 **Level I**, 25 RCTs, n=5,263). Single fraction conventional radiation therapy for painful uncomplicated bone metastases shows similar results - improvements in pain in 60% to 81% of patients with complete responses (no pain and no increase in analgesic requirements) in up to 37% (with use of 10 Gy) (Chow 2017 **Level III-3 SR**, 27 studies, n=4,071) (7 RCTs overlap).

Radiotherapy for painful bone metastases provides equivalent pain relief with different regimens, including 3 Gy in 10 fractions, 4 Gy in 6 fractions, 4 Gy in 5 fractions and 8 Gy single dose (Lutz 2017 **GL** based on 4 meta-analyses/pooled analyses, 20 RCTs & 32 studies, n=7,163; Rich 2018 **Level I** [PRISMA] 26 RCTs, n=3,059 [single fraction], n=3,040 [multiple fractions]; Chow 2014 **Level I**, 25 RCTs, n=5,617) (significant overlap of RCTs between all 3 SRs). However, after single-fraction treatment, retreatment rates are higher and there is a trend for higher rates of pathological fracture and spinal cord compression. Multiple-fraction radiotherapy is favoured for borderline complicated metastases, without any high-quality supportive evidence.

Shorter hypofractionated radiotherapy (HFRT) schedules of 4 Gy in 5 fractions were as effective as more prolonged schedules for metastatic epidural spinal cord compression (Rades 2016 **Level-II**, n=203, JS 3)

For bone metastases with a neuropathic pain component, there was little evidence for multiple fraction vs single treatment in providing longer term benefit (Roos 2005 **Level II**, n=272, JS 3).

Retreatment

Reirradiation of bone metastases improves pain in about 58% patients, with complete response in 16–28%, time to response from 3 to 5 wk, with duration of 5 to 22 wk (Huisman 2012 **Level IV SR**, 7 studies, n=2,694). Retreatment of recurrent bone pain with 8 Gy single dose confirmed its efficacy and showed no disadvantage vs 20 to 26 Gy in 5 fractions (Chow 2014 **Level II**, n=425, JS 3); therefore, European Society for Medical Oncology Clinical Practice Guidelines recommend 8 Gy single dose to be considered the schedule of choice for re-irradiation (Fallon 2018 **GL**)

Radiopharmaceuticals

For patients with pain due to widespread bone metastases, radiopharmaceuticals may provide complete reduction in pain over 1 to 6 mth with no increase in analgesic use, but with common severe adverse effects of leukopenia and thrombocytopenia (Roque 2011 **Level I** [Cochrane], 15 RCTs, n=1,146). There are limited data comparing the various isotopes used (Strontium-89 [89Sr], Samarium-153 [153Sm], Rhenium-186 [186Re] and Phosphorus-32 [32P]) showing no significant differences (Fallon 2018 **GL**). In selected patients with multiple osteoblastic bone metastases, radioisotope therapy can be highly effective in achieving pain relief in multiple sites.

Radium-223 (an alpha emitter releasing short-range radiation with little bone marrow toxicity) in patients with castrate-resistant prostate cancer demonstrated improvements in skeletal-related events (SREs), pain, QoL and survival vs placebo (Sartor 2014 **Level II**, n=921, JS 5).

8.9.7.6 | Percutaneous vertebroplasty

Where other measures fail, percutaneous vertebroplasty is a procedure that aims to stabilise vertebral compression fractures, restore function and achieve rapid pain relief by the injection of bone cement (polymethylmethacrylate). A systematic review of vertebroplasty for bone metastases and myeloma highlighted low-level evidence from heterogeneous studies and identifies pain reduction rates of 47 to 87%, with no correlation between cement volume and pain relief (Chew 2011 **Level IV SR**, 30 studies, n=987). Serious complications may result from the technique and from cement injection or extravasation, including to the epidural space. Complications were reported in 2 to 11.5% of patients and may correlate with cement volume. These included haematoma, neuropathic pain, haemothorax and pulmonary embolism of cement, with five related deaths. No good evidence currently supports superiority of kyphoplasty over vertebroplasty. In multiple myeloma, vertebroplasty or kyphoplasty are equally effective resulting in prompt and sustained reduction in pain and reduced analgesic use (Khan 2014 **Level IV SR**, 23 studies, n=923). Vertebroplasty and kyphoplasty have similar complication rates in these patients, with the most frequent complication being new vertebral fracture at untreated levels. Technical difficulties of percutaneous vertebroplasty for a patient receiving denosumab, believed related to a sclerotic bone response, highlights the need for further investigation of this issue (Mattei 2014 **CR**).

Cementoplasty, with percutaneous fluoroscopic-guided injection of bone cement into pelvic bone malignancies involving acetabulum, superior and inferior pubic rami, ischium and sacrum, is also a therapeutic option for acute intractable pain from primary or metastatic bone disease (Kim 2013b **Level IV**, n=18 [32 sites]; Kelekis 2005 **Level IV**, n=14 [23 sites]; Marcy 2000 **Level IV**, n=18; Jakanani 2010 **CR**; Harris 2007 **CR**). A combined technique of embolisation, radiofrequency ablation and cementoplasty for painful pelvic bone metastasis of renal cell cancer resulted in profound and sustained pain relief and reduction of opioid requirements for up to 6 mth (Pellerin 2014 **Level III-2**, n=52).

8.9.7.7 | Bone-modifying agents

The evidence to support an analgesic role for bisphosphonates and denosumab is weak (Porta-Sales 2017 **Level I** [PRISMA], 28 RCTs, n=8,595 [bisphosphonates] & 15 RCTs, n=7,590 [denosumab]). Bisphosphonates and denosumab appear to be beneficial in preventing pain by delaying the onset of bone pain rather than by producing an analgesic effect per se. Therefore, these agents should not be used as a primary therapy for treatment of bone pain (Swarm 2019 **GL**).

Bisphosphonates

Bisphosphonates are chemically stable derivatives of inorganic pyrophosphate with affinity for the hydroxyapatite matrix of bone, where they inhibit osteoclast-mediated bone resorption (see also Section 4.10.2). By this action, bisphosphonates reduce bone pain (see below), in addition to the primary role to decrease the risk of, and time to, skeletal-related events consequent to bone cancer, including fracture, spinal cord compression and hypercalcaemia. Hypercalcaemia is less frequent since bone-modifying agent use has increased but can still complicate widespread bone cancer and heighten the pain experience (Poon 2013 **Level I**, 11 RCTs [6 zoledronate & 4 pamidronate], n=7,834). Later generation bisphosphonates are now most widely used, have considerably greater inhibition of bone resorption, maximal effect by 3 mth, and prolong residence and duration of action in bone, for up to years for zoledronate (Kennel 2009 **NR**). Potential serious but uncommon problems include renal impairment and osteonecrosis of the jaw (ONJ); other effects include gastrointestinal symptoms, acute phase reaction with pyrexia, myalgia and arthralgia, hypocalcaemia, and idiosyncratic musculoskeletal pain or ocular inflammation. ONJ in cancer patients after bisphosphonates occurred in 6.7% of patients; the incidence is increased with time of exposure, a history of dental procedures, and zoledronate (Bamias 2005 **Level IV**, n=252). Clodronate or pamidronate use instead of zoledronate may reduce risk of ONJ but dental extractions remain the main risk factor for ONJ (RR 14.04; 99%CI 10.36 to 19.03) (Kyrgidis 2013 **Level III-2 SR**, 12 studies, n unspecified). Dental preventive measures decrease ONJ incidence (77.3%; 95%CI 47.4–90.2%) (Karna 2018 **Level III-2 SR,** 6 studies, n=2,332).

The efficacy of various bisphosphonates has been shown in a number of meta-analyses. In multiple myeloma, bisphosphonates ameliorate pain (RR 0.75; 95%CI 0.60 to 0.95) (Mhaskar 2012 **Level I** [Cochrane], 20 RCTs, n=6,692). Bisphosphonates improve pain control in patients with metastatic bone disease from lung cancer (Lopez-Olivo 2012 **Level I**, 12 RCTs, n=1,767). Zoledronate specifically reduces the likelihood of experiencing a bone-pain event in metastatic bone disease vs placebo (RR 0.83; 95%CI 0.76 to 0.89) (Zhu 2013 **Level I**, 12 RCTs, n=4,450). Analgesic effect is not shown in advanced prostate cancer (OR 1.54; 95%CI 0.97 to 2.44) (Yuen 2006 **Level I** [Cochrane], 10 RCTs, n=1,955). An IV infusion of 4 mg ibandronate gave equivalent overall pain relief to single-dose radiation therapy in prostate cancer (Hoskin 2015 L**evel-II**, n=470, JS 3).

Denosumab

Activation of osteoclasts is driven by the receptor activator of nuclear factor kappa-B ligand/ osteoprotegerin (RANKL/OPG) gradient. Denosumab is a human monoclonal antibody to RANKL that blocks osteoclast development and hence bone resorption. In patients with metastatic and primary bone cancer, denosumab reduces bone pain and slows time to worsening of pain (Prommer 2015 **NR**; Rolfo 2014 **NR**; Iranikhah 2014 **NR**).

In bone metastases from breast cancer (1 RCT, n=2,046), prostate cancer (1 RCT, n=1,901) or other solid tumours (1 RCT, n=1,597), denosumab vs zoledronate delays onset of moderate/severe pain by 1.8 mth (median 6.5 vs 4.7 mth) (HR 0.83; 95 %CI 0.76 to 0.92) and clinically meaningful increases in overall pain interference by 2.6 mth (median 10.3 vs 7.7 mth) (HR 0.83; 95%CI 0.75 to 0.92) (von Moos 2013 **Level I**, 3 RCTs, n=5,544). Denosumab also reduces strong opioid use and worsening of health-related QoL. Compared to zoledronate, denosumab delays time to

worsening of pain in patients with skeletal metastases (RR 0.84; 95%CI 0.77 to 0.91) (Peddi 2013 **Level I**, 6 RCTs, n=6,142).

Denosumab can also lead to ONJ (Diz 2012 **NR**). Use of denosumab instead of zoledronate does not reduce the risk of ONJ (RR 0.71; 99%CI 0.41 to 1.24) (Kyrgidis 2013 **Level III-2 SR**, 12 studies, n unspecified), occurring in 1.6% of patients overall (1.3% with zoledronate and 1.8% with denosumab) (Saad 2012 **Level I**, 3 RCTs, n=5,723).

Calcitonin

Although calcitonin has been used to reduce metastatic bone pain and skeletal events, the limited evidence available does not support the effectiveness of salmon calcitonin in the treatment of acute and persistent metastatic bone pain (Martinez-Zapata 2006 **Level I** [Cochrane], 2 RCTs, n=90). See also Section 4.10.1.

8.9.7.8 | Treatment of acute malignant extradural spinal cord compression

Comprehensive clinical practice guidelines exist to optimise care and pain control of patients with malignant spinal cord compression (Loblaw 2012 **GL**). Corticosteroids are indicated for neurological deficit, particularly if there is to be radiotherapy eg dexamethasone (bolus 8 to 10 mg; maintenance 16 mg/d; higher doses for dense paraparesis). Early surgical consultation is required, with due consideration of the associated morbidity. Patients unsuitable for surgery should receive radiotherapy. Selected groups suitable for stereotactic radiosurgery, with spinal cord sparing, remain to be clarified. Pain is acute and may be exacerbated during early radiotherapy, with incident pain associated with movement and positioning for treatments. See also Sections 8.9.7.3 and 8.9.7.5 above.

8.9.8 | Other acute cancer pain syndromes

8.9.8.1 | Malignant bowel obstruction

Malignant bowel obstruction frequently complicates advanced abdominal cancers, develops over days to months, and presents as generalised abdominal pain or visceral colicky pain. Very little, and heterogeneous, trial data exists to inform guidelines and choice of best medical care, surgery or endoscopic interventions, which may vary according to acuity, degree of obstruction, disease prognosis and objectives of care. Treatment should be individualised. Pharmacological management is based on glucocorticoid, analgesic, antiemetic and antisecretory agents, with attention to adequate hydration (Mittal 2014 **Level IV**, n=48 [physicians surveyed]; Ripamonti 2008 **NR**). Acute severe pain can be managed with parenteral opioids, which also reduces colicky pain by reducing bowel motility. Oral opioids should not be used due to unpredictable absorption. For exacerbations of colic, the antispasmodic hyoscine butylbromide is of benefit and less sedating than hyoscine hydrobromide. Decompression and reduction in secretions may also assist with pain in patients with inoperable bowel obstruction. Hyoscine butylbromide and the somatostatin analogues octreotide reduce gastrointestinal secretions, slow motility and decrease both continuous and colicky pain intensity (Ripamonti 2000 **Level III-1**, n=17). There is little evidence for dexamethasone (6 to 16 mg IV) to improve bowel obstruction (Feuer 2000 **Level I** [Cochrane], 3 RCTs, n=89).

For inoperable bowel obstruction with peritoneal carcinomatosis, a staged protocol with analgesic, antiemetic, anticholinergic and corticosteroid as initial therapy (Stage 1), followed by a somatostatin analogue for persistent vomiting (Stage 2) and then venting gastrostomy (Stage 3) was highly effective in relieving symptoms and avoiding permanent nasogastric tube (Laval 2006 **Level IV**, n=80). Fluoroscopic-guided, percutaneous venting gastrostomy tube placement can

be technically difficult, with 72 and 77% primary and secondary technical success, and 10% incidence of major complications; prior intraperitoneal catheter to manage ascites may reduce the technical difficulty (Shaw 2013 **Level IV**, n=89). Endoscopic stenting may offer effective and safe palliation or act as a bridging step before surgery (34 studies, n=14,356) (Frago 2014 **Level IV SR**, 59 studies, n=20,762). Complications include perforation (3.76%), stent migration (11.81%) and reobstruction (7.34%) (Sebastian 2004 **Level IV SR**, 54 studies, n=1,198). Reports of no or mild nausea increased from 10% at baseline to 100% after treatment with olanzapine in patients with inoperable and incomplete bowel obstruction (Kaneishi 2012 **Level IV**, n=20).

8.9.8.2 | Mucositis

Mucositis is a common adverse effect of high-dose chemo- and radiotherapy for malignancies affecting the head and neck, acute leukaemias and for conditioning prior to bone marrow transplants. It may be complicated by opportunistic infections including herpes simplex and candidiasis. Quality of life and nutrition can be greatly impaired by the pain of cancer-related acute mucositis. In this indication, there is no significant difference in analgesia between PCA and continuous opioid infusion, except that PCA is associated with reduced opioid requirements and pain duration (Clarkson 2010 **Level I** [Cochrane] 33 RCTs, n=1,505). IV ketamine "burst therapy" may be effective in mucositis pain that is refractory to opioid analgesia (Jackson 2005 **NR**). Retrospective studies suggest some benefit from PO gabapentin (Milazzo-Kiedaisch 2016 **NR**) with one small RCT suggesting lack of benefit (Kataoka 2016 **Level II**, n=22, JS 3).

Several topical measures have been postulated to treat the pain of oral mucositis. Topical doxepin, amitriptyline, diclofenac and benzydamine (another nsNSAID) vs placebo provide pain relief due to mucositis (Christoforou 2019 **Level I** [PRISMA], 6 RCTs, n=441). One RCT not included showed that benzydamine reduced mucositis scores, but not pain, when used as an oral rinse for the prevention and treatment of mucositis (Chitapanarux 2018 **Level II**, n=60, JS 4). Mucosal analgesia may be achieved by topical application of EMLA® cream and 5% lignocaine (Vickers 1992 **Level II**, n=60, JS 5).

Povidone-iodine mouthwash significantly reduces the severity of oral mucositis vs sterile water, however chlorhexidine was ineffective (Potting 2006 **Level I**, 7 RCTs, n=863). The lack of effect of chlorhexidine has been confirmed by a subsequent specific meta-analysis (Cardona 2017 **Level I** [PRISMA], 12 RCTs, n=876).

Two different formulations of 200 mcg dose transmucosal fentanyl citrate were equal in efficacy, tolerability and adverse-effect profile, but no better than placebo for analgesia in radiation-induced mucositis (Leenstra 2014 **Level II**, n=155, JS 5; Shaiova 2004 **Level II**, n=14, JS 5).

Topical morphine (Vayne-Bossert 2010 **Level II**, n=11, JS 5; Cerchietti 2002 **Level II**, n=26, JS 3; Cerchietti 2003 **Level III-1**), and ketamine (Slatkin 2003 **CR**) may also provide analgesia. Topical morphine mouthwash (2%) for patients with severe mucositis (associated with treatment for head and neck cancer) was more effective than mouthwash containing viscous lignocaine, magnesium aluminium hydroxide and diphenhydramine, both administered in 10 mL aliquots 3-hourly (Sarvizadeh 2015 **Level II**, n=30, JS 5). Morphine mouthwash recipients had lowered WHO grading scores for mucositis after 6 d of treatment and reported increased satisfaction with their treatment.

Preventive strategies for mucositis such as palifermin (Bensinger 2008 **GL**) or oral cryotherapy (Batlle 2014 **Level III-2**; Tayyem 2014 **NR**) may be effective in specific circumstances. Polymyxin E, tobramycin and amphotericin B (PTA), GM-CSF, oral cooling and amifostine have a preventive effect by significantly reducing the incidence and severity of oral mucositis (Stokman 2006 **Level I**, 45 RCTs, n=4,145). Oral cryotherapy by having the patient suck on ice chips or hold ice water in his/her mouth before, during, and/or after rapid infusions of systemic therapies that are

associated with mucositis has been shown to be an effective preventive treatment (NNT 4) (Riley 2015 **Level I** [Cochrane], 14 RCTs, n=1,280). Situations studied include patients receiving fluorouracil (5-FU) for solid cancers, and, to a lesser extent, patients receiving high-dose mephalan before haematopoietic stem cell transplantation, melphalan for multiple myeloma and 5-FU for solid tumours. A subsequent RCT showed similar findings (Idayu Mat Nawi 2018 **Level II**, n=88, JS 2). This approach is also recommended in guidelines (Swarm 2019 **GL**).

Low-level laser therapy (LLLT) may be effective in reducing pain intensity, severity and duration of mucositis based on moderate evidence (Anschau 2019 **Level I** [PRISMA], 5 RCTs, n=315). This is in line with findings of two small low-quality studies not included in the meta-analysis (Abramoff 2008 **Level II**, n=11, JS 2; Arora 2008 **Level II**, n=28, JS 2). LLLT used prophylactically reduces the risk of severe mucositis and pain in patients with cancer or undergoing hematopoietic stem cell transplantation (Oberoi 2014 **Level I** [PRISMA], 18 RCTs, n=1,144). This approach is recommended in a specific clinical practice guideline (Zadik 2019 **GL**).

Honey shows benefit over placebo and other treatments for moderate to severe chemotherapy induced mucositis in adults, but not in teenagers (Yang 2019 **Level I** [PRISMA] [NMA], 17 RCTs, n=1,265).

Evidence-based clinical practice guidelines for the prevention and treatment of mucositis in cancer patients have been published (Zadik 2019 **GL**; Alvarino-Martin 2014 **GL**; Lalla 2014 **GL**)

For paediatric information, see Section 10.8.3.1.

8.9.9 | Interventional therapies for acute cancer pain

Although pain is adequately controlled in the majority of patients with advanced cancer, patients with severe acute exacerbations of pain may benefit from interventions.

Where pain is prolonged, but opioid-resistant, intractable, and associated with frequent acute exacerbations of pain, including incident pain or paroxysmal neuropathic pain, and adverse effects limit other pharmacological strategies, patients with advanced disease may benefit from longer-term local anaesthetic infusions, including neuraxial infusions, or more destructive neurolytic and other ablative procedures to manage pain.

8.9.9.1 | Peripheral nerve blocks

Local anaesthetic nerve or plexus blocks including continuous peripheral nerve block (CPNBs) may be used to control pain prior to surgery eg acute or imminent fracture, during painful diagnostic or therapeutic procedures, or while awaiting a response from other therapy such as radiation therapy (Klepstad 2015 **Level IV SR**, 16 studies, n=79; Chambers 2008 **NR**) (see also Section 5.8). Unilateral continuous erector spinae plane block (ESPB) may provide sufficient analgesia in patients with end-stage pulmonary malignancy suffering from severe unilateral thoracic pain (Aydin 2018 **Level IV**, n=2).

8.9.9.2 | Neuraxial techniques

Currently, epidural or IT infusions of several classes of agents by a variety of medication delivery systems may provide effective analgesia to cancer patients with previously refractory pain, poor tolerance of oral or systemic analgesia and poor performance status (see also Sections 5.6 and 5.7). There is only limited evidence supporting neuraxial treatment of cancer pain summarised in 2 systematic reviews. There is low quality evidence supporting these techniques resulting in a weak recommendation for their use based on better pain control found for all interventions; described comparisons include neuraxial combinations of opioid and adjuvant analgesic vs opioid alone (4 RCTs), neuraxial bolus vs continuous infusion (2 RCTs), neuraxial drug vs neuraxial placebo

(1 RCT) and neuraxial opioid vs other comprehensive medical management (2 RCTs) (Kurita 2015 **Level I**, 9 RCTs, n=686). Specifically, for IT administration, the 2 RCTs show benefits of IT morphine and IT ziconotide administration (Bruel 2016 **Level IV SR**, 2 RCTs & 8 studies, n=807) (2 RCTs overlap). A retrospective chart review of neuraxial analgesia for cancer pain showed good analgesic effect in 50% of 16 epidural and in 70% of 44 IT treatments (Kiehela 2017 **Level IV**, n=60). High dose systemic opioids (in the range of 700 to 900 mg oral MED) could be discontinued or significantly reduced in 83% of patients who received neuraxial infusions of morphine, commonly combined with low-dose bupivacaine and adjuvants including clonidine and ketamine. However, catheter dislocations occurred in 27% of cases.

Consensus guidelines for the use of neuraxial analgesia in cancer pain are based largely on this weak evidence, despite broad experience in the use of IT opioids, local anaesthetics, clonidine, baclofen and other neuraxial medications (Kurita 2011 **Level IV SR**, 44 studies, n=2,116 [cancer; 7 RCT overlap with Kurita 2015]; Clarke 2017 **GL**; Deer 2011 **GL**). These consensus guidelines and other systematic or practical reviews provide a framework to optimise safety and effectiveness of these techniques that may be used in various and potentially remote palliative settings (Myers 2010 **SR** of 3 SRs, 3 consensus conferences & 12 RCTs; Gulati 2014 **NR**; Upadhyay 2012 **NR**; Mercadante 2012 **NR**).

Breakthrough analgesia with either SL ketamine or an IT local anaesthetic bolus was used successfully in palliative patients with ongoing IT analgesia (Mercadante 2005 **Level IV**). Although infrequently used, morphine by the intracerebroventricular (ICV) route may offer advantages for patients with head, neck or upper limb malignancy causing intractable pain (Ballantyne 2005 **Level IV SR** [Cochrane], 13 studies [ICV], n=337). This review noted few treatment failures and excellent analgesia reported in 73% after ICV opioids with more reports of respiratory depression, sedation and confusion, but lower incidence of nausea, urinary retention, pruritus and constipation with ICV therapy than with IT and epidural routes.

Patient-controlled IT analgesia with a number of agents (morphine, hydromorphone, fentanyl, bupivacaine, clonidine, baclofen, and ziconotide) in the management of refractory cancer-related pain resulted in improved pain control and faster onset of effect vs conventional treatment for breakthrough pain (Brogan 2015 **Level III-3**, n=58).

Patient-controlled epidural analgesia vs intravenous analgesia in patients diagnosed with advanced cancer showed that epidural analgesia is associated with improved respiratory parameters, lower pain scores, higher satisfaction scores, and less opioid related GIT side effects (He 2015a **Level II**, n=50, JS 1).

8.9.9.3 | Spinal cord stimulation

Evidence is insufficient to establish any role for spinal cord stimulation for cancer pain in adults; four case series provide the only evidence base in cancer pain and nil further in an updated Cochrane review (Peng 2015 **Level III-3 SR** [Cochrane], 4 studies, n=92).

8.9.9.4 | Destructive procedures

Coeliac plexus block

For pain due to pancreatic cancer, neurolytic coeliac plexus block has been widely used (Nagels 2013 **NR**) with improved pain scores at 4 wk (-0.42/10; 95%CI -0.70 to -0.13) and at 8 wk (-0.44/10; 95%CI -0.89 to -0.01) and reduced opioid requirements (Arcidiacono 2011 **Level I** [Cochrane], 6 RCTs, n=358). Similar findings were reported by a systematic review including additional case series (Nagels 2013 **Level IV SR**, 5 RCTs, n=295 & 61 studies, n≈4,719) (3 RCTs overlap), while a subsequent meta-analysis confirmed reduced analgesic requirements with improved pain control only at

4 and not 8 wk (Zhong 2014 **Level I**, 7 RCTs, n=403) (4 RCTs overlap with Nagels 2013; 6 RCTs overlap with Arcidiacono 2011).

Percutaneous coeliac plexus ablation for treating severe cancer pain in upper abdomen improved not only pain and performance status scores in the treatment group, but also had health economic benefits by reducing medicine-specific and total health care costs vs controls (Cao 2017 **Level III-2**, n=81). There were no differences seen between the two groups in hospitalisation, examinations, or treatment costs. Better performance status and low daily opioid use before neurolytic coeliac plexus block were independent predictors of good analgesia after the procedure in patients with unresectable pancreatic cancer (Yoon 2018 **Level III-2**, n=112).

Bilateral vs unilateral endoscopic ultrasound-guided celiac plexus neurolysis for abdominal pain management for pancreatic malignancy reduced analgesic requirements, although pain relief and response to treatment were the same (Lu 2018 **Level III-2 SR**, 6 studies, n=437).

Splanchnic nerves

There was no difference in pain outcomes or complications when comparing alcohol versus phenol based techniques in splanchnic nerve neurolysis for pain related to upper abdominal malignancies (Koyyalagunta 2016 **Level III-3**, n=93). The treatment reduced pain scores but not opioid consumption. Furthermore, the procedure resulted in improvements in anxiety, depression, thinking clearly and feeling of well-being.

Radiofrequency ablation vs chemical neurolysis of bilateral thoracic splanchnic nerves in the management of refractory cancer pain due to upper abdominal cancers provided quicker onset and longer duration of analgesia with a higher success rate, along with a better safety profile (Amr 2018 **Level II**, n=60, JS 2).

Bilateral thoracoscopic splanchnicectomy was effective for intractable pain secondary to pancreatic cancer with only 28% of patients continuing to experience abdominal pain (Bhutiani N 2017 **Level III-3**, n=48). Daily opioid dose decreased in 74% of the patients and 67% discontinued analgesics completely.

Cordotomies

Cordotomies have also been performed successfully to treat cancer pain in highly selected cases (Raslan 2011 **NR**). In pain due to mesothelioma, percutaneous cervical cordotomy may be safe and effective (France 2014 **Level IV SR**, 9 studies, n=160). In pain mainly due to malignancies, CT-guided percutaneous cervical cordotomy provided pain relief in 98.13% of cases (Kanpolat 2013 **Level IV**, n=210). In another case series, 32 of 45 patients experienced significant pain relief without relevant adverse effects (Bain 2013 **Level IV**, n=45).

Other destructive procedures

Early vs later neurolytic sympathectomy for pain from abdominal or pelvic cancer resulted in reduced oral analgesic use and improved pain control and QoL (Amr 2014 **Level II**, n=109, JS 4).

Pulsed radiofrequency was used to treat pain from infiltration of the brachial plexus by a tumour (Arai 2013b **Level IV**, n=4; Magistroni 2014 **CR**; Rana 2013 **CR**).

In selected cases, IT neurolytic blocks can be a pain-relieving intervention (Candido 2003 **NR**).

8.9.9.5 | Other Therapies

High Intensity Focused Ultrasound

A meta-analysis concluded high intensity focused ultrasound (HIFU: a non-invasive thermal ablation technique) appears to be effective for pain reduction in advanced pancreatic cancer, although the heterogeneity of the data and the lack of RCTs prevents a strong recommendation (Dababou 2017 **Level IV SR** [PRISMA], 23 studies, n=865).

Acupuncture

Acupuncture for palliative care of cancer shows conflicting evidence regarding treatment of cancer-related pain, but some evidence for its use in management of cancer-related fatigue, chemotherapy-induced nausea and vomiting and leukopenia in patients with cancer (Wu 2015 **Level IV SR**, 23 SRs of 248 primary studies, n=17,392).

Music Intervention

Music interventions may be effective in reducing pain scores (SMD -0.91; 95%CI −1.46 to −0.36) (7 studies, n=528) as well as having some beneficial effects on physiological variables (heart rate, respiratory rate and blood pressure), anxiety, pain, fatigue and QoL in people with cancer (Bradt 2016 **Level III-1 SR** [Cochrane, 52 studies, n=3,731). Most trials were at high risk of bias and, therefore, these results need to be interpreted with caution.

KEY MESSAGES

1. Intranasal, sublingual and buccal fentanyl preparations are effective treatments for breakthrough pain in cancer patients (**U**) (**Level I** [Cochrane Review]) with similar efficacy to intravenous administration (**U**) (**Level I** [PRISMA]) and superior to oral morphine (**U**) (**Level I**).
2. Radiotherapy is an effective treatment of acute cancer pain due to bone metastases (**U**) (**Level I** [Cochrane Review]), while bone-targeting agents (bisphosphonates, denosumab) are beneficial in delaying the onset of bone pain rather than providing analgesia (**W**) (**Level I** [PRISMA]).
3. Neurolytic coeliac plexus block in pancreatic cancer lowers pain intensity and opioid analgesic requirements for at least 8 weeks (**U**) (**Level I** [Cochrane Review]).
4. Opioids, via PCA or a continuous infusion, provide effective analgesia in mucositis; PCA is associated with reduced opioid requirements and pain duration (**U**) (**Level I** [Cochrane Review]).
5. Oral cryotherapy (sucking on ice chips or holding ice water in the mouth before, during, and/or after rapid infusions of systemic therapies that result in mucositis) effectively prevents mucositis (**N**) (**Level I** [Cochrane Review]).
6. Music interventions may be effective in reducing pain intensity in patients with cancer (**N**) (**Level I** [Cochrane Review]).
7. Topical treatment with doxepin (**S**), amitriptyline (**N**), diclofenac (**N**), benzydamine (**N**) (**Level I** [PRISMA]), povidone-iodine (**U**) (**Level I**) and morphine (**S**) (**Level II**) compared to placebo improve pain relief due to mucositis.
8. Low-level laser therapy reduces and when used prophylactically prevents pain and severity of mucositis (**S**) (**Level I** [PRISMA]).
9. Patient education about cancer pain is a key factor in optimising pain management (**U**) (**Level I**).
10. Opioid doses for individual patients with cancer pain should be titrated to achieve maximum analgesic benefit with minimal adverse effects (**U**) (**Level II**).

11. Analgesic medications prescribed for cancer pain should be adjusted to alterations of pain intensity (**U**) (**Level III-2**).
12. Neuropathic pain or mixed nociceptive-neuropathic pain has an estimated frequency of 30-40% in patients with cancer (**S**) (**Level IV SR**).

The following tick boxes represent conclusions based on clinical experience and expert opinion:

- ☑ Acute pain in patients with cancer often signals disease progression; sudden severe pain in patients with cancer should be recognised as a medical emergency and immediately assessed and treated (**U**).
- ☑ Prompt assessment and fast coordinated management of spinal metastases with suspected spinal cord compression is required to mitigate against neurological deficit (**U**).
- ☑ Cancer patients receiving controlled-release opioids need access to immediate-release opioids for titration of breakthrough pain; ~~s~~election of breakthrough medication should consider the time course and aetiology of the pain flare (**U**).
- ☑ If nausea and vomiting accompany acute cancer pain, parenteral opioids are needed (**U**).
- ☑ Transdermal opioids are inappropriate to control acute unstable pain (**U**).
- ☑ High interindividual variability in opioid conversion rates dictates that all opioid rotations should be individualised and monitored, particularly where higher opioid doses are in use (**U**).

8.10 | Acute pain management in intensive care

Acute pain is a common occurrence in critically ill patients. As many as 80% of intensive care unit (ICU) patients experience moderate to severe pain at some point in their ICU admission and attribute it to a source of long term psychological morbidity (Rotondi 2002 **Level III-2**, n=150; Puntillo 2001 **Level III-2**, n=6,201), while approximately 50% of both medical and surgical patients experience pain at rest (Chanques 2006 **Level III-1**, n=230). However, barriers to effective pain report exist including the presence of an endotracheal tube, sedative infusions, restraints and neurological sequelae of critical illness (eg delirium, traumatic brain injury). Despite the limitations on pain assessment and the altered physiology of critical illness, a balanced, multimodal analgesic approach targeted at the sociopsychobiomedical aetiology of acute pain is warranted.

8.10.1 | Aetiology of pain in the intensive care unit (ICU)

The aetiology of acute pain in critically ill patients is complex and synergistic (see Table 8.2). Whilst not all of these are modifiable, targeted treatment of each of the potential aetiologies may result in a profound decrease in patient suffering both in the ICU and thereafter.

Table 8.2 | Aetiology of acute pain in the ICU

Biological	Underlying Illness (eg surgery, sepsis, trauma, burns) Iatrogenic interventions (eg ETT, repositioning, drains, dressing changes, vascular access, invasive monitoring) Complications (eg nosocomial infections) Prolonged immobility Inappropriate pain management (lack of multimodal analgesia, OIH) Pharmacotherapy (Sedation type) Pre-existing chronic pain
Psychological	Fear Hallucinations Post-Traumatic Stress Disorder Sleep deprivation Delirium Anxiety Depression
Social	Isolation and Rejection Circumstances of the injury Facing own mortality

Sources: Adapted from Sigakis 2015

8.10.2 | Barriers to pain management in the ICU

There exist multiple barriers to the provision of effective, multimodal analgesia to critically ill patients (see Table 8.3). Both patient-related and provider-related barriers should be addressed in analgesic management strategies. Simple strategies such as communication boards, patient education about their likely analgesic requirements, and health provider education can result in a marked improvement to overcoming the barriers to effective analgesia. Healthcare system-related barriers require policy development (including quality improvement or QI), education, workflow analysis and change methodology when implementing unit-wide analgesic guidelines.

Table 8.3 | Barriers to effective pain management in the ICU

Patient	Inability to report pain Differential reporting to doctors and nurses Fear of the consequences of reporting pain Fear of the side effects of analgesic medications Feelings that pain should be tolerated as part of the disease process (fatalistic beliefs) Altered cognitive status giving the impression of having effective analgesia (eg hypoactive delirium)
Provider	Knowledge deficits of aetiology, assessment and management strategies (eg sedation as an analgesic, multimodal analgesia) Pain management assigned a low priority (seen as "ICU Housekeeping") Failure to assess for the existence of pain Failure to evaluate effect of analgesic treatment Inconsistent practices, particularly around periprocedural analgesia Inappropriate attitudes regarding the use of opioids Overconcern about the side-effects of analgesics (eg opioid tolerance, NSAIDs) Lack of knowledge of the types and appropriate doses of analgesics Communication difficulties between the patient and the healthcare team Personal and cultural biases
Healthcare system	Lack of accountability for unsatisfactory outcomes related to inadequate analgesic management Inadequate local guidelines to guide pain management Lack of alternative non-pharmacological therapies (eg hot or cold compresses, mobilisation therapy whilst intubated) Inadequate quality improvement processes for pain management Logistic barriers to timely analgesic administration (eg high nursing burden) Implementation of change to pre-existing methods of analgesia and sedation

Sources: Adapted from Sigakis 2015

8.10.3| Pain assessment in the ICU

Assessment of pain in the critically ill patient is difficult, owing to the barriers previously mentioned and outlined in Table 8.3. A patient's subjective index of pain is often not possible or reliable because of altered cognitive status or co-administered sedative agents. In addition, a health provider's own biases may prevent recognition of pain. In a study of patient recollections, the presence of the endotracheal tube was rated on average as being 6/10 (5/10 at best and 8/10 at worst) (Rotondi 2002 **Level III-2**, n=150). For this reason, a patient post-laparotomy may be more likely to be assessed for pain compared with a patient receiving mechanical ventilation due to severe pneumonia. Hence, it is important to have a structured, consistent approach to analgesic assessment, regardless of the admission diagnosis.

The Society of Critical Care Medicine's (SCCM) Pain, Agitation, Delirium, Immobility and Sleep (PADIS) Guidelines (Devlin 2018 **GL**) advocate for self-reporting scales to be used as first line for pain assessment, followed by behavioural pain scores in those unable to self-report.

In responsive patients, the numerical rating scale (NRS) is the reference standard for pain assessment. The presence of an endotracheal tube should not prevent self-reporting, and the use of communication adjuncts (communication board, pen and paper, visual aid) should be encouraged. In unresponsive patients, the NRS is not applicable. Instead, the observation of behavioural and physiological responses may be the only information available to modify pain management (Puntillo 2002 **Level IV**; Puntillo 1997 **Level IV**; Chong 2003 **NR**). The use of such behavioural scales is recommended but only validated, reliable and feasible scales should be used (Gelinas 2013b **NR**).

The critical care pain observation tool (CPOT) has been developed and validated in sedated, mechanically-ventilated critically ill patients (Gelinas 2011 **Level III-2**; Gelinas 2006 **Level III-2**), including the cohorts with a brain injury (Joffe 2016 **Level III-2**), post-operative elective neurosurgical patients (Echegaray-Benites 2014 **Level III-2**) and delirium (Kanji 2016 **Level III-2**). The behavioural pain score (BPS) has also been described and validated for the evaluation of pain in sedated, mechanically ventilated, unresponsive patients (Aissaoui 2005 **Level III-1**; Payen 2001 **Level III-1**; Gelinas 2013b **NR**). The use of BPS vs CPOT resulted in a higher specificity (91.7% vs 70.8%), but a lower sensitivity (62.7% vs 76.5%) (Severgnini 2016 **Level III-2**).

8.10.4 | Analgesic management strategies in the ICU

The management of acute pain in intensive care requires an individualised, multimodal analgesic approach targeted at the sociopsychobiomedical aetiology of acute pain. Although there is a paucity of evidence to guide specific analgesic practices, the SCCM PADIS guidelines provide a framework for this challenging group (Devlin 2018 **GL**).

The use of protocolised analgesia management consisting of regular assessment of pain, analgosedation protocols, sedation assessment and management, delirium screening and management, and targeted analgesia was associated with improved analgesia, decreased duration of mechanical ventilation, ICU LOS, duration and dose of opioid and sedative infusions and decreased mortality (Georgiou 2015 **Level IV SR** [PRISMA], 10 studies, n=3,547; Mansouri 2013 **Level II**, n=216, JS 3; Chanques 2006 **Level III-1**; Barnes-Daly 2017 **Level III-2**, n=6,064; Payen 2009 **Level III-2**; De Jonghe 2005 **Level III-3**).

A summary of the principal recommendations of evidence-based pain guidelines includes (Devlin 2018 **GL**):

- An analgosedation-based protocol for assessment and management should be used (ie assess and treat pain first, followed by agitation/sedation assessment and management,

followed by delirium screening and management and withdrawal assessment/ management during weaning);
- Pain should be routinely monitored in ICU, using the BPS and the CPOT for patients who are unable to self-report;
- Vital signs alone should not be used for pain assessment;
- Opioids are recommended as first-line analgesics for non-neuropathic pain, administered at the lowest possible dose to achieve adequate analgesia;
- Paracetamol should be used as an adjuvant to opioids in pain management;
- Conditional recommendations for NSAIDs as an adjunct to opioids in pain management;
- Ketamine should be used to reduce opioid consumption in postsurgical ICU patients;
- Neuropathic pain medications should be used with an opioid for neuropathic pain.

Current practice still falls well short of these recommendations. In an Australian and New Zealand point-prevalence study, fewer than half of patients in the participating ICUs had their pain assessed within the 4 h period audited and 22% of those assessed were considered to have moderate or severe pain (Elliott 2013 **Level IV**, n=41 [ICUs]).

8.10.5 | Nonpharmacological analgesic management

As there may be a large psychosocial influence in development of acute pain in the critically ill patient, non-pharmacological interventions have the potential to act as powerful analgesic adjuvants. Attention to detail with positioning, pressure care, comfortable fixation of invasive devices, care in the management of secretions and excretions, minimisation of noise from spurious alarms and unnecessary equipment (such as the uncritical application of high-flow mask oxygen) can substantially lessen the burden of discomfort for the patient (Puntillo 2004 **Level III-3**; Chong 2003 **Level IV**; Aaron 1996 **Level IV**). Maintenance of a day-night routine (lighting and activity) is thought to aid sleep quality, which may reduce pain perception (Horsburgh 1995 **NR**).

Specific to analgesic management, cognitive behavioural techniques such as distraction therapy and music therapy, simple massage and facilitation of family presence were agreed by patients and nursing staff as the most effective non-pharmacological analgesic adjuvants (Gelinas 2013a **Level IV**). Massage may have beneficial effects in reducing pain and anxiety in ICU patients (Jagan 2019 **Level I** [PRISMA], 12 RCTs, n=779).

8.10.6 | Pharmacological analgesic management

Management of acute pain may be difficult in the presence of co-administered sedation. It is important, however, to attempt to monitor both processes with sedation scoring (via the Richmond Agitation-Sedation Scale: RASS) and an observational pain assessment tool. This may allow titration of both sedative and analgesic medications separately and decrease the risk of inappropriate therapies (eg increased sedation for agitation due to acute pain).

The mainstay of treatment of acute pain in mechanically ventilated ICU patients is parenteral opioid analgesia (Devlin 2018 **GL**). Despite this, multimodal analgesia should be the goal; the use of non-opioids as adjuvants to opioids in the ICU setting has beneficial effects (Zhao 2019 **Level I** [PRISMA], 12 RCTs, n=910). In particular in ICU patients with Guillain-Barre-Syndrome and after surgery, non-opioids reduce pain intensity, opioid requirements and nausea and vomiting. In addition to multimodal analgesia, sedative type may play a role in analgesic management. In healthy volunteers, moderate sedation with midazolam increased the pain perception of temperature and electrical pain, whilst propofol reduced ischaemic pain and dexmedetomidine reduced both ischaemic and cold pain (Frolich 2013 **Level II EH**, n=86, JS 2). This raises the possibility that midazolam may lower pain thresholds.

8.10.6.1 | Paracetamol

Paracetamol is a safe non-opioid analgesic in the critically ill cohort. IV paracetamol 1 g every 6 h in ICU patients with fever or suspected infection did not increase the incidence of hepatic dysfunction vs placebo (Young 2015 **Level II**, n=700, JS 5). In elective, post-operative surgical ICU patients, the addition of paracetamol improved analgesia, reduced opioid consumption and time to extubation (Memis 2010 **Level II**, n=40, JS 5).

However, IV paracetamol can result in hypotension (Chiam 2015 **NR**). The use of IV propacetamol and IV paracetamol and associated hypotension has been reported (with variable definitions: systolic vs MAP change in absolute value or 15-20% decrease) in mostly critically ill (often cardiac) patients (14/19 studies) (Maxwell 2019 **Level IV SR**, 19 studies [5 RCTs, 6 open-label trials & 8 retrospective reviews], n=3,470). Hypotension appears to be more prevalent with IV vs nasogastric paracetamol in an RCT included in the systematic review (Kelly 2016 **Level II**, n=50, JS 3).

8.10.6.2 | NSAIDs

Non-steroidal anti-inflammatory drugs (NSAIDs) are effective analgesics. Their use, however, is restricted in the critically ill cohort due to the perceived increased risk of acute kidney injury, gastrointestinal bleeding, platelet inhibition and acute myocardial infarction.

When ketoprofen was added for 24 h to an opioid infusion in post-operative major abdominal surgery patients, the result was a reduction in pain scores, opioid consumption (by approximately 20%) and nausea and vomiting (Oberhofer 2005 **Level II**, n=44, JS 4). There were no reported bleeding events or episodes of acute kidney injury. The use of ketorolac in patients with rib fractures decreased the incidence of pneumonia and ventilation times, with no apparent increase in the risk of bleeding or renal failure (Yang 2014 **Level III-2**, n=619).

In a study comparing ibuprofen 10 mg/kg (max. 800 mg) four times daily to placebo in septic ICU patients, there was no increase in the incidence of acute kidney injury, renal replacement therapy, bleeding, or gastrointestinal bleeding (Bernard 1997 **Level II**, n=455, JS 4). Interestingly, the exclusion criteria for renal dysfunction was a creatinine >354 micmol/L. Despite this, there was no increase in renal adverse events in the ibuprofen group vs placebo. Hence, the incidence of side effects in the critically ill may be overestimated.

8.10.6.3 | Opioids

Type of opioid

Currently, there are no head-to-head studies comparing the main opioids used in ICU. Morphine and fentanyl are the predominant parenteral opioids administered in the ICU. Analysis of the opioid infusions in the SPICE 3 trial revealed that 80.0% of patients received fentanyl compared to 30% receiving morphine (some patients received more than 1 opioid) (Shehabi 2019 **Level II**, n=4,000, JS 5). Morphine was traditionally the first-line agent in patients without renal impairment, whereby accumulation of the active metabolite, morphine-6-glucuronide could potentiate the opioid effects (Casamento 2019 **NR**). Fentanyl has a short duration of action after a single dose due to redistribution, but its long elimination half-life leads to accumulation when given in high doses for long periods (Mather 1983 **NR PK**). The replacement of a fentanyl infusion with enteral methadone in mechanically ventilated patients was associated with a shorter weaning time (Wanzuita 2012 **Level II**, n=68, JS 4). Hydromorphone also lacks an active metabolite, but the inactive metabolite, hydromorphone 3-glucuronide may accumulate in renal failure and result in neuroexcitation (manifesting as delirium, altered mental status) (Murray 2005 **NR**). Parenteral oxycodone is being used more in the critical care setting, but there is a lack of

evidence to guide its use, particularly in the setting of end-organ dysfunction. Remifentanil, due to its pharmacokinetics, has the potential to lead to improved outcomes in ICU. However, remifentanil vs either another opioid or hypnotic agent has no benefits in mortality, duration of mechanical ventilation, ICU LOS or risk of agitation (Tan 2009 **Level I**, 11 RCTs, n=1,067). The use of remifentanil is only associated with a reduction in the time to extubation after cessation of sedation (2.04 h; 95%CI 0.39 to 3.69). A subsequent study confirmed this by failing to identify superiority of remifentanil over fentanyl in terms of analgesia, duration of ventilation or morbidity (Spies 2011 **Level II**, n=60, JS 5). There are ongoing concerns about remifentanil with regard to the development of OIH and acute opioid tolerance in the perioperative setting, which may also have implications in the ICU (Kim 2014d **Level IV SR** & **EH**, number of studies unspecified, n unspecified).

Opioid delivery: intermittent bolus vs continuous infusion

The use of intermittent boluses of opioids has the potential benefit of decreasing the duration of mechanical ventilation, opioid-related side-effects such as gastric stasis and nausea and vomiting and development of opioid tolerance. Patients initiated on a continuous infusion of fentanyl experienced more delirium than intermittent boluses of fentanyl (Wolf 2017 **Level III-2**, n=60). The duration of mechanical ventilation, ICU and hospital LOS and self-extubation were similar between the two groups. Unfortunately, pain scores and opioid consumption were not recorded. In another study, intermittent boluses of fentanyl were compared to parenteral paracetamol, with no difference in pain scores for 48 h in mechanically ventilated ICU patients (Kouchek 2013 **Level II**, n=40, JS 2).

Prolonged infusion and tolerance

In ICU patients receiving mechanical ventilation for a prolonged period, there is potential for opioid tolerance to occur (Martyn 2019 **NR**). This may manifest upon cessation of the opioid with a withdrawal syndrome and delirium. In a study looking at ICU patients receiving >7 d of continuous opioid and sedative infusions, abrupt cessation resulted in an acute withdrawal syndrome in 32.1% of patients (Cammarano 1998 **Level III-2**, n=28). Acute withdrawal was associated with a higher daily opioid dose. In another study of general ICU patients, the incidence of withdrawal was 16.7%; higher median cumulative opioid dose and duration of opioid infusion >6 d were associated with withdrawal syndrome, although this study was underpowered (Wang 2017b **Level III-2**, n=54). Hence, cautious opioid weaning should be considered in patients that have received a high cumulative dose of opioid or have been exposed to prolonged duration of infusion (>6 d).

See also Section 9.7 and for paediatric opioid tolerance Section 10.4.6.

8.10.6.4 | Alpha-2 agonists

The alpha-2 agonists have analgesic effects and may aid in analgesia both through the management of psychological contributors for acute pain (eg delirium, agitation and anxiety) and through the avoidance of potentially antalgesic sedatives (Frolich 2013 **Level II EH**, n=86, JS 2). However with use of dexmedetomidine, there was no difference in 90-day mortality, delirium-free or ventilator-free days, with an increased risk of adverse events, namely hypotension, bradycardia and an increased mortality in patients <65 y old (Shehabi 2019 **Level II**, n=4,000, JS 5). However in one RCT, dexmedetomidine was associated with lower morphine requirements than propofol-based sedation after cardiac surgery (Herr 2003 **Level II**, n=295, JS 2). It is also of note here that dexmedetomidine facilitated patient interaction such as the ability to use a VAS for pain assessment vs midazolam and propofol (Ahmed 2013 **Level II**, n=500, JS 5).

8.10.6.5 | Ketamine

Unlike other analgesics and sedatives in ICU, ketamine acts as a potent analgesic, sedative agent and bronchodilator that has positive effects on haemodynamics (Patanwala 2017 **Level IV SR** [PRISMA], 6 RCTs, n=223 & 6 studies, n=39). Its use as an adjunct to opioid therapy reduced cumulative morphine consumption by 27.5% in awake postsurgical ICU patients (Guillou 2003 **Level II**, n=101, JS 2). In mechanically ventilated patients in a surgical ICU, administration of low-dose ketamine infusion resulted in a decrease in morphine consumption by 20%, with a decrease in sedative requirements and vasopressor use (Buchheit 2019a **Level III-3**, n=40). There was, however, an increase in the number of patients with a Richmond Agitation-Sedation Scale (RASS) >0 (10 point scale -5 to +4). This may be due to the psychomimetic effects of ketamine or the reduced dose of propofol sedation. Additionally, opioid infusions were ceased within 24 h in 50% of patients receiving a ketamine infusion.

8.10.6.6 | Regional analgesia

Regional analgesic modalities are covered elsewhere (see Sections 5.6 to 5.8). The ICU patients who may derive benefit are those that receive thoracic epidural analgesia for abdominal aortic aneurysm surgery (Nishimori 2006 **Level I** [Cochrane], 13 RCTs, n=1,224 patients), traumatic rib fractures (Carrier 2009 **Level I**, 8 RCTs, n=232; Stundner 2012 **NR**) or thoracoabdominal procedures (Popping 2014 **Level I** [PRISMA], 125 RCTs, n=9,044).

Furthermore, there is an increasing utilisation of peripheral nerve blocks as techniques of regional analgesia. See also Sections 5.8 and 8.2.2.

8.10.6.7 | Guillain-Barré Syndrome

Gabapentin and carbamazepine, but not methylprednisolone, have analgesic efficacy in Guillain-Barré syndrome but the evidence is limited and of low quality (Liu 2013 **Level I** [Cochrane], 3 RCTs, n=277). IV lidocaine may be useful in the treatment of acute neuropathic pain in Guillain-Barré syndrome based on evidence of benefit in other neuropathic pain disorders (Kalso 1998 **Level I**, 17 RCTs, n=450).

Plasma exchange in acute Guillain-Barré syndrome was associated with a shortened duration of disease and improved outcomes, including pain (Raphael 2012 **Level I** [Cochrane], 6 RCTs, n=649). However, corticosteroids do not offer any benefits in this indication and may even delay recovery, while causing adverse effects (Hughes 2012 **Level I** [Cochrane], 6 RCTS, n=587).

8.10.6.8 | Periprocedural analgesia

There is often an assumption that patients who are intubated and sedated in an ICU will not recall or perceive pain during procedures. Lines and catheters are sometimes inserted without supplementary anaesthesia. A survey suggests that specific treatment of procedure-related pain occurs less than 25% of the time (Payen 2007 **Level IV**, n=1,381). Of patients who have memories of ICU, 54% recall discomfort and 12% overt pain.

Endotracheal tube suctioning and other medical interventions are consistently reported as being uncomfortable or painful (Jeitziner 2012 **Level III-2**, n=21). Therefore, adequate local and/or parenteral anaesthesia should be provided during any noxious procedure (Casey 2010 **Level II**, n=60, JS 5; Puntillo 2004 **Level IV**). Use of dexmedetomidine as the sole agent for painful procedures does not reliably prevent recall or acute stress disorder (MacLaren 2015 **Level II**, n=23, JS 5).

Bolus remifentanil at a dose of 1 or 0.5 mcg/kg prior to removal of chest drains after cardiac surgery was superior to placebo with the higher dose causing more respiratory depression (Casey 2010 **Level II**, n=60, JS 5). In a dose-response study, the 90% effective dose (ED_{90}) of sufentanil was 0.15 mcg/kg for turning patients during the first 5 d of sedation (Chaveron 2012 **Level II**, n=25, JS 5).

KEY MESSAGES

1. Plasma exchange in acute Guillain-Barre syndrome improves outcome including analgesia (**U**) (**Level I** [Cochrane Review]).
2. Carbamazepine and gabapentin may reduce the pain associated with Guillain-Barre syndrome, based on limited and low-quality evidence (**U**) (**Level I** [Cochrane Review]).
3. Non-opioids including NSAIDs and paracetamol improve analgesia in selected intensive care unit patients (**S**) (**Level I** [PRISMA]).
4. Remifentanil provides no advantages over other opioids in ventilated intensive care unit patients (**U**) (**Level I**).
5. Ketamine decreases cumulative opioid doses in mechanically ventilated patients, with positive effects on haemodynamics and reduced requirements for sedation, but with an increased risk of psychomimetic adverse effects (**N**) (**Level II**).
6. The formal assessment and management of pain and agitation in ventilated intensive care unit patients decreases the incidence of pain, the duration of ventilation, the length of ICU stay and mortality (**U**) (**Level III-1**).
7. Prolonged opioid infusions for >6 days and higher cumulative opioid dose increase the risk of acute withdrawal if the opioid infusion is abruptly ceased (**N**) (**Level III-2**).
8. Procedures such as endotracheal tube suctioning are consistently reported as uncomfortable and painful (**U**) (**Level III-2**).

The following tick boxes represent conclusions based on clinical experience and expert opinion.

- ☑ The aetiology of acute pain in critically ill patients is complex and encompasses all domains of the sociopsychobiomedical model of pain (**N**).
- ☑ Observation of behavioural and physiological responses permits assessment of pain in unconscious patients (**U**).
- ☑ Routine monitoring for pain in sedated intensive care patients should be performed, using the Behavioural Pain Scale or the Critical-Care Pain Observation Tool (**U**).
- ☑ Analgesia management should be targeted to the potential aetiologies of acute pain (**N**).
- ☑ Opioids are the recommended first-line analgesic agents in ventilated intensive care patients (**U**).
- ☑ The risk of NSAIDs in critically ill patients may be overestimated; NSAIDs may provide effective analgesia as a part of multimodal analgesia (**N**).
- ☑ Regional analgesia techniques should be considered in patients undergoing large intra-abdominal surgical procedures and trauma (**N**).
- ☑ Intensive care unit patients should be provided with appropriate analgesia prior to and during potentially painful procedures, in particular as recall of discomfort, pain and procedures can be a source of post-traumatic stress (**S**).

8.11 | Acute pain management in emergency departments

Pain is the most common reason for presentation to the emergency department (ED) and many patients will self-medicate for pain before attending (Kelly 2008 **NR**). Analgesia should be simple to administer, safe, patient- and condition-specific and, where appropriate, based on local-regional rather than systemic techniques. Systems should be adopted to ensure adequate pain assessment, timely, adequate and appropriate analgesia, frequent monitoring and reassessment of pain and additional analgesia as required.

As in many other areas of health care, patients in EDs around the world can receive suboptimal pain management (Gueant 2011 **Level IV**, n=11,670), although this has been challenged (Cinar 2012 **Level III-3**, n=15,387; Green 2012 **NR**). A substantial proportion of patients in pain refuse pain medications (Kant 2019 **Level IV**, n=651). Although 70% of patients presenting to an ED rated their analgesia as "good" or "very good", patient satisfaction with analgesia did not correlate with pain scores at presentation or discharge or change in pain scores (Kelly 2000 **Level IV**, n=54). This indicates that other factors are involved (Shill 2012 **Level III-2**, n=476) including a strong association with staff compassion (Brown 2018 **Level IV**, n=115).

Strategies to improve analgesic administration in the ED include nurse-initiated processes (Shaban 2012 **Level III-3**, n=52 [Australian hospital EDs]), however, nurse-initiated analgesia was not associated with high satisfaction (Shill 2012 **Level III-2**, n=476). Other strategies include the introduction of a protocol-based opioid titration regimen (Curtis 2007 **Level III-3**), whilst mandatory pain scoring at triage was also associated with a faster time to analgesia (Vazirani 2012 **Level III-1,** n=35,628). A review of ED interventions to encourage measurement of pain, remove barriers which delay analgesia, improve staff attitudes to pain relief, employ multi-faceted interventions, or investigate specific departmental diagnostic analysis of problems in pain management did not recommend wide-spread adoption of any interventions (Sampson 2014 **Level III-3 SR**, 42 studies, n≈76,856).

Often, procedural sedation is required as part of the analgesic management in the emergency department. In Australian EDs, reductions of fracture/dislocated shoulders (26.7%), wrist/forearm fractures (15.5%) and tibia/fibula fractures (13.1%) were the most common procedures requiring additional procedural sedation (Bell 2011 **Level IV**, n=2,623 (in 11 Australian EDs). As analgesics preprocedural morphine (34.1%) and fentanyl (12.3%), either on their own or combind with other sedative medications. Sedatives used alone were propofol (38.5%), midazolam (10%) and ketamine (7.4%).

8.11.1 | Systemic analgesics

8.11.1.1 | Paracetamol and NSAIDs

Both paracetamol and NSAIDs are useful for treating mild to moderate trauma pain, musculoskeletal pain, renal and biliary colic and some acute headaches, as discussed elsewhere (see Sections 4.1 and 4.2). Paracetamol and NSAIDs have comparable analgesic efficacy in adult patients in ED with minor musculoskeletal injuries, with no significant benefit if given together (Ridderikhof 2019 **Level I** [PRISMA], 7 RCTs, n=2,100). However, the combination of oral paracetamol and NSAIDs is generally more effective than the use of either agent alone in postoperative pain (Ong 2010 **Level I**, 21 RCTS, n=1,909) or dental pain (Bailey 2013 **Level I** [Cochrane], 7 RCTs, n=2,241). In acute musculoskeletal injuries in ED, addition of ibuprofen and codeine did not improve the analgesic effect of paracetamol but significantly more adverse events were recorded in the combination group (Gong 2019 **Level II**, n=119, JS 5). Addition of codeine or oxycodone to

paracetamol and ibuprofen did not result in improved analgesia in patients with extremity pain (Chang 2017 **Level II**, n=416, JS 5), and more adverse events occurred in the group receiving oxycodone (Graudins 2016 **Level II**, n=182, JS 4).

IV paracetamol (mostly 1 g) is supported by limited evidence as a primary analgesic for acute pain in the ED based on RCTs with various methodological issues; 3 of 14 RCTs showed superior pain relief over comparators (IV morphine 2 RCTs, IM piroxicam 1 RCT) and 8 of 14 RCTs showing no differences in pain scores between IV paracetamol and comparators (opioids, NSAIDs, buccal paracetamol) (Sin 2016 **Level I** [PRISMA], 14 RCTs, n=1,472). Two subsequent RCTs showed IV morphine 0.1 mg/kg was superior to IV paracetamol for sciatica, with both superior to placebo (Serinken 2016 **Level II**, n=300, JS 2) and IV hydromorphone (1 mg) was superior to IV paracetamol in acute severe pain, again with both causing meaningful analgesia (Barnaby 2019 **Level II**, n=220, JS 5). The addition of IV paracetamol 1 g to IV hydromorphone 0.5 mg did not improve analgesia in acute severe pain (Chang 2019 **Level II**, n=162, JS 3). IV paracetamol was comparable to IV dexketoprofen in acute musculoskeletal pain (Demirozogul 2019 **Level II**, n=200, JS 5; Yilmaz 2019 **Level II**, n=200, JS 5). In a comparison of PO to IV paracetamol as analgesia following an initial dose of IV opioid, both groups had modest and comparable improvements in pain scores at 30 min, with high proportions of participants in each group requiring rescue medications (Furyk 2018 **Level II**, n=142, JS 5). Consideration should be given to IV paracetamol when other analgesics are contraindicated.

Dose comparison studies showed similar efficacy for IV ketorolac (10 mg vs 15 mg vs 30 mg) across doses for acute moderate to severe pain in the ED (Motov 2017b **Level II**, n=240, JS 4), and for PO ibuprofen 400 mg vs 600 mg vs 800 mg (Motov 2019 **Level II**, n=225, JS 4). This suggests an analgesic ceiling for NSAIDs in this setting.

For severe pain, IV parecoxib 40 mg reduced pain scores similarly vs IV morphine 0.1 mg/kg with less adverse effects (Baharuddin 2014 **Level II**, n=32, JS 4). Similar results were found comparing morphine to IV dexketoprofen (Eken 2014 **Level II**, n=137, JS 5), IV ibuprofen (Pan 2016 **Level II**, n=293, JS 2) or PO hydrocodone/paracetamol (Pan 2018 **Level II**, n=206, JS 2). For soft tissue injuries, PO naproxen 250 mg and PO oxycodone 5 mg had comparable analgesic effects, but oxycodone required more rescue analgesic medication with higher rates of adverse effects (Fathi 2015 **Level II**, n=150, JS 5).

8.11.1.2 | Conventional and atypical opioids

In the ED, opioids are frequently prescribed for the treatment of severe pain and should preferably be titrated via the IV route, given the wide interindividual variability in dose response and the delayed absorption via the IM or SC routes (Motov 2018 **GL**). There is no clear consensus on what constitutes the most effective IV opioid and dosing regimen for analgesia in the ED. A comparison of IV opioids to treat severe pain in the ED shows no clinically significant differences in efficacy or adverse effects between all opioids studied (Patanwala 2010 **Level I**, 10 RCTs, n=2,095). Single IV doses below 0.1 mg/kg of morphine, 0.015 mg/kg of hydromorphone or 1 mcg/kg of fentanyl may be inadequate for severe acute pain without subsequent titration. Nurse-initiated or patient-driven protocols can provide better and faster analgesia but opioid titration is often poorly done, leading to suboptimal dosing and analgesia (Bijur 2012 **Level IV**, n=281).

Higher initial opioid doses may be associated with more rapid onset of analgesia but studies comparing high- vs low-dose titration regimens for IV morphine (Bounes 2008 **Level II**, n=106, JS 3) and hydromorphone (Chang 2013a **Level II**, n=334, JS 3) show similar pain relief by 30 min and a trend towards fewer adverse effects in the lower dose range. Patients require close observation for sedation, respiratory depression and occasionally hypotension (Coman 1999 **Level IV**, n=401).

Although studies have heterogenous results, PCA in the ED is at least comparable in analgesic effect to usual care with titrated opioid analgesia, but consistently improves patient satisfaction (Bijur 2017 **Level II**, n=636, JS 3; Smith 2015 **Level II**, n=200, JS 3; Birnbaum 2012 **Level II**, n=211, JS 3; Rahman 2012 **Level II**, n=96, JS 3).

In patients with difficult IV access, intraosseous morphine (Von Hoff 2008 **Level II**, n=22, JS 3), IN fentanyl (Hansen 2013 **Level I** [PRISMA], 3 RCTs, n=301), IN hydromorphone (Wermeling 2010 **Level III-1**) and nebulised morphine (Grissa 2015 **Level II**, n=300, JS 5; Farahmand 2014 **Level II**, n=90, JS 5) have similar pharmacokinetic and clinical profiles. Buprenorphine SL demonstrates effective analgesic effects for acute pain in the ED (Vlok 2019 **Level I**, 9 RCTs, n=826) as did IN sufentanil in several RCTs (Blancher 2019 **Level II**, n=157, JS 5; Sin 2019 **Level II**, n=60, JS 5; Lemoel 2019 **Level II**, n=144, JS 5). IN fentanyl 2 mcg/kg was more efficacious than IV morphine 0.1 mg/kg in adults with abdominal pain (Deaton 2015 **Level II**, n=40, JS 5). Oral opioids in situations with delayed or difficult IV access are another option (Miner 2008 **Level II**, n=320, JS 3); oral oxycodone 0.125 mg⁄kg in a suspension vs IV morphine 0.1 mg⁄kg resulted in delayed onset of analgesia and lower patient satisfaction but similar efficacy at 30 min. Fentanyl 200 mcg buccal tablets had similar analgesic efficacy to PO oxycodone 10 mg/paracetamol 650 mg (Arthur 2015 **Level II**, n=50, JS 3).

In children requiring analgesia in the ED, fentanyl IN (Borland 2007 **Level II**, n=67, JS 5), inhaled (nebulised) (Furyk 2009 **Level II**, n=73, JS 5) or oral transmucosal (Mahar 2007 **Level II**, n=87, JS 3) provided effective analgesia (see Sections 5.5 and 10.9.1 for details). The use of IN fentanyl improves the time to analgesia in younger children without adverse effects (Holdgate 2010a **Level III-2**, n=118).

With regard to atypical opioids, IV tramadol had similar analgesic efficacy to IV morphine in equianalgesic doses (100 to 200 mg tramadol vs 5 to 20 mg morphine) (Vergnion 2001 **Level II**, n=105, JS 5). In patients with right lower quadrant pain, presumed to be due to appendicitis, IV tramadol reduced pain and did not affect the clinical examination (Mahadevan 2000 **Level II**, n=68, JS 5). For renal colic, tramadol was less effective than pethidine (Eray 2002 **Level II**, n=47, JS 1). For acute musculoskeletal pain, IM tramadol was similar to ketorolac in efficacy and adverse effects, also when both were combined with oral paracetamol (Lee 2008 **Level II**, n=78, JS 3). They were also equally effective administered SL in children with suspected fractures or dislocations (Neri 2013b **Level II**, n=131, JS 5). However, for musculoskeletal pain in the ED, oral tramadol 100 mg provided inferior analgesia to hydrocodone 5mg/paracetamol 500 mg (Turturro 1998 **Level II**, n=68, JS 5).

Opioid-tolerant patients pose a special challenge in the ED and their management is discussed in Section 9.7.

8.11.1.3 | Inhalational analgesics

In patients with moderate to severe traumatic pain in the ED, self-administered nitrous oxide (N_2O) 65% in oxygen inhaled by face mask was effective in acute pain management vs 100% oxygen placebo, with a low frequency of minor adverse events (Gao 2019 **Level II**, n=60, JS 5). Inhaled N_2O in oxygen is more effective than oxygen as an analgesic adjunct to IV fentanyl 50 mcg for relieving pain in patients with renal colic in the ED (Ahmadi 2018 **Level II**, n=120, JS 5). The difference was evident particularly 10 min from the start of the intervention but the difference between groups disappeared after a further dose of fentanyl.

Inhaled N_2O in oxygen (see Section 4.5.1) provided effective analgesia and anxiolysis for minor procedures in both adults and children (Gerhardt 2001 **Level II**, n=11, JS 5; Burton 1998 **Level II**, n=30, JS 5; Gregory 1996 **Level II**, n=28, JS 3; Gamis 1989 **Level II**, n=30, JS 5) and may be useful as a temporising measure while definitive analgesia is instituted (eg insertion of a digital nerve block for finger injury) (see also Section 10.7.4).

Methoxyflurane (see Section 4.5.2) is used most commonly in prehospital emergency care. In ED patients aged ≥12 y, methoxyflurane was significantly more efficacious than placebo, with only mild transient adverse effects such as dizziness (Coffey 2014 **Level II**, n=300, JS 4). Onset of analgesia was rapid at 4 min; peak analgesia was at 18.5 min. Safety was assessed over 14 d following administration and no significant adverse effects, including renal toxicity, were found. Since no RCTs comparing methoxyflurane and N_2O directly have been performed, an indirect comparison showed no significant differences between the two agents (Porter 2018 **Level I** [NMA], 2 RCTs, n=263). As part of a multimodal analgesic protocol, methoxyflurane with paracetamol and oxycodone decreased pain in the first 5 to 10 min of care, with further decrease in pain intensity over 1 h (Viglino 2019 **Level IV**, n=200).

8.11.1.4 | Ketamine

Low dose IV ketamine 0.1 to 0.3 mg/kg was considered a safe and efficacious analgesic in the ED either as single therapy or in combination with IV morphine 0.1 mg/kg (Karlow 2018 **Level I** [PRISMA], 3 RCTs, n=261; Ghate 2018 **Level IV SR** [PRISMA], 6 RCTs, n=544 & 2 studies, n=65) (2 RCTs overlap). There are comparable improvements in pain intensity and need for rescue analgesia when comparing IV morphine 0.1 mg/kg with low dose IV ketamine 0.1 to 0.3 mg/kg (Lee 2016a **Level I**, 6 studies, n=438) (2 & 4 RCTs overlap). There is a higher rate of neurological and psychological adverse events with ketamine, but more major cardiopulmonary adverse events in the opioid group. Administering ketamine as a 15 min infusion decreased the proportion of patients with adverse events (particularly feeling of unreality and sedation) vs an IV bolus dose, with no differences in analgesic efficacy (Clattenburg 2018 **Level II**, n=62, JS 5; Motov 2017a **Level II**, n=48, JS 5).

As an adjunct to IV morphine, IV ketamine improves pain relief in the first 15 to 30 min and may have a lower rate of additional analgesic requirement in the ED (Sin 2019 **Level II**, n=60, JS 5; Abbasi 2014 **Level II**, n=220, JS 4).

IN Ketamine (0.5 to 1 mg/kg) was an effective analgesic in the ED (Shrestha 2016 **Level IV**, n=34; Andolfatto 2013 **Level IV**, n=40; Yeaman 2013 **Level IV**, n=28) and had comparable effects to IV morphine 0.1 mg/kg, but faster onset of analgesia than IM morphine 0.15 mg/kg (Shimonovich 2016 **Level II**, n=90, JS 3) (see also Section 4.6.1.1).

Ketamine/midazolam was more effective and had fewer adverse effects than fentanyl/midazolam or fentanyl/propofol for fracture reduction in children in the ED (Migita 2006 **Level I**, 8 RCTs, n=1,086).

8.11.1.5 | Centrally acting muscle relaxants

Adding cyclobenzaprine (or oxycodone/paracetamol) to naproxen did not improve pain or functional outcome at 1 wk in patients with acute low back pain (Friedman 2015 **Level II**, n=323, JS 5). Similar results were found with with adding other centrally acting muscle relaxants to ibuprofen or naproxen including orphenadrine, methocarbamol (Friedman 2018 **Level II**, n=240, JS 5), diazepam (Friedman 2017a **Level II**, n=114, JS 5), or baclofen, metaxolone or tizanidine (Friedman 2019 **Level II**, n=300, JS 5). IM benztropine for acute non-traumatic neck pain (wry-neck) was not effective for analgesia or to improve movement, and anti-cholinergic side effects were common (Asha 2015 **Level II**, n=30, JS 3)

8.11.1.6 | Lidocaine

IV lidocaine has mixed results in treatment of painful conditions presenting to ED (Silva 2018 **Level IV SR**, 6 RCTs and 2 studies, n=536; Masic 2018 **Level IV SR**, 4 RCTs & 9 studies, n= 512) (4 RCTs overlap).

There is limited evidence for effectiveness in critical limb ischaemia and renal colic when vs IV morphine, but inferior to standard treatments for migraine and no better than NSAIDs for radicular low back pain. IV lidocaine 1.5 mg/kg was as effective as IV morphine 0.1 mg/kg for decreasing pain scores in patients with extremity fractures experiencing moderate or severe pain (Farahmand 2018 **Level II**, n=50, JS 5; Forouzan 2017 **Level II**, n=280, JS 2). IV lidocaine was as effective as IV morphine in patients with undifferentiated severe pain in the ED, and could provide an opioid-sparing effect (Clattenburg 2019 **Level II**, n=32, JS 3), but was less effective than IV hydromorphone (Chinn 2019 **Level II**, n=154, JS 5). Safety data is limited with 20 adverse events (rate 8.9%; 95%CI 5.5% to 13.4%) (6 studies, n=225) reported with use of IV lidocaine in the ED (19 nonserious and 1 classified as serious) (Silva 2018 **Level IV SR**, 6 RCTs and 2 studies, n=536).

IN lidocaine did not improve analgesia when used as an adjunct to metoclopramide for the treatment of migraine (Avcu 2017 **Level II**, n=162, JS 5).

8.11.1.7 | Corticosteroids

In low back pain, corticosteroid administration for analgesia has mixed results. For patients with low back pain with radiculopathy, in addition to routine care, a single dose of IV dexamethasone 8 mg was better than placebo in reduction of 24 h pain scores and decreased ED LOS but had no effect on functional scores (Balakrishnamoorthy 2015 **Level II**, n=58, JS 5). However, a 5 d course of oral prednisone 50 mg for patients discharged from ED with acute low back pain showed no benefit (Eskin 2014 **Level II**, n=79, JS 5).

For the treatment of acute gout in ED, prednisolone (30 mg/d) was as efficacious as indomethacin (initially 50 mg three times per d) in the first 2 h after commencement of treatment in ED, and for the subsequent 2 wk (Rainer 2016 **Level II**, n=416, JS 5). Paracetamol was used in both groups. Prednisolone was associated with a lower incidence of adverse events, particularly gastrointestinal symptoms. These findings were confirmed in a systematic review, where only two of the RCTs recruited patients in the ED (Billy 2018 **Level I**, 6 RCTs, n=817). There is insufficient evidence for the use of IA corticosteroids for the treatment of gout (Wechalekar 2013 **Level I**, 0 RCTs, n=0). Low dose colchicine is also recommended as treatment for acute gout, but no studies have compared corticosteroids and colchicine (van Echteld 2014 **Level I** [Cochrane], 2 RCTs, n=124).

8.11.2 | Analgesia in specific conditions

8.11.2.1 | Abdominal pain

Patients and physicians differ in their assessment of the intensity of acute abdominal pain in the ED, with physician estimates of severity of abdominal pain being significantly lower than patient reports (Marinsek 2007 **Level IV**, n=185). Administration of analgesia correlated with the physician's assessment of a pain score greater than 60/100. A patient's satisfaction with analgesia correlated with a reduction in pain of at least 20/100 and titration of analgesia to the patient's pain reports. Nevertheless, 60% of patients presenting to the ED with abdominal pain were satisfied with their analgesia on discharge. It is therefore reassuring that in patients presenting with abdominal pain to an ED (over a 10 y period) analgesia administration increased and time to administration decreased (Cinar 2013 **Level IV**, n=2,646).

Early pain relief (usually in the form of opioids) does not interfere with the diagnostic process in acute abdominal pain in adults (Manterola 2011 **Level I**, 8 RCTs, n=922; Kang 2015 **Level II**, n=213, JS 5) or in children (Green 2005 **Level II**, n=108, JS 5; Kim 2002 **Level II**, n=60, JS 5) and does not lead to increased errors in clinical management (Ranji 2006 **Level I**, 12 RCTs, n=1,389).

See also Section 8.6.1.

8.11.2.2 | Renal colic

NSAIDs are effective in the treatment of renal colic vs placebo or antispasmodics (Afshar 2015 **Level I** [Cochrane], 50 studies, n=5,734). For renal colic in patients with adequate renal function, treatment with NSAIDs provides effective and the most sustained pain relief, with fewer side effects, vs IV opioids or IV paracetamol (Pathan 2018 **Level I**, 36 RCTs, n=4,887; Al 2018 **Level II**, n=300, JS 4; Cenker 2018 **Level II,** n=200, JS 4).

For renal colic, the onset of action of NSAIDs is faster when given IV vs IM, PO or PR administration (Tramer 1998 **Level I**, 26 RCTs, n=2,225).

See Section 8.6.1.2

8.11.2.3 | Biliary colic

NSAIDs significantly reduce biliary pain and complications (eg acute cholecystitis, acute pancreatitis, jaundice, cholangitis) vs placebo or spasmolytic drugs (Fraquelli 2016 **Level I** [Cochrane], 12 RCTs, n=828).

See Section 8.6.1.3.

8.11.2.4 | Acute cardiac chest pain

See Section 8.6.3.

8.11.2.5 | Acute pain and sickle cell disease

See Section 8.6.4.1 and in children see Section 10.9.5.1.

8.11.2.6 | Headache

While a number of different classes of medicines are effective in the treatment of acute migraine, other more serious causes of headache, particularly subarachnoid haemorrhage and CNS infection, should always be considered during clinical assessment (American College of Emergency Physicians Clinical Policies Subcommittee on Acute Headache 2019 **GL**). Clinical improvement with medication directed at migraine relief is not specific and does not rule out alternative causes of headache (Pfadenhauer 2006 **Level IV**).

Simple treatment with oral NSAIDs, especially aspirin, is effective in ED patients with migraine who are not vomiting (Kirthi 2010 **Level I** [Cochrane], 13 RCTs, n=4,222). In patients unable to tolerate oral therapy, phenothiazines such as chlorpromazine and prochlorperazine (Kelly 2009 **Level I**, 13 RCTs, n=917), selective serotonin agonists especially sumatriptan (Derry 2012 **Level I** [Cochrane], 35 RCTs, n=9,365) and butyrophenones (however with significant adverse effects) (Leong 2011 **Level I**, 6 RCTs, n=574) provide effective analgesia in up to 80% of patients in the ED. A systematic review of treatment of migraine pain in ED settings supports these results with strong evidence in favour of prochlorperazine and moderate evidence for chlorpromazine, metoclopramide, sumatriptan and IV lysine acetylic acid (Orr 2015 **Level I** [PRISMA], 44 RCTs, n unspecified). A subsequent systematic review confirmed these results with neuroleptics providing the greatest pain reduction in the first h, with metoclopramide and NSAIDs also providing significant relief, but combinations of medications were not superior to single agents (Westafer 2018 **Level I**, 40 studies, n=3,489) (significant overlap between all SRs).

Dexamethasone is recommended to prevent headache recurrence vs placebo (OR 0.60; 95%CI 0.38 to 0.93) (3 RCTs, n=358) (Orr 2016 **Level I**, 68 RCTs, n unspecified). Recurrence following discharge from ED was comparable between IM dexamethasone 10 mg or IM

methylprednisolone acetate 160 mg given in ED with IV metoclopramide (Latev 2019 **Level II**, n=220, JS 5).

IV Paracetamol 1 g was comparable to IV dexketoprofen 50 mg for acute migraine (Turkcuer 2014 **Level II**, n=200, JS 5). The addition of IV paracetamol to prochlorperazine and diphenhydramine for the treatment of headache resulted in an improvement of pain score and less need for rescue analgesia (Meyering 2017 **Level II**, n=90, JS 5) although there has been no direct comparison of adjunctive PO versus IV paracetamol.

Opioids are not recommended in the treatment of migraine or acute primary headache as the recommended medicines provide superior analgesia in comparisons with fewer adverse effects (American College of Emergency Physicians Clinical Policies Subcommittee on Acute Headache 2019 **GL**; Orr 2015 **GL**; Worthington 2013 **GL**) The following medications demonstrated worse or no better analgesia than standard treatment: IV ketamine (Etchison 2018 **Level II**, n=34, JS 5; Zitek 2018 **Level II**, n=54, JS 5), IN ketamine (Benish 2019 **Level II**, n=53, JS 5), caffeine (Derry 2014a **Level I** [Cochrane], 20 RCTs, n=7,238; Baratloo 2016 **Level II**, n=110, JS 5), IV valproate (Friedman 2014b **Level II**, n=330, JS 5), magnesium (Miller 2019 **Level I** [PRISMA], 7 RCTs, n=545), and propofol (Moshtaghion 2015 **Level II**, n=91, JS 5). The addition of IV fluids to standard therapy had no effect on analgesia (Jones 2019a **Level II**, n=49, JS 5; Balbin 2016 **Level III-2**, n=570).

Evidence-based recommendations for the treatment of migraine in ED settings are published (Orr 2015 **GL**).

See Section 8.6.5 for a more detailed review of the treatment of migraine and other acute headache syndromes and Section 10.9.3 for migraine treatment in children.

8.11.2.7 | Hip fracture

Regional blockade reduces pain after hip fracture, and is associated with a decreased risk of pneumonia, reduced time to mobilisation, and reduced cost of analgesia (Guay 2017 **Level I** [Cochrane], 31 RCTs, n=1,760). Regional nerve blockade in the ED is at least as effective and possibly superior to standard analgesia (opioids or NSAIDs) after a hip or femoral neck fracture and decreases overall opioid consumption (Ritcey 2016 **Level I**, 9 RCTS, n=447). FICB (Steenberg 2018 **Level I**, 11 RCTs, n=1,062), FNB (Riddell 2016 **Level I**, 7 RCTs, n=224) or 3-in-1 blocks (4 RCTs, n=199) (Ritcey 2016 **Level I** [PRISMA], 9 RCTs, n=547) are superior to systemic opioids in reducing pain on movement, decrease preoperative opioid requirements and lengthen time to rescue analgesia. These findings are consistent even in patients with dementia (Unneby 2017 **Level II,** n=266, JS 2).

Although opioids alone are not particularly effective in providing analgesia and have the potential for significant adverse effects such as respiratory depression and delirium in the older patient cohort, regional nerve blocks are underutilised in EDs in Australia (Holdgate 2010b **Level IV**, n=646) and the United Kingdom (Rashid 2014 **Level IV**, n=147 [responding EDs]).

Guidelines to direct care of hip fracture patients are published (ANZFHR Steering Group 2014 **GL**); integrated orthogeriatric care, utilisation of care bundles and adherence to clinical care standards improves outcomes in hip fracture patients (ACSQHC 2016 **GL**).

For more details, see also section 8.4.

8.11.2.8 | Shoulder dislocation

The majority of shoulder dislocations requiring reduction in an ED occur with procedural sedation and analgesia. Entonox® (inhaled N_2O:Oxygen) as a single agent is not as effective as procedural sedation using fentanyl and midazolam with regard to analgesia and patient satisfaction (Mahshidfar 2011 **Level II**, n=120, JS 3).

IA lidocaine (injected via landmark technique) for anterior shoulder dislocations provides analgesia comparable to systemic analgesics with fewer adverse effects (Wakai 2011 **Level I**

[Cochrane], 5 RCTs, n=211; Jiang 2014 **Level I**, 9 RCTs, n=438) (5 RCTs overlap). US guided suprascapular nerve block (Tezel 2014 **Level II**, n=41, JS 2) and ultrasound guided interscalene block (Blaivas 2011 **Level II**, n=42, JS 2) showed similar benefits.

8.11.2.9 | Wounds

Local anaesthesia is frequently required for the treatment of wounds in the ED. Agents most commonly used for local infiltration are lignocaine or the longer acting bupivacaine, ropivacaine or levobupivacaine, depending on the duration of anaesthesia required and whether analgesia following the procedure is desirable.

It is less painful to infiltrate local anaesthesia by injection through the wound rather than in the tissues surrounding it (Bartfield 1998 **Level II**, n=63, JS 4). Buffering of lignocaine with bicarbonate reduces the pain of infiltration, particularly when using lignocaine with adrenaline (Cepeda 2010 **Level I** [Cochrane], 23 RCTs, n=1,067).

Digital nerve block with 0.75% ropivacaine significantly prolonged analgesia and reduced rescue analgesia requirements to 24 h, without a clinically significant increase in time to block onset vs 2% lignocaine (Keramidas 2007 **Level II**, n=70, JS 2).

Topical application of local anaesthetics has advantages over local injection although there is little evidence to choose one preparation over another for use on simple lacerations (Tayeb 2017 **Level I** [Cochrane], 25 RCTs, n=3,278). Topical tetracaine, liposome-encapsulated tetracaine, and liposome-encapsulated lignocaine are as effective as EMLA® cream for dermal instrumentation (eg cannulation) analgesia in the ED (Eidelman 2005 **Level I**, 25 RCTS, n=2,096). For simple lacerations in children, topical anaesthetic preparations such as ALA (adrenaline, lignocaine, amethocaine) are effective alternatives to infiltration with local anaesthesia without the pain of local injection (Ferguson 2005 **Level I**, 7 RCTs, n=1,260). Topical lignocaine and adrenaline applied to a wound in sequential layers significantly reduced reports of pain during initial application vs a 2% lignocaine injection, but with no difference in pain scores during suturing (Gaufberg 2007 **Level II**, n=100, JS 3). A topical gel dressing containing morphine was no more effective than other gel dressings in reducing burns injury pain in the ED (Welling 2007 **Level II**, n= 49, JS 3).

8.11.3 | Nonpharmacological management of pain

Although analgesic agents may be required to treat pain in the ED setting, the importance of nonpharmacological treatments should not be forgotten. These include ice, elevation and splinting for injuries and explanation of the cause of pain and its likely outcome to allay anxiety. Psychological techniques such as distraction, imagery or hypnosis may also be of value (see Sections 7.1 and 10.7.5).

In young children, interventions such as distraction, positioning, sucrose and cold application may be helpful to manage pain in the ED (Wente 2013 **Level IV SR**, 14 studies, n=1,459).

In general, acupuncture is comparable to standard analgesic care, and provides superior analgesia when used as an adjunct to standard care in the ED (Jan 2017 **Level I** [PRISMA], 14 RCTs, n=1,210). This included studies of renal colic and back pain. Ear acupuncture shows significant improvements in pain score vs sham acupuncture or standard analgesic care and when used as an adjunct to standard care (Jan 2017 **Level IV SR** [PRISMA], 4 RCTs, n=286 & 8 studies, n=458). Acupuncture had lower pain scores at 60 min vs morphine 0.1 mg/kg in the treatment of patients with renal colic in the ED (Beltaief 2018 **Level II**, n=115, JS 5). Acupuncture and/or standard pharmacotherapy provided comparable reductions in pain within 1 h of administration for back pain, ankle sprain or migraine (Cohen 2017 **Level II**, n=528, JS 3). For more details see Section 7.3.2.1.

Spinal manipulation or exercise therapy for patients presenting to ED with nonradicular low back pain of less than 12 wk duration is no more effective than analgesic pharmacotherapy alone (Rothberg 2017 **Level I**, 2 RCTs, n=344 [spinal manipulation]; 4 RCTs, n=930 [exercise therapy]).

Physical interventions (physical therapy, mobilisation, mechanical support, manipulation), direct interventions (acupuncture, TENS, ultrasound), and indirect interventions (music therapy, aromatherapy, hypnosis, guided imagery) initiated in the ED, all significantly reduce pain vs controls in the short term (immediately in ED) and up to 12 wk later (Sakamoto 2018 **Level I** [PRISMA], 7 RCTs, n=593 [physical interventions]; 9 RCTs, n=975 [direct interventions]; 4 RCTs, n=375 [indirect interventions]). However, most of the included studies had high risk of bias, variable outcome measures, and heterogeneity across interventions.

KEY MESSAGES

1. Paracetamol, in particular if administered IV, and NSAIDs are effective primary analgesics for use in the emergency department (**N**) (**Level I** [PRISMA]).
2. Sublingual buprenorphine (**N**) (**Level I** [PRISMA]) or intranasal fentanyl (**N**) (**Level I**) are effective alternatives to parenteral opioids in the emergency department.
3. Low dose ketamine is a safe and effective analgesic alone or when combined with opioids in the emergency department, but increases neuro-psychological adverse events (**N**) (**Level I** [PRISMA]).
4. Appropriate doses of intravenous opioids are effective in treating acute severe pain in the emergency department and ideally should be titrated according to nurse-initiated and patient-driven protocols; there is no preference for a specific opioid (**U**) (**Level I**).

Abdominal pain

5. Provision of analgesia does not interfere with the diagnostic process in acute abdominal pain and does not increase the risk of errors in clinical management (**U**) (**Level I** [Cochrane Review]).

Migraine

6. NSAIDs, triptans (**S**) (**Level I** [Cochrane]), phenothiazines (prochlorperazine, chlorpromazine), butyrophenones and metoclopramide are effective to treat migraine in the emergency department (**U**) (**Level I**).

Fractured neck of femur

7. Lower limb nerve blocks with local anaesthetics reduce pain, analgesia requirements and lengthen time to rescue analgesia in hip fracture patients compared to systemic analgesia; there is no advantage of a specific nerve block, insertion technique or continuous versus single injection administration (**S**) (**Level I** [Cochrane Review]).

Shoulder Dislocation

8. Intra-articular local anaesthetics provide comparable analgesia for reduction of gleno-humeral dislocation to procedural sedation and analgesia methods with fewer adverse events (**N**) (**Level I** [Cochrane Review]).

Wounds

9. Buffering of lignocaine with bicarbonate reduces the pain of infiltration, particularly when using lignocaine with adrenaline (**U**) (**Level I** [Cochrane Review]).

10. Topical local anaesthetic agents (including those in liposomal formulations) (**S**) (**Level I** [Cochrane Review]) or topical local anaesthetic-adrenaline agents (**U**) (**Level II**) provide effective analgesia for wound care in the emergency department.

Musculoskeletal Pain

11. Centrally acting muscle relaxants do not improve analgesia in the acute treatment of lower back pain (**N**) (**Level II**).

Non-pharmacological management of pain

12. Acupuncture may provide effective analgesia as a single agent or adjunct in the emergency department (**N**) (**Level I** [PRISMA]).

The following tick box represents conclusions based on clinical experience and expert opinion:

☑ To ensure optimal management of acute pain, emergency departments should adopt systems to ensure adequate assessment of pain, provision of timely, adequate and appropriate analgesia, frequent monitoring and reassessment of pain (**U**).

8.12 | Prehospital analgesia

The previous section considered management of acute pain in patients admitted to EDs. However, many of these patients will also have required prehospital pain relief while under the care of paramedic or medical retrieval teams. While the term "prehospital" is also used to cover a greater variety of prehospital locations, it is beyond the scope of this document to look at pain relief administered in more complex situations such as medical retrievals, interhospital transfers, wilderness medicine, medical coverage for large public gatherings and disaster or war settings.

Although there is a paucity of specific research (particularly RCTs), the literature consistently suggests that substantial improvement in the provision of prehospital analgesia is needed (Parker 2015 **NR**), and a possible link between poor quality prehospital analgesia and post-traumatic stress disorder has been raised (Parker 2015 **NR**; Ellerton 2014 **NR**).

Pain may require management prior to and during transport, and the nature of the prehospital environment presents many challenges in addition to most of the issues seen in the hospital. These issues are often related to the relative paucity of resources, fewer treatment options (including medications and equipment), and a working environment where light, sound and issues of hygiene will impact on how pain can and should be managed. Furthermore, the patient is often in the acute or evolving stage of their condition, which may change rapidly. Guidelines for prehospital analgesia have been published (Gausche-Hill 2014 **GL**) as well as those for treatment of pain in remote environments (Russell 2014 **GL**) and a systematic review of guidelines (Yousefifard 2019 **GL SR**).

8.12.1 | Incidence and undertreatment of acute pain in prehospital settings

Pain in the prehospital setting is common, with pain severity rated as moderate to severe in up to 64% of ambulance patients (Galinski 2010 **Level IV**, n=2,279). In these patients, the factors associated with severe pain were cardiac pain and trauma, yet the proportion of patients given analgesics (opioid or inhalational) prior to transfer to an ED varies significantly. Subsequent surveys of ambulance services report an incidence of 28% of moderate to severe pain during ambulance transport (Friesgaard 2018 **Level IV**, n=41,241) and an incidence of 17% of severe and intolerable pain in ambulance attendances for trauma (Hebsgaard 2016 **Level IV**, n=985).

Factors associated with under-treatment of pain in a setting of physician-managed prehospital care were severe pain at initiation of treatment (OR 8.8; 95%CI 5.1 to 15.2), treatment by a female physician (OR 2.0; 95%CI 1.0 to 4.0), and relative inexperience of the physician measured in years of postgraduate experience (4 to 5 y [OR 1.3]; 3 to 4 y [OR 1.6]; 2 to 3 y [OR 2.6]; < 2.0 y [OR 16.7]) (Albrecht 2013 **Level IV**, n=1,202 [patients] & n=77 [emergency physicians]). In a subsequent study, male patients were more likely to receive opioids than females (OR 1.5; 95%CI 1.29–1.79), while sex of the paramedic did not influence opioid use (Lord 2014 **Level III-3**, n=42,051). Other factors reported to be associated with under-treatment of pain include children <15 y and non-white ethnicity in the USA (Hewes 2018 **Level IV**, n= 276,925 [ambulance attendances]) Another single municipality study from the USA showed that analgesia after falls was provided to 8.2% of patients with factors influencing this rate being ethnicity (less often to black vs white patients (OR 0.19; 95%CI 0.08 to 0.44)), an initial higher pain score (9.1/10 [95%CI 8.7 to 9.5] vs 5.8/10 [95%CI 5.5 to 6.2]) and injury location (extremity and hip injury vs head and neck injury) (Infinger 2014 **Level IV**, n=1,200).

Pain in children is less often assessed and treated than in adults (Browne 2016 **Level IV**, n=1,368 [paediatric ambulance attendances]; Rahman 2015a **Level IV**, n=202 [paramedics]) In paediatric patients <15 y, 55% with severe pain (≥8/10) did not receive any analgesia (Lord 2016 **Level IV**, n=38,167 [ambulance records]). In paramedic led services, barriers to providing pain relief to paediatric patients were concerns about pain and fear caused by IV cannulation (59.5%), parental influences (51.6%), difficulty assessing pain in children (47.2%), and concerns about allergic reactions (45.6%) (Whitley 2017 **Level IV**, n=127 [paramedics]). Other factors were perceived negative attitudes from receiving EDs (30.4%) and negative scrutiny from supervisors (11.8%). Similarly to adults, non-white ethnicity was associated with less pain score documentation (OR 0.52; 95%CI 0.44 to 0.62) and provision of analgesics (OR 0.64; 95%CI 0.50 to 0.82) (Johnson 2014 **Level IV**, n=5,057). In children and adolescents (0 to 15 y) admitted to a burns centre within 24 h of injury, pre-burn-centre analgesic administration (paracetamol, NSAID and/or opioid) increased over time (68 to 79%: from 2002-2004 to 2007-2008); flame burns and more extensive burns were predictors of receiving pre-burn-centre analgesics, whilst transfer/referral by ambulance services or general practitioners were predictors of not receiving pre-burn-centre analgesics (Baartmans 2016 **Level III-3,** n=622). For paediatric information, see Section 10.9.1.1.

In a survey of a number of emergency services in the Netherlands, nonpharmacological pain control was used in less than 50% of trauma cases, pharmacological treatment deviated from guidelines in 73 to 99% and time of administration of medication was not documented in 73 to 100% of cases (Scholten 2015 **Level IV**, n=1,066). Similarly in Germany, patients with a hip fracture reported an average pain score of 6.8/10 (± 2.7) with 22% rating their pain as 10/10; however only 28% received analgesia despite its effectiveness (mean pain score reduced from 7/10 [± 2.6] to 2.8 [± 1.4] at hospital arrival) (Oberkircher 2016 **Level III-2**, n=156) (See also Section 8.4). In the setting of a Swiss helicopter rescue service, patients who received pain management had higher initial pain scores (7.4/10 ± 2.0) vs those who did not (2.8/10 ± 1.8) (Eidenbenz 2016 **Level IV**, n=1,156). Beside high pain scores, diagnosis of a fracture was associated with increased analgesic use. Fentanyl (84%) was preferred over ketamine (14%), but ketamine was preferred by more experienced doctors and those with an anaesthesia background.

The presence of cognitive impairment in patients managed by ambulance staff is associated with markedly less analgesic administration despite having significant injuries (McDermott 2014 **Level IV**, n=224). "*Unnecessary pain*" was the second most common type of injury in 56 of 272 claims against ambulance trusts in the UK between 1995 and 2005 (Dobbie 2008 **Level IV**).

A survey of adult patients with suspected extremity fractures showed that just 18 (1.7%) were given any analgesia and only 2 received morphine (White 2000 **Level IV**, n=1,073). A later survey showed that only 12.5% of patients with isolated extremity injuries received any prehospital parenteral pain relief (Abbuhl 2003 **Level IV**, n=706). This trend continues with older patients and those with hip fractures being less likely to be given analgesia prior to arrival in the ED (McEachin 2002 **Level IV**, n=124). In contrast, another group reported that 51% of elderly patients with a fractured neck of femur were given prehospital analgesia; methoxyflurane in 47% of cases, N_2O in 10% and morphine in 6% (Vassiliadis 2002 **Level IV**, n=176).

A large (NSW Ambulance service) audit of ambulance patients who received analgesia found that 87% of all patients received single analgesic therapy (Bendall 2011b **Level IV**, n=97,705). Overall, inhaled methoxyflurane was the most commonly used analgesic (given to 60% of patients), followed by morphine IV (26%) and fentanyl IN (19%).

8.12.2 | Opioid use in the prehospital setting

Despite concerns about opioids in the community, prehospital use of these medications may be increasing. In a 2005 survey, 29% of patients with isolated extremity injuries were given morphine (Michael 2007 **Level IV**, n=953) and 13% of females and 17% of males in pain were given morphine (Lord 2009 **Level IV**, n=3,357). Adequate use of morphine during the early treatment of acute pain after military trauma may significantly reduce the risk of developing post-traumatic stress disorder (OR 0.47; 95%CI 0.34 to 0.66) (Holbrook 2010 **Level III-2**, n=696). With use of systemic opioids, 60 to 70% of prehospital care patients have pain scores above 30/100 at 10 min, falling to 30% at 30 to 40 min (Park 2010 **Level I**, 21 RCTs, n=6,212). Only two patients required naloxone and none needed ventilatory support.

The trend towards increasing opioid use is not universal in adults, and certainly does not seem to flow through to the paediatric patients seen in the prehospital environment. One study of children with fractures or soft tissue injuries reported that 37% received prehospital analgesic medicines (Rogovik 2007 **Level IV**, n=310). Another, which included patients with a diagnosis of limb fracture or burns, reported that analgesia was given to 51% of children between the ages of 5 and 15 y, but not to any child aged <5 y; a greater proportion of this younger group (70 vs 54%) were given opioid analgesia once in the ED (Watkins 2006 **Level IV**, n=45). Undertreatment in children under 5 y of age is a repeated finding of many prehospital investigations. A large study of adult and paediatric ambulance patients found that when a single agent was used, females were less likely to receive opioid analgesia than males (RR 0.83; 95%CI 0.82 to 0.84) (Bendall 2011b **Level III-2**, n=97,705). In contrast to the earlier series above, opioid use increased with increasing age; those aged >60 y were the most likely to receive opioids. While, children were less likely to receive opioids vs methoxyflurane (RR 0.65; 95%CI 0.63 to 0.67) and when given, IN fentanyl was the most common opioid. Prehospital administration of opioids to children (and assessment of pain intensity) occurred infrequently despite implementation of several best practice recommendations in a USA ambulance service; factors associated with opioid use were presence of vascular access (OR 11.89; 95%CI 7.33 to 19.29), longer patient transport time (OR 1.07; 95%CI 1.04 to 1.11), age (OR 0.93; 95%CI 0.88 to 0.98) and pain score documentation (OR 2.23; 95%CI 1.40 to 3.55) (Browne 2016 **Level IV**, n= 1,368 [paediatric ambulance attendances]).

8.12.3 | Principles of management of acute pain in the prehospital setting

Although pain relief has been acknowledged as a key area for investigation, evidence regarding management of acute pain in patients in the prehospital setting remains limited. Many analgesic techniques that work in hospital environments have been transcribed to the prehospital environment, but these do not always comply with the ideal of simplicity, safety and effectiveness when used in the field. Attitudes toward analgesia by the prehospital caregivers may be another factor in the apparent underuse of prehospital analgesia. In a small survey of experienced paramedics, the following themes arose as reasons why analgesia was withheld: reluctance to administer opioid unless there were significant signs (for example an obvious fracture), concerns regarding malingering behaviour, uncertainty regarding the endpoint ("*pain free*" or "*take the edge off*"), concern regarding analgesia masking diagnostic symptoms and a reluctance to use larger initial opioid doses (>5 mg morphine) (Walsh 2013 **Level IV**, n=15 [paramedics]).

System wide interventions in an emergency medical service including education and implementation of a pain management protocol resulted in increased frequency of opioid administration, but only a limited and not sustained increase in pain score documentation (Haley 2016 **Level III-3**, n=15,228; Brown 2014 **Level III-3**, n=3,491). Telemedically delegated analgesic

administration by paramedics in ambulances following an algorithm vs physician-administered analgesia was safe and similarly effective (Brokmann 2016 **Level III-3**, n=160).

Table 8.4 | Factors that influence the provision of prehospital analgesia and the direction of this influence

Factors	Negatively affected by:	Variably affected by:
Patient	Paediatric patients Female sex Physiological instability Comorbidities	Reported pain score Culture Severity of injury
Clinician	Perceived negative response from receiving hospital Concerns regarding IV cannulation in children Lack of training Lack of confidence Fear of adverse events	
Other	Guardian/parental refusal in paediatrics Presence/lack of IV access Resource limitations Limitation of therapeutic options Urgency of transport	

(compiled from Hewes 2018; Whitley 2017; Samuel 2015; Rahman 2015a; Albrecht 2013)

8.12.1 | Assessment of pain in the prehospital environment

As in other settings, pain intensity is best assessed using patient self-report measures such as VAS (Galinski 2005 **Level II**, n=54, JS 4; Kober 2002 **Level II**, n=60, JS 5), VNRS (Bounes 2008 **Level II**, n=106, JS 5; Rickard 2007 **Level II,** n=258, JS 3; McLean 2004 **Level IV**, n=1,227; Woollard 2004 **Level II**, n=175, JS 3), VDS (Vergnion 2001 **Level II**, n=105, JS 5; McLean 2004 **Level IV**, n=1,227) or faces pain scale (Rogovik 2007 **Level IV**, n=301). In a comparison between VAS and VNRS in the prehospital setting, both performed comparably (r 0.87 to 0.93) with a preference by patients and paramedics for VNRS (Ismail 2015 **Level III-2**, n=133). A ruler incorporating both visual analogue and faces pain scales has also been used to measure pain in patients prior to arrival at hospital (Lord 2003 **Level IV**). A cohort study of ambulance patients having had acute trauma showed that patients had poor recall of initial pain scores at 1–2 d after injury (Easton 2012 **Level III-3**, n=88). In some instances, it may not be possible to obtain reliable self-reports of pain (eg patients with impaired consciousness or cognitive impairment, young children [see Section 10.3], elderly patients [see Section 9.2.2], or where there are failures of communication due to language difficulties, inability to understand the measures, unwillingness to cooperate or severe anxiety). In these circumstances other methods of pain assessment based on observation of patient behaviours should be used. For further details on assessment tools, see Chapter 2.

In a survey of a number of emergency services in the Netherlands, standardised tools to assess pain in trauma patients were used in 0 to 52% (depending on the service); reassessment of pain following treatment was only performed in 50% of patients under the care of a helicopter-based service, and not performed by any other services (Scholten 2015 **Level IV**, n=1,066).

8.12.4 | Systemic analgesics

The ideal prehospital analgesic agent should be simple to use, safe (both in terms of side effects and adverse effects on the patient's condition), effective, not lead to delays in transport and have a rapid onset and short duration of action, so that it can be repeated as often as necessary and titrated to effect for each patient (Alonso-Serra 2003 **NR**). Consideration should be given to both choice of analgesic medicine and route of administration.

In a systematic review, PO and IV paracetamol and IV opioids (morphine and fentanyl) are identified as effective analgesics in the prehospital trauma setting, while results for NSAIDs are mixed (Dijkstra 2014 **Level IV** SR, 10 RCTs & 15 studies [12 prehospital], n=5,339).

8.12.4.1 | Paracetamol and NSAIDs

The use of parenterally administered paracetamol and NSAIDs has been suggested for prehospital analgesia (McManus 2005 **NR**; Alonso-Serra 2003 **NR**) and their use seems to be increasing. However, their slower onset of effect as well as the risk of adverse effects (eg bleeding, renal impairment; see Section 4.2), especially in patients who have lost blood and may be hypovolaemic, means they are often overlooked (Scholten 2015 **Level IV**, n=1,066). Similarly, injectable paracetamol is not commonly used. Oral paracetamol or other analgesics may have a limited role in the prehospital management of moderate to severe pain.

8.12.4.2 | Conventional and atypical opioids

The administration of systemic opioids as an effective prehospital analgesic is widespread in ambulance services staffed by paramedics. Their application is influenced by the knowledge and judgment required to use them and the differing legislation for the drugs of dependence between countries. In this setting, use of IV or IN routes will enable a more rapid and predictable onset of action than other routes of administration. Opioids should not be administered IM/SC in the prehospital environment, because of unpredictable pharmacokinetics in the poorly perfused patient. Following resuscitation, morphine may undergo reabsorption from earlier IM administration, which may lead to a potential risk of delayed adverse effects.

Both morphine and fentanyl are commonly used for prehospital analgesia. Morphine (Friesgaard 2016 **Level IV**, n=2,348; Fullerton-Gleason 2002 **Level IV**; Bruns 1992 **Level IV**, n=69), fentanyl (Kanowitz 2006 **Level IV**, n=2,129) and tramadol (Ward 1997 **Level IV**, n=142) have been shown to provide effective and safe pain relief in patients being transported by road. Fentanyl was also safe and effective when given to patients during helicopter transportation (Krauss 2011 **Level IV**, n=1,055; Thomas 2005 **Level IV**, n=213 [doses in 177 patients]). Morphine was the most used opioid by the NSW ambulance service, followed by fentanyl, then ketamine (with no difference in the rate of vomiting between all three) (Zhang 2018 **Level III-3**, n=196). IV fentanyl in a dose of 1 to 3 mcg/kg is an effective analgesic in the prehospital care of children (Samuel 2015 **Level IV SR**, 19 studies [13 paediatric, 6 mixed adult/paediatric], n>67,287).

IV morphine doses of 0.1 mg/kg followed by 0.05 mg/kg every 5 min as needed provided more rapid pain relief and patient satisfaction than doses that were 50% lower (Bounes 2008 **Level II**, n=106, JS 5). Similarly, a liberal treatment protocol (3 mcg/kg) vs a standard treatment protocol (2 mcg/kg) of fentanyl administration resulted in use of higher doses (117.7 mcg [95% CI 116.7 to 118.6] vs 111.5 mcg [95%CI 110.7 to 112.4]) with a higher proportion of patients achieving sufficient pain control (44.0% [95%CI 41.8 to 46.1] vs 37.4% [95%CI 35.2 to 39.6]; aOR 1.47 [95%CI 1.17 to 1.84]) (Friesgaard 2019 **Level II**, n=5,737, JS 3).

Comparisons of IV fentanyl and morphine bolus for prehospital analgesia demonstrated no difference in analgesic efficacy or incidence of adverse effects (Galinski 2005 **Level II**, n=54, JS 4).

This was also confirmed in ischaemic chest pain (Weldon 2016 **Level II**, n=207, JS 5). Similarly, there was no difference in pain relief or adverse effects reported in a comparison of IV tramadol and morphine (Vergnion 2001 **Level II**, n=105, JS 5).

A comparison of IV nalbuphine 5 mg and 10 mg given and repeated at 3 min intervals to a total of 20 mg showed that use of the larger dose led to better pain relief but higher patient-reported drowsiness; over half the patients in both groups still had significant pain on arrival at the hospital (Woollard 2004 **Level II**, n=175, JS 3).

In rural and suburban settings with ambulance services relying on basic life support emergency technicians instead of paramedics, SC fentanyl (maximum first dose 1.5 mcg/kg) has been used successfully to treat pain with only 1.6% of patients experiencing minor adverse effects not requiring intervention (Lebon 2016 **Level IV**, n=288).

IN fentanyl is often used in the prehospital setting for treating acute pain in both children and adults (19% of patients) (Bendall 2011a **Level III-2**, n=3,312; Murphy 2017a **Level IV**, n=94). This route requires a small volume (high-concentration preparation of fentanyl 300 mcg/mL and 50 mcg/mL have been used) and ideally atomisation eg with a metered aerosol device MAD® attached to a syringe. In Australia, this route is sanctioned under an exemption from the TGA. Fentanyl has a relatively high lipid-solubility that enables rapid absorption from the nasal mucosa. Compared with IV fentanyl, the IN route shows similar pharmacokinetics (Foster 2008 **PK**). Bioavailability is 89% with an interpatient variability of 30%. Absorption and onset of analgesia are slightly delayed vs IV fentanyl (T_{max} 13 vs 6 min) (see Section 5.5.2). The analgesic efficacy of IN fentanyl vs alternatives (IV morphine, methoxyflurane) for the treatment of pain in the prehospital setting is unclear but appears to be favourable (Murphy 2017a **Level IV**, n=940). There is only low-quality evidence to support the use of IN fentanyl prehospital (Hansen 2013 **Level III-3 SR**, 4 studies, n=47,407). The one included prehopsital RCT found no difference in pain score reduction between IN fentanyl and IV morphine (Hansen 2013 **Level III-3 SR**, 1 RCT: Rickard 2007 **Level II**, n=258, JS 3). The study was likely underpowered and the findings complicated by use of IV morphine as the rescue analgesic in the IN fentanyl group. Oral transmucosal fentanyl (Actiq®) in battlefield casualties showed suitable effectiveness and safety with ease of administration (Wedmore 2012 **Level IV**, n=286).

For paediatric information, see also Section 10.9.1.1.

8.12.4.3 | Inhalational agents

Nitrous Oxide

Inhalational analgesics can provide early pain relief in the prehospital environment. However, variations in the availability of different agents have a marked impact on regional practices. In one series, patients with extremity fractures were more likely to receive N_2O than morphine (White 2000 **Level IV**, n=1,073), whereas in another series N_2O was not used at all (Rogovik 2007 **Level IV**, n=310).

N_2O is included in prehospital management protocols for manipulation, splinting and transfer of patients with lower limb fracture (Lee 2005b **NR**) and as a second-line in burns patients if opioids are not available (Allison 2004b **GL**). Although N_2O has been reported to provide pain relief in >80% of patients requiring prehospital analgesia (Thomas 2008 **NR**), this practice was not based on RCTs (Faddy 2005 **NR**) and there are few studies comparing efficacy with other agents. In one paediatric series, a higher proportion of children receiving N_2O rather than opioids had pain on arrival in the ED but interruption of delivery during transfer from the ambulance may have contributed (Watkins 2006 **Level IV**, n=45). Based on data from hospital studies, N_2O has been suggested as a safe analgesic in prehospital settings, although specific contraindications (such as pneumothorax and decreased consciousness) may be particularly relevant in this patient group

(Faddy 2005 **NR**) (see Section 4.5.1 for further details). Administration of 50% N_2O vs medical air to trauma patients in the prehospital setting showed effective analgesia; 67% of the N_2O group had pain score ≤3/10 at 15 min compared with only 27% in the air group (Ducasse 2013 **Level II,** n=60, JS 4).

Provision of N_2O in ambulances is hampered by difficulties providing scavenger systems that minimise occupational exposure and the bulk/logistical issues associated with managing cylinders of oxygen and N_2O (Entonox® cylinders are a mixture of 50% N_2O and 50% oxygen) that separate at low temperatures. The demand valves are costly and require maintenance, and the inability to activate the valve and effectively use Entonox® equipment has been rated as a major factor limiting use in children <5 y (Watkins 2006 **NR**).

Methoxyflurane (Penthrane®)

Methoxyflurane is not available in most countries, but in Australia and New Zealand it has largely replaced N_2O in prehospital settings with reviews on its characteristics available in the literature (Blair 2016 **NR**). Methoxyflurane is delivered by a Penthrox® inhaler which contains 3 mL of methoxyflurane and lasts for 25–30 min (Medical Developments International 2001). It is now licensed in the UK, but not in the European Union nor the USA. It is more costly per dose than opioid analgesics (>$20/dose). Methoxyflurane is contraindicated in patients with renal impairment, which is difficult to reliably assess in the acute prehospital environment. Caution against its use has been expressed by one UK medical college until further studies have been undertaken (Fairhurst 2011 **GL**).

Methoxyflurane use reduced pain scores (mean 2.47/10 ± 0.24) in adults, the majority of whom had musculoskeletal pain (Buntine 2007 **Level IV**, n=83); the incidence of nausea was 8%, and 11% had increased drowsiness. Results on the efficacy of methoxyflurane when compared to Fentanyl (IV or IN) or IV morphine are mixed. Methoxyflurane produced greater initial reduction in pain scores than IN fentanyl (2.0 vs 1.6/10) but IN fentanyl produced greater pain reduction by the time of arrival at hospital (3.2 vs 2.5/10) (Johnston 2011 **Level III-3**, n=1,024). Methoxyflurane reduced NRS pain score by ≥30% for 78% of children (aged 5 to 15 y), while among those who received IV morphine and IN fentanyl this was achieved for 88 and 90% respectively (Bendall 2011a **Level III-2**, n=3,312). In a smaller series, methoxyflurane also reduced pain scores in children and adverse effects were reported (Babl 2006 **Level IV**, n=105); the overall incidence of drowsiness was 27% but the risk of deep sedation was significantly higher in younger children (see also Section 10.9.1.1). Yet a further review reported IN Fentanyl or IV morphine to be of superior analgesic efficacy with moderate to severe pain (Blair 2016 **NR**).

There have been no reports of toxicity with analgesic use of methoxyflurane if doses are limited to 3 mL repeated once per event with a maximum of 15 mL per wk or a maximum of 0.5% for 1 h (Grindlay 2009 **NR**) (see also Section 4.5.2). A large population database study found no long term (up to 14 y) adverse effects in patients who had been given methoxyflurane by an ambulance service (Jacobs 2010 **Level IV**, n=17,629).

8.12.4.4 | Ketamine

Ketamine has been administered for prehospital procedural analgesia and sedation in both adults (Bredmose 2009b **Level IV**, n=1,030; Porter 2004 **NR**) and children (Bredmose 2009a **Level IV**, n=164) for many years (Henderson 2016 **NR**). A preference for ketamine has been reported in adult cases with severe pain but less so in paediatric patients. A case-series of patients treated by paramedics trained in the use of ketamine/midazolam found it was highly efficacious (reduction of mean pain score from 8/10 to 3/10) and safe (adverse effects 2.8%, no change in vital signs) (Haske 2014 **Level IV**, n=528). IV ketamine provided similar analgesia to IM morphine for trauma patients in rural areas (Tran 2014 **Level II**, n=308, JS 2). The ketamine group had a higher rate of

agitation and hallucinations (11 vs 1.5%) but a lower rate of vomiting (5 vs 19%). After trauma, patients who responded poorly to a first dose of IV morphine 5 mg had better analgesia with subsequent IV ketamine than morphine bolus doses but with more minor adverse effects (Jennings 2012 **Level II**, n=135, JS 3). In a low-resource rural trauma service in Iraq, provision of prehospital analgesia with IV ketamine vs IV pentazocine resulted in better physiologic severity scores vs no analgesic recipients (respiration and blood pressure); IV ketamine achieved positive change for blood pressure in more severely injured patients (Losvik 2015 **Level III-2**, n=1,876).

8.12.5 | Anxiolytics

Anxiolytics, for example low doses of midazolam, are sometimes used to alleviate some of the acute anxiety or agitation that may complicate effective control of pain in stressful prehospital conditions (McManus 2005 **NR**). However, there are no studies looking at efficacy and safety, and midazolam does not enhance the analgesic effect of morphine in a prehospital setting (Auffret 2014 **Level II**, n=91, JS 5). It should be remembered that the combination with opioids will increase the risk of respiratory depression and that anxiety and agitation may be indicators of other more serious underlying conditions such as a head injury or hypoxia (McManus 2005 **NR**). Low-dose IV midazolam (1 mg typically) in combination with ketamine administered by ambulance officers did not produce any drug-related adverse effects (Haske 2014 **Level IV**, n=528).

8.12.6 | Regional analgesia

Use of regional analgesia in the prehospital setting (excluding war or disaster situations) is uncommon but increasing. Initiation of a fascia iliaca compartment block (FICB) for analgesia in patients with isolated femoral shaft fractures reduces pain intensity across all studies; success rate is 90% with only one adverse event (Hards 2018 **Level IV SR**, 1 RCT, 5 studies & 1 CR, n=254 [blocks]). In the included studies, these blocks were administered by physicians (3 studies), paramedics (1 RCT: McRae 2015 **Level II**, n=24, JS 3), anaesthetists (1 study & 1 CR) and emergency medical service nurses (1 study: Dochez 2014 **Level IV**, n=108 [blocks])

The approach was supported by paramedics in a survey (Evans 2019 **Level IV**, n=11 [paramedics]).

Prehospital treatment of dislocated extremity fractures with US-guided PNBs (FNB, sciatic nerve block, brachial plexus block) vs analgosedation (midazolam/ketamine or midazolam/fentanyl) by anaesthetists resulted in lower pain intensity during the reduction (median 0/10 [IQR 0 to 0] vs 6/10 [IQR 0 to 8]) and on the first POD (1/10 [IQR 0 to 5] vs 5/10 [IQR 5 to 7]), as well as higher rate of successful reduction and patient satisfaction (Buttner 2018 **Level II**, n=30, JS 2).

8.12.7 | Nonpharmacological management of pain

Although analgesic agents are often used to treat pain in the prehospital setting, the importance of nonpharmacological treatments should not be forgotten. The role of psychological intervention with reassurance and distraction in the management of acute pain in an anxious patient is often undervalued.

Physical interventions specific for traumatic injuries include ice, elevation and splinting and these can be effectively delivered in the prehospital environment. Local active warming resulted in analgesia for females in pelvic pain during prehospital transport (Bertalanffy 2006 **Level II**, n=100, JS 3).

TENS used in the prehospital setting reduced pain intensity vs pain before TENS use (MD 38/100; 95%CI 28 to 44) and vs sham TENS (MD 33/100; 95%CI 21 to 44), as well as acute anxiety

secondary to pain (Simpson 2014 **Level I** [PRISMA], 4 RCTs, n=261). The logistical and practical implications of implementing TENS into widespread prehospital practice is unclear.

Acupressure performed by paramedics using "*true points*" led to better pain relief and less anxiety than acupressure using "*sham points*" (Lang 2007 **Level II**, n=32, JS 5) or sham or no acupressure (Kober 2002 **Level II**, n=60, JS 5).

8.12.8 | Analgesia in specific conditions

8.12.8.1 | Acute cardiac pain

The mainstay of analgesia in acute coronary syndrome is the restoration of adequate myocardial oxygenation, including the use of supplemental oxygen (Pollack 2008 **GL**; Cannon 2008 **GL**) and glyceryl trinitrate (Henrikson 2003 **Level IV**, n=459). Whether supplemental oxygen is beneficial or harmful (especially if used in a nontargeted way) when used in acute coronary syndrome remains unclear (Cabello 2013 **Level I** [Cochrane], 4 studies, n=430). Current guidelines by the Australian and New Zealand Cardiology Society (Chew 2016 **GL**) and NICE (NICE 2016b **GL**) state that the use of supplemental oxygen is not recommended unless hypoxia (oxygen saturation [SpO_2] <94%) is present because of these concerns.

When used to treat acute cardiac chest pain during prehospital transfer, IV alfentanil provided more rapid relief than IV morphine (Rickard 2007 **Level II**, n=258, JS 3; Silfvast 2001 **Level II**, n=40, JS 4). In two cohort studies, prehospital use of morphine vs non-use was not associated with worse in-hospital complications and 1 y survival (HR 0.69; 95%CI 0.35 to 1.37) (Puymirat 2016 **Level III-3**, n=2,438 [1,726 survival analysis]).

See also Section 8.6.3 above.

8.12.8.2 | Abdominal pain

As noted in Section 8.6.1 above, administration of opioids does not interfere with the diagnostic process in acute abdominal pain.

8.12.8.3 | Patients with head injury

Caution is often expressed about the use of opioids for pain relief in patients with a head injury (Thomas 2008 **NR**). This is largely because of the potential adverse effects of opioids and their ability to interfere with recovery and neurological assessment, as well as the concern that OIVI will lead to hypercarbia and increased intracranial pressure (Nemergut 2007 **NR**). While there is little specific information regarding the use of opioids in patients with a head injury in the prehospital setting, opioids have been safely used in patients after craniotomy (see Section 8.1.8 above).

The use of opioids in patients with a head injury in the prehospital environment will need to be based on an individual risk-benefit assessment for each patient.

KEY MESSAGES

1. Transcutaneous electrical nerve stimulation TENS provides pain relief in the prehospital setting (**N**) (**Level I** [PRISMA]).
2. Intravenous morphine, fentanyl and tramadol are equally effective in the prehospital setting (**S**) (**Level II**).
3. Nitrous oxide is an effective analgesic agent in prehospital situations (**U**) (**Level II**).
4. Methoxyflurane, in low concentrations, is an effective analgesic with rapid onset in the prehospital and hospital setting with good safety data (**U**) (**Level II**).
5. Ketamine is a safe and effective analgesic in the prehospital setting (**U**) (**Level II**).
6. Moderate to severe pain is common in both adult and paediatric patients in the prehospital setting (**S**) (**Level IV**) and is often poorly managed (**N**) (**Level III-2**).
7. Fascia iliaca compartment block is an effective analgesic technique for patients with isolated femoral shaft fractures in the prehospital setting (**N**) (**Level IV SR**).
8. The prehospital setting presents challenges beyond those encountered in hospital to the assessment, documentation, treatment and reassessment of pain in both adult and paediatric patients (**N**) (**Level IV**).

The following tick box represents conclusions based on clinical experience and expert opinion:

☑ Nonpharmacological measures are effective in providing pain relief and should always be considered and used if practical (**U**).

8.13 | Discharge opioid medication for acute pain management

The number of patients discharged from hospital with opioid medication is rising (Macintyre 2014 **NR**), partially because the range of patients and procedures considered suitable for short-stay or early discharge are increasing (see Section 8.1.7).

Ideally, multimodal analgesia approaches should be the cornerstone of the discharge analgesic regimen (Desai 2018 **Level III-2**, n=42,000). A multimodal bundle of standardised use of preoperative paracetamol, postoperative comfort education, simethicone, postoperative gum chewing and abdominal binders reduced opioid requirements in hospital and with more women receiving <20 tablets of oxycodone at discharge (96.7% vs 26.3%) (Burgess 2019 **Level III-1**, n=9,313).

In a multimodal regimen for discharge, oral immediate release opioid is prescribed if required, to be used on an 'as needed' (prn) basis, ideally for a defined period. Not all, but many patients will require opioid medications at discharge to manage moderate to severe postoperative pain and optimise recovery and rehabilitation (Association of Anaesthetists of Great 2011 **GL**; Steyaert 2013 **NR**).

Before prescribing discharge opioids, consideration needs to be given to possible opioid adverse effects including the potential risks of long term opioid use, drug diversion, misuse or abuse, and death from accidental overdose (Roughead 2019 **Level III-3**, n=24,854; Desai 2018 **Level III-2**, n=42,000; Macintyre 2014 **NR**). See further discussion below in 8.13.2.

Anaesthetists are ideally placed to enforce opioid stewardship (Macintyre 2014 **NR**); they and surgeons need to take responsibility for discharge opioid prescribing as they are in a good position to influence behaviour (Dunn 2017b **NR**). Furthermore, emergency departments play a central role in community opioid supply with need for better coordination between community and hospital specialities (Allen 2014 **NR**).

For discharge medication after ambulatory surgery, see also Section 8.1.7.4.

For discharge opioid prescribing in children, see also Section 10.4.5.

8.13.2 | Adverse effects of opioids

8.13.2.1 | Opioid-related deaths

Opioid overdose in 2016 resulted in death for 1,045 Australians aged 15 to 64 y (Roxburgh 2018 **Level IV**). The majority of these deaths (76%) were attributable to prescription opioids. There has been a significant increase over the last 10 y in opioid-related deaths, from 3.8 to 6.6 deaths per 100,000 Australians per year. Similarly, but on a lower scale, the rate of opioid-related deaths in New Zealand has increased by 33% from 2001 to 2012, with more than half (n=179) being unintentional opioid overdoses (Shipton 2017 **Level IV**, n=325). In the USA, over a similar period, over 183,000 deaths have been attributed to prescription opioids with numbers increasing each year (Morrison 2017 **NR**). There is evidence that illicit fentanyl is significantly contributing to the growth in opioid deaths in the USA and Canada, but not in Australia or New Zealand (Roxburgh 2018 **Level IV**, n=1,045).

Non-fatal overdose events are 7 to 11 times more common than fatal events and lead to significant morbidity. Most of the non-fatal overdose events occur in patients who have used opioids for <90 d (ie acute, not chronic opioid users) (Brat 2018 **Level III-2**, n=1,015,116).

As the average daily dose (in oral morphine equivalent doses [MED]) increased, so did the opioid overdose death rate (Zedler 2018 **Level III-2**, n=18,365,497; Mudumbai 2016 **Level III-3**, n=64,391; Garg 2017 **Level IV**, n=150,821). The daily opioid dose correlated with risk of fatal overdose in patients prescribed opioids (Garg 2017 **Level IV**, n=150,821). Compared to patients

taking between 1 and 19 mg/d, the adjusted HRs (aHR) were 2.3 (95%CI 1.4 to 4.1) for 50 to 89 mg/d, 4.0 (95%CI 2.2 to 7.3) for 90 to 119 mg/d, 3.8 (95%CI 2.1 to 6.9) for 120 to 199 mg/d and 4.9 (95%CI 2.9 to 8.1) for ≥200 mg/d

In the same study, compared to use of opioids only, using opioids in combination with sedatives and hypnotics increased the risk of overdose death (aHR 6.4; 95%CI 5.0 to 8.4), even with lower opioid doses between 1 and 19 mg/d (aHR 5.6; 95%CI; 1.6 to 19.3). The highest risk was recorded with opioids combined with oral benzodiazepines and centrally acting skeletal muscle relaxants (aHR 12.6; 95%CI 8.9 to 17.9).

Co-prescription of pregabalin and opioids is associated with increased mortality in a dose dependent fashion: higher doses of pregabalin were associated with a higher risk of opioid-related death and low doses associated with a lower, but still statistically significant, increased risk (Gomes 2018 **Level III-2**, n=6,514). The mechanism of the association is unclear, but alpha-2-delta-ligands can augment the ventilatory impairment associated with opioids (Morrison 2017 **NR**) and have reversed opioid tolerance in rodent studies (Nicolodi 1995 **BS**). Data from many countries (USA, UK, Germany, Finland, India, South Africa and France) show that over 75% of deaths attributable to alpha-2-delta-ligands also involve opioids (Smith 2016b **Level IV SR**, 34 studies [including 23 CR], n=49,570).

See also section 4.8.

Contribution of discharge opioids to overdoses and overdose mortality

Although relatively rare, there is a small increased risk of opioid overdose in the month after discharge from hospital following surgery (Mudumbai 2019 **Level III-3**, n=64,391; Ladha 2018 **Level III-3**, n=1,305,715). Immediately after discharge (0-30 d) the risk of overdose is much higher than later (31 to 365 d) (RR 10.80; 95%CI 8.37 to 13.92) (n=476) and this risk may increase stepwise as intensity of discharge opioid increases: from no opioids; tramadol only; short-acting opioid only; long-acting only; to short- and long-acting combined (Mudumbai 2019 **Level III-3**, n=64,391). Patients on short- and long-acting opioids combined had the highest risk of overdose (HR 4.84; 95%CI 3.28 to 7.14). Preoperative use of high doses of opioids was another risk factor (Ladha 2018 **Level III-3**, n=1,305,715).

An analysis of deaths related to opioid toxicity in Canada found that the source of opioid in 6.6% of cases was an acute pain prescription (Madadi 2013 **Level III-3**, n=2,330 [drug-related deaths]). While in the USA in people who died of prescription drug overdose, 5% of prescriptions came from emergency or urgent care specialists and anaesthetists provided only 1.7% of the total prescriptions involved (Lev 2016 **Level III-3**, n=4,336 [prescriptions]).

8.13.2.2 | Opioid-induced Ventilatory Impairment (OIVI)

For inpatients, OIVI is estimated to occur in less than 0.5% of acute pain patients using opioids post-operatively (Dahan 2010 **NR**). The time periods of greatest risk of OIVI occurrence being the day of and the night following surgery has implication for discharge of short-stay surgery patients (Lee 2013a **Level IV**, n=341); in children following tonsillectomy with or without adenoidectomy most clinically significant OIVI cases occurred within 2 d of the procedure (FDA 2013 **GL**). Positive predictors identified for inpatient OIVI include: age over 70 y, male sex, major organ failure (including cardiac, respiratory and renal disease) and opioid naïvety (Khanna 2018 **Level IV**, n=1,650). Other risk factors have included: sleep disordered breathing (Lee 2013a **Level IV**, n=341; Macintyre 2011 **NR**); increasing daily opioid doses (Zedler 2018 **Level III-2**, n=18,365,497; Garg 2017 **Level IV**, n=150,821); and, for chronic opioid users, a history of alcohol dependence (Gomes 2011 **Level III-2**, n=1,463 opioid-associated deaths [498 age matched controls]). These have presumed but unproven significance in patients discharged home postoperatively with opioids.

For outpatients, risk factors for OIVI have included:

- The combination of long-acting plus short-acting opioids (Garg 2017 **Level IV**, n=150,821);
- Additional non-prescribed opioids; alcohol and other nonopioid sedating medications such as benzodiazepines (Garg 2017 **Level IV**, n=150,821), antidepressants (Gomes 2011 **Level III-2**, n=2,122 deaths [498 opioid-associated]; Rintoul 2011 **Level IV**, n=320; Webster 2011 **NR**) and pregabalin (Gomes 2011 **Level III-2**, n=2,122 deaths [498 opioid-associated]);
- Magnitude of prescribed daily opioid dose (a significant positive correlation starts at MED 20 mg/d, with the highest risk in those prescribed MED >100 mg/d) (Garg 2017 **Level IV**, n=150,821)
- Duration of opioid use (users with 31 to 89 d cumulative duration 4 times more likely to have an opioid related death than those using opioids for <30 d) (Garg 2017 **Level IV**, n=150,821);
- History of opioid dependence; hospitalisation during the 6 mth prior to the event; liver disease; co-prescription of sedatives including benzodiazepines, skeletal muscle relaxants and pregabalin; and the use of long-acting opioids (Zedler 2018 **Level III-2**, n=18,365,497).

For outpatients at perceived increased risk of OIVI due to opioid overdose, WHO is recommending the provision of take-home naloxone (WHO 2014 **GL**). In Australia, an IM and an IN naloxone preparation suitable for take home use are commercially available and guidelines for their use have been proposed (Lintzeris 2020 **GL**).

On the basis of these identified risk factors, risk prediction tools for OIVI have been proposed for both inpatients and outpatients prescribed opioids (Zedler 2018 **Level III-2**, n=18,365,497). Although these factors have been identified to increase the risk of significant OIVI, no patient can be said to be risk free. As total opioid dose increases, the risk of respiratory depression increases but some patients experience respiratory depression with very small opioid doses.

Older patients may be at greater risk of OIVI, but young patients with no identified comorbidities have died of OIVI post-operatively (Lee 2013a **Level IV**, n=341). Thus, it has been recommended that health care professionals involved in prescribing, administering or dispensing opioids should adopt a cautious and standardised approach, consider every patient at risk of adverse events and titrating dose to effect and side-effects (NPS Medicinewise 2019 **GL**; Macintyre 2014 **NR**).

8.13.2.3 | Patient falls

Patients treated with opioids for any reason may be at increased risk of falling.

Those using opioids chronically for noncancer pain may be at greater risk of falling and requiring hospital admission than those not on opioid medication; the overall risk is greatest in week 1 following initial prescription and decreases over time (Rolita 2013 **Level III-2**, n=13,354). Patients newly treated with opioids may similarly be at increased risk of falling. There is an increased risk of presentation to hospital with a falls related injury in the 2 to 4 weeks following the filling of an opioid prescription (Daoust 2018 **Level III-2**, n=67 929; Soderberg 2013 **Level III-2**, n=167,257). In an analysis of fall-injured patients 4.5% had a first opioid prescription less than 28 d prior to their fall (Soderberg 2013 **Level III-2**, n=167,257). Fall risk was greatest in younger patients (18 to 29 y) and decreased with increasing time from initial prescription. In a similar study, 4.9% of fall-injured patients had filled an opioid prescription in the 2 wk prior to the injury and were more likely to have a fall related injury than through another mechanism (aOR 2.42; 95%CI 1.94 to 3.02) (Daoust 2018 **Level III-2**, n=67,929).

Despite the correlation of opioid prescription and increased fall risk, there is no evidence of causation. The mechanism by which prescribed opioids may trigger injurious falls is unclear; it may be directly due to adverse opioid effects (sedation, dizziness or cognitive impairment),

underlying patient risk factors or comorbidities that make the prescription of opioids more likely, or increase of risky activities which the opioid analgesic effect allows (Soderberg 2013 **Level III-2**, n=167,257).

8.13.2.4 | Impaired driving

Prescription opioid use is associated with a significantly increased risk of fatal crash involvement; 5.0% of US drivers involved in fatal crashes tested positive for prescription opioids vs 3.7% of drivers overall (OR 1.72; 95%CI 1.37 to 2.17) (Li 2019a **Level III-2**, n=19,206). Of drivers involved in fatal crashes, 56% tested positive for alcohol only vs 7% of roadside tested drivers (aOR 17.9; 95%CI 16.19 to 19.84); 2.2% tested positive for both prescription opioids and alcohol vs 0.2% of roadside tested drivers (aOR 21.89; 95%CI 14.38 to 33.32). The interaction with alcohol is in line with previous data (EMCDDA 2012 **Level III-2**; Brady 2014 **Level IV**, n=23,591). Pooled data for prescription opioids only showed increased risk for accidents (OR 2.29; 95%CI 1.51 to 3.48) and for culpability (OR 1.47; 95%CI 1.01 to 2.13) (Chihuri 2017 **Level III-3 SR**, 15 studies, n=926 to 72,685). Self-reported driving under the influence of prescription opioids was also asscoiated with an increased risk of collision (aOR 1.97; 95%CI 1.08 to 3.60) (Wickens 2018 **Level IV**, n=7,857).

Opioids are known to cause sedation, to diminish reaction times, reflexes and coordination and to decrease the ability to concentrate (Wilhelmi 2012 **Level IV SR**, 58 studies, n>80,940); they reduce attention specifically in cognitive tests and this effect increases when used together with antidepressants or anticonvulsants (Allegri 2019 **Level III-2 SR** [PRISMA], 9 studies, n=683). They may thus interfere with the ability to perform a complicated task such as driving. These effects are both subjectively and objectively evident when opioid naïve patients take medicinal opioids in commonly prescribed amounts, although some studies have found less significant objective than subjective impairment (Wilhelmi 2012 **Level IV SR**, 58 studies, n unspecified). Attention and visual function are most sensitive in experimental studies, where doses up to 5 mg morphine IV (leading to plasma concentrations of 50 nmol/L [≈14.3 ng/mL]) had very few effects on traffic-relevant performance tasks (Strand 2017 **Level I EH**, 15 RCTs, n=324 [tests performed]). The overall degree of driving impairment by prescription opioids was similar to that of a blood alcohol reading of 0.05 to 0.08 g/dL (EMCDDA 2012 **Level III-2**); no attempt was made in this analysis to distinguish between acute and chronic opioid use.

In chronic pain patients, it has been traditionally considered that as tolerance develops the driving performance of patients on long term stable opioids may not be negatively affected by their medication and may not have an increased crash risk (Wilhelmi 2012 **Level IV SR**, 58 studies, n unspecified; Dassanayake 2011 **Level III-2 SR**, 21 studies [13 case control n>26,603 drivers in accidents vs n>60,508 controls]). In this setting, no significant impact of regular therapeutic opioid agonists on people's driving-related psychomotor skills has been found (Ferreira 2018 **Level III-3 SR** [PRISMA], 3 studies, n=426). However, driving risk may be increased in the first few weeks following the initiation of a prescription opioid (Dassanayake 2011 **Level III-2 SR**, 21 studies [5 opioid n unspecified]) and may be dose dependent (EMCDDA 2012 **Level III-2**). Similarly, when patients on long term opioids have their dose increased, their psychomotor impairment returns (Wilhelmi 2012 **Level VI SR**, 58 studies, n unspecified). These findings may have implications for the discharge management of acute postoperative pain.

8.13.2.5 | Risk of inducing long term opioid use

Between 2 and 10% of patients continue to use opioid medication for months or even years following its postoperative initiation (Roughead 2019 **Level III-2**, n=24,854; Brat 2018 **Level III-2**, n=1,015,116; Stark 2017 **Level III-2**, n=1,013). Any post-discharge prescription of opioids at all seems

to be a risk factor for ongoing use, but risk increases with every further repeat prescription or refill in all dose ranges (Brat 2018 **Level III-2**, n=1,015,116).

In Australia, 15.7% of patients admitted to mainly private hospitals under the veteran care system for a surgical admission were discharged on opioids, of which 3.9% became chronic users of opioids (Roughead 2019 **Level III-2**, n=24,854). Similarly, in Canada, 3.1% of opioid naïve patients having major elective surgery showed prolonged opioid use after being discharged on opioids (Clarke 2014 **Level III-2**, n=39,140).

Even after day-stay surgery, patients receiving an opioid prescription within the 7 d following surgery were more likely to use opioids within the next year in comparison to those without a prescription (OR 1.44; 95%CI 1.39 to 1.50) (Alam 2012 **Level III-2**, n=391,139). Discharge NSAID prescriptions were also more likely to be associated with persistent NSAID use (OR 3.74; 95%CI 3.27 to 4.28).

Risk factors for prolonged opioid use have included the type of surgical procedure with higher rates in orthopaedic and spinal surgery (Stark 2017 **Level III-2**, n=1,013); after surgical procedures odds ratios ranging from 1.28 (95%CI 1.12 to 1.46) for Caesarean section to 5.10 (95% CI 4.67 to 5.58) for TKA have been reported (Sun 2016 **Level IV**, n=641,941 [surgical patients]). Risk factors have also included medical comorbidities such as diabetes, heart failure and chronic lung disease, behavioural and social factors such as lower household income (Clarke 2014 **Level III-2**, n=39,140; Namba 2016 **Level III-3**, n=12,859), mental health comorbidities including depression, anxiety and psychosis (Brummett 2017 **Level III-2**, n=36,177; Lalic 2018 **Level III-3**, n=431,963; Namba 2016 **Level III-3**, n=12,895), preoperative pain disorders (Brummett 2017 **Level III-2**, n=36,177) and preoperative use of certain medications, specifically benzodiazepines, SSRIs and ACE inhibitors (Carroll 2012 **Level III-2**, n=109; Sun 2016 **Level IV**, n=641,941 [surgical patients]). Preoperative prescription opioid use, alcohol and substance use disorders and depressive or anxiety symptoms have, in some studies, more accurately predicted prolonged opioid use than the duration or severity of postoperative pain (Stark 2017 **Level III-2**, n=1,013; Carroll 2012 **Level III-2**, n=109).

Characteristics of the initial opioid prescribing pattern have been linked to long term opioid use. In a database analysis of the records of opioid naïve patients who received a new prescription for opioids in the US, with each additional day's supply of opioids in the initial prescription, the probability of chronic opioid use increased (Shah 2017 **Level IV**, n=1,294,247). The sharpest increases in chronic opioid use occurred after the fifth and thirty-first day of continual use, after the second prescription and after a cumulative opioid dose of 700 MME. In this study there was no distinction made between perioperative patients, acute non-operative patients and chronic pain patients.

However, the greatest risk for prolonged opioid use after surgery may be preoperative opioid use (Mohamadi 2018 **Level IV SR** [PRISMA], 37 studies, n=1,969,953; Dunn 2018b **Level III-3**, n=1,477 [patient records reviewed]; Bedard 2018 **Level III-3**, n= 35,894). Of over 6,000 USA veterans undergoing TKA that did not subsequently require revision, 60% had used an opioid in the year prior to surgery (Hadlandsmyth 2018 **Level IV**, n=6,653). In patients on long term opioids at the time of surgery, 69% received opioids for at least 6 mth and 57% for at least 12 mth after TKA. In patients not on long term opioids at the time of TKA, only 4% received opioids for at least 6 mth and 2% for at least 12 mth after TKA. Similarly, with patients having lower limb arthroplasty who used opioids at least 80% of the time for >4 mth preoperatively, over 70% became persistent users (Kim 2017c **Level IV**, n=57,545).

Australian pharmaceutical benefit (PBS) scheme data show persistent opioid use is more likely if initiated with transdermal preparations, higher doses, in older patients, with comorbid depression (Sullivan 2018 **NR**) or psychotic illness, and prior dispensing of pregabalin or benzodiazepines (Lalic 2019 **Level IV**, n=769,334).

For paediatric information, see Section 10.4.5.4.

There is a growing awareness of prescription opioid abuse in the general population and among injecting drug users (Degenhardt 2013 **Level IV**; Fischer 2010 **NR**). This has been described by some as a major public health problem and is associated with prescription opioid-related overdoses and deaths (Cicero 2017 **Level IV SR** [PRISMA], 17 studies, n=816).

Overprescribed and subsequently unused opioids prescribed for postoperative pain are potentially a large reservoir for opioid abuse, misuse and diversion. Following urological surgery, 67% of those who filled their prescriptions for opioids had leftovers, which 91% planned to keep (Bates 2011 **Level IV**). After dermatological surgery, 35% of those prescribed an opioid did not use it at all and 55% of these planned to keep the leftover tablets (Harris 2013 **Level IV**). Following upper limb surgery, 31% of 245 patients used fewer than half of the opioid tablets prescribed with over 4,000 tablets in total unused (Rodgers 2012 **Level IV**). In opioid naïve patients discharged to home after major gastrointestinal or colorectal surgery, 85% of patients were prescribed an opioid and only 38% of prescribed tablets were taken (Hill 2018a **Level IV**, n=333). For paediatric information, see Section 10.4.5.6.

These opioids are not just a danger to the patient for whom they are prescribed. Patients who retain unused tablets are usually willing to share them. It has been estimated that 71% of chronic opioid users receive their medications through diversion (Hill 2018a **Level IV**, n=333). After receiving opioid prescriptions for an acute episode, 64% of patients kept unused opioids and 34% shared them with others (Lewis 2014 **Level IV**, n=191). In the USA, one third of college students prescribed an analgesic for acute pain report having diverted opioids to others (Arria 2011 **Level IV**, n=192).

Sharing opioid medication may expose the user to an increased risk of adverse reaction or drug interaction as there is often no assessment made of the underlying cause of the opioid requirement and no advice given by a doctor or pharmacist (Ward 2011 **Level IV**, n=641; Ellis 2009 **NR**).

Hoarded medication may also be a source of opioids for nonmedical use (Macintyre 2014 **NR**). The most common source of prescription opioids for nonmedical use in both the USA (Lipari 2013 **Level IV**, n≈10,700,000) and Australia (Belcher 2014 **Level IV**, n=952) is a friend or relative, with no charge incurred.

The total duration of opioid use post-operatively may be the strongest predictor of subsequent opioid misuse (Brat 2018 **Level III-2**, n=1,015,116). Prescribing patterns and their association with subsequent misuse events were considered in a study of surgical claims from a linked medical and pharmacy administrative database in the USA. Each additional week of opioid use was associated with a 34% increase in the rate of misuse. For example, one refill in addition to the opioid prescription on discharge doubled the rate of misuse, and each additional prescription increased the rate by 70%. In this study, the dosage prescribed was a far weaker predictor of misuse. Even high doses (>MED 150mg/d) were associated with only small increases in misuse risk when the duration of prescription was short. For prescriptions <2 weeks, misuse rates for MED 40-50 mg/d were similar to rates for MED 100 to 150 mg/d.

Other risk factors associated with opioid misuse events have included benzodiazepine use, bariatric surgery, tobacco use disorder, other chronic pain and major depressive disorder (Brat 2018 **Level III-2**, n=1,015,116).

For paediatric information, see Section 10.4.5.5.

8.13.2.7 | Discharge opioid prescribing regimens

"*Over-prescription*" of opioids is common on discharge and may be explained by difficulties in estimating the postoperative opioid analgesic requirements of patients following day surgery or short inpatient stay. For post-operative patients, post-discharge opioid requirement may best be predicted by opioid use the day prior to discharge (Hill 2018a **Level IV**, n=333); the number of opioid tablets used at home was associated with the number of tablets taken the day before discharge and the patient age, but not the type of surgery. The following regimen satisfied home opioid requirements of 85% of the patients discharged: if a patient took no opioids the day prior to discharge, no prescription was required; if 1-3 tablets were taken the day prior to discharge, then a prescription for 15 pills was appropriate; and if 4 or more pills were used then 30 pills were given. Such an individualised approach to opioid prescribing is supported after Caesarean section (predicted based on each patient's inpatient opioid use), where individualised vs standard prescription (30 PO oxycodone 5 mg tablets) resulted in 50% reduced unused tablets and, most interestingly, 50% reduced opioid use (8 vs 15 tablets) with no difference in pain scores (Osmundson 2018 **Level II**, n=190, JS 3).

Although this approach may seem intuitive, it is not commonly done. Even when opioid requirements have been established, excessive prescription commonly occurs; 19% of postoperative patients prescribed oxycodone for discharge from a large Australian teaching hospital had not needed any opioid in the 24 h prior to discharge (Platis 2011 **Level IV**) and of the 36% of an American surgical cohort who received no opioids in the 24 h prior to discharge, 46% were prescribed opioids to take home (Chen 2018 **Level IV**, n=18,343).

Opioid prescribing limits for acute pain are a prominent component of the USA response to the opioid epidemic, often limiting prescription to "*7 days*" (Chua 2019 **NR**). Due to the heterogeneity of patient requirements, such prescribing limits may be either excessive for some patients, contributing needlessly to the community's "*opioid pool*", or inadequate for others, resulting in inadequate pain control and an increased risk of pseudoaddiction, chronic pain and potentially overdose (Brat 2018 **Level III-2**, n=1,015,116).

Many patients discharged from EDs with opioid medication do not safely store and dispose of these medicines (Hill 2018a **Level IV**, n=333). Other studies have shown that less than 10% of patients take unused opioid tablets back to the pharmacy or to a safe box drop (Bicket 2017 **Level III-3 SR** [PRISMA], 6 studies, n=810), some flush them down the toilet, some simply discard them and others keep them at home (Hill 2018a **Level IV**, n=333).

Patients should be advised of these risks and also of the safe way to dispose of unused opioid medicines; in Australia this is to return them to a pharmacy (Macintyre 2014 **NR**). In the USA when patients were provided with a written brochure describing how to dispose of unused opioids, disposal rates increased from 11% to 22% (Hasak 2018 **Level III-3**, n=334). A clear plan for analgesia reduction after discharge and robust systems for communication with usual treating practitioners in the community is essential and will assist in avoiding unintended dose escalation (Hanna 2019 **NR**; Katz 2015a **NR**). In ED, the introduction of education sessions, a staff information email, posters within the ED, and a patient information brochure resulted in a 22% (95%CI 13 to 31%) relative reduction of oxycodone on discharge (Kline 2019 **Level III-3**, n=43,814). Pain specialists and clinics have a role in assisting with transition of these patients to the community postoperatively and future developments may include transitional pain services for those discharged home with high dose opioids (Katz 2015 **NR**, De Pinto 2012 **NR**). Pharmacist led "*opioid exit plans*" can also assist with care on discharge (Genord 2017 **NR**).

For paediatric information, see Section 10.4.5.7.

8.13.3 | Selection of opioid for discharge medication

A position paper by ANZCA and FPMANZCA advises that slow-release (SR) conventional opioids (including transdermal opioid patches and methadone) are not recommended for routine use in the management of opioid naïve patients with acute pain (ANZCA 2018 **GL**). This position is based on the following facts:

- The inappropriate use of slow-release opioids for acute pain has been associated with sedation and respiratory depression resulting in severe adverse reactions and deaths;
- There is significant variation in opioid responsiveness between individuals which makes accurate dose prediction of slow release opioids difficult;
- Initial opioid dose should be titrated to effect and side effects, with the initial dose of immediate release opioid age-based;
- Acute pain intensity normally reduces rapidly over a few days, and so should opioid doses and controlled-release preparations do not allow for this rapid tapering;
- The use of controlled-release opioids in the initial treatment of pain is associated with an increased risk of long term opioid use and subsequent prescribed opioid dependence (Shah 2017 **Level IV**, n=1,294,247).

These recommendations are equally applicable to inpatient and discharge opioid medication.

There is no strong evidence that any one immediate release oral opioid is best for the management of pain on discharge following surgery (Macintyre 2014 **NR**). Hydromorphone or oxycodone, when used as the initial discharge opioid, have both been associated with a higher rate of long term misuse than other opioids (hydrocodone, codeine and tramadol) in opioid naïve patients undergoing surgery in the USA (Brat 2018 **Level III-2**, n=1,015,116). In Australia, the most commonly abused prescription opioids are oxycodone, tramadol and morphine (AIHW 2018a **Level IV**).

8.13.4 | Identification of patients at risk of opioid misuse

Many screening tools have been proposed to predict the risk of opioid misuse before opioid prescription in chronic pain patients (Chou 2009 **Level IV SR**, 16 studies, n=2,570; Passik 2008 **NR**) and are often recommended and utilised in the chronic pain setting (Webster 2011a **NR**). Their validity has, however, been questioned (Clark 2018 **Level IV**, n=225; Dowell 2016 **GL**). No risk prediction tool has been validated for use in acute pain patients although many have been proposed (Calcaterra 2018 **Level IV**, n=12,933) and an informal 'risk assessment' is often advocated using the risk factors discussed above.

8.13.5 | Practical opioid prescribing on discharge

It has been recommended that prescribing physicians use a "universal precautions" approach to opioid prescribing. Universal precautions have been described as a "systematic set of procedures and tools that aid the physician in gathering relevant information, help the physician interpret the information collected and provide a pathway for responsible decisions" (Webster 2010 **NR**).

Strategies include:

- **Risk assessment** for chronic opioid use and misuse (the type of surgical procedure, behavioural and social factors, medical comorbidities and preoperative pain disorders, the use of benzodiazepines, alpha-2-delta ligands, antidepressants (SSRIs), antipsychotics and ACE inhibitors, prescription opioid use, alcohol and substance use disorders and depression or anxiety (Carroll 2012 **Level III-2**, n=109; Sun 2016 **Level IV**, n=641,941 [surgical patients]);

- **The use of a multi-modal analgesic** regimen including non-opioid pain medications if they are not contraindicated (Dowell 2016 **GL**);
- **Appropriate opioid dose** when applicable is best predicted by usage the day before discharge home (Chen 2018 **Level IV**, n=18,343; Hill 2018a **Level IV**, n=333);
- **Limited prescribing and duration of therapy** (which should be communicated clearly to the patient) (Dowell 2016 **GL**). Patients should be instructed (verbal and written) on the expected duration of needing opioids, and recommendations should be individualised based on patient factors and anticipated pain trajectory after discharge;
- **Appropriate patient education** about the risk of opioids, including OIVI and addiction, and the safe disposal of opioids (Dowell 2016 **GL**) eg by the provision of educational material such as (NPS Medicinewise 2019 **GL**);
- **Monitoring of effect and compliance** (close follow-up of at-risk patients after discharge) and having a plan should opioid abuse, misuse or diversion be suspected (Thorson D 2014 **GL**; Webster 2010 **NR**; Passik 2009 **NR**).

A consensus statement for the prescription of discharge medications after surgery has been published in Canada (Clarke 2020 **GL**).

Pre-operative opioid users may be included in this strategy. However, patients who are taking high doses of opioids, long-acting opioids, or have a pain management contracts preoperatively fall outside of these recommendations and a postoperative pain management plan should be developed before surgery in coordination with their primary prescriber (Dowell 2016 **GL**). In using a multimodal discharge analgesic regimen, oral immediate release opioid should be prescribed only if required (based on prior in hospital use), to be used on an 'as needed' basis, for a defined period. Discharge planning should include a discussion of the plan for reduction and discontinuation of opioids as the acute pain resolves (Chou 2016 **GL**). If further opioid analgesia is required, the patient should first be reviewed by a medical officer (AMWG 2017 **GL**).

KEY MESSAGES

1. Short-term opioid therapy may lead to long term opioid use and misuse (**S**) (**Level III-2**); risk factors for prolonged postoperative use include preoperative opioid use, type of surgery, slow-release opioids, psychological and social factors and pre-existing alcohol or substance use disorder (**N**) (**Level III-2**).
2. Recent introduction of opioid therapy may increase the risk of falls (**S**) (**Level III-2**).
3. Recent introduction of opioid therapy or recent dose escalation may impair driving (**S**) (**Level III-2**), thereby leading to increased driving accidents (**N**) (**Level III-3 SR**); this risk is further increased by combined use of opioids and alcohol (**N**) (**Level III-2**).
4. Many patients who retain unused opioid tablets are willing to share them with others (**S**) (**Level III-2**); this contributes to increased risks of abuse and adverse effects in the recipients (**N**) (**Level IV**).
5. The most common source of prescription opioids for nonmedical use is a friend or relative (**N**) (**Level III-3**).

The following tick boxes represent conclusions based on clinical experience and expert opinion:

☑ Unused opioids prescribed for postoperative pain are potentially a large reservoir for opioid abuse, misuse and diversion (**S**).

☑ A "universal precautions" approach for opioid prescribing should be used in the setting of prescribing discharge medications (**S**).

☑ Prescribing discharge medications should be done in consideration of opioid requirements on the day before discharge, avoiding slow-release opioids and for a limited duration (**N**).

☑ Patient education about risks of opioids and safe disposal of unused medication by return to a pharmacy and follow-up by GP or pain medicine services in case of ongoing issues improve safety of discharge medications (**N**).

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9

Other specific patient groups

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Dr Richard Halliwell, Prof Stephan A Schug

9.1.1 | Management of acute pain during pregnancy

9.1.2 | Pain syndromes in pregnancy

Contributor: Dr Karin Jones

9.1.3 | Management of acute pain during labour and birth

9.1.4 | Pain management during lactation

9.1.5 | Pain in the puerperium

Contributor: Dr Maggie Wong

9.2 | The older patient

Contributors: Prof Stephen Gibson, A/Prof Benny Katz

9.3 | Culturally responsive care for Culturally and Linguistically Diverse patients

Contributor: Ms Monita Mascitti-Meuter

9.3.1 | Aboriginal and Torres Strait Islander peoples

Contributors: Dr Luke Arthur, Prof Alex Brown

9.3.2 | Māori peoples and pain

Contributor: Prof Edward A Shipton

9.4 | The patient with sleep-disordered breathing including obstructive sleep apnoea

Contributor: Dr Christina Denman

9.5 | The obese patient

Contributor: Dr Sonya Ting

9.6 | The patient with concurrent renal or hepatic disease

Contributor: Dr Andrew Stewart

9.7 | The opioid-tolerant patient

9.8 | The patient with a substance use disorder

Contributor: Dr Lindy Roberts

9.1 | The pregnant patient

9.1.1 | Management of acute pain during pregnancy

Pregnant women with pain that is severe enough to need pharmacological treatment (over the counter or by prescription) represent a challenging group as medications given to them almost always cross the placenta. While most medications are safe, there are particular times of concern, notably the period of organogenesis (wk 4 to 10) and just before birth. Where possible, nonpharmacological treatment options should be considered before analgesic medications are used. Most of the data reported in this setting are from episodes of prolonged use (eg for chronic conditions) and there is a lack of data on the risk of short-term exposure such as in the treatment of acute pain during pregnancy. Ongoing analgesic use requires close liaison between the pregnant woman, the health professional managing the pregnancy, and the health professional managing the pain.

9.1.1.1 | Medications used in pregnancy

Studies of analgesic use during pregnancy are often confounded by the indication (the condition the analgesic was being taken for may alter birth and childhood outcomes), recall bias and the lack of an active comparator. This is evident in various cohort studies discussed below that have explored the associations of analgesic medication use and different pregnancy or birth outcomes and childhood issues and results should be interpreted with caution.

Medication use during pregnancy is common and the data on which to make clear statements about fetal risk is limited (Daw 2011 **Level IV SR**, 17 studies, n unspecified; Lupattelli 2014 **Level IV**, n=9,459; Black 2019 **NR**; Price 2017 **NR**). Medications that may be prescribed during pregnancy have been categorised according to fetal risk by the TGA (TGA 2011 **GL**) in Australia, and the same categories are used in New Zealand (Medsafe 2013 **GL**). The categories used are listed in Table 9.1. It is important to note that the system is not hierarchical and that medications in Category B are not necessarily safer than those in Category C. The classification of some of the medications that might be used in pain management is summarised in Table 9.2. A list of these medications, including regular updates, is maintained by the TGA (TGA 2020 **GL**) .

The United States has moved away from a '*letter based*' categorisation of medication safety in pregnancy to providing a description of risk about individual agents that providers can then use to discuss risk with their patients (FDA 2014 **GL**).

Paracetamol

Paracetamol is classed a Category A medication by the TGA and is regarded as the analgesic of choice during pregnancy (Bisson 2019 **GL**) as no increased prevalence of congenital anomalies has been reported with its use (Rebordosa 2008 **Level III-3**; Scialli 2010 **NR**).

There was also no association of paracetamol with an increased risk of spontaneous abortion (OR 1.2; 95%CI 0.8 to 1.8) (Li 2003 **Level III-2**). However, it has been suggested that its potential influence on prostaglandin synthesis may have adverse effects in women at high risk of pre-eclampsia (Sahlman 2019 **Level III-2**, n=2,508; Zelop 2008 **NR**). A yet to be replicated Danish cohort study suggested an increased risk of preterm birth following paracetamol exposure in early pregnancy in mothers with pre-eclampsia (OR 1.55; 95%CI 1.16 to 2.07), but not in women without pre-eclampsia (OR 1.08; 95%CI 0.97 to 1.20) (Rebordosa 2009 **Level III-3**, n=98,140).

Childhood asthma

Paracetamol exposure has also been examined as a potential contributor to the increasing prevalence of childhood asthma, although there are likely multiple confounders. Plausibility is related to the potential for paracetamol to cause depletion of glutathione, an airway antioxidant. In observational cohort studies any paracetamol use during the first trimester was associated with an increased risk of childhood asthma (pooled OR 1.39; 95%CI 1.01 to 1.91) (5 studies) (Cheelo 2015 **Level III-2 SR**, 11 studies, n=3,663,454). However, there was marked between-study heterogeneity (I^2=63%) and only one of the studies adjusted for maternal respiratory tract infections. The association was weakened when adjustments for a range of factors, including respiratory infections was made.

Cryptorchidism

Association between paracetamol exposure in utero and cryptorchidism has been of interest due to the potential for paracetamol to act as an endocrine disrupter. A systematic review finds little evidence for an association between 'ever' use of analgesia and risk of cryptorchidism (pooled crude OR 1.11; 95%CI 1.00 to 1.23), including when separated into subgroups of case-control studies (OR 1.23; 95%CI 0.85 to 1.78) or cohort studies (OR 1.09; 95%CI 0.97 to 1.22) (Gurney 2017 **Level III-2 SR** [PRISMA], 10 Studies, n=501,456). There was a high degree of heterogeneity among studies.

Other childhood issues

Cohort studies have identified weak associations between intrauterine exposure to paracetamol and other childhood issues including neurodevelopmental conditions such as ADHD and ASD (for details see section 10.4.1).

There is also a potential association between premature closure of ductus arteriosus and maternal paracetamol use in pregnancy (Allegaert 2019 **Level IV SR**, 12 studies, n=25). Given paracetamol has been shown to be as effective as ibuprofen for closure of a patent ductus arteriosus in preterm neonates (Ohlsson 2018 **Level I** [Cochrane], 8 RCTs, n=916), it seems reasonable to recommend that (as with all medications) use should be limited to the minimum dose and duration that is clinically necessary.

Overall there is insufficient evidence to warrant changing guidelines on early life paracetamol exposure at this time.

Nonsteroidal anti-inflammatory drugs

Nonselective NSAIDs and coxibs are Category C medications, except celecoxib which is Category B3.

Spontaneous abortion

Exposure to an nsNSAID or coxib was not identified as an independent risk factor for spontaneous abortion (Daniel 2014 **Level III-2**, n=65,457 [n=4,495 exposed to NSAIDs]). There was an increased risk with indomethacin found (aHR 2.8; 95%CI 1.70 to 4.69), but the authors warn that this is possibly due to reverse causation bias, as indomethacin is a tocolytic medication used in preterm labour. This is supported by the finding that the association with indomethacin use disappeared when omitting all indomethacin use during the last four d before the spontaneous abortion. The same authors found in a further analysis of the same database associations of spontaneous abortion with use of nsNSAIDs in general, and specifically for diclofenac and indomethacin, which disappear again when exposures occurring on the day before the spontaneous abortion for nsNSAIDs and when exposures in the last week for indomethacin are excluded (Daniel 2015 **Level III-2**, n=65,457 [n=4,495 exposed to NSAIDs]). The authors regard these results as confirmation of an indication bias of these findings.

Congenital malformations

Intrauterine exposure to nsNSAIDs was not associated with increased risk for major congenital malformations (Daniel 2012 **Level III-2**, n=110,783 [n=5,267 exposed to NSAIDs]). This was also confirmed in another smaller study (Van Marter 2013 **Level III-3**, n=1,213) and four older cohort studies (Bloor 2013 **NR**). Major congenital malformations, structural heart defects and infant survival did not differ in offspring of women who took one of four different nsNSAIDs (ibuprofen, diclofenac, naproxen and piroxicam) during early pregnancy vs controls (Nezvalová-Henriksen 2013 **Level III-2**, n= 90,417 [n=6,511 exposed to NSAIDs]). The use in the second trimester of ibuprofen (aOR 1.7; 95%CI 1.3 to 2.3) or diclofenac (aOR 3.1; 95%CI 1.1 to 9.0) was associated with low birth weight, possibly related to maternal inflammatory conditions.

A cohort study of 174 women who took coxibs in the first trimester of pregnancy did not find a significantly increased risk of birth defects in their offspring (2.9% vs. 2.7%) (Dathe 2018 **Level III-2**, n=174).

While relatively safe to use in early and mid-pregnancy, NSAIDs can precipitate fetal cardiac and renal complications in late pregnancy, as well as interfere with fetal brain development and the production of amniotic fluid and thus should be discontinued from gestational wk 32 (Bloor 2013 **NR**).

Other neonatal and childhood issues

Fetal exposure to NSAIDs has been associated with persistent pulmonary hypertension in the newborn in one study (Alano 2001 **Level III-2**, n=40 [cases] vs n=61 [controls]), but not another (Van Marter 2013 **Level III-2**, n=377 [cases] vs n=836 [controls]). In the third trimester, associations between NSAID use and renal injury, oligohydramnios, necrotising enterocolitis and intracranial hemorrhage have also been reported (Bloor 2013 **NR**); the incidence may be increased with exposure occurring closer to delivery.

There is also an increased risk of premature closure of the ductus arteriosus (OR 15.04; 95%CI 3.29 to 68.68) (Koren 2006 **Level I** [Cochrane], 8 RCTs, n=438).

Ibuprofen use in the second (aOR 1.5; 95%CI 1.2 to 1.9) and third trimesters (aOR 1.5; 95%CI 1.1 to 2.1) was also associated with asthma in 18 mth old children (Nezvalová-Henriksen 2013 **Level III-2**, n= 90,417 [n=6,511 exposed to NSAIDs]).

One observational study showed an increased association between maternal aspirin use during pregnancy and the development of psychotic symptoms during adolescence (Gunawardana 2011 **Level III-3**, n=6,437]). However, this association may be related to the presence of maternal indications, for which the aspirin is taken, rather than the aspirin itself being causative itself (Khandaker 2013 **Level III-2 SR**, 21 studies, n unspecified)**.**

Conventional Opioids

Large increases in the use of prescription opioids in Western countries has been reflected in women of child bearing age and is a major public health concern affecting pregnant women and their infants (Lind 2017 **Level III-2 SR**, 68 studies, n unspecified; Yazdy 2015 **NR**). Rates of opioid use in Australia and New Zealand are possibly less than those seen in North America. One Australian study estimated that 1% of pregnant women took prescription opioids in a two-week period (Miller 2019 **Level III-2,** n=192,617 [pregnant patients] vs n=5,448,771 [controls]). In comparison, a Canadian cohort (studied between 2001 and 2013) where opioid use was 6.7 % before pregnancy, reducing to 4.2%, 3.0% and 2.4% in first, second and third trimesters respectively (Falk 2017 **Level III-2**, n=174,848).

Congenital malformations

The risk of congenital malformation related to opioid exposure in early pregnancy is difficult to clarify due to these being rare events and bias due to inaccurate self-reporting about opioid use (Yazdy 2015 **NR**).

Data from the long running US National Birth Defects Prevention Study (1997-2011) was used to calculate an adjusted odds ratios for risk of a range of birth defects in offspring exposed in the periconceptual period to paracetamol, NSAID or opioid (Interrante 2017 **Level III-2**, n=29,078 [treated patients] vs n=10,962 [controls]). In utero opioid exposure (n=196 [treated patients] vs n=110 [controls]) was associated with tetralogy of Fallot, perimembranous ventricular septal defect and atrio-ventricular septal defect (aOR range 1.8 to 2.3), whereas the use of both opioids and NSAIDs (n=191 and n=86) was associated with gastroschisis, cleft palate, spina bifida, hypoplastic left heart syndrome, and pulmonary valve stenosis (aOR range 2.0 to 2.9). It was not possible to tell whether the effects were due to the drug or confounding due to the condition for which the drug was taken.

The impact of periconceptual opioid exposure for all indications on the risk of neural tube defects was studied in a well-designed case control study. This found an overall increased risk vs non-malformed controls (aOR 2.2; 95%CI 1.2 to 4.2) and malformed controls (aOR 1.9; 95%CI 1.0 to 3.4) (Yazdy 2013 **Level III-2**, n=305 [cases] vs 7,125 [non-malformed controls] vs 13,405 [malformed controls]). When opioids were used for pain control, the most common indication reported, there was no significant increase in neural tube defects.

A systematic review of the risk of teratogenic effects with opioid exposure in utero analysed 30 studies where statistical analysis was presented (Lind 2017 **Level III-2 SR**, 68 studies, n unspecified). Seventeen of these 30 studies (10 of 12 case control studies and 7 of 18 cohort studies) found positive associations for a range of congenital malformations, with the most common being for orofacial clefts, ventricular or atrial septal defects and, for the cohort studies, club foot. The authors noted few of these studies were of high quality, and many had been performed before 1999, and could not differentiate between groups taking opioids for substance use disorder vs chronic pain.

Neonatal abstinence syndrome

Neonates exposed to regular opioid in utero, particularly in the last three mth of pregnancy, are at risk of neonatal abstinence syndrome (NAS) and should be monitored for it after delivery. A population based USA cohort study reported the risk of NAS in infants born to women prescribed opioids during pregnancy (Desai 2015 **Level III-2**, n=290,605 [1,705 cases of NAS]). The absolute risk was low (0.59%; 95%CI 0.56 to 0.62). Both the duration (cumulative dose) and timing (later use; in the 90 d prior to birth) increased the risk. Maternal history of opioid misuse or dependence, alcohol, psychoactive medication use or smoking were also associated with increased risk of NAS. Long-term known opioid misuse had higher absolute risk 22% (95%CI 20 to 24%) vs short-term known misuse (19%; 95%CI 18 to 21%).

The longer term impact of NAS is of concern but clouded by the complexity of the effects of medication, small sample sizes and lack of control for confounding variables such as poverty and maternal psychopathology (Conradt 2018 **NR**).

Other issues are the lack of appropriate tools for its assessment and the lack of early recognition of NAS symptoms resulting in possible underreporting and, as a consequence, inappropriate and too early neonatal discharge from hospital (Wolff 2014 **NR**). Guidelines for the management of NAS have been published (Wiles 2014 **GL**).

Other neonatal issues

Preterm infants, prenatally exposed to opioids, had increased rates of intermittent hypoxaemia (defined as episodes with SpO_2<80% on continuous pulse oximetry), which persisted beyond the immediate postnatal period (Abu Jawdeh 2017 **Level III-2**, n=14 [exposed] vs n=68 [unexposed]).

A small study suggested that neonatal outcome was better in mothers receiving opioids for chronic pain rather than addiction, although differences in dose and other environmental factors may contribute (Sharpe 2004 **Level III-2**, n=43), but minimising the use of opioid therapy for chronic pain during pregnancy has been recommended (Chou 2009 **GL**).

Neurodevelopmental outcomes

Neurodevelopmental abnormalities resulting from opioid exposure are mechanistically plausible due to multiple effects of opioids on maternal and fetal physiology, as well as direct receptor mechanisms; potential confounders such as psychosocial issues leading to childhood deprivation must also be considered. A pilot study suggested that on MRI scans brain volumes of opioid-exposed babies may be smaller than controls, in particular in specific regions such as basal ganglia (Yuan 2014 **Level IV**, n=16). Cognitive outcomes of children exposed to opioids in utero have been described, showing marked developmental functional impairments vs non-exposed children (Farid 2008 **NR**; Winklbaur 2008 **NR**).

However, a systematic review found no significant impairments for cognitive, psychomotor or observed behavioural outcomes after chronic intrauterine opioid exposure in infants (4 studies, n=423) and preschool children (3 studies, n=455) vs non-exposed controls (Baldacchino 2014 **Level III-2 SR** [PRISMA], 5 studies, n unspecified). There were significant limitations of this systematic review (small number of studies analysed, heterogeneous populations, small numbers within the individual studies).

The school age academic performance (NAPLAN testing) of Australian grade 3, 5 and 7 children (assessed from year 2000 to 2006) who had suffered neonatal abstinence syndrome (NAS) (n=2,234) vs a matched control cohort (n=4,330) and population results (n=598,265) found significantly poorer outcomes in NAPLAN testing (Oei 2017 **Level III-2**). The risk of not meeting minimum NAPLAN test result standards was independently associated with a history of NAS (aOR 2.5; 95%CI 2.2 to 2.7).

Beside impairment of general cognitive abilities, children exposed to heroin prenatally show problems in several behavioural areas, in particular with regard to attention, when assessed by parents and teachers at 4.5 and 8.5 y of age, but these are not specific and not more severe than the effect on cognitive function (Nygaard 2016 **Level III-2**, n=72 [exposed] vs 58 [not exposed]).

For the management of acute pain in pregnant patients with an addiction see Section 9.8.9 below.

Atypical Opioids

Among women identified from the Swedish Medical Birth Register 1997 to 2013, 1,751 mothers (n=1,776 infants) had used tramadol and 96 of the infants had a congenital malformation (Kallen 2015 **Level III-2,** n=1,682,846 [mothers]; n=1,797,678 [infants]). Tramadol was associated with increased odds ratios for cardiovascular defects (OR 1.56; 95%CI 1.04 to 2.29) and for pes equinovarus (club foot) (OR 3.63; 95%CI 1.61 to 6.89).

Alpha-2-delta ligands

Evidence regarding the effects of exposure to alpha-2-delta ligands in utero remains scant. While registries of antiepileptic drug and pregnancy outcomes were established in different countries ≈15 y ago, gabapentin and pregabalin have been used relatively rarely vs other antileptic agents and no relevant outcomes could be reported for the two medications (Veroniki 2017 **Level III-2 SR**, 29 studies, n=5,100).

Data on gabapentin use in pregnancy suggest its safety currently, although the number of documented exposures is small (Guttuso 2014 **Level IV SR**, 6 studies & 2 case reports, n=294 [gabapentin exposures in first trimester]). The rate of congenital malformations (1.7%) was not different from the rate in comparable general populations (1.6 to 2.2%). There were also equivalent rates of premature birth (including maternal hypertension/eclampsia premature birth) and similar birth weight after correction for gestational age at delivery with gabapentin use vs the general population (n=261). Based on similarly small numbers in another study, gabapentin exposure was not associated with increased rates of small for gestational age infants (aOR] 2.03; 95%CI 0.68 to 6.01), low birth weight (aOR 1.86; 95%CI 0.56 to 6.15) or preterm delivery (aOR 1.214; 95%CI 0.501 to 2.946) (Wade 2015 **Level III-2**, n=53 [gabapentin exposures]). In contrast, another cohort study revealed no increased rate of malformations, but a higher rate of preterm births and birth weight <2,500 g in the gabapentin group (Fujii 2013 **Level III-2**, n=223 [gabapentin exposures] vs n=223 [unexposed controls]).

Of 477 infants exposed to pregabalin during the first trimester, 5.9% had congenital malformations vs 3.3% in non-exposed infants (RR 1.80; 95%CI 1.26 to 2.58). However, propensity score adjustment suggested no teratogenic effect of pregabalin (aOR 1.16; 95%CI 0.81 to 1.67), confirmed by analysis of a second database (n=174 [exposed to pregabalin]) (aRR 1.03; 95%CI 0.56 to 1.90) (Patorno 2017 **Level III-2**, n=1,323,432 [pregnancies followed]).

Data from the Medical Birth Registry of Norway showed no increase of congenital malformations with gabapentin (n=39) and pregabalin (n=30), however, based on very low numbers of exposures (Veiby 2014 **Level III-2**, n=2,600 [exposed to any anticonvulsant] vs n=774,012 [unexposed controls]). Similarly, a systematic review examining neurodevelopmental effects from intrauterine exposure to anticonvulsants could not provide information on gabapentin or pregabalin due to too few exposures (Bromley 2014 **Level III-2 SR** [Cochrane], 28 studies [22 prospective cohort, 6 registry-based studies], n unspecified).

Withdrawal syndromes can occur in neonates exposed during pregnancy to gabapentin (combined with other substances), with re-introduction of gabapentin being a suggested treatment for this syndrome (Carrasco 2015 **CR**).

Table 9.1 | TGA medicine categorisation according to fetal risk

A	Medicines which have been taken by a large number of pregnant women and women of childbearing age without any proven increase in the frequency of malformations or other direct or indirect harmful effects on the fetus having been observed.
B1	Medicines which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed. Studies in animals have not shown evidence of an increased occurrence of fetal damage.
B2	Medicines which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed. Studies in animals are inadequate or may be lacking, but available data show no evidence of an increased occurrence of fetal damage.

B3	Medicines which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed. Studies in animals have shown evidence of an increased occurrence of fetal damage, the significance of which is considered uncertain in humans.
C	Medicines which, owing to their pharmacological effects, have caused or may be suspected of causing, harmful effects on the human fetus or neonate without causing malformations. These effects may be reversible. Accompanying texts should be consulted for further details.
D	Medicines which have caused, are suspected to have caused or may be expected to cause, an increased incidence of human fetal malformations or irreversible damage. These medicines may also have adverse pharmacological effects. Accompanying texts should be consulted for further details.
X	Medicines which have such a high risk of causing permanent damage to the fetus that they should not be used in pregnancy or when there is a possibility of pregnancy.

Notes: For medicines in the B1, B2 and B3 categories, human data are lacking or inadequate and subcategorisation is therefore based on available animal data. The allocation of a B category does NOT imply greater safety than the C category. Medicines in category D are not absolutely contraindicated in pregnancy (eg anticonvulsants). Moreover, in some cases the 'D' category has been assigned on the basis of "suspicion".

Due to legal considerations in Australia, sponsoring companies have, in some cases, applied a more restrictive category than can be justified on the basis of the available data.

In some cases there may be discrepancies between the published product information and the information in this table due to the process of ongoing document revision.

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Table 9.2 | Categorisation of medicines used in pain management

Medicine	Cat	Comments
Opioids alfentanil, buprenorphine, dextromoramide, dextropropoxyphene, fentanyl, hydromorphone, methadone, morphine, oxycodone, papaveretum, pentazocine, pethidine, phenoperidine, remifentanil, tramadol	C	Opioid analgesics may cause respiratory depression in the newborn. Withdrawal symptoms in newborns have been reported with prolonged use of this class of medicines including tramadol
codeine, dihydrocodeine	A	Prolonged high-dose use of codeine prior to birth may produce codeine withdrawal symptoms in the newborn
Paracetamol	A	
Aspirin	C	Aspirin inhibits prostaglandin synthesis. When given late in pregnancy, it may cause

Medicine	Cat	Comments
		premature closure of the fetal ductus arteriosus, delay labour and birth. Aspirin increases the bleeding time both in the newborn and in the mother because of its antiplatelet effects. Products containing aspirin should be avoided in the last trimester. Low-dose aspirin (100 mg/d) does not affect bleeding time.
Other nsNSAIDs diclofenac, diflunisal, ibuprofen, indomethacin, ketoprofen, ketorolac, mefenamic acid, nabumetone, naproxen, phenylbutazone, piroxicam, sodium salicylate, sulindac, tenoxicam, tiaprofenic acid	C	These agents inhibit prostaglandin synthesis and, when given during the latter part of pregnancy, may cause closure of the fetal ductus arteriosus, fetal renal impairment, inhibition of platelet aggregation and delayed labour and birth. Continuous treatment with NSAIDs during the last trimester of pregnancy should only be given on sound indications. During the last few days before expected birth, agents with an inhibitory effect on prostaglandin synthesis should be avoided.
Coxibs celecoxib parecoxib	 B3 C	
Local anaesthetics bupivacaine, cinchocaine, lignocaine (lidocaine), mepivacaine, prilocaine etidocaine, ropivacaine procaine hydrochloride levobupivacaine	 A B1 B2 B3	
Antidepressants *SSRIs:* citalopram, fluoxetine, fluvoxamine, sertraline,	 C	SSRIs have had limited use in pregnancy without a reported increase in birth defects. The use of SSRIs in the third trimester may result in a withdrawal state in the newborn.
paroxetine	D	Category changed Sept 2005
Tricyclic antidepressants: amitriptyline, clomipramine, desipramine, dothiepin (dosulepin), doxepin, imipramine, nortriptyline, protriptyline, trimipramin	 C	Withdrawal symptoms in newborn infants have been reported with prolonged maternal use of this class of medicines.
Other antidepressants:		

Medicine	Cat	Comments
mirtazapine, moclobemide, nefazodone, duloxetine venlafaxine, desvenlafaxine	B3 B2	
Anticonvulsants carbamazepine	D	Spina bifida occurs in about 1% of pregnancies in which carbamazepine is used as monotherapy. Carbamazepine taken during pregnancy also has been associated with minor craniofacial defects, fingernail hypoplasia and developmental disability. Carbamazepine also can cause coagulation defects with consequent risk of haemorrhage in the fetus and the newborn, which may be preventable by the prophylactic administration of vitamin K to the mother prior to the birth.
phenytoin sodium	D	This medicine taken during pregnancy has been associated with craniofacial defects, fingernail hypoplasia, developmental disability, growth retardation and, less frequently, oral clefts and cardiac anomalies. This clinical pattern is sometimes called the “fetal hydantoin syndrome”. Phenytoin can also cause coagulation defects with consequent risk of haemorrhage in the fetus and the newborn, which may be preventable by the prophylactic administration of vitamin K to the mother prior to the birth.
sodium valproate	D	Sodium valproate is contraindicated in pregnancy. A broad range of congenital malformations can occur in babies born to women who take sodium valproate during pregnancy, and the risk of malformations increases with increasing dose of valproate. If taken in the first trimester of pregnancy, sodium valproate (valproic acid) is associated with a one to two percent risk of neural tube defects (especially spina bifida) in the exposed fetus. Sodium valproate should not be used during pregnancy and in women of child-bearing potential unless alternative treatments are ineffective or not tolerated because of the high risk of malformation and risk of developmental disorders in infants exposed to valproate before birth. Avoid use of valproate in women of child-bearing age for all non-

Medicine	Cat	Comments
		seizure indications. For seizure indications, consider alternatives if they exist. Always use the lowest effective dose. Patients and prescribers should reconsider benefit and risk at regular treatment reviews, at puberty and urgently when a woman of child-bearing potential treated with valproate plans a pregnancy or becomes pregnant. Folic acid supplementation (5 mg) should be commenced four weeks prior to and continue for twelve weeks after conception; specialist prenatal diagnosis including detailed mid-trimester ultrasound should be offered.
lamotrigine	D	Category changed June 2006
clonazepam	C	Clonazepam is a benzodiazepine. These medicines may cause hypotonia, respiratory depression and hypothermia in the newborn if used in high doses during labour. Withdrawal symptoms in newborns have been reported with this class of medicines.
gabapentin,	B1	Used for neuropathic pain
tiagabine, topiramate, pregabalin	B3	
Lamotrigine Levetiracetam	D B3	Anticonvulsants for partial complex seizures, possibly mood stabilising and antineuropathic
Antiemetics, antinauseants *Phenothiazines:* prochlorperazine, promethazine, thiethylperazine	C	When given in high doses during late pregnancy, phenothiazines have caused prolonged neurological disturbances in the infant.
Others: dimenhydrinate, diphenhydramine, metoclopramide	A	
dolasetron, granisetron, ondansetron	B1	
domperidone, hyoscine, hyoscine hydrobromide	B2	
tropisetron	B3	

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KEY MESSAGES

1. Short-term use of NSAIDs in late pregnancy is associated with an increase in the risk of premature closure of the ductus arteriosus (**U**) (**Level I** [Cochrane Review]).
2. The chronic use of opioids during pregnancy may be associated with some teratogenic effects, childhood neurocognitive delay and/or negative neurobehavioural outcomes; however, it is difficult to separate the influence of multiple confounders in this patient group (**Q**) (**Level III-2 SR**).
3. Retrospective epidemiological studies linking paracetamol use in pregnancy to later development of childhood asthma are inherently confounded (**U**); when adjusted for respiratory tract infections in the child the association is lost (**Q**) (**Level III-2 SR**).
4. The use of common nsNSAIDS during pregnancy is not associated with increased risk of major congenital malformations, structural heart defects or difference in infant survival (**N**) (**Level III-2**).
5. Exposure to an nsNSAID or coxib is not an independent risk factor for spontaneous abortion (**Q**) (**Level III-2**)
6. The safety of alpha-2-delta ligand use in pregnancy remains unclear; limited data has not raised safety concerns (**N**) (**Level III-2**).

The following tick boxes represent conclusions based on clinical experience and expert opinion:

☑ For pain management in pregnancy, nonpharmacological treatment options should be considered where possible before analgesic medications are used (**U**).

☑ Use of medications for pain in pregnancy should be guided by published recommendations; ongoing analgesic use requires close liaison between the patient, the health professional managing the pregnancy and the health professional managing the pain (**U**).

☑ Most of the data reported in this setting are from episodes of prolonged use (eg for chronic conditions) and there is a lack of data on the risk of short-term exposure such as in the treatment of acute pain (**N**).

☑ Studies of analgesic use during pregnancy may be confounded by the indication, recall bias and often the lack of an active comparator; this is exemplified by reported associations between NSAID use in pregnancy and low birth weight and asthma confounded by the maternal indications for their use (ie inflammatory diseases) (**N**).

☑ Nonselective NSAIDs and Coxibs should be used with caution in the last trimester of pregnancy and should be avoided after the 32nd week (**U**).

☑ Emerging evidence suggests that maternal paracetamol use may influence premature closure of the fetal ductus arteriosus (**N**).

☑ Neonates exposed to regular opioid in utero, particularly in the last three months of pregnancy, are at risk of neonatal abstinence syndrome and should be monitored for it after delivery (**N**).

9.1.2 | Pain syndromes in pregnancy

9.1.2.1 | Musculoskeletal pain syndromes

Low back pain (LBP) or pelvic girdle pain (PGP) alone or in combination are common during pregnancy (Casagrande 2015 **NR**). Low back pain in pregnancy refers to pain in the lumbar spine without radicular component or pain reproduced with repeated range of motion activity. Pelvic girdle pain is experienced between the posterior iliac crest and the gluteal fold, particularly in the vicinity of the sacroiliac joint, may radiate to the posterior thigh or be perceived in the pubic symphysis (Vleeming 2008 **GL**). The endurance capacity for standing, walking and sitting is diminished. The pattern may change during the course of pregnancy and following delivery with 76% of women reporting some form of back or pelvic pain during singleton pregnancy (Weis 2018 **Level IV**, n=287). Point and period prevalence were respectively 15.7%/17.8% for LBP, 15.3%/33.4% for PGP and 27.9%/30.7% for the combination.

Risk factors for pelvic pain during pregnancy include previous LBP and pelvic trauma (Elden 2016 **Level IV**, n=371). The group with pre-existing pain may present a more complex picture that may be more resistant to interventions, although studies do not always examine this group separately. Recommendations to improve the consistency of reporting in research using a Core Outcome Set for PGP have been proposed (Wuytack 2018 **GL**).

Exercise

A Cochrane review of interventions to prevent or reduce pain severity, functional disability or absenteeism (in addition to usual prenatal care) examined 15 RCTs in LBP, 6 RCTs in PGP and 13 RCTs in LBP/PGP combination (Liddle 2015 **Level I** [Cochrane], 34 RCTs, n=5,121). For women with pregnancy related LBP, comparing land-based exercise with usual care provides low quality evidence for exercise leading to reduced LBP and disability (SMD -0.64; 95%CI -1.03 to -0.25) (7 RCTs, n=645). For PGP alone, low quality evidence shows no significant difference in the number of women reporting pain when comparing exercise with information about pain management and usual prenatal care (RR 0.97; 95%CI 0.77 to 1.23) (2 RCTs, n=374). For combined LBP and PGP, there was moderate quality evidence for reduced pain and related sick leave after participation in a 12 wk program of land-based exercise in various formats (RR 0.76; 95%CI 0.62 to 0.94) (4 RCTs, n=1,062).

Two further systematic reviews investigated the preventive beneficial effect of exercise. The first assessed prenatal exercise impact on LBP, PGP and lumbopelvic pain (Davenport 2019 **Level III-3 SR**, 23 RCTs & 9 studies, n=52,297) (13 RCTs overlap with Liddle 2015). Prenatal exercise does not reduce the incidence of these conditions (13 RCTs), either in pregnancy or the postpartum period, but exercise in pregnancy is associated with lower pain severity during pregnancy and the early postpartum period vs non-exercisers (SMD -1.03; 95%CI -1.58 to -0.48) (15 RCTs). Exercise in pregnancy reduces the risk of LBP in pregnancy by 9% (RR 0.91; 95%CI 0.83 to 0.99) (7 RCTs, n=1,175), whereas it has no protective effect on PGP (RR 0.99; 95%CI 0.81 to 1.21) (4 RCTs, n=565) or lumbopelvic pain (RR 0.96; 95%CI 0.90 to 1.02) (8 RCTs, n=1,737) (Shiri 2018 **Level I** [PRISMA], 11 RCTs, n=2,347) (7 RCTs overlap with Liddle 2015 and 9 RCTs overlap with Davenport 2019). However, exercise prevented new episodes of sick leave due to lumbopelvic pain (RR 0.79; 95%CI 0.64 to 0.99) (3 RCTs, n=1,168).

In a cohort prevention intervention study, not included in the above systematic reviews, women who undertook high impact exercise 3 to 5 times per wk had a lower risk of developing PGP in pregnancy vs non-exercisers (RR 0.86; 95%CI 0.77 to 0.96) (Owe 2016 **Level III-2**, n=39,184).

Manual therapies

Manual therapy interventions (including craniosacral therapy, osteopathic manipulative treatment, chiropractic interventions, massage and partner-delivered massage) reduce the intensity of pregnancy-related back and pelvic pain vs usual care and relaxation, but not to sham interventions (Hall 2016 **Level I** [PRISMA], 10 RCTs, n=1,198).

Pelvic belts

Use of a soft vs rigid pelvic belt was examined in two small non-blinded RCTs, with no non-treatment arm. There was no difference in function but pain was reduced vs the previous 24 h (Flack 2015 **Level II**, n=20, JS 2). Combining data from both groups, function and pain were improved at three wks (MD -2.3/10; 95%CI -1.2 to -3.5). In de novo PGP, two different pelvic support belts were well tolerated and reduced pain intensity by 20/100 (Bertuit 2018 **Level II**, n=46, JS 2).

Magnesium

Oral magnesium therapy did not reduce the frequency or severity of painful leg cramps during pregnancy (Nygaard 2008 **Level II**, n=45, JS 2).

9.1.2.2 | Meralgia paraesthetica and other compressive neuropathies

These variable conditions comprise some or all of the sensations of pain, tingling and numbness in the lateral thigh affects pregnant women more than a nonpregnant population (OR 12.0; 95%CI 1.2 to 118.0) (van Slobbe 2004 **Level III-2**). Multiple therapies have been reported but have not been fully evaluated or compared, including ice packs, local infiltration with steroid and local anaesthetic, topical lignocaine or capsaicin, TENS, pharmacological therapy (TCAs, antiepileptics) and surgical intervention (Harney 2007 **NR**; Van Diver 1995 **NR**). Other compressive neuropathies, such as carpal tunnel syndrome and Bell's palsy, also occur more commonly during pregnancy (Sax 2006 **NR**).

9.1.2.3 | Diastasis symphysis pubis

Diastasis of the symphysis pubis is defined as the separation of the pubic bones. It may occur during pregnancy, and following either operative or non-operative delivery. This occasionally disabling disorder (sometimes also called osteitis pubis or diastasis pubis) has a quoted incidence of 1:600 (Taylor 1986 **Level IV**) and can produce persistent pain; but there are limited data to inform management (Aslan 2007 **NR**).

Severe traumatic separation is rare and is heralded by a sensation of the separation occurring, associated with severe pain and swelling at the pubic symphysis. Evidence regarding management is from case series (Urraca-Gesto 2015 **Level IV SR**, 4 studies & 14 case reports, n=47 [diastasis symphysis pubis]; Chawla 2017 **Level IV**, n=2). Recommended management often initially includes lateral decubitus bed rest with a pelvic girdle and analgesia followed by mobilisation and physiotherapy to reinstate mobility. Rarely surgery is required for cases that do not resolve with spontaneous treatment (Buitendyk 2018 **CR**).

KEY MESSAGES

1. Exercise reduces low back and pelvic girdle pain during pregnancy (**S**) (**Level I** [Cochrane Review]).
2. Manual therapy interventions reduce intensity of pregnancy-related back and pelvic pain versus usual care and relaxation, but not to sham interventions (**N**) (**Level I** [PRISMA])

The following tick box represents conclusions based on clinical experience and expert opinion:

☑ The use of a pelvic support belt may reduce pelvic girdle pain during pregnancy (**N**).

9.1.3 | Management of acute pain during labour and after birth

Pain during labour and birth represents a complex interaction of multiple physiological and psychological factors involved in parturition. Women's desires for and expectations of pain relief during labour and delivery vary widely. High-quality pain relief does not necessarily equate with a high level of satisfaction. Non-analgesic interventions (eg support person during labour or education) can provide a significant improvement in satisfaction with the experience of labour and childbirth (Taheri 2018 **Level I** [PRISMA], 20 RCTs, n=22,800).

Severe pain during labour is one of several factors associated with post-traumatic stress symptoms following birth (Slade 2006 **NR**). Personality traits, anxiety and analgesic expectations partially predict labour pain, epidural analgesic consumption and satisfaction (Carvalho 2014 **Level IV**, n=39).

9.1.3.1 | Systemic analgesia in labour pain

Nonopioids

A variety of nonopioids (NSAIDs, paracetamol, antispasmodics, sedatives and antihistamines) have been investigated with regard to their effect in labour pain (Othman 2012 **Level I** [Cochrane], 19 RCTs, n=2,863). Most of these studies are very old (>30 y) and show very limited efficacy vs placebo and inferior efficacy vs opioids. Sedatives may have a limited benefit vs placebo with regard to analgesia and satisfaction. There is insufficient evidence for the effectiveness of nonopioids to manage pain during labour.

However, a few studies subsequent to this review show some efficacy of nonopioids in labour pain. IV paracetamol 1 g and IM tramadol 1 mg/kg provide similar analgesia in labour, but tramadol recipients had a longer first stage of labour and more sedation and nausea (Kaur Makkar 2015 Level II, n=60, JS 1). IV paracetamol 1 g reduced labour pain slightly at 2, 3 and 4 h after injection (Zutshi 2016 **Level II**, n=200, JS 4), but was inferior to IV morphine (Ankumah 2017 **Level II**, n=40, JS 3). As an adjunct to patient-controlled epidural analgesia (PCEA), IV paracetamol 1 g decreased mean epidural infusion rate (7.03 ml/h [± 0.83] vs 8.12 ml/h [± 1.34]) and demand bolus requirements (1.0 [±0.93] vs 1.43 [±SD 0.90]) (Gupta 2016 Level II, n=80, JS 5).

Opioids

Systemic opioids are used in labour, although practice varies, and their use in Australia is declining (21.8% at 2011) (Li 2011 **Level IV**).

The following conclusions are for healthy women with an uncomplicated pregnancy giving birth at or near term when parenteral opioids were compared to no treatment, placebo, another opioid or TENS (Smith 2018b **Level I** [Cochrane], 61 RCTs, n>8,000):

- Parenteral opioids provide moderate pain relief in labour;
- Maternal satisfaction is variable where reported;
- Opioids cause sedation, nausea and vomiting;
- For most outcomes there was no good quality evidence of differences between treatment groups.

There was insufficient evidence to assess the safety of opioids in labour. The quality of the evidence for pain and pain relief outcomes was predominantly poor or very poor.

Opioid analgesia vs epidural analgesia provides inferior pain relief overall (5 RCTs, n=1,133), with less maternal satisfaction (17 RCTs, n=1,911) (Anim-Somuah 2018 **Level I** [Cochrane], 40 RCTs, n=12,389).

IN or SC fentanyl was preferred by parturients to IM pethidine, when surveyed six wk after birth (Fleet 2017 **Level II**, n=116, JS 2)

Remifentanil intravenous PCA

In comparison to other systemic opioids, remifentanil offers an advantage due to its rapid metabolism. In some countries, remifentanil IV PCA is used for labour analgesia as an alternative to both epidural analgesia and other systemic opioids (Devabhakthuni 2013 **NR**). In the UK, 49% of obstetric wards use IV PCA with remifentanil as the most common agent followed by morphine and fentanyl. In Belgium, 36% of obstetric wards use IV PCA, with remifentanil being the most commonly used opioid (77%).

Remifentanil IV PCA in women with low-risk pregnancies (higher risk groups were excluded) was compared with other forms of parenteral analgesia in labour (Weibel 2017 **Level I** [Cochrane], 19 RCTs, n=3,569):

Satisfaction

- Women receiving remifentanil IV PCA are more satisfied with pain relief than women having other forms of opioids (IV/IM) (SMD 2.11; 95%CI 0.72 to 3.49) (4 RCTs, n=216), but satisfaction is less than for women in the epidural group (SMD 0.22; 95%CI 0.04 to 0.40);

Note: reversal of conclusion
This reverses the Level I key message in the previous edition of this document; preceding RCTs had described remifentanil IV PCA as providing superior satisfaction vs epidural techniques.

Pain relief

- Remifentanil IV PCA vs other opioids administered IV/IM provides better pain relief at 1 h (SMD -1.58/10; 95%CI -2.69 to -0.48);
- Remifentanil IV PCA vs epidural analgesia shows higher pain scores at 1 h (SMD 0.57; 95%CI 0.31 to 0.84) (6 RCTs, n unspecified);

Additional analgesia

- Remifentanil IV PCA lowers the risk of needing additional analgesia vs other opioids (IV/IM) (RR 0.57; 95%CI 0.4 to 0.81), while there is no evidence that remifentanil IV PCA reduces the requirement for additional analgesia vs other opioids via PCA;
- Remifentanil IV PCA is associated with a higher risk of needing rescue analgesia vs epidural analgesia (RR 9.27; 95%CI 3.73 to 28.03) (6 RCTs, n=1,037);

Adverse events

- Data on adverse events is limited. Low quality evidence demonstrates women receiving remifentanil IV PCA experience more maternal respiratory depression vs epidural analgesia (SMD 0.91; 95%CI 0.51 to 1.62) (3 RCTs, n=687);
- Newborns of mothers receiving remifentanil IV PCA vs epidural analgesia, do not have an increased risk of Apgar scores < 7 at 5 min (5 RCTs, n=1,322).

There is mostly low-quality evidence to inform practice; further work is needed on maternal and fetal safety outcomes (maternal respiratory depression, Apgar score) and on optimal mode and regimen of remifentanil administration (Weibel 2017 **Level I** [Cochrane], 19 RCTs, n=3,569). A concurrent SR, comparing remifentanil IV PCA to epidural analgesia, finds higher pain scores at 1 h (WMD 1.33/10; 95%CI 0.30 to 2.36) and increased rates of hypoxaemia (OR 7.48; 95%CI 3.42 to 16.36); there were no differences at 2 and 3 h for analgesia, satisfaction or adverse effects except for overall reduced rates of pruritus (OR 0.54; 95%CI 0.32 to 0.89) (Lee 2017 **Level I** [PRISMA], 8 RCTs, n=2,351) (7 RCTs overlap).

Parturients having remifentanil IV PCA vs IM pethidine prn had lower pain scores (MD 13.9/100; 95%CI 21.4 to 6.4), lower conversion to epidural analgesia (19 vs 41%) but with a greater frequency of needing supplemental oxygen (41 vs 1%) (Wilson 2018 **Level II**, n= 401, JS 3). Remifentanil IV PCA achieved better median pain relief scores vs inhaled nitrous oxide (N_2O) (2.5/10 vs 0.5) (Volmanen 2005 **Level II**, n=15, JS 3).

As a potent opioid, remifentanil carries the risk of severe maternal respiratory depression (Van De Velde 2016 **NR**; Muchatuta 2013 **NR**). Oxygen desaturation (<90%) is frequent (70% of women studied) even when continuous supplemental oxygen is administered (Messmer 2016 **Level IV**, n=61). A number of respiratory (Bonner 2012 **CR**; Pruefer 2012 **CR**) and even cardiorespiratory arrests (Marr 2013 **CR**) have been reported with its use. Therefore, use of remifentanil IV PCA is only recommended if there is one-on-one continuous presence of a midwife, with both continuous oxygen saturation and cardiotocograph (CTG) monitoring (as an indirect method of detecting global hypoxaemia) (Goudra 2013 **NR**; Muchatuta 2013 **NR**). In view of these risks and the monitoring required, remifentanil IV PCA should not be regarded as an alternative to epidural analgesia based purely on economic considerations or convenience (Kranke 2013 **NR**). Remifentanil IV PCA has been recommended when neuraxial techniques are contraindicated.

9.1.3.2 | Inhalational analgesia

A meta-analysis of inhaled analgesia for pain management in labour compared various volatile agents (flurane derivatives) and N_2O to each other, placebo or no analgesia (Klomp 2012 **Level I** [Cochrane], 26 RCTs, n=2,959). Flurane derivatives (multiple volatiles studied, most recently sevoflurane) provide better pain relief than inhaled N_2O in first stage of labour; they result in lower pain intensity (MD 14.4/100; 95%CI 4.4 to 24.4) (3 RCTs, n=70) and higher pain relief scores (MD -16.3/100; 95%CI -26.9 to -5.8) (2 RCTs, n=70) but cause more drowsiness. Inhaled N_2O causes more nausea vs flurane derivatives (RR 6.60; 95%CI 1.85 to 23.52) (2 RCTs, n=98). However, trial design was often poor including lack of blinding for volatile agents.

Subgroup analysis of inhaled N_2O shows minimal difference in analgesic effect vs placebo (RR 0.06; 95%CI 0.01 to 0.34) (MD -3.5/100; 95%CI -3.75 to -3.25) (Klomp 2012 **Level I** [Cochrane], 3 RCTs [N_2O], n=819). A subsequent systematic review confirms some analgesic efficacy in labour, but only two studies were of good quality (Likis 2014, **Level IV SR**, 58 studies, n=20,266) (1 RCT overlap). Inhaled N_2O provides less pain relief than epidural analgesia, but more than pethidine, bathing, showering or acupuncture. Maternal satisfaction with analgesia during their birth experience is heterogeneous and difficult to assess. A majority of women using inhaled N_2O report a positive

experience (57%), but also report less satisfaction with analgesia (54%) vs epidural analgesia (94%) (Likis 2014, **Level IV SR**, 58 studies, n=20,266). The maternal adverse effects of inhaled N_2O are nausea (RR 43.1; 95%CI 2.6 to 707) (1 RCT, n=509), vomiting (RR 9.1; 95%CI 1.2 to 69) (2 RCTs, n=619), dizziness (RR 114; 95%CI 7.1 to 1,834) (1 RCT, n=509) and drowsiness (RR 77.6; 95%CI 4.8 to 1,255) (1 RCT, n=509) (Klomp 2012 **Level I** [Cochrane], 3 RCTs [N_2O], n=819); the wide confidence interval in the latter two outcomes suggests significant uncertainty in the estimate. Apgar scores are not different for inhaled N_2O vs no analgesia.

9.1.3.3 | Neuraxial analgesia in labour pain

Ultrasound guidance for epidural and intrathecal needle insertion

The use of ultrasound as an aid to improve successful placement of an epidural catheter or intrathecal needle is helpful. It can reduce the risk of failed (RR 0.21; 95%CI 0.10 to 0.43) or traumatic intrathecal needle and epidural catheter positioning (RR 0.27; 95%CI 0.11 to 0.6) and the number of needle insertions and redirections (Shaikh 2013 **Level I** [PRISMA], 14 RCTS, n=1,334)

Epidural analgesia

Epidural analgesia vs systemic opioid analgesia

Epidural analgesia vs opioid analgesia (Anim-Somuah 2018 **Level I** [Cochrane], 40 RCTs, n=12,389 [34 RCTs vs opioids, n=10,440]):

- Provides better pain relief overall (SMD -2.64; 95%CI -4.56 to -0.73) (5 RCTs, n=1,133), with a higher proportion rating their pain relief as 'excellent' or 'very good' (RR 1.47; 95%CI 1.03 to 2.08) (17 RCTs, n=1,911);

Note: reversal of conclusion
This reverses the Level I key message in the previous edition of this document; a preceding meta-analysis had described no difference in maternal satisfaction with epidural analgesia vs systemic opioid analgesia.

- Achieves substantial decreased need for additional analgesia vs opioid analgesia (RR 0.10; 95%CI 0.04 to 0.25) (16 RCTs, n=5,099);
- Achieves lower rate of respiratory depression needing supplemental oxygen administration (RR 0.23; 95%CI 0.05 to 0.97) (5 RCTs, n=2,031);
- Achieves less nausea and/or vomiting (RR 0.62; 95%CI 0.45 to 0.87) (15 RCTs, n=4,440);
- Increases duration of first stage (MD 32.28 min; 95%CI 18.34 to 46.22) (9 RCTs, n=2,259) and second stage of labour (MD 15.4 min; 95%CI 9.0 to 21.8) (16 RCTs, n=4,979);
- May increase oxytocin augmentation (RR 1.12; 95%CI 1.00 to 1.26) (19 RCTs, n=8,351);
- Increases the rate of assisted vaginal delivery (RR 1.44; 95%CI 1.29 to 1.60) (30 RCTs, n= 9,948). However, a post-hoc analysis (assessing only trials after 2005, which used lower concentrations of local anaesthetic) found no increase in assisted vaginal birth (RR 1.19; 95%CI 0.97 to 1.46);
- Does not increase the rate of Caesarean section overall (RR 1.07, 95%CI 0.96 to 1.18) (33 RCTs, n=10,350) or the rate of Caesarean section for fetal distress (RR 1.32, 95%CI 0.97 to 1.79) (12 RCTs, n=5,753);
- Reduces the risk of fetal acidosis (cord pH<7.2) (RR 0.81; 95%CI 0.69 to 0.94) (8 RCTs, n=4,783) and need for naloxone administration to newborns (RR 0.15; 95%CI 0.10 to 0.23) (10 RCTs, n=2,645); with no increase in admission to a special care/neonatal

intensive care unit (8 RCTs, n=4,488) and no increase in the rate of Apgar score < 7 at 5 min (1 RCT, n=60);
- Does not increase long-term backache (2 RCTs, n=814), headache (4 RCTs, n=1,938), postnatal depression (1 RCTs, n=313) or itching (8 RCTs, n=2,900).

The most common complications caused by epidural analgesia are maternal hypotension (RR 11.34; 95%CI 1.87 to 67.95) (10 RCTs, n=4,212), motor block (RR 31.67; 95%CI 4.16 to 245) (3 RCTs, n=322), urinary retention (RR 14.18; 95%CI 4.52 to 44.45) (4 RCTs, n=343) and maternal fever (RR 2.51; 95%CI 1.67 to 3.77) (9 RCTs, n=4,276) (Anim-Somuah 2018 **Level I** [Cochrane], 40 RCTs, n=12,389).

These Cochrane review results are influenced by substantial heterogeneity for pain relief, maternal satisfaction, need for additional means of pain relief, length of second stage of labour and oxytocin augmentation. This heterogeneity did not seem to relate to subgroup or sensitivity confounders, where data could be analysed. None of these studies reported on the rare, serious adverse effects of epidural analgesia (see Sections 5.6.5.1 to 5.6.5.3). However, despite evidence for safety, in a case series of women before childbirth, 39% expressed concerns about neuraxial analgesia and 46% of 129 women deciding against epidural analgesia did so because of concerns about the technique (Toledo 2013 **Level IV**, n=509). Safety data from the above Cochrane review could help inform pregnant women about these concerns.

Epidural vs no analgesic pharmacological treatment

Epidural analgesia vs no analgesic pharmacological treatment (Anim-Somuah 2018 **Level I** [Cochrane], 40 RCTs, n=12,389 [7 RCTS vs no pharmacological treatment, n=897]):
- Epidural analgesia results in less pain (SMD -9.55; 95%CI -12.91 to -6.19) (2 RCTs, n=120);
- Epidural analgesia achieves a higher proportion rating their satisfaction with pain relief as excellent or very good (RR 1.32, 95%CI 1.05 to 1.65) (1 RCT, n=70);
- Epidural analgesia is associated with a lower Caesarean section rate vs placebo or no treatment (RR 0.46, 95%CI 0.23 to 0.90) (5 RCTs, n=578);
- There are no differences between groups for the following outcomes: nausea and vomiting (2 RCTs), pruritus (1 RCT), fever (1 RCT), shivering (1 RCT), drowsiness (1 RCT), and urinary retention (2 RCTs);
- Other maternal adverse events and fetal outcomes were not reported.

Epidural vs acupuncture

Epidural analgesia vs electrical acupoint stimulation results in lower pain scores (SMD -53/100; 95%CI -58 to -48) (1 RCT, n=60) (Anim-Somuah 2018 **Level I** [Cochrane], 40 RCTs, n=12,389).

Epidural versus continuous midwifery support (one-to-one, with non-epidural analgesia):

All 493 women receiving epidural analgesia, and 494 out of 499 women receiving continuous midwifery support rated their pain relief as 'excellent or very good' (RR 1.01, 95% CI 1.00 to 1.02); however, pain intensity was not reported (1 RCT, n=992) (Anim-Somuah 2018 **Level I** [Cochrane], 40 RCTs, n=12,389). No woman receiving epidural analgesia requested additional means of pain relief vs 262 out of 499 receiving continuous midwifery support (1 RCT, n=992).

Timing of epidural

A meta-analysis assessed outcomes of early vs late initiation of epidural analgesia for labour, showing no clinically significant differences dependent on timing of epidural analgesia (Sng 2014 **Level I** [Cochrane], 9 RCTs, n=15,752). Specifically, there are no differences in rate of instrumental birth (RR 0.93; 95%CI 0.86 to 1.01) (8 RCTs, n=15,379), duration of second stage of labour (MD -3.22 min; 95%CI -6.71 to 0.27) (8 RCTs, n=14,982) or adverse fetal outcomes.

The use of labour epidural analgesia given to every parturient at the onset of labour (routine use), when compared to maternal request for epidural analgesia, found no significant increase in Caesarean deliveries (34.8% vs 26.7%; 95%CI -0.1 to 16.3) (Wassen 2015 **Level II**, n= 493, JS 3). There was more hypotension (difference 9.5%; 95%CI 4.2 to 14.9) and motor blockade (difference 6.8%; 95%CI 1.1 to 12.5) in the routine use group.

Local anaesthetic concentrations

Epidural analgesia with low concentrations of bupivacaine (≤0.1%) or ropivacaine (≤0.17%) vs non-epidural methods of analgesia shows no differences in the duration of the first or second stage of labour, or the rate of instrumental birth or Caesarean section (Wang 2017 **Level I** [PRISMA], 10 RCTs, n=1,809).

A prior meta-analysis favours lower concentrations of bupivacaine (≤0.1%) (8 RCTs, n=852) or ropivacaine (≤0.17%) (3 RCTs, n=293) over higher concentrations for epidural analgesia in labour (Sultan 2013 **Level I**, 11 RCTs, n=1,145). Low concentrations are associated with fewer assisted vaginal births (OR 0.70; 95%CI 0.56 to 0.86), a shorter second stage of labour (WMD -14.03 min; 95%CI -27.52 to -0.55), less motor block (OR 3.9; 95%CI 1.59 to 9.55), greater ability to ambulate (OR 2.8; 95%CI 1.1 to 7.14), and less urinary retention (OR 0.42; 95%CI 0.23 to 0.73) but no difference in Caesarean section rate (OR 1.05; 95%CI 0.82 to 1.33).

However, lower vs higher concentrations may be associated with increased pruritus (OR 3.36; 95%CI 1.00 to 11.31) and are associated with a higher rate of Apgar scores <7 at 1 min (OR 1.53; 95%CI 1.07 to 2.21), but not persisting at 5 min. No differences are apparent for pain, nausea and vomiting, hypotension, fetal heart rate abnormalities or need for neonatal resuscitation.

Comparison of ropivacaine vs bupivacaine (alone or with fentanyl)

Use of bupivacaine vs ropivacaine as the sole agent for epidural analgesia shows no difference with regard to mode of birth, maternal satisfaction or neonatal outcomes (Halpern 2003 **Level I**, 23 RCTs, n=2,074).

The combination of fentanyl, with either ropivacaine or bupivacaine, exhibits comparable efficacy and safety (Li 2015 **Level I**, 9 RCTs, n=556). However, ropivacaine with fentanyl resulted in a significantly lower frequency of motor block (OR 0.31; 95%CI 0.18 to 0.51) despite a longer second stage than bupivacaine/fentanyl (MD 6.87; 95%CI 10.98 to 2.77). The concentrations used varied widely (by a factor of 30), and equipotent concentrations were not compared.

Adjuvant dexamethasone

The analgesic effect of dexamethasone when added to epidural local anaesthetic improves analgesia, but this may be due to a systemic effect. The addition of dexamethasone 8 mg to epidural analgesia in labour (levobupivacaine with fentanyl via PCEA) resulted in a reduced requirement for the PCEA solution (7.0 ml ± 1.2 vs 8.4 ml ± 2.6) (Dhal 2018 **Level II**, n=60, JS 5). The addition of dexamethasone 4 mg to single dose epidural levobupivacaine extended the duration of analgesia (81.6 min ± 14.4 vs 63.8 min ± 12.8) (Wahdan 2019 **Level II**, n=60, JS 4), this may be due a systemic effect (see also Section 4.12.2).

Adjuvant alpha-2 agonists

Epidural alpha-2 agonists (clonidine and neostigmine) as adjuvants to local anaesthetics in labour prolong analgesia (MD 37.79; 95% CI 9.37 to 66.21) and reduce hourly local anesthetics and opioid administration (MD -5.49; 95% CI -6.78 to -4.21) (Zhang 2015 **Level III-2 SR**, 4 studies, n=280). There is no effect on total duration of labour, mode of delivery and Apgar scores.

The addition of dexmedetomidine to epidural local anaesthetic improved labour analgesia as bolus 0.5mcg/kg (Zhao 2017 **Level II**, n=80, JS 3) or infusion 0.5mcg/mL (Zhang 2018 **Level III-2 EH**, n=60). An RCT has compared 0.25, 0.5, 0.75 and 1 mcg/mL (with no local anaesthetic only arm) and the optimum dose is uncertain (Wangping 2017 **Level II**, n=100, JS 3) (see also Section 4.9.2.1).

Adjuvant neostigmine

Adding neostigmine (in widely varying doses) to local anaesthetics (bupivacaine or ropivacaine) ± opioid for neuraxial administration in labour analgesia and postoperative analgesia after Caesarean section permits reduction of local anaesthetic doses (MD -4.08 mg/h; 95% CI -6.7 to -1.5) (Cossu 2015 **Level I**, 16 RCTs, n= 1,186). Only IT neostigmine (5 RCTs, n=275), but not epidural neostigmine (11 RCTs, n=911), increases risk of nausea (OR 9; 95%CI 4.7 to 17.1). Neuraxial neostigmine reduces risk of pruritus (OR 0.4; 95%CI 0.2 to 0.7) (6 RCTs), but does not increase hypotension, sedation or affect fetal outcome (see also Section 4.13.2).

Technique of epidural administration

Patient-controlled epidural analgesia (PCEA) for labour pain

PCEA can provide effective analgesia but the optimal settings are not clear (Leo 2008 **Level IV**; Loubert 2011 **NR**). A meta-analysis of PCEA in labour concluded that dilute concentrations of bupivacaine (0.125%) or ropivacaine (≤ 0.16%), with and without background infusion provide acceptable analgesia (6 RCTs, n=789) and that use of large bolus doses (6 RCTs, n=588) and background infusions (7 RCTs, n=573) with PCEA may improve analgesia and result in reduction of unscheduled clinician interventions vs other interventions (Halpern 2009 **Level I**, 30 RCTs, n=4,033 [bupivacaine vs ropivacaine 11 RCTs, n=2,083]).

A meta-analysis comparing PCEA with and without a background infusion shows that continuous background infusion was associated with increased instrumental vaginal birth (RR 1.66, 95%CI 1.08 to 2.56), prolonged second stage of labour (WMD 12.3 min, 95%CI 5.1 to 19.5), reduced requirement for physician-administered boluses (RR 0.35, 95%CI 0.25 to 0.47), with no difference in Caesarean section rate (RR 0.83, 95%CI 0.61 to 1.13) (Heesen 2015 **Level I** [PRISMA], 7 RCTs, n=891).

Programmed intermittent epidural boluses (PIEB)

PIEB for analgesia in labour reduces breakthrough pain incidence vs continuous epidural infusion (20 vs 33%) (RR 0.60; 95%CI 0.39 to 0.92) (Sng 2018 **Level I**, 10 RCTs, n=797). There are no differences for Caesarean section and assisted vaginal delivery rates, duration of labour or Apgar scores. Hourly local anaesthetic dose in the PIEB group is reduced, but the clinical significance of the difference is unclear (MD −1.1 mg/h; 95%CI −1.8 to −0.4) (12 RCTS, n=1,121). Maternal satisfaction is higher in the PIEB group (5 of 7 RCTs, n=570; data unable to be pooled for effect size). See also Section 5.6.1.5.

Combined spinal-epidural (CSE) and dural puncture epidural analgesia for labour pain

CSE analgesia provides slightly more rapid onset of pain relief than epidural techniques alone (Simmons 2012 **Level I** [Cochrane], 37 RCTs, n=3,274). In comparison to traditional epidural techniques (local anaesthetic concentration ≥0.25% bupivacaine), the time to onset is shorter (MD -2.9 min; 95%CI -5.1 to -0.7) (2 RCTs, n=129), with reduced need for rescue analgesia (RR 0.31; 95%CI 0.14 to 0.70) (1 RCT, n=42), lower rates of urinary retention (RR 0.86; 95%CI 0.79 to 0.95) (1 RCT, n=704) and instrumental birth (RR 0.81; 95%CI 0.67 to 0.97) (6 RCTs, n=1,015). However, a comparison of CSE with low-dose epidurals (local anaesthetic concentration equivalent to bupivacaine <0.25%; reflecting current practice) shows a faster onset of effect (MD -5.4 min; 95%CI -7.3 to -3.6) (5 RCTs, n=461), but no difference in maternal satisfaction (RR 1.01; 95%CI 0.98 to 1.05) (7 RCTs, n=520) and an increased rate of mild pruritus (RR 1.80; 95%CI 1.22 to 2.65) (11 RCTs, n=959).

The risk of unilateral block is reduced after CSE vs epidural analgesia (RR 0.48, 95%CI 0.24 to 0.97) (Heesen 2014 **Level I** [PRISMA], 10 RCTs, n=1,722).

Non-reassuring fetal heart rate tracings may be more common with CSE than epidural analgesia alone (RR 1.31, 95%CI 1.02 to 1.67) (Hattler 2016 **Level I** [PRISMA], 17 RCTS, n=3,947). The

mechanism of this effect may be from an abrupt transient reduction in circulating catecholamines (Segal 2008 **BS**).

CSE techniques may be associated with a lower failure rate (6.6%) than standard epidural analgesia (1.6%) (Booth 2016 **Level III-3**, n=2,395).

Dural puncture epidural analgesia is a technique similar to CSE, where dural puncture is performed but no medication is injected intrathecally. There appears to be no certain benefit for this technique vs standard epidural analgesia (Heesen 2019 **Level I** [PRISMA], 5 RCTs, n=581).

Intrathecal analgesia for labour pain

Single-injection intrathecal opioids

Single-injection IT opioids are as effective as epidural local anaesthetics for the management of pain in early labour and they do not affect the rate of nausea or mode of delivery (Bucklin 2002 **Level I**, 7 RCTs, n=332). IT opioids increase the risk of fetal bradycardia (NNH 28) and maternal pruritus (NNH 1.7) in comparison with non-IT opioid analgesia (Mardirosoff 2002 **Level I**, 24 RCTs, n=3,513). Adding IT morphine ≤250 mcg to single bolus IT labour analgesia with bupivacaine/fentanyl or bupivacaine/sufentanil prolongs duration of analgesia (60.6 min, range 3 to 155) with no effect on SMD of pain intensity (Al-Kazwini 2016 **Level I** [PRISMA], 5 RCTs, n=286).

Respiratory depression related to epidural or IT opioids during labour is rare (Carvalho 2008 **NR**); see Section 5.7.1.3 for more details.

Intrathecal catheters for labour analgesia

IT microcatheters (24- to 28-gauge) are used infrequently for labour analgesia but may be useful in some specific cases, such as those patients who are morbidly obese, have significant cardiac disease or previous spinal surgery (Palmer 2010 **NR**). Continuous IT medication infusion improved early analgesia, with no differences in neonatal or obstetric outcomes but more technical difficulties vs epidural administration (Arkoosh 2008 **Level II**, n=429, JS 3); this trial used 28-gauge catheters and there were no safety concerns. Subsequent case series have used larger catheters: two have used 23-g successfully (Tao 2015 **Level IV**, n=113; Tao 2011 **Level IV**, n=7) with the larger study reporting a low PDPH rate (2.6%) and a failure rate of 11%, while a further study described a higher failure rate (20%) with 22-g and 24-g catheters (n=92) and a higher incidence of PDPH (29%), requiring a blood patch in 18% of these patients (Alonso 2009 **Level IV**). The authors of this study concluded the risks outweigh the benefits of IT microcatheters as a primary method for labour analgesia.

Placement of an epidural catheter (20- to 22-g) in women who have experienced an unintentional dural puncture is widely practised. A study comparing IT placement with epidural placement of an epidural catheter after unintentional dural puncture (n=97) reported a similar PDPH incidence (72 vs 62%) but easier establishment of neuraxial analgesia with the IT method (Russell 2012 **Level III-1**). Another study found a lower rate of PDPH (42% for IT placement vs 62% for epidural placement) (OR 2.3; 95%CI 1.04 to 4.86) (Verstraete 2014 **Level III-2**, n=128).

Comparison of intrathecal ropivacaine with bupivacaine

Single dose IT ropivacaine 0.15%/sufentanil 0.2mcg/mL vs IT bupivacaine 0.125%/sufentanil 0.2mcg/mL for labour pain resulted in lower pain scores (over the time period from 10 min until full cervical dilatation), and higher satisfaction (94.7% vs 84%) (Li 2018 **Level II**, n=300, JS 2).

9.1.3.4 | Regional analgesia in labour pain

Paracervical block and pudendal nerve block are the most commonly performed local anaesthetic PNBs, with a long history of use for pain management in labour.

Local anaesthetic nerve blocks (11 RCTs paracervical; 1 RCT pudendal), using various agents, are effective (8 RCTs), and superior to placebo (1 RCT, n=200), opioid (2 RCTs, n=129) and nonopioid

analgesia (1 RCT, n=100) (Novikova 2012 **Level I** [Cochrane], 12 RCTs, n=1,549); however it is noted that these findings are based on RCTs of unclear quality and limited numbers. Adverse effects are more common in comparison with placebo (1 RCT, n=200). There is no difference in quality of analgesia and satisfaction with analgesia between different local anaesthetics (4 RCTs, n=789). Specifically in comparison to placebo, paracervical blocks with lignocaine 2% are associated with higher patient satisfaction (RR 32.3; 95%CI 11 to 99) but more adverse effects (RR 29.0; 95%CI 1.8 to 480) (Novikova 2012 **Level II** [Cochrane], 1 RCT [vs placebo], n=200). In comparison with opioids (IM pethidine or fentanyl IV PCA), nerve blocks provide better pain relief (RR 2.52; 95%CI 1.65 to 3.83), without an increase in the rate of assisted vaginal birth (RR 1.02; 95%CI 0.56 to 1.87) or of Caesarean section (RR 0.23; 95%CI 0.03 to 1.87) (Novikova 2012 **Level I** [Cochrane], 2 RCTs [vs opioids], n=129).

Paracervical block was equally efficacious but required supplementation more frequently than epidural analgesia (Manninen 2000 **Level II**, n=44, JS 3) and was less effective than single-injection IT analgesia (Junttila 2009 **Level III-2**). Serious fetal complications may occur (Shnider 1970 **NR**), so this technique should be limited to hospitals without other obstetric anaesthesia services (Levy 1999 **Level III-2**) or for patients with contraindications to neuraxial techniques (Junttila 2009 **Level III-2**).

9.1.3.5 | Complementary and other methods of pain relief in labour

Continuous or one-to-one support by a midwife or trained layperson during labour reduces analgesic use, rate of instrumental and operative birth and dissatisfaction, especially if the support person is not a member of the hospital staff, was present from early labour, or if an epidural analgesia service was not available (Hodnett 2013 **Level I** [Cochrane], 22 RCTs, n=15,288). The effect of continuous midwifery support, with and without epidural analgesia is described above (see Section 9.1.3.3).

A qualitative systematic review has assessed women's experiences of pharmacological and non-pharmacological pain relief for labour (Thomson 2019 **Level IV SR**, 24 studies, n unspecified). Overall, experiences were mixed with pharmacological methods assessed as effective, but with adverse effects, while non-pharmacological were described as not as effective, but facilitating bonding.

For some nonpharmacological or complementary therapies there is weak evidence of effectiveness vs standard care:

- Water immersion during labour has limited benefit. There is no difference in mode of delivery (spontaneous, instrumental or Caesarean), perineal trauma or blood loss. There is a small reduction in the requirement for regional analgesia (epidural, intrathecal, paracervical) vs no immersion (39% vs 43%) (RR 0.91; 95%CI 0.83 to 0.99) (5 RCTs; n=2,439) (Cluett 2018 **Level I** [Cochrane] 15 RCTs, n=3,663). Other maternal outcomes were not reported. There is insufficient evidence to determine the impact on neonatal intensive care unit admissions (2 RCTs, n=1,511) or neonatal infection rates (5 RCTs, n=1,295).

- Acupuncture/Acupressure in labour (Smith 2020 **Level I** [Cochrane], 28 RCTs, n=3,960) (see also Section 7.3.2.3):
  - Acupuncture vs sham does not reduce pain scores (2 RCTs, n=325), but does increase satisfaction with pain relief (RR 2.38; 95%CI 1.78 to 3.19) (1 RCT, n=150) and decreases use of pharmacological analgesia (RR 0.75; 95%CI 0.63 to 0.89);

- Acupuncture vs usual care reduces pain scores (4 RCTs, n=495) and use of pharmacological analgesia (6 RCTs, n=1,059) but does not improve satisfaction (2 RCTs, n=343);
- Acupuncture vs no treatment reduces pain scores (1 RCT, n=163);
- Acupuncture vs water injection does not reduce use of pharmacological analgesia (1 RCT, n=128);
- Acupressure vs sham lowers pain scores (MD -1.93/10; 95%CI -3.31 to -0.55) but has no effect on use of pharmacological analgesia (6 RCTs, n=472);
- Acupressure vs usual care reduces pain scores (SMD -1.07; 95%CI -1.45 to -0.69) (8 RCTs, n=620) and improves satisfaction (1 RCT, n=105);
- Acupressure vs both placebo and usual care reduces pain scores (SMD -0.42; 95%CI -0.65 to -0.18) (2 RCTs, n=322) and marginally increases satisfaction with analgesia (1 RCT, n=212);
- There was no effect on Caesarean section rate;
- Overall, evidence was of low quality with no study at a low risk of bias on all domains. There is a need for high-quality research that includes sham controls and comparisons to usual care.

- Massage vs standard care reduces pain during first stage of labour (SMD −0.81, 95%CI −1.06 to −0.56) (6 RCTs, n=362), but not second (SMD −0.98/10; 95%CI −2.23 to 0.26) (2 RCTs, n=124) or third stages (SMD −1.03/10; 95%CI −2.17 to 0.11) (2 RCTs, n=122) (Smith 2018a **Level I** [Cochrane], 10 RCTs, n=1,055). Massage also lessens anxiety during the first stage of labour (MD -16.27; 95%CI −27.03 to −5.51) (1 RCT, n=60), increases sense of control (MD 14.05; 95% CI 3.77 to 24.33) (1 RCT, n=124) and satisfaction (unable to quantify due to methodology) (see also Section 7.5.2).
- The use of birth ball (Swiss ball) exercises for labour pain relief improves pain vs non-use (SMD -0.9/10; 95% CI -1.3 to -0.6) (Makvandi 2015 **Level I**, 3 RCTs, n=205). The quality of the studies was mixed, with most providing little information on the exact methods they used**;**
- Hypnosis (eight antenatal and one intrapartum intervention) for labour pain reduces analgesic use (RR 0.73; 95%CI 0.57 to 0.94) (8 RCTs, n=2,916), but has no effect on rate of spontaneous vaginal birth (6 RCTs, n=2,361), sense of coping with labour (1 RCT, n=420) or satisfaction with pain relief when combined with either pethidine (1 RCT, n=72) or epidural analgesia (1 RCT, n=127) (Madden 2016 **Level I** [Cochrane], 9 RCTs, n=2,954);

Note: reversal of conclusion
This reverses the Level I key message in the previous edition of this document; a preceding meta-analysis had described no effect of hypnosis in the management of labour pain.

- Relaxation techniques (including yoga, music or audio) has limited and low to very low quality evidence for reduction in labour pain or improved satisfaction (Smith 2018a **Level III-1 SR** [Cochrane], 15 studies, n=1,731).

For the following interventions, the evidence is not supportive.

- Biofeedback does not affect the use of pharmacological pain relief or the rates of assisted vaginal birth or Caesarean section (Barragan Loayza 2011 **Level I** [Cochrane], 4 RCTs, n=186);
- Sterile water injections, intra- or subcutaneously, vs saline injection do not reduce labour pain during the first stage of labour, or affect mode of birth or other maternal or fetal outcomes (Derry 2012 **Level I** [Cochrane], 7 RCTs, n=766);

- Aromatherapy has no effect on any primary or secondary outcomes in labour (Smith 2011 **Level I** [Cochrane], 2 RCTs, n=535);
- In labour, TENS has no effect on pain, interventions or outcomes vs sham TENS (10 RCTs) or routine care (7 RCTs), when applied to the back (13 RCTs, n=1,150) or cranium (2 RCTs, n=140), with the exception of a reduction of reports of severe pain when applied to acupuncture points (2 RCTs, n=190) (Dowswell 2009 **Level I** [Cochrane], 17 RCTs, n=1,466). The findings of no analgesic effect were confirmed by two subsequent meta-analyses (Bedwell 2011 **Level I**, 14 RCTs, n=1,456) (14 RCTs overlap) (Mello 2011 **Level I**, 9 RCTs, n=1,076) (3 RCTs overlap) (see also Section 7.2).

9.1.3.6 | Analgesia for forceps delivery

Rates of assisted vaginal birth vary throughout the world (10 to 15% in high-resource settings). Neuraxial analgesia is commonly used for forceps delivery in these settings but local infiltration and pudendal nerve block are also used, while the rate of general anaesthesia is very low (Osterman 2011 **Level IV**). Studies in this setting are limited and old (Nikpoor 2013 **Level I** [Cochrane], 4 RCTs, n=388). Three of these RCTs compared diazepam to other agents for provision of general anaesthesia, without finding clinically relevant differences. In one RCT, IT analgesia vs pudendal nerve block resulted in more women regarding their analgesia as adequate (RR 3.36; 95%CI 2.46 to 4.60), with fewer reporting severe pain (RR 0.02; 95%CI 0.00 to 0.27) (Nikpoor 2013 **Level I** [Cochrane], 1 RCT [IT]: Hutchins 1980 **Level II**, n=183, JS 1). The authors conclude that there is a lack of evidence to guide practice.

9.1.3.7 | Pain after Caesarean section

Pain after Caesarean section has been treated by multiple analgesic techniques and multimodal analgesia is recommended (Sutton 2017 **NR**); a multimodal bundle of standardised use of preoperative paracetamol, postoperative comfort education, simethicone PO, postoperative gum chewing and use of abdominal binders reduced morphine requirements by 61% (Burgess 2019 **Level III-1**, n=9,313). This approach led to more women receiving less than 20 tablets of oxycodone (5 mg or 10 mg) at discharge (96.7% vs 26.3).

Pain on POD 1 may be higher than that from many other types of major surgery (Gerbershagen 2013 **Level III-2**, n=456 [Caesarean sections] of total n=70,764).

When asked to rate their pain after Caesarean section, patients using pain scores had increased pain reporting and a worse experience during the postoperative period than the comfort score reporting group (Chooi 2013 **Level II**, n=300, JS 4).

Important considerations in this patient group include transfer of medications via breast feeding, and facilitating postoperative mobility of the mother for care of the neonate.

Systemic analgesia

Oral analgesia

A meta-analysis of oral analgesia (opioids, tramadol, paracetamol, NSAIDs, coxibs, gabapentin) for pain after Caesarean section identified mainly small RCTs with contradictory results, not permitting definitive conclusions regarding the most effective or safest approach (Mkontwana 2015 **Level I** [Cochrane], 8 RCTS, n=962). Opioids and nonopioids showed little effect in comparison to placebo and each other with significant heterogeneity except for ketoprofen 100 mg (RR 0.55; 95%CI 0.39 to 0.79) (1 RCT, n=72). This Cochrane review states based on a single RCT that gabapentin reduces the need for additional analgesia vs placebo (Short 2012 **Level II**, n=132, JS 5). However, the results were incorrectly calculated and the conclusion replaced by a subsequent systematic review (including this trial) which finds: gabapentin 600 mg improves pain scores on

movement at 24 h only (MD -11.58/100 VAS; 95%CI -23.04 to -0.12) and increases satisfaction scores after Caesarean section, with no difference in opioid use, nausea, vomiting, pruritus or sedation (Felder 2019 **Level I** [PRISMA], 6 RCTs, n=656). Oral oxycodone was as effective as IV PCA piritramide (opioid) in this setting, but there was no placebo comparator (Dieterich 2012 **Level II**, n=239, JS 3). Oral naproxen or tramadol were similarly effective, with fewer adverse effects with naproxen (Sammour 2011 **Level II**, n=120, JS 3). A study comparing oral oxycodone with IT morphine on top of background oral nonopioid analgesia found comparable analgesia and less pruritus, but lower maternal satisfaction (McDonnell 2010 **Level II**, n=111, JS 5).

Parenteral analgesia

IV paracetamol, given before the commencement of Caesarean section, vs placebo reduces postoperative pain (measured immediately after surgery or during the recovery period) (SMD −0.72/10; 95%CI −1.31 to −0.13) and reduces postoperative opioid consumption (SMD −0.46; 95%CI -0.828 to -0.092) (Ng 2019 **Level I** [PRISMA], 5 RCTs, n=409). In women having either Caesarean section or hysterectomy, IV paracetamol vs oral paracetamol reduced LOS (-11%), use of opioids (-1.6 mg daily morphine equivalent) and opioid-related adverse effects (Urman 2018 **Level III-3**, n=29,124).

Parenteral (but not oral or rectal) NSAIDs vs placebo after Caesarean section reduce pain scores at 12 and 24 h, opioid requirements, drowsiness and sedation, but not PONV (Zeng 2016 **Level I**, 22 RCTs, n=1,313). In combination with IV PCA morphine, parecoxib and ketorolac had similar efficacy, but without a placebo control (Wong 2010 **Level II**, n=66, JS 2).

As mentioned above, IV PCA piritramide (opioid) was as effective as oral oxycodone, but with no placebo comparator (Dieterich 2012 **Level II**, n=239, JS 3). A continuous IV infusion of tramadol vs IV PCA tramadol resulted in higher tramadol consumption and lower patient satisfaction (Demirel 2014 **Level II**, n=40, JS 1).

Dexmedetomidine (by IV or neuraxial routes) vs placebo for Caesarean section improves sensory block and duration of postoperative analgesia (4 RCTs [IT local anaesthetic], n=352) and reduces PONV and shivering (RR 0.26; 95%CI 0.11 to 0.60), with no harmful effects on umbilical blood gases and Apgar scores at 1 and 5 min (Zhang 2017 **Level I** [PRISMA], 6 RCTs, n=458). Review of further systemic dexmedetomidine studies reveal beneficial effects on PONV and shivering (Bao 2017 **Level I**, 12 RCTs, n=986) (2 RCT overlap); however, IT dexmedetomidine reduces only shivering, without an effect on PONV (Miao 2018 **Level I** [PRISMA], 6 RCTs, n=360) (2 & 3 RCTs overlap). Dexmedetomidine had an opioid-sparing effect when combined with sufentanil PCA (Nie 2014 **Level II**, n=120, JS 5); this was more pronounced when dexmedetomidine was continued in the PCA after an initial bolus than if an initial bolus only was administered.

IV dexamethasone 10 mg reduced nausea and vomiting following Caesarean section under bupivacaine/morphine spinal anaesthesia, with fewer complaints of pain at rest and on movement in the first 24 h vs saline control (Cardoso 2013 **Level II**, n=70, JS 5). However, IV dexamethasone 8 mg vs placebo had no effect on opioid consumption after Caesarean section (Ituk 2018 **Level II**, n=52, JS 5).

Low-dose ketamine bolus and subsequent low-dose infusion for 12 h resulted in an opioid-sparing effect for 24 h without any further benefits or improved long-term outcome (Suppa 2012 **Level II**, n=56, JS 4). However, three different intraoperative IV bolus doses of ketamine (0.25, 0.5, and 1 mg/kg) had no effect on postoperative pain, opioid requirements or long-term outcomes after Caesarean section (Bilgen 2012 **Level II**, n=140, JS 4). Similarly, there were no obvious benefits when IV ketamine 10 mg was added to IT morphine and IV ketorolac (Bauchat 2011 **Level II**, n=188, JS 5). In contrast, IV ketamine 0.15 mg/kg given in addition to a bupivacaine spinal anaesthetic resulted in a longer duration and better quality of early postoperative analgesia (Menkiti 2012 **Level II**, n=60, JS 4). There are conflicting RCTs examining the effect of low dose ketamine on

reduction of pain after Caesarean section and no conclusion about efficacy can be made in this patient group (Rahmanian 2015 **Level II**, n=160, JS 2; Behdad 2013 **Level II**, n=60, JS 4; Han 2013 **Level II**, n=40, JS 2).

Neuraxial analgesia

Neuraxial alpha-2 agonists

Neuraxial clonidine 50 to 150 mcg (epidural and IT) modestly enhances postoperative analgesia in women having Caesarean section under neuraxial anaesthesia (Allen 2018 **Level I** [PRISMA], 12 RCTs [IT administration] [9 RCT overlap with Crespo 2017] & 6 RCTs [epidural administration: 2 RCTs bolus followed by infusion, 2 RCTs repeated bolus, 2 RCTs single bolus], n=1,169). Neuraxial clonidine reduces morphine consumption (MD -8.7 mg; 95% CI -15.3 to -2.0); this effect is less with IT administration (MD -4.3 mg; 95%CI -7.0 to -1.5) than with epidural administration (MD -18.9 mg; 95%CI -34.8 to -3.0). It also increases the time to first analgesic request (MD 150 min; 95%CI 110 to 190) vs placebo, but does not improve pain scores on movement at 0 to 6 h. Neuraxial clonidine increases the risk of intraoperative hypotension (49%) vs placebo (33%) and of intraoperative sedation. Risks for bradycardia, nausea/vomiting and pruritus are inconclusive. There was no case of respiratory depression and neonatal outcome was not different in control and study group.

Epidural local anaesthetics

A comparison of four different concentrations of ropivacaine (0.2, 0.1, 0.05, or 0.025%) with fentanyl 3 mcg/mL and adrenaline 0.5 mcg/mL, showed that the very low concentration 0.025% is effective for PCEA after Caesarean section (Cohen 2015 **Level II**, n=48, JS 5). All patients receiving this concentration could ambulate, and none had urinary retention.

PCEA with 0.2% ropivacaine vs epidural morphine 2 mg every 12 h, provided equivalent analgesia (Chen 2011 **Level II**, n=120, JS 5); although it resulted in more motor weakness, this did not impair ambulation. Other adverse effects (pruritus, nausea, vomiting and urinary retention) occurred more often after epidural morphine, resulting in improved satisfaction scores with PCEA ropivacaine. Intrathecal morphine may be more cost-effective than PCEA after Caesarean section (Vercauteren 2002 **Level II**, n=53, JS 2). No differences were found between PCEA with 0.1% levobupivacaine vs 0.06% combined with fentanyl 2 mcg/mL (Chen 2014 **Level II**, n=80, JS 4).

Epidural opioids

After Caesarean section, single-dose epidural morphine (1 to 8 mg) increases the time until rescue analgesic is required and decreases pain and postoperative morphine requirements for 24 h vs systemic opioid analgesia (Bonnet 2010 **Level I** [QUOROM], 10 RCTs, n=431); however, there is an increased incidence of pruritus (RR 2.7; 95%CI 2.1 to 3.6) and nausea (RR 2.0; 95%CI 1.2 to 3.3). The requirement for rescue IV opioid reduces as the morphine dose increases from 1.25 to 3.75 mg, with no apparent additional benefit from 5 mg (Palmer 2000 **Level II**, n=60, JS 5). Epidural morphine 1.5 mg was noninferior to 3 mg and caused fewer adverse effects (Singh 2013b **Level II**, n=90, JS 5). Extended-release epidural morphine 10 mg decreased supplemental opioid use and improved functional ability scores for 48 h vs 5 mg of conventional epidural morphine (Carvalho 2005 **Level II**, n=79, JS 3).

Epidural magnesium

Bupivacaine/morphine/magnesium for epidural administration was superior to bupivacaine/morphine or bupivacaine/magnesium with regard to pain relief, time to rescue analgesia and patient satisfaction (Sun 2012 **Level II**, n=200, JS 5), but the neurotoxicity of neuraxial magnesium has not been adequately investigated (Albrecht 2013b **Level I** [PRISMA], 25 RCTs [IV magnesium], n=1,461).

Intrathecal analgesia

Intrathecal opioids

IT morphine and other opioids effectively reduce pain and analgesic requirements post Caesarean section (Dahl 1999 **Level I**, 15 RCTs, n=535).

Lower-dose (50 to 100mcg) vs higher-dose intrathecal morphine (>100 to 250mcg) has shorter time to first request for analgesia (MD 4.5 h; 95%CI 1.9 to 7.1) but with less nausea and vomiting (OR 0.44; 95%CI 0.27 to 0.73]) and pruritus (OR 0.34; 95%CI 0.20 to 0.59) (Sultan 2016 **Level I**, 11 RCTs, n=480). Acknowledging the combined sample size is small, there is no difference in pain score at 12 h nor in morphine consumption at 24 h after surgery. Thus, the higher dose provides some additional analgesic benefit at the expense of greater adverse effects.

A retrospective study of IT morphine 200 mcg vs 100 mcg had similar findings with sparing of additional opioids, but more nausea requiring treatment and more pruritus (Wong 2013 **Level III-2**, n=241).

IT morphine 100 mcg added to IT fentanyl vs IT fentanyl alone was superior with regard to analgesia and its duration as well as patient satisfaction, despite increased adverse effects (pruritus, nausea and vomiting) (Sawi 2013 **Level II**, n=60, JS 4).

IT hydromorphone 40 mcg produced similar outcomes to IT morphine 100 mcg () (Beatty 2013 **Level III-2,** n=114) and IT diamorphine 250 mcg similar outcomes to IT morphine 100 mcg (Barkshire 2001 **Level II**, n=60, JS 4).

IT tramadol 10 mg vs IT fentanyl 10 mcg added to spinal anaesthesia with bupivacaine increased the duration of analgesia and reduced postoperative shivering (Subedi 2013 **Level II**, n=80, JS 5).

Intrathecal alpha-2 agonists

IT clonidine 30 to 150 mcg as an adjuvant to neuraxial anaesthesia during Caesarean section prolongs the duration of sensory block (MD 128 min; 95%CI 82 to 175) and motor block (MD 45 min; 95%CI 9 to 81) (Crespo 2017 **Level I** [PRISMA], 12 RCTs, n=1,280). IT clonidine increases sedation (RR 3.92; 95%CI 1.17 to 13.14), but does not increase the risk of hypotension, affect pruritus or PONV.

In obstetrics patients, the time to achieve highest sensory and complete motor block was less and duration of analgesia was longer when clonidine and hyperbaric bupivacaine were administered sequentially, compared to the mixing of the two medicines in a single syringe (Sachan 2014 **Level II**, n=60, JS 4).

There is no human or animal evidence of neurotoxicity when preservative-free clonidine is administered IT (Hodgson 1999 **NR**). Epidural clonidine is approved by the FDA for relief of chronic cancer pain. For details see Section 4.9.2.1.

Intrathecal midazolam

IT midazolam gave short duration postoperative analgesia (Prakash 2006 **Level II**, n=60, JS 3). The safety of midazolam with respect to neurotoxicity is not established.

Safety of neuraxial opioids after Caesarean section

The prevalence of OIVI (author-reported, individual study definition) with use of neuraxial diamorphine and morphine after Caesarean section is 61/10,000 (95%CI 51 to 74) (Sharawi 2018 **Level IV SR**, 78 studies [54 RCTs, 21 studies & 3 case reports], n=18,455). However, when classified as clinically significant OIVI, highest prevalence with all doses of neuraxial opioids was 8.67/10,000 (95%CI 4.20 to 15.16) and lowest was 5.96/10,000 (95%CI 2.23 to 11.28). These rates dropped even further with the use of lower but clinically relevant doses of neuraxial morphine: IT dose ≤150 mcg 1.63/10,000 (95%CI 0.62 to 8.77) (31 RCTs [IT]) or epidural dose ≤3 mg 1.08/10,000

(95%CI 0.24 to 7.22) (32 RCTs [epidural]). No cases were reported for IT diamorphine ≤400 mcg or epidural diamorphine ≤5 mg.

Other regional techniques

Peripheral regional blocks are useful analgesic techniques after Caesarean section (Mitchell 2019 **NR**; Patel 2019 **NR**). Local anaesthetic techniques in general (wound infiltration, bupivacaine-soaked gelatin sponge placement or catheter infusions, ilioinguinal/ iliohypogastric block, TAP block) reduce opioid consumption following Caesarean section performed under general or regional anaesthesia vs placebo (Bamigboye 2009 **Level I** [Cochrane], 20 RCTs, n=1,150). The reduction in opioid consumption is most beneficial where abdominal nerve blocks are used to supplement regional anaesthesia (MD -25.8 mg; 95%CI -50.4 to -5.4) (4 RCTs, n=175).

Wound infiltration or infusion

After Caesarean section, either continuous wound infusion or single-dose infiltration with local anaesthetics vs placebo reduces parenteral morphine consumption at 24 h (MD -9.69 mg; 95%CI -14.85 to -4.52) and pain at 24 h at rest (MD -0.36/10; 95%CI -0.58 to -0.14) and with movement (MD -0.61/10; 95%CI -1.19 to -0.03) with no difference between the techniques (Adesope 2016 **Level I** [PRISMA], 21 RCTs, n=1,435). These effects are not shown in patients receiving IT morphine and only with catheter placement below the fascia. PONV and pruritus are not reduced. RCTs not included in this systematic review confirm these results. Continuous wound infiltration with ropivacaine was superior to epidural morphine with regard to pain relief, adverse effects, need for nursing care and hospital LOS (O'Neill 2012 **Level II**, n=58, JS 3). Combining a pre- with a postincisional wound infiltration with lignocaine 1% had superior efficacy to a pre- or postincisional infiltration alone (Fouladi 2013 **Level II**, n=281, JS 4).

There is benefit from adding diclofenac (Lavand'homme 2007 **Level II**, n=92, JS 3) or low-dose ketorolac, but not hydromorphone, to a 48 h continuous bupivacaine wound infusion (Carvalho 2013 **Level II**, n=60, JS 5). Ketorolac reduced pain scores and need for analgesia and also inflammatory cytokines (IL-6 and IL-10) in the wound exudate. Adding tramadol (1.5 mg/kg) to levobupivacaine wound infiltration reduced pain scores early in the postoperative period but there was no systemic control group (Demiraran 2013 **Level II**, n=90, JS 4). SC pethidine or tramadol improved analgesia and were opioid sparing vs infiltration of bupivacaine 0.25% or placebo (Jabalameli 2016 **Level II**, n=120, JS 3). Placing a multi-orifice catheter for wound infiltration with ropivacaine/ketoprofen below the superficial abdominal fascia resulted in improved analgesic efficacy vs placement above (Rackelboom 2010 **Level II**, n=56, JS 5).

The number of factors influencing efficacy of local anaesthetic wound infiltration in post Caesarean section analgesia - catheter placement (superficial versus deep to transversalis fascia), local anaesthetic dose (high /low volume and concentration) and methods of administration (intermittent boluses versus continuous infusion) - need to be evaluated with further studies.

Ilioinguinal-iliohypogastric block (II-IH block)

Bilateral II-IH block (local anaesthetic vs saline placebo) used in addition to IT morphine improved analgesia, lowered analgesic requirements and increased satisfaction (Wolfson 2012 **Level II**, n=34, JS 5). However in another study, US-guided II-IH blocks with bupivacaine, combined with IT morphine (variable dosing), conferred no further benefit (Vallejo 2012 **Level II**, n=50, JS 4). US-guided II-IH blocks vs TAPB provided similar early analgesia with similar adverse event rates; however at later time points (24 h and 48 h), analgesia was superior with US-guided II-IH block (Jin 2019 **Level III-1**, n=242).

Transversus abdominis plane block (TAPB)

After Caesarean section, TAPB vs placebo (9 RCTs) or no block (3 RCTs) reduces pain at rest at 6 h (-3.6/10; 95%CI -6.3 to -0.9), to a lesser extent at 24 h (-1.1/10; 95%CI -2.1 to -0.01) and morphine

requirements at 2 to 24 h (Champaneria 2016 **Level I SR** [PRISMA], 18 RCTs, n=1,353). TAPB/IT morphine vs IT morphine only reduces pain at rest (-0.5/10; 95%CI -1.0 to -0.1) and with movement (-1.0/10; 95%CI -1.7 to -0.4).

In a preceding SR, TAPB has varying outcomes depending on the comparator, and if added to multimodal analgesia (IT morphine, or placebo, in combination with paracetamol and NSAID and/or PCA opioids) (Fusco 2015 **Level I** [PRISMA], 11 RCTs, n=727) (9 RCTs overlap with Champaneria 2016). TAPB in addition to multimodal analgesia may not confer additional analgesic benefit. This uncertainty is affected by the heterogeneity of analgesic treatment in RCTs. Opioid related side effects may be reduced. In this systematic review the outcomes were not suitable for quantitative assessment; TAPB reduces opioid consumption vs IT opioid (3 of 4 RCTs), time to first analgesic request (5 of 7 RCTs), PONV (10 of 10 RCTs) and pruritus (4 of 7 RCTs). TAPB alone and with IT opioid does not improve postoperative analgesia vs IT opioid (3 RCTs each), but TAPB/IT opioid vs placebo reduces pain intensity (4 RCTs).

Following Caesarean section, local anaesthetic TAPB reduces postoperative opioid requirements for 24 h and pain scores for 12 h but only when IT morphine is not used (Mishriky 2012 **Level I** [PRISMA], 9 RCTs, n=524) [7 RCT overlap with Fusco 2015]; Abdallah 2012 **Level I** [PRISMA], 5 RCTs, n=312 (all 5 RCTs overlap)); IT morphine provides better analgesia than TAP blocks but with an increased rate of adverse effects.

RCTs with small patient numbers of TAPB used in combination with IT morphine have shown no (McKeen 2014 **Level II**, n=83, JS 5) vs early 0–24 h analgesic benefit (Lee 2013a **Level II**, n=51, JS 5; Onishi 2013 **Level III-2**; Singh 2013a **Level II**, n=60, JS 5). The latter study compared high-dose (3 mg/kg) with low-dose ropivacaine (1.5 mg/kg) and found only high-dose ropivacaine produced benefits for up to 12 h.

Single-dose US-guided TAPB and continuous wound infusions were compared in women having Caesarean section under spinal anaesthesia without morphine (Chandon 2014 **Level II**, n=65, JS 3). The trial was abandoned after a generalised seizure in the TAPB group; however, there were no differences between the groups with regard to analgesia and pain at 1 mth. In a similar study, there was also no difference in morphine use or pain when TAPB and SC wound infiltration with bupivacaine 0.25% and adrenaline were compared (Telnes 2015 **Level II**, n=60, JS 5).

With regard to TAPB technique and duration of effect, the posterior approach (4 RCTs) reduced opioid consumption and rest and dynamic pain scores over 48 h vs controls; longer than that from a lateral approach where rest pain scores only were lower than controls at 12 h (8 RCTs) (Abdallah 2013 **Level I** [PRISMA], 12 RCTs [8 Caesarean sections], n=641). Subanalysis of the varying agents and dose equivalents administered was not performed.

TAPB are associated with high peak plasma concentrations of local anaesthetic after 30 min (Torup 2012 **PK**) and mild toxicity is reported after total doses of ropivacaine of ≥2.5 mg/kg (Griffiths 2013 **Level IV**) and convulsions after 150 mg of levobupivacaine (Weiss 2014 **CR**).

Quadratus lumborum (QL) block

Quadratus lumborum block after Caesarean section in comparison to TAPB provided effective and prolonged analgesia with a mean time to first analgesic request of 68.8 h (SD 1.74) vs 13.3 h (SD 1.21) (Verma 2019 **Level II**, n=60, JS 3)

Risk of chronic pain following Caesarean section

Persistent postsurgical pain has been reported in 1 to 18% of women following Caesarean section (Landau 2013 **NR**). In two studies with detailed follow-up, the incidence of persistent pain was 14.6% at 2 mth, reducing to 4.2% at 12 mth (n=426) (Liu 2013 **Level IV**) and 11% at 8 wk, reducing to 0.6% at 12 mth (n=381) (Ortner 2014 **Level III-2**). For repeat Caesarean section, preoperative scar hyperalgesia (seen in 41% of patients) is a risk factor for postoperative pain (Ortner 2013 **Level III-**

2). Patients with chronic postsurgical pain had higher rates of general vs spinal anaesthesia (37% general vs 17% in the no-pain group; p=0.02); in this study the incidence of significant pain at 10 mth postoperatively was 5.9 % (Nikolajsen 2004 **Level III-2**). A variety of regional analgesia techniques reduces CPSP at 3 to 8 mth following Caesarean section (NNT 19) (OR 0.46; 95%CI 0.28 to 0.78) (4 RCTs, n=551) (Weinstein 2018 **Level I** (Cochrane), 63 RCTs, n=3,027).

Prior Caesarean section is also a risk factor for chronic pelvic pain (Latthe 2006 **Level III-3 SR**, 63 studies, n=64,286). See also Section 1.4.

KEY MESSAGES

Neuraxial and regional analgesia for pain in labour

1. Epidural and combined spinal-epidural analgesia provides superior pain relief for labour and delivery compared with all other analgesic techniques (**S**) along with improved maternal satisfaction (**R**) (**Level I** [Cochrane Review]).
2. Epidural analgesia compared to systemic opioid reduces maternal nausea and/or vomiting (**N**) and need for maternal oxygen supplementation (**N**), but increases the duration of the first and second stage of labour slightly (**Q**) (**Level I** [Cochrane Review]).
3. Epidural analgesia compared to systemic opioid does not increase the rate of Caesarean section (**S**), long-term backache (**S**), headache (**N**), pruritus (**N**) or postnatal depression (**N**) (**Level I** [Cochrane Review]).
4. Epidural analgesia compared to systemic opioids reduces the risk of fetal acidosis (**S**) and the need for neonatal naloxone administration with no increase in special care/neonatal intensive care unit admissions (**N**) (**Level I** [Cochrane Review]).
5. Epidural analgesia may increase the rate of assisted vaginal delivery (**U**), but not with contemporary techniques of epidural analgesia (use of low-concentrations of local anaesthetics) (**Q**) (**Level I** [Cochrane Review]).
6. Lower concentrations of local anaesthetics for epidural analgesia in labour result in a shorter duration of second stage of labour, fewer assisted vaginal deliveries, greater ambulation and less urinary retention than higher concentrations (**S**) (**Level I** [Cochrane Review]).
7. Early versus late initiation of epidural analgesia leads to no clinically significant differences in outcome (**S**) (**Level I** [Cochrane Review]).
8. In comparison with epidural analgesia, combined spinal-epidural analgesia reduces time to effective analgesia (**U**), does not increase maternal satisfaction (**U**), increases the incidence of mild pruritus (compared to low-dose epidurals) (**U**) (**Level I** [Cochrane Review]) and reduces the risk of unilateral block (**N**) (**Level I** [PRISMA]).
9. Local anaesthetic nerve blocks (in particular paracervical blocks) provide better analgesia than placebo, nonopioids and opioids for labour pain, but at an increased rate of adverse effects (**U**) (**Level I** [Cochrane Review]).
10. Non-reassuring fetal heart rate tracings can be more common with combined spinal-epidural analgesia than epidural analgesia in labour (**N**) (**Level I** [PRISMA]).

11. Ultrasound guidance improves the success of epidural catheter insertion and intrathecal needle placement and reduces traumatic insertions (**N**) (**Level I** [PRISMA]).

12. Patient-controlled epidural analgesia provides effective analgesia for labour (**U**) but optimal settings (**U**) (**Level I**) and the need for a background infusion remain unclear (**U**) (**Level I** [PRISMA]).

13. Programmed intermittent epidural bolus versus continuous epidural infusion reduces the incidence of breakthrough pain without increasing adverse outcome (**S**) (**Level I** [PRISMA]).

14. Dural puncture epidural analgesia does not appear to offer benefit over standard epidural analgesia (N) (**Level I** [PRISMA]).

15. There is no difference between the use of bupivacaine and ropivacaine for epidural analgesia in labour for any outcome (**U**), except ropivacaine may reduce the incidence of motor block (**Q**) (**Level I**).

16. Single-injection intrathecal opioids provide comparable early labour analgesia to epidural local anaesthetics, with increased pruritus but no difference in nausea (**U**) (**Level I**). Adding single injection intrathecal morphine (≤250 mcg) to local anaesthetic combined with shorter acting opioids increases time to first analgesic request, but is associated with increased adverse effects **(N)** (**Level I**).

Systemic analgesia for pain in labour

17. Analgesic concentrations of inhaled volatile anaesthetics provide superior analgesia in labour but more drowsiness, compared to inhaled nitrous oxide (**U**) (**Level I** [Cochrane Review]).

18. Inhaled nitrous oxide has some analgesic efficacy in labour pain (**U**), increases maternal adverse effects (nausea, vomiting, dizziness) (**U**) but has no adverse effects on the newborn (**U**) (**Level I** [Cochrane Review]); pain relief is comparable to pethidine but inferior to epidural analgesia (**U**) (**Level IV SR**).

19. Use of nonopioid analgesics alone for labour analgesia is not supported by current evidence (**U**) (**Level I** [Cochrane Review]).

20. Parenteral opioids other than remifentanil intravenous PCA provide moderate analgesic effects in labour pain (**S**), are inferior to epidural analgesia (**S**) and cause increased adverse maternal effects (sedation, nausea, vomiting) (**S**) and adverse effects on the newborn remain unclear (**Q**) (**Level I** [Cochrane Review]).

21. Remifentanil intravenous PCA is inferior to epidural analgesia (**U**), but provides better analgesia in labour compared to other parenteral opioids (**S**) (**Level I** [Cochrane]).

Complementary and other methods of pain relief in labour

22. Continuous or one-to-one support by a midwife or trained layperson during labour reduces analgesic use, rate of assisted and operative birth and dissatisfaction (**S**) (**Level I** [Cochrane Review]).

23. Immersion in water during labour may reduce the requirements for regional and neuraxial analgesia, with no difference in other maternal outcomes and insufficient evidence for neonatal outcomes compared to no immersion (**W**) (**Level I** [Cochrane Review]).

24. Relaxation by use of yoga, music or audio has limited benefit for pain relief or satisfaction in labour (**Q**) (**Level I** [Cochrane Review]).

25. Acupuncture and acupressure for labour pain may reduce pain, use of pharmacological pain relief and increase satisfaction with pain management vs standard care or placebo (**Q**) (**Level I** [Cochrane Review]); Caesarean section rates are unchanged (**R**) (**Level I** [Cochrane Review]).
26. Acupressure (vs sham) reduces labour pain, but has no effect on the use of pharmacological analgesia (**Q**) (**Level I** [Cochrane Review]).
27. Massage may decrease pain in the first stage of labour pain compared to standard care (**S**) (**Level I** [Cochrane Review]).
28. Transcutaneous electrical nerve stimulation has no effect on pain, interventions or outcomes in labour (**U**) (**Level I** [Cochrane Review]).
29. Biofeedback, sterile water injections intra- or subcutaneously and aromatherapy have no effect on labour pain or other outcomes (**U**) (**Level I** [Cochrane Review]).
30. Use of a birth ball may improve labour pain (**N**) (**Level I**).
31. Heat packs may reduce labour pain during the first and second stages (**N**) (**Level I** [Cochrane Review]).
32. Hypnosis (mostly antenatal interventions) may reduce analgesic requirements for labour pain (**R**) (**Level I** [Cochrane Review]).

Pain relief after Caesarean section

33. Local anaesthetic wound infiltration, in particular abdominal nerve blocks, reduces opioid consumption following Caesarean section (**U**) (**Level I** [Cochrane Review]).
34. Local anaesthetic transversus abdominis plane blocks reduce postoperative opioid requirements and pain scores after Caesarean section but only when intrathecal morphine is not used (**S**) (**Level I** [PRISMA]).
35. In relation to controls only and with no direct comparison between the two approaches, local anaesthetic transversus abdominis plane blocks performed by a posterior approach provide a longer duration of benefit versus the lateral approach after lower abdominal incision surgery including Caesarean section (**U**) (**Level I** [PRISMA]).
36. Intravenous paracetamol given before incision reduces opioid analgesic requirements after Caesarean section (**N**) (**Level I** [PRISMA])
37. Epidural (**U**) (**Level I** [QUOROM]) and intrathecal morphine (**U**) (**Level I**) and patient-controlled epidural analgesia (**U**) (**Level II**) provide effective analgesia after Caesarean section, but neuraxial morphine increases the rate of pruritus and nausea compared with systemic administration (**U**) (**Level I** [QUOROM]).
38. Intrathecal morphine (range of 100 mcg to 250 mcg) increases time to first analgesic request after Caesarean section, but pain scores and opioid consumption are unchanged, and postoperative nausea, vomiting and pruritus increased (**N**) (**Level I**).

The following tick boxes represent conclusions based on clinical experience and expert opinion:

☑ Remifentanil IV PCA for relief of labour pain carries a risk of maternal respiratory depression; use is recommended only if there is one-on-one continuous presence of a midwife, continuous oxygen saturation monitoring and continuous cardiotocograph monitoring (as an indirect method of detecting global hypoxaemia) (**U**).

☑ Transversus abdominis plane blocks after Caesarean section may result in high plasma concentrations of local anaesthetic and potential toxicity; minimum effective doses should be used (**U**).

9.1.4 | Pain management during lactation

Several general principles apply when administering analgesic and antiemetic medications for pain management during lactation:

- The choice of medications should be based on knowledge of their potential impact on breastfeeding and on the breastfed infant secondary to transfer in human milk;
- The lowest possible effective maternal dose of analgesic for the shortest possible duration is recommended (Reece-Stremtan 2017 **GL**);
- Breastfeeding is best avoided at times of peak medication concentration in milk and the infant should be observed for effects of medication transferred in breast milk.

A useful regularly updated peer reviewed resource is the USA National Library of Medicine's Drugs and Lactation Database (LactMed®) (https://www.ncbi.nlm.nih.gov/books/NBK501922/) (LactMed **GL**); this replaces the previously associated Toxicology Data Network (Toxnet) and LactMed@NIH smartphone/mobile applications. Alternative websites here are (https://www.infantrisk.com) and an Australia-based website with information for parents, too (https://www.breastfeeding-anaesthesia.info).

Importantly, the use of many analgesic and antiemetic medications during lactation is off-label and the effects have not been adequately investigated, leaving clinical decisions to be made on evidence derived from pharmacokinetic or observational studies, case reports and anecdotes. For most medications, information on infant outcome is inadequate (based on single dose or short-term administration or on case reports) or absent, so maternal consent is advisable and caution is warranted.

The principles of the passage of medications in human milk (LactMed **GL**; Verstegen 2019 **NR**; Ilett 2005 **NR**) including medications relevant to pain management (Ito 2018 **NR;** Bar-Oz 2003 **NR**; Spigset 2000 **NR**) have been reviewed. The maternal plasma concentration, which is influenced by the dose and the ability of the mother to metabolise the medication, is an important determinant of medication concentrations in breast milk. High lipid solubility, low molecular weight, low protein binding and the unionised state favour secretion into breast milk. Most medications have a milk-to-plasma ratio of ≤1 (Ito 2000 **NR**). Relative infant dose (RID) is a weight-adjusted time averaged (eg daily) dose of drug in milk ingested by the infant, expressed as a percentage of the time averaged maternal therapeutic dose on a body weight basis; a RID of 100% is the same as directly receiving a therapeutic dose per weight.

Infant exposure is often 0.5 to 4% of the maternal dose but infant medication metabolism may be impaired and much of the data is from single maternal dose studies rather than chronic therapy (LactMed **GL**; Berlin 2005 **NR**). A safe level of infant exposure to a medication has been arbitrarily defined as no more than 10% of the therapeutic dose for infants (or the adult dose

standardised by weight if the infant dose is not known) (Ito 2000 **NR**). Until mature milk breastfeeding is established, only very small volumes of colostrum are secreted, so early breastfeeding is unlikely to pose a hazard (as overall dose is low including in the setting of lipophillic medications when concentrated vs plasma)(LactMed **GL**).

Guidelines include the following general recommendations (Mitchell 2020 **GL**; Martin 2018 **GL**; Reece-Stremtan 2017 **GL**). These recommendations are limited by the sparse clinical trial data in this patient population. Guidance is based on the experience of historical use, case series and pharmacokinetics (usually presented as relative infant dose [RID]% in breast milk related to the weight-adjusted maternal dose).

- Intracellular junctions between lactocytes close after 7 to 10 d postpartum. Exposure to maternal medications may be highest during 3 to 10 d postpartum;
- Opioids are the most concerning group of analgesics – dose and duration should be limited;
- Analgesic effectiveness needs to be weighed against adverse effects and safety concerns (particularly for opioids) because when maternal pain is well treated, breastfeeding outcomes are improved;
- There are differences in risk between different opioids. Codeine should be avoided as some mothers who are ultrarapid metabolisers produce higher concentrations of morphine with transfer into breast milk. Warnings against codeine use have been made (TGA 2016 **GL**) and extended to tramadol by some regulatory bodies (Medsafe 2020 **GL**; FDA 2019 **GL**) (see also Sections 10.4.4.5 and 10.4.4.12);
- Long acting opioids, and those with active metabolites (eg pethidine, morphine), have been associated with respiratory depression, cyanosis and bradycardia in neonates. Inconclusive evidence suggests doses of cumulative epidural fentanyl >150mcg may be associated with less successful breastfeeding;
- Mothers of healthy full-term infants can breastfeed as soon as they have recovered from anaesthesia. However, infants at risk of sensitivity (eg low birth weight, premature) should probably not be breastfed/receive maternal breast milk until 6 to 12 h after anaesthesia;
- Breastfed infants of mothers on high dose or long-term opioids need observation for drowsiness, poor feeding and neonatal abstinence syndrome (NAS);
- Neonatal observation and monitoring is warranted if there is evidence of maternal CNS depression;
- Regional anaesthesia should have a lower risk than general anaesthesia for babies of breastfed mothers, because systemic absorption is very low, and postoperative regional analgesia may minimise the requirement for opioid analgesia;
- Neuraxial morphine and multimodal analgesia (including regional techniques such as transversus abdominis plane block and wound infiltration with local anaesthetic) reduces systemic opioid requirements.

Advice about specific agents includes:

- Paracetamol is widely used. Transfer into milk is low and appears to be less than the dosage given to infants;
- Aspirin in doses < 81mg/d has undetectable concentrations in human milk. Its use as chronic anti-platelet therapy is considered safe. Variable transfer into milk reflects nonlinear metabolism at higher analgesic dosages and these should be avoided (Mitchell 2020 **GL**);
- nsNSAIDs and Coxibs have a low transfer into milk (low %RDI) however they should be avoided in infants with ductal dependent cardiac lesions;

- Concentrations in breast milk after oral ketorolac are low, but have not been measured after parenteral administration;
- For diclofenac, limited studies demonstrate undetectable concentrations after oral or IM administration;
- For naproxen, milk transfer is low and safe with short-term use (<1 wk), but there have been reports of neonatal GI disturbances after prolonged maternal use;
- For indomethacin, milk transfer is low and is considered safe in the postpartum period;

- The effect of epidural analgesia on breastfeeding is uncertain (French 2016 **SR Level III-**2, 23 studies, n=36,128);
  - There is minimal data on effects of inhaled nitrous oxide by mothers on neonates. A review reported no adverse effect on suckling.

9.1.4.1 | Nonopioids

Paracetamol

The weight-adjusted maternal dose of paracetamol transferred to the newborn was 1.85% of a 1 g dose (Notarianni 1987 **Level IV PK**). Although glucuronide conjugation may be deficient in the newborn, the medication is considered safe as there have been no reports of adverse effects and concentrations in breast milk are a fraction of the recommended neonatal doses.

NSAIDs

Short-term maternal NSAID use during lactation appears safe for the healthy term infant; aspirin <150 mg/d maybe indicated for long-term use (Bloor 2013 **NR**). Despite similar proportional transfer to paracetamol, salicylates are eliminated slowly by the newborn, cause platelet dysfunction and have been associated with Reye's syndrome; aspirin in analgesic doses cannot be recommended as safe (Bar-Oz 2003 **NR**).

NSAIDs must be considered individually but, in general, concentrations in breast milk are low because they are weak acids and extensively plasma protein bound. In particular, ibuprofen has very low transfer (<1% weight-adjusted maternal dose), is short acting, free of active metabolites and has the best documented safety (Ito 2000 **NR**). Ibuprofen is therefore considered the ideal agent in this group (Montgomery 2012 **GL**).

Diclofenac and ketorolac are minimally transported into breast milk and short-term or occasional use is compatible with breastfeeding (Rathmell 1997 **NR**). The safety of naproxen is less clear but it is also considered compatible. Indomethacin has been associated with central maternal adverse effects, such as agitation and psychosis, in previously healthy postnatal women (n=32) (Clunie 2003 **Level IV**).

Following a single 200 mg dose of celecoxib, <0.5% of the weight-adjusted maternal dose was present in breast milk, suggesting that breastfeeding during routine dosing poses a minimal risk (Gardiner 2006 **Level IV PK**; Hale 2004 **Level IV PK**). The relative infant dose of parecoxib and valdecoxib after a single dose of maternal parecoxib is very low (<1%) and neonatal neurobehavioural scores are within the normal range (Paech 2012 **Level IV PK**).

9.1.4.2 | Conventional and atypical opioids

With some provisos, the short-term use of opioids (2 to 3 d) is generally considered safe during lactation as most opioids are secreted into breast milk in low doses (LactMed **GL**; Ito 2018 **NR**; Hendrickson 2012 **NR**); the RID of opioids is usually low in the range of 1% to 5%, although individual variations exist (Ito 2018 **NR**).

Conventional opioids

An association between opioid exposure in breast milk and episodes of apnoea and cyanosis in infants has been described (Naumburg 1988 **Level IV**), leading some to suggest that opioids should be avoided if the newborn experiences such events during the first week of life. Cases of infant toxicity due to human milk exposure are reported (LactMed **GL**; Madadi 2007 **CR**), mostly involving codeine in infants <2 mth of age, therefore infants should be monitored for drowsiness (Hendrickson 2012 **NR**) (see also Sections 1.7.3 and 4.1.1).

RID (relative infant dose) of morphine is 2 to 3%, however, M6G exposure might be higher (Ito 2018 **NR**). The oral bioavailability in the infant is low (about 25%), so smaller amounts reach the infant's plasma (Feilberg 1989 **Level IV PK**). In mothers treated with IV PCA morphine for 48 h following Caesarean section, concentrations of morphine and M6G were low in breast milk, suggesting minimal medication would be transferred to the newborn (Baka 2002 **Level IV PK**). Compared with IV PCA pethidine (meperidine), there is significantly less neurobehavioural depression with IV PCA morphine (Wittels 1990 **Level III-2**). Overall, short-term morphine use post-partum is compatible with safety in breast feeding (Ito 2018 **NR**).

Pharmacokinetic studies suggest the more lipophilic opioids, such as fentanyl and alfentanil, are unlikely to cause problems. Following a single dose of IV fentanyl, the weight-adjusted maternal dose received by the newborn was 3%, concentrations in colostrum became undetectable within several hours and the nursing infant appeared unaffected (Steer 1992 **Level IV PK**; Nitsun 2006 **Level IV PK**).

Breastfed infants whose mothers received IV PCA pethidine were less alert and oriented to auditory cues after Caesarean section than infants of mothers receiving morphine (Wittels 1997 **Level III-2**, n=47). As norpethidine (normeperidine) accumulates in breast milk with repeated use and has a very slow neonatal elimination, pethidine use during breastfeeding is not recommended (Ito 2000 **NR**). The American Academy of Pediatrics (AAP) recommends against use of IV pethidine in breastfeeding mothers (Sachs 2013 **GL**). Pethidine PCEA results in much lower plasma concentrations than systemic pethidine, with lower infant exposure to pethidine and norpethidine (1.8%) (Al-Tamimi 2011 **Level IV PK**) and may be a low risk method during very early lactation (Sakalidis 2013 **Level III-2**).

Caution has been advised regarding the use of codeine during breastfeeding (FDA 2019 **GL**; TGA 2016 **GL**). Codeine has a milk-to-plasma ratio of slightly more than 1 and was previously suggested to be generally safe with short-term use, but should be used with caution when dosing is repeated (Meny 1993 **PK**; Hendrickson 2012 **NR**). A case-control study that included a newborn who died while breastfed by a mother taking codeine, has highlighted that breastfed infants of mothers who are extensive or ultrarapid metabolisers (20–40% of the population, depending on ethnicity, with duplications of CYP2D6 gene) are at increased risk of life-threatening CNS depression (Madadi 2009 **Level III-2**). A number of similar cases have been reported and healthcare workers and breastfeeding mothers should be aware of this risk (Madadi 2008 **Level IV**, n=35). A relationship between infant CNS symptoms (decreased alertness, lethargy, poor feeding) and maternal symptoms, codeine dose and, in some cases CYP2D6 phenotype, has been identified (Madadi 2009 **Level III-3**, n=72 [17 symptomatic]). Pharmacokinetic simulation suggests potentially toxic morphine concentrations can be reached in the newborn within 4 d of repeated maternal codeine administration (Willmann 2009 **PK**).

Oxycodone shows a relative infant dose (RID) of 1.5 to 8.5%; it has high oral bioavailability and is concentrated in human breast milk, so breastfed infants may receive >10% of a therapeutic dose, and a USA guideline cautions against its use (Sachs 2013 **GL**), while others suggest a maximum maternal daily dose of 30 to 40 mg (LactMed **GL**; Mitchell 2020 **GL**). Poor CYP2D6 metabolisers may have decreased clearance of oxycodone and ultrarapid metabolisers higher concentrations of the more potent metabolite oxymorphone, leading to sedation (Samer 2010

Level II PK, n=10 [5-arm crossover], JS 5). The safety with repeated maternal dosing has been questioned (Ito 2000 **NR**; Lam 2012 **Level III-2**); a case of opioid toxicity in a breastfed newborn of a mother taking oxycodone has been reported (Timm 2013 **CR**). Oxycodone use during breastfeeding resulted in increased rate of CNS depression of the newborn vs paracetamol (20.1 vs 0.5%) (OR 46.16; 95%CI 6 to 344) but no difference to codeine (16.7%) (OR 0.79; 95%CI 0.46 to 1.38) (Lam 2012 **Level III-2,** n=533). As a component of multimodal analgesia in the first 72 h after Caesarean section, there may be minimal risk to breastfeeding infants as only a low volume of milk is ingested during this period. Only 1 of 44 newborns had detectable plasma concentrations and none were over sedated despite maternal exposure up to 90 mg/d (Seaton 2007 **Level III-3**).

After IN hydromorphone exposure of the mother, 0.67% of the maternal dose of hydromorphone (adjusted for body weight) is transferred into breast milk (Edwards 2003 **Level IV PK**).

Hydrocodone is metabolised in small quantities to a more potent metabolite, hydromorphone, and ultrarapid metabolisers exist. The RID is 2.4% (Sauberan 2011 **Level IV PK**) and possible infant toxicity has been reported (Hendrickson 2012 **NR**).

Methadone is considered compatible with breastfeeding; even with high methadone doses, breast milk concentrations were relatively low at 2.1–3.5% (Bogen 2011 **Level IV PK**). Plasma concentrations of methadone were low in infants of breastfeeding mothers on methadone-maintenance programs and no effect on infant neurobehavioural outcomes were found on d 3, 14 and 30 following birth (Jansson 2008 **Level III-3**). Breastfeeding reduced NAS in newborns of mothers on methadone substitution and is encouraged (McQueen 2011 **Level III-2**).

Atypical opioids

Buprenorphine has very low passage into breast milk and the combined RID of both buprenorphine and its active metabolite norbuprenorphine is <1% (Ilett 2012 **Level IV PK**). When used for drug substitution therapy in breastfeeding mothers, buprenorphine did not lead to adverse effects in newborns up to 4 wk postnatally (Gower 2014 **Level IV**).

Information regarding tapentadol in lactaction is limited to 4 case reports of infant exposure during breastfeeding, with no adverse reactions reported (LactMed **Level IV**).

Tramadol (100 mg every 6 h) on d 2–4 after Caesarean section was associated with a milk-to-plasma ratio of 2.2, a relative infant dose of 2.9% and no detectable behavioural effects in the infants (Ilett 2008 **Level III-2**). However, as with other medications, these data cannot be directly extrapolated to long-term use at later postpartum stages when the volume of ingested milk is higher. The use of tramadol during pregnancy and in lactation has been reviewed (LactMed Database 2019 **GL**; Bloor 2012 **NR**); the opinion being that during early lactation short-term use of tramadol appears unlikely to cause harm to healthy term infants. However, the USA's FDA has elected to apply the same warning as for codeine to tramadol (FDA 2019 **GL**); New Zealand has followed this lead (Medsafe 2017 **GL**), but not the Australian TGA to date.

9.1.4.3 | Other analgesics and medications related to pain relief

Epidural local anaesthetics

After epidural administration, local anaesthetics showed acceptable milk-to-plasma ratios of 1.1 for lidocaine (lignocaine), 0.34 for bupivacaine (Ortega 1999 **PK**) and 0.25 for ropivacaine (Matsota 2009 **PK**). These are considered safe (Rathmell 1997 **NR**), including for anaesthesia and analgesia during very early lactation (Hirose 1996 **Level II**, n=30, JS 2; Matsota 2009 **Level IV**, n=25). Use of epidural analgesia (local anaesthetic ± fentanyl) during labour (Chang 2005 **Level III-3**) or as PCEA after Caesarean section (Matsota 2009 **Level IV**) did not influence neurobehavioural scores in healthy term infants.

The possible effect of epidural analgesia on breastfeeding is complex and may not only be related to medications administered, with selection bias (lack of randomised trials), nonstandardised breastfeeding evaluations and failure to control for confounding variables making firm conclusions impossible (Szabo 2013 **NR**). In a study of 1,054 nulliparous women randomised to different methods of epidural analgesia in labour and matched with 351 nonepidural controls, there was no association with breastfeeding initiation (Wilson 2010 **Level III-2**, n=1,405). However, epidural analgesia in labour was associated with an increased risk of breastfeeding cessation at 30 d after adjusting for demographic and intrapartum factors (HR 1.26; 95%CI 1.1 to 1.44) (Dozier 2013 **Level III-2**, n=772).

Alpha-2 agonists

The effects of clonidine on breastfeeding have not been studied, but a single neuraxial dose is unlikely to have any adverse effect. As a neuraxial adjuvant, it may reduce requirements for systemic opioids in the postpartum period (Martin 2018 **GL**).

Dexmedetomidine has been used as an adjuvant infusion during Caesarean section; a breastfeeding infant would receive a negligible dose of 0.04 to 0.098% RID (Nakanishi 2017 **Level IV PK**).

Alpha-2 delta ligands

The alpha-2-delta ligands are increasingly popular analgesics for acute pain after operative birth, especially among women with neuropathic pain, opioid tolerance or where opioid dose minimisation is recommended. For gabapentin, the milk-to-plasma concentration was 0.86, the RID was 2.4% and no adverse effects were noted in the infant (Ohman 2005 **Level IV PK**). While suggestive of safety during lactation, a careful individual risk-benefit analysis was suggested (Kristensen 2006 **CR PK**). There are also limited human data on pregabalin during breastfeeding. Pregabalin is a small molecule that undergoes negligible metabolism and is thus expected to be excreted in breast milk. A breastfed infant of a mother on long-term pregabalin (for epilepsy) had serum concentrations of about 8% of the maternal concentrations, although no adverse effects were observed (Ohman 2011 **Level IV PK**). During a much later stage of lactation, the mean milk-to-plasma ratio was 0.53 to 0.76; and 0.2% of the maternal daily dose was secreted into breast milk, representing 7% of the body weight normalised maternal dose (Lockwood 2014 **Level IV PK**). The medication was well tolerated and the overall safety of anticonvulsants in breastfeeding mothers is regarded as high, with continuation of breastfeeding recommended (Reimers 2012 **NR**). Gabapentin is considered the safer of the two agents given its less likely transfer in breast milk (Reece-Stremtan 2017 **GL**).

Ketamine

Ketamine has limited data on transfer to breast milk. Given the uncertainty over neurodevelopmental effects with infant/toddler ketamine anaesthesia exposure, concerns exist over its use (Yan 2014 **Level III-3**). There is insufficient evidence to support its long-term safety when this agent is used as an infusion in breastfeeding mothers (Martin 2018 **GL**). A single study found there was no effect on duration of breast feeding (Suppa 2012 **Level II**, n=56, JS 4).

Antiemetics

There is very little information about antiemetic use and breastfeeding and, in almost all cases, the manufacturers (approved product information) do not recommend their use during lactation; although in practice most antiemetics are used, with the best data for metoclopramide (Pistilli 2013 **NR**). Metoclopramide is used both for cancer chemotherapy and to increase milk production, so although it concentrates in human milk the RID is much lower than the therapeutic dose in paediatrics (Kauppila 1983 **Level IV PK**) and authors have reported the absence of adverse effects in newborns whose mothers were exposed (Pistilli 2013 **NR**). Animal studies

suggest possible CNS effects in the newborn but human anecdotal experience is favourable with medications such as metoclopramide, domperidone and dexamethasone. Ondansetron (and other 5HT-3 blockers), dexamethasone, and metoclopramide are recommended over the more sedating agents prochlorperazine and promethazine, which are considered safe, but could cause maternal sedation (Martin 2018 **GL**).

Laxatives

Stool softeners and laxatives (docusate, senna and bisacadoyl) are minimally absorbed from the gastrointestinal tract, and are thus considered safe for use during lactation (LactMed **GL**).

See Table 9.3 for recommendations.

Table 9.3 | The breastfeeding patient and medications used in pain management

Medication	Comments
Paracetamol	Safe to use
Aspirin	Avoid analgesic doses due to theoretical risk of Reye's syndrome; however, single doses of aspirin can be taken. Low-dose aspirin (75–150 mg daily) safe.
Other NSAIDs	
Non-selective NSAIDs	Safe to use, ibuprofen is preferred
COX-2 selective inhibitors	Limited data but appear safe
Opioids	
Buprenorphine, codeine, fentanyl, hydromorphone, methadone, morphine, oxycodone, pethidine, tramadol, tapentadol	Safe to use occasional doses but avoid codeine. Use repeated doses with caution, especially if infant is preterm or <4 weeks old; monitor infant for sedation and other adverse effects
SSRIs	
Citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline	Considered safe to use (adverse effects, eg drowsiness, irritability, occasionally occur in breastfed babies). Avoid fluoxetine due to long half-life; some think sertraline one of the preferred antidepressants in breastfeeding as its levels in breast milk are low
TCAs	
Amitriptyline, clomipramine, dothiepin, doxepin, imipramine, nortriptyline, trimipramine	Avoid doxepin if possible (neonatal respiratory depression has been reported)
SNRIs	
Duloxetine, desvenlafaxine, milnacipran, venlafaxine	Concentrations in breast milk are low but check baby for sedation and adequate weight gain; consider using alternatives to duloxetine or milnacipran until more is known about them

Medication	Comments
Anticonvulsants	
Carbamazepine	Safe to use; monitor infant for drowsiness and poor suckling
Phenytoin	May be used
Valproate	Should be safe to use (1 report of adverse effects); consider monitoring baby for petechial rash
Clonazepam	Few data; avoid repeated doses if possible, as lethargy and poor feeding may occur due to drug accumulation in the baby
Gabapentin, pregabalin, lamotrigine, topiramate	Pass into breast milk; contact one of the Pregnancy drug information centres
Antiemetics	
Prochlorperazine	Safe to use
Domperidone	Safe to use
Metoclopramide	Safe to use
Granisetron, ondansetron, tropisetron, palonosetron	No data available, although 1 or 2 doses after delivery should not be a concern
Droperidol, haloperidol	Avoid if possible; there are few data regarding long-term effects
Local anaesthetics	
Bupivacaine, levobupivacaine, lidocaine, prilocaine, ropivacaine, tetracaine	Unlikely to cause problems
Other	
Ketamine	Limited data

Source: Modified information taken with permission from data published in Australian Medicines Handbook 2020; see also LactMed and Mitchell 2020.

KEY MESSAGES

1. Local anaesthetics, paracetamol and several NSAIDs, in particular ibuprofen, are considered to be safe in the lactating patient (**U**) (**Level IV**).
2. Morphine, fentanyl, methadone, and short-term oxycodone immediately after delivery are considered to be safe in the lactating patient and are preferred over pethidine (**U**) (**Level IV**).
3. Repeated dosing of codeine or oxycodone in lactating patients should be avoided if possible and the infant monitored for central nervous system depression (**S**) (**Level IV**).

The following tick boxes represent conclusions based on clinical experience and expert opinion:

☑ Prescribing medications during lactation requires consideration of possible transfer into breast milk, uptake by the infant and potential adverse effects for the infant; it should follow available prescribing guidelines (**U**).

☑ Breastfed neonates and infants may become sedated from the transfer of maternal medications; in this case, observation and monitoring of the infant and seeking medical advice is warranted. Maternal sedation may be an early warning sign (**N**).

9.1.5 | Pain in the puerperium

Pain during the puerperium is common and of multiple aetiologies, most often being perineal or uterine-cramping pain initially, and breast pain from postpartum d 4. In the first 6 mth postpartum, backache was reported by 44% of women and perineal pain by 21% (Brown 1998 **Level IV**). Headache has multiple aetiologies, mainly primary causes such as tension, migraine and musculoskeletal headache and, in a large observational study was reported by 40% of women one wk after delivery (Goldszmidt 2005 **Level IV**, n=985). Severe perineal and uterine pain limited mobility during maternal-infant bonding and perineal trauma and pain was associated with delayed resumption of sexual intercourse after birth (Williams 2007 **Level IV**). Breast, especially nipple, pain may result in abandonment of breastfeeding (Morland-Schultz 2005 **Level III-3 SR**). Chronic postnatal pain is also a risk factor for postnatal depression (Gaudet 2013 **Level IV**).

9.1.5.1 | Perineal pain

Perineal pain - prevention and physical treatments

Many obstetric and surgical factors contribute to perineal trauma and episiotomy. After adjusting for parity, perineal trauma and length of labour, women with instrumented vs unassisted vaginal deliveries reported more perineal pain (Thompson 2002 **Level IV**; Fahey 2017 **NR**). Restrictive use vs routine mediolateral episiotomy reduced the rate of episiotomy from 75 to 28% and reduced the risk of severe perineal trauma and the requirement for suturing but did not influence the incidence or degree of perineal pain (Carroli 2009 **Level I** [Cochrane], 8 RCTs, n=5,541).

In comparison with interrupted suturing methods, continuous suturing reduced pain incidence for up to 10 d (particularly suturing of all layers) (RR 0.65; 95%CI 0.60 to 0.71) (4 RCTs, n=2,488) but not for skin only (RR 0.89; 95%CI 0.73 to 1.07) (2 RCTs, n=1,217) and reduced postpartum analgesic use (RR 0.70; 95% CI 0.58 to 0.84) (for all layers 2 RCTs and skin only 2 RCTs, n=2,973) (Kettle 2007 **Level** [Cochrane], 7 RCTs, n=3,822).

There is only limited evidence to support the effectiveness of local cooling treatments (ice packs, cold gel pads, cold/iced baths) for relieving perineal trauma pain vs various alternatives or no interventions (East 2012 **Level I** [Cochrane], 10 RCTs, n=1,825). Ice packs provided superior analgesia vs no treatment for 24–72 h postpartum (RR 0.61; 95%CI 0.41 to 0.91) (1 RCT, n=208).

Although improvement in perineal pain has been reported with US, there is insufficient evidence to fully evaluate efficacy (Hay-Smith 2000 **Level I** [Cochrane] 4 RCTs, n=659). Ear acupressure did not relieve perineal trauma pain in the first 48 h after birth (Kwan 2014 **Level II**, n=266, JS 5)

For women without prior vaginal birth, antenatal perineal massage (from 35 wk gestation) reduced the incidence of perineal trauma requiring suturing (NNT 15; 95%CI 10 to 36) and the

requirement for an episiotomy (NNT 21; 95%CI 12 to 75) (Beckmann 2013 **Level I** [Cochrane], 4 RCTs, n=2,497). Effects on acute postpartum pain have not been reported, but a reduction in the incidence of perineal pain at 3 mth postpartum was found in women who used antenatal perineal massage and had previously given birth vaginally (NNT 13; 95%CI 7 to 60) (1 RCT, n=376).

Perineal pain - pharmacological treatments

More women with perineal pain experience pain relief from paracetamol than from placebo (RR 2.14; 95%CI 1.59 to 2.89) (Chou 2013 **Level I** [Cochrane] 11 RCTs, n=1,367); fewer women require additional analgesia (RR 0.34; 95%CI 0.21 to 0.55) (8 RCTs, n=1,132).

A single dose of NSAID vs placebo provided adequate pain relief at 4 h (RR 1.9; 95%CI 1.64 to 2.23) (10 RCTs, n=1,573) and 6 h (RR 1.92; 95%CI 1.69 to 2.17) (17 RCTs, n=2,079) after administration (Wuytack 2016 **Level I** [Cochrane], RCTs 28, n= 4,181). NSAIDs were more effective than paracetamol at 4 h (RR 1.54; 95%CI 1.07 to 2.22) (3 RCTs, n=342), but not at 6 h after administration.

Suppositories of nsNSAIDs reduce perineal pain in the first 48 h postpartum more effectively than placebo (Hedayati 2003 **Level I** [Cochrane], 3 RCTs, n=249). Rectal indomethacin was as effective as rectal diclofenac (Yildizhan 2009 **Level** II, n=200, JS 3). IV dexketoprofen was as effective as IV paracetamol (Akil 2014 **Level II**, n=95, JS 5). Both oral celecoxib and diclofenac reduced perineal pain, with celecoxib showing a slight advantage with respect to pain scores at rest and the incidence of gastrointestinal symptoms (Lim 2008 **Level II**, n=329, JS 5).

Topical local anaesthetics (lignocaine, cinchocaine, pramoxine plus hydrocortisone preparations) or placebo did not improve perineal pain in the 24 h postpartum (Hedayati 2005 **Level I** [Cochrane], 8 RCTs, n=976). The use of systemic analgesics was not standardised across these studies and maybe a confounding factor. Following mediolateral episiotomy repair under epidural analgesia, a pudendal block with ropivacaine improved pain scores and reduced the proportion of women requiring additional analgesia (Aissaoui 2008 **Level II,** n=42, JS 4).

9.1.5.2 | Postpartum breast and nipple pain

Painful breasts are a common reason for ceasing breastfeeding (Amir 2003 **NR**). Management is firstly directed toward remedying the cause, whether this is infant-related (incorrect attachment, sucking, oral abnormalities), lactation-related (breast engorgement, blocked ducts or forceful milk ejection), nipple trauma, dermatological or infective problems (candida or mastitis) or other causes. There is insufficient evidence to recommend glycerine gel dressings, breast shells with lanolin, lanolin alone or an all-purpose nipple ointment for treatment of nipple pain (Dennis 2014 **Level III-1 SR** [Cochrane], 4 studies, n=656). Irrespective of treatment, nipple pain resolves by 7 to 10 d postpartum for most women. Guidance regarding the usual duration of pain may help women to continue to breastfeed.

Symptomatic treatments for breast engorgement have been assessed (Mangesi 2016 **Level III-3 SR**, 13 studies, n=919): acupuncture (2 studies), acupressure (1 study), scraping therapy (*Gua Sha*) (1 study), cabbage leaves (3 studies), cold gel packs (1 study), electromechanical massage (1 study) and pharmacological treatments (3 studies) did not result in a faster resolution of symptoms vs no treatment.

Mastitis is defined by at least two breast symptoms (pain, redness or lump) and at least one of fever or flu-like symptoms. The incidence is 17–33% of breastfeeding women, most episodes occurring in the first 4 wk postpartum (Amir 2007 **Level IV**). Infective mastitis is most commonly due to *Staphylococcus aureus* and noninfective mastitis is equally common. There is insufficient evidence to confirm the efficacy of antibiotics in relieving symptoms, with only two trials meeting the inclusion criteria for analysis (Jahanfar 2013 **Level I** [Cochrane], 2 RCTs, n≈125).

9.1.5.3 | Postpartum uterine pain

Uterine pain or "after pains" often worsen with increasing parity and are experienced by most multiparous women. Uterine contraction results from the release of oxytocin from the posterior pituitary gland, especially in response to breastfeeding. Lower abdominal pain may be mild to severe, accompanied by back pain and is described as throbbing, cramping and aching. Ergot alkaloids during the third stage of labour increase the requirement for analgesia for pain after birth due to persistent uterine contraction (RR 2.53; 95%CI 1.34 to 4.78), but also decreases mean blood loss and the incidence of postpartum haemorrhage vs no uterotonic medications (Liabsuetrakul 2007 **Level I** [Cochrane], 6 RCTs, n=3,941).

NSAIDs are superior to placebo (3 RCTs, n=204) and paracetamol (1 RCT, n=48) for the relief of "after pains" following vaginal birth (Deussen 2011 **Level I** [Cochrane], 18 RCTs, n=1,498). Paracetamol is no better than placebo (1 RCT, n=48). Data on opioids are contradictory and do not permit an assessment of their efficacy for this indication.

High-intensity TENS was more effective than low-intensity TENS for treating postpartum uterine pain but also produced more local discomfort (Olsen 2007 **Level III-2**).

KEY MESSAGES

1. Routine episiotomy does not reduce perineal pain (**U**) (**Level I** [Cochrane Review]).
2. Continuous suturing of all layers compared with interrupted suturing for repair of episiotomy or second-degree tears reduces perineal pain and analgesic use in the postpartum period (**U**) (**Level I** [Cochrane Review]).
3. Paracetamol and NSAIDs are effective in treating perineal pain after childbirth compared with placebo (**S**) (**Level I** [Cochrane Review]).
4. NSAIDs, but not paracetamol, are effective in treating pain from uterine cramping after vaginal birth (**U**) (**Level I** [Cochrane Review]).
5. There is limited evidence to support the effectiveness of local cooling treatments in treatment of perineal pain after childbirth (**U**) (**Level I** [Cochrane Review]).
6. Topical local anaesthetic preparations are not effective for perineal pain after childbirth (**U**) (**Level I** [Cochrane Review]).
7. There is insufficient evidence to recommend any specific treatments for nipple pain and breast engorgement (**U**) (**Level I** [Cochrane Review]).

The following tick boxes represent conclusions based on clinical experience and expert opinion:

☑ Pain after childbirth requires appropriate treatment as it coincides with new emotional, physical and learning demands and may trigger postnatal depression (**U**).

☑ Management of breast and nipple pain should target the cause (**U**).

9.2 | The older patient

The need to manage acute pain in older patients is becoming more common as the population ages. Advances in anaesthetic and surgical techniques mean that increasingly older patients, including patients >100 y old (Konttinen 2006 **Level IV**), are undergoing major surgery (Kojima 2006 **Level IV**). Medical conditions are more likely in older people and may lead to acute pain; these include acute exacerbations of arthritis, osteoporotic fractures of the spine, cancer and also pain from other acute medical conditions including ischaemic heart disease, herpes zoster and peripheral vascular disease. Furthermore, older adults are more likely to undergo potentially painful medical procedures, and experience trauma as well as surgery.

Adults of advanced age are a particularly vulnerable group. Factors that can combine to make effective control of acute pain in the older person more difficult than in younger patients include: a higher prevalence of coexistent diseases and concurrent medications, which increases the risk of drug-drug and disease-drug interactions; the presence of common geriatric syndromes, including cognitive impairment and frailty; age-related changes in physiology, pharmacodynamics and pharmacokinetics; altered responses to pain; and difficulties with assessment of pain, including problems related to cognitive impairment (Gibson 2018 **NR**).

National guidelines on pain management in the elderly have been developed (APS 2019 **GL).** Specific geriatric perioperative guidelines have been developed for general surgery (Mohanty 2016 **GL**) and hip fracture surgery (ACSQHC 2016 **GL**).

Furthermore, the elderly may fail to report pain because they think it is a normal part of ageing, or they acquiesce to family members/medical staff or have fears about intervention or the unwanted effects of analgesics, especially opioids (Fine 2012 **GL**). Sensory impairment and social isolation may further impair the effective treatment of pain. Lastly, the relative paucity of dedicated age-specific research on pain and its management, including the lack of randomised controlled trials conducted in older populations compounds vulnerability due to the lack of appropriate evidence to help guide clinical practice (Reid 2015 **NR**). Information on the safety, efficacy and pharmacokinetics in the elderly patient (>65 y) is often missing from drug registration trials and regulatory body documents. A structured cross-sectional review of publicly available initial drug registration data (FDA) found that limited data on older patients was present in the following areas: pharmacokinetics (62%) and safety (42%) and efficacy (45%) (Ruiter 2019 **Level IV SR**).

9.2.1 | Physiology and perception of pain

Several reviews summarise the age-related changes that occur in the neurophysiology of nociception and pain perception (Gagliese 2005 **Level III-2**; Gibson 2018 **NR**; Farrell 2012 **NR**; Gibson 2004 **NR**; Yezierski 2012 **NR BS**). Compared with a younger person's nervous system, there are extensive changes in the older person's structure, neurochemistry and function of both peripheral and central nervous systems, including neurochemical deterioration of the opioid and serotonergic systems. Therefore, there may be changes in nociceptive processing, including impairment of pain-inhibitory systems.

9.2.1.1 | Neurophysiological changes

In the peripheral nervous system there is a decrease in the function and density of both myelinated and, particularly, unmyelinated peripheral nerve fibres (Kemp 2014 **EH**; Heft 2017 **NR**). There are also increased number of fibres with damage or degeneration and conduction velocity

slowing. In rats, reductions in substance P, CGRP and somatostatin levels have been reported (Yezierski 2012 **NR BS**). Similar structural and neurochemical changes have been noted in the CNS. In older humans, there are sensory neuron degenerative changes and loss of myelin in the dorsal horn of the spinal cord as well as reductions in substance P, CGRP and somatostatin levels. Age-related loss of neurons and dendritic connections is seen in the human brain, particularly in the cerebral cortex; including those areas involved in nociceptive processing. The synthesis, axonal transport and receptor binding of neurotransmitters also change. Opioid-receptor density is decreased in the brain but not in the spinal cord, and there may be decreases in endogenous opioids. However, the functional consequences of such age-related changes remain a subject of debate. Functional MRI studies show more age-related similarities than differences in the magnitude of activation in response to acute noxious mechanical stimulation (Cole 2010 **EH**; Farrell 2012 **NR**). A specific difference that has been identified was reduced activation in the middle insular cortex and primary somatosensory cortex in response to noxious heat (Tseng 2013 **EH**).

Variations in pain perception are best determined in controlled situations where the severity of the noxious stimulus is standardised, and psychopathology (such as impaired cognitive function or mood) is absent (Radinovic 2014 **Level IV**; Kunz 2009 **EH**). Assessment of variation can be done with experimental pain stimuli or, to a lesser extent, with standard medical procedures such as venipuncture and wound dressings.

Studies of the effects of experimental pain stimuli (brief noxious stimuli without tissue injury) on pain thresholds are conflicting and results depend on the type of stimulus used. Psychophysical studies using experimental pain provide limited evidence for a modest increase in pain threshold (ie reduced sensitivity to mild pain) with advancing age, particularly for thermal pain stimuli (Tseng 2013 **EH**; Gibson 2004 **NR**) and radiant more than contact heat (Lautenbacher 2017 **Level III-2 SR EH** [PRISMA], 31 studies [pain threshold], n=2,912; 9 studies (pain tolerance threshold], n=11,295). The results for electrical, mechanical and ischaemic stimuli are equivocal, with reports of no change or even decreased pain thresholds in adults of advanced age (El Tumi 2017 **Level III-2 SR EH** [PRISMA], 12 studies, n unspecified). Of note, there were racial differences similar to those found in younger patients and increased decrement in the lower extremities (Riley 2014 **Level III-3 EH**). The applicability of these experimental observations to pain occurring with tissue injury remains uncertain. These findings could indicate some deficit in the early warning function of pain with reduced capacity to identify a painful stimulus and that it might cause tissue injury (Hadjistavropoulos 2014 **NR**; Gibson 2006 **NR**). For example, in patients with an acute myocardial infarction, greater intensity of chest pain was inversely correlated with lower pain threshold (Granot 2007 **Level III-3 EH**); presentation and treatment of those patients with less pain may therefore be delayed.

Studies looking at age-related changes in pain tolerance are limited, but in general, using a variety of experimental pain stimuli, there is a reduced ability in older people to endure or tolerate intense pain (Farrell 2012 **NR**; Gibson 2003 **NR EH;**). Lessened ability to tolerate pain could mean that severe pain may have a greater impact on the more vulnerable older person.

Also, in the elderly, there are significantly smaller increases in pain thresholds following prolonged noxious stimulation and a prolonged recovery from hyperalgesia (Zheng 2009 **EH**; Gibson 2006 **EH**; Zheng 2000 **EH**). Using experimental pain stimuli in the elderly, there is a lower threshold for temporal summation (Lautenbacher 2012 **Level III-2 SR EH**, 25 studies, n= 13,580; Naugle 2017 **Level III-2 EH**, n=189; Gibson 2004 **EH**); older subjects showed temporal summation with trains of brief electrical stimuli at all stimulation frequencies, unlike younger subjects where this was not seen at the lower frequencies. Temporal summation of thermal stimuli was increased in older subjects vs younger subjects. Summation was more prolonged but otherwise temporal summation of pressure pain showed no age-related effects. After topical application of capsaicin, the magnitude and duration of primary hyperalgesia was similar in both older and younger

subjects but secondary hyperalgesia (tenderness) resolved more slowly in older people. The proposed underlying mechanism for these findings is impaired descending inhibitory mechanisms and reduced capacity to down-regulate after sensitisation thereby leading to prolonged recovery in the older person (Gagliese 2005 **NR**). Findings from human psychophysical studies support the contention of impaired function in endogenous pain inhibitory systems in older adults (Riley 2017 **Level III-2 EH**, n=17; Grashorn 2013 **Level III-2 EH**, n=64), and this is also consistent with many earlier animal studies (Gagliese 2000b **BS**).

9.2.1.2 | Clinical implications

Several clinical reports (summarised in Cole 2006 **Level III-3 EH**; Pickering 2005 **NR**; Gibson 2003 **NR**) suggest that pain symptoms and presentation may change in the older patient; pain becomes a less frequent or a less severe symptom of a variety of acute medical conditions. Examples of differences in reports of acute pain are commonly related to abdominal pain (eg associated with infection, peptic ulcer, cholecystitis, or intestinal obstruction) or chest pain (eg myocardial ischaemia or infarction or pneumonia) and are in general agreement with the experimental finding of increased pain thresholds in the older person.

Compared with the younger adult with the same clinical condition, the older adult may report less pain or atypical pain, report it later or report no pain at all (Pickering 2005 **NR**). Examples in older patients include the absence of right upper quadrant or epigastric pain in 85% with cholecystitis, in 30% of those with peptic ulcer disease and up to 90% with pancreatitis, while in those with advanced peritonitis, pain may be a symptom in only 55%. Chest pain is absent, or pain is atypical, in up to 33% of older patients with acute myocardial infarction and 50% with unstable angina. This suggests a contradiction to data on experimental pain (reduced tolerance to intense pain – see Section 9.2.1.1 above); however, many clinical states are characterized by moderate to strong pain, but not intense pain (approaching tolerance levels). Age-related decrease in the efficiency of ascending pathways (noted by an increased pain threshold) and a concomitant decrease in the efficiency of descending inhibitory pathways (as noted by reduced pain tolerance) may explain this discrepancy.

Pain intensity after surgery may also be less. Older patients, matched for surgical procedure, reported less pain in the postoperative period: pain intensity decreased by 10 to 20% each decade after 60 y of age (Thomas 1998 **Level III-2**). Older men undergoing radical prostatectomy reported less pain on a present pain intensity scale and MPQ (but not a VAS) in the immediate postoperative period and used less PCA opioid than younger men undergoing the same procedure (Gagliese 2003 **Level III-2**). In a study of pain following IV cannula placement (a relatively standardised pain stimulus), older patients reported significantly less pain than younger patients (WMD -15/100; 95%CI -26 to -4) (Li 2001 **Level III-2**). An observational study of patients undergoing painful procedures (wound care, drain and femoral sheath removal, tracheal suctioning, turning, and central line insertion) found there was no age-related difference in pain scores (NRS) between the young and the elderly (>65 y), however the younger patients reported more pain-related distress (Stotts 2007 **Level III-2**, n=5,957).

9.2.2 | Assessment of pain

The need for specific methods to assess pain in the elderly is recognised in national guidelines (Schofield 2018 **SR GL).** These also emphasise the need for education of healthcare staff in the use of patient appropriate pain assessment tools (Sirsch 2020 **SR GL**).

Even though cognitively impaired patients are just as likely as cognitively intact patients of the same age to have painful conditions and illnesses, the number of pain complaints and the reported pain intensity decreases with increasing cognitive impairment (Radinovic 2014 **Level IV**; Hadjistavropoulos 2014 **NR**; Lukas 2012 **NR**). Reasons for this could include diminished memory, impairment of capacity to report, or it could be that less pain is experienced.

Dementia

Studies in patients with dementia suggest that they may not experience less pain (Monroe 2014 **Level III-2**; Hadjistavropoulos 2014 **NR**). Functional MRI responses following mechanical pressure stimulation showed no evidence of diminished pain-related activity in patients with Alzheimer's disease vs age-matched controls, indicating that pain perception and processing were not diminished in these patients (Cole 2006 **Level III-2**). Moreover, in those with dementia, facial expressions are increased in response to controlled levels of noxious stimulation (Kunz 2009 **Level III-2 EH;** Kunz 2007 **Level III-2 EH**) and immediately following a uniform clinical pain stimulus, such as venipuncture, pain on mobilisation (Hadjistavropoulos 2014 **NR**) or dental local anaesthetic injection (Hsu 2007 **Level III-2**). The increased facial expressions in response to pain could suggest an increased sensitivity to pain in persons with dementia (Kunz 2007 **Level III-2**) or that facial actions represent a different aspect of the pain experience: a reflexive, automatic response which may be disinhibited in persons with cognitive impairment. In support of this conclusion, persons with dementia have also been found to display enhanced nociceptive flexion withdrawal reflexes (RIII) (Kunz 2009 **Level III-2 EH;** Kunz 2007 **Level III-2 EH**). In contrast, autonomic responses typically associated with the onset of acute pain (ie increased heart rate, blood pressure, galvanic skin resistance, breathing) appear to be blunted in persons with dementia (Plooij 2011 **Level III-2 SR EH,** 6 studies, n=395). Much of the typical elevation in autonomic indices occurs in anticipation of an impending painful stimulus, yet this anticipatory response is lacking in those with dementia (2 studies, n=135). Group differences in the poststimulus autonomic response, particularly in heart rate change, are less obvious (1 study, n=95) or unchanged (2 studies, n=103) including to stronger intensity pain (1 study, n=40).

Another study assessed the placebo component of analgesic therapies by looking at the effect of both "overtly applied" and "covertly applied" local anaesthetic on pain after venipuncture in patients with Alzheimer's disease (Benedetti 2006 **Level III-2**). The patients with reduced Frontal Assessment Battery scores (a measure of frontal executive function) had a reduced placebo component to their pain relief and dose increases were required to produce adequate analgesia.

Undertreatment of acute pain is more likely to occur in cognitively impaired patients (Forster 2000 **Level III-2**; Morrison 2000 **Level III-2**; Feldt 1998 **Level III-2**), although this may be improving (Paulson 2014 **Level III-2**).

Delirium

Acute perioperative neurocognitive disorders include delayed neurocognitive recovery (dNCR - formerly postoperative cognitive dysfunction) and delirium (Evered 2018 **NR**). From a pain management perspective, delirium is the more significant. Delirium is an acute deterioration in cognitive state associated with a fluctuating course, inattention, confusion and altered conscious state. It is most common in the elderly, especially those with pre-existing cognitive impairment, and occurs in medical patients and in up to 65% of postoperative patients. Delirium is associated with increased postoperative morbidity, impaired rehabilitation and prolonged hospital LOS (O'Regan 2013 N**R**). It is also prevalent during acute illnesses in the older person. It is estimated that delirium can be prevented in up to 40% of hospitalised patients; risk factors including age,

infection, emergency surgery, pre-existing cognitive impairment, metabolic disturbance, polypharmacy and unrelieved pain (Thompson 2018 **Level IV**, n=668; American Geriatrics Society 2015 **GL**).

Delirium presents clinically in both hyperactive and hypoactive forms, of which the latter is more common (Rudolph 2011 **NR**) and mixed forms can occur. Although restlessness and agitation (hyperactive delirium) may trigger assessment, which identifies a trigger associated with pain, the more frequent hypoactive delirium may mask pain, especially in the elderly.

Effective pain management contributes to strategies to reduce the incidence of delirium, but some analgesics, especially opioids, also contribute to delirium either through anticholinergic activity (eg pethidine) or by causing sedation and confusion (Swart 2017 **Level III-2 SR,** 6 studies, n≈22,000; American Geriatrics Society 2015 **GL**).

9.2.2.2 | Measurement of pain

Patient self-report measures of pain

Unidimensional measures of pain intensity are more commonly used to quantify pain in the acute pain setting than multidimensional measures (see also Section 2.2). Unidimensional measures used in younger adult populations, and which have been shown to be appropriate for use in the older patient, include the VNRS, FPS, VDS alone and with calorimetry (Iowa pain thermometer) and the NRS, with equivocal support for use of the VAS (Hadjistavropoulos 2014 **NR;** Paulson 2014 **NR**). Completion rate is high for VNRS in the older patient but this decreases with increasing cognitive impairment. Several studies confirm that VDS is often the preferred tool and use of familiar words such as “none, slight, mild, moderate, severe and extreme” is felt to be the most reliable in the older patient, including those with mild to moderate cognitive impairment. Trialling of different self-assessment scales may be warranted including in those with severe impairment and the patients may need more time to understand and respond to questions regarding pain. Immediate reports of present pain may be reasonably accurate and as valid as those of cognitively intact patients but recall of past pain is less likely to be as reliable. Further comparative studies in the elderly include patients with fractured hips (Leino 2011 **Level IV**) and after cardiac surgery (Pesonen 2008 **Level IV**), where VAS was also the least reliable and the VDS and Red Wedge Scale were most applicable.

Other measures of pain

Assessment of pain in noncommunicative patients is more difficult. Behaviours such as restlessness, frowning and grimacing or sounds such as grunting or groaning have been used in attempts to assess pain. In cognitively intact adults, some of these behaviours have been shown to correlate with patient self-report of pain (Bell 1997 **NR**). However, they may not always be valid indicators of pain in the nonverbal adult (Farrell 1996 **NR**) and can be difficult to interpret (Herr 2011 **NR**; Herr 2006 **NR**).

There is some argument that observations of facial expressions and sounds may be accurate measures of the presence of pain but not pain intensity in patients with advanced dementia (Herr 2006 **NR**), although this position has been challenged in recent studies (Lukas 2013 **Level III-2**).

More than 28 different observational pain assessment scales have been developed and used in patients with varying degrees of dementia (Lichtner 2014 **Level IV SR of SRs**, 8 SRs; Herr 2011 **NR**). Scales with the strongest evidence of utility include: FPSs, Abbey Pain Scale, Pain Assessment in Advanced Dementia (PAINAD) (a simple, reliable and validated five-item observational tool), Pain Assessment Checklist for Seniors with Limited Ability to Communicate and Mobilization-Observation-Behavior-Intensity-Dementia Pain Scale.

For more detailed and critical review of pain-assessment tools for use with nonverbal adults see (Lichtner 2014 **Level IV SR of SRs**, 8 SRs; Hadjistavropoulos 2014 **NR**; Herr 2011 **NR**; Herr 2006 **NR**; Zwakhalen 2006 **NR**).

See also Section 2.2.

9.2.3 | Pharmacokinetic and pharmacodynamic changes

The changes in physiology and effects on pharmacokinetics and pharmacodynamics in older people, and consequent alterations that might be required in some drug regimens are summarised in Table 9.4. The information in this table centres on opioids, given their widespread use. These changes have variable prevalence and are generally attributable to ageing alone but may be compounded by the higher incidence of degenerative and other concurrent diseases in older people.

Assessment of the pharmacodynamic changes associated with ageing is difficult. When such studies have been done with opioids, most have used a surrogate measure of effect other than clinical pain relief. For example, in studying the effects of fentanyl and alfentanil on the EEG, the pharmacokinetics were shown to be unaffected by age, but the sensitivity of the brain to these opioids was increased by 50% in the older person (Scott 1987 **EH**). It is unclear whether this can be attributed to changes in the number or function of opioid receptors in the CNS (in older rats there are fewer mu- and kappa-opioid receptors) (Yezierski 2012 **NR BS**; Vuyk 2003 **NR**), or whether it is due to an increased penetration of opioids into the CNS. Some of the changes that may lead to increased drug sensitivity in the older patient are discussed below; see Section 9.2.2 above.

Table 9.4 | Physiological changes in older people, resulting changes of pharmacokinetic variables and consequences for pharmacological treatment

Body system or process	Parameter and changes	Resulting pharmacokinetic/ pharmacodynamic changes	Changes in pharmacological treatment
Body composition	body fat ↑ 10–50%	for lipophilic medicines ↑ V_d ↑ $t_{1/2}$	calculate doses of lipophilic medicines on total body weight
	muscle ↓ 20%	no relevant effect	none
	body water ↓ 10%	for hydrophilic medicines ↓ V_d	calculate doses of hydrophilic medicines based on lean body weight
	plasma volume ↔	None	none
Liver	Liver size ↓ 25–40%	↑ bioavailability of oral medicines ↓ hepatic CL of high extraction medicines (eg morphine)	↔ IV bolus dose ↓ oral dose of some medicines
	Hepatic blood flow ↓ 25–40%		

Body system or process	Parameter and changes	Resulting pharmacokinetic/ pharmacodynamic changes	Changes in pharmacological treatment
	Phase 1 metabolism ↓ 25%	↓ hepatic CL of some low extraction medicines (eg ibuprofen	↓ maintenance doses of some medicines (eg morphine)
Kidney	Kidney size ↓ 30%	↓ clearance of renally excreted medicines ↔ effect on opioids, but often clearance of metabolites (eg morphine [M6G], tramadol [M1])	↓ maintenance dose of renally excreted medicine (alpha-2-delta ligands: gabapentin, pregabalin) or medicines with renally excreted metabolites (morphine, tramadol, pethidine) monitor for accumulation of renally excreted medicines
	Renal blood flow ↓ 10% / decade		
	GFR ↓ 30–50%		
	Creatinine clearance (Cl) ↓ 50–70%		
Heart	Cardiac output ↔ or ↓ to 20%	↓ central compartment volume ↑ peak concentration after IV bolus	↓ initial IV bolus doses ↓ IV injection speed
CNS	Cerebral blood flow, volume and metabolism ↓ 20%	↓ distribution to the CNS ↓ apparent volume in the CNS	minimal clinically relevant changes for most drugs, but: ↓ bolus doses of medicines during titration ↓ maintenance doses of some medicines
	Blood brain barrier transport ↓ (medicine specific effect)	↑ apparent volume in the CNS ↑ apparent increase in CNS sensitivity	
Absorption of Medicines	oral and transmucosal absorption	no relevant effect of ageing	however oral bioavailability of some medicines due to first-pass effect
	IM absorption	↔	none
	SC absorption	↔	none
	transdermal absorption	↓ hydrophilic medicines ↔ lipophilic medicines	no clinically relevant effect for TD opioids
Protein binding of medicines	Plasma albumin ↓ 20%	↑ unbound fraction of medicines	

Body system or process	Parameter and changes	Resulting pharmacokinetic/ pharmacodynamic changes	Changes in pharmacological treatment
	Alpha-1-acid glycoprotein ↑ 30–50%	↑ cerebral uptake of medicines ↔ hepatic clearance of high extraction medicines ↑ hepatic clearance of low extraction medicines	possibly changed clearance and oral bioavailability possibly changed cerebral effects

Source: Modified and adapted from Macintyre 2008 and Coldrey 2011

9.2.4 | Drugs used in the management of acute pain in older people

In general, there is limited evidence about the use of analgesic medications in older patients; as because of their age, comorbidities or concurrent medications, they are often specifically excluded from clinical trials (McLachlan 2011 **NR**).

The American Society of Geriatrics publishes and regularly updates a list of drugs that can be associated with increased adverse effects when used in the elderly: American Geriatrics Society Updated Beers Criteria® for Potentially Inappropriate Medication Use in Older Adults (American Geriatrics Society 2019 **GL**). This list comprises drugs that should be prescribed with caution in the elderly, as well as drug-drug interactions and drugs which have additional risk in specific disease states.

Drugs used to treat pain which are on the list include:

- Pethidine – may cause delirium
- nsNSAIDs – risk of GI bleeding in high risk groups, including > 75 y
- Drugs with anti-cholinergic effects – tricyclic antidepressants (TCA), hyoscine
- Falls risk – opioids, antidepressants (TCA, SSRI, SNRI), clonidine (CNS effects, orthostatic hypotension)
- Opioids in combination with gabapentin or pregabalin – this combination increases risk of sedation, OIVI and death.
- Heart failure – caution with nsNSAIDs and Coxibs (avoid if symptomatic heart failure)
- Cognitive impairment – drugs with anticholinergic effects eg TCAs
- Chronic kidney disease (GFR < 30 mL/min) – nsNSAIDs, Coxibs
- Hyponatraemia or Risk of Syndrome of inappropriate antidiuretic hormone secretion (SIADH) – SNRIs, SSRIs, TCAs, Tramadol

Concern is often expressed about the safety of pharmacological approaches to pain management in older adults due to the increased risk of adverse drug reactions. Analgesics may be responsible for >5% of adverse drug reactions and can lead to emergency department visits in the older population (Oscanoa 2017 **Level IV SR**, 42 studies, n>≈7,000,000 [>≈265,000 admissions]; Shehab 2016 **Level IV**, n=42,585); only anticoagulants and antidiabetic agents result in more frequent admissions (Shehab 2016 **Level IV**, n=42,585). Older patients are particularly vulnerable to adverse drug reactions because of the age-associated changes in pharmacokinetics and pharmacodynamics. In addition, comorbid medical conditions and geriatric syndromes that commonly occur in older people can increase adverse drug reactions (eg for NSAIDs) (Bhala 2013

Level I, 754 RCTs, n=353,809). For instance, the presence of frailty, defined as "*a progressive age-related decline in physiological systems, which confers extreme vulnerability to stressors and increases the risk of a range of adverse health-outcomes*" (WHO 2015 **NR**) may raise several concerns in formulating an appropriate pharmacological treatment of pain (Lohman 2017 **Level IV**, n=3,652). Frailty is often characterised by the coexistence of multiple diseases states, resulting in multiple medications with increasing risk of drug-drug and drug-disease interactions, and an associated increase in the risk of adverse drug reactions (Onder 2018 **GL**). The known association between frailty and inflammation may potentially down-regulate drug metabolism and transporter pathways, thereby impacting upon the clinical pharmacology of analgesics (McLachlan 2011 **NR**). Likewise, frailty is often characterized by chronic undernourishment, which could alter the distribution of some drugs as well as changes in pharmacokinetic parameters (Onder 2018 **GL**). Therefore, when pain medications are prescribed in older adults it is important to consider their potential side effects, but also possible interacting drugs or diseases in order to prevent ADRs.

While this and the following section concentrate on the use of analgesic drugs and techniques in the older patient, physical and psychological strategies should also be employed as with other patients (APS 2019 **GL**; Abdulla 2013 **GL**; Makris 2014 **NR)**.

9.2.4.1 | Paracetamol, nonselective NSAIDs and Coxibs

Paracetamol is recommended as a first-line therapy in older adults for both mild to moderate pain (Abdulla 2013 **GL**; O'Neil 2012 **GL**; American Geriatrics Society 2009 **GL**; Makris 2014 **NR**). There is inconsistent evidence on the effect of ageing and frailty on clearance of paracetamol, with earlier authors recommending no dose adjustment (Bannwarth 2001 **PK**; Miners 1988 **PK**; Divoll 1982 **PK**) but more recent reviews recommending that dose adjustment is prudent (McLachlan 2011 **NR**; Mitchell 2011b **NR**). In a small cohort comparison, spot paracetamol plasma concentrations on d 5 of 3 to 4 g/d therapy were in the therapeutic range in 21 of 23 older and frail older patients and elevated in 2 (but less than twice therapeutic range) (Mitchell 2011a **Level III-3**, n=71). Plasma alanine aminotransferase (ALT) levels after 5 d were not elevated in any of the older and frail participants. Overdose may lead to severe hepatotoxicity and the wide availability of paracetamol often marketed under different names, presentations and combinations may increase this risk in older persons living at home (Tittarelli 2017 **NR**). A detailed review of paracetamol induced liver injury found no good quality evidence to indicate that older patients are at increased risk of liver injury when treated with paracetamol at normal doses (Caparrotta 2018 **NR**)

NSAIDs may offer more effective control of inflammatory pain, but older patients are more likely to suffer gastric and renal adverse effects following administration of nsNSAIDs (Abdulla 2013 **GL**) and may also be more likely to develop cognitive dysfunction (Juhlin 2005 **Level II**, n=14, JS 4; Pilotto 2003 **Level III-2**; Peura 2004 **NR**) (see also Section 4.2). In elderly (age >65 y) medical inpatients, use of nsNSAIDs was a significant risk factor for renal function deterioration occurring in 6.1% of patients exposed; other risk factors were loop diuretics, hypernatraemia and low serum albumin levels (Burkhardt 2005 **Level IV**, n=343). Use of oral nsNSAIDs often does not align with current clinical guidelines in the older population and particularly regarding the prolonged duration of use and lack of PPI coadministration (Gnjidic 2014 **Level III-2**).

NSAIDs should be used with care in elderly patients given their cardiovascular, gastrointestinal and renal adverse effects, and patients should be monitored closely (O'Neil 2012 **GL**; Fine 2004 **GL**; Makris 2014 **NR**). For this reason, opioids are sometimes used in preference to NSAIDs. A cohort study of elderly patients with arthritis (mean age 80 y) started on nsNSAIDs, coxibs or opioids challenge the assumption that opioids are safer in this population (Solomon 2010

Level III-2, n=12,840). This study found increased rates of fracture, hospital admission and all-cause mortality in the opioid cohort and similar or higher rates of cardiovascular, renal and gastrointestinal adverse effects. Overall the nsNSAID cohort appeared to have the lowest risk for adverse effects.

Coxibs have a significantly lower incidence of upper gastrointestinal complications (Jarupongprapa 2013 **Level I**, 9 RCTs, n=7,616) and have no antiplatelet effects (Munsterhjelm 2006 **Level II EH**, n=18, JS 4), which might be of some advantage in the older patient. The risk of other adverse effects, including effects on renal function (Zhang 2006 **Level I**, 114 RCTs, n=116,094), hypertension and exacerbation of cardiac failure may be lower too, at least for celecoxib (see Section 4.2.2.2). Compared with paracetamol and placebo, only transient reduction of creatinine clearance was seen after 3 d treatment with parecoxib 40 mg/d in elderly patients undergoing major orthopaedic surgery (Koppert 2006 **Level II**, n=75, JS 5).

Use of both coxibs and nsNSAIDs (possibly lowest with naproxen and celecoxib) can increase the risk of cardiovascular and cerebrovascular events (Trelle 2011 **Level I**, 31 RCTs, n=116,429) and regular use of nsNSAIDs may interfere with the clinical benefits of low-dose aspirin (for details see Section 4.2). Extra precautions are therefore required in older patients.

Topical nsNSAID agents may be a preferred route of administration (due to lower systemic levels and less gastrointestinal adverse effects) in older adults where there is appropriate and localised pain (Massey 2010 **Level I** [Cochrane] 47 RCTs, n=3,455; Klinge 2013 **Level I**, 6 RCTs, n=600; Zacher 2008 **Level I**, 19 RCTs, n>≈3,000; Makris 2014 **NR**) (significant overlap between all three SRs) (see also Section 4.2.3.6).

9.2.4.2 | Conventional and atypical opioids

Despite the age-related changes listed in Table 9.4, there may be few differences in the older patient in fentanyl (Scott 1987 **EH**), morphine, oxycodone (Villesen 2007 **PK**) and buprenorphine pharmacokinetics (Kress 2009 **NR**).

After oral administration, the bioavailability of some drugs may be increased, leading to relatively higher plasma concentrations (Gupta 2012 **NR**; Mangoni 2004 **NR**).

Opioid dose

Older patients require less opioid than younger patients to achieve the same degree of pain relief (Gagliese 2000a **Level IV**; Woodhouse 1997 **Level IV**; Macintyre 1996 **Level IV**; Upton 2006 **PK**); however, a large interpatient variability still exists and doses must be titrated to effect in all patients. The decrease is much greater than would be predicted by age-related alterations in physiology and seems to have a significant pharmacodynamic component (Gupta 2012 **NR**; Macintyre 2008 **NR**).

In the clinical setting, there is evidence of an age-related 2 to 4-fold decrease in morphine and fentanyl requirements (Gagliese 2000a **Level IV**; Woodhouse 1997 **Level IV**; Macintyre 1996 **Level IV**). The decrease is in agreement with previous findings that the sensitivity of the brain to fentanyl and alfentanil was increased by 50% in older people (Scott 1987 **EH**). It has been suggested that doses of fentanyl, sufentanil and alfentanil should be reduced by up to 50% in older patients (Shafer 1997 **NR**); reductions in the doses of other opioids are also advised (Macintyre 2008 **NR**). In general, patients aged 80 y should receive 50% of the opioid dose of a 40-y-old patient due to pharmacodynamic changes and increased sensitivity (Gupta 2012 **NR**).

In patients >75 y, the elimination half-life of tramadol is slightly prolonged (Scott 2000 **NR**); lower daily doses have been suggested (Barkin 2005 **NR**). Awareness and consideration of drug interactions in the elderly is necessary, particularly with the high incidence of polypharmacy and antidepressant use (Makris 2014 **NR**).

Opioid metabolites

Reduced renal function in the older patient could lead to a more rapid accumulation of active opioid metabolites (eg M6G, M3G, H3G, nordextropropoxyphene, norpethidine and M1) (see Section 4.1).

Adverse effects of opioids

The concern regarding respiratory depression in older people, especially those with respiratory disease, often leads to inadequate doses of opioid being given for the treatment of their pain. However, as with other patients, significant respiratory depression can generally be avoided if appropriate monitoring (in particular, of sedation) is in place (see Section 4.3.1.4).

The incidence of nausea/vomiting and pruritus in the postoperative period lessens with increasing age (Quinn 1994 **Level IV**). In older patients, IV PCA fentanyl may cause less postoperative cognitive dysfunction than morphine (Herrick 1996 **Level II**, n=96, JS 2). There is an increased risk of delirium in the elderly with use of pethidine (Swart 2017 **Level IV SR**, 3 studies [pethidine], n=877) and tramadol (Swart 2017 **Level IV SR**, 1 study [tramadol]: Brouquet 2010 **Level IV**, n=133) and a potential protective effect with fentanyl and hydromorphone; however, the underlying studies are small and of low quality. However, administration of an appropriate opioid medication is often associated with higher levels of cognitive function and undertreatment of postoperative pain with lower levels (Morrison 2000 **Level III-2**, n=541; Lynch 1998 **Level IV**). Constipation is a common adverse effect of treatment with opioids and is a relevant consideration in older adults, many of whom already exhibit altered gastrointestinal function. Prophylactic management of constipation should be commenced whenever opioids are prescribed (Hunold 2013 **Level IV**; Makris 2014 **NR**).

See also Section 4.3.1.4

9.2.4.3 | Local anaesthetics

Age-related decreases in clearance of bupivacaine (Veering 1987 **Level III-2**; Veering 1991 **PK**) and ropivacaine (Simon 2006 **PK**) have been shown. Older patients may be more sensitive to the effects of local anaesthetic agents because of a slowing of conduction velocity in peripheral nerves and a decrease in the number of neurons in the spinal cord (Sadean 2003 **NR**). Localised neuropathic pain may be suitable for treatment with topical lignocaine (lidocaine) patch, in particular in older patients with increased comorbidities and polypharmacy, as systemic adverse effects are rare (Finnerup 2015 **GL Level I** [PRISMA], 229 RCTs, n unspecified; Fine 2012 **GL**; Makris 2014 **NR**).

9.2.4.4 | Ketamine

There are no good data on the need or otherwise to alter ketamine doses in the older patient. In aged animals, however, changes in the composition of the NMDA-receptor site and function have been reported (Clayton 2002 **BS**; Magnusson 2002 **BS**; Vuyk 2003 **NR**). Young and elderly rats, given the same dose of ketamine on a mg/kg basis showed similar EEG changes but these changes were quantitatively greater in the older rats (Fu 2008 **BS**). These data suggest that, apart from any pharmacokinetic changes, the older person may be more sensitive to the effects of ketamine and doses may need to be lower in this patient group.

9.2.4.5 | Tricyclic antidepressants

Clearance of TCAs may decrease with increasing patient age and lower initial doses are recommended in older people (Ahmad 2002 **NR**).

Older people may be particularly prone to the adverse effects of TCAs (Abdulla 2013 **GL**; Fine 2004 **GL**; Ahmad 2002 **NR**) including sedation, confusion, orthostatic hypotension, dry mouth, constipation, urinary retention, and increased risk of mortality and dementia (Coupland 2019 **Level III-2**, n=284,343; Fox 2011 **Level III-2**). Adverse effects appear to be most common with amitriptyline, and so nortriptyline may be preferred in this patient group (Argoff 2005 **NR**; Ahmad 2002 **NR**). Clinical conditions that may require TCAs to be administered with caution are more common in older people and include prostatic hypertrophy, narrow-angle glaucoma, cardiovascular disease and impaired liver function; ECG abnormalities may be a contraindication to the use of TCAs in older people (Ahmad 2002 **NR**).

Overall in elderly patients, TCAs should generally be avoided, as the use of medications with anticholinergic activity increases the risk of cognitive impairment and even mortality in this patient group (Fox 2011 **Level III-2**).

9.2.4.6 | Serotonin–norepinephrine-reuptake inhibitors

Duloxetine has been shown to be effective and safe for the treatment of painful diabetic peripheral neuropathy in older patients (mean age 60 y) (Goldstein 2005 **Level II**, n=547, JS 4). Duloxetine was effective and well tolerated for the treatment of osteoarthritis pain of the knee in older patients (mean age 62 y) (Chappell 2009 **Level II**, n=231, JS 4).

9.2.4.7 | Anticonvulsants

As liver and renal function decline with increasing age, elimination of anticonvulsants such as carbamazepine and gabapentin may be reduced (Ahmad 2002 **GL**). As with TCAs, initial doses should be lower than for younger patients and any increases in dose should be titrated slowly.

The “second generation” drugs such as gabapentinoids and topiramate may be less likely to result in adverse effects in the older patient (Argoff 2005 **NR**), although the relatively high frequency of adverse effects such as somnolence and dizziness with pregabalin may be a problem in this group of patients (Goodman 2017 **NR**; Guay 2005 **NR**). However, pooled data from RCTs with pregabalin in neuropathic pain showed an increase of adverse effects only with increasing doses, but not related to the age of patients (Semel 2010 **Level III-3**, n=2,516 [65 to 74 y: n=766] & [≥75 y: n=514]). Efficacy was comparable to that in younger age groups; the lack of drug interactions may be an advantage in particular in older patients.

9.2.5 | Patient-controlled analgesia

PCA is an effective method of pain relief in older people but its use may be limited by the presence of cognitive impairment or development of postoperative delirium (Mann 2000 **Level II**, n=70, JS 3; Gagliese 2000a **Level III-2**; Mann 2003 **NR**). Compared with younger patients (mean age 39 y), older patients (mean age 67 y) self-administered less opioid than the younger group but there were no differences in pain relief achieved, satisfaction with pain relief and pain scores or concerns about pain relief, adverse drug effects, risks of addiction or use of the equipment (Gagliese 2000a **Level III-2**).

Compared with IM morphine analgesia in older men, PCA resulted in better pain relief, less confusion and fewer severe pulmonary complications (Egbert 1990 **Level II**, n=83, JS 2). In older patients, PCA also resulted in significantly lower pain scores vs intermittent SC morphine injections (Keita 2003 **Level II**, n=40, JS 3).

9.2.6 | Epidural analgesia

In the general patient population, epidural analgesia can provide the most effective pain relief of all analgesic therapies used in the postoperative setting (see Section 5.6). Epidural analgesia significantly reduces many of the complications that occur in the elderly after surgery (Popping 2014 **Level I** [PRISMA], 125 RCTs, n=9,044). Older patients given epidural PCA using a mixture of bupivacaine and sufentanil had lower pain scores at rest and movement, higher satisfaction scores, improved mental status and more rapid recovery of bowel function vs use of IV PCA (Mann 2000 **Level II**, n=70, JS 3). After hip fracture surgery, epidural analgesia with bupivacaine and morphine also provided better pain relief both at rest and with movement but this did not lead to improved rehabilitation (Foss 2005 **Level II**, n=60, JS 5). Epidural analgesia, after colectomy for cancer in patients aged >65 y of age, may be associated with improved long-term survival (Cummings 2012 **Level III-2**, n=42,151). Patients having colectomy for cancer had better 5-y survival in the epidural group vs the nonepidural group (61 v 55%; HR 0.91; 95%CI 0.87 to 0.94). In a retrospective study, epidural analgesia was associated with reduced cancer recurrence in patients aged >64 y having colectomy (Gottschalk 2010 **Level III-2**). The postulated mechanism is reduced impairment of immune function in patients having epidural analgesia, although overall data are contradictory (see also Section 5.6.1.2).

Older patients are more likely to have ischaemic heart disease where coronary blood flow may be reduced rather than increased in response to sympathetic stimulation. In a study of patients (average age 67 y) with multivessel coronary artery disease, high (T2 to T3) thoracic epidural analgesia using 0.5% bupivacaine instituted before CABG surgery was able to partly normalise myocardial blood flow in response to sympathetic stimulation (Nygard 2005 **Level III-2**). In a small trial of perioperative analgesic regimens initiated preoperatively for hip fracture repaired under spinal anaesthesia, older patients who had received epidural bupivacaine/fentanyl analgesia had significantly better postoperative pain relief than those who were given IM oxycodone; there was no difference in the number of patients who developed postoperative continuous ECG-detected ischaemia or hypoxia (Scheinin 2000 **Level II**, n=77, JS 3). However, the number of episodes and total duration of ischaemia in each patient was markedly greater in the oxycodone group.

Epidural morphine requirements decrease as patient age increases (Ready 1987 **Level IV**). However, a comparison of PCA epidural fentanyl in patients aged >65 y with those aged 20–64 y showed no difference in fentanyl requirements or pruritus; although pain relief on coughing at 24 h was better in the older patient group (Ishiyama 2007 **Level III-3**).

Age is also a determinant of the spread of local anaesthetic in the epidural space and the degree of motor blockade (Simon 2004 **Level III-2**; Simon 2002 **Level III-2**). Thus, smaller volumes may be needed to cover the same number of dermatomes than in a younger patient. When the same volume of local anaesthetic was given, the concentration required to produce effective motor block decreased as patient age increased (Li 2006 **Level III-1**). Combinations of a local anaesthetic and opioid are commonly used for epidural analgesia, so it would seem reasonable to use lower infusion rates in older patients (Macintyre 2008 **NR**).

Older patients may be more susceptible to some of the adverse effects of epidural analgesia, including hypotension (Simon 2002 **Level III-2**; Crawford 1996 **Level IV**; Veering 2006 **NR**).

9.2.7 | Intrathecal opioid analgesia

IT morphine using a variety of doses provided more effective pain relief after major surgery vs other opioid analgesia, although the risk of respiratory depression and pruritus was greater (Meylan 2009 **Level I**, 27 RCTs, n=645).

With neuraxial opioids, advanced patient age is considered by some to be a risk factor for respiratory depression and it has been suggested that patients >70 y be monitored in an ICU setting (Gwirtz 1999 **Level IV**). However, others report that older patients (average age 69 y) given up to 200 mcg IT morphine at the time of spinal anaesthesia for peripheral vascular and other surgery have been safely nursed on general wards by nursing staff who have received additional education and managed by an APS according to strict guidelines (Lim 2006 **Level IV**).

The optimal dose of IT morphine for older patients remains unknown. The evidence for the "best" dose is provided by data from small trials and remains inconsistent. IT morphine doses of 200 mcg given in addition to general anaesthesia in older patients (average age 70 y) undergoing abdominal aortic surgery led to better postoperative analgesia and reduced postoperative analgesia requirements vs general anaesthesia only (Blay 2006 **Level II**, n=30, JS 4). No conclusion could be made about adverse effects, as total patient numbers were small. A comparison of three doses of IT morphine (50 mcg, 100 mcg and 200 mcg) given to older patients after hip surgery concluded that the 100 mcg dose provided the best balance between good pain relief and pruritus (Murphy 2003 **Level II**, n=60, JS 4). There was no difference seen in the incidences of nausea and vomiting or respiratory depression.

Use of IT morphine 300 mcg in addition to IV PCA morphine in elderly patients led to better pain relief and PCA morphine requirements vs PCA morphine alone (Beaussier 2006 **Level II**, n=59, JS 5). However, sedation was increased and there were no differences in time to ambulation, hospital LOS or incidence of confusion.

9.2.8 | Other regional analgesia

The advantages of regional block in older patients include improved pain relief and a reduction of the adverse effects of opioids (Halaszynski 2009 **NR**). After hip fracture fixation, those who received patient-controlled femoral nerve analgesia, in addition to regular paracetamol and metamizol, were less likely to develop postoperative delirium, were able to sit at the bedside at an earlier stage, and required no SC morphine vs those getting paracetamol and metamizol only (28% required additional morphine analgesia) (Rosario 2008 **Level III-3**).

The duration of action of sciatic nerve (Hanks 2006 **Level III-2**) and brachial plexus blocks (Paqueron 2002 **Level III-2**) is prolonged in the older patient.

In older (>65 y) patients undergoing urological surgery via a flank incision, PVB of the lumbar plexus using either ropivacaine or bupivacaine has been shown to provide good analgesia with no changes in the patients' heart rate or blood pressure (Akin 2005 **Level II**, n=60, JS 1).

Unlike epidural analgesia, age did not influence the spread of bupivacaine in the thoracic paravertebral space (Cheema 2003 **Level III-2**).

KEY MESSAGES

1. Topical nsNSAIDs for localised pain provide effective analgesia (**U**) (**Level I** [Cochrane Review] with lower plasma concentrations and fewer gastrointestinal adverse effects than oral nsNSAIDs (**U**) (**Level I**); this may improve safety in the elderly.
2. PCA and epidural analgesia are more effective in older people than conventional opioid regimens (**U**) (**Level II**).
3. Experimental pain thresholds to thermal stimuli are modestly increased in older people (**U**) (**Level III-2 SR**).

4. Reported frequency and intensity of acute pain in clinical situations may be reduced in the older person (**U**) (**Level III-2**).
5. Common unidimensional self-report measures of pain can be used in the older patient in the acute pain setting, but need to be appropriate for the individual patient; the verbal descriptor and numerical rating scales are preferred in patients who can self-report (**U**) (**Level III-2**), while in the older patient with cognitive impairment, specific pain assessment tools are more appropriate (**N**) (**Level IV SR**).
6. Undertreatment of acute pain is more likely to occur in cognitively impaired patients (**U**) (**Level III-2**).
7. The use of nsNSAIDs and coxibs in older people requires caution, although use of opioids may result in more complications (**U**) (**Level III-2**); paracetamol is the preferred nonopioid analgesic (**U**) (**Level III-2**).
8. The under-representation of older patients in clinical drug trials limits information about efficacy, safety and pharmacokinetics of many types of medications including analgesic medications **(N) (Level IV SR**}
9. The older patient is at increased risk from adverse effects of medications including many analgesics (**N**) (**Level IV**).
10. Delirium is common in elderly hospitalised patients, including after surgery; risk factors include inadequate pain management and excessive use of opioids and other sedating analgesics (**N**) (**Level IV**).
11. There is an age-related decrease in opioid requirements; significant interpatient variability persists (**U**) (**Level IV**).
12. The age-related decrease in opioid requirements is related more to the changes in pharmacodynamics that accompany ageing than to the changes in pharmacokinetics (**U**) (**Level IV).**

The following tick box represents conclusions based on clinical experience and expert opinion:

☑ The assessment of pain and evaluation of pain relief therapies in the older patient may present problems, arising from differences in reporting, cognitive impairment and difficulties in measurement (**U**).

☑ Measures of present pain may be more reliable than past pain, especially in patients with some cognitive impairment (**U**).

☑ The physiological changes associated with ageing are progressive; while the rate of change can vary markedly between individuals and is related to frailty, these changes may decrease the dose (maintenance and/or bolus) of drug required for pain relief and may lead to increased accumulation of active metabolites (**U**).

☑ The high prevalence of frailty in the older patient is an independent risk factor for increased adverse drug effects to analgesic medications (**N**).

☑ The use of regional analgesics techniques, as an alternative to systemic analgesics, can confer benefits of improved pain relief, and minimise adverse effects (cognitive, pulmonary) (**N**).

☑ Cognitive impairment in the older patient may limit the appropriate use of PCA (**N**).

9.3 | Culturally responsive care for Culturally and Linguistically Diverse patients

Growth in the cultural, linguistic and religious diversity of the Australian community reflects the diversity of migrant communities from many countries, this being a clear shift from early migrant communities predominantly of European background. The 2016 Census states that about 49% of Australians were born overseas or have at least one parent born overseas and 21 % speak a language other than English with slight variations across states (ABS 2017). The Aboriginal and Torres Strait Islander community comprises 2.8% of the total population. The five most common languages spoken at home (other than English) were Mandarin (2.5%), Italian (1.2%), Vietnamese (1.2%), Arabic (1.4%), Cantonese (1.2%) and Greek (1.0%). The top five non-Christian religions in 2016 were Islam (2.6% of the population), Buddhism (2.4%), Hinduism (1.9%), Sikhism (0.5%) and Judaism (0.4%). The New Zealand 2018 census (Stats NZ 2019) shows the following ethnic groups: European (64.1%), Māori (16.5%), Chinese (4.9%), Indian (4.7%), Samoan (3.9%); with the top 3 foreign countries of birth being England (4.5%); Peoples Republic of China (2.9%) and India (2.5%) and the languages spoken at home (other than English) were te reo Māori (4%), Samoan (2.2%), Northern Chinese (including Mandarin) (2%), and Hindi (1.5%).

Economic globalisation and current world events are compelling many communities to seek a home elsewhere. This facilitates ongoing migration, which has a direct impact on the cultural diversity of many countries. A major '*immigration nation*', Australia has been made home by over 7.5 million people since 1945 (Phillips 2017 **NR**). Recent migration patterns and the humanitarian program in Australia have resulted in the arrival of a variety of cultural groups, the majority of which came from Iraq, Syria, Afghanistan and Myanmar in 2016-17 (Refugee Council of Australia 2019).

Culture, language and religious convictions have an impact on the clinical encounter. This background drives a need to understand different cultures when considering pain assessment and management. This extends beyond the language spoken, because an individual's culture, faith and migration history influence their linguistic expression, metaphorical language, beliefs, attitude, need for social support, framework of meaning, health literacy, expectations, perception, methods of communication, norms of behaviour and pain relief preferences. This also applies to the culture and attitudes of the health professional (Xu 2018 **Level III-2**; Al-Harthy 2016 **Level III-2**; Holt 2018 **Level IV**; Park 2017 **Level IV**; Martin 2017 **Level IV**; Rahavard 2017 **NR**; Brady 2017 **NR**; Brady 2016 **NR**; Pillay 2015 **NR**). These principles, and culturally competent practices, are supported by the ANZCA Statement on Cultural Competence PS 62 (ANZCA 2017 **GL**). Similarly, culturally competent practices are endorsed by The Australian Medical Council, the Medical Board of Australia, and the Medical Council of New Zealand (Medical Board of Australia 2014 **GL**).

Consequently, a health professional needs to consider their own cultural assumptions and preconceived biases as well as address the cross-cultural elements that underpin their patients' individual responses. A person's empathy and ability to perceive pain in the other differs across cultures (Atkins 2016 **Level III-3**; Rosa 2018 **NR**). Some evidence shows variation in assessment and the severity of pain particularly in the case of African American patients; ethnicity can influence the health care relationship (Vigil 2016 **Level IV**; Hirsh 2015 **Level IV**). Investigation into medication adherence and patient–physician ethnicity/language concordance supports the need for cultural responsiveness (Ali 2017 **Level IV**; Ohana 2015 **Level IV**). The need for cross-cultural sensitivity is particularly important when addressing verbal and nonverbal indicators of pain and being aware

of stoic and emotive responses to pain as they may have different meaning across cultures (Ford 2015 **Level IV**). Overall, researchers have found significant cultural differences in self-care when managing pain which affects pain-relief seeking behaviour (Xu 2018 **Level III-2)**. These behavioural differences occur as it relates to ethnicity (Meints 2016 **Level III-3 SR,** 19 studies, n=6,489; Meints 2018 **Level III-2 EH**; Meints 2017 **Level III-2 EH**, n=172). On a broader scale, some cultural attitudes may limit pain-relief seeking behaviour (Wechkunanukul 2016 **Level IV SR**, 10 studies, n=1,511,382). Similarly, a patient may vocalise (Burri 2018 **Level III-2**; Meints 2015 **Level III-2 EH**, n=190; Brady 2016 **NR**), or appear stoic in managing pain (Cagle 2017 **NR**). For example, it may be perceived by some patients as inappropriate to use a nurse's time to ask for pain relief as it may be seen as a weakness/shameful, or an unnecessary interruption of their time (Carrion 2015 **Level III-3**). In some collectivist cultures, the concept of patient autonomy is foreign and interdependence is preferred. This behaviour may result in patients waiting for a health professional to offer pain relief as the latter is seen as the primary medical decision maker (Martin 2017 **Level IV**; Pillay 2014 **NR**). Health literacy influences a patient's ability to understand and act on medical advice (Xu 2018 **Level III-3 SR,** 23 studies, n=6,110; Teo 2018 **Level III-3**; Wilkinson 2014 **Level IV**). Cross-cultural perception of pain may be a learned behaviour with links that have been made between culture and pain-related caregiver behaviours (Kristjansdottir 2018 **Level III-3**). This may explain why, cross-culturally, there is a difference in how a patient might approach their ability to manage their pain (or not). A recent study highlighted that the cross-cultural perception of the causation of pain as something external, impeded the capacity to express it in biomedical terms: *'The women reported that not eating the right food, old age and stress could cause pain, with an overlying belief that pain was often caused by hard work or tiredness.'* (Holt 2018 **Level IV**). Spiritual coping needs to be considered as well; faith informs many patients to respond to pain positively without seeking pain relief. Hindu culture, for instance, understands pain and suffering within the context of gaining better karma (Dewar 2015 **Level IV**). Buddhism emphasises the need for stoicism and fatalism, articulating that pain has the ability to strengthen the body, purify the soul and deepen the spirit (Cheng 2017 **NR**; Waikakul 2016 **NR**). Prayer has also demonstrated a powerful way of tolerating pain in both the African American and Latino community (Meints 2015 **Level III-2 EH**, n=190; Gagnon 2014 **NR**). Research about the impact of the refugee experience on patients with health professionals, advises to provide care with great cultural sensitivity, and that mental health symptoms and chronic pain are commonly experienced by refugee patients (Crosby 2013 **NR**).

Communication problems caused by variable linguistic (and non-verbal) proficiency of either the patient or the health professional, make it difficult to adequately assist patients with interactive pain management (eg PCA use, requesting analgesia when needed), to gain consent for invasive analgesic techniques (eg epidural or regional catheters) and to assess their pain (Taylor 2017 **Level III-2**; Ali 2017 **Level IV;** Ford 2015 **Level IV**). When language is an obstacle, there should be caution when using nonprofessional interpreters (eg family, friends), because their linguistic ability/accuracy in the other language has not been tested and may be variable. In addition, nonprofessional interpreters may inadvertently omit, edit and impose their own values when conveying the information to the clinician, and the patient may be reluctant to openly express themselves in front of people they know.

Direct correlation with longer length of hospital admission, as well as higher readmission rates, longer delay times, not to mention poorer outcomes in emergency treatment (eg lower likelihood of receiving analgesia or attending to hospital, lower self-reported quality of life and poorer end-of-life care) have been made with failure to use an interpreter (Wechkunanukul 2016 **Level III-2 SR**, 10 studies, n=1,511,382; Taylor 2017 **Level III-2**; Asghar 2016 **Level III-2**; Kilkenny 2018 **Level III-3**; Santos 2013 **Level III-3**; Silva 2016 **Level IV SR**, 10 studies, n unspecified; van Rosse 2016 **Level IV**; Lindholm 2012 **Level IV**). This is in addition to poorer outcomes due to possible delays in seeking

help, which can be culturally influenced as well (Wechkunanukul 2016 **Level IV SR**, 10 studies, n=1,511,382)

The use of alternative methods of communication through translation apps such as Google Translate™ in the clinical setting is either not advised or non-conclusive with the risk to the patient being considered too great (Silvera-Tawil 2018 **Level IV**; Panayiotou 2019 **NR**). The use of health-care specific language translation apps may therefore only be considered as an alternative option in low risk situations such as non-clinical communication in the sub-acute setting (eg daily routine communication) when formal healthcare interpreter services are not available. An accredited healthcare interpreter should always be engaged to communicate the important points in the continuum of patient care. To date only two language translation apps, "Talk to Me" and "CALD Assist" are regarded safe to use when communicating with culturally and linguistically diverse patients in the sub-acute setting. Both apps incorporate basic questions around pain and were developed in Australia (in November 2019 only available for Apple IOS 10® [iPad®] in the case of CALD Assist and both [iPad®] and [iPhone®] in the case of "Talk to Me"), therefore incorporating languages reflecting the local migrant communities (Panayiotou 2019 **NR**).

Cultural differences in response to pain in both experimental and clinical settings have been reported. A person's expression of pain is something that will not change irrespective of the length of settlement in a host country (Zborowski 1969 **NR**). In addition, the pain experience is socialised and therefore one will encounter cultural variances in language of distress when experiencing pain. Studies conducted using experimental pain stimuli found that cultural differences indeed influenced clinically relevant pain (Lee 2016 **Level III-2**), pain tolerance and threshold (Kim 2017 **Level III-2 EH SR**, 41 studies, n unspecified; Mahadeva 2015 **Level III-3**; Aufiero 2017 **EH**; Morris 2015 **EH**). In a cohort study on large colorectal and lung cancer, African American patients reported higher sensitivity to pain than Caucasian patients (Martinez 2014 **Level III-2**). Similarly, African American and Latino/a patients were found to experience a greater 'ethnicity effect' when it came to pain related anxiety, severity and vocalising pain than their Caucasian counterparts (Gagnon 2014 **NR**).

Several systematic reviews looked at the perception of pain across cultures and the effect of patient ethnicity on pain response, assessment and management across a variety of clinical pain settings (Lee 2019a **Level III-2 SR** [PRISMA], 14 studies, n=11,733; Xu 2018 **Level III-3 SR,** 23 studies, n=6,110; Rahavard 2017 **Level III-3 SR**, 42 studies, n unspecified; Kim 2017 **Level III-3 EH SR**, 41 studies, n unspecified; Krupic 2019 **Level IV SR**, 10 studies, n unspecified; Hampton 2015 **Level IV SR**, 5 studies, n unspecified). A review of the cultural impact on the pain management of Chinese cancer patients highlighted that analgesic use, adherence and pain reporting in Chinese cancer patients is poor, as it is culturally influenced by feelings of '*fatalism, desire to be good, low pain control belief, pain endurance beliefs, and negative effect beliefs*.' (Xu 2018 **Level III-3 SR**, 23 studies, n=6,110). Similarly, another study compared opioid consumption after major abdominal surgery between Hong Kong patients and Caucasian patients in Australia found that the Hong Kong patients requested less opioid, but that their pain scores were higher (Konstantatos 2012 **Level III-2**). Further marked disparities in effective pain treatment were reported; in the United States, African Americans and Hispanics were less likely to receive opioid analgesics and were more likely to have their pain undertreated vs Caucasian patients (Groenewald 2018 **Level IV**; Dickason 2015 **Level IV**). This disparity was reported for all types of pain visits, was more pronounced with increasing pain intensity and was unaffected by adjustment for pain severity. A study which looked at a patient receipt of an opioid prescription after a dental diagnosis, found that indeed ethnicity also mattered (Janakiram 2018 **Level IV**).

Interestingly, the research that focused on analgesic prescriptions to children in US EDs, raises the point that the level of opioids is dependent on whether the patient has an ethnic-concordant health care provider (Groenewald 2018 **Level IV**). This may explain the differences

reported in patients of different ethnic groups attending EDs and requiring analgesia (Lee 2019a **Level III-2 SR** [PRISMA], 14 studies, n=11,733), while some studies find little to none (Ly 2019 **Level III-2**; Jacob 2017 **Level III-2**; Shavit 2018 **Level IV**; Shavit 2016 **Level IV**).

Prescription of opioids also varied with patient ethnicity independent of health professional bias. There are innate genetic factors that may explain pain disparity in Indian, Malay and Han Chinese patients, which demonstrates that opioid requirements are indeed ethnicity dependent and have to be administered as such (Somogyi 2016 **Level IV**).

To ensure culturally responsive care, it is imperative that health professionals continually improve their cultural competence by increasing their cross-cultural knowledge, skills and self-awareness through cultural competency training (Jongen 2018 **Level IV SR** [PRISMA], 64 studies [16 studies specific to health work force], n unspecified). Additionally, it is important to use accredited healthcare interpreters to improve communication between health professionals and patients who have difficulty communicating in the main language (Berger 2014 **Level IV**; Cadoret 2014 **NR**). Other strategies used to facilitate cross-cultural pain education and management include bilingual handouts describing varying methods of pain control and Visual Analog Scale (VAS) with carefully chosen anchor terms or the use of faces scales (see Chapter 2). With some studies showing a preference for the Faces Pain Scale – Revised, these scales might not be effective on their own (Pathak 2018 **Level IV**). A comparative study involving the assessment of Verbal Descriptor Scale (VDS), the Visual Analog Scale (VAS), the Faces Pain Scale (FPS), the McGill Pain Questionnaire-Short Form (MPQ-SF) and the Brief Pain Inventory-Short Form (BPI-SF) found that more than a single tool may be needed to ensure diagnostic accuracy and consistency in assessing severe pain in patients of CALD backgrounds (Ham 2015 **Level IV**). A series of pain scales in a number of different languages has also been produced by the British Pain Society to assist in the assessment of people whose first language is not English and these are available on their website (BPS 2014 **GL**). Limitations with the latter are that it is not available in Italian (one of the largest cultural groups in Australia) and it assumes a certain level of literacy of the patient. While there is evidence of differences in pain reports and analgesic use in different cultures or ethnic groups, this should not be used to stereotype patients or promote assumptions about differences in assessment and management of pain or response to pain therapies. Rather, it should only be used to inform of possible cultural preferences. Culturally responsive care in this context is used as an extension of person-centred care and therefore provision of effective analgesia requires not a culturally specific approach but a sensitivity to a patient's ethnicity, spirituality, cultural practices and beliefs, level of acculturation and their behavioural expression of pain. The large individual differences in pain behaviours and analgesic requirements that exist in any patient group mean that pain is best assessed and managed on an individual basis rather than on the basis of what might be expected in a patient from a particular cultural, ethnic or spiritual background (Cadoret 2014 **NR**).

KEY MESSAGES

1. Disparities in assessment, analgesic requirements and effective treatment of pain exist across ethnic groups (**S**) (**Level III-2 SR**).
2. Ethnic and cultural background of both healthcare professional and patient can influence the ability to assess and treat acute pain (**N**) (**Level III-2 SR**).

The following tick boxes represent conclusions based on clinical experience and expert opinion:

☑ Cultural competence of health professionals supported by specific training improves health outcomes for culturally and linguistically diverse patients (**U**).

- ☑ Pain assessment and management should be done on an individual patient basis. Differences between ethnic and cultural groups should not be used to stereotype patients but should only be used to inform of possible cultural preferences (**U**).
- ☑ Multilingual printed information and pain measurement scales are useful in managing patients from different cultural or ethnic backgrounds (**U**).
- ☑ If language proficiency poses a communication barrier, then an accredited health care interpreter should be included when conducting a pain assessment, to ensure correct assessment; the use of friends, family or staff member should be avoided (**N**).
- ☑ The use of health-care specific language translation apps may be only considered as an alternative option in non-clinical situations in the sub-acute setting (eg daily routine communication) when formal healthcare interpreter services are not available (**N**).

9.3.1 | Aboriginal and Torres Strait Islander Peoples

Evidence from the Australian Institute of Health and Welfare highlights that when compared to non-Indigenous Australians; "*Indigenous Australians, on average, have worse heal*th", experience "*large disparities in health outcomes*" and "*report greater difficulty in accessing affordable health services that are close by*" (AIHW 2018 **NR**). Despite limited and predominantly weak levels of evidence regarding acute pain and its management in Indigenous Australians; this chapter seeks to identify key themes, barriers, concerns and opportunities for improvement (see also Table 9.5).

Importantly for clinicians navigating this chapter, findings drawn from patient populations may not be generalisable beyond the cohort where they were originally documented; however, exploration of these original papers may provide guidance to practitioners working with these populations. Additionally, examples selected from the literature for this chapter are not to suggest a universal approach to pain assessment, but instead highlight heterogeneity in this population, the need to counter racial profiling and ensure delivery of individualised care. There is a need for personalised care and variable patient preferences were identified for different mediums of patient information regarding lower back pain (Lin 2017 **Level III-1**); it was suggested that the need for "*communication to be individualised, flexible, and patient centred*".

The ramifications of profiling on pain management have been highlighted within the literature. One example regards pain experience related to vulvar cancer surgery where "*Although pain was noted as an issue by the Indigenous women, one of the health professionals interviewed did not see it as an issue and indicated that Indigenous peoples have high pain thresholds.*"(McGrath 2015 **Level IV**). Practitioners should be aware that historical literature which suggests high pain tolerance or pain threshold has been broadly criticised by contemporary authors, who have highlighted a potential risk of harm to patients if these beliefs are followed (McGrath 2015 **Level IV**; Fenwick 2004 **Level IV**; Fenwick 2006 **NR**).

Contemporary studies have instead identified unique, culturally appropriate pain behaviours among Indigenous patients (Fenwick 2004 **Level IV**) which may have been misinterpreted by health practitioners as "*a high pain threshold*" (McGrath 2015 **Level IV**). Examples of culturally appropriate pain behaviours may include **"***verbal and nonverbal silence in response to pain*" as reported in a study of postoperative pain in Central Australian Indigenous women (Fenwick 2004 **Level IV**). Multiple authors highlight study populations where pain may not be vocally communicated in a manner "*expected*" by Western health professionals which suggests that health professionals may be required to change their methods of assessment in order to identify

pain expression in this population (McGrath 2006 **Level IV**; Fenwick 2004 **Level IV**; Honeyman 1996 **Level IV**). Other examples of "*silent*" pain performance may include the feigning of sleep, turning a head away or grimacing, also documented in a Central Australian study (Fenwick 2001 **Level IV**). Authors propose multiple reasons for this style of pain expression; ranging from respect for the health professional (Fenwick 2006 **NR**), an individual's position within their community (McGrath 2006 **Level IV**), a belief that the practitioner can "*see within*" the patient akin to the skills of a traditional healer (Fenwick 2004 **Level IV**), fear of the healthcare system (Fenwick 2001 **Level IV**) or due to fear of the cause of pain (Fenwick 2004 **Level IV**). Examples of the latter include cohorts where "*illness and pain are understood in relation to the external world and can be caused by such things as, breaking of tradition or violation of taboos, crossing into forbidden land or speaking to the wrong relative at the wrong time… possibly making the (pain) sufferer too ashamed to complain*" (Fenwick 2004 **Level IV**). Beliefs regarding the cause of pain must however be contrasted with the findings in regional and remote Western Australia, where the majority of participants with chronic low-back pain believed their pain resulted from problems in spinal anatomy or structure (Lin 2013 **Level IV**). Drawing from this evidence, clinicians need to acknowledge the breadth of pain expression and associated beliefs and how this may influence the establishment of appropriate pharmacological and non-pharmacological therapeutic regimes.

Consideration should also be given to the systemic factors which may also play a role in an individual's decision to report pain. Examples from the literature include patients being reluctant to disclose pain due to "*a lack of established trust relationships with health care providers*", perception that they were not listened to by health professionals and that negative stereotypes were affecting their treatment (Strong 2015 **Level IV**). Additionally, some patients may become "*quiet and withdrawn*" when hospitalised and may therefore "*not be sufficiently assertive to indicate their need for pain relief"* (McGrath 2015 **Level IV**). The impact of historical factors influencing an individual's decision to express pain must also not be overlooked (Fenwick 2006 **NR**).

9.3.1.1 | Assessment

Problems with the utility of frequently used assessment tools have been identified in a variety of studies exploring pain assessment in Aboriginal and Torres Strait Islander patients. In a review of the impact of an Acute Pain Service on postoperative pain, a higher proportion of patients were able to complete a verbal rating scale than a numerical pain scale (Sartain 1999 **Level III-3**). This was expanded by later authors who suggested that in some patient populations, linguistic nuances may favour the use of verbal rating scales and recommend the use of verbal descriptors based on the patient's language (Fenwick 2006 **NR**).

Not appreciating individual differences in pain expression or an individual's expectations regarding the assessment of their pain may lead to inadequate pain management. (Fenwick 2006 **NR**) An example from postoperative pain management in Central Australian Aboriginal women, highlighted that non-Aboriginal nurses expected pain to be expressed in a manner familiar to their own culture (e.g. vocalising pain); whereas the Aboriginal women expected pain to be interpreted in a manner similar to traditional healers such as "*to see within*" (Fenwick 2004 **Level IV**).

One particular challenge which may further exacerbate cultural differences and expectations across the patient/health care professional's interaction involves the role of communication. A prospective study identified that anaesthetists were more likely to be unsure if Aboriginal or Torres Strait Islander patients understood explanations vs non-Aboriginal patients (Howe 1998 **Level III-3**); subsequently leading to a higher rate of change to the patient's proposed treatment plan. From a patient perspective, patients were noted to experience "*difficulty describing their*

pain problems to health professionals, in making themselves understood and in understanding what they were being told" (Strong 2015 **Level IV**). Adding to this, language barriers and the use of jargon have been identified as potential impediments to communication (Strong 2015 **Level IV**; Lin 2014 **Level IV**). Suggestions for health practitioners to address this include personalising communication (as discussed above), avoiding the use of jargon (Strong 2015 **Level IV**; Lin 2014 **Level IV**), consider the use of visual aids ((Strong 2015 **Level IV**; Lin 2014 **Level IV**; Cusack 2013 **Level IV**), and investing in trust development (Mitchell 2018 **Level IV**; Strong 2015 **Level IV**; McGrath 2006 **Level IV**; Fenwick 2006 **NR**).

The health professional may be required to modify their methods of history-taking within some populations in order to improve communication (Fenwick 2001 **Level IV**). Resources developed for pain management in Central Australian Aboriginal people highlight that asking two questions in one sentence or asking questions with obvious answers may cause confusion or result in no answer being forthcoming from the patient respectively. They recommend the health professional ask one question at a time and avoid asking "*nonsense*" questions where the answer is clear, such as asking about the presence of pain when the experience of pain is obvious. Likewise, health professionals should be aware that periods of silence may occur following asking questions of some Australian Aboriginal people, possibly out of respect for the individual asking the question (Taylor 2014 **NR**; Fenwick 2006 **NR**). Alternate suggestions for health professionals include using a conversational style of history taking (Lin 2014 **Level IV**; Lin 2013 **Level IV**; Taylor 2014 **NR**; Fenwick 2006 **NR**), which is noted by some authors to improve patient-practitioner trust (Fenwick 2006 **NR**).

9.3.1.2 | Treatment

Negative interactions with health care professionals may "*deter Indigenous people from seeking further services*" (Strong 2015 **Level IV**). Conversely, the development of trust between the healthcare provider and patient is noted to improve information disclosure and "*participants taking an active role in their management*" (Lin 2014 **Level IV**).

Variation in treatment or inconsistent use of pain relief has been identified in the literature. Examples include a recent publication which identified the inconsistent use of pain reducing techniques for children receiving repeated penicillin injections during acute rheumatic fever management (Mitchell 2018 **Level IV**). In this paper the author notes that only a minority of patients were able to "*negotiate about the pain of their injection*" with the children's ability to negotiate being linked to "*a trusting relationship with clinicians*". As a result, for repeated procedures Mitchell suggests "*a decolonising stance would ensure that pain reduction measures are mandated for every instance*" referencing current paediatric procedural pain management guidelines (RACP 2006 **GL**). Additionally, one study suggested that Indigenous Australian patients may be less likely to receive complex analgesia than non-indigenous patients in the postoperative period (RR 0.45; 95%CI 0.18 to 1.15]) (Howe 1998 **Level III-3**). Another author suggests Indigenous Australian patients receiving vulvar cancer treatment were "*were undermedicated for pain*" (McGrath 2015 **Level IV**). These findings have not been explored further, and the implications remain unclear.

Finally, higher levels of medical comorbidities such as renal failure have been identified within the Indigenous Australian population (Howe 1998 **Level III-3**; AIHW 2011 **Level IV**). These comorbidities may influence analgesic choice as reflected within other chapters.

Table 9.5 | Barriers to effective Pain Management:

Barrier	Recommendations to address these barriers
Communication difficulties during patient/health care practitioner interaction	
Pain expression in Aboriginal and Torres Strait Islander Peoples may not reflect that which is expected by the health professional's cultural background (Fenwick 2004 **Level IV**)	• Health practitioners should understand nuances of pain expression and beliefs within such populations. Using frameworks such as cultural safety/cultural competency may be of assistance (The Wardliparingga Aboriginal Research Unit of the South Australian Health and Medical Research Institute 2017 **GL**; Fenwick 2006 **NR**) • Seek the assistance of caretakers in assessment of pain (Fenwick 2006 **NR**)
Language difficulties may exist between the patient and health care practitioner (Lin 2014 **Level IV**; Strong 2015 **Level IV**)	• Seek the assistance of an Aboriginal health worker or interpreter to assist in the bilateral communication between patient and health care team (Howe 1998 **Level III-3**; Cusack 2013 **Level IV**; Taylor 2014 **NR**) • Provide support, give information and improved explanations to patients (Strong 2015 **Level IV**; McGrath 2006 **Level IV**) • Avoid jargon (Lin 2014 **Level IV;** Strong 2015 **Level IV**) • Consider visual aids, (Strong 2015 **Level IV**; Lin 2014 **Level IV**) however this should be personalised to the individual. (Lin 2017 **Level III-1**)
Systemic factors may affect pain disclosure by the patient to health care practitioner (Fenwick 2006 **Level IV**; Strong 2015 **Level IV**)	• Develop trust with the patient (Mitchell 2018 **Level IV**; Strong 2015 **Level IV**; McGrath 2006 **Level IV**; Fenwick 2006 **NR**) • Consider cross-cultural competency/cultural safety Frameworks (see above) • Consider input from Aboriginal Health Workers • Consider self-exploration of practitioner's own culture, and the impact this can have on patients of other cultures (process of becoming culturally sensitive) (Fenwick 2006 **NR**)
Racial Profiling	• Acknowledge that previous views about pain tolerance can be harmful to patient care (McGrath 2015 **Level IV**; Fenwick 2004 **Level IV**; Fenwick 2006 **NR**)
Assessment Use of culturally inappropriate measures (Fenwick 2004 **Level IV**)	• The verbal pain descriptors may be a better choice of pain measurement tool than numerical rating scales in some Aboriginal Australian Peoples (Fenwick 2006 **NR**)
Treatment Potential variation, under-treatment or disparities	• Recognition of the risk of harm due to racial profiling (see above)

treatment of pain for Indigenous Australian patients (Lin 2018 **Level IV SR**, 18 studies n unspecified; Howe 1998 **Level III-3**; McGrath 2015 **Level IV**)	• Taking a "decolonising stance" to address power imbalance, examples include ensuring "that pain reduction measures are mandated for every instance" (Mitchell 2018 **Level IV**) of paediatric procedure related pain as guided by current guidelines. (RACP 2006 **NR**)

KEY MESSAGES

1. Verbal descriptor scales may be a better choice of pain measurement tool than verbal numerical rating scales in some Aboriginal and Torres Strait Islander Peoples (**U**) (**Level III-3**).
2. Medical comorbidities such as renal impairment are more common in Aboriginal and Torres Strait Islander Peoples and may influence the choice of analgesic agent (**U**) (**Level IV**).

The following tick boxes represent conclusions based on clinical experience and expert opinion:

☑ Heterogeneity between differing populations of Aboriginal Peoples may require tailoring of the service delivered to the population and individual being serviced (**U**).

☑ Pain expression in Aboriginal and Torres Strait Islander Peoples may not reflect that which is expected by the health professional's cultural background. This places the onus on the health professional to understand nuances of pain expression and beliefs within such populations (**U**).

☑ Aboriginal and Torres Strait Islander Peoples are at increased risk of underrecognition and undertreatment of pain (**N**).

9.3.2 | Māori peoples

Māori peoples make up 16.5% (775,836 people) of the New Zealand population (Stats NZ 2019 **NR**). In 1840 in New Zealand, the Treaty of Waitangi, Māori and the Crown contracted to recognise British sovereignty in exchange for guarantees that indigenous rights to customary resources would be protected. This treaty has impacted on the health resources for this indigenous population (Durie 2012 **NR**). Cultural factors play a role in pain experiences in terms of a person's pain expression, threshold and tolerance (McGavock 2012 **NR**; Davidhizar 2004 **NR**) and also influence interaction with health professionals and adherence to advice provided (Magnusson 2011 **Level IV**, n=15). Māori views on health and healing, and the care of Māori people who are in pain, are different to the biomedical views prevalent in Western culture (McGavock 2012 **NR**). Māori perceive pain as a multidimensional experience affecting them physiologically, psychologically and socially (Magnusson 2011 **Level IV**, n=15). For example, in the Te Whare Tapa Whā model, health is seen as the interaction between te taha tinana (physical health), te taha hinengaro (mental health), te taha wairua (spirituality) and te taha whānau (family) (Pitama 2011 **NR**; Durie 1985 **NR**). Commonly used and widely accepted descriptors and phrases relating to pain and established pain measures in Western medicine are appropriate to use when assessing Māori patients (Magnusson 2011 **Level IV**; Pitama 2011 **NR**).

Demographic data of patients attending for an initial assessment in 2015 were requested from all District Health Boards that offered a multidisciplinary chronic pain service (Lewis 2018 **Level III-3**, n=2002). Māori patients scored significantly worse than patients of European descent on all clinical assessment measures. Māori vs to non- Māori had higher pain, and greater disability, increased levels of stress, anxiety and depression, lower self-efficacy to manage pain, greater levels of pain-related fear and more catastrophic thoughts that were related to pain. In another study, data were collected via a comprehensive questionnaire given to consecutive new patients seen at a New Zealand multidisciplinary Pain Service over a four-year period (Burri 2018 **Level III-3**, n=798). Cross-cultural comparison discovered that Māori patients reported highest pain levels, the largest number of pain sites, the greatest pain interference, as well as highest levels of stress, anxiety, depression, and psychological distress, when vs all other ethnicities.

There has been limited data published about Māori perspectives on pain (Magnusson 2011 **Level IV**). Some of the quantitative research of Māori health has covered acute experimental pain (Azariah 1984 **Level III-2 EH**), acute postoperative pain (Mahmoud 2006 **Level IV**), pain associated with giving birth (Nelson 2006 **Level IV**), dental pain in children (Jamieson 2006 **Level III-2**) and prescription rates for analgesia (Crengle 2005 **Level III-2**).

Using the ischaemic arm test, Māoris were able to tolerate ischaemic pain for longer durations vs their European counterparts (Azariah 1984 **Level III-2 EH**, n=60). After accounting for various behavioural and material factors, Māori children were more likely to experience dental pain (OR 1.35; 95%CI 1.08 to 1.70) in a model considering demographic factors only, and Pacific Islander children were less likely to have received a general anaesthetic for dental work than New Zealand European children (OR 0.44; 95%CI 0.24 to 0.82) (Jamieson 2006 **Level III-2**, n=3,275).

Māori women were less likely to receive a range of medical interventions during childbirth, including Caesarean sections or epidural analgesia, vs non-Māori women (Harris 2007 **Level III-2**; Sadler 2002 **Level III-2**; Nelson 2006 **Level IV**). Māori and Pacific Islander women had a 15% epidural analgesia rate vs 25% in other New Zealand women, despite the fact that Māori and Pacific women were more likely to have pre-existing health conditions that would dictate a higher need for epidural analgesia (Nelson 2006 L**evel IV**). A retrospective observational study was conducted in New Zealand Māori and New Zealand Europeans with data collected over 21 mth on patients who had received intrathecal morphine for postoperative pain management (Woods 2018 **Level III-3**, n=96). New Zealand Māori experienced a significantly higher rate and intensity of pruritus than New Zealand Europeans which was less likely to be treated.

From accident registry data, high levels of adverse outcomes were observed three mths post-trauma among a Māori cohort (Maclennan 2013 **Level IV**, n=566). Almost half were experiencing problems with mobility. A majority were having difficulties performing their usual activities and most were suffering some or extreme pain or discomfort. Over half were experiencing an increased level of psychological distress as well. Prevalence of disability due to injury in a household survey was slightly higher among Māori (31.4%) than non-Māori (29.3%) aged ≥15 y (Office for Disability Issues and Statistics New Zealand 2010 **Level III-2**). Overall, these outcomes highlight the importance of improved prevention strategies and post-injury care.

New Zealand continues to have some of the highest healthcare inequalities in the world with Māori having a two to three times higher mortality from non-communicable disease than non-Māori populations (Lilic 2015 **Level III-2**; Kerr 2014 **Level III-2**; Di Cesare 2013 **Level IV**; Hsiang 2013 **Level IV**). Māori were slightly less likely to consult general practitioners for back pain or regional pain disorders than European New Zealanders but were more likely to present with gout (Taylor 2004 **Level III-3**). Māori have one of the highest prevalence of gout internationally. A qualitative general inductive approach guided by Māori community principles ('Kaupapa') was used on 12 Māori (aged 48-79 years) with gout (Te Karu 2013 **Level IV**). Many put up with the pain

and put the needs of others before themselves. NSAIDs, prednisone, and colchicine were mostly used with allopurinol used late in the disease. This showed that early preventive treatment in a culturally sensitive health care system was needed. In a prospective observational study, patients with gout for <10 y were recruited from primary and secondary care settings (Dalbeth 2013 **Level III-2**, n = 291 [37 Māori, 35 Pacific Islanders and 219 who were neither Māori nor Pacific Islanders]). Māori and Pacific Islander participants had 9 y earlier age of onset, higher flare frequency and more features of joint inflammation. Māori and Pacific Islander patients also reported greater pain and activity limitation and lower health-related quality of life.

Similarly, joint replacement registry data collected between 2005 and 2009 demonstrated that Māori patients experience higher pain and poorer mobility on self-report questionnaires one year following total joint arthroplasty than non-Māori patients (Singleton 2013 **Level III-2**). A validated Monte Carlo computer simulation model estimated quality-adjusted life years (QALYs) lost due to knee osteoarthritis in the New Zealand (NZ) adult population (aged 40 to 84 y) over their lifetimes until death (Abbott 2017 **NR**). Data were obtained from the NZ Health Survey, NZ Burden of Diseases, NZ Census, and from the relevant literature. QALY losses were found to be lower for Māori than non-Māori due to lower life expectancy. A prospective cohort study of rotator cuff repairs (March 2009 to December 2010) from the New Zealand Rotator Cuff Registry showed that Māori present younger with more pain and with significantly poorer function (Maher 2017 **Level III-2**, n=1,383). Māori suffer disproportionately from the pain of ischaemic heart disease with hospitalisation rates for Māori found to be 1.4 times that of non-Māori (Curtis 2010 **Level III-2**); mortality rates were more than twice that of non-Māori.

Alongside inequalities in access to, and quality of care, Māori also experience greater discrimination than non-Māori (Harris 2006 **Level III-2**). Research on acute pain suggests that experiences of Māori may differ from those of other New Zealanders in terms of tolerance, healthcare access or treatment, including receipt of pain-relief medication (McGavock 2012 **NR**). Given entrenched health disparities across a wide range of conditions and diseases, Māori carry a disproportionate burden of pain. The development and implementation of cultural competence training should provide pathways for health professionals to work more effectively with Māori patients (Pitama 2011 **Level IV**).

KEY MESSAGES

1. Experimental ischaemic pain is tolerated for longer in Māori people than in European New Zealanders (**U**) (**Level III-2**).
2. Māori people report higher levels of pain and/or disability with dental pain, gout and after trauma and joint replacement surgery than European New Zealanders (**U**) (**Level III-2**).

The following tick boxes represent conclusions based on clinical experience and expert opinion:

☑ High healthcare inequalities exist regarding access and quality of care (across age ranges, genders and for various medical conditions) between the Māori and Pacific Islander peoples compared with New Zealanders of European origin (**S**).

☑ Māori culture embraces the multidimensional aspects of pain experiences (**S**).

9.4 | The patient with sleep-disordered breathing including obstructive sleep apnoea

Sleep-disordered breathing (SDB) is a spectrum of disorders where partial or complete cessation of breathing occurs many times during sleep. Obstructive sleep apnoea (OSA) is the most common form of SDB and is the condition most studied in surgical patients. As the prevalence of OSA is increasing and numbers of patients having surgery is large, the population at risk is significant (Memtsoudis 2013 **NR**). Acute pain management in a patient with OSA presents several potential problems; identification of patients at significant risk, choice of the most appropriate form of analgesia, the most suitable location in which to provide care and the level of monitoring required. These difficulties arise primarily from the risk of exacerbating OSA by the administration of opioid or other medicines with sedative effects (in particular benzodiazepines, but also butyrophenone or phenothiazine antiemetics and alpha-2-delta ligands). Importantly, patients with OSA suffer sleep disturbance on postoperative night one, and an increased frequency of SDB on postoperative night three (Chung 2014 **Level III-2**, n=38).

The prevalence of moderate and severe OSA in the general adult population is estimated to be 6 to 17%, and in older age groups (>60y) 49% or more (Senaratna 2017 **Level IV SR,** 24 studies, n=3,807). However, a large proportion of OSA patients remain clinically undiagnosed and untreated. There is a variable prevalence in the surgical population, with an estimated 60 to 70% prevalence in patients undergoing bariatric surgery of which one-third have moderate or severe OSA, and would benefit from CPAP (de Raaff 2017 **GL**). Therefore, many patients with undiagnosed OSA will have had treatment for acute pain without significant morbidity. The risk will depend on the severity of OSA, the nature and extent of surgery, the type of anaesthesia and analgesia and the extent of postoperative monitoring.

Patients with known OSA are at increased risk of postoperative complications vs other patients (Memtsoudis 2013 **NR**). However, the main risk may lie more with the body size and build of the patient, especially those who are morbidly obese, rather than the fact they have a specific diagnosis of OSA (Loadsman 2009 **NR**).

The simple to use STOP-Bang screening questionnaire has been validated for the identification of patients with OSA (Nagappa 2017 **Level III-2 SR** [PRISMA], 10 studies, n=23,609). A score ≥3 has been demonstrated to have high sensitivity for detecting moderate to severe OSA, whereas patients with a score <3 are considered to be low risk. Patients at high risk of OSA (STOP-BANG ≥3) have been demonstrated to have higher rates of perioperative complications. Specifically, in 7,877 high risk patients for OSA vs 15,732 low risk patients undergoing different surgeries, postoperative complications (6.86% vs 4.62: OR 3.93; 95%CI 1.85 to 7.77) and LOS (5.0 d ± 4.2 vs 3.4 ± 2.8: MD 2.01 d; 95%CI 0.77 to 3.24) are increased. Similarly, preoperative apnoea-hypopnoea index (AHI) and identification of nocturnal hypoxemia by oxygen desaturation index (ODI), cumulative sleep time percentage with SpO_2 <90% (CT90), minimum SpO_2, mean SpO_2, and longest apnoea duration are associated with postoperative complications (Suen 2019 **Level IV SR**, 21 studies, n unspecified).

A large retrospective database study using the USA Nationwide Inpatient Sample compared postoperative respiratory outcomes in surgical patients either with or without OSA based on ICD-9 coding on discharge and matched by propensity scoring (Memtsoudis 2011 **Level III-2**, n=6,051,703). Coding for OSA was associated with respiratory complications after both orthopaedic and general surgery: aspiration pneumonia (OR 1.41; 95%CI 1.35 to 1.47 and OR 1.37; 95%CI 1.33 to 1.41 respectively), acute respiratory distress syndrome (OR 2.39; 95%CI 2.28 to 2.51 and OR 1.58; 95%CI 1.54 to 1.62 respectively) and requiring intubation/mechanical

ventilation (OR 5.20; 95%CI 5.05 to 5.37 and OR 1.95; 95%CI 1.91 to 1.98 respectively). The relative contribution of each component of perioperative care (eg type of analgesia or anaesthesia) is impossible to ascertain. Several other studies have analysed patient outcomes using the Nationwide Inpatient Sample database. These studies found:

- SDB was independently associated with postoperative cardiopulmonary complications (atrial fibrillation, intubation with mechanical ventilation, noninvasive ventilation) but not with an increased rate of in-hospital death (Mokhlesi 2013b **Level III-2**, n=1,058,710);
- For the subgroup of bariatric surgery patients, a diagnosis of SDB/OSA was surprisingly negatively associated with inhospital mortality (OR 0.34; 95%CI 0.23 to 0.50) (Mokhlesi 2013a **Level III-2**), n=91,028), while being positively associated with increased risk of atrial fibrillation (OR 1.25; 95%CI 1.11 to 1.41), need for intubation (OR 4.35; 95%CI 3.97 to 4.77) and of noninvasive ventilation (OR 14.12; 95%CI 12.09 to 16.51);
- For patients having shoulder arthroplasty, there was no association with adverse outcomes (Griffin 2013 **Level III-2**, n=22,988);
- In patients having revision hip or knee arthroplasty, OSA was associated with increased inhospital mortality (OR 1.9; 95%CI 1.3 to 2.8), as well as pulmonary embolus (OR 2.02; 95%CI 1.3 to 2.9) and wound complications (D'Apuzzo 2012 **Level III-2**, n=258,455).

OSA has been associated with a higher risk of postoperative cardiac adverse effects (OR 2.07; 95%CI 1.23 to 3.50) and acute respiratory failure (OR 2.43; 95%CI 1.34 to 4.39) (Kaw 2012 **Level III-2 SR**, 13 studies, n=3,942). Desaturation and ICU transfer were also more likely, but these two findings were hindered by a high degree of heterogeneity in the studies.

Following outpatient surgery, there was no association between preoperative diagnosis of OSA and an increase in adverse effects or unplanned hospital admission (Bryson 2012b **Level III-2**, n=674; Sabers 2003 **Level III-3**, n=234).

A major limitation of these studies is the reliance on existing diagnostic codes to identify patients with OSA using administrative data which may significantly underestimate the risk of undiagnosed OSA. This question was subsequently investigated. Patients presenting for general and vascular surgery were categorised into three groups: no diagnosis or low risk OSA; documented OSA without therapy or suspicion of OSA (STOP-Bang ≥3); and diagnosis of OSA with treatment. Untreated OSA, was independently associated with an increase in cardiopulmonary complications (risk-adjusted rates 6.7% versus 4%; aOR 1.8), especially unplanned reintubation (aOR 2.5) and myocardial infarction (aOR 2.6) (Abdelsattar 2015 **Level III-2**, n=26,842). Furthermore, the available evidence was recently reviewed by the Society of Anesthesia and Sleep Medicine Task Force (USA) which concluded that despite the low level of evidence, the majority of studies suggest OSA is associated with an increased risk of postoperative complications, including pulmonary and cardiovascular complications (Opperer 2016 **Level III-2 SR** [PRISMA], 61 studies, n=8,969,583). These findings are confirmed by subsequent studies: The rates of a composite outcome (myocardial injury, cardiac death, heart failure, thromboembolism, atrial fibrillation, and stroke within 30 d of surgery) were 30.1% for patients with severe OSA, 22.1% for patients with moderate OSA, 19.0% for patients with mild OSA, and 14.2% for patients with no OSA (Chan 2019c **Level III-2**, n=1,364). The association between composite outcome and OSA was significant only for patients with severe OSA (aHR 2.23; 95%CI 1.49 to 3.34). A hospital registry study assessing a bundle intervention for perioperative screening and management of patients with suspected OSA (BOSTN) identified associations between high BOSTN score (≥2) and a number of outcomes vs low scores; increased risk of postextubation desaturation (aOR 1.34; 99.3%CI 1.21 to 1.48) and increased LOS (3.7 d vs 4.3: aRR 0.87; 99.3%CI 0.84 to 0.91) but reduced requirement for postoperative invasive ventilation (aOR 0.89; 95%CI 0.80 to 0.98) (Raub 2020 **Level III-2**, n=3,834).

Despite the evidence presented above, in a Canadian survey, 50% of anaesthetists continue to rely on their clinical suspicion and only 30% on a screening tool to identify patients with OSA preoperatively (Cordovani 2016 **Level IV**, n=992). Furthermore, 47% did not know of or had no access to a specific institutional policy for perioperative management of OSA, and 40% would send a patient with OSA home after ambulatory surgery. An accompanying editorial criticises this situation on the basis of 12 perioperative deaths in OSA patients the author assessed as an expert witness (Benumof 2016 **Level IV**, n=12).

In light of the increased postoperative risks associated with OSA, recent studies have aimed to determine the effect of treatment on outcome. A prospective cohort study screened patients for OSA risk and after surgery instituted extra care and observation (options included continuous pulse oximetry, oxygen, CPAP/BiPAP and others) for those identified as high risk, but the actual usage of these interventions was not recorded (Lockhart 2013 **Level III-2**, n=14,962). There was no increase in 30 d or 1 y postoperative mortality; however, it is not possible to determine if this was due to the use of the targeted interventions.

9.4.1 | Opioids and obstructive sleep apnoea

One of the main concerns in patients with OSA is that administration of opioids for the treatment of acute pain may lead to an increase in the number and severity of obstructive episodes and oxygen desaturation. OSA is associated with an increased sensitivity to opioid analgesia, possibly due to upregulation of opioid receptors secondary to recurrent hypoxia, and increased sensitivity to pain, due to chronic sleep fragmentation, in both adult volunteers (Doufas 2013 **Level III-2 EH**, n=43) and children (Brown 2009 **NR**) (see also 10.10.3). Furthermore, CPAP treatment appears to reduce pain sensitivity in patients with OSA, likely by the restoration of sleep continuity and improved ventilation (Cozowicz 2018 **Level IV SR** [PRISMA], 40 studies, n unspecified).

Patients assessed to be at risk of having OSA (by history, BMI and physical examination) vs control patients had more obstructive events during the first postoperative night (39±22 vs 14±10 events/h) and spent more time with oxygen saturation levels <90% (Blake 2008 **Level III-2**, n=63). There was no difference between the groups in the cumulative morphine dose over that time or frequency of central and mixed apnoeas. Classification of risk for OSA correlated with an increased number of desaturation events per h in patients monitored for 48 h postoperatively (Gali 2009 **Level III-3**, n=693).

Furthermore, while perioperative morphine dose is predictive of central apnoeas regardless of OSA status, patients at risk of OSA experienced significantly more severe hypoxaemia, largely due to obstructive respiratory events (Cozowicz 2018 **Level III-SR** [PRISMA], 40 studies, n=223,368).

OSA was a risk factor for OIVI in surgical patients (OR 1.4; 95%CI 1.2 to 1.7) (Gupta 2018b **Level IV SR** [PRISMA], 12 studies, n = 841,424). In patients with OSA, opioids attenuated the arousal response to hypoxia and prolonged airway obstruction.

Two early studies concluded that opioid administration in the postoperative period led to episodes of pronounced oxygen desaturation while the patients were asleep, and this was more commonly the result of obstructive and central apnoea than a decrease in respiratory rate (Catley 1985 **Level III-2**, n=32; Clyburn 1990 **Level III-2**, n=10). Those studies, however, involved bolus doses of opioids in the PACU and subsequent infusion rates of IV morphine that would now be considered much larger than current practice. A subsequent study using continuous infusion doses of remifentanil calculated to be analgesic in volunteers with moderate OSA demonstrated a substantial increase in the number of central events, while the number of obstructive events was reduced (possibly secondary to the REM-suppressing effect of opioids); minimum arterial haemoglobin oxygen saturation during the night was significantly lower in patients receiving remifentanil (Bernards 2009 **Level II**, n=19, JS 4). In another study, the central apnea index and

obstructive apnea index on postoperative night 1 were correlated with the first 24-h opioid requirements (Chung 2014 **Level III-2**, n=38).

Despite a Cochrane review (Mason 2015 **Level I** [Cochrane], 14 studies, n=293: including Bernards 2009 **Level II**), there remains a paucity of information regarding the effects of analgesics, including opioids, in the acute pain setting in patients with OSA and therefore limited data on which to base recommendations for their postoperative care (ASA 2014 **GL**).

The apparent ceiling effect on respiratory depression, but not analgesia in healthy young patients, has favoured the use of buprenorphine in patients with SDB. Buprenorphine has unique pharmacological properties - it is a mixed agonist-antagonist, with a higher affinity for the mu-opioid receptor and consequent long half-life (166 min) (White 2018 **Level I** [Cochrane], 28 studies, n=2,210). However, in the setting of acute pain management, buprenorphine was found to have no difference in pain scores or the incidence of respiratory depression or sedation vs morphine in adults (White 2018 **Level I** [Cochrane], 28 studies, n=2,210) and children (Murray 2018 **Level I** [Cochrane], 4 studies, n=195). Buprenorphine's effect on respiratory drive may have potentially profound adverse effects in acute pain management, especially in patients with SDB.

A small study in children undergoing adenotonsillectomy for OSA showed a trend to fewer episodes of postoperative desaturation in children given tramadol vs morphine, but the difference was only significant for the second h after surgery (Hullett 2006 **Level II**, n=66, JS 4). In patients with a BMI ≥28 and with signs or symptoms suggestive of OSA, there was no difference in the numbers of respiratory events (obstructive apnoeas, hypopnoeas or central apnoeas) in patients receiving IV morphine PCA and those receiving an "opioid-sparing" analgesic regimen (IV tramadol PCA, parecoxib and "rescue-only" morphine); however there was a correlation between >15 respiratory events/h and total morphine dose (Blake 2009, **Level II**, n=65, JS 4).

Multimodal, opioid-sparing, analgesia has also been examined in adult OSA patients undergoing elective lower extremity arthroplasty (Cozowicz 2019 **Level III-2**, n=181,182). Assessment of this higher perioperative risk population demonstrated a step-wise reduction in opioid dose prescription and PCA use (26.6% in opioid only vs 19.2%, 13.7%, and 7.7%) with increasing modes of multimodal analgesia over 10 y. With regards to postoperative complications, there were significantly reduced odds for postoperative mechanical ventilation (OR 0.23; 95%CI 0.16 to 0.32) and critical care admission (OR 0.60, CI 0.48; 0.75) with the addition of two or more non-opioid analgesic modes. Of note, the most commonly used components of multimodal analgesia included paracetamol, coxibs, nsNSAIDs, gabapentin or pregabalin, regional analgesia, ketamine and corticosteroids.

In a number of case reports, the use of opioid medications by various regimens (intermittent IM, IV PCA and PCEA) in patients with OSA appeared to be a common factor for complications, including death (Parikh 2002 **Level IV**, n=19; Ostermeier 1997 **Level IV**, n=3; Etches 1994 **Level IV**, n=8; Lofsky 2002 **NR**; Cullen 2001 **CR**; Reeder 1991 **CR**; VanDercar 1991 **CR**). However, caution is required when interpreting these reports. Most of the cases involved excessive opioid doses (eg excessive bolus dose or a background infusion with PCA) and/or inadequate monitoring for respiratory depression (Macintyre 2005 **NR**). It appeared there was an over-reliance on monitoring respiratory rate; and sedation levels were not checked and/or increasing sedation was not recognised as an early indicator of respiratory depression.

Examination of the legal literature provides a similar story. From analysis of the Anesthesia Closed Claims Project database, OSA or suspected OSA was identified in 24% of patients with postoperative OIVI (Lee 2015 **Level IV**, n=357). Furthermore, the majority of critical events (88%) occurred within 24 h of surgery and nearly half of patients had a continuous opioid infusion at the time of the event, highlighting the requirement for appropriate postoperative monitoring in high risk patients. A retrospective review of the legal literature between 1991 and 2010 found 24 cases in which OSA (a known diagnosis in 96%) was directly implicated in the postoperative

adverse outcome (death in 45.6% and anoxic brain injury in 45.6%) (Fouladpour 2016 **Level IV**, n=24). The most common complications were respiratory arrest in an unmonitored environment and difficulty in airway management. Furthermore, opioid use was thought to play a role in 38% of cases. Finally, examination of case reports of critical complications (death, near-death, and critical respiratory events) in surgical patients with OSA reinforced the importance of early postoperative monitoring, with 80% of events occurring within the first 24 h and 67% on the general hospital ward (Subramani 2017 **Level IV**, n=60).

An updated ASA task force report (USA) on the perioperative management of patients with OSA concluded that there remains only limited evidence to evaluate the effects of various postoperative analgesia techniques in patients with OSA and no good comparisons between conventional opioids such as morphine, and tramadol or nonopioid analgesics (ASA 2014 **GL**). Expert opinion, however, consistently suggests that nonopioid analgesics and regional techniques should be considered, either as an alternative to opioids or to help limit the amount of opioid required both for adults (ASA 2014 **GL**) and children (Patino 2013 **NR**).

9.4.2 | Obesity as a risk factor

The prevalence of obesity continues to grow, from 5 to 8% in 1980 to 13% in 2015 (WHO 2017), and is strongly associated with OSA (Young 2004 **NR**). Using polysomnography, OSA was identified in 71% of patients presenting for bariatric surgery (Frey 2003 **Level IV**, n=40) and an estimated one third of these patients suffer from moderate to severe OSA (de Raaff 2017 **Level IV**, n=15 [experts surveyed]). It is still unclear if the use of PCA, with appropriate bolus doses and monitoring, in morbidly obese patients is less safe than regional analgesia or other systemic opioid analgesic techniques.

In patients having bariatric surgery, all of whom underwent preoperative polysomnography and were prescribed CPAP therapy preoperatively if indicated, complications were common (33%) but, while age, open surgery and BMI were associated with those complications, OSA severity was not (Weingarten 2011a **Level III-2**, n=797). In morbidly obese children having tonsillectomy, obesity was similarly associated with adverse outcome, independently of OSA (Gleich 2012 **Level III-2**, n=100).

For further information see Sections 9.5 and on paediatric patients see Section 10.10.3.

9.4.3 | Approaches to treatment

9.4.3.1 | Oxygen

While oxygen therapy alone may not prevent the disruptions of sleep pattern or symptoms such as daytime somnolence and altered mental function that may occur in patients with OSA, it can reduce the likelihood of significant hypoxaemia (Landsberg 2001 **Level III-3**, n=43; Phillips 1990 **Level III-3**, n=8). As patients with OSA are more at risk of hypoxaemia after surgery or when given opioids, the use of supplemental oxygen would seem appropriate (ASA 2014 **GL**) despite concerns about reducing respiratory drive during apnoeic periods and potential life-threatening respiratory depression (Lofsky 2002 **NR**) from removing hypoxaemia as a key trigger for respiratory arousal. However, in patients with newly diagnosed (AHI >5 per h on preoperative polysomnography) and untreated OSA, postoperative supplemental oxygen 3 L/min via nasal prongs improved oxygenation, and decreased the AHI, mainly due to a decrease in hypopnea index and, to a smaller degree, central apnoea index (Liao 2017 **Level II,** n=123, JS 3). Furthermore, there was no significant difference in $PaCO_2$ measured by transcutaneous CO_2 monitor, however, patients with COPD and obesity hypoventilation syndrome (OHS) (serum $HCO3^-$ level >30 mmol/L) were excluded from this study and a significant proportion of patients (11.4%)

experienced CO_2 retention, especially those receiving supplemental oxygen on postoperative night one.

9.4.3.2 | Continuous positive airway pressure

The perioperative use of CPAP may theoretically help to reduce postoperative risk and is recommended for patients with OSA (ASA 2014 **GL**). The effectiveness of CPAP (used appropriately and in highly supervised environments) for the management of OSA in the postoperative setting was initially supported by case reports (Rennotte 1995 **Level IV**, n=16; Mehta 2000 **NR;** Reeder 1991 **CR**). However, a number of studies examining perioperative initiation of both fixed and autotitrated CPAP for patients considered or known to be at risk, have demonstrated very poor adherence by those accepting the therapy (Liao 2013 **Level II**, n=177, JS 2; Guralnick 2012 **Level IV**, n=211), with no obvious outcome benefit (O'Gorman 2013 **Level II**, n=133, JS 2). Poor patient adherence may be improved by initiation of CPAP prior to surgery with more effective education and individualisation of therapy.

The effective *de-novo* use of CPAP in the setting of acute pain management likely requires a higher level of supervision than that available in the general surgical ward; most reports of the successful use of postoperative CPAP utilise extended periods of high-dependency nursing with staff educated and experienced in its use (Rennotte 1995 **Level IV**, n=16; Mehta 2000 **NR;** Reeder 1991 **CR**). Established CPAP use may, however, be associated with a lower risk of perioperative complications, as cardiovascular complications in particular (cardiac arrest and shock) were increased in patients with untreated OSA vs those previously established on CPAP in a study using a Manitoban health administrative database (OR 2.20; 95%CI 1.16 to 4.17) (Mutter 2014 **Level III-3**, n=20,488).

In adult patients with OSA undergoing surgery, there was no significant difference in postoperative adverse events between CPAP and no-CPAP treatment groups, but postoperative CPAP reduced the AHI vs preoperative baseline AHI values without CPAP (37 ± 19 events/h vs 12 ± 16 events/h) (Nagappa 2015 **Level IV SR** [PRISMA], 6 studies, n=904). In patients in PACU following bariatric surgery, CPAP treatment decreased AHI, decreased oxygen desaturations, and increased the mean oxygen saturation by 3% (Zaremba 2016 **Level III-1**, n=45). Patients with a known diagnosis of OSA, who are currently using CPAP at home, should therefore have CPAP continued while in hospital (ASA 2014 **GL**). As such, the Society of Anaesthesia and Sleep Medicine guidelines recommend the perioperative usage of CPAP therapy (prescribed setting) to reduce the risk of postoperative respiratory failure and cardiac events in patients with OSA who are either adherent, or poorly adherent, to CPAP therapy (Chung 2016 **GL**).

In paediatric patients with CPAP intolerance and moderate to severe OSA, there are limited data that high-flow air via nasal cannula (10 to 50 L/min) reduced respiratory events, improved oxygenation, and reduced heart rate (Hawkins 2017 **Level III-2**, n=10).

Evidence indicates that the risk of CPAP causing gastric distension and anastomotic leaks after all types of oesophageal and upper abdominal surgery appears to be unfounded in adults (Weingarten 2011b **Level III-2**, n=797; Huerta 2002 **Level III-2**, n=1,067). In patients undergoing bariatric surgery postoperative CPAP usage was not a risk factor for suture line disruption and leakage (de Raaff 2018 **Level III-2**, n=2,153).

9.4.3.3 | Monitoring and environment

Advice on the most appropriate environment for the care of OSA patients requiring analgesia, along with the level of monitoring required, is based on expert opinion only and suggests that the severity of SDB, efficacy of any current therapy, relevant comorbidities (eg cardiac) and the analgesia required all be taken into consideration both for adults (ASA 2014 **GL**; Joshi 2012 **GL**) and

children (Patino 2013 **NR**). The ASA recommends continuous pulse oximetry monitoring and supplemental oxygen use after discharge from the recovery room in patients at increased risk of respiratory compromise from OSA until baseline oxygen saturation can be maintained on room air (ASA 2014 **GL**). Recommendations for postoperative monitoring of OSA patients after bariatric surgery include a minimum of continuous pulse oximetry in a designated surgical ward or a medium care unit, independent of CPAP usage (de Raaff 2017 **GL**).

Continuous pulse oximetry monitoring has the potential disadvantage of delaying the detection of hypoventilation when supplemental oxygen is administered. However, when continuous pulse oximetry was compared with standard monitoring (intermittent nursing spot-checks) in postoperative patients prescribed opioids, the detection of oxygen desaturation was 15 times more common, with a trend toward less ICU transfer in the pulse oximetry group (Lam 2017 **Level I** [PRISMA], 9 RCTs, n unspecified).

See also Section 4.3.1.4.

KEY MESSAGES

1. Continuous pulse oximetry compared to intermittent nursing spot-checks detects more episodes of hypoxaemia in postoperative patients with obstructive sleep apnoea prescribed opioids (**N**) (**Level I**).
2. The STOP-Bang questionnaire has high sensitivity for the identification of patients at risk of moderate to severe obstructive sleep apnoea (**S**) (**Level III-2 SR**).
3. Patients with sleep-disordered breathing, including obstructive sleep apnoea, having surgery are at increased risk of adverse cardiac and respiratory effects (**S**) (**Level III-2 SR**), in particular cardiac arrest/shock, atrial fibrillation, aspiration pneumonia, acute respiratory distress syndrome and need for intubation, mechanical and noninvasive ventilation (**N**) (**Level III-2**) and increased hospital length of stay (**N**) (**Level III-2 SR**).
4. Patients with obstructive sleep apnoea have an increased risk of exacerbation of obstructive episodes and hypoxaemia during the postoperative period (**U**) (**Level III-2**), in particular in the first 72 hours with peaks on the first and third postoperative night (**N**) (**Level III-2**).
5. Morbidly obese patients may be at increased risk of postoperative hypoxaemia, independent of a diagnosis of obstructive sleep apnoea (**U**) (**Level III-2**).
6. Continuous positive airway pressure does not increase the risk of anastomotic leak after upper gastrointestinal surgery (**S**) (**Level III-2**).
7. Increasing severity of obstructive sleep apnoea is associated with increased risk of postoperative respiratory complications including opioid-induced ventilatory impairment (**Q**) (**Level III-3**).
8. The prevalence of obstructive sleep apnoea in the surgical patient population is high and the majority (80%) of these patients are undiagnosed (**S**) (**Level IV SR**).
9. Higher preoperative apnoea-hypopnoea index and identification of nocturnal hypoxemia are risk factors associated with postoperative complications in patients with sleep-disordered breathing (**N**) (**Level IV SR**).

10. Patients with obstructive sleep apnoea have increased sensitivity to pain that improves with use of continuous positive air way pressure (**N**) (**Level IV SR**).
11. Opioids in patients with obstructive sleep apnoea attenuate arousal to hypoxia and prolong airway obstruction, and thereby lead to more severe hypoxaemia (**S**) (**Level IV SR**).

The following tick boxes represent conclusions based on clinical experience and expert opinion:

☑ Preoperative screening for obstructive sleep apnoea combined with treatment (ideally instituted preoperatively) and increased postoperative observation may decrease postoperative morbidity and mortality (**S**).

☑ Management strategies that may increase the efficacy and safety of pain relief in patients with obstructive sleep apnoea include multimodal nonsedating opioid-sparing analgesia such as regional techniques, continuous positive airway pressure, monitoring and supervision (in a high-dependency area if necessary) and supplemental oxygen (**U**).

☑ Perioperative commencement of continuous positive airway pressure may be beneficial in patients with obstructive sleep apnoea but requires high levels of supervision; significant problems are poor patient acceptance and postoperative adherence (**U**).

☑ In patients with obstructive sleep apnoea, monitoring should be extended beyond 24 hours to capture the high-risk period for late postoperative hypoxaemia (**N**).

9.5 | The obese Patient

Over the past three decades, the prevalence of obesity has increased significantly and is a major public health concern worldwide (Arroyo-Johnson 2016 **NR**). Obesity is associated with many comorbidities, with obstructive sleep apnoea (OSA) and the risk of hypoventilation being of particular concern with regards to acute pain management. As more obese patients are presenting for surgery, the need to manage acute pain safely in these patients becomes increasingly relevant. Multimodal analgesia and opioid-sparing techniques provide superior pain relief, improve perioperative outcomes and enhanced recovery in bariatric surgical care.

9.5.1 | Definitions of obesity

Obesity can be defined according to either anthropometric or body composition diagnostic criteria (Lang 2017 **NR**). Body mass index (BMI) is commonly used to define obesity, calculated by using weight in kilograms divided by height in metres squared. Other methods, including waist circumference, central and peripheral fat mass have also been used (Engin 2017 **NR**). The World Health Organization has established an international adult classification of BMI, whereby a BMI of 30 kg/m2 or higher is defined as obese (Arroyo-Johnson 2016 **NR**). Obesity can be further sub-classified into class 1 (30 to 34.9 kg/m2); class 2 (35 to 39.9 kg/m2) and class 3 or morbid obesity (greater than 40 kg/m2) (Engin 2017 **NR**). Currently, there is no consensus on an international classification of obesity for the paediatric population.
See Section 10.10 for paediatric issues.

9.5.2 | Prevalence

In Australia, 67% of adults are currently overweight or obese (AIHW 2019c **Level IV**). In New Zealand, 30.9% of adults are obese with differences by ethnicity (66.5% of Pacific Islanders, 48.2% of Māori, 29.1% of European/Other and 13.8% of Asian) (NZ MoH 2019 **Level IV**); the adult obesity rate has increased from 29% in 2011/12. Worldwide, the prevalence rate for being overweight or obese between 1980 and 2013 increased 27.5% for adults and 47.1% for children, to a total of 2.1 billion individuals considered overweight or obese (Ng 2014 **NR**). It has been predicted that by 2030, up to 86% of adults in the USA will be overweight or obese (Wang 2008 **NR**).

9.5.3 | Morbidity associated with obesity

Obesity has been linked to decreased life expectancy by approximately 3 to 18 y and large increases in healthcare expenditures (Leung 2015 **NR**). For every 5 unit increase in BMI above 25 kg/m2, overall mortality increases by 29%, vascular mortality by 41% and diabetes-related mortality by 210% (Prospective Studies 2009 **Level IV SR**, 57 studies, n=894,576).

Body mass is an important determinant of respiratory function, which can manifest as reduced lung volume, derangements in lung and chest wall compliance, increased resistance and moderate to severe hypoxaemia (Wang 2008 **NR**). These physiological alterations are more marked in obese patients with OSA. In surgical patients, the OSA prevalence is 40% in obese female and 50% in obese males, and OSA incidence increases to approximately 70% in morbid obesity (Lang 2017 **NR**).

The incidence of hypertension, dyslipidaemia, type 2 diabetes mellitus and cerebrovascular disease are directly proportional to BMI (Engin 2017 **NR**)**.** Obesity is also associated with increased

risk of several cancer types and certain pro-inflammatory conditions such as osteoarthritis and chronic pain (Belcaid 2019 **NR**).

Common characteristics in obese persons with pro-inflammatory conditions include fatigue, lethargy, social withdrawal, irritability as well as anxiety and depression (Seaman 2013 **NR**; Hoftun 2012 **Level IV**, n=7,373). Obesity is an independent risk factor for major depressive disorder (OR 5.25; 95% CI 1.41 to 19.58) (Kasen 2008 **Level IV**, n=544). Obese patients with high depression, anxiety and alexithymia levels rated their postoperative pain as more intense and requested more analgesia vs obese patients with normal psychological indicators (Aceto 2016 **Level IV**, n=120).

9.5.4 | Pharmacokinetic impact of obesity

Unfortunately, obese subjects are often excluded from clinical trials during the drug development process (Hanley 2010 **NR**). As a result, information regarding the impact of obesity of the pharmacokinetics and pharmacodynamics of the majority of drugs remains limited.

Absorption

Although gastric emptying and gut permeability are affected by obesity (Teixeira 2012 **Level III-2**, n=40; Cardoso-Junior 2007 **Level III-2**, n=38; Xing 2004 **NR**), oral bioavailability and absorption does not appear to be altered in obese individuals, and may increase in morbid obesity (Cheymol 2000 **NR**; Blouin 1999 **NR**).

Distribution

Total blood volume, cardiac output and plasma protein binding are increased in obesity (Cooney 2016 **NR**). Volume of distribution (Vd) changes in the obese patient appear to be drug-specific and for the most part, can be attributed to the physiochemical properties of the individual drug (Hanley 2010 **NR**). However, it is clear that Vd is influenced by many factors and its obesity related changes are therefore difficult to predict on the basis of drug properties such as lipophilicity alone (Belcaid 2019 **NR**; Smit 2018 **NR**).

Metabolism and Elimination

Obese patients appear to undergo TBW-proportional increases in phase II conjugation of paracetamol (Abernethy 1982 **Level III-2**). There is limited evidence of an increase in cytochrome P450 (CYP) 2E1 activity with obesity, with a reduction in activity noted after weight loss (Emery 2003 **Level III-2**, n=32; O'Shea 1994 **Level III-2**, n=24). The clinical relevance of this is unclear and probably not significant. Although hepatic clearance is usually unchanged or increased in the early stages of obesity, it could eventually become reduced due to hepatic steatosis, liver fibrosis and cirrhosis (Leykin 2011 **NR**; Adams 2000 **NR**)

The direct effect of obesity on renal clearance is unclear. Studies of creatinine have found increased, decreased or similar GFR estimates in obese versus non-obese individuals. Presently, there is no single, well validated weight descriptor to characterise drug clearance in the obese population (Belcaid 2019 **NR**; Hanley 2010 **NR**).

9.5.4.1 | Indirect measures of body composition

A number of indirect measures to assess body composition have been developed for clinical use, including BMI, total body weight (TBW), ideal body weight (IBW), lean bodyweight (LBW) and predicted normal weight (PNWT).

Methods for calculating indirect measures of body composition are as follows (Duffull 2004 **Level III-3 PK**):

- IBW (kg) = 45.4 (49.9kg if male) + 0.89 x (height in cm – 152.4)
- LBW (kg) = 1.07 (1.1 if male) x TBW – 0.0148 (0.0128 if male) x BMI x TBW.
- PNWT (kg) = 1.75 (1.57 if male) x TBW – 0.0242 (0.0183 if male) x BMI x TBW – 12.6 (10.5 if male)

There is a lack of evidence regarding dose adjustments of analgesia in the obese and morbidly obese patient and no clear consensus on what measures to use (Budiansky 2017 **NR**). It is advisable not to use TBW to calculate doses in obese patients to avoid risk of overdosing. Additionally, it is important to consider that LBW does not increase proportionally with fat mass in obesity. Normal fat mass is a size descriptor that partitions total body mass into fat and fat-free components. It uses allometric theory to calculate the fraction of fat mass that will make fat equivalent to fat-free mass. The value of normal fat mass is drug specific and specific to a PK parameter (eg Vd or CL) (Anderson 2017 **NR PK**). Calculating normal fat mass for drug dosing has been proposed as a principle-based approach that explains size and body composition effects on PKs of all drugs in adults of all sizes.

9.5.5 | Drugs used in the management of acute pain in the obese patient

An overarching systematic review of pain management after laparoscopic gastric bypass surgery shows that the administration of NSAIDS (1 RCT, n=47), dexmedetomidine (2 RCTS, n=157), ketamine (1 RCT, n=60) and intraperitoneal (2 RCT, n=188) or subfascial/subcutaneous (1 RCT, n=40) local anaesthetics or by transversus abdominis plane block (TAP) (2 RCTs, n=157) may improve analgesia vs placebo/controls (Andersen 2014 **Level I** [PRISMA] 9 RCTs, n=644).

Specifically for laparoscopic sleeve gastrectomy, a systematic review identified paracetamol (2 RCTs, n=161), NSAIDs (1 RCT, n=28) and opioids as rescue analgesics as well as TAP block (5 RCTs, n=247), but preferably port-site infiltration instead (1 RCT, n=147) as evidence-based analgesic options (Macfater 2019 **Level I** [PRISMA], 18 RCTs, n unspecified.; alpha-2-delta ligands (3 RCTs, n=253), while effective, should be used with caution in this population due to the risk of increasing OIVI (Belcaid 2019 **NR**).

RCTs included in the above two systematic reviews are partially mentioned again in the following more detailed paragraphs.

9.5.5.1 | Paracetamol

IV paracetamol improves pain scores (MD -0.66/10; 95%CI -1.03 to -0.28) and reduces opioid consumption (MD -6.44 mg; 95%CI -9.26 to −3.61) during the first 24 h after laparoscopic bariatric surgery vs placebo (Lee 2019b **Level I** [PRISMA], 4 RCT, n=349 patients).

The use of paracetamol in morbidly obese patients undergoing laparoscopic sleeve gastrectomy reduces opioid consumption, hospital LOS and reduces the number of emergency representations postoperatively due to abdominal pain (Cooke 2018 **Level II**, n=127, JS 5; El Chaar 2016 **Level II**, n=100, JS 5). The combined use of IV paracetamol with IV ketorolac has been shown to provide similar analgesic efficacy vs hydromorphone patient-controlled analgesia (PCA) after gastric bypass surgery (Ziemann-Gimmel 2013 **Level III-3**, n=181).

Pharmacokinetics in morbidly obese young adults appears to be altered as serum concentrations are virtually undetectable two h after administration of 1000 mg IV paracetamol (Hakim 2019 **Level IV PK**, n=11). This suggests that morbidly obese patients may require dose adjustment, although there is currently no consensus on what dosing regimen to use.

9.5.5.2 | Non-steroidal anti-inflammatories (NSAIDs)

In the absence of contraindications, the use of non-selective NSAIDs following bariatric surgery has been shown to reduce opioid consumption and improve pain scores and postoperative nausea and vomiting (PONV) (Govindarajan 2005 **Level II**, n=50, JS 2). IV ibuprofen vs IV paracetamol provided better reduction in pain scores and similar reductions in post-operative opioid consumption (Erdogan Kayhan 2018 **Level II**, n=80, JS 5). Intraoperative ketorolac was associated with reduced haemoglobin, although there was no difference in transfusion requirements (Klein 2012 **Level III-2**, n=162).

9.5.5.3 | Conventional Opioids

The use of conventional opioids for acute pain management in obese patients is a challenge due to the increased risk of OIVI. An opioid-sparing approach with multimodal techniques and individualised pain management may mitigate the risks.

Comparisons between opioids offer conflicting evidence and slight differences in outcomes. Sufentanil vs remifentanil infusions offered better quality of recovery (Aldrete score, psychomotor recovery) despite slower awakening times in morbidly obese patients undergoing laparoscopic gastroplasty (Bidgoli 2011 **Level II**, n=100, JS 5).

Studies comparing remifentanil and fentanyl in patients with class 2 and 3 obesity undergoing laparoscopic gastric banding surgery provided conflicting results, however remifentanil had predictably faster recovery of respiratory parameters (Kontrimaviciute 2012 **Level II**, n=66, JS 3; Bidgoli 2011 **Level II**, n=100, JS 5; De Baerdemaeker 2007 **Level III-3**, n=40).

Pharmacologic dosing models for fentanyl in morbidly obese patients have not yet been developed, but data suggest that fentanyl should be dosed based on LBW or IBW (Belcaid 2019 **NR**; Lang 2017 **NR**). One small trial demonstrated the pharmacokinetic mass versus TBW curve was essentially linear below 100 kg and approached a plateau above 140 kg (Shibutani 2004 **Level III-2 PK**, n=109). Prolonged infusions of fentanyl in obese patients have been associated with prolonged effects (Porhomayon 2013 **NR**). Remifentanil infusion dosing is governed by either IBW or LBW (Egan 1998 **Level III-2 PK**, n=24). Metabolism of morphine does not appear to be altered in morbidly obese patients, however, decreased elimination of active metabolites is evident, prolonging duration of action and exposure to these metabolites (de Hoogd 2017 **Level III-2**, n=40).

9.5.5.4 | Tramadol

After laparoscopic bariatric surgery, tramadol was superior to morphine in providing postoperative analgesia, with lower opioid requirements, lower hypopnoea episodes, earlier ambulation, early PACU discharge and shorter hospital LOS (Bamgbade 2017 **Level III-3**, n=412). Drawbacks for routine use include potential interactions with multiple antidepressants, which is particularly relevant as obesity is associated with a higher risk of developing depressive disorders (Kasen 2008 **Level IV**, n=544; Apovian 2016 **NR**).

9.5.5.5 | NMDA receptor antagonists

Intraoperative ketamine vs placebo improved early analgesia and reduced opioid requirements in patients undergoing laparoscopic gastric bypass surgery when added to remifentanil infusion) (Hasanein 2019 **Level II**, n=60, JS 3). Addition of low dose ketamine to morphine appears to significantly reduce opioid consumption and improve oxygen saturation and lung function vs patients using morphine alone (Kamal 2008 **Level II**, n=80, JS 4). The use of ketamine combined with clonidine or dexmedetomidine also reduces intra- and post-operative opioid consumption, along

with reduction of PONV and earlier time to extubation. This combination may cause significant drowsiness however (Sollazzi 2009 **Level II**, n=50, JS 3). A single dose of ketamine (0.4 mg/kg) resulted in no significant difference in pain intensity, however a clinically significant improvement in the affective component of pain was observed (Wang 2019 **Level II**, n=100, JS 5).

There is limited data available regarding ketamine dosing in obese patients. One study examining dose adjustments for induction of anaesthesia suggests using LBW or IBW (Sollazzi 2009 **Level II**, n=50, JS 3).

Perioperative IV magnesium sulfate vs placebo lowered pain scores and morphine consumption in patients undergoing sleeve gastrectomy (Kizilcik 2018 **Level II**, n=80, JS 5).

9.5.5.6 | Alpha-2-delta ligands

A single preoperative administration of pregabalin 150 mg demonstrated reductions in morphine consumption and pain scores with a low incidence of adverse effects after laparoscopic sleeve gastrectomy (Cabrera Schulmeyer 2010 **Level II**, n=80, JS 5). A single dose of preoperative gabapentin was found to have similar effects after laparoscopic gastric bypass surgery in patients with morbid obesity (Hassani 2015 **Level II**, n=60, JS 5). Caution with the routine use of these agents is required in the obese population, as they are known to cause sedation and may increase the risk of OIVI (Belcaid 2019 **NR**).

9.5.5.7 | Alpha-2 agonists

Dexmedetomidine in class 3 obese patients undergoing bariatric surgery results in improved analgesia, reduced opioid requirements and PONV with the most common infusion dose being used at 0.2 to 0.4 mcg/kg/hr (Singh 2017 **Level I** [PRISMA], 6 RCTs, n=362). This is confirmed by a subsequent RCT; intraoperative dexmedetomidine infusion reduced pain scores, morphine consumption and improve the quality of recovery after laparoscopic sleeve gastrectomy (Sherif 2017 **Level II**, n=150, JS 5). Clonidine vs dexmedetomidine had comparable effects on pain scores, quantity of analgesic consumption, return to normal function and patient satisfaction after laparoscopic sleeve gastrectomy (Naja 2014 **Level II**, n=60, JS 5).

9.5.5.8 | Corticosteroids

In postoperative obese patients undergoing laparoscopic sleeve gastrectomy, the addition of dexamethasone 8 mg and haloperidol 2 mg to ondansetron 8 mg vs ondansetron 8 mg only reduced pain intensity, morphine consumption and nausea (Benevides 2013 **Level II**, n=90, JS 5).

9.5.5.9 | Systemic local anaesthetics

Intraoperative systemic lidocaine infusion in the obese population undergoing laparoscopic gastric reduction surgery reduced pain scores, opioid consumption and improved quality of recovery (Sherif 2017 **Level II**, n=150, JS 5; De Oliveira 2014a **Level II**, n=50, JS 5).

9.5.5.10 | Cannabinoids

Self-reported marijuana use is associated with higher perioperative opioid use in the context of obesity and weight loss surgery (Bauer 2018 **Level III-2**, n=434).

9.5.6 | Local and regional anaesthetic techniques used in the management of acute pain in the obese patient

9.5.6.1 | Wound infiltration including wound catheters

Continuous SC and subfascial infusion of bupivacaine provided similar analgesia to IV PCA pethidine with reduced opioid requirements following laparoscopic gastric bypass surgery (Cottam 2007 **Level II**, n=40, JS 2).

Intraperitoneal local anaesthetic infusions for bariatric surgery reduce postoperative pain, decrease opioid consumption (Andersen 2014 **Level I** [PRISMA] 2 RCTs [intraperitoneal], n=188); Omar 2019 **Level II**, n=100, JS 3; Sherwinter 2008 **Level II**, n=30, JS 5) and are associated with earlier mobilisation, earlier intake of oral fluids and a shorter hospital LOS (Ruiz-Tovar 2018 **Level II**, n=110, JS 5). However, spraying 20 mL of 2.5% (?dosing error in manuscript) bupivacaine vs placebo onto the diaphragm during a laparoscopic gastric bypass did not reduce pain or opioid consumption (Schipper 2019 **Level II**, n=127, JS 4).

Preperitoneal bupivacaine infiltration reduced acute pain intensity, opioid consumption and the incidence of chronic post-surgical pain after bariatric surgery (Boerboom 2018 **Level II**, n=100, JS 4).

9.5.6.2 | Continuous and single-injection peripheral nerve blocks

Obesity was associated with a higher rate of peripheral block failure using landmark techniques (Franco 2006 **Level III-3**, n=2,020) and lower rates of patient satisfaction (Hanouz 2010 **Level III-2**, n=605). The use of US-guided regional blocks in obese patients improved procedural time, efficacy and patient satisfaction vs nerve stimulation (Lam 2014 **Level II**, n=24, JS 5). Even with the use of US guidance, elevated BMI is associated with an increased time required for block placement and higher pain scores and opioid consumption in PACU (Schroeder 2012 **Level IV**, n=528).

Ambulatory hernia repairs under local anaesthesia appear to be feasible and safe in obese patients with a BMI up to 45 kg/m2 (Acevedo 2010 **Level III-3**, n=2,031).

There is conflicting evidence regarding the analgesic benefit of a single injection US-guided TAP blocks in morbidly obese patients undergoing laparoscopic bariatric surgery (De Oliveira 2014b **Level II**, n=19, JS 5; Wassef 2013 **Level II**, n=35, JS 3). There was a short-term reduction in pain scores by US-guided TAP blocks, however other parameters including opioid consumption, time to ambulation or hospital LOS were similar to placebo (Saber 2019 **Level II**, n=90, JS 5). Another RCT found no difference in pain scores or opioid consumption with US-guided TAP blocks (Albrecht 2013a **Level II**, n=70, JS 5). Continuous local anaesthetic infusions appear to be more successful, with reduced pain scores and opioid consumption, earlier oral intake and ambulation times with US- guided (Said 2017 **Level II**, n=90, JS 2) or laparoscopic guided TAP block catheter placement (Ruiz-Tovar 2018 **Level II**, n=140, JS 4).

Brachial plexus blocks have been shown to provide safe and effective analgesia in patients with morbid obesity (Melton 2017 **Level III-2**, n=28; Franco 2006 **Level III-3**, n=2,020; Schroeder 2012 **Level IV**, n=528; Schwemmer 2006 **Level IV**, n=70). However, concern has been raised regarding the safety of supraclavicular blocks following a case report of severe respiratory distress in a morbidly obese patient who received a US-guided block (Guirguis 2012 **CR**).

There is currently no evidence-based recommendation for peripheral nerve block local anaesthetic dosing in patients with morbid obesity. Based on expert opinion, IBW should be used (Leykin 2011 **NR PK**; Ingrande 2010 **NR PK;** Adams 2000 **NR**).

9.5.6.3 | Neuraxial techniques

Neuraxial blocks are challenging in obese obstetric patients, with a significant increase in failure rate at times (Kula 2017 **Level IV**, n=2,485; Vaananen 2017 **Level IV**, n=842). US guidance is likely to improve success rate (Shaylor 2016 **Level IV**, n=63), and estimated epidural depth visualised on ultrasound is strongly correlated with actual distance upon successful needle placement (Balki 2009 **Level IV**, n=46). A handheld ultrasound device provides comparable depth estimates to a console ultrasound machine (Carvalho 2019 **Level III-2**, n=47).

Obese parturients report significantly lower efficacy from labour epidurals (Bonnet 2017a **Level IV**, n=9,337). After an accidental dural puncture, the incidence of postdural puncture headaches (PDPH) is less in obese parturients vs non-obese (Peralta 2015 **Level III-2**, n=518 [dural punctures]).

The effect of obesity on the spread and block height in spinal anaesthesia remains controversial (Ngaka 2016 **Level III-2**, n=50; Kim 2015 **Level III-2**, n=209). More extensive spread of spinal anaesthesia is noted in females with central obesity vs those with non-central obesity (Chang 2017 **Level III-2**, n=57).

The addition of IT morphine vs placebo as part of a multimodal analgesic regimen after laparoscopic bariatric surgery markedly reduced postoperative pain, systemic opioid consumption and hospital LOS (El Sherif 2016 **Level II**, n=100, JS 4).

Epidural administration of local anaesthetic in obese patients has been associated with increased risk of cephalad spread (Carvalho 2017 **Level II,** n=40, JS 5; Lamon 2017 **Level III-2**, n=5,015; Kim 2015 **Level III-2**, n=209; Vricella 2011 **Level III-2**, n=250), thus dose reductions are likely to be required.

Thoracic epidural infusions of morphine at 200 mcg/h have been used safely in patients with class 3 obesity (Zotou 2014 **Level II**, n=48, JS 5). A loading dose of epidural morphine appears to offer no additional benefit in pain control and prolongs delay to normal bowel function and ambulation. Post laparotomy, the use of a thoracic epidural offers better measurements on spirometry function tests and quicker recovery of respiratory function (von Ungern-Sternberg 2005 **Level III-2**, n=84). Thoracic epidural use in obese patients undergoing off-pump coronary artery bypass surgery was shown to provide better analgesia, early tracheal extubation and shorter ICU LOS (Sharma 2010 **Level II**, n=60, JS 3).

PCA morphine vs epidural analgesia in gastric bypass surgery resulted in similar pain control, time to ambulation, bowel recovery or hospital LOS (Charghi 2003 **Level III-3**, n=86). Epidural analgesia was associated with an increased incidence of wound infections (39% vs 15%).

9.5.7 | Non-pharmacological techniques used in the management of acute pain in the obese patient

Various non-pharmacological therapies have been assessed in small trials for their efficacy in improving postoperative pain, though none are common practice.

Pulmonary recruitment manoeuvres reduced pain intensity and opioid requirements in the first 24 h after laparoscopic bariatric surgery (Pasquier 2018 **Level II**, n=150, JS 5).

A single session of postoperative prefrontal repetitive transcranial magnetic stimulation vs sham was associated with a 40% reduction in PCA morphine use in gastric bypass surgery patients (Borckardt 2008 **Level II**, n=20, JS 5).

The use of lavender aromatherapy in the post-anaesthesia care unit has been found to reduce the total analgesic and opioid requirements of patients undergoing laparoscopic gastric banding (Kim 2007 **Level II**, n=54, JS 3).

9.5.8 | Multimodal concepts

Introduction of a multimodal protocol for analgesia in laparoscopic sleeve gastrectomy (preoperative etoricoxib, intraoperative and postoperative paracetamol with optional postoperative tramadol) vs historic control (previous standard care) resulted in reduced opioid requirements, reduced adverse effects of opioids (8.8% vs 33%) with similar analgesic efficacy (Ng 2017 **Level III-3**, n=158).

KEY MESSAGES

1. Perioperative dexmedetomidine infusion reduces pain intensity, opioid requirements and PONV after bariatric surgery (**N**) (**Level I** [PRISMA]).
2. Intraoperative peritoneal local anaesthetic administration reduces pain intensity and opioid requirements after bariatric surgery (**N**) (**Level I** [PRISMA]).
3. Paracetamol (multi-dosing) r educes opioid requirements, hospital length of stay and representations for pain after bariatric surgery (**N**) (**Level II**).
4. Intraoperative systemic lidocaine infusions reduce pain intensity, opioid requirements and improve the quality of recovery after bariatric surgery (**N**) (**Level II**).
5. Epidural administration of local anaesthetics in obese patients has been associated with increased risk of cephalad spread (**N**) (**Level III-2**).
6. Obesity increases the failure rate of neuraxial and peripheral nerve blocks (**N**) (**Level IV**); ultrasound guidance improves the success rate (**N**) (**Level IV**).

The following tick boxes represent conclusions based on clinical experience and expert opinion:

☑ Obesity has significant detrimental effects on respiratory function and is linked to an increased rate of obstructive sleep apnoea (**N**).

☑ Obesity influences pharmacokinetic and pharmacodynamic parameters of analgesic medications leading to uncertainty about dosing and caution should be used with weight-based dosing (**N**).

☑ Multimodal analgesic techniques including use of regional techniques result in opioid-sparing effects and thereby improve safety of acute pain management after bariatric surgery (**N**).

9.6 | The patient with concurrent renal or hepatic disease

The efficacy and effectiveness of most analgesic medicines is altered by impaired renal or hepatic function. This change is not only because of altered clearance of the parent medicine, but also through the accumulation of therapeutically active or toxic metabolites. Some analgesic agents can aggravate pre-existing renal and hepatic disease, causing direct damage and thus altering their metabolism.

A brief summary of the effects that renal or hepatic disease may have on some of the medicines used in pain management, as well as alterations that might be required in analgesic medicine regimens, is given in Tables 9.6 and 9.7.

9.6.1 | Patients with renal disease

The degree to which analgesic medicine regimens require alteration in patients with renal impairment depends largely on the extent of renal impairment. Some medicines have active metabolites that are dependent on the kidney for excretion, and the medicine or its metabolites may further impair renal function.

A standard definition for chronic kidney disease (CKD) is provided by the US National Kidney Foundation (kidney.org) Kidney Disease Outcome Quality Initiative Advisory Board; patients with CKD should have either a glomerular filtration rate (GFR) <60 mL/min/1.73 m^2 for ≥3 mth or structural/functional kidney damage with or without changes in GFR **(**Levin 2014 **GL**). This definition quantifies five stages from Stage 1 (kidney damage with normal or increased GFR) via Stage 2 (mild reduction in renal function and GFR), Stages 3 and 4 (moderate to severe impairment of renal function and reduction in GFR) to Stage 5 (end-stage kidney disease requiring dialysis or renal replacement therapy).

There is some limited information about the ability of dialysis to clear many medicines and/or their metabolites. Molecules are more likely to be removed by dialysis if they have a low molecular weight, greater water solubility and lower volume of distribution; while a higher degree of protein binding and use of lower-efficiency dialysis techniques will reduce removal (Trainor 2011 **NR**; Dean 2004 **NR**).

The available data indicate the following (see Table 9.6 for references):

- Analgesics that exhibit the safest pharmacological profile in patients with renal impairment are alfentanil, buprenorphine, fentanyl, ketamine, paracetamol (except with compound analgesics) and sufentanil. None of these medicines deliver a high active metabolite load or have a significantly prolonged clearance.
- Oxycodone can usually be used without any dose adjustment in patients with renal impairment. Its metabolites do not appear to contribute to any clinical effect in patients with normal renal function.
- Amitriptyline, bupivacaine, levobupivacaine, lignocaine, ropivacaine, clonidine, gabapentin, pregabalin, codeine, hydromorphone, methadone, morphine, tramadol and tapentadol have been used in patients with renal disease but may need dosing adjustment depending on the degree of impairment. For local anaesthetics and prolonged administration, a reduction in dose may be required. Levobupivacaine, with similar clearance mechanisms, and ropivacaine may be safer than bupivacaine due to their higher therapeutic ratio. Haemodialysis clears some medicines, and so a supplemental dose may be needed at the end of dialysis (eg gabapentin, pregabalin).

- NSAIDs (both nsNSAIDs and coxibs), dextropropoxyphene and pethidine should not be used in the presence of significant renal impairment.
- Carbamazepine, sodium valproate and lamotrigine require no dose reduction. Caution is advised for the use of lamotrigine in patients with an eGFR <15 mL/min/1.73m^2
- Oxcarbazepine and topiramate require dose reduction in renal disease

Detailed reviews of pain management in patients with CKD have been published (Nagar 2017 **Level III-3 SR** [PRISMA], 12 studies, n unspecified; Sande 2017 **Level IV SR**, 18 studies, n unspecified; Davison 2019 **NR**; Pham 2017 **NR**; Nayak-Rao 2011 **NR**), also with an emphasis on the perioperative period (Tawfic 2015 **NR**) and on paediatric patients (Reis 2018 **NR**). Reviews of perioperative management (Trainor 2011 **NR**) and of prescribing for the dialysis patient has also been published (Smyth 2016 **NR**).

Additional information can be found in the *Australian Medicines Handbook* (AMH 2019 **GL**).

Table 9.6 | Analgesic medicines in patients with renal impairment

Medicine	Comments	Recommendations*
Opioids		
Alfentanil	No active metabolites 92% protein bound; increases in free fraction may result from alterations in protein binding (Sande 2017; Tawfic 2015)	No dose adjustment required unless renal failure is severe
Buprenorphine	Pharmacokinetics unchanged; predominantly biliary excretion of metabolites Pharmacokinetics also unchanged with dialysis (Davison 2019; Pham 2017; Sande 2017)	No dose adjustment required
Codeine	Accumulation of active metabolites can occur; prolonged sedation and respiratory arrest have been reported in patients with renal impairment No good data on removal by dialysis (Davison 2019; Pham 2017; Sande 2017)	Dose adjustment recommended or use an alternative opioid
Dextro-propoxyphene	Accumulation of active metabolite (nordextropropoxyphene) can lead to CNS and cardiovascular system toxicity. Contraindicated if creatinine clearance <40 mL/min. Blood concentrations not significantly changed during dialysis (Davison 2019; Niscola 2010)	Use of alternative agent recommended
Dihydrocodeine	Metabolic pathway probably similar to codeine Time to peak concentration and terminal half-life prolonged (Pham 2017; Craig 2008; Murtagh 2007)	Insufficient evidence: use not recommended

Medicine	Comments	Recommendations*
Fentanyl	No active metabolites Not removed to any significant degree by dialysis (Davison 2019; Sande 2017; Pham 2017; Tawfic 2015)	No dose adjustment required; may be used in patients with severe renal impairment
Hydromorphone	Neurotoxicity from accumulation of H3G possible H3G is effectively removed during HD; PD no data (Davison 2019; Sande 2017; Pham 2017; Tawfic 2015)	Dose adjustment recommended or use alternative opioid
Methadone	Methadone and its metabolites are excreted in urine and faeces; in anuric patients it may be mostly in faeces High protein binding, high volume of distribution and moderate water solubility would suggest that it is likely to be poorly removed by HD (Davison 2019; Pham 2017; Opdal 2015; Nayak-Rao 2011)	Dose adjustment may be required in severe renal impairment
Morphine	Major metabolites M3G and M6G excreted via kidney and accumulate in renal impairment M6G is an opioid agonist that crosses the blood-brain barrier slowly; delayed sedation from M6G has been reported in renal failure Neurotoxicity from accumulation of M3G possible Oral administration results in proportionally higher metabolite load Morphine and its metabolites are cleared by most HD procedures but may not be significantly affected by PD M6G also removed but slow diffusion from CNS delays response (Davison 2019; Sande 2017; Pham 2017; Tawfic 2015)	Dose adjustment recommended or use alternative opioid

Medicine	Comments	Recommendations*
Oxycodone	The metabolite oxymorphone is active but plasma levels are normally negligible and therefore it has an insignificant clinical effect in patients with normal renal function Higher blood concentrations of oxycodone and metabolites with moderate to severe renal impairment; half-life significantly increased in end-stage renal disease Oxycodone and its metabolites are dialyzable (HD, no data on PD) (Davison 2019; Samolsky Dekel 2017; Pham 2017; Sande 2017)	No dose adjustment required in most patients Monitor and adjust if necessary
Pethidine	Norpethidine is the only active metabolite and is renally excreted; it is dialysable (HD) Accumulation of norpethidine can lead to neuroexcitation including seizures (Tawfic 2015; Craig 2008; Launay-Vacher 2005)	Use of alternative agent recommended
Sufentanil	Minimally active metabolite (Sande 2017; King 2011; Murphy 2005)	No dose adjustment required
Tramadol	Increased mu-opioid effects from active metabolite O-desmethyltramadol (M1) as renally excreted Tramadol is removed to some extent by HD (Davison 2019; Pham 2017; Tawfic 2015)	Dose adjustment recommended Use of alternative agent recommended in significant renal impairment
Tapentadol	Metabolised by glucuronidation Major metabolite will accumulate in renal failure but significance unknown Likely to be removable by HD (AMH 2019; Pham 2017; Xu 2010)	Do not use in severe renal impairment (Creatinine clearance <30 mL/min)
Nonopioids		
Paracetamol	Terminal elimination half-life may be prolonged Is dialysable (Nayak-Rao 2011; Kuo 2010; Craig 2008)	May need to increase dose interval if renal impairment is severe Some evidence that it may accelerate the rate of progression to chronic renal failure

Medicine	Comments	Recommendations*
NsNSAIDs and coxibs	Can affect renal function Behaviour during dialysis not clearly elucidated for most NSAIDs (Nayak-Rao 2011; Kuo 2010; Launay-Vacher 2005)	Some evidence that they may accelerate the rate of progression to chronic renal failure, in particular in dehydration. Progression of renal disease more likely with nsNSAIDs than coxibs
Anticonvulsants		
Alpha-2-delta ligands	Gabapentin: impaired renal function reduces clearance in direct proportion to creatinine clearance; about 35% cleared by dialysis (Davison 2019; Asconape 2014)	Dose adjustment recommended on basis of creatinine clearance
	Pregabalin: Impaired renal function reduces clearance in direct proportion to creatinine clearance; highly cleared by dialysis (Davison 2019; Asconape 2014)	Dose adjustment recommended on basis of creatinine clearance
Carbamazepine	No dose adjustment necessary Highly protein bound, poorly dialysed (Bansal 2015)	No dose adjustment needed
Lamotrigine	Limited data (Bansal 2015)	Dose reduction if GFR<15 ml/min
Topiramate	Up to 80% renal excretion unchanged (Bansal 2015)	Dose reduction
Valproic acid	Hepatic elimination (Bansal 2015)	No dose reduction
Other medicines		
Local anaesthetics	There may be no significant difference in plasma concentration of levobupivacaine, bupivacaine or ropivacaine in patients with chronic renal failure unless renal failure is severe, or continuous infusions are used or repeated doses are used Increases in free fraction may result from alterations in protein binding Higher peak plasma concentrations of ropivacaine in uraemic patients but no difference in free fraction; uraemic patients have significantly higher alpha-1-acid glycoprotein plasma concentrations (AMH 2019; De Martin 2006; Jokinen 2005; Crews 2002)	Risk of toxicity may be affected by abnormalities in acid-base balance and/or potassium levels Doses may need to be reduced if prolonged or repeated administration (eg continuous infusions)

Medicine	Comments	Recommendations*
Clonidine	Half-life is increased in severe renal failure 50% metabolised by the liver; remainder excreted unchanged by the kidney (Khan 1999; Lowenthal 1993)	Limited data; dose adjustment has been recommended
TCAs	Amitriptyline is metabolised in the liver to nortriptyline, the active agent Not significantly removed by dialysis (Davison 2019; Raymond 2008; Dargan 2005)	Limited data; metabolite accumulation may occur and increase the risk of adverse effects but little evidence to indicate need for dose reduction
SNRIs	Duloxetine Venlafaxine (AMH 2019; Raymond 2008)	Dose reduction if creatinine clearance <30 mL/min
Ketamine	Dehydronorketamine levels are increased but it has only 1% of potency of ketamine Ketamine is not removed well by HD (Davison 2019; Tawfic 2015)	Limited data; probable that no dose adjustment is required

*Note: * Doses must still be titrated to effect for each patient.*
HD – haemodialysis
PD – peritoneal dialysis

9.6.2 | Patients with hepatic disease

Not all patients with hepatic disease have impaired liver function. In patients with hepatic impairment, most analgesic medicines have reduced clearance and increased oral bioavailability but the significance of these changes in the clinical setting has not been studied in depth.

Patients with cirrhotic liver disease may have renal impairment despite a normal serum creatinine. This can affect clearance of renally excreted medications and dose adjustment may be required.

The available data indicate the following (see Table 9.7 for references).

- While there are limited data, dose adjustments are usually not required for alfentanil, buprenorphine, fentanyl, morphine, oxycodone and sufentanil. However, all opioids carry an increased risk of toxicity and hepatic encephalopathy.
- Tramadol may need to be given at lower doses.
- Methadone should be used with caution in the presence of severe liver disease because of the potential for accumulation due to impaired clearance.
- Combination preparations of slow-release oxycodone and naloxone (Targin®) should be avoided in hepatic impairment as the reduced naloxone clearance leads to increased systemic levels and potential antagonism of the analgesic action of the oxycodone.
- The clearance of local anaesthetics may be significantly impaired; doses may need to be decreased if use is prolonged.
- Carbamazepine and valproate should be avoided in patients with severe hepatic impairment.
- It may be wise to reduce the dose of paracetamol in patients with significant degrees of hepatic impairment.

Detailed reviews of analgesic use in hepatic disease have been published (Dwyer 2014 **NR**; Imani 2014 **NR**; Bosilkovska 2012 **NR)** other detailed but lower quality reviews have also been published (Soleimanpour 2016 **NR**). Additional information can be found in the *Australian Medicines Handbook* (AMH 2019 **GL**).

Table 9.7 | Analgesic medicines in patients with hepatic impairment

Medicine	Comments	Recommendations*
Opioids		
Alfentanil	No significant difference in half-life found in children undergoing liver transplant In alcoholic cirrhosis, plasma clearance and protein binding decreased and elimination half-life increased after single dose (Davis 1989; Ferrier 1985)	Limited data: no dose adjustment required in most patients
Buprenorphine	Lower blood concentrations of buprenorphine and norbuprenorphine Chronic use in patients with HIV or HCV associated with increased incidence of hepatic enzyme rise (Tetrault 2016; Dwyer 2014; Johnson 2005)	Limited data: no dose adjustment required

Medicine	Comments	Recommendations*
Dextro-propoxyphene	Reduced oxidation leading to reduced clearance (Tegeder 1999)	Limited data: dose adjustment may be required
Fentanyl	Disposition appears to be unaffected (Dwyer 2014; Chandok 2010)	Limited data: no dose adjustment required
Methadone	Increased half-life but limited significance (Dwyer 2014; Lugo 2005)	Limited data: no dose adjustment required in stable chronic liver disease
Morphine	Hepatic impairment does not appear to have a significant effect on morphine pharmacokinetics; even in patients with cirrhosis there is a large hepatic reserve for glucuronidation Blood concentrations of morphine but not morphine metabolites higher after liver resection; blood concentrations also higher in patients with liver cancer Increased oral bioavailability of morphine due to its normal high first pass metabolism when given via this route Morphine pharmacokinetics altered in Nonalcoholic Steatohepatitis (NASH) (Pierre 2017; Rudin 2007; Kotb 2005)	In most patients no dose adjustment required
Hydro-morphone	Increased half-life of hydromorphone (AMH 2019; Soleimanpour 2016; Chandok 2010)	Consider dose reduction
Oxycodone	Decreased oxycodone clearance with mild to moderate hepatic impairment Avoid fixed dose combination with naloxone (Targin®) in moderate to severe hepatic impairment as systemic absorption of naloxone may be increased (AMH 2019; Riley 2008; Kalso 2005)	Limited data: no dose adjustment required in most patients
Pethidine	Reduced clearance (Tegeder 1999)	Limited data: dose adjustment may be required; use not recommended
Sufentanil	No difference in clearance or elimination (Tegeder 1999; Chauvin 1989)	No dose adjustment required
Tramadol	Reduced clearance (Dwyer 2014; Kotb 2008; Tegeder 1999)	Limited data: dose adjustment may be required if impairment is severe

Medicine	Comments	Recommendations*
Tapentadol	Elimination by hepatic glucuronidation (AMH 2019; Xu 2010)	Avoid in severe hepatic impairment (Child-Pugh score 10–15) Adjust dose in moderate hepatic impairment (Child-Pugh score 7–9)
Nonopioids		
Paracetamol	Metabolised in the liver; small proportion metabolised to the potentially hepatotoxic metabolite N-acetyl-p-benzoquinone imine. This is normally inactivated by hepatic glutathione Clearance is reduced (Hayward 2016; Dwyer 2014; Imani 2014; Graham 2013; Chandok 2010)	Commonly suggested that it should be used with caution or in reduced doses or frequency with active liver disease, alcohol-related liver disease and glucose-6-phosphate dehydrogenase deficiency However, others report that it can be used safely in patients with liver disease and is preferred to NSAIDs, and that therapeutic doses of paracetamol, at least for short-term use, are an unlikely cause of hepatotoxicity in patients who ingest moderate to large amounts of alcohol Dose reduction for chronic use
nsNSAIDs	Metabolised in liver. Altered metabolism and bioavailability in cirrhosis. Avoid if renal impairment present or risk of hepato-renal syndrome (Dwyer 2014; Imani 2014; Chandok 2010)	May be used in mild chronic liver disease Avoid in cirrhosis COX2 selective agents may be safer

Medicine	Comments	Recommendations*
Anticonvulsants		
Alpha-2-delta ligands	Eliminated renally (Asconape 2014; Dwyer 2014; Chandok 2010)	Safe in liver disease
Carbamazepine	Transient rises in hepatic enzymes occur in 25–61% of patients treated; has been reported to cause hepatic failure (rare) Primarily metabolised in the liver (Asconape 2014; Ahmed 2006)	Dose adjustment may be required; use not recommended in severe hepatic impairment
Valproate	Transient rises in hepatic enzymes occur in 10–15% of patients treated; has been reported to cause hepatic failure (rare) Primarily metabolised in the liver (Asconape 2014; Ahmed 2006)	Dose adjustment may be required; use not recommended in severe hepatic impairment
Other medicines		
Local anaesthetics	Amide-type local anaesthetics undergo hepatic metabolism and clearance may be reduced in hepatic disease Increased plasma concentrations of ropivacaine after continuous infusion but not a single dose (AMH 2019; Jokinen 2007; Jokinen 2005; Bodenham 1990)	Limited data; dose adjustment may be required with prolonged or repeated use
TCAs	Amitriptyline is metabolised in the liver to nortriptyline, the active agent (Dwyer 2014; Chandok 2010)	Reduce dose if hepatic impairment is severe
SNRIs	Duloxetine Venlafaxine (Dwyer 2014; Chandok 2010)	Duloxetine should not be used in hepatic impairment Venlafaxine dose reduction in hepatic impairment Desvenlafaxine may be safer
Ketamine	In acute use, rare incidence of hepatic enzyme rise Prolonged infusion associated with hepatic enzyme rise Chronic use possibly associated with sclerosing cholangitis (Wong 2014; Noppers 2011)	Monitor hepatic enzymes when continuous infusion is prolonged beyond about five d

*Note: *Doses must still be titrated to effect for each patient*

KEY MESSAGE

The following tick box represents conclusions based on clinical experience and expert opinion:

☑ Consideration should be given to the choice and dose regimen of analgesic agents in patients with hepatic and particularly renal impairment (**S**).

9.7 | The opioid-tolerant patient

With increased opioid prescribing for chronic pain, partly due to an ageing population, and increased use and misuse of prescription opioids, increasing proportions of patients with acute pain are opioid-tolerant. The proportion of opioid-tolerant patients varies widely with country and context. For example, it is higher in those presenting for orthopaedic and spinal surgery (Hilliard 2018 **Level IV**, n=34,186).

9.7.1 | Definitions

Misunderstandings in the terminology related to addiction (see also Section 9.8 below), tolerance, and physical dependence may confuse health professionals and patients, leading to inappropriate and/or suboptimal acute pain management as well as stigmatisation (Patel 2017 **Level IV**, n=216). Terms such as addiction, substance abuse, substance dependence and dependence are often used interchangeably. Relevant terms are defined in Table 9.8.

The definitions of many of these terms were not developed for people suffering with chronic pain. Consensus statements from the IMMPACT and ACTTION panels address definitions for the patient with chronic pain (O'Connor 2013 **GL**; Smith 2013 **GL**) as follows:

- Misuse: opioid use contrary to the directed or prescribed pattern of use, regardless of the presence or absence of harm or adverse effects
- Abuse: intentional use of the opioid for a nonmedical purpose, such as euphoria or altering one's state of consciousness
- Addiction: Pattern of continued use with experience of, or demonstrated potential for, harm.

Table 9.8 | Definitions of relevant terms

Aberrant drug-related behaviours	"*Behaviours that may be suggestive of the development of abuse, addiction or misuse*" (Moore 2009)
Addiction	A disease that is characterized by aberrant drug-seeking and maladaptive drug-taking behaviours that may include cravings, compulsive drug use and loss of control over drug use, despite the risk of physical, social and psychological harm While psychoactive drugs have an addiction liability, psychological, social, environmental and genetic factors play an important role in the development of addiction Unlike tolerance and physical dependence, addiction is not a predictable effect of a drug "*Primary chronic disease of brain reward, motivation, memory and related circuitry. Dysfunction in these circuits leads to characteristic biological, psychological, social and spiritual manifestations*" (AAPM 2001 **GL**)
Chemical coping	"*The use of opioids to cope with emotional distress, characterized by inappropriate and/or excessive opioid use*" (Kwon 2015 **NR**)

Dependence syndrome (ICD 10)	"*A cluster of behavioural, cognitive, and physiological phenomena that develop after repeated substance use and that typically include a strong desire to take the drug, difficulties in controlling its use, persisting in its use despite harmful consequences, a higher priority given to drug use than to other activities and obligations, increased tolerance, and sometimes a physical withdrawal state*" (AAPM 2001 **GL**)
Diversion	Sharing, selling or trading prescribed drugs to someone for whom they are not prescribed (Arria 2011 **Level IV**) Sourcing activities or paths which redirect psychoactive prescription drugs from legitimate production or medical-use environments into the hands of nonmedical consumers (Fischer 2010 **NR**)
Medication assisted treatment	Use of medications in combination with counselling and behavioural therapies for the treatment of substance use disorders (SAMHSA 2019 **GL**)
Non-medical prescription opioid use (NMPOU)	Used by National Survey on Drug Use (SAMHSA 2019 **GL**)
Opioid Induced Hyperalgesia (OIH)	"*State of nociceptive sensitization caused by exposure to opioids*" (Ramasubbu 2011 **NR**) Declining nociceptive threshold after opioid exposure without overt withdrawal signs (Mao 2015 **NR**)
Physical dependence	A physiological adaptation to a drug whereby abrupt discontinuation or reversal of that drug, or a sudden reduction in its dose, leads to a withdrawal (abstinence) syndrome Withdrawal can be terminated by administration of the same or similar drug
Pseudoaddiction	Behaviours that may seem inappropriately drug-seeking but are a result of undertreatment of pain and resolve when pain relief is adequate (Weissman 1989 **NR**)
Substance use disorder (SUD)	The essential feature of a substance use disorder is a cluster of cognitive, behavioural and psychological symptoms indicating that the individual continues using the substance despite significant substance-related problems (American Psychiatric Association 2013b)
Tolerance (pharmacological)	A predictable physiological decrease in the effect of a drug over time so that a progressive increase in the amount of that drug is required to achieve the same effect Tolerance develops to desired (eg analgesia) and undesired (eg euphoria, opioid-related sedation, nausea or constipation) effects at different rates
Tolerance (associative, psychological)	"*Can arise for all the central effects of opioids, including euphoria and dysphoria, sedation, analgesia and nausea. This type of tolerance involves learning, and its development is linked to environmental or contextual cues*" (Ballantyne 2017 **NR**)

*Source: Adapted from (AAPM 2001 **GL**) and the references in the table.*

9.7.2 | Clinical implications of opioid tolerance and opioid-induced hyperalgesia

Opioid exposure can lead to desensitisation processes commonly described as opioid tolerance and pronociceptive processes referred to as opioid-induced hyperalgesia (OIH) (Mao 2015 **NR**). OIH may be modulated by amongst others NMDA and GABA receptors and possibly the innate neuroimmune system (Arout 2015 **BS NR**) as well as peripheral mu-opioid receptors (Weber 2017 **NR**).

The relative roles played by tolerance and OIH in the patient who is taking long-term opioids are unknown and both may contribute to increased pain (Higgins 2019 **Level III-3 EH SR** [PRISMA], 26 studies, n=2,706; Weber 2017 **NR**). It is also possible that different opioids vary in their ability to induce OIH and tolerance (see Section 4.1.1). Studies of OIH are confounded by factors such as pain modality tested, route of administration and opioid type (Weber 2017 **NR**). Psychological factors such as pain-related distress and catastrophising might also affect pain sensitivity in those taking opioids for chronic pain (Edwards 2011 **Level III-2**; Eyler 2013 **NR**). Illicit substance use, affective characteristics, and coping styles may also play a role (Higgins 2019 **Level III-3 EH SR** [PRISMA], 26 studies, n=2,706).

There are some features of OIH that may help to distinguish it from pre-existing pain. With OIH, pain intensity may be increased above the level of the pre-existing pain; the distribution tends to be beyond that of the pre-existing pain as well as being more diffuse; and QST may show changes in pain thresholds and tolerability (Higgins 2019 **Level III-3 EH SR** [PRISMA], 26 studies, n=2,706; Weber 2017 **NR**; Lee 2011 **NR**; Ramasubbu 2011 **NR**). Additionally, increasing opioid dose will worsen OIH (Colvin 2019 **NR**). Practical clinical challenges include lack of consensus on "the" diagnostic test, and overlap with tolerance, withdrawal and neuropathic pain.

OIH is identified by reduced pain tolerance to noxious thermal (hot and cold), but not electrical stimuli, in patients with chronic opioid exposure (Higgins 2019 **Level III-3 EH SR** [PRISMA], 26 studies, n=2,706); pain detection thresholds remain unchanged. However, an attempt to identify a quantitative sensory testing method to detect hyperalgesia in chronic pain patients on long-term opioids failed, as none of the measures could be used as a definitive standard (Katz 2015b **Level IV EH SR**, 14 studies, n unspecified). The methods investigated include pain due to cold, heat, pressure, electrical stimulus, ischemia, and injection; only heat pain sensitivity showed some promise.

In subjects in methadone-maintenance programs, the presence of chronic pain may differentially increase pain thresholds and there may be a dose-related effect on abnormal pain processing (Chen 2009 **Level III-2 EH**; Peles 2011 **Level III-3 EH**; Hooten 2010 **Level IV EH**). In chronic pain patients on opioid treatment, patients with negative affect (ie more distressed) show more features of OIH (Edwards 2016 **Level III-2**, n=31). There is controversy about the impact of opioid cessation, with some evidence suggesting resolution of OIH after a few months opioid abstinence (Treister 2012 **Level III-3 EH**) and others showing that heat and pain perception remain abnormal even after abstinence for at least 6 mth (Prosser 2008 **Level III-2 EH**).

After intraoperative use of remifentanil (at ≥0.1 mcg/kg/min), there is evidence of acute opioid tolerance and OIH of limited clinical relevance (Kim 2014 **Level IV SR**, number of studies unspecified, n unspecified; Rivosecchi 2014 **Level IV SR**, 35 studies, n unspecified). Another meta-analysis confirms clinically small but statistically significant OIH only after high-dose remifentanil (≥0.3 mcg/kg/min) with insufficient data on fentanyl and sufentanil (Fletcher 2014 **Level I** [PRISMA] 27 RCTs, n=1,494). Patients had increased postoperative pain scores at 1 h (MD 9.4/100; 95%CI 4.4 to 14.5) up to 24 h (MD 3/100; 95%CI 0.4 to 5.6) and higher opioid requirements over 24 h (SMD 0.7; 95%CI 0.37 to 1.02). Overall, the effect of remifentanil is dose dependent (Angst 2015 **NR**). Gradual (by 0.6 ng/ml target concentration every 5 min) vs abrupt withdrawal of a remifentanil infusion (target concentration 2.5 ng/ml for 30 min) induced no OIH (pain similar to placebo) measured with the

heat pain test, but not the cold pressor test (Comelon 2016 **Level II EH**, n=19, JS 5). This was confirmed in a clinical setting of thyroidectomy, where gradual tapering of a high-dose remifentanil infusion (from 0.3 to 0.1 mcg/kg/min over at least 30 min) reduced postoperative pain at 1 and 2 h and rescue analgesia requirements (Han 2015 **Level II**, n=62, JS 5).

NMDA-receptor antagonists (mainly ketamine [8 RCTs] but also magnesium [5 RCTs] and amantadine [1 RCT]) reduce the development of acute tolerance/OIH associated with remifentanil use (Wu 2015 **Level I** [QUOROM], 14 RCTs, n=729). Pregabalin had an attenuating effect (Lee 2013b **Level II**, n=93, JS 5; Jo 2011 **Level II**, n=60, JS 5) as did propofol in a subgroup analysis (6 RCTs, n=341) of a systematic review (Fletcher 2014 **Level I** [PRISMA], 27 RCTs, n=1,494) as well as N_2O (Wehrfritz 2016 **Level II EH**, n=21, JS 5; Echevarria 2011 **Level II**, n=50, JS 4). Low-dose naloxone (0.25 mcg/kg/h intraoperatively) also reduced postoperative opioid requirements when combined with high dose remifentanil (and improved time to bowel recovery) (Xiao 2015 **Level II**, n=75, JS 5).

The challenge faced by the health professional is that if inadequate pain relief is due to OIH, reducing the opioid dose may help; if it is due to opioid tolerance, increased doses may provide better pain relief (Colvin 2019 **NR**; Huxtable 2011 **NR**; Mao 2008 **NR**). There are case reports of patients with cancer and chronic noncancer pain taking high doses of opioid who developed OIH and whose pain relief improved following reduction of their opioid dose (Chang 2007 **CR**; Angst 2006 **CR**). There are no data in the acute pain setting.

When a patient who has been taking opioids for a while (either legally prescribed or illicitly obtained) has new and ongoing tissue injury with resultant acute pain, a reasonable initial response to inadequate analgesia, after an evaluation of the patient and in the absence of evidence to the contrary, is a trial of higher opioid doses (Huxtable 2011 **NR**; Chang 2007 **NR**). If the pain improves, this would suggest that the inadequate analgesia resulted from tolerance; if pain worsens, or fails to respond to dose escalation, it could be a result of OIH (Chang 2007 **NR**). Fortunately, some of the strategies that may be tried in an attempt to attenuate opioid-tolerance in the acute pain setting may also moderate OIH (see below).

Other reasons for increased pain and/or increased opioid requirements should also be considered. These include acute neuropathic pain, pain due to other causes including postoperative complications, major psychological distress and aberrant drug-seeking behaviours (see Section 9.8 below) (Edwards 2011 **Level III-2**; Macintyre 2015 **NR**; Gourlay 2008 **NR**).

9.7.3 | Patient groups

Four main groups of opioid-tolerant patients are encountered in acute pain settings.

1. Patients with chronic noncancer pain (CNCP) being treated with opioids, where acute presentations may be due to a new acutely painful condition (eg surgery, trauma) or to exacerbation of the underlying chronic condition (eg sickle cell crisis, pancreatitis) (Quinlan 2012 **NR**). Opioids for CNCP are associated with increased risk of acutely painful injuries, including fractures (Teng 2015 **Level III-2 SR**, 8 studies, n=500,819), other injury and overdose (Landsman-Blumberg 2017 **Level III-2**, n=21,203), with increasing risk as opioid dose increases (Bedson 2019 **Level III-2**, n=98,140; Murphy 2018 **Level IV**, n=19,480 [SAEs]). In USA veterans, chronic opioid use is more likely at younger ages, in males, in rural areas, in smokers, in the presence of back pain, and in those with post-traumatic stress disorder (PTSD) and major depression (Hudson 2017 **Level III-2**). Australian pharmaceutical benefit (PBS) scheme data show persistent opioid use is more likely if initiated with transdermal preparations, higher doses, in older patients, with comorbid depression (Sullivan 2018 **NR**) or psychotic illness, and if there is prior dispensing of pregabalin or benzodiazepines (Lalic 2019 **Level IV**, n= 769 334). Some of the patients in this group may exhibit features of OUD.

2. Patients with cancer pain being treated with opioids, who may be at various stages of their illness including active treatment (eg surgery), palliation and in remission. In the latter case, survivors of cancer may experience specific issues relating to "survivorship" (Yazdani 2014 **NR**). Some of these issues will be similar to those in patients with chronic noncancer pain.
3. Patients with a OUD with current status ranging from using illicit prescription or non-prescription opioids and/or on an opioid-maintenance treatment program, or in remission; many patients with active or past OUD report chronic non-cancer pain (see also Section 9.8 below).
4. Patients who have developed acute or subacute opioid tolerance (or OIH) due to perioperative opioid administration, particularly opioids of high potency, in high dose and for "extended" periods (e.g. in an ICU).

Recognition of the presence of opioid tolerance or OIH may not be possible if the patient's history is not available or accurate (eg following major trauma with ICU admission or if the patient is unconscious at presentation). If a patient is requiring much larger than expected opioid doses and other factors that might be leading to the high requirements have been excluded, opioid tolerance or OIH should be considered.

See Sections 10.6.3.1 and 10.7 for paediatric issues.

9.7.3.1 | Overlap between chronic pain (cancer- or non-cancer related) treatment and opioid use disorder

Chronic non-cancer related pain (CNCP)

The past twenty years have seen a multi-fold rise in opioid prescription for CNCP, primarily in developed countries (Karanges 2016 **Level IV**; Dowell 2016 **GL**) including Australia, which experienced a a 15-fold increase in opioids dispensed over the 20 years to 2015 (Donovan 2020 **Level IV SR**, 24 studies, n unspecified). This is despite evidence of only small and probably clinically insufficient improvements in pain, physical function and social functioning, and no improvement in emotional functioning vs placebo, and no evidence of better outcomes than most non-opioid alternatives (Busse 2018 **Level I** [PRISMA], 96 RCTs, n=26,169). There is insufficient evidence of long-term benefit (Chou 2015 **Level IV SR**, 39 studies, n unspecified; Dowell 2016 **GL**).

Concurrently, there has been a rising incidence of opioid-related harms, including opioid use disorder (OUD), opioid diversion, traumatic injury such as road trauma, myocardial infarction, overdose (intentional and unintentional) and mortality (Els 2017 **Level I** [Cochrane] 14 SRs of 61 RCTs, n=18,679; Tucker 2019 **Level I** [PRISMA], 14 RCTs, n=3,071; Ray 2016 **Level III-2**, n=22,912 [prescription episodes]; Chou 2015 **Level IV SR**, 39 studies, n unspecified; Dowell 2016 **GL**). Adverse events are more likely at higher doses, typically greater than 100 mg oral MED/d (Chou 2015 **Level IV SR**, 39 studies, n unspecified; Dowell 2016 **GL**; Ballantyne 2017 **NR**) and with greater dose variability (Glanz 2019 **Level III-2**, n=14,898).

The relationship between CNCP and addiction exists on a continuum with a "*complicated reciprocity*" between the two conditions (Manhapra 2018 **NR**). Ballantyne defines "*complex persistent dependence*" in CNCP by the inability to taper opioids, accompanied by OUD-like behaviours on attempted cessation (Ballantyne 2012 **NR**). CNCP and addiction have overlapping mechanisms with disruption of reward in both, noting that acute pain in the context of CNCP may have "*positive reinforcing qualities*" (Elman 2016 **NR**).

Observed rates of OUD in CNCP depend on the definitions used. The varying criteria in DSM-IV, DSM-V, ICD-9, -10 and -11 classifications lead to different estimates (Kaye 2017b **NR**), noting that these definitions were not developed for those with concurrent pain (Campbell 2016 **Level IV**, n=1,134).

- In those with CNCP, "misuse" prevalence was 21 to 29% (95%CI 13 to 38%), and "addiction" 8 to 9% (95%CI 3 to 17%) (Vowles 2015 **Level IV SR** [PRISMA], 38 studies, n=1,026,427).
- Using IMMPACT and ACTTION consensus statements in mixed studies of chronic non-cancer and cancer pain, the pooled incidence of "dependence/abuse" was 4.7% (95%CI 2.1 to 10.4%) (Higgins 2018 **Level IV SR** [PRISMA], 12 studies, n=310,408).
- The Australian POINT Study found 18% of community members with CNCP prescribed opioids met DSM-V 'opioid use disorder' criteria, 19% ICD-11 'dependence' criteria, and 24% the 'addiction' definition used in pain medicine, with substantial concordance (Campbell 2016 **Level IV**, n=1,134).

In USA veterans, chronic opioid use is more likely if younger, male, white, married, living in in a rural area, PTSD (OR 1.22; 95%CI 1.2 to 1.25), major depression (OR 1.14; 95%CI 1.12 to 1.17), tobacco use disorder (OR 1.18; 95%CI 1.15 to 1.2), back pain (OR 2.50; 95%CI 2.45 to 2.55), and with increasing pain severity (Hudson 2017 **Level IV**, n=1,397,946). American patients on higher opioid doses for musculoskeletal pain are less likely to be working, with greater depression, more fear-avoidance, decreased pain self-efficacy and greater primary care and pain clinic visits (Morasco 2017 **Level III-3**, n=517). Depressed patients are twice as likely to transition to long-term opioid use for CNCP; depression increases risk of abuse or non-medical prescription opioid use (although dose and duration contribute to this risk, duration is more important) (Sullivan 2018 **NR**).

These factors are similar to the factors that are associated with SUD. In patients presenting for surgery, a higher Screener and Opioid Assessment for Patients with Pain-Revised (SOAPP-R) score is associated with increased likelihood of preoperative prescribed and illicit opioid use and increased postoperative surgical site pain (Hah 2015 **Level IV**, n=107). OUD is more likely in the presence of psychosocial factors, particular if the person has a genetic predisposition (Kaye 2017b **NR**). Past-year "dependence" is increased in younger people and if there is a history of benzodiazepine dependence (Campbell 2015 **Level IV**, n=1,424). There is a strong association with psychiatric illness including mood disorders, antisocial personality disorder and PTSD, and a history of SUD (Kaye 2017b **NR**). In one USA series, of those prescribed opioids long-term, 73.1% had a comorbid psychiatric diagnosis (Glanz 2019 **Level III-2**, n=14,898).

In those with chronic pain and history of SUD, pain catastrophising is associated with greater likelihood of prescription opioid misuse (Morasco 2017 **Level III-3**, n=517). High-dose opioid prescription also increases the likelihood of self-reported heroin use (adjusted HR 2.54; 95%CI 1.26 to 5.10) in USA veterans, although long-term opioid prescription did not increase this risk (Banerjee 2019 **Level III-2**, n=3,570). In Canada, prescription of opioids is a common pathway to OUD requiring addiction treatment, more commonly in women; those taking this route are older and more educated with chronic pain a significant association (Sanger 2018 **Level III-2**, n=976). Addiction treatment outcomes may be worse in those with pain volatility (Worley 2015 **Level IV**, n=149). There is growing evidence that buprenorphine maintenance therapy may be preferred in those with combined CNCP and addiction (Berna 2015 **NR**) (see Section 9.8 below).

Screening for risk of OUD is addressed in Section 9.8.5 below.

Cancer pain

Those with cancer pain exist on a continuum in terms of disease stages, conforming roughly to three main groups – those undergoing active treatment with curative intent, those undergoing palliative care/treatment with reduced life expectancy and those in remission.

In a palliative care setting, physician-assessed "chemical coping", defined as "using prescribed opioids to control non-nociceptive symptoms", was found in 18% (95%CI 14 to 21%) and (on multivariate analysis) more likely in patients who were younger, CAGE ("cut-annoyed-

guilty-eye" screening questionnaire for problematic alcohol use) positive, with better function, higher pain and lower wellbeing scores (Kwon 2015 **Level IV**). There was high prevalence of positive SOAPP-SF and CAGE in a palliative care clinic, noting approximately one quarter had no evidence of ongoing disease and one quarter had CNCP; there were also positive urine drug screens in those with cancer and active treatment (56% of the subsample) (Childers 2015 **Level IV**, n=323)

With improved oncological treatment, there is a growing population of cancer "survivors", defined by the American Cancer Society as survival at least 5 y following a cancer diagnosis. In this group, CNCP is common and multifactorial due to surgery, radiotherapy, chemotherapy and incidental causes (Carmona-Bayonas 2017 **NR**). An integrative review estimated that at least one in five cancer patients may be at risk of OUD (Carmichael 2016 **NR**). Cancer survivors are more likely than the general population to be prescribed long-term benzodiazepines and opioids, with such prescriptions often not conforming to professional guidelines (Fredheim 2019 **Level IV**, n=21,426). Particular issues arise in those with co-morbid psychiatric disorders including an addiction history (Carmona-Bayonas 2017 **NR**). Surveys of USA palliative care providers and hospice social workers found limited systems in place to screen for and manage OUD in this context (Merlin 2019 **Level IV**, n=157 [health care professionals]; Sacco 2017 **Level IV**, n=107 [US Medicare certified hospices]).

The American Society of Clinical Oncology practice guidelines recommend a universal precautions approach to chronic pain in survivors of adult cancers, with regular screening for pain, multidisciplinary care for complex situations, preference for non-opioids, opioid trials in selected patients with clear goals and regular risk assessment (Paice 2016 **GL** [based on SR of 63 studies]).

9.7.4 | Chronic opioid use and perioperative outcomes

9.7.4.1 | Effects on perioperative outcomes

A growing body of evidence, primarily in patients undergoing elective orthopaedic and spinal surgery and primarily retrospectively collected, shows an association between chronic preoperative opioid use and worse postoperative outcomes. This includes increased likelihood of 90-d complications (Sing 2016 **Level III-2**, n=174), revision arthroplasty following primary arthroplasty (Bedard 2018a **Level III-2**, n=17,695; Bedard 2018b **Level III-2**, n=35,894; Weick 2018 **Level III-2**, n=324,154; Ben-Ari 2017 **Level III-2**, n=32,636) and periprosthetic joint infection (Bell 2018 **Level III-2**, n=23,754).

In primary knee arthroplasty, preoperative opioid use was associated with poorer outcomes – longer hospital LOS, more additional surgeries for stiffness or pain, more referrals to pain specialists and worse knee society scores (Zywiel 2011 **Level III-2**, n=98). In spinal surgery, opioids increase the risk of 90 d wound complications, readmission and revision spinal fusion (Jain 2018a **Level III-2**, n=29,101; Jain 2018b **Level III-2**, n=24,610). Likewise, opioid abuse and dependence (defined by ICD-9 codes) are associated with increased aggregate morbidity (OR 2.3; 95%CI 2.2 to 2.4), surgical site infection (OR 2.5; 95%CI 2.0 to 3.0), pneumonia (OR 2.1; 95%CI 1.8 to 3.2) and prolonged LOS (OR 2.5; 95%CI 2.4 to 2.5) following joint arthroplasty and spinal fusion (Menendez 2015 **Level III-2**, n=9,307,348). Greater preoperative opioid use is associated with worse general health, quality of life and disability at 3 and 12 mth following spinal surgery (Lee 2014 **Level III-2**, n=583). However, evidence is conflicting, with multivariate analysis of spinal surgery showing preoperative opioid use not being associated with complications (identified on retrospective chart review), but only with increased LOS (Armaghani 2016 **Level III-2**, n=583). On multivariate analysis, preoperative opioid use is associated with longer LOS, more complications,

more readmissions and increased (covariate-adjusted) costs following abdominal and other surgeries (Gupta 2018a **Level III-2**, n=16,016,842; Cron 2017 **Level III-2**, n=2,413; Waljee 2017 **Level III-2**, n=200,005).

Chronic opioids may also suppress the hypothalamic-pituitary-adrenal axis. As many as one in five patients on chronic opioids may have low cortisol levels, although is not clear which patients should be screened (Demarest 2015 **NR**). This led the US Food and Drug Administration (FDA) in 2013 to issue a warning to be added to all opioid labelling (FDA 2013 **GL**). Addisonian crises have been described in some postoperative patients (Fountas 2018 **NR**). Although the prevalence is unknown, the implications for perioperative care include investigation should patients present with symptoms and signs suggesting adrenal insufficiency.

9.7.4.2 | Strategies for outcome improvement

Preoperative opioid use may be a modifiable risk factor for perioperative outcomes. There is limited low quality evidence that ceasing opioids preoperatively may ameliorate perioperative risk (Jain 2018a **III-2**, n=29,101; Nguyen 2016 **Level III-2**, n=177).

Opioid tapering should be considered prior to elective surgery, although there is limited evidence as to the best strategy in terms of efficacy and safety (Eccleston 2017 **Level I** [Cochrane], 5 RCTs, n=278; Berna 2015 **GL**). Whatever strategy is used, it should consider patient-centred barriers (fear of withdrawal and that nonopioids might be ineffective) and facilitators (social support and a trusted practitioner) along with reassurance about long-term benefits (including improved pain and quality of life) (Goesling 2019 **Level IV**, n=49; Frank 2016 **Level IV**, n=24).

Expert advice is for shared decision making, reduction by 5 to 20% every 4 wk (Pergolizzi 2018 **GL**), and support for self-efficacy, resilience and alternative pain management strategies (McAnally 2017 **GL**). The USA Department of Veterans Affairs has developed an opioid tapering tool (U.S. Department of Veterans Affairs 2016 **GL**). Alpha-2 agonists such as clonidine are effective for withdrawal symptoms, although have side effects including hypotension (Gowing 2014 **Level I** [Cochrane], 25 RCTs, n=1,668).

In opioid-tolerant patients, improved compliance with enhanced recovery after surgery (ERAS) protocols may mitigate the impact of opioid tolerance on postoperative complications (Owodunni 2019 **Level III-2**, n=646). ERAS may provide a framework to reduce the risk of ongoing opioid use; it is multidisciplinary, patient-centred, includes multimodal analgesia (which decreases opioid reliance), includes site-specific regional analgesia, promotes more comprehensive preoperative assessment, and has formalised pathways for community transition; it is a logical extension for ERAS to guide use of post discharge opioids including tapering and follow-up (Stone 2017 **NR**).

9.7.5 | Chronic opioid use and sleep-disordered breathing

Opioids can affect ventilatory function via decreases in central respiratory drive, level of consciousness and upper airway tone causing opioid-induced ventilatory impairment (OIVI) (Macintyre 2011 **NR**).

Long-term opioid use is a risk factor for sleep-disordered breathing (SDB) (prevalence in this population 24%) (Correa 2015 **Level III-3 SR**, 8 studies, n=560); SDB (in particular central sleep apnoea) is strongly associated with morphine equivalent daily dose (high risk >200 mg MED/d) with body mass index inversely related to the severity of SDB. A study not included in this systematic review has similar findings (Rose 2014 **Level IV**, n=24); severe SDB (again mainly central sleep apnoea) was found in 46 % of patients on opioids in a dose-dependent fashion and of these 45% had daytime hypercapnia, indicating chronic respiratory failure.

In patients undergoing methadone-maintenance treatment, SDB was common (35.2% OSA and 14.1% central sleep apnoea), but not related to methadone dose and subjective sleep complaints (Sharkey 2010 **Level IV**, n=71). Patients on methadone-maintenance programs were more likely to have sleep abnormalities, especially central sleep apnoea, than were matched controls, although the effect was confounded by greater use of benzodiazepines in the methadone group (Teichtahl 2001 **Level III-2**, n=19).

Particular care should be taken when the total opioid dose is rapidly escalated above the usual dose and when other sedative agents are coadministered (Macintyre 2011 **NR**).

See also Section 9.4 above.

9.7.6 | Assessment and management of acute pain

A number of articles, chapters and a book (Bryson 2012a **NR**) have been published outlining suggested strategies for the assessment and management of acute pain in the patient taking long-term opioids for chronic pain or because they have a SUD, perhaps treated in a drug treatment program. These focus on postoperative (Coluzzi 2017 **NR**; Simpson 2017 **NR**; Buckley 2014 **NR**; Tumber 2014 **NR**; Eyler 2013 **NR**; De Pinto 2012 **NR**; Geary 2012 **NR**; Quinlan 2012 **NR**; Schug 2012 **NR**; Huxtable 2011 **NR**) and post-traumatic pain (Karamchandani 2019 **NR**).

Evidence for the most appropriate assessment and management in these patients is very limited and the advice given in these papers remains based primarily on case series, case reports, expert opinion and personal experience. Opioid-tolerant patients are heterogeneous and thus difficult to study, and thus are often excluded from studies of acute pain management. The past few years have seen a growing number of RCTs in opioid-tolerant patients or inclusion of these patients in broader studies, often after spinal or orthopaedic surgery. However, details of the opioid tolerance and pre-existing pain are sometimes not well described. In general, assessment and management of these patients should focus on:

- Coordinated care that includes an interdisciplinary approach and liaison with other treating health professionals and specialist teams, as required,
- Effective analgesia;
- Use of strategies that may attenuate tolerance or OIH;
- Prevention of withdrawal;
- Appropriate discharge planning to ensure continuity of long-term care.

9.7.6.1 | Models of care and clinical pathways

Given that opioid-tolerant patients may present complex assessment and management challenges, there is an international trend towards improved perioperative coordination of care with interdisciplinary input. This aims to provide patient-centred care, robust preoperative risk stratification, planning, optimisation and consent, reduced practice variability and care continuity, including bidirectionally in transition from hospital to the community. These models promote safe opioid management that conforms to professional guidelines, by identifying those at risk, offering tapering strategies, ensuring ongoing follow-up, and promoting coordination and communication with other providers.

One such integrated model of care is the Perioperative Surgical Home, which has been extensively discussed in the literature (Kaye 2017a **NR**) and might be of particular value in the setting of high risk patients including the opioid-tolerant patient (Pozek 2017 **NR**). Other models have been described which involve pain medicine physicians (and others) early in the preoperative and then the postoperative phase; these are either described as a Transitional Pain Service (Huang 2015 **NR**; Katz 2015a **NR**) or an Acute Pain Outpatient Service (Tiippana 2016 **Level IV**, n=200). There are limited data supporting successful opioid reduction by such services (Huang

2016 **Level IV**, n=51; Tiippana 2016 **Level IV**, n=200). There is the suggestion that such services could become an integrated part of the Perioperative Surgical Home (Vetter 2017 **NR**).

"Ambulatory pain physicians" based in ambulatory surgical centres could be another approach (Vadivelu 2016a **NR**), in particular as the management of opioid-tolerant patients in this setting is often even more complex (Vadivelu 2017 **NR**).

Interdisciplinary management of patients with aberrant opioid-related behaviour has been successfully implemented in the palliative care setting (Arthur 2018 **Level IV**, n=30). Peer-reviewed clinical pathways including standardised postoperative analgesia orders for opioid-tolerant patients developed with multidisciplinary input improved pain management and PACU discharge readiness (Naqib 2018 **Level III-3**, n=169). A Safer Opioid Prescribing Protocol (SOPP) introduced in an electronic medical record at a level 1 trauma centre improved prescribing of non-opioids and reduced high-dose opioid prescribing (Baird 2019 **Level III-3**, n=507).

9.7.6.2 | Assessment

Assessment using unidimensional measures is frequently inadequate, in particular in these complex patients (Radnovich 2014 **NR**; Gandhi 2011 **NR**). The need for multidimensional assessment is recognised in the ACTTION-APS-AAPM pain taxonomy which uses five dimensions (core criteria, common features, modulating factors, impact/functional consequences, putative pathophysiologic pain mechanisms) to better describe pain complexity (Kent 2017 **GL**). The USA is abandoning pain scores and pain as "the fifth vital sign", as an unintended consequence has been excess opioid administration to chase pain scores (viewed as a contributor to the opioid epidemic). This has been exacerbated by the direct link between pain self-report and reimbursement; the Hospital Consumer Assessment of Healthcare Providers and Systems (HCAHPS) survey uses pain scores as a surrogate measure of care quality. Treating unidimensional scores may lead to increased adverse events like oversedation and should be avoided (Levy 2019 **NR**). This is in particular true in the setting of opioid-tolerance and chronic pain (Allen 2014 **NR**).

Other considerations in acute pain assessment in opioid-tolerant patients include:

- Psychological and social, as well as biological, triggers for pain deterioration in those with chronic pain should be identified (Quinlan 2012 **NR**);
- Specific factors that should be sought in all opioid-tolerant patients, those with chronic pain and those with SUD (see Table 9.9) (Huxtable 2011 **NR**);
- Practitioners determining the need for elective procedures (eg surgeons, physicians, radiologists) or for labour analgesia planning (obstetricians, general practitioners) should refer patients early for pain management planning and optimisation (Tumber 2014 **NR**);
- Previous records should be reviewed and information about prior experiences of acute pain management should be sought to avoid or optimise strategies that were ineffective and to replicate those that were effective (Tumber 2014 **NR**);
- Meaningful engagement of the patient and their family or other caregivers (Geary 2012 **NR**), is key to assessment, management and adherence to the proposed plan (Haber 2009 **NR**) through expectation management, addressing concerns and education;
- Communication should involve engagement, empathising, educating, enlisting and end by summarising, reviewing and indicating next steps (Jamison 2011 **NR**).

Table 9.9 | Pain-related assessment in opioid-tolerant patient

Information from all opioid-tolerant patients	Additional information in patients with CNCP or cancer pain	Additional information in patients with a substance use disorder
Current treatment providers	Pain diagnosis	Opioid substitution therapies and doses (methadone, buprenorphine)
Opioid and nonopioid medications	Usual pain scores	Other prescribed or diverted prescription medicine or illicit substance use (polyabuse is common)
Dose verification of all relevant medications	Functional status	Routes of administration
Nonprescribed drugs (eg over-the-counter and illicit drugs, alcohol, nicotine)	Prognosis (cancer pain)	Where relevant, registered prescriber and dispensing pharmacy
Drug allergies and reactions	Psychospiritual issues (including end-of-life issues, anxiety, depression, coping style and strategies)	Medical and psychiatric comorbidities (eg blood-borne viruses, hepatic disease, other infections, chronic pain, personality disorder)
Experiences and expectations of acute pain management including goals of care	Where relevant, the authorized prescriber of any opioids	Concerns about opioids (especially for those in remission)
Support systems after discharge	Presence of invasive pain treatment (eg IT pump, spinal cord stimulator)	
	Medication misuse, evidence of aberrant drug-related behaviour or SUD	Comorbid chronic pain
	Expectations about their admission (eg expectation that chronic back pain will be improved after spinal surgery; palliative vs curative surgery in patients with cancer)	

Source: From Huxtable 2011; reproduced with permission and modified.

9.7.6.3 | Effective analgesia

Even more than in other patients, the basis for successful pain management in opioid-tolerant patients must be the utilisation of multimodal and interdisciplinary analgesia strategies (Schug 2012 **NR**; Huxtable 2011 **NR**). However, opioids will often be needed and then require additional considerations.

Opioids

It is known that opioid use is usually significantly higher in opioid-tolerant vs opioid-naïve patients and that the interpatient variation in the doses needed is even greater. After a variety of surgical procedures, opioid-tolerant patients using PCA (Rapp 1995 **Level III-2**, n=3,508) or epidural analgesia (de Leon-Casasola 1993 **Level III-2**, n=116) require approximately three times the dose (on average with large standard deviations) vs their opioid-naïve counterparts. The increased acute opioid dosing required to address tolerance continues to be under-recognised. Opioid-tolerant patients with cancer (78% with metastatic disease) presenting acutely to an emergency department were frequently under-dosed, due primarily to "standard dose" administration failing to account for their opioid tolerance (Patel 2017 **Level IV**, n=216). Uptake of expert opinion about managing opioid-tolerant patients for ambulatory surgery is poor, with only 37% taking their usual long-acting opioid on day of surgery and many not receiving recommended non-opioids and adjuvants (Wilson 2015 **Level IV**, n=148).

Opioid-tolerant patients reported higher pain scores (both resting and dynamic) and remained under the care of an APS longer than other patients (Rapp 1995 **Level III-2**, n=3,508). Compared with opioid-tolerant patients with cancer pain, opioid-tolerant patients with noncancer pain had higher rest and dynamic pain scores and required longer APS input but there was no difference in opioid requirements (Rapp 1995 **Level III-2**, n=3,508). In addition, staff relied more on functional measures of pain than on pain scores to assess pain intensity in these patients (Rapp 1994 **Level IV**, n=482 [health care professionals]). Their postoperative pain is initially more intense and needs therefore more time to resolve than that in opioid-naïve patients (Chapman 2009 **Level III-2**, n=138).

The incidence of opioid-induced nausea and vomiting may be lower in opioid-tolerant patients, although the risk of excessive sedation/OIVI may be higher (Rapp 1995 **Level III-2**, n=3,508) and may be particularly likely if opioid doses are rapidly escalated above the baseline level (Huxtable 2011 **NR**).

Where possible, oral or sublingual opioids should be used in preference to parenteral opioids (Donroe 2016 **NR**). IV PCA is a useful modality for pain relief in a subset of opioid-tolerant patients, including those with a SUD, provided that pain intensity and opioid consumption are carefully monitored and background requirements are provided if the patient cannot take their usual opioid; larger bolus doses will often be needed (Macintyre 2015 **NR**; Huxtable 2011 **NR**; Mitra 2004 **NR**). The size of an appropriate dose (on an individual patient basis) has been calculated by one group of investigators by using a preoperative fentanyl infusion until the patient's respiratory rate was <5/min; pharmacokinetic simulations were then used to predict the size of the PCA bolus dose and the rate of a background infusion that would be required for postoperative analgesia (Davis 2005 **Level IV PK**). It may also be based on the dose of opioid the patient is already taking (Macintyre 2015 **NR**; Hadi 2006 **NR**). Regardless of the initial dose prescribed, subsequent doses will need to be titrated to effect for each patient, bearing in mind realistic expectations about pain control and optimisation of non-opioid and non-pharmacological strategies. Caution should also be exercised as high opioid use may result in OIH (see section above).

Neuraxial opioids have been used effectively in opioid-tolerant patients, although higher doses may be required without increasing adverse effects (de Leon-Casasola 1993 **Level III-2**).

Effective analgesia using IT or epidural opioids will not necessarily prevent opioid withdrawal (Huxtable 2011 **NR**; Carroll 2004 **NR**).

Nonpharmacological strategies

Behavioural and cognitive techniques may minimise anxiety and reduce catastrophising, and physical techniques should also be considered (Tumber 2014 **NR**); however, there is limited evidence for their effectiveness in opioid-tolerant patients in acute pain settings

9.7.6.4 | Attenuation of tolerance and opioid-induced hyperalgesia

A number of strategies may attenuate opioid tolerance and OIH. These include:

- NMDA-receptor antagonists
- opioid-receptor antagonists;
- opioid rotation;
- other adjuvant medicines.

NMDA-receptor antagonists

As noted in Section 4.6, the NMDA receptor is involved in tolerance and OIH development (Chang 2007 **NR**). In rodents, the NMDA-receptor antagonist ketamine attenuates both the development of tolerance (Laulin 2002 **BS**; Shimoyama 1996 **BS**) and OIH (Van Elstraete 2011 **BS**; Minville 2010 **BS**; Haugan 2008 **BS**; Laulin 2002 **BS**).

NMDA-receptor antagonists (mainly ketamine [8 RCTs], but also magnesium [5 RCTs] and amantadine [1 RCT]) reduce the development of acute tolerance/OIH associated with remifentanil use (Wu 2015 **Level I** [QUOROM], 14 RCTs, n=729). This statement is based on reduced postoperative pain scores and opioid requirements and increased time to first analgesic request and satisfaction scores in the NMDA-receptor antagonist vs placebo groups.

After spinal surgery in opioid-tolerant patients, perioperative ketamine resulted in significantly less pain but did not reduce PCA opioid use (Urban 2008 **Level II**, n=26, JS 3) and reduced opioid requirements and pain scores in the early postoperative period and at 6 wks (Loftus 2010 **Level II**, n=101, JS 4). For multilevel spinal fusion, ketamine decreased PCA hydromorphone use in opioid-tolerant but not opioid-naïve patients, with the effect primarily from 16 h postoperatively (Boenigk 2019 **Level II**, n=129, JS 5). Intraoperative S-ketamine in opioid-tolerant patients undergoing spinal surgery resulted in reduced PCA morphine use at 24 h (MD -42 mg; 95%CI -59 to -25) with reduced sedation and without increasing other adverse effects. Furthermore, at 6 mth there was improved back pain, longer walking distance and less disability (Nielsen 2017a **Level II**, n=150, JS 5). This beneficial effect was maintained at 1 y with lower opioid use, lower dynamic pain scores, greater likelihood of working and lower disability scores (Nielsen 2019 **Level II**, n=147, JS 5).

After noncancer general surgery in a similar patient group, a postoperative ketamine infusion at 0.2 mg/kg/h decreased average pain scores (13.5% decrease vs 15.5% increase) but not opioid use (Barreveld 2013 **Level II**, n=64, JS 4).

Consensus guidelines for the use of ketamine infusions in acute pain support its use for opioid-dependent or opioid-tolerant patients undergoing surgery to limit opioid use (Schwenk 2018 **GL**).

Opioid receptor antagonists (low dose)

In rodents, ultra-low dose naloxone has been shown to attenuate opioid tolerance (Wang 2005 **BS**; Crain 2000 **BS**; Crain 1995 **BS**) and remifentanil-induced OIH (Aguado 2013 **BS**).

In the experimental pain setting in healthy volunteers, the coadministration of ultra-low doses of naloxone (La Vincente 2008 **EH**) or naltrexone (Hay 2011 **Level II EH**, n=10, JS 5) to buprenorphine significantly increased tolerance to cold-pressor pain.

Clinical studies have concentrated on the concurrent use of naloxone and an opioid given acutely, with conflicting results; improved postoperative pain and reduced opioid use as well as no differences in either have been reported (Angst 2006 **NR**; Sloan 2006 **NR**). The use of low-dose naloxone added to postoperative opioid analgesia (most commonly by PCA) decreases the risk of pruritus (OR 0.40; 95%CI 0.21 to 0.79) and nausea (OR 0.62; 95%CI 0.43 to 0.89), but not vomiting, pain intensity or opioid use (Murphy 2011 **Level I**, 8 RCTs, n=800). Use over 3 mth of a combination of oxycodone/ultra-low-dose naltrexone in patients with chronic pain vs oxycodone alone, showed that those given the combination had similar pain relief but with 12% lower daily oxycodone use, as well as less constipation, sedation, pruritus and physical dependence as assessed by a withdrawal scale (Webster 2006 **Level II**, n=719, JS 4). Low-dose naloxone (0.25 mcg/kg/h intraoperatively) also reduced postoperative opioid use when combined with high dose remifentanil (and improved time to bowel recovery) (Xiao 2015 **Level II**, n=75, JS 5).

Opioid rotation

Opioid rotation (also called "switching") is commonly used in the treatment of chronic noncancer and cancer pain when a change to another opioid can improve analgesia and reduce adverse effects (Mercadante 2012 **Level IV;** Nalamachu 2012 **NR**). Opioid rotation (eg using an opioid that is different from the preadmission opioid) may also be useful in the acute pain setting (Huxtable 2011 **NR**; Hadi 2006 **NR**). The underlying rationale is that different opioids do not act to the same degree on various opioid receptor subtypes, are metabolised differently, that cross-tolerance is likely to be incomplete (Huxtable 2011 **NR**; Mitra 2008 **NR**; Jage 2005 **NR**) and that the degree of OIH and tolerance appears to vary between opioids (see Section 4.3.1).

Adjuvants

Adjuvants are primarily used for their antitolerance, antiallodynic and antihyperalgesic effects (Huxtable 2011 **NR**).

In rats, intraoperative use of paracetamol, metamizol, ketoprofen and parecoxib abolished acute tolerance caused by remifentanil infusion (Benito 2010 **BS**). In an experimental pain setting using intradermal electrical pain stimuli, parecoxib given before but not during a remifentanil infusion modulated the hyperalgesia after withdrawal of remifentanil (Troster 2006 **Level II EH**, n=15, JS 5).

Gabapentin has also been shown to attenuate opioid tolerance (Aguado 2012 **BS**; Lin 2005 **BS**) and OIH (Wei 2012 **BS**) in rats and this effect was synergistic to ketamine (Van Elstraete 2011 **BS**). Pregabalin shows similar effects in animal models (Lyndon 2017 **BS**; Hasanein 2014 **BS**). In methadone-maintained patients, gabapentin increased cold-pressor pain threshold and pain tolerance (Compton 2010, **Level II EH**, n=26, JS 2). In the setting of OIH associated with remifentanil, 150–300 mg pregabalin preoperatively attenuated this effect after hysterectomy (Jo 2011 **Level II**, n=60, JS 5) and laparoscopic urological surgery (Lee 2013b **Level II**, n=93, JS 5).

Other adjuvants that may influence tolerance and OIH but for which there is limited evidence include alpha-2 agonists (clonidine and dexmedetomidine), buprenorphine (Lee 2011 **NR**; Ramasubbu 2011 **NR**; Patch III 2017 **CR**) and systemic lidocaine (Eipe 2016 **NR**). OIH /tolerance after remifentanil use was also reduced by propofol (6 RCTs, n=341) (Fletcher 2014 **Level I** [PRISMA], 27 RCTs, n=1,494) and N_2O (Wehrfritz 2016 **Level II EH**, n=21, JS 5; Echevarria 2011 **Level II**, n=50, JS 4).

Use of regional analgesia techniques to manage the early postoperative pain of total knee joint replacement did not reduce longer-term opioid use (1 y postop) in the overall population nor after stratification into opioid naïve patients, intermittent opioid users and chronic opioid users (Sun 2017 **Level IV**, n=120,080).

9.7.6.5 | Prevention of withdrawal

Withdrawal from opioids is characterised by excitatory and autonomic symptoms including abdominal cramping, muscle aches and pain, insomnia, dysphoria, anxiety, restlessness, nausea and vomiting, diarrhoea, rhinorrhoea and sneezing, trembling, yawning, watery eyes (epiphora) and piloerection (or "gooseflesh") (Rehni 2013 **NR**; Tetrault 2008 **NR**). Withdrawal-associated injury site pain (WISP), a temporary reactivation of pain at an old injury site that was pain-free prior to opioid initiation, has also been described (Rieb 2016 **Level IV**, n=47). The time of onset of withdrawal symptoms after cessation of the drug will depend on the duration of action of the opioid. To assess withdrawal, the use of validated withdrawal tools (Clinical Opioid Withdrawal Scale, Subjective Opioid Withdrawal Scale, Objective Opioid Withdrawal Scale) is recommended (Donroe 2016 **NR**) (See also Section 10.4.6.2 in children).

Withdrawal should be prevented by maintenance of normal preadmission opioid regimens (including on the day of surgery) or appropriate substitutions with another opioid or the same opioid via another route (Macintyre 2015 **NR**; Schug 2012 **NR**; Huxtable 2011 **NR**). It may be of benefit to check preadmission opioid doses with the patient's doctor or pharmacist; the use of unauthorised additional opioids (licit or illicit) or of lower doses than prescribed may affect both pain relief and the risk of adverse effects.

While multimodal analgesic regimens (eg NSAIDs, paracetamol, ketamine, tramadol, regional analgesia) are of analgesic benefit (Rajpal 2010 **Level III-3**), opioid-tolerant patients are at risk of opioid withdrawal if a purely nonopioid analgesic regimen or atypical opioids with low mu-receptor effects such as tramadol or tapentadol are used (Macintyre 2015 **NR**; Huxtable 2011 **NR**).

For this reason, opioid antagonists (naloxone, naltrexone) should be avoided as their use can precipitate acute withdrawal reactions (Schug 2012 **NR**; Alford 2006 **NR**).

Alpha-2 agonists such as clonidine and lofexidine are more effective than placebo in the management of opioid-withdrawal symptoms (Gowing 2014 **Level I** [Cochrane], 25 RCTs, n=1,668).

During a 10-d buprenorphine detoxification procedure, gabapentin reduced opioid use vs placebo (Sanders 2013 **Level II**, n=30, JS 5) and in a dose of 1,600 mg/d reduced withdrawal symptoms in patients during methadone-assisted detoxification (Salehi 2011 **Level III-1**). Pregabalin attenuated naloxone-induced withdrawal symptoms in opioid-tolerant rats (Hasanein 2014 **BS**) and has also been used successfully to attenuate withdrawal symptoms from a number of drugs including alcohol and benzodiazepines, although data on opioid withdrawal are limited (Freynhagen 2016 **NR).** Pregabalin added to methadone in maintenance program patients reduced methadone requirements and withdrawal symptoms vs placebo (Moghadam 2013 **Level II**, n=60, JS 5).

9.7.6.6 | Discharge planning and transition to community care

Discharge planning for opioid-tolerant patients is optimally commenced prior to admission and must consider any regulatory requirements (eg the authority to prescribe an opioid may have to be delegated to a particular physician only), the duration of use of any additional opioids prescribed for short-term acute pain management and the weaning of those drugs and, in some patients, the potential for prescribed opioids to be abused, misused or diverted. Without robust discharge systems, there is a significant risk of unintended opioid dose escalation with attendant risks (Quinlan 2012 **NR**; Schug 2012 **NR**; Huxtable 2011 **NR**).

Preoperative opioid use, especially at higher dose, is a significant risk factor for ongoing postoperative opioid prescription, even in circumstances where long-term prescription is not indicated (Dunn 2018 Level **III-2**, n=1,477; Goesling 2016 **Level III-2**, n=574). This was confirmed in an Australian population after total hip replacement, where longer preoperative opioid use increased the risk of persistent chronic use (opioid use for 157 to 224 d vs 94 to 157 d [OR=3.75; 95%CI 2.28 to 6.18] and >225 d [OR 5.18; 95%CI 2.92 to 9.19]) (Inacio 2016 **Level IV**, n=8,925). Similar findings are reported after spinal surgery, where preoperative opioid use increased the risk of prolonged postoperative requirements (OR 4.71; 95%CI 3.11-7.13) (Reid 2019 **Level III-3**, n=552). Opioid use in the year prior to elective colorectal surgery was the only risk factor for post-discharge opioid use within 1 y (Scow 2019 **Level IV**, n=367). After minor upper limb surgery (carpal tunnel release, trigger finger release, cubital tunnel release, and thumb carpometacarpal arthroplasty) 59% of patients filled an opioid prescription; patients preoperatively on opioids vs not on opioids filled more postoperative opioid prescriptions (66 % vs 59 %), were given longer-lasting prescriptions (24 d vs 5 d), received more refills (24 % vs 5 %) and 19 % vs 6% had at least one indicator of potentially inappropriate prescribing (Waljee 2016 **Level IV**, n= 296,452).

A "reverse analgesic ladder" approach is recommended, with the aim being stepwise return of the patient to their usual opioid regimen (Huxtable 2011 **NR**). Considerations include the likely duration of acute pain (and thus the amount of opioid that should be prescribed), the choice of opioid and its "abuse liability", and the use of nonopioid agents. In this context it is of note that postoperative pain resolved more slowly in opioid-tolerant than that in opioid-naïve patients (Chapman 2009 **Level III-2**).Appropriate use of nonopioid analgesics where possible, use of abuse-deterrent formulations, provision of small quantities and staged pharmacy supply, communication with the primary physician and other treating health care professionals (including a plan for cessation), and patient education and support must all be considered.

An ethical dilemma arises where the preadmission opioid regimen is not consistent with widely accepted professional guidelines for opioid prescription in chronic pain or SUD (Dowell 2016 **GL**; FPMANZCA 2015 **GL**). In these cases, and/or when there is a high risk of opioid misuse, referral to a pain specialist and/or an addiction service should be considered (Huxtable 2011 **NR**).

The USA CDC guidelines, although criticised, offer some good principles for opioid prescribing, which might be useful in the setting of discharging opioid-tolerant patients after an acute pain episode (Dowell 2016 **GL**):

- Preference for non-drug and non-opioid therapy;
- Defined goals including when opioids would be discontinued;
- Risks discussed at baseline and periodically;
- Immediate-release instead of slow-release opioids;
- Lowest effective dose – reassess at 50mg OME, avoid greater than 90 mg OME;
- For acute pain, lowest effective dose of IR for shortest duration;
- Reassess benefits and harms early and frequently;
- Evaluate risk of opioid-related harms before and episodically;
- Avoid concurrent benzodiazepines;
- If OUD, offer evidence-based treatment for this (see Section 9.8 below).

The Australian NPS MedicineWise program (NPS MedicineWise 2019 **GL**) recommends referral to an addiction or pain medicine specialist if the patient:

- is taking two or more psychoactive drugs in combination;
- is taking opioids and benzodiazepines;
- has serious psychiatric illness;
- mixes pharmaceutical and illicit drug intake;
- has been discharged from a general practitioner for problematic behaviour;

- was recently discharged from a correctional service;
- shows evidence of high-risk behaviours.

For more details on opioid use and discharge medication see Sections 9.8., 8.13. and 10.4.5.

KEY MESSAGES

1. Alpha-2 agonists (clonidine and lofexidine) reduce opioid-withdrawal symptoms (**U**) (**Level I** [Cochrane Review]).
2. Remifentanil use leads to opioid-induced hyperalgesia (**U**), which is attenuated by propofol (**U**) (**Level I** [PRISMA]), NMDA-receptor antagonists (**U**) (**Level I** [QUOROM]), pregabalin (**U**) (**Level II**), nitrous oxide (**N**) (**Level II**) and gradual tapering of remifentanil dose (**N**) (**Level II**).
3. Gabapentin and pregabalin attenuate opioid-induced hyperalgesia/tolerance and reduce opioid-withdrawal symptoms (**U**) (**Level II**).
4. In opioid-tolerant patients, ketamine improves pain relief after surgery and reduces opioid requirements (**S**) (**Level II**).
5. Long-term opioid use is a dose-dependent risk factor for sleep-disordered breathing, which requires appropriate perioperative assessment, monitoring and management (**S**) (**Level III-2 SR**).
6. Long-term opioid use is associated with dose-dependent increased risks of injuries (**N**) (**Level III-2**) including fractures (**N**) (**Level III-2 SR**) and overdose (**N**) (**Level III-2**).
7. Preoperative opioid use is associated with worse outcomes after a variety of operations (**N**) (**Level III-2**).
8. Preoperative opioid tapering may ameliorate the risk of postoperative complications and morbidity (**N**) (**Level III-2**)
9. Preoperative opioid use is a risk factor for prolonged postoperative opioid use (**N**) (**Level III-2**).
10. Opioid-tolerant patients report higher pain scores, have slower pain resolution leading to longer hospital stay and increased readmissions but have a lower incidence of opioid-induced nausea and vomiting (**U**) (**Level III-2**).
11. Opioid-tolerant patients may have significantly higher opioid requirements and interpatient variation in the doses needed than opioid-naïve patients (**U**) (**Level III-2**).

The following tick boxes represent conclusions based on clinical experience and expert opinion:

☑ Usual preadmission opioid regimens should be maintained where possible or appropriate substitutions made (**S**).

☑ Liaison with all health care professionals involved in the treatment of the opioid-tolerant patient is important (**S**).

☑ Opioid-tolerant patients are at risk of opioid withdrawal if nonopioid analgesic regimens, tramadol or tapentadol alone are used (**U**).

- ☑ PCA settings may need to include a background infusion or other background opioid to replace the usual opioid dose and a higher bolus dose (**U**).
- ☑ Neuraxial opioids can be used effectively in opioid-tolerant patients, although higher doses may be required and these doses may be inadequate to prevent withdrawal (**U**).
- ☑ Adjuvants are used for their antitolerance, antihyperalgesic, and antiallodynic effects and there is some evidence upon which to base the choice of agent (**S**).
- ☑ In patients with escalating opioid requirements, management considerations are the development of tolerance or opioid-induced hyperalgesia (**S**).
- ☑ Following short-term opioid dose escalation for acute pain, a "reverse analgesic ladder" approach, using stepwise reduction to the patient's usual opioid regimen is recommended (**S**).
- ☑ For assessment of withdrawal reactions, the use of a validated withdrawal tool in opioid-tolerant patients is recommended; management strategies vary and include weaning, rotation and adjuvant use (**N**).

9.8 | The patient with a substance use disorder

The information in this chapter overlaps with that in section 9.7 above and readers are referred to that section for information on definitions, implications of tolerance and opioid-induced hyperalgesia (OIH), overlap between chronic pain (non-cancer and cancer-related) and substance use disorders, impact of opioids on perioperative outcomes, and assessment and management of acute pain including models of care, clinical pathways and discharge planning.

Terminology

Whilst "addiction" was recommended in the consensus statement from the American Academy of Pain Medicine, the American Pain Society and the American Society of Addiction Medicine (AAPM 2001 **GL**; Ballantyne 2007 **NR**), more recently the use of the term "substance use disorder" (SUD) has been recommended by DSM-5 (American Psychiatric Association 2013a **GL**) and by ICD-11 (WHO 2018 **GL**).

For patients taking drugs that induce tolerance and physical dependence long-term, it is important to separate out these expected physiological phenomena (albeit potentially with psychological components in the case of "dependence"). This reduces the potential for stigmatisation of those who have physical dependence and tolerance (Ballantyne 2007 **NR**).

Problematic use in the setting of chronic pain is defined by the IMMPACT ACTTION consensus panels in terms of misuse, abuse and addiction (see Section 9.7.1 above)

A SUD exists when the extent and pattern of substance use interferes with the psychological and sociocultural integrity of the person (see Table 9.7). For example, there may be recurring problems with social and personal interactions or with the legal system, recurrent failures to fulfil work or family obligations, and these patients may put themselves or others at risk of harm (Haber 2009 **NR**).

The artificial divide between "good and bad drugs" is being eroded as there has been increasing misuse and abuse of legally prescribed drugs (notably prescription opioids) and drugs that were formally illegal have been legalised for therapeutic use (notably cannabinoids) (Nielsen 2017b **NR**). Although cannabis, cocaine and amphetamines are more widely abused, opioids contribute to 82% of fatal overdoses worldwide (UNODC 2016 **Level IV**)

Centres in many countries regularly monitor the use of illicit drugs, including prescription opioids and permit identification of current trends in drugs abused/misused. These include:

- internationally, the World Health Organization through the International Narcotics Control Board (https://www.incb.org) (INCB 2019);
- in Australia, the National Drug and Alcohol Research Centre (https://ndarc.med.unsw.edu.au) (Roxburgh 2018 **Level IV**), the annual overdose report from the Pennington Institute based on Australian Bureau of Statistics data (Penington Institute 2019 **Level IV**) and the annual pharmacotherapy statistics from the Australian Institute of Health and Welfare (https://www.aihw.gov.au) (AIHW 2019a **Level IV**);
- in New Zealand, the Centre for Social and Health Outcomes Research and Evaluation (https://shoreandwhariki.ac.nz/shore/) (SHORE 2014 **Level IV**);
- in the UK, the surveillance systems set up by the National Health Service under NHS Digital (https://digital.nhs.uk) which includes regular reports on drug misuse statistics;
- in the USA, the Substance Abuse and Mental Health Services of the US Department of Health and Human Services (https://www.samhsa.gov) (SAMHSA 2019), National Institute on Drug Abuse, and other schemes specifically tracking prescription opioid abuse, such as Researched Abuse, Diversion and Addiction-Related Surveillance (RADARS) (https://www.radars.org) (Murphy 2018 **Level IV**);

- in Canada, the Canadian Institute for Health Information (CIHI) (https://www.cihi.ca/en) includes reporting on opioid prescription and related harms, and other substance use.

Pain management goals

Effective management of acute pain in patients with a SUD may be complex due to:

- psychological, social and behavioural characteristics associated with the disorder; noting that SUD is more common in those with comorbid psychiatric illness (Vietri 2014 **Level IV**, n=1,242; Webster 2017 **NR**);
- presence of the drug (or drugs) of abuse including intoxication or acute withdrawal syndromes;
- medications used to assist with drug withdrawal, relapse prevention and rehabilitation;
- complications of drug abuse including organ impairment, infectious diseases and increased risk of traumatic injury and other drug-related presentations; and
- the presence of tolerance and physical dependence which are expected physiological responses to chronic use of some substances.

Impact on outcomes

SUD can impact perioperative outcomes, implying that some patients will require deferral for optimisation prior to elective procedures (eg referral for substance use and chronic pain management). In elective spinal fusion, opioid dependence (ICD-9) prolonged LOS (adj OR 2.11; 95%CI 1.78 to 2.49), increased costs, resulted in higher infection rates, higher anaemia, and higher pulmonary insufficiency and this has implications for pain management and consent (Tank 2018 **Level III-2**, n=1,826,868).

Trauma outcomes are impacted by the types of substances abused, with increased mortality in those concurrently using benzodiazepines and opioids (Cheng 2016 **Level III-2**, n=10,166). Unaddressed opioid use disorder (OUD) and subsequent undertreatment of pain leads to premature discharge, worse medical outcomes, readmission, relapse and overdose (Ward 2018 **NR**).

For impact of chronic opioid use on outcomes see Section 9.7.4 above.

9.8.1 | CNS-depressant drugs

Although not inevitable, abuse of CNS-depressant drugs (eg opioids, alcohol, benzodiazepines) is often associated with physical dependence and tolerance (see Section 9.7 above). Withdrawal from CNS-depressant drugs produces symptoms of CNS and autonomic hyperexcitability, the opposite of the effects of the drugs themselves (Quinlan 2017 **NR**).

9.8.1.1 | Opioids including prescription opioids

Acute pain in those with an opioid use disorder (OUD) should be treated using the strategies outlined in Section 9.7 above and in the remainder of this section.

United States of America

In the USA, the Centre for Disease Control (CDC) has labelled the current trends in opioid use an "opioid epidemic", as reflected in rising prescription and other opioid use, and related harms. The CDC Opioids Portal (https://www.cdc.gov/opioids/strategy.html) describes three "waves" in this epidemic from the 1990s a rise in use of prescription opioids, from 2010 of heroin and from 2013 of synthetic opioids, especially illicitly-manufactured fentanyl.

From 2002 to 2010, there were large increases in overall opioid prescriptions, followed by a slight decrease from 2011 to 2013; diversion and abuse showed large increases from 2002 to 2010, then a plateau or decline; and there have been similar patterns for opioid-related deaths

(Dart 2015 **Level IV**). The 2015 US National Survey on Drug Use and Health found that, in the general community, 37.8% had ever used prescription opioids, 4.7% had misused and 0.8% had an OUD; the most common reason for misuse was for physical pain relief (63.4%); misuse and use disorders were more common in the presence of unemployment, low income and behavioural health problems; 59.9% had used prescription opioids without a script and 40.8% had obtained them from friends or relatives (Han 2017 **Level IV**, n=52,200). Past-year rates of prescription opioid misuse amongst American adolescents and young adults have also risen (Jordan 2017 **Level IV SR** [PRISMA], 19 studies, n=503,845).

Patterns of heroin use in the USA have changed with recent users more likely to be introduced via prescription opioids, with reasons for the transition being that heroin is easier to access and cheaper, along with changing demographics of use (greater geographical spread and not now predominantly involving minorities) (Cicero 2014 **Level III-3**, n=2,851)**.** From 2013 to 2014 in the USA, there was a rapid increase in age-adjusted death rates involving fentanyl which coincided with increased availability of illicitly manufactured fentanyl, according to law enforcement reports; this underpins the need for public health, coroners and law enforcement to work together on this public health problem (Rudd 2016 **Level IV**).

Emergency departments (ED) are an important source of opioids for misuse and diversion with ED physicians amongst the top prescribers of opioids; 10% of diverted opioids originate from ED prescription, 10% of prescriptions have indicators of "inappropriate prescribing" (Lyapustina 2017 **NR**), noting that some providers prescribe opioids to expedite ED discharge (Pomerleau 2017 **Level IV**, n=443 [health care professionals]).

Systematic approaches to these issues in the USA have included support for prescribing decisions, reducing inappropriate access (eg Prescription Drug Monitoring Programs [PDMPs] and Opioid Analgesic Risk Evaluation and Mitigation Strategy [REMS]) (Bucher Bartelson 2017 **Level IV**), increasing access to overdose treatment and providing substance use treatment (Collins 2018 **NR**; Volkow 2014 **NR**).

Concerns have been raised about the inadvertent impact of such strategies on pain management and that some approaches are not evidence-based, leading to a call for pain specialists to advocate for patients to ensure adequate treatment especially for vulnerable populations (Pergolizzi 2019 **NR**) and to oppose forced opioid tapering (Darnall 2019 **NR**).

Other countries

Some authors have viewed the opioid epidemic as primarily a North American problem, with the main issues being opioid prescribing for inappropriate indications and in doses that are too high (Hauser 2016 **NR**). Although the worldwide literature shows that the highest growth in prevalence of prescription opioid use is in USA government-insured populations (Roland 2016 **Level IV SR** [PRISMA], 16 studies, n unspecified), there is ample evidence that other countries have a similar, albeit possibly less severe, issue. Prescription opioid use is also rising in the European Union, Canada and Australia (Quinlan 2017 **NR**; Hauser 2017 **NR**). Prediction estimates show opioid "dependence" is a global issue with high prevalence in Australia, New Zealand, Western Europe and North America; with lower estimates in Africa and Asia (Degenhardt 2014 **Level IV SR** [PRISMA], 31 studies, n unspecified). A comparison of five countries (USA, UK, France, Germany and Australia) via the Global Drug Survey 2015 (online anonymous) found country of residence accounted for <3% of the variance in opioid misuse or abuse (Morley 2017 **Level IV**, n=5,670). German data show that first opioid prescriptions increased by 37% from 2000 to 2010, noting professional guidelines are not always followed (Just 2016 **NR**).

In Australia in 2016, 11% of those aged ≥ 14 y had ever used a prescription opioid for non-medical purposes (3.7% in the past year); commonly multiple substances were used (alcohol in over 35%, smoking in approximately 25%, cannabis in nearly 20%); pharmaceutical opioids were

responsible for more deaths and poisonings than heroin; there was a mortality peak in 1999, followed by decline and then 62% increase in death rate from 2007 to 2016 (AIHW 2018 **Level IV**).

Opioids contributed to two-thirds of drug-induced deaths in Australia; in 2016, 1,045 opioid-induced deaths occurred in Australia (6.6/100,000 people vs 3.8/100,000 people in 2007) (Roxburgh 2018 **Level IV**) and 75% of these were prescription opioids. In 2015, a cluster of fentanyl-laced heroin deaths was reported in Melbourne, Australia, the first report of this nature outside North America (Rodda 2017 **Level IV**, n=9 [fentanyl related deaths out of ≈4,000 deaths investigated]).

Comorbid disorders

In those who use prescription opioids non-medically, the prevalence of chronic non-cancer pain is 48 to 60% (Voon 2017 **Level IV SR** [PRISMA], 18 SRs, n unspecified). For those treated with buprenorphine for OUD, relapse is more likely with increased chronic pain severity (adj OR 1.15; 95%CI 1.06 to 1.24) (Griffin 2016 **Level II**, n=148, JS 2). Long term opioid prescription receipt is more likely in those with a prior diagnosis of ADHD (HR 1.53; 95%CI 1.48 to 1.58), nonopioid SUD (HR 3.15; 95%CI 3.06 to 3.24) and prior OUD (HR 8.70; 95%CI 8.20 to 9.24) (Quinn 2018 **Level IV**, n= 1,224,520).

Abuse deterrent formulations

More recently, focus has turned to the use of "abuse deterrent" or "tamper-resistant" formulations (Schaeffer 2012 **NR**); strategies that are being assessed include the use of technologies that prevent the release of active opioid when tablets are crushed or attempts are made to extract the drugs by other means, combinations of the opioid with an opioid antagonist such as naloxone or with a second substance with aversive effects (Passik 2014 **NR**; Webster 2011 **NR**). It is important to note that such formulations are not preventing abuse in principle but are making it more difficult to abuse these opioids by routes other than the oral one (ie injecting, snorting).

Studies of opioid abuse potential can be limited by methodological issues and best practice principles have been described (Setnik 2017 **NR**). Post-marketing surveillance is significantly challenging and future studies may need to compare one abuse deterrent formulation with another, as other formulations decline in use over time.

Slow-release oxycodone, reformulated to be abuse deterrent, was introduced to the USA in 2010 and was associated with reduced intentional abuse, diversion and overdose (Larochelle 2015 **Level III-3**; Dart 2015 **Level IV**); however, this coincided with an increase in heroin overdoses. From 2012 to 2014, 25 to 30% of those with an OUD reported past-month abuse of this reformulated product, reflecting transition to oral abuse (43%), successful defeat of the formulation with ongoing inhaled or injecting use (34%), or exclusive use of the oral route (23%) (Cicero 2015 **Level IV**, n=10,784).

In Australia, reformulated slow-release oxycodone was introduced in 2014. The National Opioid Medications Abuse Deterrent (NOMAD) cohort reported cheaper street prices and lower use via tampering (injection), but no change in harms (Larance 2018 **Level III-3**; Degenhardt 2015a **Level III-3**). Whilst some tampering continued, the agent was reported as less attractive for misuse (Peacock 2015 **Level III-3**, n=522).

9.8.1.2 | Alcohol and benzodiazepines

Excessive alcohol use predisposes to particular types of acute pain eg due to trauma (77% of screened Australian trauma patients had a probable alcohol-related injury or were engaging in risky drinking regularly [Browne 2013 **Level IV**, n=729]) and pancreatic disease (RR 1.37; 95%CI 1.19 to 1.58) (Alsamarrai 2014 **Level IV SR**, 51 studies, n≈3,000,000). It may also lead to hepatic dysfunction, which may affect the metabolism of other drugs, including analgesics.

Alcohol and/or benzodiazepine use disorders are relatively common, particularly in certain subgroups of the population. The Australian POINT study of patients with CNCP prescribed opioids found a 33% lifetime prevalence of alcohol use disorder, and 16% of those who drank in the prior 12 mth did so for pain control (Larance 2016 **Level IV**, n=1,514). Heroin users also take benzodiazepines to potentiate the effects of the opioid (Bluth 2016 **NR**); concurrent use of opioids and benzodiazepines increases the risk of opioid-related overdose (Dowell 2016 **GL**).

In terms of screening for benzodiazepine use, short-acting (eg midazolam) appear in urine drug screens for 12 h and long-acting (eg diazepam) for over 7 d (Quinlan 2017 **NR**).

There is no cross-tolerance between opioids and alcohol or benzodiazepines in animal studies (Bell 1998 **BS**). The effective concentrations of remifentanil were not different between alcoholic and non-alcoholic patients (Liang 2011 **Level II**, n=60, JS 5). There is therefore no pharmacological reason to use higher than "standard" initial opioid doses in patients with an alcohol or benzodiazepine dependence.

Prevention of withdrawal should be a clinical priority in all patients. Benzodiazepines are effective for alcohol withdrawal symptoms, especially prevention of seizures (Amato 2010 **Level I** [Cochrane], 64 RCTs, n=4,309). If benzodiazepines are administered for the treatment of withdrawal symptoms and signs, patient sedation levels must be monitored, especially if patients are receiving concurrent opioids or other sedating drugs (Macintyre 2011 **NR**). Excessive sedation will limit the amount of opioid that can be given safely.

There are inconclusive results on the effect of pregabalin on alcohol withdrawal (Guglielmo 2012 **Level IV SR**, 3 studies [withdrawal], n=271).

Naltrexone is used for treatment of alcohol use disorder and this complicates acute pain management (see Section 9.8.3.3).

9.8.1.3 | Cannabinoids

Recreational use

"Recreational" cannabis users had approximately 50% greater rescue pethidine requirements, as well as higher pain intensity and dissatisfaction scores, than nonusers over the first 6 h after orthopaedic surgery (Jefferson 2013, **Level III-2**).

Synthetic cannabinoids may contain a large number of components and are more potent than the naturally occurring drug, resulting in agitation, hypertension, hypokalaemia, vomiting and seizures (Tait 2016 **Level IV SR**, 106 studies, n>4,000 [26 deaths]).

Use for chronic pain

Despite Level I evidence that cannabinoids have limited efficacy and potential for harm in CNCP (Stockings 2018 **Level IV SR** [PRISMA], 47 RCTs and 57 studies, n=9,958), the Australian POINT study found that, over a 4 y period, one quarter of those prescribed opioids for CNCP had also used cannabis, usually for pain management, with 12% meeting criteria for cannabis use disorder (ICD-10 criteria) (Degenhardt 2015c **Level IV**, n=1,514). Those using cannabis were younger, with greater pain severity and interference, lower pain self-efficacy, greater concurrent benzodiazepine prescription and greater non-adherence to the prescribed opioid regimen (Campbell 2018 **Level IV**, n=1,514). Presence of (chronic) pain may make reducing cannabis use more difficult (Sznitman 2018 **Level IV**, n=18) (see also Section 4.11).

Withdrawal syndromes

Withdrawal is usually only seen in high-dose cannabis smokers in whom tolerance develops quickly (Beaulieu 2017 **NR**). Both DSM-5 and ICD-11 define cannabis withdrawal as part of use disorders and dependence (WHO 2018 **GL**; American Psychiatric Association 2013a **GL**).

Withdrawal commences within 24-48 h and can last up to 3 wk; symptoms may include depressed mood, abdominal pain and headache, all of which can confound acute pain management (Bonnet 2017b **NR**).

Screening

In terms of screening for use, after single use, cannabis and its metabolites appear in urine drug screens for 3-4 d (Quinlan 2017 **NR**). With heavy or chronic use, they may appear in urine drug screens for up to 45 d.

For information about the use of cannabinoids for pain management see Section 4.11.

9.8.1.4 | Alpha-2-delta modulators (Gabapentinoids)

Increasingly, these are recognised as drugs of abuse with rising misuse rates (Crossin 2019 **Level IV**, n=1,201 [pregabalin misuse-related ambulance attendances]); Bonnet 2017c **Level IV SR** [PRISMA], 106 studies, n unspecified). Risk factors for abuse include prior substance abuse and psychiatric comorbidities. Rates of abuse are higher in opioid abusers than in the general population and use with opioids increases the risk of opioid-related death (OR 1.99; 95%CI 1.61 to 2.47) (Gomes 2017 **Level III-2**, n=5,875).

See also Section 4.8.1.1.

9.8.2 | CNS-stimulant drugs

Abuse of CNS-stimulant drugs (eg cocaine, amphetamines, ecstasy, ketamine) is associated with psychological rather than physical dependence and only a low degree of tolerance; these drugs do not exhibit any cross-tolerance with opioids (Buckley 2014 **NR**).

Cocaine and ecstasy (N-Methyl-3,4-methylenedioxyamphetamine or MDMA) are known to enhance the analgesic effects of morphine in animal studies (Gatch 1999 **BS**; Kauppila 1992 **BS**; Nencini 1988 **BS**). This effect may be age-dependent as exposure to methamphetamine in adolescent rats enhances morphine antinociception (and tolerance development) with inverse effects in adult rats (Cyr 2012 **BS**). In experimental-pain settings, subjects taking ecstasy have been shown to have a reduced pain tolerance (O'Regan 2004 **Level III-2 SR EH**); this was also true for abstinent previous users (lower pressure pain thresholds, increased cold pain ratings, increased pain ratings during testing of DNIC) (McCann 2011 **Level III-2 EH**). Those taking cocaine also had reduced cold pressor pain thresholds (Compton 1994 **Level III-2 EH**).

There are very few data from the clinical setting of any differences in opioid requirements. Compared with those with negative urine drug screens, trauma patients in intensive care who were urine screen positive for cocaine and/or amphetamines required similar opioid doses (Kram 2017 **Level III-2**, n=150).

Epidemiological data from the USA show rising rates of cocaine- and/or psychostimulant deaths since 2015; cocaine deaths are partially attributable to lacing with synthetic opioids (Kariisa 2019 **Level IV**). Analysis of urine drug tests in the USA show rising rates of fentanyl positivity in those positive for cocaine and methamphetamine, reflecting a growing risk to stimulant users of opioid-related overdose in that country (LaRue 2019 **Level IV**, n=1,000,000).

While behavioural and autonomic effects are seen during acute exposure, withdrawal symptoms are predominantly affective rather than physical (Quinlan 2017 **NR**). Stimulants are associated with particular types of acute pain (eg cocaine use and chest pain including acute coronary syndromes).

9.8.2.1 | Nicotine

In volunteer studies, nicotine increases pain threshold (n=393) and tolerance (n=339) and has therefore an acute small to medium analgesic effect (Ditre 2016 **Level III-2 EH SR** [PRISMA], 13 studies, n unspecified). The authors speculate, that this could make smoking more rewarding and harder to give up.

In African-American smokers, smoking abstinence increased self-reported pain, with greater abstinence-induced pain in those with pre-existing CNCP (Bello 2018 **Level III-3**, n=214). In patients attending a Danish pain clinic, smoking rates were higher than those in the general population; compared with non-smokers, smokers and ex-smokers were more likely to use opioids and at higher doses, although were not more likely to have opioid addiction (Plesner 2016 **Level IV**, n=98). Opioid-dependent smokers are more likely to be nicotine-dependent, with greater severity of nicotine dependence (Parker 2018 **Level IV**, n= 58,971).

9.8.2.2 | Cocaine

Whilst cocaine use does not induce physical dependence, its regular use is very reinforcing (ie psychological dependence) which can be managed with tricyclic antidepressants (Bluth 2016 **NR**). "Withdrawal" is described as having three phases – "crash" within h to d, "acute" for up to 3 wk, and "extinction" over several mth (Beaulieu 2017 **NR**). Cocaine is also known to enhance the effects of morphine in animal studies.

Cocaine use may present with seizures, arrhythmias, coronary vasospasm, myocardial ischaemia or stroke (Vadivelu 2018 **NR**). Dexmedetomidine may be useful to achieve sympatholysis (Vadivelu 2016b **NR**).

Cocaine appears in urine drug screens for 48 to 72 h (Quinlan 2017 **NR**).

9.8.2.3 | Amphetamines and methamphetamine

Methamphetamines are highly addictive with long-term use leading to anxiety, mood disturbance, insomnia and sometimes psychosis, all of which can impact on acute pain (Becker 2018 **NR**). There are no effective pharmacotherapies, although there is low quality evidence for methylphenidate (2 RCTs, n=88) (Chan 2019a **Level I** [PRISMA], 34 RCTs, n unspecified).

Methamphetamines, used for ADHD, are increasingly drugs of abuse especially by school students, with non-medical regular users 1.8% of Australians aged 15 to 35 y, commonly declining by mid-30s (Chan 2019b **Level III-3**, n=1,755).

Withdrawal from methamphetamines is characterised by increased sedation and appetite that can last for a few days; the severity of sleepiness correlated with the amount used (calculated by cost per mth) and length of regular use (McGregor 2005 **NR**).

Amphetamines appear in urine drug screens for 48 h (Quinlan 2017 **NR**).

9.8.3 | Drugs used in the treatment of addiction disorders

Close liaison with all treating clinicians and drug and alcohol services should occur. In the case of those receiving opioid substitution therapy (OST), this may include arrangements with the usual prescriber and pharmacist for a "takeaway" dose on the day of elective surgery/procedure admission, as well as liaison at discharge to ensure continuity of ongoing therapy (Schug 2012 **NR**; Huxtable 2011 **NR**).

Good acute pain management is particularly important for patients on OST as acute pain exposure was associated with reduced retention in treatment (aOR 0.46; 95%CI 0.23 to 0.93) (Bounes 2013 **Level III-2**, n=323 [prescribers]). The presence of chronic pain increases the odds of

craving in those on OST (aOR 3.10; 95%CI 1.28 to 7.50), which may impact outcomes in this subgroup of patients (Tsui 2016 **Level III-2**, n=105).

Continuity of OST is important, as all-cause and overdose-related mortality risk drops sharply in the first 4 wk of therapy, but rises substantially with cessation (Sordo 2017 **Level III-3 SR** [PRISMA] 19 studies, n=122,885 [methadone], n= 15,831 [buprenorphine]). With regard to mortality under OST, methadone vs buprenorphine use shows higher crude mortality, but also substantially higher relative risk reduction when time in-treatment is compared to time out-of-treatment (Bahji 2019 **Level III-3 SR** [PRISMA], 32 studies, n=150,235) (19 studies overlap with Sordo 2017). As in the previous systematic review, greatest mortality reduction occurred in the first 4 wk. Short-term detoxification is rarely effective and there is an increased risk of one-year mortality vs OST (Harrison 2018 **NR**).

A comparison of OST with methadone vs buprenorphine found no difference in self-reported opioid use or positive urine drug screens, no difference in retention (low quality evidence), but each was more effective than detoxification or psychological treatment alone (Nielsen 2016 **Level I** [Cochrane], 6 RCTs, n=607).

In Australia in 2017, 50,597 clients were receiving OST, of which 65% were male and 10% identify as Aboriginal and/or Torres Strait Islander (AIHW 2019b **Level IV**). Overall rates of OST have been stable since 2010 (20 clients per 10,000 population); there are 3,168 authorized prescribers (90 in prisons), and 2,852 dosing points (mostly pharmacies); overall there are roughly similar numbers of clients on methadone, buprenorphine (Subutex®) and buprenorphine/naloxone (Suboxone®).

9.8.3.1 | Methadone

Methadone is a long-acting opioid agonist used in the management of patients with an opioid addiction (see Section 4.3.1.3). It is commonly prescribed in doses in the range 50–120 mg and once/d, which is adequate to suppress symptoms of opioid withdrawal.

In the acute pain setting, methadone should be continued, where possible, at the usual dose. If there is any doubt about the dose (eg there is suspicion that the patient is diverting all or part of the prescribed amount), it is prudent to give part of the reported dose and repeat this over the day if needed, monitoring the patient for sedation (Huxtable 2011 **NR**; Peng 2005 **NR**). If the patient is unable to take methadone by mouth, substitution with parenteral methadone or another opioid will be required in the short-term (Huxtable 2011 **NR**; Mitra 2004 **NR**). Parenteral methadone doses were 0.7 times the oral doses (Gonzalez-Barboteo 2008 **Level IV**); half to two-thirds of the oral maintenance dose can be given in equal divided doses by SC or IM injection 2 to 4 times/d or by continuous infusion (Huxtable 2011 **NR**; Alford 2006 **NR**).

The duration of any analgesic effect from the dose is much shorter (Alford 2006 **NR**); although this is sometimes not well understood by treating physicians (Bounes 2014 **Level IV**). Dividing the daily dose on a temporary basis (eg giving half the usual daily methadone doses twice a day or one third of the usual dose every 8 h) may result in a better analgesic effect (Basu 2007 **NR**). Divided doses or continuous infusion have been recommended for palliative care management of those on methadone OST (Taveros 2017 **Level IV SR** [PRISMA], 7 studies, n=142).

Care should also be taken with concurrent administration of other drugs that prolong the corrected QT interval; although this is thought to be an issue only with very high methadone doses (Andrews 2009 **NR**).

If patient receiving methadone OST require additional opioids at discharge, consider daily dispensing; overdose prevention education and nasal naloxone prescription have also been recommended in this circumstance (Ward 2018 **NR**).

Methadone appears in urine drug screens for 7 to 8 d after cessation (Quinlan 2017 **NR**).

Patients taking methadone may have OIH (see section 9.7 above for more information including implications for management).

9.8.3.2 | Buprenorphine

Buprenorphine is a partial opioid agonist used effectively in the treatment of opioid addiction (Mattick 2014 **Level I** [Cochrane], 31 RCTs, n=5,430) and commonly prescribed for OUD in doses of 8 to 32 mg (Roberts 2005 **NR**). Regulatory controls on prescribers and those providing acute pain management vary by country and state.

Administered SL, it has a mean terminal half-life of 28 h (Johnson 2005 **NR**). It is usually given once every day or every second day, which is adequate to suppress symptoms of opioid withdrawal; like methadone the duration of any analgesic effect from the dose is much shorter (Alford 2006 **NR**).

Some preparations combine buprenorphine and naloxone (the latter is poorly absorbed by the SL route) (Orman 2009 **NR**); naloxone is added to buprenorphine with the aim of reducing parenteral abuse of the drug.

Furthermore, long-acting buprenorphine preparations are now becoming available worldwide (Harrison 2018 **NR**; Chavoustie 2017 **NR**). In Australia, two such preparations are registered for SC injection: a SC gel depot preparation (Buvidal®) previously used in France (Vorspan 2019 **NR**) for weekly or monthly injection and Sublocade® for monthly injection. There are multiple reasons why such preparations could be advantageous; they reduce need for frequent attendance at the dispensing facility, reduce inconvenience for patients and staff, reduce the risk of diversion and injecting and may result in better adherence. Guidelines for the use of these preparations in Australia are published (Lintzeris 2019 **GL**).

In opioid-naïve subjects, administration of buprenorphine resulted in decreased hyperalgesia following transcutaneous pain stimuli vs placebo, suggesting that unlike morphine and methadone, buprenorphine may exert an antihyperalgesic effect (Koppert 2005 **Level III-2**). However, both methadone-maintained and buprenorphine-maintained patients were similarly more sensitive to cold-pressor pain than opioid-naïve controls (Compton 2012 **Level III-2**).

Whilst there are still conflicting views in the literature regarding perioperative management of OST with buprenorphine, the evidence supports its continuation. A systematic literature search found limited evidence to support discontinuation (4 CR) and more support for continuation (1 Level III-1, 4 Level III-3, 3 Level IV) (Quaye 2019 **Level IV SR**, 8 studies & 4 CR, n unspecified). There is no evidence that the outcomes are worse if it is continued and limited evidence about relapse rates with discontinuation (Goel 2019 **Level IV SR** [PRISMA], 6 studies & 12 CR, n unspecified) (5 of 6 studies overlap). Significant risks of discontinuation include relapse and accidental overdose (Lembke 2019 **NR**).

As with methadone, dividing the daily doses on a temporary basis (every 8 or 12 h) may take advantage of the analgesic properties of buprenorphine (Alford 2006 **NR**).

If buprenorphine has been ceased (eg unconscious patient, intraoral surgery or trauma preventing SL administration), its reintroduction should be managed in consultation with the prescribing health professional who should also be involved in discharge planning to ensure continuity of long-term care and availability of usual replacement therapy on discharge (Huxtable 2011 **NR**).

With its metabolites, buprenorphine appears in urine drug screens for 8 d (Quinlan 2017 **NR**)

In-hospital or emergency department initiation

OST with methadone or buprenorphine are both better than clonidine and lofexidine in ameliorating withdrawal symptoms (Gowing 2017 **Level I** [Cochrane], 27 RCTs, n=3,048). This has implications for commencing OST in hospital or emergency departments.

Comparison of in-hospital OST initiation of buprenorphine and continued outpatient follow-up with a 5-day detoxification protocol using buprenorphine showed the former led to more patients receiving treatment and less illicit opioid use at 6 mth post-discharge (RR 0.60; 95%CI 0.46 to 0.73) (Liebschutz 2014 **Level II**, n=139, JS 3).

Emergency department initiation of buprenorphine/naloxone for OUD may improve engagement with and retention in treatment (D'Onofrio 2015 **Level II**, n=329, JS 3).

Management of patients treated for CNCP with transdermal buprenorphine is addressed in 9.7.

9.8.3.3 | Naltrexone

Naltrexone is a pure opioid antagonist used in the management of patients with opioid or alcohol dependence. In the USA, it is available as tablets or in a long-acting injectable form.

There is good evidence for its effectiveness in alcohol dependence (Rosner 2010 **Level I** [Cochrane], 50 RCTs, n=7,793).

There is mixed evidence for its use in opioid use disorder. Neither oral naltrexone (Minozzi 2011 **Level I** [Cochrane], 13 RCTs, n=1,158) nor long-acting naltrexone implants (Larney 2014 **Level I**, 5 RCTs, n=576 & **Level IV SR**, 4 studies, n=8,358) have good evidence of efficacy and safety. On the contrary, there is a significant excess mortality in patients on oral naltrexone vs methadone-maintenance treatment (RR 3.5; 95%CI 2.2 to 5.8) (Degenhardt 2015b **Level III-2**). There is a limited evidence base for extended release naltrexone injections with no change in mortality, except for those recently released from correctional facilities (Babu 2019 **NR**). Compared with oral naltrexone, extended release naltrexone implant (both combined with CBT) for opioid use disorder results in better treatment retention at 6 mth (Sullivan 2019 **Level II**, n=60, JS 2).

The usual oral maintenance dose is 50 mg/d; orally administered, naltrexone has an apparent half-life of about 14 h and binds to opioid receptors for over 24 h following a single dose (Vickers 2006 **NR**); this can create difficulties in the acute pain setting as opioid agonists will be antagonised. It has been recommended that, where possible, naltrexone should be stopped for at least 24 h, and preferably 72 h, before surgery (Kampman et al 2015 **GL**; Harrison et al 2018 **NR**; Vickers 2006 **NR**; Mitra 2004 **NR**).

These difficulties are even greater when the patient has an active implant (Vickers 2006 **NR**; O'Brien 2006 **NR**); the duration of efficacy of the 1.1 g implant is approximately 95 d and that of the 2.2 and 3.3 g implants approximately 140 d (Ngo 2008 **PK**). In cases where effective opioid analgesia is required, removal of the implant might be considered (Sadleir 2011 **Level IV**).

In addition, a microsphere-based formulation of naltrexone incorporated into a biodegradable matrix for IM injection (XR-NTX) is now becoming available, and is approved by the FDA for alcohol and opioid dependence (Sudakin 2016 **NR**). For this preparation (380 mg IM), the peak activity is at 7 d and duration of effect is 28 d (Harrison 2018 **NR**). Whilst it has proven difficult to provide analgesia during the first two wk post-injection, effective analgesia has been described in the last wk of the four. Elective surgery should be scheduled 4 wk after the last injection; with recommendations including a preoperative consultation with a pain and addiction specialist, development of a relapse risk management plan including with community provider input and education (Ward 2018 **NR**).

In patients receiving naltrexone therapy, multimodal analgesic regimens (eg NSAIDs, paracetamol, ketamine, tramadol, tapentadol, regional analgesia, lidocaine, dexmedetomidine, gabapentinoids, non-pharmacological strategies) should also be employed (Harrison 2018 **NR**).

There is experimental evidence of mu-opioid receptor upregulation following antagonist withdrawal (Millan 1988 **BS**) and abrupt discontinuation of naltrexone may therefore lead to a period of increased opioid sensitivity (Vickers 2006 **NR**). As the effect of naltrexone diminishes

after it has been ceased, the opioid dose required for analgesia may also need to be decreased in order to avoid opioid overdose (in particular OIVI).

Planning around cessation and reintroduction of naltrexone should be done in consultation with the prescribing health professional and an acute pain service/specialist.

9.8.4 | The therapeutic relationship and behavioural management

Pain management in patients with SUD often presents significant challenges for both clinicians and patients. Patients fear being stigmatised or discriminated against; they are concerned about inadequate pain relief with their past experiences leading to physician distrust; and they fear experiencing withdrawal (especially whilst waiting in ED or after admission, before their usual drugs are prescribed) and relapse precipitated by acute opioid exposure (Quinlan 2017 **NR**; Buckley 2014 **NR**; Eyler 2013 **NR**; Roberts 2008 **NR**).

Providers experience mistrust, concerns about drug seeking, fear of overtreatment with adverse events, concerns about diversion, and risk of discharge against medical advice. Many health professionals (and some patients) have misconceptions about acute pain management in this setting (Bounes 2014 **NR**). Evidence for the most appropriate management of acute pain in patients with an addiction is limited and thus advice is based primarily on case series, case reports, expert opinion and personal experience.

In Canada, 48% of injecting drug users report having ever been denied pain medication as inpatients and this is positively associated with using illicit drugs whilst in hospital (adj OR 1.46; 95%CI 1.14 to 1.88) (Ti 2015b **Level IV**, n=1,053). Injecting drug users who discharge against medical advice experience inadequate pain and withdrawal management, often leading to continued drug use in hospital settings (McNeil 2016 **Level IV**, n=30). Risk factors for discharge against medical advice are recent injecting drug use, "pension day", Indigenous patients (although this is likely to be multifactorial), and day of the week (more likely on weekends); rates are lower with in-hospital methadone use, community-based hospital in the home, older age and more social support (Ti 2015a **Level IV SR** [PRISMA], 17 studies, n unspecified).

A more patient-centred approach has been recommended, with a (perhaps controversial) shift in focus for these patients from abstinence-based policies to risk reduction (McNeil 2016 **Level IV**). Integration of OUD treatment into hospital care (eg as occurring in some USA emergency departments) might reduce conflict between teams and reduce discharge against medical advice (Fanucchi 2016 **NR**). A multidisciplinary addiction consultative service (IMPACT 'improving addiction care team') improved staff experiences as they felt relieved, viewed care as more humanised, understood addiction as a disease and valued the support provided by discharge referral pathways (Englander 2018 **Level IV**).

Inappropriate behaviours can be prevented to a significant extent by the development of a respectful, honest and open approach to communication and, as with all other patients, an explanation of treatment plans and the fact that complete relief of pain may not be a realistic goal, as well as involvement of the patient in the choice of plan (within appropriate boundaries) (Jones 2014 **NR**; Haber 2009 **NR**; Roberts 2008 **NR**). One communication framework is the "7 Es" (Becker 2016 **Level IV**): Express empathy, Elicit functional goals, Educate, Endorse an alternative plan, Enlist patient buy-in, Enact follow-up plan, and maintain Equanimity (calm, even-tempered, non-judgemental).

A proactive, rather than reactive, discussion about medications and behaviours is recommended (Haber 2009 **NR**) and sometimes limit setting (Huxtable 2011 **NR**). Episodes of acute pain may negatively impact upon long-term retention in addiction treatment programs and better acute pain control may improve such retention (Bounes 2013 **Level III-2**). Addiction "talking points" include the provider raising concerns, approaching management through the lens of it

being best to have treatment from a specialist (as in any chronic disease), and "[caring] enough" to set boundaries (Allen 2014 **NR**).

9.8.5 | Assessment including screening for risk of opioid use disorder and mitigation strategies

The first step in managing patients with a SUD is identifying the problem, although obtaining an accurate history can sometimes be difficult. Risk factors for OUD include past or current substance abuse, untreated psychiatric disorders, younger age, social and family factors that encourage misuse (Webster 2017 **NR**). Risk factors for opioid overdose include those of middle age, opioid use disorder and other psychiatric comorbidities. At times, it may be in the setting of unsuccessful overdose that inpatient contact occurs.

Identification of patients abusing drugs or at risk of drug abuse may be difficult. The ability of health professionals to predict which patients may misuse or abuse opioids is poor (Jung 2007 **Level IV SR**, 6 studies, n unspecified) and patient self-report of drug use may not correlate with evidence from drug screening (Sehgal 2012 **NR**).

Screening tools are widely used in chronic settings especially in the USA; and increasingly are recommended prior to short-term therapy also (Ballantyne 2015 **NR**). These tools were largely developed in an outpatient (often pain clinic) setting, and are not validated for acute hospital settings including emergency departments, so as yet it is not clear who should be screened and with what tool (Duber 2018 **NR**). Opioid Risk Tool (ORT), Screener and Opioid Assessment for Patients with Pain (SOAPP-R) and Current Opioid Misuse Measure (COMM) are poor at predicting risk of subsequent aberrant behaviours in patients with CNCP in the emergency department (Chalmers 2019 **Level IV**). The SOAPP-R applied in emergency department patients, in whom discharge opioid prescribing was being considered, had sensitivity 54%, specificity 71%, positive predictive value 26% and negative predictive value 89% for identifying subsequent high-risk behaviour (Weiner 2016 **Level IV**, n=82). A further limitation is that self-reported tools can be manipulated (Kaye 2017b **NR**).

Polysubstance use is common and many patients use drugs from different groups, the most common being CNS-depressant drugs (such as opioids, alcohol, benzodiazepines and cannabinoids) and CNS-stimulant drugs (including cocaine, amphetamines and amphetamine-like drugs). The group from which the drugs come determines their withdrawal characteristics (if any) and their interaction with acute pain treatment (Peng 2005 **NR**; Mitra 2004 **NR**). Patients should be asked about the route of administration used, as some may be injecting prescription drugs intended for oral, TD or SL use. Verification of opioid doses should be undertaken where possible or else a divided dose given with monitoring of effect, in case the reported dose is incorrect or the drug is being wholly or partly diverted (Huxtable 2011 **NR**; Alford 2006 **NR**).

Recommendations include establishing a supportive non-judgemental environment, determining what drugs are misused, developing an analgesic plan (which optimise non-opioids, increases opioids if required with careful monitoring for adverse effects and change to oral analgesia from parenteral as soon as feasible), a withdrawal management plan (continuing OST or replacing, and consider withdrawal from other drugs), minimising stress and multidisciplinary discharge planning (Quinlan 2017 **NR**).

"Universal precautions" are increasingly recommended for acute pain settings (Webster 2017 **NR**). In this context, universal precautions encompass use of multimodal analgesia, abuse-deterrent formulations, urine drug screening, use of prescription drug monitoring programs (PDMP) and risk management strategies (eg REMS programs in the USA).

An acute admission offers an opportunity to engage with the chronic condition of SUD as well as to treat the acute issues; failure to engage is a missed opportunity (Donroe 2016 **NR**). Screening,

Brief Intervention and Referral to Treatment (SBIRT) is promoted and commonly used in the USA (Kaiser 2016 **NR**)

Involvement of an addiction medicine specialist or service may be required; suggested referral criteria are (Nack 2017 **NR**):

- Abuse of medication;
- Excessive alcohol use;
- Unwilling to try other pain treatments;
- Concurrent opioid and sedative prescriptions;
- Psychiatric disorder;
- On ORT with persistent pain.

9.8.6 | Transition to community care

In all cases, close liaison with other treating health professionals and drug and alcohol services is required. This is especially important if the management plan includes additional opioids for pain relief for a limited period after discharge or if any alteration has been made, after consultation with the relevant services, to methadone or buprenorphine doses while in hospital.

In many countries, regulatory requirements will dictate that only one physician has the authority to prescribe for these patients. However, restricted use of additional opioids after discharge may be possible in some circumstances. For example, it could be arranged for the patient to pick up a limited and progressively decreasing number of tablets daily or every other day, along with their usual methadone or buprenorphine (Peng 2005 **NR**).

For those with concurrent chronic pain, referral to an outpatient pain service may be required; the patient not currently in SUD treatment may require referral to a drug and alcohol service (Huxtable 2011 **NR**).

It is necessary to notify usual prescribers of medications used in hospital as these may appear in subsequent urine drug screens (Vadivelu 2016a **NR**).

For discharge medication see also Section 8.13.

9.8.7 | Patients in recovery from substance use disorders

Patients in drug-treatment programs or in drug-free recovery may be concerned about the risk of relapse if they are given opioids for the management of their acute pain (Eyler 2013 **NR**; Markowitz 2010 **NR**). However, there is no evidence that the use of opioids to treat acute pain increases the rate of relapse; a more likely trigger is unrelieved pain, although this is primarily based on expert opinion (Ward 2018 **NR**; Buckley 2014 **NR**; Markowitz 2010 **NR**; Alford 2006 **NR**)

IV opioids may present greater risk for relapse due to more rapid and higher peak concentrations and patients may be very reluctant to receive opioids (Quinlan 2017 **NR**). Those at particular risk of relapse when given opioids include younger patients, males and those using multiple illicit drugs, especially cocaine (Markowitz 2010 **NR**). Effective communication and planning, the use of multimodal analgesic strategies, reassurance that the risk of reversion to an active addiction is small, and information that ineffective analgesia can paradoxically lead to relapse in recovered patients, are important and help avoid undertreatment (Huxtable 2011 **NR**; Mitra 2004 **NR**).

The anxiety associated with surgery might trigger conditioned responses resulting in drug craving (Volkow 2016 **NR**). Those with prior maintenance opioid addiction treatment but prolonged abstinence demonstrate increased cold sensitivity, decreased tolerance and cravings (similar to their opioid-maintained counterparts); but they had greater sense of control over these cravings which may reflect that they have developed skills to cope with pain to avoid

relapse (Wachholtz 2019 **Level III-2**, n=120). Expert opinion suggests that both uncontrolled pain and uncontrolled opioid access can trigger relapse (Ward 2018 **NR**).

9.8.8 | Acute pain in pregnant patients with an opioid use disorder

Many women with an addiction are of childbearing age (AIHW 2019a **Level IV**); the prevalence of prescription-opioid abuse is rising in this population (Klaman 2017 **GL**). The prevalence of neonatal abstinence syndrome (NAS) has risen in the USA and Canada (Filteau 2018 **Level IV**; Ko 2016 **Level IV**), although it has stabilised in Australia (Uebel 2016 **Level IV**, n=1,022,263) and England (Davies 2016 **Level IV**).

The management of acute pain in pregnant patients with an addiction must consider treatment of the mother, as well as possible effects on the foetus and newborn.

Identification of these patients during pregnancy allows time for assessment and appropriate management planning; however, this is not always possible as antenatal care is often suboptimal (Kampman 2015 **GL**; Jones 2014 **NR**). Routine screening may increase the rate of addiction detection (Jones 2014 **NR**) and validated screening tools include the 4Ps and CRAFFT (ACOG 2012 **GL**; Jones 2014 **NR**). Care is complicated in these patients by other factors related to their use of drugs such as respiratory infections, endocarditis, untreated cellulitis, abscesses, HIV/AIDS, hepatitis and social factors such as abuse, interpersonal violence and homelessness (Jones 2014 **NR**; Ludlow 2007 **NR**). Stabilisation with OST, as early as possible in pregnancy, is preferred to withdrawal management or abstinence due to risks to both mother and foetus with addiction relapse and treatment dropout (Klaman 2017 **GL**; Kampman 2015 **GL**).

Reviews of pain management in these patients (Buckley 2014 **NR**; Jones 2014 **NR**; Stanhope 2013 **NR**) as well as guidelines have been published (Klaman 2017 **GL**; Kampman 2015 **GL**). Collaborative team care is essential.

9.8.8.1 | Methadone

Methadone maintenance is regarded as the gold standard for antenatal OST (ACOG 2012 **GL**). Pregnant patients taking methadone as part of a drug-dependence treatment program should receive whatever dose is needed to prevent heroin use, and the dose may need to be increased in the third trimester because the physiological changes associated with pregnancy can alter drug pharmacokinetics (Jones 2012a **NR**; Ludlow 2007 **NR**).

9.8.8.2 | Buprenorphine

The largest study of OST in pregnancy, the Maternal Opioid Treatment Human Experimental Research (MOTHER) study compared methadone and buprenorphine and showed similar maternal outcomes (Jones 2012b **NR**, summarising results of 1 RCT: Jones 2012a **Level II**, n=175). Buprenorphine resulted in less foetal cardiac and movement suppression, lower rates of preterm labour, less severe NAS (a treatable condition), but lower maternal satisfaction and lower treatment retention rates, vs methadone maintenance (Bandstra 2012 **NR**, secondary analysis of 1 RCT: Jones 2012a **Level II**, n=175). When compared with methadone maintenance, buprenorphine maintenance may lead to better neonatal outcomes, but this might be due to systemic bias in studies (Brogly 2014 **Level III-2 SR** [PRISMA], 4 RCTs & 8 studies, n=1,380 [includes Jones 2012a]).

9.8.8.3 | Naltrexone

Although not recommended in professional guidelines, there is emerging evidence that neonatal outcomes may be no worse for those treated with implanted naltrexone when compare with

OST (Kelty 2017 **Level III-2**, n=775). Issues with naltrexone include that its induction requires an opioid-free period after detoxification and it is also more challenging for peripartum pain relief (Tran 2017 **NR**).

In the absence of specific evidence, management of pain in the peripartum period should be extrapolated from the non-pregnant patient with reliance on non-opioids including regional blocks.

9.8.8.4 | Peripartum management

Methadone maintenance should be continued without interruption in the peripartum period; if for some reason the women is unable to take it orally, it can be given subcutaneously. As with any opioid-tolerant patient, additional opioids will be required for pain relief and the newborn will require high-level neonatal care because of the risk of NAS (Jones 2012a **NR**; Jones 2008 **NR**; Ludlow 2007 **NR**). Pain scores after Caesarean section are also higher (Meyer 2010 **Level III-3**).

Buprenorphine maintenance should be continued without interruption as it does not interfere with pain control after vaginal delivery or Caesarean section (Vilkins 2017 **Level III-2**, n=273; Hoyt 2018 **Level IV**, n=14; Leighton 2017 **Level IV**, n=4). These women will also have higher opioid requirements after surgery and the newborn is still at risk (albeit maybe a lower risk) of NAS (Jones 2012a **NR**; Jones 2010 **NR**; Ludlow 2007 **NR**).

Delivery should occur at a tertiary centre and needs clear criteria for opioid use, neonatologist involvement pre-delivery and consent during pregnancy regarding NAS (Pritham 2014 **NR**). Opioid requirements during labour were not significantly increased, although methadone- and buprenorphine-maintained patients had higher pain scores and higher opioid requirements postpartum than did controls (Meyer 2010 **Level III-3**). In another study, opioid-maintained patients required epidural analgesia more often than controls (38.1 vs 14.3%) but had no higher opioid requirements after Caesarean section (Hoflich 2012 **Level III-2**).

Opioid requirements and the risk of withdrawal, for the patient and the newborn, will be higher in patients still using heroin prior to childbirth (Ludlow 2007 **NR**). In all patients with opioid addiction, naloxone is not recommended except in situations of life-threatening overdose (Kampman 2015 **GL**).

Opioid requirements in those addicted to non-opioid substances should be similar to non-pregnant patients.

For further information on maternal and neonatal outcomes see Section 9.1.

KEY MESSAGE

1. Benzodiazepines are effective for alcohol-withdrawal symptoms, in particular reducing seizures (**U**) (**Level I** [Cochrane Review]).
2. Opioid substitution therapy with methadone or buprenorphine is better than clonidine and lofexidine in ameliorating withdrawal symptoms (**N**) (**Level I** [Cochrane Review]).
3. Methadone and buprenorphine maintenance regimens should be continued throughout acute pain episodes wherever possible (**S**) (**Level III-2 SR** [PRISMA]).
4. Poorly managed acute pain episodes may decrease retention in opioid-maintenance programs (**U**) (**Level III-2**).
5. To achieve better analgesic efficacy, daily methadone maintenance doses should be divided and given 8 to 12 hourly (**S**) (**Level IV SR** [PRISMA]).

The following tick boxes represent conclusions based on clinical experience and expert opinion:

- ☑ Pain management in patients with substance use disorder often presents significant challenges for both clinicians and patients. Patients fear being stigmatised or discriminated against, are concerned about inadequate pain relief with their past experiences leading to physician distrust; they fear experiencing withdrawal (before their usual drugs are prescribed) and relapse precipitated by acute opioid exposure. The challenges for the clinician Include mistrust, concerns about drug seeking, fear of overtreatment with adverse events, concerns about diversion, and risk of discharge against medical advice (**N**).
- ☑ A "universal precautions" approach is increasingly recommended for patients with substance use disorder in acute pain settings; it may include use of multimodal analgesia, abuse-deterrent formulations, urine drug screening, use of prescription drug monitoring programs and risk management strategies (**N**).
- ☑ An acute admission offers opportunity to engage with patients with substance use disorder as well as to treat the acute issues (**N**).
- ☑ There is no cross-tolerance between alcohol or benzodiazepines or central nervous system stimulants and opioids (**U**).
- ☑ Oral naltrexone should be stopped at least 24 hours, ideally 72 hours, prior to elective surgery (**U**); naltrexone implants may need surgical removal in cases of severe acute pain where opioid responsiveness is required (**U**).
- ☑ Patients who have ceased naltrexone therapy should be regarded as opioid naïve; in the immediate post-treatment phase they may be more opioid sensitive (**U**).
- ☑ To achieve better analgesic efficacy, daily buprenorphine maintenance doses could be divided and given 8 to 12 hourly (**U**).
- ☑ Nicotine has a small to medium analgesic effect in volunteers and smoking abstinence increased self-reported pain (**N**).

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Paediatric Volume II

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10.1 | Developmental neurobiology of pain

The majority of information on this topic to date is experimental (mostly rodent) data, which presents translational challenges to the interpretation of developmental changes in the neurodevelopmental pathways of the human embryo-foetus-infant. The combination of basic science, fetal surgery and neonatal imaging studies is enhancing our understanding of pain pathway development and the influence of pacemakers and various receptors. In embryonic life, nociceptive pathways develop under the influence of (generally non-noxious) afferent input (Skaper 2018 **NR BS**; Li 2011a **BS**) and several trophic signalling pathways eg nerve growth factor and tropomyosin receptor kinase (NGF-TrK). Growth factor signalling systems are extremely important in the developing cytoarchitecture of nociceptor pathways and remain well conserved across species (Wheeler 2014 **BS**). Interspecies differences appear to stem from divergent roles played by (downstream) transcription factors (Guo 2011 **BS**). The expression of a number of molecules and channels involved in nociception are developmentally regulated. During early life, there are changes in the distribution and density of many important receptors and the levels and effects of several neurotransmitters alter significantly (Verriotis 2016a **NR**; Fitzgerald 2005 **NR**).

Animal studies confirm that activity-dependent maturation is a cornerstone of development and, in early gestation, intrinsically active neurons (endogenous pacemaker cells) contribute significantly to this (Li 2011b **BS**). Within lamina I of the spinal cord, pacemakers are positioned to regulate both the level of activity in developing motor circuits and the ascending flow of nociceptive information suggesting a role in the maturation of pain and sensorimotor networks (Li 2015 **BS**). Postnatal tuning of these pathways requires continued somatosensory (again non-noxious) input at a spinal level. The development of inhibitory pathways within nociceptor systems appears somewhat later and involves a developmentally regulated alteration in the synaptic effects of glycine and GABA (Hathway 2012 **BS**; Rajalu 2009 **BS**). Little is known about the trophic factors and essential synaptic inputs that guide the development of these pathways. Neuropeptides, receptors and ion channels implicated in the development of (and activity within) these pathways include sodium leak channels (spinoparabrachial tracts: Ford 2018 **BS**), metabotropic GABA-B receptors (Brewer 2018 **BS**) and atypical cadherins (Wang 2017 **BS**). Important signalling systems in early development include the ephrin-receptor tyrosine kinase system which influences cell movements (Wilkinson 2001 **NR**) and extracellular signal receptor kinases (O'Brien 2015 **BS**). Modulation of activity within these spinal pathways by tissue injury and inflammation appears to be mediated through glutaminergic signalling in an age-dependent fashion (Baccei 2010 **BS**). As a result, cortical coding of 'injury-induced pain states' also appears to be developmentally regulated (Chang 2016 **BS**).

Rodent studies confirm that C-fibre polymodal nociceptors are mature in their pattern of firing at stages equivalent to term gestation in humans. They are capable of being activated in the periphery by exogenous stimuli, although their central synaptic connections in the dorsal horn are initially immature. However, "wind-up" can be produced by relatively low-intensity A-fibre (rather than C-fibre) stimulation. A-beta fibres initially extend up into the spinal cord's laminae I and II and only withdraw once C fibres have matured. This overlap means there is less discrimination between noxious and non-noxious stimuli and, as the receptive fields of dorsal horn neurons are large, peripheral stimuli can excite a greater number of central neurons in early development. In addition, descending inhibitory pathways and inhibitory networks in the dorsal horn are not fully mature in early development (Schwaller 2017 **BS**). While activity of the rostroventral medial medulla (RVM) can facilitate or inhibit dorsal horn

neuron inputs in the mature animal, in young animals descending facilitation dominates and is likely generated by spontaneous brainstem activity (Hathway 2012 **BS**). Only later in postnatal life does this descending activity become modulated by ascending nociceptive inputs in a functional spinal-bulbo-spinal loop (Schwaller 2016 **BS**).

By 7 wk gestation, human primary afferent nerve fibres that innervate skin and projection neurons from the dorsal horn of the spinal cord reach the thalamus. Ascending pathways are present and functional by 25 wk gestation. Central neural projections and synaptic connections continue to mature and, from 26 wk gestation, peripheral noxious stimuli can elicit responses in the increasingly layered thalamic and cortical neurons (Verriotis 2016a **NR**).

Anatomical and electrophysiological evidence confirms that biological systems necessary for nociception are intact and functional from 26 wk gestation (Verriotis 2016a **NR**). This is clearly confirmed during fetoscopy and medical interventions in utero (Bellieni 2018 **NR**). Despite this, inferences regarding fetal pain are limited. Our understanding of the conscious, cognitive, affective and evaluative experience of pain during fetal and late gestational life remains conjectural (Derbyshire 2006 **NR**). In contrast to the protected environment *in utero* (in which the fetus is buffered from environmental stimuli and continuously exposed to the anaesthetic effects of endocrine neuroinhibitors), postnatal life brings intense afferent stimulation and wakefulness (Lagercrantz 2009 **Level IV**). With this, comes the possibility of psychological processes involving content derived from the environment (objects, people and symbols) (Derbyshire 2006 **NR**). Following birth, the neural pathways required for nociception are functional and cortical responses to noxious stimuli such as skin lancing can be demonstrated in even the most preterm neonate (Verriotis 2016a **NR**; Slater 2006 **Level IV**). However, as significant functional and structural changes occur in nociceptive pathways during the postnatal period (Hirschfeld 2012 **Level IV**), the pattern of activity evoked by tissue trauma also changes (Fitzgerald 2009 **Level IV**).

Although the underlying mechanisms may differ from adults, nociceptive pathways can be sensitised by painful stimuli in early life, as demonstrated by a reduction in reflex thresholds in neonates following repeated heel lance (Fitzgerald 1988 **Level IV**) and infants following abdominal surgery (Andrews 2002 **Level IV**). Both animal and human studies suggest that there is a relative excess of excitatory mechanisms and delayed maturation of inhibitory mechanisms in early life (Fitzgerald 2005 **NR**). Hence, neonates once thought to be less sensitive to painful stimuli in fact, produce more generalised and exaggerated reflex responses to lower intensity stimuli.

The disposition and clinical effects of drugs administered in early life are subject to many factors including changes in body composition, protein binding and membrane permeability as well as maturation of major organ systems and receptor signalling systems. Each of these may in turn be affected by disease-related alterations (van den Anker 2011 **NR**). Factors affecting the pharmacokinetic (PK) profile of analgesic drugs (body water and fat composition, plasma protein binding, hepatic metabolism and renal function) change rapidly during the first weeks of life (Funk 2012 **NR**). Postnatal changes in the PK profile of a number of analgesic drugs (eg morphine and paracetamol [acetaminophen]) result in significant age-related changes in dose requirements during infancy and childhood (Allegaert 2014 **NR**; Palmer 2008 **PK**; Prins 2008 **PK**; Bouwmeester 2004 **NR**). In addition, changes in nociceptive processing may have significant effects on the pharmacodynamic response to analgesics in early life (Walker 2008 **NR**). Therefore, developmental age and not just weight should be considered when calculating analgesic dosing (Allegaert 2014 **NR**) (see also Section 10.4 for PKs of the various analgesic drugs). Laboratory studies have demonstrated postnatal changes in the mechanism of action, analgesic efficacy and adverse-effect profile of analgesics that can inform subsequent clinical trials (Nandi 2005 **NR**; Walker 2008 **NR**; Fitzgerald 2009 **NR**).

Prolonged reductions in synaptic activity by general anaesthetics and analgesics can produce neurotoxic effects, such as accelerated apoptosis, in the developing nervous system eg in rodent models. The clinical significance of these laboratory findings remains uncertain (Mellon 2007 **NR BS**). Researchers are now assessing long term outcomes of repeated or extended exposure but the assessment of the impact of analgesic and general anaesthetic administration upon the infant's developing brain and pain pathways will always remain confounded by the underlying pathology, concomitant surgical intervention and comorbidities present (Davidson 2018 **NR**).

KEY MESSAGES

1. Following birth, even the most preterm neonate responds to nociceptive stimuli (**U**) (**Level IV**).
2. In early development, more generalised reflex nociceptive responses occur in response to lower intensity stimuli (**U**) (**Level IV**).

10.2 | Consequences of early pain and injury

10.2.1 | Early neurodevelopmental consequences

Significant reorganisation of synaptic connections occurs in the postnatal period. Activity within sensory pathways is required for normal development but abnormal or excessive activity related to pain and injury during the neonatal period may alter normal development and produce persistent changes in sensitivity that outlast the injury (Walker 2013 **NR**; Fitzgerald 2009 **NR**; Walker 2009 **Level III-2**).

However, the effect of pain in the neonatal period on neurodevelopment and the child or adult's later pain experience is difficult to quantify. In researching this, there are many factors that may confound the determination of the contribution of early pain to altered neurodevelopment and the extent to which this can be modulated by interventions. The likely patient confounders include sex, birth weight, gestational age at birth and at the time of insult, intercurrent illness type and severity (including hypotension), the extent of tissue damage (Brummelte 2012 **Level IV**), as well as genetic and epigenetic factors (Provenzi 2018 **Level IV SR** [PRISMA], 9 studies, n=1,516). While the treatment confounders that may influence neurodevelopment include type, dose and duration of analgesia (including opioids and benzodiazepines), other drugs administered (such as dexamethasone [for chronic lung disease] and anaesthetic agents (Davidson 2013 **NR**), as well as the neonatal unit's practices (which vary) and the quality of neonatal intensive care (see below: Montirosso 2012 **Level IV**). An additional confounder is the limited ability to quantify the neonate's pain experience in the intensive care setting; some studies have used the number of skin-breaking procedures (including blood tests, heel lances, vascular access and surgery) received by the neonate as a surrogate measure to then investigate impact on adverse outcomes. Nociceptive related reflex withdrawal activity and activation of higher cortical areas do not correspond well to observational pain assessment (or outward phenotype) of the neonate when compared to the adult (Fitzgerald 2015 **NR**). This means that behavioural pain assessment may not reflect physiological responses to pain. Importantly, our understanding is expanding regarding the interplay of stress exposure vs developmentally targeted care (eg in the NICU) and the influence upon epigenetics and resultant phenotypic trajectory (in terms of brain maturation, neurobehaviour, the child's current and later capacity to regulate stress, behaviour or emotions and social functioning) (Provenzi 2018 **Level IV SR** [PRISMA], 9 studies, n=1,516).

In clinical studies of ex-preterm neonates, neuroimaging studies done at the equivalent of term age showed greater pain exposure was associated with structural changes. White matter and subcortical grey matter maturation was reduced in infants born at 24–32 wk (related to the number of heel lances and single but not multiple surgical interventions), as assessed by diffusion tension and magnetic resonance spectroscopy (Brummelte 2012 **Level IV**). In a group of similarly premature infants, both neonatal pain and greater early illness severity (measured by the Score for Acute Neonatal Physiology–II) were associated with delayed microstructural development of the corticospinal tract (Zwicker 2013 **Level IV**). In MRI imaging of ex-extreme and very preterm (24–32 wk) neonates at a median of 32 and 40 wk post menstrual age (PMA), early exposure to repetitive procedural pain was associated with volume loss in the lateral thalamic (somatosensory) region with abnormal thalamocortical pathway development (Duerden 2018 **Level IV**, n=155). These changes were more pronounced in the extreme preterm infants. Neurodevelopmental outcome assessments (Bayley-III scores) showed that increased volumetric thalamic growth predicted higher cognitive and motor scores at 3 y corrected age.

Among extremely preterm infants (born at <30 wk gestation), those exposed to surgery (and anaesthesia) had greater white matter injury and smaller total brain volumes, particularly

smaller deep nuclear grey matter volume (Filan 2012 **Level III-3**). In those born at <29 wk gestation, clinical outcomes associated with greater pain exposure were delayed growth with lower body weight at 32 wk (Vinall 2012 **Level IV**) and poorer cognitive and motor function at 8 and 18 mth (Grunau 2009 **Level III-2**). No difference was seen in mental development scores at 2 y in ex-extreme preterm patients (<30 wk) who had surgery vs no surgery, following adjustment for confounders (Filan 2012 **Level III-3**).

Preterm behavioural epigenetics (PBE) is the study of the role of environmental factors such as pain-related stress, which may influence epigenetic modifications in the preterm infant and thus development and behavioural phenotype (Provenzi 2018 **Level IV SR** [PRISMA] 9 studies, n=1,516). In very preterm neonates exposed to high levels of pain-related stress, serotonin transporter gene SLC6A4 methylation in peripheral blood samples increased from birth to NICU discharge at CpG sites 5 and 6 vs neonates exposed to low pain-related stress (Provenzi 2015 **Level III-2**, n=88).

10.2.2 | Longer term consequences of early pain and injury

Longer-term consequences of early pain and injury have been well described, particularly in rodent models and ex-neonatal intensive care unit (NICU) populations. In laboratory studies, the degree of long term change varies with the type and severity of injury (Fitzgerald 2009 **NR**). Inflammation, full thickness skin wounds and skin incision produce prolonged alterations in sensitivity and the response to future injury, in the absence of any visible persistent peripheral injury. By contrast, allodynia following nerve injury is less apparent in early life (Moss 2007 **BS**; Howard 2005 **BS**). These findings are of considerable importance, as pain and injury in neonates may have effects on nociceptive processing that differ in mechanism and duration from those experienced by older children and adults. There is accumulating evidence in neonatal animal models that there are complex interactions between increased excitatory and decreased inhibitory synaptic signalling within the spinal cord in addition to changes in descending inhibitory control from the brainstem in response to tissue injury during the neonatal period (see 10.1 above and Beggs 2015 **NR**).

Neonatal pain results in an increased response to future painful stimuli months to years after the initial insult. Neonatal circumcision without anaesthesia or analgesia is associated with an increased behavioural response during immunisation at 4–6 mth when vs uncircumcised infants (Taddio 1995 **Level III-2**). Increased perioperative analgesia requirements and pain scores occurred when subsequent surgery was performed months later in the same dermatome, vs children who had no previous surgery (Peters 2005 **Level IV**). Early pain-related stress was associated with greater SLC6A4 methylation and greater behavioural problems as assessed by the Child Behaviour Checklist in ex-extreme to very preterm children at age 7 y vs full term controls, but only in individuals with the *COMT* 158 Met/Met genotype (Chau 2014 **Level III-2**, n=111).

Ex-preterm preschool children show alterations in pain-related behaviour such as increased somatisation (Grunau 1994 **Level IV**) and ex-NICU school-aged children had higher levels of pain-related catastrophisation (Hohmeister 2009 **Level III-2**). In ex-NICU preterm children and adolescents, thermal pain thresholds were reduced at age 9–14 y (Hermann 2006 **Level III-2**), and at 11 y in ex-extreme preterm children born at <26 wk gestation (along with reduced thermal and mechanical sensitivity around their neonatal thoracotomy scars) (Walker 2009 **Level III-2**). Increased gain in pain pathway signalling was seen at 11–16 y on functional magnetic resonance imaging (fMRI) in response to painful heat stimulus (Hohmeister 2010 **Level III-2**) and responses were enhanced to noxious stimuli (dolorimetry and number of tender points) vs term peers

at age 12–18 y, more so in girls (Buskila 2003 **Level III-2**). The clinical significance of these findings is uncertain.

A prospective cohort study of children born in 1958 investigated the association of chronic widespread pain in adulthood with "early trauma" (Jones 2009 **Level III-2**, n=7,571). It found no association between surgery in childhood before the age of 7 y (RR 1.0; 95%CI 0.9 to 1.1) but positive association for hospitalisation following a road traffic accident (RR 1.5; 95%CI 1.1 to 3.0). A later survey of this British cohort showed no increased risk of chronic widespread pain at 45 y in ex-premature adults (RR 1.26; 95%CI 0.95 to 1.67) (Littlejohn 2012 **Level III-2**, n=8,572).

10.2.3 | Modification by pain management intervention

Importantly, analgesia at the time of the initial painful stimulus may modulate long term adverse effects. The behavioural response to immunisation of male infants was reduced in those who had neonatal circumcision with local anaesthetic applied prior to surgery, vs neonates who had no local anaesthetic (Taddio 1995 **Level III-2**). Infants undergoing surgery in the neonatal period who received morphine did not show any increase in response to later immunisation vs infants without significant previous pain experience (Peters 2003 **Level III-2**). The quality of pain management in the NICU setting may also be important. Very preterm infants cared for in NICUs with high-quality infant pain management (ie use of pharmacological and nonpharmacological treatments for procedural pain, use of pain assessment tools and guidelines for preventing and treating pain) had better neurobehavioural outcomes vs low-quality scoring NICUs (Montirosso 2012 **Level IV**).

Further research is required to determine the most developmentally appropriate and effective analgesia regimens for modulating the effects of early pain and injury. This research will be challenged in its capacity to identify the impact of a single analgesic intervention as in- and out-patient 'care packages' have evolved including nonpharmacological intervention to support preterm and term neonates in intensive care (Provenzi 2018 **Level IV SR** [PRISMA], 9 studies, n=1,516; Valeri 2015 **Level IV SR** [PRISMA,] 13 studies, n unspecified) and procedural interventions in infants and younger children (see procedural Section 10.7).

KEY MESSAGES

1. Pain and injury in early life cause structural changes in cortical and subcortical pathways and are associated with alteration in somatosensory thresholds in later life (**U**) (**Level III-2**).
2. Analgesia may modulate the long term effects of pain and injury in early life but more information is required to determine the optimal dosing and type of agents to avoid negative impact of the pharmacological intervention itself (**U**) (**Level III-2**).
3. Improving quality of infant pain management delivery in neonatal intensive care (including pharmacological and nonpharmacological interventions) may result in improved neurodevelopmental outcomes (**U**) (**Level III-2**).
4. Understanding of the epigenetic factors that contribute to the behavioural pain trajectory is evolving; this may lead to enhanced developmentally targeted care to reduce stress exposure and long term impacts for infants (**N**) (**Level IV SR** [PRISMA]).

10.3 | Paediatric pain assessment

Pain assessment is a complex social interaction, with multiple factors contributing to the child's pain experience, its expression, subsequent interpretation and response (Voepel-Lewis 2012 **NR**). Assessment is a prerequisite to optimal pain management; it should involve a clinical interview with the child and/or their parent/carer, physical assessment and use of an age and context-appropriate pain intensity measurement tool (Howard 2008a **NR**). However, pain in hospitalised children remains common and is often under assessed and inadequately managed (Walther-Larsen 2017 **Level IV**, n=570 [4 hospitals]; Friedrichsdorf 2015a **Level IV**, n=178). Improvements in pain management and in patient, parent and staff satisfaction have been associated with regular assessment and measurement of pain (Deindl 2013 **Level IV**). Uniformity within an institution lends to staff familiarity. This and ease of use are major factors in the successful implementation of a pain management strategy. Adoption of written guidelines or pain management algorithms improved both assessment and management of pain in neonates and children (Williams 2019 **Level IV SR** 20 studies, n=6,390; Stevens 2014b **Level III-2**, n=3,822; Gharavi 2007 **Level IV**, n=225 neonatal units; Falanga 2006 **Level IV**, n=56). Clinical interventions have focussed usually on assessment of pain intensity (and rescue analgesic use). As in adults, domains of pain other than intensity (eg location, quality), the multidimensional nature of the pain experience (eg concomitant emotional distress, coping style of the child, previous pain experience) and parental expectations should be incorporated into overall assessment (Pillai Riddell 2013 **Level IV**, n=458 to 574; Liossi 2007 **Level IV**, n=45).

Verbal self-report is considered to be the best measure of pain in adults. Child self-report is desirable but not always possible, as a child's understanding of pain and their ability to describe it changes with age; while cognitive impairment alters a child's capacity to contribute to an assessment of their pain experience. Therefore, the measurement tools employed must be appropriate to the developmental stage. A range of alternative assessment methods have been established as surrogates for/or adjuncts to self-report. These include assessment scales incorporating observable behaviours, physiological markers and brain imaging techniques. Over 65 paediatric pain scales are published (Andersen 2017 **Level IV SR of S** [PRISMA], 12 SRs [number of studies & n unspecified]), examples of which are listed in Tables 10.1 to 10.4. These scales can be unidimensional (behavioural indicators only) or multidimensional (combining behavioural, physiological or contextual factors). Assessment should be expanded to evaluate aspects that are relevant to the patient and their family and the clinician, and include tools measuring global satisfaction, adverse effects, assessment of the emotional and financial impact, and physical recovery following paediatric acute pain (Walco 2018 **GL**; Berde 2012 **NR**; McGrath 2008 **GL**).

10.3.1 | Pain assessment in neonates

Noxious stimuli have deleterious short and long term effects on the developing neonate (Valeri 2015 **Level IV SR** [PRISMA], 13 studies, n unspecified) making recognition and management of pain crucial in this age group (see also Sections 10.1 and 10.2).

10.3.1.1 | Uni- and multi-dimensional neonatal pain scales

Over 40 scales have been developed for neonates and infants (Lee 2014 **NR**). These scales are comprised of overlapping combinations of surrogate measures (eg physiological signs such as increased heart rate) or behavioural responses (eg facial characteristics and cry). Choice of the most appropriate tool depends on contextual factors (the infant's age, health status), the stimulus (eg procedural or postoperative pain and whether repeated acute episodes – also

termed recurrent or “persistent” pain) and the purpose of the measurement (eg clinical care or research).

Table 10.1 lists examples of uni- and multi-dimensional scales used in neonates.

10.3.1.2 | Physiological measures used in neonatal pain assessment

Changes in physiological parameters associated with procedural interventions are assumed to indicate the presence of pain, including increases in heart rate (HR), respiratory rate, blood pressure, intracranial pressure, cerebral blood flow and palmar sweating; and decreases in oxygen saturation, transcutaneous CO_2 tension and vagal tone (Cong 2013b **NR**). As these changes are reduced by analgesia, they have been considered useful surrogate outcome measures of pain. Researchers have pursued the use of physiological parameters as objective measures of pain, particularly for preterm neonates (born at 24 to <36 wk). However, as their sensitivity and specificity are influenced by concurrent clinical conditions (eg HR increase with sepsis, illness severity, prematurity) and other factors (eg distress, environment, movement), they are predominantly experimental, have limited clinical utility and should be used in conjunction with behavioural measures.

Heart rate variability

Heart rate variability (HRV) analyses the R-R interval as a noninvasive marker of autonomic sinoatrial node input. It decreased during procedures (Padhye 2009 **Level IV**) and with postoperative pain (Faye 2010 **Level IV**). This contrasts with changes seen in adults with experimentally induced pain where HRV generally increases (Koenig 2014 **Level IV SR** [PRISMA], 20 studies, n=642).

Skin conductance

Skin conductance measures palmar/plantar stress-induced sweating electrically. In a review, skin conductance correlates with 3 unidimensional pain scales (ABC Pain Scale, 1 study; Neonatal Facial Coding System (NFCS), 1 of 2 studies; Comfortneo, 1 of 2 studies), crying time (1 study) and with one of two arousal/movement scales (Prechtl Scale: 8 studies). It has low positive predictive value for moderate pain (NFCS>4/10) and does not correlate with HR (in 6 of 8 studies), O_2sat (6 studies), respiratory rate (2 studies), or multidimensional pain scales (8 studies) (Hu 2019 **Level IV SR** [PRISMA], 28 studies, n=1,061). Study results assessing the impact of gestational (10 studies) and postnatal (9 studies) age are conflicting. Counterintuitively, skin conductance can be increased following oral (PO) glucose (Solana 2015 **Level IV**; Munsters 2012 **Level IV**). Due to the inconsistent results, skin conductance cannot be recommended for pain assessment in neonates (Hu 2019 **Level IV SR** [PRISMA], 28 studies, n=1,061).

Near infrared spectroscopy

Near infrared spectroscopy (NIRS) measures changes in haemoglobin oxygenation to calculate cerebral blood flow as a proxy for neuronal activity. Regional cerebral blood flow increases in the somatosensory cortex, contralateral to the side receiving a painful stimulus. Two systematic reviews have assessed NIRS correlations with other pain assessment scales (Relland 2019 **Level IV SR** [PRISMA], 8 studies [NIRS], n=237; Benoit 2017b **Level IV SR** [PRISMA], 9 studies [NIRS], n=272) (7 study overlap). NIRS correlated with Premature Infant Pain Profile (PIPP) particularly for the facial expression component (r 0.53 for the right prefrontal area: Ozawa 2011 **Level III-2**, n=80) (r 0.57: Slater 2008 **Level IV**, n=12 [33 tests]) and Neonatal Facial Coding System (NFCS) scores (r 0.27–0.41: Roue 2018 **Level IV**, n=133) but not with Faces Legs Arms Cry Consolability (FLACC) scores (Ranger 2013a **Level IV**, n=42) or Neonatal Infant Pain Scale (NIPS) (Bembich 2015 **Level IV**, n=16). Confounders include gestational age, activation of nearby motor cortex, sleep-wake cycle and previous pain exposure (Bembich 2016 **Level IV**, n=16; Ozawa 2011 **Level III-2**, n=80). Of note, one

third of infants showed NIRS responses without facial changes during some procedures (Slater 2008 **Level IV**, n=33 tests). Similarly NIRS and electroencephalography (EEG) changes do not consistently co-occur in neonates following innocuous cutaneous stimulation (Verriotis 2016b **Level III-2**, n=36). Use of NIRS for pain assessment requires further research.

Neurophysiological monitoring

Using scalp EEG, a pain-specific response that correlates with the spinal withdrawal reflex (1 RCT), and is reproducible, dependent on stimulus intensity and independent of sleep state is demonstrated in preterm and term neonates and infants (Relland 2019 **Level IV SR** [PRISMA], 7 studies [EEG], n=265; Benoit 2017b **Level IV SR** [PRISMA], 8 EEG, n=298) (4 study overlap). A template of brain activity that is sensitive to analgesic administration and quantifies procedural pain in neonates has been identified (Hartley 2017 **Level IV**, n=18). Data has also demonstrated temporal, topographic and amplitude patterns in EEG potentials evolving with neonate and infant neural maturation: from 28 wk gestation nonspecific neural bursts transition to specific somatosensory tactile and nociceptive potentials at 35–37 wk (Green 2019a **Level IV**, n=122; Fabrizi 2016 **Level IV**, n=18 infants & 21 adults; Fabrizi 2011 **Level IV**, n=30 term & 30 preterm). The EEG evolution correlates with development of discriminative facial expression from 33 wk gestational age (Green 2019a **Level IV**, n=122). Additionally, sex-related differences in cortical pain responses in females were consistent with those of adult females (Verriotis 2018 **Level III-2**, n=81), with individual differences in neonates in simultaneously recorded EEG and NIRS data (Verriotis 2016b **Level III-2**, n=36). Researchers reported that PO sucrose reduced PIPP score but did not alter cortical nociceptive activity to heel lance (Slater 2010 **Level II**, n=59, JS 5), and controversially concluded that sucrose may not be an effective analgesic. Scalp EEG measurement has shown promise as a surrogate measure of neonatal pain.

Functional magnetic resonance imaging

Functional magnetic resonance imaging (fMRI) to study brain responses to pain in neonates has gained attention (Benoit 2017b **Level IV SR** [PRISMA], 2 studies [fMRI]: details below). Some similarities are seen in the unique patterns of activity between the neonatal and adult brain in response to painful stimuli (Goksan 2015 **Level IV,** n=10 infants & 10 adults), including when sedated with chloral hydrate (Williams 2015 **Level IV,** n=19 infants). However, the role that this modality may play in pain assessment is still unclear.

Stress markers

Markers of stress have been measured in infant pain studies. In critically ill neonates postcardiac surgery, plasma but not urinary cortisol rose (Franck 2011 **Level IV**, n=81). In healthy newborns, salivary chromogranin and amylase did not change peri-heel lance (Shibata 2013 **Level IV**, n=47), while salivary cortisol rose after venipuncture and correlated with NFCS scores (r 0.42: Roue 2018 **Level IV**). In expreterm neonates in NICU, salivary cortisol was measured in patients receiving painful stimuli (8 studies: 5 heel lance), physical examination and heel lance (2 studies), and standard (2 studies nappy change; 1 study prone positioning) vs pleasant handling (3 studies) (Morelius 2016 **Level IV SR** [PRISMA], 16 studies, n=1,027). Plasma and salivary (but not urinary) cortisol rises with painful procedures, is modified by intervention (cocaine, prone positioning and music), while salivary cortisol does not change with non-painful handling eg nappy change. The review suggests future study designed to address the gaps in our understanding of cortisol regulation in neonates.

Integrated multimodal measurement

An integrated system (NIRS, EEG, electrocardiograph [ECG], electromyelograph [EMG], combined with physiological and behavioural indices) is likely to provide the most reliable and reproducible measurements of noxious stimulation (Roue 2018 **Level IV**, n=113; Worley 2012

Level IV, n=6). This expensive system may feasibly assist bedside tool validation but is unlikely to play a direct role in pain assessment.

10.3.1.3 | Behavioural measures used in neonatal pain assessment

Noxious stimuli produce a series of behavioural responses in neonates and infants that can be used as surrogate measures of pain including crying, changes in facial activity, torso and limb movement, consolability and sleep state (Chorney 2014 **NR**).

Crying

Crying is described in terms of presence or absence, duration, amplitude or pitch. Up to 20% of preterm and some acutely ill infants do not cry or cry inaudibly during heel stick (Johnston 1999 **Level IV**). Amplitude or audible cry occurrence did not correlate with nociceptive brain activity measured with NIRS (Bucher 1995 **Level IV**) and EEG (Relland 2019 **Level IV SR** [PRISMA], 1 study [cry response]: Maitre 2017 **Level IV**, n=54).

Facial expression

Facial expression in response to pain is widely studied and forms part of a number of pain scales, for preterm neonates up to school-aged children (Schiavenato 2012 **Level IV**, n=63) (see Tables 10.1 to 10.3). In neonatal intensive care, facial actions were more reliable than physiological measures for evaluating pain responses (Stevens 2007 **Level IV**) but may be dampened in preterm neonates (Green 2019a **Level IV**, n=122; Slater 2008 **Level IV**, n=12 [33 tests]; Holsti 2007 **Level IV**, n=92) and, like cry, may be absent (Hartley 2017 **Level IV**, n=18; Slater 2008 **Level IV**, n=33 tests), not linked to nociceptive brain responses (Hartley 2017 **Level IV**, n=18) or be present only if previous noxious stimulus has been experienced (Ozawa 2011 **Level III-2**, n=80). The use of video recordings for translation to pain scales' graphics (Schiavenato 2012 **Level IV**, n=63) has been superseded by facial recognition software. The latter has been validated with various neonatal and infant observer pain scales and provides automated identification of the expression of pain (Sakulchit 2019 **Level IV**, n=77; Xu 2018b **Level IV**, n=143; Zhi 2018 **Level IV**, n=26 [204 images]; Zamzmi 2018 **Level IV**, n=8 [15 videos]; Heiderich 2015 **Level IV**, n=30 [360 images]) and may overcome clinician bias when assessing facial expression (Blais 2019 **Level IV**, n=20 [adults]).

Contextual influences

Contextual factors include physical, psychological and social elements. A number of contextual factors influence the specificity and sensitivity of behavioural responses in ex-preterm neonates (Sellam 2011 **Level IV SR** [PRISMA], 23 studies, n=1,649). Pain can be affected by behavioural state (awake, asleep, activity prior to a stimulus), distress for other reasons (eg hunger and fatigue), age (postmenstrual and postnatal) and neuromuscular developmental status. Previous pain exposure and handling (Ozawa 2011 **Level III-2**, n=80; Holsti 2006 **Level IV**, n=43) altered both behavioural and physiological responses, eg infants experiencing higher numbers of procedures have reduced facial expression in response to pain, reduced nociceptive brain activity (Ozawa 2011 **Level III-2**, n=80), reduced brain maturation (Ranger 2013b **Level IV**, n=42; Brummelte 2012 **Level IV**, n=86) and long term alteration of their pain pathway processing on MRI (Hohmeister 2010 **Level III-3**, n=27). Sex differences are inconsistent: female vs male neonates, both preterm and term, have more facial actions (Verriotis 2018 **Level III-2**, n=81; Guinsburg 2000 **Level III-2**, n=65) but no difference in PIPP scores or cortical activity (Ozawa 2011 **Level III-2**, n=80) and, in preterm infants only, no difference in NFCS scores (Valeri 2014 **Level III-2**, n=53). In most studies, severity of illness or neurological impairment was not associated with altered behavioural pain responses. However, data in term infant NICU patients suggested that stress and illness impacts on cortical activity in the absence of behavioural changes (Jones 2017 **Level IV**, n=56). Surveyed health providers' knowledge gaps and attitude affect scoring and provision of pain relief (Cong 2013a **NR**).

Observational scales

The reliability and validity of behavioural measures is best established for procedural interventions such as heel lance but many observational scales have not been rigorously evaluated (Meesters 2019 **Level IV SR**, 9 studies, n=645). The PIPP (Stevens 2010 **Level IV SR**, 62 studies, n=3,158) and COMFORT scales (Maaskant 2016 **Level IV SR** [PRISMA], 30 studies, n=2,593) are the best validated and most widely used (McGrath 2008 **GL**). The PIPP-revised (PIPP-R) has had validation initially (Stevens 2014a **Level IV**, n=137) and after translation into 6 other languages (Bueno 2019 **Level IV**, n=187; Olsson 2018 **Level IV**, n=37; Taplak 2019 **Level IV**, n=200). The FLACC scale, developed for infants >2 mth old, was used in hospitalised neonates with simultaneous assessment with PIPP in a skin conductance study (Ahmed 2015 **Level IV**, n=85 [measurements]).

The following scales are recommended in reviews spanning a decade (Eriksson 2019 **NR**; Hatfield 2015 **Level IV SR,** 10 studies n=742; Lee 2014 **NR**; Cong 2013b **NR**; Howard 2008a **NR**). They are supported by current data (see Tables 10.1 and 10.2 with relevant references) acknowledging that the evidence supporting the psychometrics of recommended scales is usually Level III or IV (Andersen 2017 **Level I** [PRISMA], 12 SRs (number of studies & n unspecified):

- Acute procedural pain — PIPP; Neonatal Facial Coding Scale (NFCS); Neonatal Pain, Agitation and Sedation Scale (N-PASS);
- Postoperative pain — PIPP; N-PASS;
- Intensive care — COMFORT; COMFORTneo; COMFORT B (for repeated acute pain exposures termed "persistent" pain in intensive care patients); Faceless Acute Neonatal Pain Scale (FANS) (when facial expression is concealed eg with nasal continuous positive airway pressure) (Milesi 2010 **Level IV**, n=53).

10.3.2 | Pain assessment in infants and children

Observational and behavioural scales

Assessment for infants and young children is largely achieved using observational assessment scales. Many scales incorporate both physiological and behavioural parameters to determine an overall pain score and may result in more comprehensive measurement (Lee 2014 **NR**; Chorney 2014 **NR**). Some examples are included in Table 10.2 but a wider range of measures, their strengths and limitations and issues of testing reliability and validity have been reviewed (von Baeyer 2007 **Level IV SR**, 129 studies, n unspecified; Chorney 2014 **NR**; Lee 2014 **NR**; van Dijk 2012 **NR**; McGrath 2008 **GL**; Johnston 2003 **NR**). In infants and young children, behavioural items that predicted analgesic demand in the postoperative period were crying, facial expression, trunk and leg posture and motor restlessness, but physiological variables were unreliable (Buttner 2000 **Level III-2**).

There is still no single gold standard for pain assessment as requirements vary with the age and developmental stage of the child, the type of pain (eg procedural vs postoperative), and the context (eg clinical utility vs research reliability). Based on reviews summarising the wide data on this topic, the following observational/behavioural measurement tools are recommended for pain measurement in infants ≥1 y (McGrath 2008 **GL**), children and adolescents (Crellin 2015 **Level IV SR** [PRISMA], 52 RCTs & 26 psychometric studies, n unspecified; von Baeyer 2007 **Level IV SR**, 129 studies, n unspecified; Crellin 2018 **Level IV**, n=100; Chorney 2014 **NR**) (see Table 10.2):

- Acute procedural and postoperative pain — FLACC;
- Postoperative pain managed by parents at home — Parents Postoperative Pain Measure (PPPM); and
- Intensive care — COMFORT & COMFORT B scales.

10.3.3 | Self-report in children and adolescents

10.3.3.1 | The change in capacity of children to self-report with age

Self-report of pain is preferred when feasible, and is possible to an extent from 4 y of age, dependent upon the child's cognitive and emotional maturity. Scales for self-report need to consider the child's age, their ability to differentiate intensity levels, and their ability to separate the emotional from the physical components of pain (von Baeyer 2014 **NR**) (see Table 10.3). It is important that a measurement tool be used regularly and uniformly within each centre as staff familiarity and ease of use are major factors in the successful implementation of a pain management strategy. Children aged 3 y cannot provide valid graded self-report of pain intensity, and the evidence is weak for the capacity of those aged 4 y with published scales (Birnie 2019 **Level IV SR** [PRISMA], 80 studies, n unspecified; von Baeyer 2017 **Level IV SR** [PRISMA], 14 studies n=766) (8 study overlap). For 4 y olds and some 3 y olds, performance can improve by confirming pain is present, then providing an explanation of the scale with a reduced number of choices (eg 3 choices with the Simplified Faces Pain Scale or Pieces of Hurt: low, medium, high hurt). From 5 y, the standard 6 choice Faces Pain Scale-revised (FPS-R) (Figure 10.1) can be used and provides extra data (Emmott 2017 **Level II**, n=180, JS 3). At around 5 y, children have some capacity to appraise current pain and match it to previous experience, but they are more likely to choose the extremes of the scale (von Baeyer 2009b **NR**). In scales anchored with smiling or tearful faces, pain may be confused with other emotional states such as happiness, sadness or anxiety (Tomlinson 2010 **Level IV SR**, 127 studies, n=17,372).

Between ages 7–10 y, children develop numerical competency skills with measurement, classification and seriation (ie placing things in ascending or descending order). The upper end of the scale is less static than in adults changing with the individual child's ability to objectify, label and remember previous pain experiences (von Baeyer 2014 **NR**). Literacy is also important regarding the wording associated with the scales' upper anchor (such as most pain or worst pain imaginable vs very much hurt); this is also relevant for between study consistency (Castarlenas 2017 **Level IV SR** [PRISMA], 15 studies n=2,174; von Baeyer 2009a **NR**).

It is not until 10–12 y that children can clearly discriminate the sensory intensity and the affective emotional components of pain and report them independently (McGrath 1996 **Level III-2**). Verbally competent children aged ≥12 y can understand multidimensional tools designed for adults such as the McGill Pain questionnaire (MPQ) (see below).

10.3.3.2 | Unidimensional pain intensity paediatric self-report scales

Of sixty self-report scales, only eight have well established reliability and validity for acute pain assessment in children and adolescents (aged 3–18 y): Pieces of Hurt tool (scored 0–4); Faces Pain Scale-Revised (FPS-R) (0–10); Oucher pain scale photographic and numeric scales (0–10); Wong-Baker FACES Pain Rating Scale (WBFPRS) (0–10); Visual Analogue Scale (VAS) (0–100 mm), Colour Analogue Scale (CAS) (0–10) and Numeric Rating Scale NRS-11 (0–10) (Birnie 2019 **Level IV SR** [PRISMA], 80 studies, n unspecified).

Numeric Rating Scale (NRS)-11

The NRS-11 has the greatest number of studies assessing its measurement properties (Birnie 2019 **Level IV SR** [PRISMA], 24 NRS-11 studies [7 postoperative], n unspecified) including correlation between PACU scores by children aged 4–16 y with the nurse and parent (Brahmbhatt 2012 **Level IV**, n=33). This scale has been validated across a variety of paediatric settings and is available in a number of formats (verbal/printed/electronic) (Castarlenas 2017 **Level IV SR** [PRISMA], 15 studies n=2,174) (14 study overlap with Birnie 2019). Children <8 y may require screening tasks to assess numerical competency to then use the NRS-11 effectively.

Faces pain scales (FPS)

Of the fourteen FPSs, four have undergone extensive psychometric testing: FPS, FPS-R, Oucher and WBFPRS (Tomlinson 2010 **Level IV SR** [PRISMA], 127 studies, n=13,388). When given the choice, children prefer faces scales in general. The WBFPRS is most preferred but its smiling and crying anchor faces may lead to confounding with affect and it has weak recommendation for use (Birnie 2019 **Level IV SR** [PRISMA], 16 WBFPRS studies [1 postoperative], n unspecified). While the FPS-R (second to NRS-11 in the number of studies assessing measurement properties) is strongly recommended for research purposes (Birnie 2019 **Level IV SR** [PRISMA], 21 FPS-R studies [8 postoperative], n unspecified). In the ED setting, FPS-R (Tsze 2013 **Level IV**, n=620) and WBFPRS (Garra 2013 **Level IV**, n=197) have been validated. An electronic version FPS-Re has also been validated and is preferred by children (Birnie 2019 **Level IV SR** [PRISMA], 4 FPS-Re studies, n unspecified).

Coloured analogue scale (CAS)

The CAS has been assessed in the same review as the above 2 scales, mostly in English (and 4 other languages) and is strongly recommended for ≥8 y (Birnie 2019 **Level IV SR** PRISMA, 19 CAS studies [5 postoperative], n unspecified). It is coloured from small white gradations widening up to deep red, with a slider form with a 0–10 back measure or a pocket sized scale with variations in the upper anchor's wording.

Visual analogue scale (VAS)

The VAS form in children is the same as that used for adults with either a line or rule and 100mm scale, with numerical values of 0–10 or 0–100 mm. It has been assessed in children mainly in acute pain conditions with a weak recommendation for use ≥ 8 y (Birnie 2019 **Level IV SR** [PRISMA], 15 VAS studies [4 postoperative], n unspecified).

10.3.3.3 | Recommended scales according to age

Using chronological age as a guide of developmental stage, the below scales are recommended for acute pain assessment (with weaker recommendations for postoperative and chronic pain assessment) (Birnie 2019 **Level IV SR** [PRISMA], 80 studies n unspecified; von Baeyer 2017 **Level IV SR** [PRISMA], 14 studies, n=766; Tomlinson 2010 **Level IV SR** [PRISMA], 127 studies, n=13,388; Emmott 2017 **Level II**, n=180, JS 3):

- <4 y —self-report unreliable
- 4–5 y —Simplified-FPS or Pieces of Hurt
- Some 5y and ≥6y —NRS-11 (which requires numerical competency) & FPS-R
- ≥8 y —CAS & VAS

The validity of the gold standard of asking for and documenting pain scores is being questioned, due to the inherent subjective nature of self-report (von Baeyer 2014 **NR**; Berde 2012 **NR**). As is occurring in paediatric chronic pain assessment (Varni 2010 **Level IV**, n=3,048), acute paediatric pain measurement may warrant inclusion of measures of self and observed functional impairment (eg post laparotomy the child is remaining in bed vs able to sit out in chair vs attend ward play room or in-hospital school) combined with rescue analgesic use. This is particularly relevant when self-reported pain scores are either high or low and conflict with the clinical context and the paediatric clinicians' observations (von Baeyer 2014 **NR**).

Paediatric pain scale investigators argue that self-report scales of pain intensity are more valuable on a population or research level than for effective pain management for an individual child (Twycross 2015 **NR**). They suggest pain scores are best considered a primary source of information rather than a gold standard. Particularly in younger children, assessment should combine self-report with observations of activity, parental report and consideration given to psychosocial influences.

10.3.3.4 | Concordance between pain scales and subdivisions within scales

Debate continues as to concordance between the various scales (Le May 2018 **NR**; Sanchez-Rodriguez 2012 **NR**). NRS-11 correlates with FPS-R, VAS and CAS but this does not reflect agreement or interchangeability.

The minimum clinically significant difference (MCSD) for the NRS-11 is 1/10 (Castarlenas 2017 **Level IV SR** [PRISMA], 4 studies [MCSD], n=496). In the ED triage setting, for the Verbal V-NRS, MCSD and Perceived Patient Adequate Analgesia (PPAA) were both 2/10 and for the FPS-R was 2/10 and 4/10 respectively (Tsze 2019a **Level IV**, n=431 [344 VNRS and 415 FPS-R analysed]); the same group assessed FPS-R with MCSD of 2/10 vs CAS which was 1/10 (Tsze 2015 **Level IV**, n=314).

Suggested subdivisions for no, mild, moderate and severe pain are respectively: 0 to 2, 4, 6, and 8 to 10 for FPS-R vs 0 to 1, 1.25 to 2.75, 3 to 5.75 and 6 to 10 for CAS (Tsze 2018 **Level IV**, n=620).

Suggested VAS cut-offs for children and adolescents are 35 mm for mild pain and 60 mm for severe pain (in contrast to adult cut-offs of 30 mm and 70 mm respectively) (Hirschfeld 2013 **Level IV**, n=5,258). Pain intensity measurements within 12 mm on the paper VAS may be considered the same (Bailey 2012 **Level IV**, n=151).

Of importance, pain scale subdivisions or cut-offs and pain scores, as a uni-dimensional assessment, should not be used solely to guide the administration of analgesia.

10.3.3.5 | Facial recognition software applications

Types of facial recognition software applications (relevant to infants, children and adults) presented in computing conference abstracts over the last decade have been summarised (Subramaniam 2018 **NR**).

Digital burst photographs taken by iPhone® of young children during venipuncture were imported into an Emotion Application Programming Interface (Sakulchit 2019 **Level IV**, n=77). A subsequent 8 face pain scale was developed which correlated with FLACC scores (positively for 'sadness' and negatively for neutral expression) and was sensitive to EMLA use.

Facial videos of older children aged 5–18 y were taken post-laparoscopic appendicectomy at rest (ongoing pain) and with abdominal palpation (transient pain) at three time points (postoperatively, 20 h post and POD 21) to assess pain trajectory (Sikka 2015 **Level IV**, n=50). These were analysed with a computer expression recognition toolbox. The facial action units were compared to blinded self, parental and nursing report using NRS-11. A binary pain (≥4/10) vs no pain (0/10) and continuous model were developed. The computer version machine learning (CVML) system was accurate for binary classification and correlated with self and parental report (including over time). As nurses under reported pain vs child and parents, the CVML detected pain more accurately than nurses (particularly for ongoing pain). A similar CVML process was conducted in primarily Hispanic teenagers also at three time points post-laparoscopic appendicectomy (within 24 h, subsequent day, and POD 25) (Xu 2018b **Level IV,** n=143). With transfer learning, the ROC curve improved to better detect true positives and was consistent when tested on a new pain data set.

10.3.3.6 | Observer-rated or composite scales used prehospital and in EDs

The French Evaluation ENfant DOuLeur (EVENDOL) scale (0–15) for children aged 0–7 y was developed as a single observer-rated scale for pain assessment prehospital (Beltramini 2019 **Level IV**, n=422 [144 in pain]) and in EDs (Fournier-Charriere 2012 **Level IV**, n=291). It has been translated into English but not reviewed systematically.

The UK Royal College of Emergency Medicine launched the Composite Pain Scale; this combines a modified WBFPRS (4 faces) (observer-rated <8 y and self-reported ≥8 y) with an observer-rated behaviour scale, injury example prompts and NRS-11 self-report for older children (James 2017 **Level III-2**, n=117). Pain scores were then categorised as absent, mild, moderate or severe. Doctors and nurses correlated well including with the older child's face scale report, but not with the V-NRS-11 component.

10.3.3.7 | Function scales: observed vs self-report

As in paediatric chronic pain assessment (Varni 2010 **Level IV**, n=3,048), acute paediatric pain measurement may warrant inclusion of measures of self and observed functional impairment (eg post laparotomy the child remaining in bed vs able to sit out in chair vs attend ward play room or in-hospital school) and rescue analgesic use.

An in-hospital Youth Acute Pain Functional Ability Questionnaire has been developed in children admitted with sickle cell crises and subsequently validated in children post-surgery (Rabbitts 2017 **Level IV**, n=564). A 3 item short form with 5 point Likert rating of capacity to dress, wash and go outside the room was developed (assuming normal baseline capacity). Functional capacity is particularly relevant when self-reported pain scores are either high or low and conflict with the clinical context and the paediatric clinicians' observations (von Baeyer 2014 **NR**).

10.3.3.8 | Multidimensional pain intensity self-report scales for adolescents

One tool modelled after the MPQ, the Adolescent Pediatric Pain Tool assesses pain with a body diagram, word intensity scale and multiple quality descriptors (Fernandes 2014 **Level IV SR**, 23 studies, n=1,750 children & adults). It has been validated in multiple settings: acute and chronic pain, hospital, home, and in English and Spanish (pending further validation in Portuguese and Chinese). The extra dimensions are useful to examine effectiveness of pain management but pen/paper and 3–6 min time is required to complete it, and further validation in interventional studies and consistency scoring across studies is needed.

10.3.4 | Children with cognitive impairment or intellectual disability

Most children with intellectual disability (ID) or severe cognitive impairment (CI) experience pain proportional to their degree of neurological impairment (Hauer 2017 **NR**) and probably in a similar way to their peers. However, there are some examples of disorder-specific alterations in pain perception eg the higher pain and temperature threshold seen in patients with Prader-Willi syndrome (de Knegt 2011 **NR**). In addition, children with ID/CI or communication difficulties (including neonates at risk of neurological impairment in intensive care) may experience more pain episodes than other children because of their associated complex medical disorders/neurological impairment, physical comorbidities and increased need for procedures (Stevens 2003 **Level III-2**, n=194; Hauer 2017 **NR**; Breau 2009 **NR**). Both neonates (who were perceived in the past as being less responsive to painful stimuli) (Breau 2006 **Level III-2**, n=99 [clinicians]; Stevens 2007 **Level IV**, n=149) and older children with CI (Valkenburg 2012 **Level III-3**, n=45 [15 Downs syndrome]) have received less analgesia vs peers. Assessment of pain is difficult in ID/CI, particularly in the severe neurological impairment cohort, and can contribute to inadequate analgesia (Hauer 2017 **NR**). Older children with CI received less analgesia during surgery but comparable amounts and types of analgesics as cognitively intact children postoperatively (Valkenburg 2012 **Level III-3**, n=45; Long 2009 **Level III-3**, n=148; Koh 2004 **Level III-2**, n=290) contrasting with the findings in an earlier series (Malviya 2001 **Level III-3**, n=42).

10.3.4.1 | Pain assessment scales for children with neurodevelopmental disorders and severe cognitive impairment (CI)

Observer-rated scales

Specific observer-rated behavioural tools have been developed for children with neurodevelopmental disorders and severe CI (Crosta 2014 **Level IV SR**, 7 studies [4 tools], n≈270; Valkenburg 2010 **NR**) (see Table 10.4). Behaviours reported by carers to be associated with potentially painful stimuli, and that discriminate these from distressful or calm events, have been compiled in the revised Non-Communicating Children's Pain Checklist (NCCPC-R) for home (Breau 2002a **Level IV**) and postoperative use (NCCPC-PV) (Crosta 2014 **Level IV SR** 1 study: Breau 2002b **Level IV**, n=24). Cut-off scores for NCCPC-PV were developed against VAS scores, with good inter-observer reliability between primary carer and the researcher who had not met the child. It has been translated and validated in French, Swedish and German. NCCPC does not need to be individualised for the patient, it discriminates distress from pain but was rated least desirable by clinicians based on complexity and length (2 h observation) vs other scales (Quinn 2015 **NR**). The NCCPC scales have formed the basis of validated adult scales – Chronic Pain Scale for Non-verbal Adults with Intellectual Disabilities (CPS-NAID) (24 items for persistent pain) and Non-Communicating Adult Pain Checklist (NCAPC) (18 items for acute/procedural pain) (Breau 2009 **NR**).

The Paediatric Pain Profile (PPP) rates 20 behaviours to assess pain in children with neurodevelopmental disorders and severe CI (Crosta 2014 **Level IV SR,** 1 study: Hunt 2004 **Level IV**, n=140). It includes the child's pain history, baseline and ongoing pain assessments, interventions and discussion with clinicians about the child's pain but does not require knowing the individual behaviours. This scale had demonstrated potential for children with recurrent acute (persistent) pain at home but was less sensitive perioperatively. Its usability is limited by its teaching requirements and length (Crosta 2014 **Level IV SR**). The PPP is validated and used across all Gross Motor Function Classification System (GMFCS) levels of cerebral palsy (CP) (Kingsnorth 2015 **Level IV SR**, 240 studies, [54 chronic pain assessment tools screened]). It is more accurate but takes longer (5 min vs 1) and is less preferred than revised (r)FLACC (see below). Of note (as with neonates), salivary cortisol measurement in children with severe neurological disability was not found a useful marker for pain assessment (Hunt 2007 **Level IV**, n=29).

An Individualised Numeric Rating Scale (INRS), where carer proposed pain indicators are ranked on a 0–10 NRS scale, has been validated for pain assessment in children with severe CI (Crosta 2014 **Level IV SR**, 1 study: Solodiuk 2010 **Level IV**, n=50). The bedside nurse INRS scores correlated with but were lower than the carer's assessment, with only modest correlation with NCCPC-PV. INRS use fosters carer and nurse collaboration. As it is developed with input from carers and educators, it may be the best option for school nurses (Quinn 2015 **NR**).

The rFLACC scale (0–10), incorporating specific descriptors and parent-identified behaviours for individual children, has also been developed for children with severe CI (Crosta 2014 **Level IV SR**, 1 study: Malviya 2006a **Level IV**, n=52). It remains the easiest, preferred and most flexible tool to use in the acute hospital setting (Crosta 2014 **Level IV SR**, 7 studies, n≈270). Compared to VAS-observer (0–10), rFLACC (Danish) was valid and reliable for pain assessment post-orthopaedic surgery in children with CP GMFCS II–V; 2 nurse observers experienced in nursing children with CP scored video-recordings and had high intra-rater reliability (Pedersen 2015 **Level IV**, n=27). When assessing videotapes without audio of children with CP (all GMFCS grades I to V) having physiotherapy, the Child Facial Coding System (which codes 13 facial actions; 10 of which indicate pain not present) correlated with observer-rated NRS-6 (Hadden 2016 **Level IV**, n=85). Future work using pain expression facial coding combined with facial recognition software and computer

learning algorithms may be useful in children who cannot self-report, as is being explored for adults with dementia (eg PainChek®) (Atee 2018 **NR**).

Self-report scales in children with neuromuscular disorders and lower degrees of cognitive impairment

Self-report scales may not be reliable even in those with mild to moderate CI (Quinn 2015 **NR**). For physically disabled children aged 8–20 y with various neuromuscular disorders and no CI, self-report with NRS outperformed the WBFPRS (4 faces) and 6 point Verbal rating scale (Miro 2016 **Level IV**, n=113). A study assessed self-report NRS-6 (0–5) vs observer-rated NCCPC-PV in children with CP of varying severity (diplegic 32% to quadriplegic 54 %) having physiotherapy (Hadden 2015 **Level III-2**, n=63). The children had their hearing, vocabulary and receptive knowledge assessed and 52% were able to self-report. Carer ratings were lower than ratings by researcher, physiotherapist and the child capable of self-report.

10.3.4.1 | Children with Autism Spectrum Disorder (ASD)

ASD is a developmental disorder affecting communication, socialisation and sensory processing to varying degrees, which may influence the reliability of the pain assessment scales (Allely 2013 **Level IV SR** [PRISMA], 10 studies & 5 case reports, n=1,137). Assessment is further complicated by the frequent comorbidities of altered perception (hypo and hypersensitivity), anxiety, attentional deficient disorder and ID. Typical pain behaviours (pain expression) may be absent in some patients, which does not reflect an absence of pain perception and can lead to underappreciation, even by carers. In fact, individuals with ASD who self-injure may have pain insensitivity (Allely 2013 **Level IV SR** [PRISMA] , 10 studies & 5 case reports, n=1,137) or enhanced pain expressions (Courtemanche 2016 **Level III-3**, n=51). For children with limited understanding of graded response, carers should be asked to complete individualised pain behaviours on the rFLACC scale. For children with ASD who are verbal and can grade response, a qualitative perioperative study recommends the following (Ely 2016 **Level IV**, n=40):

- Individualise care by using words familiar to each child;
- Describing pain is possible and often preferred to using a numerical scale – extremes are selected when using self-report scales;
- Locating pain is a favoured technique to start with – most can describe but some find this anxiety provoking;
- Children frequently rely on their parents to confirm or validate their report or to interpret behaviours/social cues;
- Facial expressions and body language often do not match pain scores or descriptors of pain intensity.

For pain assessment in less acute daily living, NCCPC (French) with some modifications for ASD behaviours was useful (Dubois 2017 **Level IV**, n=35).

KEY MESSAGES

1. Pain measurement tools are available for children of all ages (**S**) (**Level IV SR**).
2. Paediatric pain measurement tools must be matched to the age and development of the child (**U**) (**Level IV SR**).
3. Adoption of written guidelines or pain management algorithms improves both assessment and management of pain in neonates and children (**N**) (**Level IV SR**).

The following tick boxes represent conclusions based on clinical experience and expert opinion:

☑ Pain assessment and measurement are important components of paediatric pain management (**U**).

☑ Pain scores generated from different pain scales may not be congruent and this should be considered when used clinically and in research (**N**).

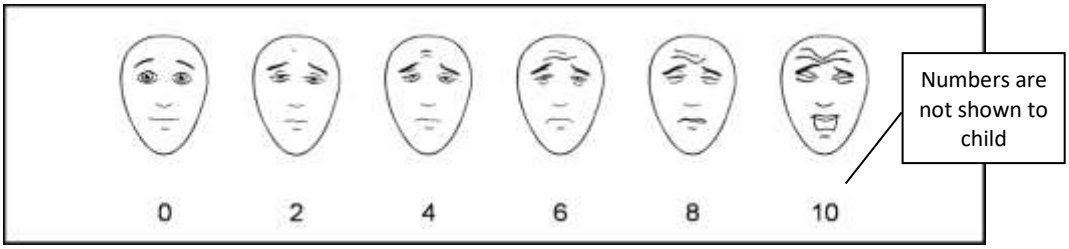
☑ Pain scores and pain score subdivisions (cut-offs) should not be used as a sole guide to administration of analgesia (**N**).

☑ Children with neurodevelopmental disorders (with and without cognitive impairment and varying levels of physical disability) may be more susceptible to pain and communicate it in different ways (**N**).

☑ Pain measurement tools must be appropriate for the clinical context, be explained and used consistently (**U**) and be validated when translated into other languages (**Q**).

☑ Facial recognition software applications may reduce clinician bias and become useful bedside tools in neonates and children with and without cognitive impairment (**N**).

Figure 10.1 | Faces Pain Scale — Revised



Note: *The full-size version of the FPS-R, together with instructions for administration (available in many languages), are freely available for non-commercial clinical and research use from www.iasp-pain.org/FPSR.*

Source: *FPS-R; (Hicks 2001); adapted from (Bieri 1990).*
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Table 10.1 | Acute pain intensity measurement tools — neonates

Scale	Indicators	Score	Utility
Unidimensional			
NFCS Grunau 1987 Johnston 1993	Brow bulge Deep nasolabial fold Eyes squeezed shut Open mouth Taut tongue Horizontal mouth stretch Vertical mouth stretch Pursing of lips Chin quiver Tongue protrusion	Presence or absence of action during discrete time intervals scored	Preterm to 4 mth Procedural pain
Multidimensional			
PIPP Stevens 1996 PIPP-Revised (PIPP-R) Stevens 2014a	Postmenstrual age Behavioural state Heart rate Oxygen saturation Brow bulge Eye squeeze Nasolabial furrow	Each scored on 4-point scale (0,1,2,3) ≤6 = minimal pain; >12 = moderate to severe pain In the revised form postmenstrual age and behavioural state points are only applied if other variables indicate pain.	Procedural pain in preterm and term neonates; Postoperative pain in term neonates
Neonatal Infant Pain Scale (NIPS) Lawrence 1993	Facial expression Cry Breathing patterns Arms Legs State of arousal	Each scored on 2 (0,1) or 3-point (0,1,2) scale; total score: 0–7	Preterm and term neonates; Procedural pain
CRIES Krechel 1995	Crying Requires oxygen for SaO_2 >95% Increased vital signs (heart rate/blood pressure) Expression Sleeplessness	Each scored on 3-point scale (0,1,2); total score: 0–15	32–60 wk Postoperative pain

Scale	Indicators	Score	Utility
N-PASS Hummel 2008	Crying/irritability Behavioural state Facial expression Extremities tone Vital signs (heart rate/blood pressure/SaO_2)	Each scored on 5-point scale (-2,-1,0,1,2); Total score: -10 to +10 with minus scores reflecting responses if sedated Extra point added for prematurity <30 wk Score >3 indication for treatment	23–40 wk Postoperative pain; Procedural pain; Persistent pain; Sedation level
COMFORTneo Modified from COMFORT B van Dijk 2009	Alertness Calmness/agitation Respiratory response (ventilated) or crying (spontaneous ventilation) Body movement Facial tension Muscle tone	Each scored on 5-point scale (1–6); total score: 6–30 Score >14 indicating moderate-severe pain/distress	24–42 wk Prolonged pain; Sedation
FANS Milesi 2010	Acute discomfort Limb movements Vocal expression Heart rate variation	Each scored differently; total score: 0–10 Nonintubated but face not visible	30–35 wk Procedural Pain

Note: Further details available in Lee 2014; Cong 2013b; Howard 2008a; Bandstra 2008.

Table 10.2 | Composite scales for infants and children

Scale	Indicators	Score	Utility
CHEOPS Chorney 2014	Cry Facial expression Verbal expression Torso position Touch Leg position	Each scored as 0, 1, 2 or 3; total score 4–13	1–7 y Postoperative pain; Procedural pain
FLACC Merkel 1997 Crellin 2015	Face Legs Activity Cry Consolability	Each scored on 3-point scale (0,1,2); total score 0–10	Young children Postoperative pain
COMFORT scale Ambuel 1992	Alertness Calmness/agitation Respiratory response Physical movement	Total score 8–40	Newborn to adolescent Distress in paediatric intensive care unit;

Scale	Indicators	Score	Utility
COMFORT B scale (behavioural elements) van Dijk 2000	Muscle tone Facial expression Mean arterial pressure Heart rate		Postoperative pain 0–3 y (van Dijk 2000); Downs Syndrome 0–3 y (Valkenburg 2011); Burns 0– 5 y (de Jong 2010); Post-cardiac surgery in term infants (Franck 2011)

Further details available in Chorney 2014 and Howard 2008a.

Table 10.3 | Self-report tools for children

Scale	Components	Anchors	Utility
Poker Chip Tool Hester 1979	4 chips=pieces of "hurt"	± white "no pain" chip; 1 chip="a little hurt"; 4 chips="most hurt you could ever have"	4–6 y Procedural; Acute and Postoperative pain
FPS-R Hicks 2001	6 graphically depicted faces Simplified version for 4 y electronic versions available	Neutral anchors Verbal anchors: No pain to Very much pain	>5/ 6 y Acute pain; Postoperative pain; Chronic pain
WBFPRS Wong 1988	6 cartoon faces (and 4 cartoon faces) culturally adapted versions	Faces graded from smiling to tears with verbal anchors from "no hurt" to "as much as you can imagine"	6 y Acute pain; Procedural pain
Coloured Analogue Scale McGrath 1996	Modification of 10 cm horizontal VAS; scored 0–10 in 0.25 increments ruler or flat Electronic version	Gradations in colour (white to deep red) and area (progressively wider tetragon); verbal labels "no pain" to "most pain"	>6 y Acute pain; Postoperative pain
Numeric Verbal Scale (NRS-11) Miro 2009	Pain intensity from 0–10 Electronic version	0=No pain or hurt 10 worst pain or hurt you can imagine/possible	>6 y Acute pain; Postoperative pain; Chronic Pain

Further details available in Birnie 2019 and von Baeyer 2014.

Table 10.4 | Sample of observational pain assessment scales for intellectually disabled children

Scale	Components	Score	Utility
NCCPC-PV Breau 2002b NCCPC-R for home setting Breau 2002a	Facial Vocal Social Activity Body and limbs Physiological (Eating/sleeping in NCCPC-R)	27 items over 6 domains, rated 0–3 based on frequency of behaviour over a 10 min observation period; total score 0–81 score 6–10/81 mild pain >11/81 mod pain (≥3 on VAS) (NCCPC-R 30 items scored over a 2 h period: >7/90 indicates pain)	Nonverbal/ID 3–18 y Postoperative pain Familiarity with child not necessary Other languages Requires 2 h observation
PPP Hunt 2004	20 typical pain behaviours selected based on interview and questionnaire	20 items scored 0–3 based on frequency of behaviour; total score 0–60 14/60 moderate pain	1–18 y Pain Takes 5 min
Revised (r)FLACC Malviya 2006a	Face Legs Activity Cry Consolability	5 items each scored on 3-point scale (0,1,2); total score 0–10 4/10 Moderate Pain Can individualise	4–19 y ID Postoperative pain Takes 1 min
INRS Solodiuk 2010	Individual Pain indicators proposed by carers	0–10 NRS scale with pain indicators superimposed Needs to be collaboratively individualised	6–18 y Nonverbal ID Postoperative pain Needs time to design

Further details available in Chorney 2014, Crosta 2014 and Valkenburg 2010.

10.4 | Analgesic agents

The following section describes the evidence supporting the use of various medications as analgesics in children. Most medications listed (beyond paracetamol, ibuprofen and morphine) are not licensed for paediatric use. Consequently, they are often used off-label (Kimland 2012 **Level IV SR**, 18 international hospital & primary care studies) for acute (and also chronic) pain management, or are used below licensed age cut-offs (such as 6 or 12 mth or 12, 16 and 18 y) or by non-licensed novel routes, with both being accepted practice. The result is varying locally and regionally accepted regimens. Commonly doses for 'routine and non-routine off-label' use (TGA 2013 **GL**) are extrapolated from adult dosing and this is frequently unsupported by either paediatric pharmacokinetic (PK) data (in particular) or pharmacodynamic (PD) study. Considerations pertinent to paediatrics are that countries differ in their licensing for single agents including nonuniformity of age cut-offs and in the formulation types and strengths available. Further to this, when a suspension is not available, adult tablets and capsules require cutting/crushing/dispersing and often disguising (eg in food to improve palatability), which has implications for compliance and dose administration error.

10.4.1 | Paracetamol (acetaminophen)

Paracetamol is effective for mild to moderate pain in children (Allegaert 2017 **NR**; Marzuillo 2014 **NR**). The dose required for analgesia is greater than for antipyretic effect. The proposed mechanism of analgesic action includes inhibition of prostaglandin synthesis and central cannabinoid/TRPV1 receptor (Allegaert 2017 **NR**; de Martino 2015 **NR**; Graham 2013 **NR**) and indirect serotonergic effects (see also adult Section 4.1.1). The serotonergic mechanism has been investigated in adults, and subsequently in children undergoing tonsillectomy (Ramirez 2015 **Level II**, n=69, JS 4). Children received paracetamol, corticosteroid, fixed dose morphine/ nonselective non-steroidal anti-inflammatory drugs (nsNSAIDs) and ondansetron vs droperidol intraoperatively. More ondansetron vs droperidol recipients required rescue morphine in PACU (57 vs 21%), suggesting ondansetron suppressed paracetamol's analgesic effect.

10.4.1.1 | Efficacy

Paracetamol has similar efficacy to nsNSAIDs depending on the surgery type assessed. Paracetamol is a useful adjunctive treatment as part of multimodal analgesia for more severe pain. A systematic review of paracetamol has defined the NNT for different doses in adults, with no evidence of dose-dependent effect (see Section 4.1.2 and in Chapter 5 Table 5.1); this has not been defined for children. Paracetamol is established as opioid-sparing in adults (see Section 4.1.2). In children, opioid-sparing efficacy is variably demonstrated and dependent upon the route of administration, the duration of therapy and follow-up, and dose size used. The RCTs and subsequent systematic reviews are challenged by variable timing of administration and various outcomes. Interpretation is complicated by study heterogeneity and inclusion of surgical procedures with low postoperative analgesic requirements, as well as the lack of data regarding equipotent dosing between the different comparators (Marzuillo 2014 **NR**). In many instances, paracetamol is considered the standard of care in various RCTs where additional medication intervention is then assessed. It has been recommended as part of routine multimodal therapy for post tonsillectomy analgesic protocols by various bodies (Mitchell 2019 **GL**). The RCTs where paracetamol is one of the treatment arms are presented below.

Paracetamol use in neonates and infants

A review has been performed of use in neonates and infants in heterogeneous painful conditions (Ohlsson 2016 **Level I** [Cochrane], 9 RCTs, n=728):

- Post major thoracic (noncardiac) or abdominal surgery, IV paracetamol 30 mg/kg/d reduced cumulative morphine dose in the first 48 h postoperatively (MD -157 mcg/kg; 95%CI -27 to -288) but did not reduce pain scores or opioid-related adverse effects (Ohlsson 2016 **Level I** [Cochrane], 1 RCT: Ceelie 2013 **Level II,** n=71, JS 5). While in a similar patient group, PR paracetamol was not morphine-sparing (Wong 2013b **Level I** [PRISMA], 1 RCT: van der Marel 2007 **Level II**, n=71 [57 analysed], JS 5);
- Following heel lance, PO paracetamol given 60–90 min prior did not reduce pain vs placebo (water or cherry elixir) or EMLA cream applied at 60 min (3 RCTs, n=346); PO glucose-treated infants had lower pain scores 3 min after heel lance vs those paracetamol-treated (MD 2.21/21; 95% CI 0.72 to 3.7) (1 RCT, n=38) (Ohlsson 2016 **Level I** [Cochrane], 9 RCTs, n=728);
- For eye examinations, RCT results conflicted for PO paracetamol 15–20 mg/kg 30 to 60 min prior vs water or sucrose 24% 0.2 mL: in two RCTs, no difference was found in pain scores taken in the first 45 s, last 45 s and 5 min after the examination, whilst the third and largest RCT reported lower pain scores vs water during the examination (Ohlsson 2016 **Level I** [Cochrane], 3 RCTs [eye], n=213).

For PICC placement in very preterm neonates <32 wk, paracetamol vs PO sucrose 24% 0.5–1 mL had similar median pain scores: 8/21 (IQR 6–10.5) for 10 mg/kg, 7 (IQR 6–9) for 15 mg/kg and 8 (IQR 6–10) for both 20 mg/kg paracetamol group and 24% sucrose (Roofthooft 2017 **Level II**, n=80, JS 5).

For pain management in very preterm neonates <32 wk, IV paracetamol 20 mg/kg load then multidosing with 7.5 mg/kg 6 hly (mean dose number 17 [SD 11.7]) decreased cumulative morphine requirements from median 0.37 mg/kg (SD 0.96) (prior to its introduction) to 0.17 mg/kg (SD 0.45) (Harma 2016 **Level III-2**, n=218). For postoperative pain management in term neonates, IV paracetamol 20 mg/kg initial dose then dosed according to age below or above 30 d of 10 or 15 mg/kg 6 hly was administered first line in preference to IV morphine infusion, with 99% adherence to the protocol (Baarslag 2018 **Level IV**, n=75).

Perioperative Analgesia

In a systematic review of paediatric use comparing paracetamol (IV, PO and PR routes) to placebo or nsNSAIDs or in combination, 7 of 13 RCTs are positive with an opioid-sparing effect in cleft palate repair (1 RCT), inguinal surgery (2 RCTs), ureteroneocystostomy (1 RCT), adenoidectomy and tonsillectomy (3 RCTs) (Wong 2013b **Level I** [PRISMA], 31 RCTs, n=2,624). A further systematic review of multiple opioid-sparing adjuvant medications lists outcomes for the paracetamol trials individually (Zhu 2017 **Level I**, 11 RCTs [paracetamol], n=1,011) (3 RCT overlap). While a subsequent systematic review of systematic reviews does not include these two systematic reviews but includes the other reviews (including the Cochrane reviews) discussed later in this chapter (Radman 2019 **Level I** [PRISMA], 17 SRs: 72 RCTs [42 both agents, 17 paracetamol], n unspecified). This systematic review assesses paracetamol and ibuprofen in combination or each agent alone concluding that the evidence is disappointingly limited considering these two medications listings as WHO essential medicines.

In young children following ureteroneocystostomy, IV paracetamol (15 mg/kg initial bolus and subsequent infusion with bolus prn) vs placebo added to IV fentanyl (infusion with bolus prn) had similar pain scores, with reduced fentanyl requirements (POD 1 and 2), reduced vomiting (16% vs 56) and sedation (10% vs 47) (Zhu 2017 **Level I**, 1 RCT: Hong 2010 **Level II**, n=63, JS 5).

Following scoliosis surgery, IV paracetamol 90 mg/kg/d for 24 h reduced pain scores vs placebo, but not opioid use or PONV (Zhu 2017 **Level I**, 1 RCT: Hiller 2012 **Level II**, n=36, JS 5).

Post cleft palate repair, paracetamol 12.5 mg/kg IV and 15 mg/kg PO (given every 6 h for 24 h) reduced postoperative morphine requirements vs placebo (Nour 2014 **Level II**, n=48, JS 5).

Post paediatric dental restorations, patients who received IV paracetamol 15 mg/kg vs IM pethidine 1 mg/kg had modestly higher pain scores but with less sedation and 10 min earlier discharge from PACU (Zhu 2017 **Level I**, 1 RCT: Alhashemi 2007 **Level II**, n=40, JS 5). Preemptive administration of very low dose paracetamol prior to dental treatment under local anaesthesia did not have benefit over placebo (2 RCTs, n=120) (Ashley 2016 **Level I** [Cochrane], 3 RCTs [paracetamol], n=165).

For inguinal herniorrhaphy in young children, both PR and IV paracetamol 15 mg/kg reduced pain scores (0–2 h) and vomiting postoperatively vs placebo (Khalili 2016 **Level II**, n=120, JS 3). For the same procedure, addition of PR paracetamol 30 mg/kg to caudal block had similar time to first rescue analgesia vs caudal block alone (while PR diclofenac 1 mg/kg with caudal block was superior to both) (Nnaji 2017 **Level II**, n=90, JS 4).

Post paediatric (adeno)tonsillectomy, paracetamol by different routes has had varying analgesic benefits:

- PO vs PR 40 mg/kg reduced opioid requirements (Anderson 1996 **Level II**, n=100, JS 5);
- PR 40 mg/kg vs IV 15 mg/kg resulted in a longer time to first rescue analgesic request (median 10 h vs 7) (Capici 2008 **Level II**, n=50, JS 5);
- PR 15 mg/kg vs IV 10 mg/kg had slightly lower pain scores at 4 and 6 h, with more patients pain free (44% vs 10) and a longer time to analgesic rescue (5 h vs 3.8) (Haddadi 2014 **Level III-1**, n=96);
- PO 15 mg/kg, as a single preoperative dose, resulted in lower early pain scores vs ibuprofen 10 mg/kg and placebo (Mahgoobifard 2014 **Level II**, n=60, JS 5);
- PO 12 mg/kg and 6 mg/kg ibuprofen, alone and in combination, were similarly effective over 48 h, with similar area under the curve for pain scores at rest and on swallowing (Merry 2013 **Level II**, n=152, JS 5);
- IV 15 mg/kg provided similar analgesic effects to IV tramadol 1 mg/kg in the early postoperative period (Uysal 2011 **Level II**, n=64, JS 5) and was similarly effective vs IM pethidine 1 mg/kg with similar pain scores, slightly less sedation and 10 min earlier discharge from PACU. However, 17 vs 0% of patients required morphine rescue (Alhashemi 2006 **Level II**, n=80, JS 4); and
- There were no differences in pain intensity between patients administered PO paracetamol (alone or in combination with codeine or hydrocodone) as required vs fixed schedule for 3 d despite the 33 to 68% lower dose/volume of analgesia used in the prn groups (Erskine 2015 **Level I** [Cochrane], 3 RCTs, n=207).

PO paracetamol 15 mg/kg with PO diclofenac 1 mg/kg provides equivalent analgesia to PO paracetamol 30 mg/kg (Hannam 2014 **Level I PK**, pooled data from 3 RCTs, n=466).

A subsequent PK-PD study has determined analgesic plasma concentrations for ibuprofen and paracetamol (Hannam 2018 **PK**, n=251 [1,168 paracetamol and ibuprofen samples]). The simulated time concentration effect profiles for varying doses demonstrate that ibuprofen alone decreased pain scores further and for longer than paracetamol alone. In combination, the simulated effect was additive: clinically used doses of paracetamol 15 mg/kg combined with ibuprofen 4.5 mg/kg decreased the pain score by 65%. Adding tramadol 0.5–1 mg/kg to this combination model maintained the pain score <6/10 for a further 7 h.

Paracetamol use in other painful conditions (non-surgical)

For acute otitis media [AOM], monotherapy with either PO paracetamol 15 mg/kg or PO ibuprofen 10 mg/kg had more children pain free at 48 h (90 and 93%) vs placebo (75%) (1 RCT n=148) (RR [paracetamol] 0.38, 95%CI 0.17 to 0.85; NNT 7) with no difference at 24 h, 48 to 72 h or 4–7 d (Sjoukes 2016 **Level I** [Cochrane], 3 RCTs, n=327 [AOM]).

For musculoskeletal injuries in children presenting to the ED, PO paracetamol 15 mg/kg vs codeine 1 mg/kg were both inferior to ibuprofen 10 mg/kg analgesia 1 h post dose (Clark 2007 **Level II**, n=300, JS 5), and paracetamol combined with codeine was equivalent to ibuprofen (Friday 2009 **Level II**, n=68, JS 4) (both RCTs in Le May 2016 **Level I** [PRISMA], 8 RCTs, n=1,169).

10.4.1.2 | Pharmacokinetics and pharmacodynamics

Paracetamol's bioavailability is dependent on the route of administration. Oral bioavailability is high (hepatic extraction 0.11–0.37) (Anderson 2014a **PK**) and peak plasma concentrations are reached in 30 min with the liquid and effervescent formulations (longer with tablet and capsule) (Marzuillo 2014 **NR**; Gibb 2008 **NR**); the equilibration halftime ($t_{1/2keo}$) between plasma and effect compartment is 53 min (Anderson 2001 **PK**). Rectal administration is associated with slower and less predictable absorption and PR loading doses of 30–40 mg/kg paracetamol may be required to achieve therapeutic plasma concentrations associated with analgesia (eg 10 mg/L which correlates with VAS reduction of 2.6/10) (Howell 2003 **Level II,** n=24, JS 2; Anderson 1996 **Level II**, n=100, JS 5). Neonates generally have delayed oral absorption, attributed to slower gastric emptying which reaches adult rates at 6–8 mth of age (Marzuillo 2014 **NR;** Gibb 2008 **NR**). An IV formulation of paracetamol achieves more predictable concentrations, because PK variability attributable to absorption is avoided, but also has more rapid offset than a PR formulation that has slow delayed absorption (Capici 2008 **Level II**, n=50, JS 5) as explored with simulation (Anderson 2014a **PK**).

Clearance is reduced in neonates and increases with age to reach adult rates during infancy (using allometric scaling expressed as L/h/kg). The volume of distribution (Vd: L/kg) is increased in neonates and rapidly reduces in the first year of life (Wang 2014 **PK**; Allegaert 2013 **NR**; Mohammed 2012 **PK**; Allegaert 2011a **PK**). Dose regimens that target a steady state plasma concentration of 10–20 mg/L have been determined. There is some evidence for analgesic efficacy at this concentration in children and neonates (Allegaert 2013 **NR**; Anderson 2001 **Level III-1 PK**). A PK model based on data from 220 subjects (neonatal up to adult) proposes dosing to achieve a concentration of 9 mg/L, chosen as this concentration is predicted with the clinically used schedule of 15 mg/kg every 6 h (for patients weighing 10–50 kg) (Wang 2014 **PK**). For paracetamol dosing see Table 10.5 where expert opinion is combined with supportive PK data, where available.

Table 10.5 | Suggested paracetamol dosing for infants and children

Postmenstrual age or weight	Oral (PO)/ Rectal (PR) dose	IV dose	Maximum daily dose	References
Infants 28–29 wk	Nil data	10 mg/kg 12 hly proposed	20 mg/kg/d proposed	Caution against use: van den Anker 2011 Note: Limited data in extreme premature Allegaert 2011a **PK**; Allegaert 2013 **NR**; Veyckemans 2014

Postmenstrual age or weight	Oral (PO)/ Rectal (PR) dose	IV dose	Maximum daily dose	References
Infants 30–31 wk	Nil data	10 mg/kg 8–12 hly	25–30 mg/kg/d	
(Weight 0.5–2 kg)		Initial bolus 12 mg/kg; 6–7 mg/kg 6 hly		Wang 2014 **PK**
Infants 32–44 wk (Weight 3–5 kg)	15 mg/kg 8 hly	Initial bolus 0–20 mg/kg; 10 mg/kg 6 hly	IV: 40 mg/kg/d PO: 45 mg/kg/d	Palmer 2008 **Level IV PK**; Allegaert 2011a **PK**; Allegaert 2013 **NR**; Wang 2014 **PK**; Veyckemans 2014.
Infants >45 wk		15 mg/kg 6 hly	IV/PO: 60 mg/kg/d	Veyckemans 2014; Palmer 2007 **Level IV**; Howard 2008b **NR**; Wang 2014 **PK**
Older children 6 mth–12 y	15–20 mg/kg 4–6 hly	15 mg/kg 6 hly	IV: 60 mg/kg/d PO: 90 mg/kg/d suitable for acute administration for 2–3 d	Anderson 2002 **PK**; Wang 2014 **PK**

10.4.1.3 | Adverse effects and safety

Overall safety

Paracetamol use at therapeutic doses can generally be considered safe. Dosing recommendations have been revised and capped at 75–80 mg/kg/day for PO and IV acute use (Ajjan 2016 **Level IV**, n=72) and 60 mg/kg/day for short term use (eg in the British National Formulary or Australian Medicines Handbook), but the margin for safety particularly in ill children and adults weighing less than 50 kg is unclear (Caparrotta 2018 **NR**). A review assessing a range of adverse effects (including abdominal, hepatic, skin, respiratory and neurological effects) suggests paracetamol and ibuprofen have similar safety and tolerability profiles vs placebo if prescribed and administered at recommended doses in children (Southey 2009 **Level IV SR**, 24 RCTs, n=119,166 & 12 studies, n=221,459).

Safety in neonates and preterm infants

Data regarding safety of paracetamol (all routes) in neonates is scant and cautious dosing and monitoring of hepatic function is recommended (Anderson 2009 **NR**). There is minimal safety data in preterm <32 wk (Allegaert 2011a **PK**). Dosing practices in NICUs vary (with decreasing dose and or frequency) and are not informed by pharmacodynamic data (Allegaert 2017 **NR**).

Limited data on liver function during repeated IV (Palmer 2008 **Level IV**, n=50) and PR dosing for pain or fever (Chen 2018 **Level IV**, n=25) suggest alteration was contributed to by factors other than paracetamol.

Use of paracetamol for patent ductus arteriosus (PDA) closure also provides some limited safety data in preterm neonates ≤34 wk (Ohlsson 2018a **Level I** [Cochrane], 8 RCTs, n=916). Paracetamol has equivalent efficacy for this indication to NSAIDs, with reduced gastrointestinal bleeding vs ibuprofen (RR 0.28; 95%CI 0.12 to 0.69) (4 RCTs, n=537), higher platelet counts (2 RCTs [ibuprofen], n=287; 1 RCT [indomethacin], n=200), lower bilirubin (2 RCTs [ibuprofen], n=290) and less renal impact with lower creatinine (4 RCTs [ibuprofen], n=537; 1 RCT [indomethacin], n=200), less oliguria (3 RCTs [ibuprofen] ,n=337) and greater daily urine output (1 RCT [ibuprofen], n=200; 1 RCT [indomethacin], n=200).

In extreme preterm neonates ≤28 wk, PO paracetamol 15 mg/kg 6 hly for 3 d vs ibuprofen 10 mg/kg d 1, 5 mg/kg d 2 and 3 was as effective for PDA closure 89 vs 84%, with similar side effect profile in terms of intestinal, liver and renal function (Karabulut 2019 **Level III-2**, n=87).

Hepatotoxicity

Paracetamol is metabolised in the liver, predominantly via glucuronidation and sulphation. Increased production of a reactive oxidative product, N-acetyl-p-benzoquinone imine (NAPQI), occurs if the usual metabolic enzyme systems become saturated (eg acute overdose) or if glutathione is depleted (eg with prolonged fasting). An increased contribution of sulphation to metabolism and reduced production of oxidative metabolites may reduce the risk of toxicity in neonates, particularly in the presence of unconjugated hyperbilirubinaemia (Palmer 2008 **Level IV**, n=50) but, as overall clearance is reduced, a lower dose is appropriate. Hepatotoxicity has been reported in infants aged 3–7 wk having received PO dosing of 60 mg/kg/d for 3 and 6 d and 100 mg/kg/d for 2 d (Bucaretchi 2014 **Level IV**, n=3).

Risk factors for paracetamol hepatotoxicity may include fasting (malnourished state), vomiting, dehydration, systemic sepsis, pre-existing liver disease and prior paracetamol intake, however the situation remains unclear (Caparrotta 2018 **NR**; Kaplowitz 2004 **NR**) (see also 4.2.3). Hepatic injury results from the NAPQI metabolite. Single overdoses in children of 120 to 150 mg/kg have caused hepatic injury (AAP 2001 **NR**). Notably, acute liver failure has occurred with 3–4 d dosing of 68–82 mg/kg/d in 4 young children in an Australian and New Zealand cohort (Rajanayagam 2015 **Level IV**, n=14 [paracetamol]). Hepatic failure in this paediatric series (age range 0.7–13 y) was mostly associated with medication error involving higher multiday (median 4 d, range 2 to 24) dosing: 7/14 (50%) received >120 mg/kg/d and the remainder had double doses or excessive frequency, were coadministered other medications containing paracetamol or received regular dosing. Ten survived without requiring transplant, 2 survived post-transplant; while 2 died (1 without and 1 post-transplant). A Spanish series documents similar reported acute and chronic dosing with accidental overdose in younger children (n=38) and attempted suicide in teenagers (n=43) with 50% receiving acetylcysteine, 4 patients developing acute liver failure with none requiring transplant or dying (Tong 2017 **Level IV**, n=90). In adolescent overdose, early predictors of severity of paracetamol hepatotoxicity included the initial INR elevation, presence of hyperbilirubinaemia and hypophosphataemia, the number of prehospital vomiting episodes (≥3) and time to acetylcysteine administration (Hedeland 2014 **Level IV**, n=25). In contrast to adults, no relationship was found for the severity of hepatoxicity and the amount ingested (either as overall dose [mean 16.4 g, range 6.5–60 g] or when weight adjusted). All patients received acetylcysteine and recovered; none required transplant.

Repeated paracetamol ingestion (dose known for 78 patients as >76 mg/kg/d [median 120] for median 3 d [IQR 2–5]) resulted in severe hepatic damage (ALT/AST ≥1000 IU/L) (93%), liver failure (69%) and death (39%) (Acheampong 2016 **Level IV SR**, n=199 [78 children ≤6 y]).

The commonest prescribing error in paediatrics is a ten-fold dosing error. This has significant impact when involving paracetamol, as occurred for an infant where 2 doses of 150 mg/kg were given (detected after the 2nd dose) with hepatotoxicity; successfully treated with NAC (Aslan 2019 **CR**).

A review of therapeutic dosing of paracetamol beyond 24 h in children assessed hepatic adverse effects (Lavonas 2010 **Level IV SR**, 62 studies, n=32,414). It reports no cases of liver disease, need for antidote or transplantation or death (0.0%; 95%CI 0.000 to 0.009) and only 10 children experienced major or minor hepatic adverse effects (0.031%; 95%CI 0.015 to 0.057). This review identified 22 case reports of hepatotoxicity associated with therapeutic doses of paracetamol; in 9 cases, Naranjo scoring suggested probable causation.

Of note, the guidelines for the management of paracetamol poisoning have been revised (Chiew 2020 **GL**). Specifically for younger children <6 y who have ingested an excessive dose of the more rapidly absorbed liquid preparation, an earlier measurement of plasma concentration from at least 2 h is recommended (rather than at ≥4 h for tablet ingestion) and intervention tailored to whether this is >150 mg/L. The guideline also incorporates response to modified release paracetamol overdoses, large or massive overdose and repeated supratherapeutic ingestions. The three infusion NAC dosing schedule has been revised to two (Chiew 2018 **Level I** [Cochrane], 4 RCTs [NAC route and dose regimens in adults], n=518), with the recommendation to double the 2nd infusion if the plasma concentration is greater than twice the height of the paracetamol toxicity nomogram line.

Cardiovascular effects of paracetamol

Paracetamol has poorly understood vasoactive effects. It is as effective as ibuprofen for closure of a PDA in preterm neonates (Ohlsson 2018a **Level I** [Cochrane], 8 RCTs, n=916). There is also a potential association between constriction and premature ductus arteriosus closure and maternal paracetamol use in pregnancy (see below: Allegaert 2019 **Level IV**, n=25).

The overall effect of paracetamol on blood pressure in adults and children remains unclear (see also adult Section 4.1.3.3). Observational studies show a variable association between PO paracetamol use and hypertension, but RCTs are inconsistent (Turtle 2013 **Level III-3 SR**, 6 RCTs, n=152 & 4 studies n=155,910). While use of IV propacetamol and IV paracetamol and hypotension has been reported (with variable definitions: systolic vs MAP change as absolute value or 15–20% decrease) in mostly critically ill (often cardiac) patients (14/19 studies) (Maxwell 2019 **Level IV SR**, 19 studies (5 RCTs, 6 open label trials & 8 retrospective reviews), n=3,470 [2 paediatric, n=680]). Clinically significant hypotension appears to be an issue when patients have cardiovascular compromise prior to administration; importantly regular four times daily dosing with IV paracetamol where mannitol is the stabilising agent exposes the patient to 0.23 mg/kg/d mannitol (with its diuretic and secondary hypotensive effect) (Chiam 2015 **NR**). Within the above systematic review, IV paracetamol (with mannitol excipient) vs mannitol vs placebo reduced MAP by only 1.8 mmHg in healthy adult volunteers (Chiam 2016 **Level II**, n=24, JS 5). Of the two paediatric studies, the first included neonates receiving IV propacetamol where a minor decrease in MAP (-3 mmHg) occurred 60 min post dose (Allegaert 2010, **Level IV**, n=72). This may reflect analgesic effect, although the 8 neonates who developed hypotension all had lower baseline MAP prior to administration. Further to this, 5% of young children in a cardiac PICU (mostly postsurgical), whose MAP had started to decline prior to IV paracetamol administration, progressed to clinically significant hypotension (≥15% decrease in MAP from baseline) within 30–75 min of IV paracetamol, and 20% experienced a 10–14% decrease (Achuff 2019 **Level IV**, n=608 [777 doses]). This series excluded patients who had a vasoactive medication within 1 h before or after paracetamol. Severe hypotension and cardiac arrest is also described in a toddler with febrile neutropenia occurring 5 min into the infusion (Yaman 2016 **CR**).

Paracetamol hypersensitivity

Hypersensitivity to paracetamol is uncommon (Gabrielli 2018 **Level IV SR** [PRISMA], 85 studies, n=1,030). The classification of reaction types and mechanisms of immune reaction in children are summarised (Kidon 2018 **GL)** (and discussed further below in nsNSAID hypersensitivity Section 10.4.2.3).

Most reported cases of hypersensitivity to paracetamol involve the skin, including nonimmediate cutaneous eruptions, fixed drug eruptions, Stevens-Johnson syndrome (SJS)/toxic epidermal necrolysis (TEN) and urticarial/angioedema/anaphylaxis. Reactions to paracetamol have been reported usually in association with suspected nsNSAIDs reactions; with its proposed weak cyclooxygenase (COX) effect, paracetamol was presumably included to explore cross sensitivity with nsNSAIDs. Three such paediatric series have focussed on nsNSAIDs hypersensitivity, skin and oral drug provocation testing and explored associations eg with atopy (Arikoglu 2017 **Level IV**, n=106; Topal 2016 **Level IV**, n=64; Cousin 2016 **Level IV**, n=107). Paracetamol was either implicated directly or was coadministered with nsNSAIDs at the time of reaction; as with nsNSAIDs most reactions were cutaneous or urticarial/angioedema. No anaphylaxis to paracetamol was reported in these series. One confirmed two patients with positive skin testing to paracetamol and two further (aged 6 and 15 y) skin test positive to a nsNSAID then reacting to 'high-dose oral provocation' with 90–120 mg paracetamol (Topal 2016 **Level IV**, n=18 confirmed [2 paracetamol] of 64 evaluated). The second explored applicability of the European Network of Drug Allergy (ENDA) classification to children and association of allergy with urticaria and atopy; it confirmed 7 reactions to paracetamol with 'urticaria/angioedema or anaphylaxis' (defined as 'single agent reaction' as the patients tested negative with at least one other nsNSAID; where paracetamol was not implicated in the patient subgroup with cross-intolerant hypersensitivity) (Cousin 2016 **Level IV**, n=107). While the third also explored the ENDA concepts of selective responders vs cross intolerant and confirmed patients with nsNSAID allergy (with skin and/or drug provocation testing) (Arikoglu 2017 **Level IV**, n=33 confirmed of 106 evaluated [6 paracetamol; 27 nsNSAIDs]). Paracetamol was frequently implicated on history (59%) but oral provocation was only positive for 6 patients (two of whom tested negative on skin prick testing). The majority of patients with confirmed nsNSAID allergy in this series subsequently had oral drug provocation with paracetamol establishing its use as a safe alternative for the nsNSAID allergic children (see also Section 10.4.2.3). A subsequent meta-analysis (including the first of these series) established a pooled estimate for paracetamol hypersensitivity prevalence in children who reported a previous reaction to paracetamol and underwent an oral challenge of 10.1% (95% CI 4.5–15.6) (Gabrielli 2018 **Level IV SR** [PRISMA], 10 studies [meta-analysed] [5 mixed/ 5 paediatric], n=259]. Skin testing has not been developed as a diagnostic tool for paracetamol (and other nsNSAIDs beyond aspirin).

In 2013, the USA's Food and Drug Administration (FDA) investigated paracetamol as a rare cause of SJS/TEN syndrome (FDA 2013a **Level IV**, n=91, 6 [probable]; 85 [possible]). While, a French pharmacovigilance study reported 112 cases involving 574 suspected drugs (5.1 per case) (Lebrun-Vignes 2018 **Level IV**, n=23 [children]). In 80 cases, drugs other than paracetamol had a higher suspicion for causality; in a further 12 paracetamol was unlikely to be involved. In the remaining 20 cases, paracetamol was possibly or probably involved, but in 14 there was protopathic confounding bias (where the drug is taken for a symptom or illness).

Anaphylactic reactions to paracetamol have been reported rarely, mostly following PO administration and one following IV (Sørensen 2014 **Level IV**, n=12). Six (50%) of these children notably had negative skin tests with initial or subsequent reactions to low dose, high dose provocation or therapeutic dosing.

Pregnancy and early childhood exposure and association with various childhood issues

Paracetamol is a Category A medicine and is regarded as the analgesic of choice during pregnancy and infancy in Australia and New Zealand (currently unassigned in the USA). There are numbers of observational cohort studies in the literature claiming modest associations between paracetamol exposure in utero and various early infancy and childhood issues (as presented below). Caution should be used with interpretation of these retrospective analyses because of the possible effect of unknown or unmeasured confounding factors; the relevance of these reports to limited acute use remains unclear.

Childhood asthma

The scientific literature has debated whether paracetamol can precipitate asthma (by increased *de novo* myeloperoxidase production) or causes a shorter less severe asthmatic episode in aspirin-sensitive people with asthma (Graham 2013 **NR**). An important potential confounder of the below epidemiological study is protopathic: where the indication for paracetamol is fever due to viral upper respiratory tract illness (in mother and or the child), which in itself precipitates asthma.

Two systematic reviews, with no overlap of included studies, report an association between paracetamol use in pregnancy and subsequent childhood wheezing (OR 1.5; 95%CI 1.1 to 2.1) (Etminan 2009 **Level III-3 SR**, 5 studies [wheezing], n unspecified) and asthma (OR 1.28; 95%CI 1.13 to 1.39) (Etminan 2009 **Level III-3 SR**, 4 studies [asthma], n unspecified) (OR 1.21; 95%CI 1.02 to 1.44) (Eyers 2011 **Level III-2 SR**, 6 studies, n=28,038). A subsequent systematic review of heterogeneous studies (with 2 study overlap with each of the above SRs) revealed any paracetamol use was associated with increased childhood asthma risk: during the first trimester (pooled OR 1.39; 95%CI 1.01 to 1.91) (5 studies, n unspecified) and during the second and third trimesters (OR 1.49; 95%CI 1.37 to 1.63) (3 studies, n unspecified) (Cheelo 2015 **Level III-2 SR** (PRISMA), 11 studies, n=910,054 [4 pregnancy studies n=896,313; 2 pregnancy and infant studies n=9,527; 4 infant-toddler studies n=4,241]). Importantly, only one study adjusted for maternal respiratory tract infections.

The epidemiological literature has also reported an association between childhood asthma and paracetamol exposure in children in the year prior to diagnosis (pooled OR 1.60; 95%CI 1.48 to 1.74) (3 studies, n unspecified) and in the first year of life (pooled OR 1.47, 95%CI 1.36 to 1.56) (3 studies, n unspecified), with one study reporting an association with high doses (Etminan 2009 **Level III-3 SR**, 19 studies, n=425,140 [15 paediatric, n=361,018]). However, when adjusted for respiratory tract infections in the child, increasing frequency of use (defined as doubling of dose) of paracetamol during infancy (up to 6, 12 and 24 mth) was no longer associated with increased odds of childhood asthma (OR 1.06; 95% CI 0.92 to 1.22) (Cheelo 2015 **Level III-2 SR** (PRISMA), 3 studies [infant & toddler use], n=3,327).

A subsequent RCT in children with mild persistent asthma (on glucocorticoid and leukotriene receptor antagonist inhaler treatment) assessed acute use of paracetamol vs ibuprofen for pain or fever and frequency of asthma exacerbations (over a 48 wk period) (Sheehan 2016 **Level II**, n=300, JS 5). Participants received a median of 5.5 doses (IQR 1 to 15) with no difference in the number of asthma exacerbations (RR 0.94, 95%CI 0.69 to 1.28), asthma-control days (85.8 and 86.8%), albuterol rescue inhaler use (2.8 vs 3.0 inhalations per week) or unscheduled health care utilisation for asthma (0.75 and 0.76 episodes per participant).

Childhood atopy

Paracetamol exposure during pregnancy has been implicated in childhood atopy (nutritional, eczema, wheezing) in early infancy (Allegaert 2017 **NR**). Certain maternal antioxidant gene polymorphisms may modify this relationship, as is also relevant to asthma above (Shaheen 2010 **Level IV**, n=4,000 [mothers]). At present, the association may be explained by confounders.

Cryptorchidism

Association between paracetamol exposure in utero and cryptorchidism has been of interest due to paracetamol's potential to act as an endocrine disrupter. For the association between 'ever' use of paracetamol and cryptorchidism in highly heterogeneous studies, the pooled crude OR was 1.11 (95%CI 1.00 to 1.23), and when separately analysed as study type no association was shown for case-control studies (OR 1.23; 95%CI 0.85 to 1.78) or cohort studies (OR 1.09; 95%CI 0.97 to 1.22) (Gurney 2017 **Level III-2 SR** [PRISMA], 10 Studies, n=501,456).

Premature closure of the ductus arteriosus

Maternal paracetamol use in pregnancy has been proposed as causal in premature constriction or closure of the ductus arteriosus: 4 certain and 11/25 probable (Allegaert 2019 **Level IV**, n=25).

Childhood neurobehavioural outcomes

The relationship of paracetamol exposure in utero and early childhood to neurobehavioural outcomes has been explored. Suggested mechanisms for an effect of paracetamol include impact on cerebral inflammation and metabolite production eg cannabinoids or again this may reflect a protopathic bias. Three overlapping reviews have included birth cohort studies with follow-up at various ages (18 mth vs 3, 5, 7 and 11 y) including different assessments for several neurobehavioural outcomes eg attention deficit hyperactivity disorder (ADHD) (4 studies, n=75,633), conduct and emotional problems (1 study, n=7,796), attention/executive function (1 study, n=1,491), and autistic spectrum disorder (ASD) with hyperkinetic disorder (HR 1.51; 95%CI 1.19 to 1.92) (1 study, n=1,491) (Bauer 2018 **Level III-2 SR,** 9 studies, n=176,955; Masarwa 2018 **Level III-2 SR** [PRISMA], 7 studies, n=132,738; Allegaert 2017 **Level III-2 SR,** 7 studies, n=174,732) (6 to 7 study overlap). Lower IQ (by 3.4 points; 95%CI 0.3 to 6.6) was reported (1 study, n=1,491); where an earlier study (included in the 1st and 3rd review) had found no effect (Streissguth 1987 **Level III-2**, n=421). Duration of exposure (<28 vs >28 d) was assessed in 2 studies and was associated with reduced communication/motor attainment and greater hyperactivity (Bauer 2018 **Level III-2 SR**, 1 study: Brandlistuen 2013 **Level III-2**, n=48,631 [2,919 same sex sibling matching]); when adjusted for confounders, delayed motor milestone attainment remained an association (OR 1.35, 95%CI 1.07–1.70), but not communication issues (OR 1.38, 95%CI 0.98 to 1.95) (Bauer 2018 **Level III-2 SR**, 1 study: Vlenterie 2016 **Level III-2**, n=51,200). In the largest study (in all 3 reviews), the use of paracetamol in pregnancy was associated with child hyperkinetic disorder (HR 1.37; 95%CI 1.19 to 1.59), use of ADHD medications (HR 1.29; 95%CI 1.15 to 1.44) and ADHD-like behaviours at age 7 y (RR 1.13; 95%CI 1.01 to 1.27) (Liew 2014 **Level III-2**, n=64,322). The third review determined mean duration of use as 4-7 d and range 4 to more than 28 d (Masarwa 2018 **Level III-2 SR** [PRISMA], 7 studies, n=132,738). It calculated increased risk for ADHD (RR 1.34; 95%CI 1.21 to 1.47) (6 studies, n=118,085), hyperactivity symptoms (RR 1.24; 95%CI 1.04 to 1.43) (5 studies, n=124,264) and ASD (RR 1.19; 95%CI 1.14 to 1.25) (5 studies, n=117,214). A subsequent study analysed the number of days of use of paracetamol in pregnancy and after adjustment for family history also revealed association with childhood ADHD for longer >29 d (HR 2.2; 95%CI 1.5 to 3.2) but not short term <8 d use (HR 0.9; 95%CI 0.8 to 1.0) (Ystrom 2017 **Level III-3**, n=112,973 [2,246 ADHD]).

In addition, a birth cohort study subsequently linked to administrative data, paracetamol was used in 49% of pregnancies and was associated with a modest increase in numbers of cerebral palsy (CP) affected children (OR 1.3; 95%CI 1.0 to 1.7) and unilateral spastic CP (OR 1.5; 95%CI 1.0 to 2.2), where confounders (use for fever and viral illness) are again likely relevant (Petersen 2018 **Level III-2**, n=185,617).

KEY MESSAGES

1. Post tonsillectomy in children, paracetamol (alone or combined with opioids) administered as required compared to fixed schedule achieved similar pain scores over 3 days; with lower dosing administered in the as required groups (**N**) (**Level I** [Cochrane Review]).
2. For pain of acute otitis media in children, paracetamol is similar to ibuprofen and both are superior to placebo in achieving pain freedom at 48 hours, but not other time points (**N**) (**Level I** [Cochrane Review]).
3. Paracetamol is effective for moderately severe pain and decreases opioid requirements after major and minor surgery in children (**U**) (**Level I** [PRISMA]).
4. Paracetamol has a similar safety and tolerability profile compared with ibuprofen and placebo if prescribed and administered at recommended doses in children (**U**) (**Level IV SR**).
5. Retrospective epidemiological studies linking paracetamol use in pregnancy or infancy to later development of childhood asthma are inherently confounded (**U**); when adjusted for respiratory tract infections in the child the association is lost (**Q**) (**Level III-2 SR** [PRISMA]).
6. Retrospective epidemiological studies report modest association of paracetamol use in pregnancy with childhood neurodevelopmental disorders such as attention deficit and hyperkinetic disorders; this is strengthened when adjusted for longer term use (>28 days) and disappears for short term use (<8 days) (**Q**) (**Level III-2 SR** [PRISMA]).
7. Paracetamol has unclear vasoactive effects; in critically ill children, hypotension is reported with both IV formulations (**N**) (**Level IV SR**).

The following tick boxes represent conclusions based on clinical experience and expert opinion:

☑ Safe dosing of paracetamol requires consideration of the age and body weight of the child and the duration of therapy (**U**).

☑ Paracetamol related hepatotoxicity generally occurs in children who have received doses greater than 120 mg/kg, as single or repeated daily dosing; with contributions from rounding up or 10-fold dosing error and formulation substitution or confusion by prescribers and parents (**N**).

☑ Paracetamol is recommended routinely following tonsillectomy and pharmacokinetic/pharmacodynamic simulation is exploring the optimal combinations of multimodal analgesia in this surgical model (**N**).

☑ There is insufficient pharmacokinetic/pharmacodynamic and safety data of use of paracetamol in preterm and term neonates; use for patent ductus arteriosus closure in preterm neonates provides limited data in this age group of an improved safety profile compared with nsNSAIDs (**N**).

☑ Emerging evidence suggests that maternal paracetamol use may influence premature closure of the fetal ductus arteriosus (**N**); use in pregnancy should be limited to the minimum dose and duration that is clinically necessary.

☑ Intravenous paracetamol in haemodynamically unstable patients has been associated with hypotension (**N**).

10.4.2 | Nonselective NSAIDs

For mild to moderate pain, nonselective non-steroidal anti-inflammatory drug (nsNSAIDs) are effective analgesic agents. The product information states that safety in children <2 y is unestablished, while the lower age limit for licensing varies by country and by NSAID agent. Despite this, nsNSAIDs have been studied and used in all age groups including infants, as reported by surveyed anaesthetists (Eustace 2007 **Level IV**, n=314) and German anaesthetic departments (Emons 2016 **Level IV**, n=342 [hospitals treating children]). Use of nsNSAIDs for analgesia is generally not approved for infants aged <3 mth; some authors suggest caution under 6 mth of age due to a paucity of data (Tobias 2014 **NR**). There is off-label use in neonates postoperatively (Moffett 2006 **Level IV**; Papacci 2004 **Level IV**) and in patent ductus arteriosus [PDA] closure and intraventricular haemorrhage prevention providing limited safety data (Aranda 2017 **NR**). The choice between ibuprofen, diclofenac, ketorolac, naproxen, ketoprofen and others mainly depends on available formulations and convenience of administration.

10.4.2.1 | Pharmacokinetics and pharmacodynamics

Data on pharmacokinetics (PKs) for the commonly used NSAIDs are available for children but pharmacodynamic (PD) studies are few. The clearance (CL) of diclofenac (Litalien 2001 **NR**), ketorolac (Lynn 2007 **PK**) and ibuprofen (Anderson 2019 **PK**; Kyllonen 2005 **PK**) is immature in neonates and matures within the first year of life. Equilibration half times of drug concentration with clinical effect ($t_{1/2\ keo}$) are 14 min for diclofenac (Hannam 2014 **Level II**, n=151, JS 3), 24 min for ketorolac (Mandema 1996 **PK**) and 28 min for ibuprofen (vs 53 min for paracetamol) (Li 2012a **PK**). Studies of analgesic effects are frequently flawed by failing to account for the variations in time to onset when assessing outcomes. A paediatric pain consortium has determined acute pain clinical trial models to improve study design for analgesic trials in children (Walco 2018 **GL**).

Rectal bioavailability of diclofenac is high in children (van der Marel 2004 **PK**). A population PK study estimated diclofenac CL as 16.5 L/h/70 kg and bioavailability as 35% for dispersible tablet or suspension and 63% for suppository (Standing 2011 **PK**). Dosing for children aged 1–12 y was predicted as IV 0.3 mg/kg, PR 0.5 mg/kg and PO 1 mg/kg. A PK-PD study revealed the maximum effect of both paracetamol and diclofenac (VAS reduction 4.9/10; 95%CI 4.7 to 5.2) (Hannam 2014 **Level II**, n=151, JS 3) as similar to that described for ibuprofen in adults (Li 2012a **PK**). Combination therapy of PO diclofenac 1 mg/kg with PO paracetamol 15 mg/kg is predicted to achieve equivalent analgesia to PO paracetamol 30 mg/kg. Synergistic interaction is complex as the drugs have different onset and half-lives. Studies must take this into account to determine the optimum combination-dosing schedule to improve or extend duration of analgesia.

Plasma and cerebrospinal fluid (CSF) concentrations after PO naproxen have been studied in children (mean age 5–6 y, range 0.25–12 y), establishing that CL and Vd <5 y of age are similar to values for adults and children >5 y (Valitalo 2012 **PK**). High unbound naproxen concentrations in CSF suggest an active uptake mechanism. Ketoprofen PKs are summarised in a narrative review (Kokki 2010 **NR**). PKs in children (aged 0.25–13 y) after PO and IV flurbiprofen have been reported, with increased concentrations in CSF vs plasma (Kumpulainen 2010 **PK**).

Adult data suggest ketorolac has a half maximal effective concentration (EC_{50}) of 0.37 mg/L (Mandema 1996 **PK**). PK modelling demonstrates that current IV dosing regimens of 0.5 mg/kg every 6 h maintain a trough concentration above this EC_{50} in children (aged 0.75–16 y) (McLay 2018 **PK**). In adolescents, the PKs of IN ketorolac 15–30 mg (via metred aerosol device) has good bioavailability (81%) and similar time to maximum plasma concentration (T_{max}) and clearance to adults. A 30 mg dose reached a predicted effect compartment concentration of 0.37 mg/L at 30 min and remained above this target for 10 h (Drover 2012 **PK**).

For ibuprofen, clearance maturation, as studied with use in ductus arteriosus closure in neonates and analgesic use in young infants and older children, was rapid with near adult values 90% at 44 wk PMA and mature 98% at 53 wk PMA (Anderson 2019 **PK**). Clearance informed ibuprofen dosing predictions to achieve steady state plasma concentrations >7.2 mg/L (in all ages) matching 10 mg/kg dose recommendations three to four times daily in children >3 mth. Of note, analgesic plasma concentrations of >7.2 mg/L have been suggested post paediatric inguinal hernia repair (Kokki 2007 **NR**). Target analgesic concentrations (ideally surgery-specific) for other NSAIDs, developmental changes in PDs, and the impact of different stereoisomer forms and the influences of various covariates (including weight, postmenstrual and postnatal age, renal function, obesity, enzyme maturation and influence of ethnicity/pharmacogenomics and comedications) on the differential PK, efficacy and adverse-effect profile require further evaluation (Admiraal 2014 **NR**; Anderson 2011 **NR**).

10.4.2.2 | Efficacy

Clinical studies of nsNSAIDs and paracetamol suggest similar (Shepherd 2009 **Level II**, n=72, JS 3; Riad 2007 **Level II**, n=108, JS 3; Hiller 2006 **Level II**, n=120, JS 5; Tay 2002 **Level II**, n=63, JS 2) or superior efficacy of nsNSAIDs (Wong 2013b **Level I** [PRISMA], 4 RCTs (nsNSAIDs vs paracetamol), n=330). Benefit is dependent on dose and route (absorption PKs eg via PR vs IV routes), timing (preop/intra/postoperative), intermittent vs regular and duration of administration, and type of surgery (eg cleft palate, hernia repair vs laparotomy).

Three systematic reviews on use of NSAIDs in paediatrics are published, reporting results differently. The 2017 review does not perform meta-analysis and references the earliest meta-analysis and 2 further tonsillectomy trials detailed below (Zhu 2017 **Level I**, 1 meta-analysis [27 RCTs, n=978] and 2 RCTs, n=443). The earliest meta-analysis includes two RCTs using coxibs and finds NSAIDs, alone or as a component of multimodal analgesia, decrease opioid consumption in PACU and at 24 h (Michelet 2012 **Level I** [QUOROM], 27 RCTs, n=985). NSAIDs also reduce pain intensity in PACU but not in the first postoperative 24 h. The second meta-analysis overlaps by 24 RCTs, including 1 coxib RCT, but also incorporates outcomes for paracetamol (13 RCTs) (Wong 2013b **Level I** [PRISMA], 31 RCTs, n=2,624). NSAIDs (and/or paracetamol) reduce opioid consumption in 38 of 48 treatment arms (21 of 31 RCTs), with a higher proportion positive in NSAID-only trials and with this being more apparent in moderate to major surgery. Where systemic opioids were available via patient-controlled or nurse-controlled analgesia (PCA/NCA) (ie after major surgery), mean opioid consumption was reduced by 32% (95%CI 17 to 47) (7 RCTs) when studied for >24 h and not reduced when studied for ≤6 h (24%; 95%CI -1.7 to 50) (3 RCTs). Where systemic opioids were available by intermittent bolus (21 RCTs, usually short or day-stay surgery), opioid consumption was decreased by 24% (95%CI 6.3 to 43). Pain scores, reported in various ways, were reduced in 16 of 29 RCTs. The impact on adverse effects is difficult to interpret due to study heterogeneity and small study size.

In a review of diclofenac studies only, diclofenac reduces the need for postoperative rescue analgesia vs placebo (5 RCTs) and paracetamol (NNT 3.6; 95%CI 2.5 to 6.3, 2 RCTs) (Standing 2009b **Level I** [Cochrane], 7 RCTs [analgesic rescue], n=404) (1 & 2 RCT overlap with above meta-analyses).

In a review of low quality ketorolac only studies with 3 and 4 RCT overlap with the above 2 reviews there was no difference in PACU rescue (4 RCTs) or PACU opioid requirement (3 RCTs), with a small reduction in postoperative morphine requirement (1.58 mg; 95%CI -2.58 to -0.57 mg, 2 RCTs) in the 4 postoperative h only vs placebo (McNicol 2018 **Level I** [Cochrane], 13 RCTs, n=920).

Additional trials have found NSAIDs effective with reduced pain scores and rescue morphine use post inguinal hernia repair (Riad 2007 **Level II**, n=108, JS 5), reduced need for early rescue

analgesia post tonsillectomy (Pickering 2002 **Level II,** n=103, JS 5), reduced pain scores post multiple dental extractions (Gazal 2007 **Level II,** n=201, JS 5) and reduced pain scores and need for rescue opioid 0–48 h post cleft palate repair (more so when combined with paracetamol) (Mireskandari 2011 **Level II**, n=120, JS 5). A ketorolac infusion was more effective than fentanyl infusion following ureteric-bladder surgery with less bladder spasm (4% vs 30) and less rescue analgesic administration over 48 h (21% vs 65) (Jo 2011 **Level II**, n=52, JS 5). SL ketorolac was equianalgesic vs SL tramadol for moderate and severe pain post fracture or dislocation (Neri 2013 **Level II**, n=131, JS 5). Intraoperative IV ibuprofen resulted in a small reduction in early postoperative fentanyl rescue administration after adenotonsillectomy surgery vs placebo (Moss 2014 **Level II**, n=161, JS 4). A combination of individually titrated intraoperative opioids and regularly administered perioperative nonopioid analgesics (NSAID and/or paracetamol) is recommended for pain management following paediatric tonsillectomy (Hamunen 2005 **Level I**, 36 RCTs, n=2,309). The combination of paracetamol (48 mg/kg/d) and ibuprofen (24 mg/kg/d) was not superior to either agent alone following tonsillectomy (Merry 2013 **Level II**, n=152, JS 5). Ketoprofen has been studied using IV, PO and PR route (Kokki 2010 **NR**). It is not currently used in children in Australia and New Zealand, where it is available as CR and topical forms only.

A Cochrane review of nsNSAIDs (and paracetamol) found ibuprofen use for acute otitis media reduces the number of patients in pain at 48 h vs placebo (7 vs 25%) (RR 0.28; 95%CI 0.11 to 0.70: NNT=6) (3 RCTs, n=146) with similar efficacy to paracetamol (Sjoukes 2016 **Level I** [Cochrane], 3 RCTS, n=327).

A Cochrane review of efficacy of NSAIDs in paediatric cancer found no RCTs (Cooper 2017b **Level I** [Cochrane], 0 RCTs).

Nonselective NSAIDS and reduction of postoperative nausea and vomiting

Diclofenac use in acute pain is associated with reduced nausea and vomiting (or both) vs placebo, paracetamol and opioids (OR 0.58; 95%CI 0.47 to 0.73: NNT 7.7; 95%CI 5.3 to 14.3) (Standing 2009b **Level I** [Cochrane], 13 RCTs, n=775). NSAIDs do not affect vomiting in PACU but reduce vomiting over 24 h (OR 0.75; 95%CI 0.57 to 0.99) (Michelet 2012 **Level I** [QUOROM], 17 RCTs, n=1,302 [events analysed]). Less vomiting occurs following tonsillectomy when nsNSAIDs are part of the analgesic regimen (RR 0.72; 95%CI 0.61 to 0.85) (Lewis 2013 **Level I** [Cochrane], 13 RCTs, n=1,021). The suggested mechanism is through improved pain relief, rather than reduced opioid rescue requirement. A fourth meta-analysis, of heterogeneous surgery types, found no association (with confidence interval overlap) between opioid-sparing effect and PONV reduction; 47% (95%CI 22 to 72) for those reporting PONV reduction vs 26% (95%CI 20 to 31) for those reporting equivalent PONV rates (Wong 2013b **Level I** [PRISMA], 31 RCTs, n=2,624).

10.4.2.3 | Adverse effects of nsNSAIDs in children

Overall safety

In large series of children with febrile illnesses (n=55,785), the risk of serious adverse effects following short term use of ibuprofen was low, and similar to that following the use of paracetamol (Lesko 1995 **Level II**, n=84,192, JS 4) including in the subgroup of children aged <2 y (Lesko 1999 **Level II**, n=27,065, JS 4). Diclofenac use for postoperative pain is also safe, with an overall serious adverse effect rate (including bleeding) of 8 in 10,000 (95%CI 2 to 24) (Standing 2009b **Level IV SR** [Cochrane], 18 RCTs and 54 studies [diclofenac], n=3,611). See also Section 4.2.1.2.
Ketorolac has been used as an analgesic in preterm and term neonates with no reported adverse effects (Gupta 2004 **Level III-1,** n=70; Moffett 2006 **Level IV,** n=53; Papacci 2004 **Level IV,** n=18). In children (<19 y) admitted to hospital with community acquired pneumonia, pre-hospital exposure to NSAIDs is associated with empyema in 4 of 5 studies, but use at home may

reflect illness, pain and fever severity rather than causation (Voiriot 2019 **Level III-3 SR**, 5 paediatric studies, n=1,753).

Nonselective NSAID hypersensitivity

NsNSAID hypersensitivity reactions may be immune or non-immune mediated. Immune mediated include immediate reactions (IgE mediated, onset <1 h), which may be single or multiple nsNSAID induced, and delayed reactions (T cell mediated, onset >24 h) (Kidon 2018 **GL;** Blanca-Lopez 2015 **NR**). Non-immune nsNSAID hypersensitivity includes NSAID-exacerbated respiratory disease (NSAID-ERD) (see below), NSAID exacerbated cutaneous disease and NSAID induced urticaria/angioedema; a mixed phenotype is common in children (Cousin 2016 **Level IV**, n=107). These reactions are COX-1 mediated with consequent excessive release of leukotrienes, and present within several hours of nsNSAID exposure (Cavkaytar 2019 **NR**). Also called cross-intolerance hypersensitivity, these accounted for most of the reaction types (67-85%) in a group of drug provocation test positive children (Arikoglu 2017 **Level IV**, n=106; Cousin 2016 **Level IV**, n=107).

Cutaneous symptoms of NSAID hypersensitivity reactions vary from urticaria/angioedema to more rare severe cutaneous reactions (Stevens-Johnson Syndrome [SJS] and toxic epidermal necrolysis [TEN]). The skin reactions are confounded by the use of the nsNSAID for the possible underlying viral or bacterial infection (Blanca-Lopez 2015 **NR**). Chronic urticaria (OR 7.74; 95%CI 3.38 to 18.30), atopic status (OR 2.51; 95%CI 1.50 to 4.36) and allergic rhino-conjunctivitis (1.80; 95%CI 1.14 to 2.84) are risk factors for nsNSAID hypersensitivity (Cousin 2016 **Level IV**, n=107).

Life-threatening NSAID-exacerbated respiratory disease (ERD) (see section below) and anaphylaxis are rare events. Anaphylaxis rates to nsNSAIDs are very low (0/100,000 hospitalisations; 95%CI 0 to 5.4) (Lesko 1995 **Level II**, n=84,192, JS 4). Allergic reactions are infrequently reported with diclofenac: one fatality from study data (Standing 2009b **Level IV SR** [Cochrane], 18 RCTs and 54 studies [diclofenac], n=3,611) and nine nonfatal from case reports (Standing 2009a **Level IV**). The frequency of implication of a particular nsNSAID in published series of children with allergic reactions likely reflects local prescribing and parental administration practices and has included all subclasses of nsNSAIDs (and also paracetamol) (Arikoglu 2017 **Level IV**, n=106; Topal 2016 **Level IV**, n=64). These children have been admitted for skin testing and/or oral provocation tests with either the drug implicated or aspirin. Predictors include:

- Onset of the reaction within 1 h of administration - OR 3.0; 95%CI 1.2 to 7.7 (Arikoglu 2017 **Level IV,** n=33 confirmed of 106 evaluated [6 paracetamol, 27 nsNSAIDs]) and OR 26.4; 95%CI 1.7 to 403 (Topal 2016 **Level IV**, n=18 confirmed of 64 evaluated [2 paracetamol, 16 nsNSAIDs]);
- Reported history of multiple nsNSAID-hypersensitivity (OR 27; 95%CI 1.5 to 482) (Topal 2016 **Level IV**) and (OR 2.9; 95%CI 1.2 to 7.6) (Arikoglu 2017 **Level IV**); and
- Family history of atopy (OR 4.0; 95%CI 1.50 to 10.82) (Arikoglu 2017 **Level IV**).

In these two series, the proven allergic children were subsequently tested to find a safe alternative. This is a better approach than telling the families to avoid all nsNSAIDs in their child as recommended by a prior paediatric series (Quiralte 2007 **Level IV**, n=223) referenced in this book's previous edition. Cross sensitivity may be limited to those in the same chemical group eg arylpropionic agents (ibuprofen and ketoprofen), arylacetic derivatives (diclofenac and aceclofenac) and pyrazolones (propyphenazone and dipyrone) (Blanca-Lopez 2015 **NR**).

Aspirin or NSAID-exacerbated respiratory disease (NSAID-ERD)

NSAID-ERD prevalence is reported at 1.8-44%; the variability is influenced by whether the population is from the community self-reporting sensitivity or a patient cohort with known sub-classified severity of their asthma and nasal disease, assessed with spirometry or provocation tests vs admitted to intensive care units (Kowalski 2019 **NR**). Age is relevant: younger children are stated to have reduced prevalence vs adults, with case series mostly of older children with

moderate to severe asthma (usually with coexistent nasal disease/polyps) developing NSAID-ERD (Kanabar 2017 **NR;** Tuttle 2016 **Level IV**, n=3; Karagol 2015 **Level IV**, n=10; Cavkaytar 2015 **Level IV**, n=161**;** Palmer 2005 **CR**). Old series (referenced in the two narrative reviews) report prevalence of 5% in children, but a lower value of 2% (95% CI 0.2 to 7.0) in older asthmatic children reporting sensitivity (n=100) assessed with spirometry post ibuprofen provocation. In most children with mild asthma, nsNSAIDS are likely to be safe. Single-dose diclofenac had no significant effect on respiratory function tests (spirometry) in children with asthma (Short 2000 **Level III-3**) and short term use of ibuprofen (vs paracetamol) reduced the risk of outpatient visits for asthma (RR 0.56; 95%CI 0.34 to 0.95) (Lesko 2002 **Level II**, n=1,879, JS 4). In toddlers with mild persistent asthma, no difference in asthma control or the exacerbation frequency was found between as-needed use of paracetamol and ibuprofen over 48 wk (Sheehan 2016 **Level II**, n=300, JS 4).

Reye's syndrome

Aspirin should be avoided in children with a febrile illness, as it has been associated with Reye's syndrome (encephalopathy and liver dysfunction) (Schror 2007 **NR**). The Therapeutic Goods Administration (TGA 2004 **GL**), Medsafe (Medsafe 2015 **GL**), the FDA (FDA 2003 **GL**) and the Medicines and Healthcare Products Regulatory Agency (MHRA 2003 **GL**) all recommend against aspirin under the ages of 12, 12, 12 and 16 y respectively.

Platelet effects and bleeding

The issue of nsNSAIDs and postoperative bleeding risk remains controversial.

Diclofenac use for various surgery types was not associated with increased bleeding risk requiring reoperation (OR 1.25; 95%CI 0.31 to 5) (Standing 2009b **Level I** [Cochrane], 7 RCTs, n=463).

In children (median 5 y, IQR 0.7-12) having neurosurgery (mostly major cranial and spinal interventions), perioperative ketorolac (dose unspecified) was not associated with an increase in clinically significant bleeding events (OR 0.69; 95% CI 0.15 to 3.1) or radiographic haemorrhage (OR 0.81; 95% CI 0.43 to 1.51) (Richardson 2016 **Level III-2**, n=1,451 [955 ketorolac]). In three small trials, ketorolac did not increase the risk of bleeding complications in infants after congenital cardiac (Gupta 2004 **Level III-1**, n=70; Moffett 2006 **Level IV**, n=53) or general surgery (Papacci 2004 **Level IV**, n=18).

Bleeding after tonsillectomy is of clinical significance but occurs infrequently: 1–5% in children depending on how bleeding is defined – any bleeding (which can have rates up to 10%), postoperative primary or secondary (>24 h) vs those requiring admission/transfusion/surgical intervention. Past studies have been small with contradictory results. Bleeding risk has been the subject of several meta-analyses with varying conclusions (6–7 RCT overlap). Ketorolac use is associated with increased post tonsillectomy bleeding in adults (RR 5.64; 95%CI 2.08 to 15.27) (n=246) but not children (RR 1.39; 95%CI 0.84 to 2.30) (n=1,111) (Chan 2014 **Level III-2 SR** [PRISMA], 10 studies [7 paediatric], n=1,357). An earlier review of only paediatric tonsillectomy trials (with 7 ketorolac RCT overlap) demonstrates no increased bleeding requiring either nonsurgical or surgical intervention (Lewis 2013 **Level I** [Cochrane], 15 RCTS, n=1,101). A larger tonsillectomy review also found no increased bleeding risk (surgical or nonsurgical) for all NSAIDs in adults and children, children only or for specific NSAIDs (Riggin 2013 **Level I**, 36 RCTs, n=3,193 [1,747 children]). Importantly, to definitively answer the question of whether NSAIDs increase bleeding post tonsillectomy, a study size of 2,400 is required (Lewis 2013 **Level I** [Cochrane], 15 RCTS, n=1,101).

Of note, the majority of studies in these meta-analyses have used a single dose of NSAID vs placebo. A multicentre RCT in children (median 5 y, range 2 to 18) comparing ibuprofen and paracetamol (with an overall rate of any bleeding of 9.4%) was unable to show non-inferiority for returns to theatre for bleeding post tonsillectomy (1.2 vs 2.9%: difference of 1.7% where non-inferiority margin was set at 3%) (Diercks 2019 **Level II**, n=741, JS 5). Multiple postoperative dosing for some days is routine clinical practice and has not been prospectively studied, with regard to

the issue of bleeding, and surgical techniques are evolving. In a single institution with low return to theatre for post-tonsillectomy bleeding (3.3% in 3.5 years), postoperative ibuprofen exposure (n=2,122 of 6,710) did not increase post-tonsillectomy haemorrhage requiring surgical intervention (OR 0.90; 95%CI 0.68 to 1.19), but of those returning to theatre, ibuprofen users had a 3-fold greater transfusion rate than non-users (OR 3.2; 95%CI 1.0 to 9.9) (Mudd 2017 **Level III-3**, n=6710 [222 return to theatre: 15 transfusion requiring]). Predictors for post-tonsillectomy haemorrhage requiring surgical intervention included age ≥12 y (OR 2.74; 95% CI 1.99 to 3.76) and preoperative diagnosis of recurrent tonsillitis (OR 1.52; 95% CI 1.12 to 2.06) but not obstructive indications. Cumulative dose data per patient was not reported.

Gastrointestinal effects

Epigastric discomfort, gastric or duodenal inflammation, oesophageal and peptic ulceration has occurred in association with nsNSAID use for fever and pain in children (Kanabar 2017 **NR**; Cardile 2016 **Level IV**, n=51). Following ibuprofen use for fever management, the incidence of hospital admission for gastrointestinal bleeding was low at 7.2 per 100,000 (95%CI 2 to 18) and similar to those treated with paracetamol (Lesko 1995 **Level II**, n=84,192, JS 4). A prospective series of young children admitted with gastroduodenal symptoms, haematemesis or melaena after mostly short term use had increased upper gastrointestinal complications with ibuprofen (OR 2.9; 95% CI 2.1 to 4.0), PO steroids (OR 2.9; 95% CI 1.7 to 4.8) and paracetamol (OR 2.0; 95% CI 1.5 to 2.6) vs non-use (Bianciotto 2013 **Level III-2**, n=486).

Although NSAIDs are used infrequently for analgesia in young infants, limited data on adverse gastrointestinal effects is available following PO, IV, bolus and infusion for PDA closure. Ibuprofen is as effective as indomethacin (indometacin) for PDA closure (PO or IV; 32 RCTs, n=1,862) with reduced risk of necrotising enterocolitis (18 RCTs, n=1,292) (Ohlsson 2018b **Level I** [Cochrane], 39 RCTs, n=2,843) – of relevance recent trials comparing NSAID with paracetamol for this indication suggest equivalent efficacy for paracetamol with reduced gastrointestinal bleeding (4 RCTs, n=537) and lower creatinine (4 RCTs) and bilirubin (2 RCTs) (Ohlsson 2018b **Level I** [Cochrane], 8 RCTs, n=916).

Renal effects

Renal blood flow, glomerular filtration and renal drug clearance are affected by nsNSAIDs (Allegaert 2005a **PK**). Acute kidney injury and renal failure (due to acute tubular necrosis or interstitial nephritis) in association with nsNSAID use is a serious but rare complication. It has occurred in all age groups (Misurac 2013 **Level IV**; de Martino 2017 **NR**; Musu 2011 **NR** with reviewed case series overlap;) from newborns (after maternal use), neonates (Andreoli 2004 **NR**), and infants to older children (Taber 2006 **NR**). A review has shown the risk in children is lower than in adults but paediatric fatalities have occurred (Musu 2011 **NR**). No renal impairment with ibuprofen exposure was observed in a large fever trial including the subgroup of patients admitted to hospital (risk 0/100,000; 95%CI 0 to 5.4) (Lesko 1995 **Level II**, n=84,192 [n=55,785 ibuprofen], JS 4). NSAID induced acute renal failure is usually reversible with cessation of the drug (Musu 2011 **NR**). Children susceptible to dehydration (eg with high fever, vomiting and diarrhoea) may be at increased risk of nephrotoxicity.

Retrospective analysis of the FDA's spontaneous reporting system suggests increased risk of acute kidney injury with ibuprofen alone, which is higher when paracetamol was coprescribed (Yue 2014 **Level IV**). However, no data on illness type, severity, comorbidity or suspected causation (determined by expert panel review) was provided.

Vascular effects

Neonatal bolus and short term use for PDA closure can alter pulmonary (although no pulmonary hypertensive events were reported in Ohlsson 2018b **Level I** [Cochrane], 3 RCTs [pulmonary hypertension], n=255), cerebral (Naulaers 2005 **NR**), gastrointestinal and renal blood flow (Aranda 2006 **NR;** Allegaert 2005b **PK**) with oliguria (Ohlsson 2018b **Level I** [Cochrane], 6 RCTs [oliguria], n=576; Musu 2011 **NR**). Ibuprofen for PDA closure is associated with reduced risk of transient renal insufficiency vs indomethacin (Ohlsson 2018b **Level I** [Cochrane], 6 RCTs [oliguria], n=576 and 11 RCTs [creatinine levels], n=918). Subsequent to findings in non-RCT data (Musu 2011 **NR;** Ment 2004 **Level III-2,** n=431 [65 events]), the relative effects of indomethacin on the risk of intraventricular haemorrhage (IVH) continue to be debated: of relevance, RCTs do not have a placebo arm, they differ in their report of outcomes eg severity grade of the bleed including all IVH grades (83 events/524 [7 RCTs]) vs severe grades (71/798 [10 RCTs]) or the consequence of cystic periventricular leukomalacia 37/573 [6 RCTs]) and duration of follow-up (Ohlsson 2018b **Level I** [Cochrane], 39 RCTs, n=2,843).

Bone healing effects

NSAID use following orthopaedic injury and surgery remains controversial. NSAIDs do improve analgesia, increase mobility and reduce opioid consumption following orthopaedic (including spinal) surgery, but they are also used to suppress and treat heterotopic bone ossification. The paediatric data is limited and we still do not have an understanding of the effects on bone healing and, more specifically, the impact of dosing schedules, timing and duration of exposure and whether they only delay union or contribute to non-union (Borgeat 2018 **Level III-2 SR** [PRISMA], 5 studies [paediatric], n=1,602) (see also Section 4.2.1.2). In this review, the three small retrospective reports of paediatric spinal fusion patients did not find adverse effects from <14 d of ketorolac use (total n=415) (Horn 2010 **Level III-3**; Sucato 2005 **Level III-3**; Vitale 2003 **Level III-3**). Specifically the incidence of pseudoarthrosis and revision surgery was not increased. Two retrospective series of fracture and osteotomy surgery (with one surgeon) report no delayed or non-union with perioperative ketorolac (0.5 mg/kg every 6 h) (n=468 ketorolac treated vs n=80 not) (Kay 2011 **Level III-3** in neither above nor below review; Kay 2010 **Level III-3** in both reviews). Ibuprofen exposure in children presenting to ED with a fracture (tibia, femur, humerus, scaphoid, or fifth metatarsal) and followed in orthopaedic clinic did not increase bone healing complications (OR 0.8; 95% CI 0.4 to 1.8) (DePeter 2017 **Level III-2**, n=808). The cohort were initially managed conservatively or by closed reduction or surgery. Data on ibuprofen dosing and duration was not reported.

A meta-analysis of 4 of the above studies concludes that NSAID exposure did not increase delayed or non-union risk (OR 0.58; 95%CI 0.27 to 1.21) (Wheatley 2019 **Level III-3 SR** [PRISMA], 4 studies [paediatric], n=2,017 [analysed as broken bones]) (4 study overlap with Borgeat).

The balance of low-level evidence suggests that a short-duration NSAID regimen is safe for post fracture or osteotomy pain control and for postoperative use in spinal fusion surgery.

Local necrosis following intramuscular injection

Serious local necrosis following IM injection of diclofenac is reported in six patients (Standing 2009a **Level IV**).

Table 10.6 | Common nsNSAIDs and dosing recommendations in children

nsNSAID	Suggested age cut-off	Recommended Dose	Suggested dosing frequency	References
Ibuprofen (PO)[#]	>3 mth (>5 kg) Some suggest >6 mth	5–10 mg/kg (max 400-800 mg)	6–8 hly (max 30-40 mg/kg/d)	Ziesenitz 2017 **NR PK**
Diclofenac (PO/PR)	1–12 y	1-2 mg/kg (max 50 mg)	PO: 6–8 hly PR: 12 hly	Hannam 2014 **PK**
Ketorolac* (parenteral) Australia	>16 y	0.2–0.25mg/kg (Aust.: max 10 mg)	6 hly	Marzuillo 2018 **NR**; McLay 2018 **PK**
Ketorolac (parenteral) USA	>3 mth–2 y 2–16 y >16 y	0.5 mg/kg (USA: <50 kg max 15 mg; ≥50 kg max 30 mg)	6 hly	

[#] IV formulation of ibuprofen is minimally used clinically to date as it is more costly than ketorolac

** These dosing recommendations are based upon study data: ketorolac does not have regulatory approval in Australia for use under 16 y (and is not available in New Zealand).*

KEY MESSAGES

1. Nonselective NSAIDs do not increase the risk of either surgical or nonsurgical intervention for bleeding after paediatric tonsillectomy (**U**) (**Level I** [Cochrane Review]); however this was not supported by a large non-inferiority RCT where surgical intervention was increased with ibuprofen versus paracetamol (**Q**) (**Level II**).
2. Nonselective NSAID (ibuprofen) use for acute otitis media reduces pain (at 48 hours) vs placebo, with similar efficacy to paracetamol (**N**) (**Level I** [Cochrane Review]).
3. Nonselective NSAIDs are effective for moderately severe pain and decrease opioid requirements after major paediatric surgery (**U**) (**Level I** [PRISMA]) and postoperative nausea and vomiting (**U**) (**Level I** [QUOROM]).
4. Serious adverse effects after nonselective NSAIDs are rare in children over 6 months of age (**U**) (**Level II**).
5. Ibuprofen may increase severity of haemorrhage post tonsillectomy in patients returning to theatre (**N**) (**Level III-3**).
6. Short term use of ketorolac or ibuprofen do not increase bone healing complications in children undergoing posterior spinal fusion, osteotomy, or fractures managed surgically (**S**) (**Level III-3**) or conservatively (**N**) (**Level III-3**).

The following tick boxes represent conclusions based on clinical experience and expert opinion:

☑ Aspirin for acute pain indications should be avoided in children (**U**).

☑ Combined population pharmacokinetic-pharmacodynamic modelling is required to inform targeted dosing recommendations of analgesics in children (**U**).

10.4.3 | Coxibs

Paediatric trial data is limited and thus the understanding of the degree of COX-2 selectivity, the pharmacokinetic-pharmacodynamic (PK-PD) relationship and adverse effects of these agents in children remains poor and paediatric use is again off-licence.

10.4.3.1 | Pharmacokinetics

The PKs of a celecoxib suspension, capsule sprinkles and the commercial capsule have been compared (Krishnaswami 2012 **PK**). The different formulations achieve similar areas under the curve post ingestion. For pain relief in juvenile idiopathic arthritis (JIA), a suggested dosing regimen is 2–4 mg/kg bd. Although metabolism and excretion processes are typically fully functional by age 2 y, absolute oral clearance (L/h) of celecoxib is reduced in younger patients; by 40% in infants weighing 10 kg and by 24% in children weighing 25 kg vs a 70 kg adult. The major clearance pathway for celecoxib is via CYP2C9 (Murto 2015 **Level II**, n=195, JS 5). Other drugs cleared by this pathway (eg ibuprofen) have increased clearance (L/kg/h) in childhood. It is reported that clearance may be further increased in children with oncological disease (Stempak 2002 **PK**).

Parecoxib is a prodrug metabolised to the active valdecoxib, which reaches peak serum concentration at 27 min (Tan 2016 **PK**). A pooled PK analysis of parecoxib demonstrates no change in clearance with age for children over 1 y (Tan 2016 **PK**, n=112). The first year of life is when the major clearance pathways for parecoxib mature. Parecoxib dose-response relationship modelling suggest a ceiling analgesic effect at doses of less than 1 mg/kg (Tan 2016 **Level II**, n=59, JS 5). Allometric dosing of parecoxib IV (0.9 mg/kg for 2 y, 0.75 mg/kg for 7 y and 0.65 mg/kg 12 y: 40 mg max) is suggested to maintain the concentration of valdecoxib above the *in vitro* 50% inhibitory concentration for cyclooxygenase for >12 h. This achieves dose equivalence of 40 mg in a 70 kg adult, where 12 h dosing may be appropriate for both adult and paediatric age groups (Tan 2016 **PK** incorporated data from Hullett 2012 **PK**). A dose reduction or increased dosing interval is suggested for children aged <2 y. In practice for older children, paediatric centres are using 1 mg/kg (max 40 mg).

10.4.3.2 | Efficacy

Celecoxib (6mg/kg pre-induction then 3 mg/kg 12 h for 3 days) reduced early pain (POD 0-2) and co-analgesic use following adenotonsillectomy (Murto 2015 **Level II**, n=195, JS 5). Carriers of the *CYP2C9*3* allele are slow celecoxib metabolisers and demonstrate less pain and improved functional recovery. This suggests dosing may need to be more frequent than 12 h for normal metabolisers. Celecoxib use has previously been reported in children with chronically painful medical conditions. Celecoxib (3–6 mg/kg twice/d) was as effective as naproxen (7.5 mg/kg twice/d) in children with JIA (Foeldvari 2009 **Level II**, n=242, JS 5). Celecoxib use was reported in a series of JIA patients (n=68; 68 person-years) vs nsNSAID treatment (mostly naproxen, meloxicam, and nabumetone) (Sobel 2014 **Level III-2**, n=268 [person-years]) and in a small series of haemophiliac patients (Rattray 2006 **Level IV**).

Parecoxib 0.5–1.5 mg/kg for various surgery types reduces pain scores at 2 h (MD -1.9/10; 95%CI -3.0 to -0.8) and 12 h (MD -2.0; 95CI -2.3 to – 1.8) (Bu 2015 **Level I** [PRISMA], 6 RCTs [pain scores], n=350). Its use reduces PONV (4 RCTs) vs fentanyl and tramadol and postoperative opioid consumption (2 RCTs) (Bu 2015 **Level I** [PRISMA], 12 RCTs, n=994). Parecoxib 1mg/kg for post tonsillectomy pain was modestly effective in the immediate postoperative period (Li 2016 **Level II**, n=60, JS 5; Tan 2016 **Level II**, n=59, JS 5). IV parecoxib 20–40 mg (alone and combined with topical local anaesthetic) was superior to IV fentanyl 2 mcg/kg for pain after repair of corneal

perforation, with reduced rescue analgesic requirements and PONV (Subramaniam 2007 **Level II**, n=90, JS 3).

10.4.3.3 | Adverse effects of Coxibs in children

Overall safety

Prospective data from 3–12 mth use in JIA patients had similar incidence of treatment related adverse events to nsNSAIDs (Sobel 2014 **Level III-2**; Krishnaswami 2012 **PK**). None were serious which is reassuring but sample size was limited (overall n=220) (See Section 4.2.2.2 for discussion of safety and adverse effects in adults).

Safety in overdose

Paediatric overdose of celecoxib was reported in children aged 0–5 y (Forrester 2009 **Level IV**, n=177). For 92 patients, the dose was known and was large; mean 506 mg (range 10–2,300 mg) equating to mean ingested amounts of 22–39 mg/kg (for the half with documented weight) across the age groups. This resulted in no adverse effects in 96%, and minor adverse effects (rash, abdominal pain, vomiting, agitation or drowsiness) in only 4%.

NSAID hypersensitivity including NSAID-exacerbated respiratory disease (ERD)

Based upon adult data (see Section 4.2.2), coxibs are generally considered safe for use in paediatric patients with asthma and aspirin- or NSAID-exacerbated respiratory disease. In 223 patients (aged 5–78 y) with various levels of allergic reaction to nsNSAIDs or paracetamol (cutaneous/angioedema/urticaria/rash [61%], naso-ocular/cutaneous/asthma [15%], respiratory alone [9%] and anaphylaxis [16%]) having placebo-controlled multidrug oral challenges (n=697), celecoxib precipitated no events and meloxicam one event (Quiralte 2007 **Level IV**). Other smaller series have reported cross-sensitivity for coxibs in patients with cutaneous or naso-ocular reactions. In 28 nsNSAID-sensitive patients (aged 10–61 y), use of rofecoxib and valdecoxib produced urticaria or angioedema in 3 (10%) (Sanchez-Borges 2005b **Level IV**). Of 58 similarly aged patients, 5 (9%) had reactions to celecoxib and 3 (5%) had reactions to etoricoxib (Sanchez-Borges 2005a **Level IV**). As a small percentage of patients have reactions suggesting cross-sensitivity, oral challenge under medical supervision for 2 h is advisable (see Section 10.4.2.3 regarding detail of Anaphylaxis and allergy, and of NSAID-ERD with nsNSAIDs in children).

Platelets effects and bleeding

In adolescent haemophiliac patients, etoricoxib and rofecoxib treated patients had similar numbers of presentations for bleeding vs placebo (Tsoukas 2006 **Level II**, n=102, JS 5). Bleeding following paediatric tonsillectomy has been assessed (Lewis 2013 **Level I** [Cochrane], 15 RCTS, n=1,101) (see Section 10.6.5.1). This meta-analysis includes only one small coxib trial, with no differences in bleeding rates of rofecoxib vs ibuprofen vs placebo (added to paracetamol) (Pickering 2002 **Level II**, n=98, JS 5). A subsequent still relatively small trial found no difference in post tonsillectomy bleeding rates for celecoxib vs placebo (Murto 2015 **Level II**, n=195, JS 5).

Gastrointestinal effects

In children with JIA treated chronically (where 68–71% were receiving disease-modifying agents, with the number on corticosteroids unspecified), rates of abdominal pain were similar between those treated with nsNSAIDs (15/100 patient-years; 95%CI 10 to 19 [n=225 patient-years]) and celecoxib (18/100 patient-years; 95%CI 8 to 28 [68 patient-years]) and not statistically different from patients in “off-NSAID” periods (8/100 patient-years, 95%CI 2 to 15 [n=75 patient-years]) (Sobel 2014 **Level III-2**). One patient experienced gastrointestinal ulceration in an off-NSAID period. Nausea and vomiting rates were similar in the three groups.

Renal effects

Two unspecified renal disorders (not categorised as serious) occurred in chronically celecoxib-treated children with JIA during 68 patient-years of therapy (Sobel 2014 **Level III-2**). Celecoxib's safety profile for acute kidney injury in adults is specified in Section 4.2.2.2.

Table 10.7 | Coxib dosing recommendations in children

Coxib Drug	Age	Recommended Dose	Dosing frequency	References
Celecoxib (PO)*		3-6 mg/kg (max 200mg)	12 h (2-4 mg/kg repeat dosing)	Murto 2015 **Level II**
Parecoxib (IV)*	>2 y	1 mg/kg (max 40 mg) was studied: to derive allometric dose scaling see doses in text.	Single intraop. dose, >12 h before next NSAID dose	Tan 2016 **PK** Hullett 2012 **PK**

** These dosing recommendations are based upon study data; at the time of writing neither coxib is licensed for acute postoperative pain indication under 18 y.*

KEY MESSAGES

1. Parecoxib use in children reduces early postoperative pain scores, PONV (compared to tramadol and fentanyl) and postoperative opioid consumption (**N**) (**Level I** [PRISMA]).
2. Parecoxib may have a ceiling analgesic effect in children in doses less than 1 mg/kg (**N**) (**Level II**).

The following tick boxes represent conclusions based on clinical experience and expert opinion:

☑ The safety profile of coxibs in the setting of allergy or contraindication to nonselective NSAID in adults and children is encouraging; but safety data specific to short term use in the perioperative period is limited (**Q**).

☑ Celecoxib for 3 days reduces pain and additional analgesic requirement post-tonsillectomy in children (**N**).

☑ Some paediatric centres retain the 1 mg/kg (40 mg) maximum daily dosing schedule for Parecoxib for off license use (**N**).

10.4.4 | Conventional and atypical opioids

There are significant developmental changes in the pharmacokinetic (PK) handling and pharmacodynamic (PD) response to opioids (Allegaert 2014 **NR**; Anderson 2014b **NR**; Holford 2012 **PK**). Doses must therefore be adjusted according to age, body weight, coexistent liver or renal impairment, and individual response. Routine and regular assessment of pain severity, the analgesic response, and the incidence of adverse effects (particularly nausea, vomiting, sedation and opioid induced ventilatory impairment [OIVI]) is essential, with titration of opioid treatment according to individual needs. As with adult patients, appropriate dose regimens, guidelines for monitoring, documentation, management of adverse effects, and education of staff and carers are required (Ellis 2011 **Level IV**; Wrona 2007 **Level IV**) (see Section 4.3.1 and subsection 4.3.1.5).

The issue of sleep-disordered breathing (SDB) is discussed here under the individual opioid adverse events subheadings and not as a subsection (See also the adult Section 9.4 on sleep-disordered breathing and subsection 9.4.1 Opioids and obstructive sleep apnoea). The issue of opioid-related tolerance and withdrawal in children and adolescents is discussed in Section 10.4.6.

10.4.4.1 | Pharmacogenomics

The evidence for the effect of pharmacogenetics on opioid responses is accumulating. Examples of relevant polymorphisms include: the liver enzyme cytochrome-P450 CYP2D6 (Balyan 2017a **PK**, n=30; Yee 2013 **Level IV**; Friedrichsdorf 2013 **Level IV;** Soderberg Lofdal 2013 **NR**; Kelly 2012 **Level IV**); enzymes involved in glucuronidation (UGT1A1) (Toce 2019 **CR)**; liver cell transporter proteins (OCT1) (Fukuda 2013 **Level IV**), ATP-binding cassette (ABC) subfamily member *B1* (or MDR1) (Horvat 2017 **Level III-3**, n=63; Sadhasivam 2015b **NR**) and ABCC3 (Chidambaran 2017c **Level III-3**, n=316; Venkatasubramanian 2014 **Level III-3**); opioid receptor subtypes (Anderson 2014a **NR**), including OPRM1 genes involved in pain perception (Sadhasivam 2015c **Level III-3**, n=259; Lee 2016 **Level III-3**, n=88) and COMT, a regulating enzyme involved in pain pathways (Elens 2016 **Level III-3**, n=34; Sadhasivam 2014 **Level IV**). Genome wide association studies have also identified single nucleotide polymorphisms associated with opioid effects in children (Cook-Sather 2014 **Level IV**). Further considerations are the differential risk with genetic differences and varying prevalence of racial/ethnic phenotypes (Anderson 2014a **NR**) and consequent variability in sensitivity to adverse effects (Balyan 2017b **Level III-3**, n=30; Chidambaran 2017a **Level III-3**, n=101; Sadhasivam 2015c **Level III-3**, n=259; Fukuda 2013 **Level IV**; Jimenez 2012 **Level III-3**) (see also Sections 1.7.2 and 1.7.3). Despite a growing understanding of the genetic factors determining drug effects, the link between genetic polymorphisms and the relevance to the observed clinical outcome is not always clear (Balyan 2017b **PK**). For some of the best understood polymorphisms, genetic screening to support clinical decision making is being explored (Gammal 2016 **Level IV**, n=2,468 [621 sickle cell disease])**.**

10.4.4.2 | Medication prescribing errors

Medication errors continue to be problematic, particularly in children. Ten-fold dose errors in prescribing made up a small proportion of hospital prescribing errors (3.8%) but were associated with significant morbidity when involving opioids (Doherty 2012 **Level IV**, n=6,643). In a single paediatric centre 5 y audit (≈1,320 medication error reports per year), the most frequently implicated drug class was opioids (8.5%) (Doherty 2012 **Level IV**) and drug was morphine (3.2%) (Mc Donnell 2011 **Level IV**). This is concerning due to the frequency of prescription within hospitals and the community and the adverse effect profile of opioids.

Conventional opioids

10.4.4.3 | Morphine

Morphine has a long history of use in paediatric acute pain management as either the gold standard comparator or rescue agent in analgesic trials.

Pharmacokinetics and pharmacodynamics

Morphine clearance is influenced by postmenstrual/postnatal age and weight (Holford 2012 **PK**; Krekels 2011 **PK**). Morphine clearance is reduced and half-life prolonged in neonates and infants, achieving adult values from age 2 y, related to the maturation of glucuronidation. Within age groups, individual variability in kinetics results in large interindividual variation in clearance, from

2 to 20 fold (Altamimi 2015 **NR**), with subsequent variability in observed maximum plasma concentration, including after PO administration (Dawes 2017 **PK**, n=34). In neonates, infants and children to 3 y, age is the most important factor affecting morphine requirements and plasma morphine concentrations (Bouwmeester 2003b **Level II**, n=68, JS 2). Mechanical ventilation reduces hepatic blood flow (up to 45%) and is associated with reduced clearance, as is renal failure (Anderson 2014b **NR**). Post cardiac surgery, there was no difference in morphine PKs seen between patients with Down syndrome vs without (Goot 2018 **Level III-2 PK**, n=42; Valkenburg 2016 **Level III-2 PK**, n=38). Pharmacodynamics also change with age eg the change seen in older children for average patient-controlled morphine requirements (Hansen 1996 **Level IV**) with contribution, as outlined above, from genetics with resultant racial differences (Anderson 2014b **NR**).

The risk of respiratory depression is reduced when infusions are targeted to plasma morphine concentrations <20 mcg/L. However, no minimum effective concentration for analgesia has been determined (Anderson 2014b **NR**). No clear relationship between plasma concentration and analgesia has been identified due to variability in individual requirements, clinical state of the child, type of surgery, assessment measure used and small sample size in many studies.

Efficacy

Morphine (administered via IV, epidural, IM and IT routes) has analgesic efficacy in comparison with inactive controls, but with significantly increased vomiting and sedation (Duedahl 2007 **Level I**, 36 RCTs, n=1,908). The majority of studies analysed compared single perioperative doses and only one study evaluated a postoperative infusion of morphine. A further trial in bilateral myringotomy demonstrated equivalence of IN fentanyl, IV and IM morphine (Hippard 2012 **Level II**, n=171, JS 5). In children with SDB post tonsillectomy, more desaturation events per h occurred with PO morphine vs ibuprofen, leading to early RCT termination (Kelly 2015 **Level II**, n=91, JS 3).

In children having minor day-stay orthopaedic surgery with low pain scores, multidosing with prn PO morphine 0.5 mg/kg (max 20mg) was not more effective than ibuprofen 10 mg/kg (max 600mg) and, similar to above, was associated with more adverse effects (Poonai 2017 **Level II**, n=154, JS 5). While in a systematic review of single and repeat dosing, IV morphine 50–150 mcg/kg is inferior to IV buprenorphine 1.5–6mcg/kg in time to rescue analgesia in a range of paediatric surgeries (MD: 115 min; 95% CI 43 to 186) (Murray 2018 **Level I**, 4 RCTs, n=137).

10.4.4.4 | Fentanyl

Fentanyl is a highly lipophilic and potent mu-opioid agonist and is used in paediatric acute pain management.

Pharmacokinetics

Fentanyl's rapid redistribution contributed to its relatively rapid offset of action following single IV bolus doses (Tibboel 2005 **NR**). Fentanyl is metabolised by CYP3A4 to inactive metabolites and clearance is only 70–80% of adult levels in neonates but rapidly matures within the first 2 weeks of life, when standardised using allometric scaling. Clearance is greater per kg than adults in older infants and children 3 mth and 6 mth to 6 y (Ziesenitz 2018 **Level IV SR PK**, 24 studies [IV fentanyl], n=777).

After transbuccal administration, when children retained the lozenge in the cheek, the bioavailability was 50% vs other studies of lozenge (2 studies) vs solution (1 study), where swallowing likely contributed to the lower bioavailabilities of 33 to 36% (Lotsch 2013 **NR PK**; Ziesenitz 2018 **Level IV SR PK**, 3 studies [oral transmucosal fentanyl citrate], n=67) (1 study overlap).

Intranasal (IN) fentanyl PKs have been assessed in adults demonstrating high bioavailability (and rapid onset of effect), but not in children to date. Small volumes are necessary to reduce delivery to the posterior pharynx (where it is swallowed).

TD fentanyl has high bioavailability. In children vs adults, the time to reach steady state serum drug concentrations following TD application is longer, and the elimination half-life is shorter as clearance is enhanced (Ziesenitz 2018 **Level IV SR PK**, 1 study [TD fentanyl]: Paut 2000 **PK**, n=8).

Efficacy

Fentanyl has been administered for perioperative pain management in neonates and children (APAGBI 2012 **GL**) and also in the intensive care setting (Anand 2013a **Level III-2**) by multiple routes, including IV bolus (He 2013 **Level I,** 3 RCTs, n=283; Elshammaa 2011 **Level II**, n=60, JS 4), infusion (Jo 2011 **Level II**, n=52, JS 5), patient-controlled analgesia (PCA) (Antila 2006 **Level II** n=45, JS 4) (see Section 10.5.2), IT injection (Duman 2010 **Level II**, n=50, JS 5; Batra 2008 **Level II**, n=56, JS 5) and as an additive to peripheral nerve and epidural infusions and patient-controlled epidural analgesia (PCEA) (Saudan 2008 **Level III-3**) (see Section 10.6.3.3).

Due to its rapid onset and short duration of action, fentanyl can be used alone or in combination with sedatives to control procedural pain (see Section 10.7.2 and APAGBI 2012 **GL**; Tibboel 2005 **NR**).

Due to its high lipophilicity, fentanyl can also be administered via transmucosal (transbuccal, IN, nebulised) and TD routes. Transmucosal fentanyl is attractive when IV access is challenging or unavailable. Transbuccal fentanyl has been used for children having burns dressing changes and lumbar punctures (see Section 10.7.2).

In the prehospital or ED setting for orthopaedic trauma, 10–15 mcg/kg by transbuccal route (Davis 2011 **Level IV SR**, 1 RCT [paediatric]: Mahar 2007 **Level II**, n=87, JS 3) and 1–4 mcg/kg IN have been used effectively (O'Donnell 2013 **Level III-3**, n=946; Karlsen 2014 **Level IV**, n=903). It has also been used to manage pain from abdominal, back and other conditions (Bendall 2011a **Level III-2**, n=3,312). In paediatric EDs, IN fentanyl (INF) 1.5–2 mcg/kg (usual max 100 mcg) was used for pain from injured extremities (Schoolman-Anderson 2018 **Level IV**, n=132; Setlur 2018 **Level IV SR** [PRISMA], 4 RCTs, n=281 and 2 studies (fracture) n=1800), burns, the abdomen and other sources (Hansen 2012 **Level IV SR**, 7 studies [paediatric], n=878 analysed). A second systematic review describes efficacy of similar dosing in three ED studies (one of fractures, one mixed pain types and one in burns [see Section 10.9.1 and 10.9.2]) and four perioperative myringotomy studies (Mudd 2011 **Level IV SR**, 12 studies, n=1,743) (5 study overlap). Further myringotomy studies have also been published (Dewhirst 2014 **Level II**, n=100, JS 5; Karlsen 2014 **Level IV**, n=903; Hippard 2012 **Level II,** n=171, JS 5). A Cochrane review did not perform meta-analysis due to the 3 different active comparator arms studied (Murphy 2014b **Level I** [Cochrane], 3 RCTs, n=313) (1 & 2 RCT overlap with above & below). In a fourth systematic review (1 & 3 study overlap: 2 RCTs and the largest prehospital study above), INF 1.5–2 mcg/kg in a variety of settings was superior to placebo and IM morphine and similar to IN and IV ketamine and IV morphine in reducing pain scores (Setlur 2018 **Level IV SR** [PRISMA], 6 RCTs, n=350; 4 retrospective studies n=5,595). In acute care settings, use of INF vs IV morphine achieved earlier time to analgesic administration in 2 cohorts by 24 and 29 mins (Borland 2008 **Level III-3**, n=617); and in a further study by 8.5 min (Schoolman-Anderson 2018 **Level III-3**, n=132). A subsequent RCT in procedural pain showed INF added to nitrous oxide (N_2O) did not improve analgesia over N_2O alone in children with low preprocedural pain scores and short procedure duration (Seiler 2019 **Level II**, n=402, JS 5). No serious adverse effects of INF were reported in the above studies with a total of >6,000 patients.

Data on nebulised fentanyl in children is limited showing similar reduction in pain scores vs IV fentanyl and IV morphine (Thompson 2016 **Level I** [PRISMA], 2 RCTs (paediatric), n=118). There have been no randomised trials of efficacy of the TD route.

Adverse effects to morphine and fentanyl in children

Side effects

Mild to moderate but not life threatening opioid-related adverse effects that greatly disturb children, and their parents, include nausea, vomiting, constipation, dizziness, sedation, dysphoria, nightmares, itch/skin rash and urinary retention. They occur commonly; no large scale comparative data is available. See data for other opioids in Table 10.8.

Major adverse events

Respiratory complications, coma and death have occurred with these two opioids. Younger aged children may have increased risk postoperatively (Tait 2016 **Level III-2**, n=678; Chidambaran 2014 **Level IV**, n=38), including post tonsillectomy (Sadhasivam 2015a **Level IV**, n=275). Comorbidities are likely to contribute (see below) but the degree of interplay of other factors such as variation in opioid potency, prescriber error (dosing or with change of opioid) and severity of pathology is unknown. National outpatient 'weak and strong opioid' prescription data has been published for New Zealand (HQSC 2019 **Level IV**, n=58,272), Australia (Bell 2019a **Level IV**, n=78,320) and USA (Chung 2018a **Level IV**, n=1,362,503), with low level (0 to 3.5%) oral morphine prescription in children.

Certain groups of paediatric patients are at higher risk of opioid induced ventilatory impairment (OIVI). Children with neurodevelopmental disabilities (eg cerebral palsy, Down's syndrome and encephalopathy) experienced more OIVI than children without (1.1 vs 0.6%; OR 1.8) with similar median dosing of morphine infusions POD 0-2 (Jay 2017 **Level III-3**, n=12,904). Children with SDB receiving postoperative opioids following various surgery types (frequently tonsillectomy in the SDB group) triggered oxygen desaturation alarms, required escalation of care and treatment with naloxone more than children without SDB (53 vs 27%: OR 2.0; 95%CI 1.6 to 2.5) (Tait 2016 **Level III-2**, n=678). Additionally, children with SDB who have worse night time oxygen desaturation (<85% nadir) required half the morphine dose to achieve the same analgesic effect (Brown 2006 **Level III-2**, n=22). Amongst hospital inpatients (n=60,467), 38 (0.06%) opioid-induced respiratory events requiring naloxone occurred, with higher incidence in those patients who were under pain service care (0.23%) (Chidambaran 2014 **Level IV**, n=38). Most patients were postoperative (71%) and were more likely to have had recent airway surgery, be underweight or obese, age <1 y and ex-premature vs pain service patients who did not receive naloxone. See also the adult Section 9.4 on sleep-disordered breathing and subsection 9.4.1 Opioids and obstructive sleep apnoea. Of three patients with renal failure who received morphine, two experienced OIVI and one died, with likely contribution of metabolite accumulation (Niesters 2013 **Level IV**, n=27).

Fentanyl-related deaths are described in children unrelated to therapeutic use. Illicitly manufactured fentanyl has caused death in a teenager and two toddlers (related to parental administration) (DeRienz 2018 **Level IV**, n=3). The transdermal patch formulation has resulted in poisonings in young children (mostly in boys with 48% mortality: Stoecker 2016 **Level IV**, n=25) and has been deliberately misused in an adolescent suicide attempt (five 100 mcg/h patches applied) (Lyttle 2012 **CR**). Partial occlusion of fentanyl patches does not reduce the dose received (Nelson 2009 **NR**). Thus the practice of applying an occlusive dressing to the skin surface of a transdermal fentanyl delivery system to limit drug delivery is not supported; some authors have inappropriately suggested this practice (Mitchell 2010 **NR**).

10.4.4.5 | Codeine

Codeine has been used for decades in paediatric acute pain. Multiple factors have led to reduced prescription of this opioid prodrug. These include the publications of codeine-related deaths, increased understanding of the relevant pharmacogenomics (see below), upscheduling (eg in Australia) and removal by the World Health Organisation (WHO) of codeine from its tiered analgesic ladder for treatment of (persistent) pain in children (WHO

2012 **GL**) in response to the blacklabelling by the USA's Food and Drug Administration (FDA) (2012 statement archived: FDA 2013b **GL**) and European Medicines Agency (EMA) (EMA 2013 **GL**). National USA data is available for 1996 to 2013 with opioid use in trauma, dental pain, outpatient procedures, postsurgery and for infections, where codeine comprised 27-40% of prescriptions (Chung 2018a **Level IV**, n=547,726 [codeine]; Livingstone 2017 **Level IV**, n=1.03 million [codeine in 2013]; Groenewald 2016 **Level IV**, n=917,700 [codeine in 2012]). Comparison of USA adenotonsillectomy claim data pre and post FDA investigation assessed children who received opioid prescriptions (Chua 2017b **Level III-3**, n=362,992 [246,459 prescriptions]). In Jan 2010 vs Dec 2015, codeine decreased from 46.8% to 9.1% of prescriptions (while hydrocodone increased from 48.4 to 72.7%). In Dec 2015, off label prescription of codeine occurred for 5.1% of all children and 3% of children with OSA. While still in 2017, codeine made up the majority of community opioid prescriptions in Australia for children <17 y (50.5%: AIHW 2019 **Level IV**) and in New Zealand for <24 y (54.3%: HQSC 2019 **Level IV**).

Pharmacokinetics

PO codeine has a similar time to peak effect but decreased total absorption vs PR and IM delivery (McEwan 2000 **PK**). Administration IV should be avoided as severe hypotension may result (Shanahan 1983 **Level IV**).

Pharmacogenomics and adverse effects

Relevant to codeine as a prodrug, the numerous CYP2D6 enzyme's polymorphisms result in four phenotypes, which demonstrate an overlapping spectrum of activity (Chidambaran 2017b **NR**) (see also Sections 1.7.3 and 4.3.1.2). The phenotypes are variably represented in populations of different ethnicities. The most common (>70% of Caucasians to 92% of Asians) "normal" phenotype, termed extensive metabolisers, has 1–2 x CYP2D6 activity and analgesic effect with codeine. Intermediate metabolisers have reduced (0.5 x CYP2D6 activity) and poor metabolisers no effect (nil CYP2D6 activity) from codeine: affecting 46% of a group of UK children having tonsillectomy (Williams 2002 **Level II PK**, n=96, JS 4) and 49% (intermediate 44% and poor 5.3%) of children with sickle-cell disease (Yee 2013 **Level IV**, n=75); while ultra metabolisers (>2 x activity) attain high peak morphine levels and are at risk of sedation and respiratory depression (Chidambaran 2017b **NR**; Yee 2013 **Level IV**, n=75; Racoosin 2013 **Level IV**, n=7) (case report overlap). Somnolence, lethargy and respiratory depression have been reported with antitussive use of codeine (Paul 2018 **Level IV**, n=98 [38 codeine related]). Several paediatric deaths associated with codeine administration have been reported, some with confirmed ultra and extensive metaboliser phenotype. Subgroups at particular risk included breastfeeding neonates (whose ultra/extensive metaboliser mothers were taking codeine in the puerperium) (Madadi 2007 **CR**), toddlers (Racoosin 2013 **Level IV**, n=7; Kelly 2012 **Level IV**, n=3 [2 deaths]) and obese older children following adenotonsillectomy (Chidambaran 2017b **NR**, case report summary including Friedrichsdorf 2013 **Level IV**, n=3 [obese]).

The USA's FDA has subsequent to 2013 contraindicated against codeine use in all children under 12 y and in adolescents who are obese or having adenotonsillectomy (with a recommendation against use by breastfeeding mothers) (FDA 2017 **GL**). The EMA has extended their 2013 contraindication to also exclude use as an antitussive (EMA 2015 **GL**). Australia's Therapeutic Goods Administration (TGA) applied the same warnings as the FDA in 2017 (TGA 2017 **GL**) and further limited access with upscheduling of combination codeine containing products in 2018 (TGA 2019 **GL**). New Zealand applied the same warnings in children and breastfeeding mothers in mid 2018 (Medsafe 2018 **GL**) and plans scheduling changes in 2020. Several paediatric hospitals have removed codeine from their drug formularies (Tremlett 2013 **NR**).

Efficacy

Codeine efficacy data has been published in a few RCTs prior to 2009. In the majority of studies with a codeine treatment arm (see below), CYP2D6 activity is not accounted for and is a significant confounder contributing to conflicting reports of efficacy for postoperative pain. Early perceived advantages of codeine include less respiratory depression in neonates and reduced nausea and vomiting vs morphine (at one only of four time points) (Williams 2002 **Level II**, n=96, JS 4). These conclusions are probably compromised by low levels of active metabolites and resultant reduced efficacy (Williams 2001 **NR**). Comparison of codeine and morphine for tonsillectomy has shown either no difference (Semple 1999 **Level II**, n=40, JS 4) vs an increased requirement for rescue analgesia following codeine (Williams 2002 **Level II**, n=96, JS 4). Codeine was less effective than ibuprofen for acute musculoskeletal pain in children (Clark 2007 **Level II**, n=336, JS 5). Addition of codeine to paracetamol has been reported to improve analgesia (Pappas 2003 **Level II**, n=120, JS 5) or have no effect (Moir 2000 **Level II**, n=79, JS 5) and was as effective as ibuprofen for fracture pain but ibuprofen-treated patients had fewer adverse effects and better functional outcomes (Drendel 2009 **Level II**, n=336, JS 5). Use of codeine in paediatric neurosurgical case series has been published (Bronco 2014 **Level IV**; Teo 2011 **Level IV**).

10.4.4.6 | Oxycodone

Oxycodone is increasingly used in paediatric acute pain management. USA prescription data for children is available. One tertiary USA centre has documented oxycodone as the most commonly prescribed opioid (72.5%) by mostly surgical services, with decreased annual codeine prescription over 7 y from 377 to only 3 prescriptions (George 2016 **Level IV**, n=34,218). The USA's national community opioid prescription data has not yet reflected this change with only 4.6% and 15.5% being for oxycodone vs the more commonly prescribed codeine and hydrocodone (Chung 2018a **Level IV**, n=62,675 [oxycodone]; Groenewald 2016 **Level IV**, n=314,650 [oxycodone]; see Table 10.8 for data detail). In the USA's adenotonsillectomy claim analysis pre and post FDA investigation, oxycodone prescription increased from 3.8% in 2010 to 17.4% in 2015, outranked by increased hydrocodone (Chua 2017b **Level III-3**, n=362,992 [246,459 prescriptions]). Community prescription of oxycodone for children in 2017 was low in New Zealand at 1.3% of all opioid prescriptions (HQSC 2019 **Level IV**), while in Australia oxycodone was commonly prescribed comprising 36.5% of opioid prescriptions for children (AIHW 2019 **Level IV**).

Pharmacokinetics and pharmacogenomics

In children aged >6 mth, the PK profile of oxycodone is similar to adults and dosing can be based on weight (El-Tahtawy 2006 **PK**). Similar absorption is seen following buccal and SL administration (Kokki 2006 **PK**). PK variability remains large, exacerbated by CYP2D6 polymorphism, as is the case with other opioids (Soderberg Lofdal 2013 **NR**). In expreterm to term neonates and infants, the half-life is prolonged with an inverse relationship to age (reflecting the lower body weight adjusted clearance and higher apparent Vd) and increased variability in kinetics is seen even following IV administration (Valitalo 2017 **PK**, 3 Studies, n=119). The body weight adjusted clearance is lowest and the apparent Vd is highest in preterm babies, which results in elimination half lives typically around 8 h in extremely preterm neonates. The parent compound contributes the majority of drug effect but the impact of polymorphisms and cotherapies that influence CYP2D6 and CYP3A4 enzymes, and thus metabolite (eg oxymorphone, noroxymorphone and noroxycodone) concentration, has been debated (Kokki 2012a **NR**) (see Section 1.7.3). In children, a difference in the plasma concentrations of oxycodone metabolites relating to CYP2D6 genotypes was found, but the clinical significance has not yet been explored (Balyan 2017a **PK**, n=30). See adult Section 1.7.3.4.

Efficacy

Oxycodone's efficacy has been shown in various paediatric settings: PO use of 0.1–0.2 mg/kg in the ED for children with orthopaedic injuries (Charney 2008 **Level II**, n=107, JS 5; Koller 2007 **Level II**, n=66, JS 5), use of a PO controlled-release (CR) preparation as a step-down following PCA in adolescents after spinal fusion (Czarnecki 2004 **Level IV**), IV bolus dose administration for postoperative rescue analgesia (Kokki 2006 **Level IV**) and IV PCA in adolescents and adults (Silvasti 1999 **Level II**, n=52, JS 4). Oxycodone CR (OxyContin®) has been approved in the USA for use in children >11 y who are 'opioid-tolerant' defined as minimum 5 d prior oxycodone therapy of >20 mg/d (Product information: FDA 2018b), but use is off-label elsewhere. There has been no study reporting paediatric use of the CR oxycodone/naloxone combination (eg Targin®) to date.

Adverse effects

Like for the other commonly used opioids, large scale data on mild to moderate adverse effects is not available for oxycodone specifically. USA data following outpatient opioid prescription and subsequent ED presentation with an adverse event likely related to the prescribed opioid is summarised in Table 10.8 below. See also 10.4.5 Issues with discharge opioid prescriptions for children.

Literature search reveals no data specific to oxycodone and QT prolongation in children, however this is different for adults. See adult Section 4.3.1.5 Adverse effects of opioids where the issue of cardiac effects of opioids and also nausea and vomiting and QT prolongation related to antiemetics is discussed.

Table 10.8 | Opioid prescription data (USA) for children and adolescents including subtypes of opioids and adverse events

Author Year	**Groenewald 2016**	**Chua 2017b**	**George 2016**	**Chung 2019**	**Chung 2018a**
Data type	**National**	**National**	**One hospital**	**One state[#]**	**National**
Prescriptions, n	2,030,000 in 2012	246,459	34,218	529,731 prescriptions for 201,940 adolescents	1,362,503
Years	1996-2012	2010-2015	2007-2014	1999-2011	1999-2014
Prescribed opioids* (%)					
Hydrocodone	42.1	72.7	2	59	42.1
Codeine	39.9	9.1	7.3	27	40.2
Oxycodone	15.5	17.4	73	8.6	4.6
Hydromorphone	NS	--	3.7	NS	NS
Morphine	NS	NS	1.1	NS	NS
Tramadol	NS	--	NS	5.5	2.9
Other	--	0.8	--	--	5.2 (meperidine)
Adverse events related to opioids, n (per prescription)			25 (7/1 million)	275 (5/1 million)	437 (3/1 million)

Author Year	Groenewald 2016	Chua 2017b	George 2016	Chung 2019	Chung 2018a
Adverse event subtype n (%)					
Death			NS	1 (0.36%)	3 (0.7%)
Resp. depression				10 (3.3%)	12 (2.8%)
CNS depression				71 (25.8%)	97 (22.2%)
Neuro-psychiatric				83 (30.2%)	83 (30.2%)
Gastrointestinal				57 (20.7%)	134 (30.7%)
Dermatological				51 (18.5%)	102 (23.3%)
Allergic				35 (12.7%)	77 (17.6%)
Other				4 (1.5%)	15 (3.4%)
Prescriber error			25 total 16 patients with weight entry error: 14 with <10% error; two with >15% error -one under and one over		

 # Tennessee **(alone or as combined products)* *NS= not specified* *Resp.=respiratory*

Other conventional opioids

A large number of opioid preparations have been used in children (see below), but availability varies by country and many have not been investigated in controlled trials. For additional details see (APAGBI 2012 **GL**).

10.4.4.7 | Hydromorphone

Hydromorphone has no advantage over other opioids in terms of analgesic efficacy or adverse-effect profile, administered by PO, IV, caudal or epidural route (Quigley 2002 **Level I** [Cochrane], 4 RCTs [paediatric], n=122). Oral hydromorphone prescriptions were uncommonly dispensed from a single USA paediatric institution over 8 years (George 2016 **Level IV**, n=1,266 prescriptions). IV Hydromorphone has been used in the PICU setting usually as second or third line opioid therapy for analgesia and sedation for malignancy and following trauma with a median dose 10 mcg/kg/h (Reiter 2012 **Level IV**). IN Hydromorphone was titrated in children presenting to the ED with various painful conditions (such as fracture or abdominal pain); 30–60 mcg/kg over 30 min total achieved ≥3/10 pain reduction (Tsze 2019b **Level IV**, n=35).

See Section 10.6.3.3 and 10.6.6 for neuraxial use and Section 10.8.1 and 10.8.3 for use in paediatric cancer.

10.4.4.8 | Hydrocodone

Hydrocodone is not available for analgesic use in Australia or New Zealand. In other countries, it is generally used in combination with paracetamol (Sutters 2010 **Level II**, n=123, JS 3; Rees 2019 **Level IV**, n=1,246). In the USA in 2014, hydrocodone (combination product with paracetamol) was upscheduled. As documented in Table 10.8, it has been the most commonly prescribed opioid for children in the USA over a 16 year period, with no evidence base.

Oral clearance is higher in children (weight adjusted) vs adults; weight-based dosing in children thus leads to reduced exposure which is overcome if body surface area adjusted dosing is used for children aged 6–17 y (Liu 2015 **PK**, n=17). Hydrocodone is metabolised by CYP2D6 to

hydromorphone and CYP3A4 to norhydrocodone. Inhibition of these enzymes by coadministered antibiotics and anticonvulsants resulted in a child's death where hydrocodone was being used for antitussive effect (Madadi 2010 **CR**). Three further fatalities have been reported in children <12 y associated with antitussive use of hydrocodone combined with antihistamine and a further 57 patients had respiratory depression, somnolence and/or lethargy (Paul 2018 **Level IV**, n=98). The FDA has limited hydrocodone (along with codeine) containing cough and cold products to adults ≥18 y (FDA 2018a **GL**).

10.4.4.9 | Methadone

Methadone is used in children for persistent pain, for opioid weaning (Dervan 2017 **Level IV SR** [PRISMA], 12 studies, n=459; Johnson 2012 **Level IV**, n=96) and as part of a multimodal approach to complex surgeries. In adolescent posterior spinal fusion patients receiving intraoperative remifentanil infusion up to 0.3 mcg/kg/min, the addition of IV methadone 0.1 mg/kg reduced intraoperative hydromorphone administration with resultant lower overall 0–24 h requirement of 0.26 ± 0.10 mg/kg vs magnesium (50 mg/kg bolus then intraoperative infusion 10 mg/kg/h) 0.38 ± 0.10 mg/kg vs remifentanil alone 0.34 ± 0.11 mg/kg, with no difference in pain scores (Martin 2018 **Level II**, n=60, JS 4). Methadone has also been used for the Nuss procedure (Singhal 2016 **Level III-2**, n=125) and as a third line intervention for acute neuropathic pain in children post limb salvage surgery (Anghelescu 2011a **Level IV**, n=6/150). The more extensive published use in children is in oncology and palliative care (Habashy 2018 **NR**; Mott 2018 **Level IV**, n=16) and in neonatal abstinence syndrome.

There is limited PK information in children, but the available data show similar parameters in neonates, infants and children to adults (Ward 2014 **PK**). The conversion to methadone from other opioids is complex and dependent on recent opioid exposure. Patients with higher opioid exposure require relatively lower methadone conversion ratios (Mott 2018 **Level IV**, n=16).

In children receiving methadone for cancer pain, some QT prolongation was seen in patients taking a median dose of 0.37 mg/kg/day (most of whom were on other QT prolonging agents), but there have been no published reports of severe dysrhythmias in children receiving methadone for pain (Habashy 2018 **NR**).

See adult sections 4.3.1.2 Methadone and 4.3.1.5 Cardiac effects of opioids for discussion of QT prolongation.

10.4.4.10 | Sufentanil, Alfentanil and Remifentanil

Sufentanil

Sufentanil PKs have been assessed after IV use, and clearance maturation is the same as for other drugs metabolised by CYP3A4 eg fentanyl (Ziesenitz 2018 **Level IV SR PK**, 8 studies [sufentanil], n=129). After IN sufentanil 2 mcg/kg, maximum concentration (Cmax) occurred at 15-30 min with syringe dropper technique (Ziesenitz 2018 **Level IV SR PK**, 1 study [IN sufentanil]: Haynes 1993 **PK**, n=15).

IN sufentanil 0.5 mcg/kg combined with IN ketamine via actuating device spray was effective for various procedures (n=50) with respective bioavailabilities of 25 and 36% and a Cmax at 13.8 min (Nielsen 2014 **Level IV**). IV sufentanil infusion was used to manage post-thoracotomy pain in intubated preterm neonates at 0.1–0.2 mcg/kg/h initially and subsequently reduced to 0.03–0.04 mcg/kg/h, with no difference in time to extubation (Soreze 2017 **Level III-3**, n=109).

Epidural sufentanil use alone and with local anaesthetic is described in Section 10.6.3.

There is no current data on SL sufentanil use in children.

Alfentanil

Alfentanil PKs have been reviewed (Ziesenitz 2018 **Level IV SR PK**, 15 studies [alfentanil], n=244). Use of IN alfentanil 10 mcg/kg (in low volume solution 0.2 mL) is described in the ED for analgesic management of mostly orthopaedic injuries (Brenchley 2006 **Level IV**, n=36). Only intraoperative and not postoperative use of alfentanil in children has been described. Caudal epidural administration with local anaesthetic is described in Section 10.6.3.

Remifentanil

Remifentanil PKs have been reviewed (Ziesenitz 2018 **Level IV SR PK**, 7 studies [remifentanil], n=118). Mostly intraoperative use of remifentanil in children has been described. Extension of use into PACU has been reported for modification of emergence agitation (and is not presented here). Use in neonates having non cardiac surgery and while in NICU to facilitate endotracheal tube tolerance and sedation has been described (Kamata 2016 **NR;** Allegaert 2016 **NR**), as well as in PICU for sedation without documenting pain scores (Hungerford 2019 **Level IV**, n=38).

See Sections 10.7.2.2 for use in procedural intervention in children with cancer and 10.7.2.9 for use of remifentanil in combination with propofol for procedural intervention in burns.

See Section 10.4.7 and adult Sections 4.6.1.1 and 4.6.1.3 for data on the adjuvant use of ketamine and magnesium to reduce remifentanil induced tolerance.

10.4.4.11 | Diamorphine (diacetylmorphine, heroin)

This opioid is not available for analgesic use in Australia and New Zealand. In the UK, it is used IN in paediatric EDs (by 118 of 205 surveyed paediatric EDs) (Hadley 2010 **Level IV**) for trauma pain management eg alone post fracture (Kendall 2001 **Level II**, n=404, JS 3; Kidd 2009 **Level III-2**; Regan 2013 **Level III-3**; Kendall 2015 **Level IV**, n=226) or for fracture reduction with N_2O (Kurien 2016 **Level IV**, n=100), and for sickle cell crises (Telfer 2009 **Level IV**) (see Section 8.6.4.1). The bioavailability following IN drop installation is 33%, with T_{max} of 10 min (Kidd 2009 **Level III-2**).

Atypical opioids: Tramadol, Buprenorphine and Tapentadol

10.4.4.12 | Tramadol

Tramadol, first launched as an opioid, is now recognised as an atypical opioid with its multimodal antinociceptive and antineuropathic effects. Its two enantiomers act via noradrenaline and serotonin reuptake inhibition and mu-receptor agonistic effect, where for the latter the metabolite O-desmethyl-tramadol (or M1) has greater efficacy than the parent compound (Anderson 2017b **NR**). Evidence for tramadol use in paediatric acute pain is still limited by studies of small sample size and difficulty determining comparative analgesic doses. With the 2012 FDA black box warning for young children and tonsillectomy, codeine prescription has decreased post-tonsillectomy (Van Cleve 2017 **Level IV,** n=230 [477 tonsillectomies]). Meanwhile from 2012 to 2015, tramadol use has increased in the USA by 23% from 170 to 209 per 1,000 population (Bigal 2019 **Level IV**, n=18.8 million [12 to 64 y olds]); but it is not known how many prescriptions are paediatric or post-tonsillectomy. Interestingly codeine prescription over the same period, after an initial decrease, has also increased. Subsequent to codeine's relabeling, the FDA has applied the same warning against tramadol use in paediatric acute pain (FDA 2017 **GL**). Frequent off label use occurs in young children with variable paediatric licensing internationally: over 1–3 y in Europe (country-dependent) (Rodieux 2018 **NR**) vs ≥12 y previously in Australia (with June 2019 revised Consumer medicine information leaflets for the oral capsule stating 'should not be used in children') (NPS Medicinewise 2019a **GL**) with New Zealand changing its licensing from ≥2 y

(Medsafe 2017 **GL**) to follow the USA FDA with contraindication <12 y and <18 y following tonsillectomy/adenoidectomy (Medsafe 2020 **GL**).

Pharmacokinetics and pharmacogenomics

Oral bioavailability is 68–75% post single dose in adults (See section 4.3.1.3) and is likely similar in children. Due to extensive first-pass hepatic metabolism and higher hepatic blood flow in children and infants, plasma concentrations are lower (Vandenbossche 2015 **PK**; Allegaert 2011b **PK**). Rectal bioavailability is good with low interindividual variability (Zwaveling 2004 **PK**, n=12 in Bozkurt 2005). Maximum plasma concentrations post IV, PO and PR dosing are achieved between 0.3–2.4 h (Bozkurt 2005 **Level III-3 SR PK**, 3 studies, n=164), with peaks post PO at 1–2 h for tramadol and 3 h for M1 (Vandenbossche 2015 **PK**, 3 studies, n=97). Analgesic efficacy is associated with a plasma concentration of tramadol of 100 ng/mL in adults and children and M1 of 15 ng/mL (Garrido 2006 **PK**).

Tramadol is transported to the liver via the organic cation transporter-1 (OCT1). Reduced OCT-1 function resulted in lower tramadol requirements in adults (Stamer 2016 **PK**, n=205). It is metabolised primarily to M1 by the hepatic enzyme CYP2D6 (Anderson 2017b **NR**) (see also Sections 1.7.3 and 4.3.1.3). CYP2D6 activity matures with age increasing rapidly from 25 wk postmenstrual age to 50% of the adult value by 44 wk postmenstrual age and to 90% by 1 y of age (Allegaert 2011b **PK**). M1 is primarily inactivated via glucuronidation, most extensively by UGT2B7 and UGT1A8 (with the glucuronide forms then renally excreted) (Lehtonen 2010 **BS**). The relevance of the UGT enzymes is now being explored. In addition to this, M1 is eliminated renally but preterm neonates, because of their reduced renal function, have relatively higher plasma M1 concentrations (Allegaert 2008 **PK**). While, infant size and postmenstrual age constitute the greater contribution (53%) to inter-individual variability in tramadol and M1 metabolism and clearance, significantly more so than CYP2D6 activity score in the very young (Allegaert 2008 **PK**). In older children, tramadol clearance is linked to weight (Bressolle 2009 **PK**). OCT1 expression and function is highly genetically variable and may be a further consideration, alongside CYP2D6 phenotype, in at risk groups (Tzvetkov 2017 **NR BS**) (see also Section 10.4.4.5).

The poor, normal, extensive or ultra metaboliser CYP2D6 phenotype has been the reason for codeine's black box warning, but the clinical significance in terms of tramadol/M1's analgesic efficacy and adverse effect profile is still unknown.

Dose and efficacy

Systemic administration

In children IV dosing is the same as in adults (1–2 mg/kg every 6 h), with an initial IV dose 2 mg/kg recommended, followed by IV infusion rates of 0.25–0.41 mg/kg/h (6–10 mg/kg/24 h) (Allegaert 2011b **PK**; Bressolle 2009 **PK**). Lower infusion rates have been reported (Alencar 2012 **Level II**, n=160, JS 5; Moyao-Garcia 2009 **Level II**, n=24, JS 5).

A meta-analysis has graded the existing heterogeneous RCTs as low in quality with methodological problems (Schnabel 2015 **Level I** [Cochrane], 20 RCTs, n=1,170). It finds single doses of IV tramadol 0.5–3 mg/kg for postoperative pain relief in children is superior to placebo reducing the number of patients in moderate to severe pain (2 RCTs, n=94), need for rescue analgesia in PACU (RR 0.4; 95%CI 0.2 to 0.8) (5 RCTs, n=189), with similar efficacy in terms of rescue use (0–24 h) to morphine (3 RCTs, n=127), fentanyl (1 RCT, n=42), pethidine 1 mg/kg (2 RCTs, n=120) and nalbuphine (2 RCTs , n=110).

For tonsillectomy, PO tramadol 2.5 mg/kg was more effective than low-dose PR paracetamol (Pendeville 2000 **Level II**, n=50, JS 5), IV 1 mg/kg had similar efficacy to IV paracetamol 15 mg/kg (Uysal 2011 **Level II,** n=64, JS 5), IV 1–2 mg/kg had similar efficacy to IV morphine 0.1 mg/kg (Engelhardt 2003 **Level II**, n=60, JS 5) as did PCA IV tramadol bolus of 0.2mg/kg vs 0.02 mg/kg morphine for 24 h postoperatively (Ozalevli 2005 **Level III-1**). Conversely IV 1 mg/kg was less effective than IV pethidine

1 mg/kg (Ozer 2003 **Level II**, n=50, JS 3), PO dextromethorphan 1 mg/kg (Ali 2008 **Level II**, n=90, JS 1), ketoprofen (IV initial bolus 2 mg/kg and 6 h infusion of same dose) (Antila 2006 **Level II**, n=45, JS 4) and ropivacaine infiltration, while being similarly effective to placebo (Cocelli 2012 **Level II**, n=90, JS 3) (all 4 RCTs in Schnabel 2015 **Level I** [Cochrane]). Multidosing post tonsillectomy in 4–15 y olds for 5–10 d of PO tramadol 1.05 mg/kg (max 52.5 mg) alone 6 hly provided comparable analgesia to combination paracetamol 7.2 mg/kg with codeine 0.72 mg/kg (max 36 mg) (Friedrichsdorf 2015b **Level II**, n=84, JS 2). More paracetamol-codeine treated patients were sedated only on POD 1 (21 vs 3%), while the tramadol-treated experienced more itch in the 10 d (33 vs 13%).

Post abdominal surgery, IV tramadol 2 mg/kg was similarly effective to IV pethidine 1 mg/kg (Ekemen 2008 **Level II**, n=110, JS 3). In postoperative ventilated neonates, multidosing of IV tramadol 2 mg/kg 6 hly vs placebo in addition to IV paracetamol and morphine infusion did not offer clinical benefit in pain scores, morphine requirements or time to extubation (Olischar 2014 **Level II**, n=71, JS 5). In ventilated neonates following major abdominal and minor surgery, IV tramadol infusion (0.1–0.2 mg/kg/h) was similar to fentanyl infusion (1–2 mcg/kg/h) in terms of pain scores over 72 h, time to extubation and to full enteral feeding (Alencar 2012 **Level II**, n=160, JS 5). In children having various surgery types, IV tramadol infusion 0.12 mg/kg/h for 72 h was trialled against nalbuphine infusion (Schnabel 2015 **Level I** [Cochrane], 1 RCT [nalbuphine]: Moyao-Garcia 2009 **Level II**, n=24, JS 5).

For further data on IV tramadol administration to children: see Section 10.5.2 for PCA and 10.5.3 for NCA.

Sublingual administration

SL tramadol 2 mg/kg use in paediatric fracture pain was effective and comparable to SL ketorolac 0.5 mg/kg at 100 min (Neri 2013 **Level II**, n=131, JS 5), but PK data to support this route is not available.

Neuraxial administration

After neuraxial administration, efficacy has generally not been compared to systemic administration; the safety of this route remains uncertain (Walker 2012c **NR**; Engelman 2012 **Level I** [PRISMA], 9 RCTs [tramadol], n=258). Caudal tramadol 1–2 mg/kg added to caudal local anaesthetic prolongs the time to first rescue analgesic (4.5 h; 95%CI 2.8 to 6.1) at the expense of increased vomiting (OR 2.5; 95%CI 1.3 to 4.6), with no IV comparator.

For inguinoscrotal surgery, caudal tramadol 2 mg/kg added to bupivacaine and levobupivacaine was similarly effective (Sezen 2014 **Level II**, n=68, JS 5). Post abdominal surgery, epidural tramadol 2 mg/kg added to epidural ropivacaine 0.2% was superior to ropivacaine alone, with lower pain scores, reduced rescue requirement and longer time to first analgesic request (14.5 h vs 5) (Inanoglu 2010 **Level II**, n=44, JS 5). For lower abdominal, urological and lower extremity surgery in young children, caudal tramadol 1 mg/kg added to caudal bupivacaine 0.25% 1 mL/kg increased time to first analgesia vs local anaesthetic alone (7.8 h vs 4) (Regmi 2017 **Level II**, n=60, JS 5). As a sole agent for urological surgery (without a systemic arm or epidural local anaesthetic comparator), epidural tramadol 2 mg/kg vs morphine 0.1 mg/kg had similar pain scores and time to first rescue analgesic, but with reduced adverse effects (Demiraran 2005 **Level II**, n=80, JS 3) (see also Section 10.6.3.1 and 10.6.3.3).

Infiltration and topical administration

Whether tramadol has clinically useful local anaesthetic effects has been debated. Peritonsillar infiltration of tramadol 2 mg/kg has been studied in several small RCTs and was effective for control of early (0–8 h) postoperative pain following adenotonsillectomy. Its benefits were similar to lidocaine (Heiba 2012 **Level II**, n=60, JS 4), similar (Ugur 2013 **Level II**, n=75, JS 5) and superior to ketamine infiltration (Ayatollahi 2012 **Level II**, n=126, JS 4), superior to placebo (Atef 2008 **Level II**,

n=40, JS 5) and, when combined with IV ketamine, superior to either agent alone and placebo (Honarmand 2013 **Level II**, n=75, JS 5). Only one small systemic comparator trial is available, which found infiltration of tramadol 2 mg/kg to be superior to IM administration and placebo (Ugur 2008 **Level II**, n=45, JS 5).

For inguinal herniorrhaphy in young children, preincisional infiltration of tramadol 2 mg/kg was as effective as bupivacaine 0.25% with regard to pain scores and time to first analgesic use (Numanoglu 2014 **Level II**, n=52, JS 4). While infiltration post hernia repair of SC tramadol 2 mg/kg resulted in higher initial pain scores but similar time to first rescue analgesic request vs bupivacaine infiltration, with both having a longer effect than IM tramadol (6.7 h vs 6 vs 4.5) (Demiraran 2006 **Level II**, n=75, JS 5).

For awake circumcision, ring block combined with pudendal nerve block with tramadol 5%/adrenaline was effective and superior to prilocaine/adrenaline with reduced rescue requirements (Kargi 2010 **Level II**, n=40, JS 4), but was ineffective vs lidocaine/adrenaline (Polat 2013 **Level II**, n=47, JS 4).

A small tonsillectomy study showed no benefit on POD 0 following single topical application of tramadol 5%, but pain scores were reduced on POD 6 (Akbay 2010 **Level II**, n=40, JS 5). Tonsillar application of tramadol 40 mg/ketamine 20 mg was superior to placebo, with similar pain scores and rescue analgesic requirements on POD 0 (Tekelioglu 2013 **Level II**, n=60, JS 5).

Adverse effects

Tramadol has similar or reduced rates of nausea and vomiting (10–40%), sedation and fatigue to those found with conventional opioid use, generally with lower rates of constipation and pruritus (Bozkurt 2005 **Level III-3 SR**, 20 studies, n unspecified). Following a large tramadol overdose with plasma level >1 mg/mL, a seizure and cardiogenic shock have been reported in a child; cardiac function normalised within 48 h (Perdreau 2015 **CR**). Anaphylaxis (Mori 2015 **CR**) and deaths have been reported (see below).

Nausea and vomiting

In mixed surgery types, PONV is not reduced in tramadol vs placebo recipients in PACU (RR 0.84; 95%CI 0.28 to 2.52) (3 RCTs, n=215) or to 24 h (RR 0.78; 95%CI 0.54 to 1.12) (4 RCTs, n=150) (Schnabel 2015 **Level I** [Cochrane], 20 RCTs, n=1,170). In accidental and intentional overdose, nausea and vomiting rates were 16 to 25% (Stassinos 2019 **Level IV** n=1,115; Hassanian-Moghaddam 2015 **Level IV**, n=20; Tsutaoka 2015 **Level IV**, n=3,051 [tramadol exposures in children under 19y]; Marquardt 2005 **Level IV**, n=190).

Sedation and ventilatory impairment

Lower sedation rates with tramadol vs conventional opioids have been described (Schnabel 2015 **Level I** [Cochrane], 7 RCTs, n=526); the heterogeneity of the included RCTs documenting sedation scores did not permit subanalysis. Drowsiness is common post overdose with rates in adults of 27% (Marquardt 2005 **Level IV**, n=190) and 55–100% in children (mean dose of 13.1 mg/kg) (Stassinos 2019 **Level IV**, n=1,115 [symptomatic children] of 7,334 exposures; Tanne 2016 **Level IV**, n=7; Hassanian-Moghaddam 2015 **Level IV**, n=20; Marquardt 2005 **Level IV**, n=8 [<5 y]) and may or may not be associated with miosis.

In the Cochrane review, no tramadol-treated child had ventilatory impairment, but sample sizes were small. Subanalysis of tramadol vs placebo (3RCTs, n=165) and multiple opioid comparator arms (8 RCTs, n=532) revealed non-estimable or minimal effect sizes (Schnabel 2015 **Level I** [Cochrane], 20 RCTs, n=1,170). In an RCT included in the Cochrane involving tonsillectomy in children with OSA, fewer desaturation events were reported with tramadol 2 mg/kg than with morphine 0.1 mg/kg, significant only between 1–2 h postoperatively (Schnabel 2015 **Level I** [Cochrane], 1 RCT: Hullett 2006 **Level II**, n=66, JS 4). Three ex-premature infants given tramadol

2 mg/kg (with local anaesthetic drops: for outpatient eye examination) experienced prolonged sedation, returned and were admitted (Bilgili 2012 **Level IV**, n=20). One experienced frequent apnoea required continuous positive airway pressure (CPAP) and transfusion, one required supplemental oxygen and one was observed only.

Following mostly supratherapeutic doses or accidental/intentional overdose, ventilatory impairment is reported in both adults (following a high mean dose of 2,125 mg, range 200-4,600) (Hassanian-Moghaddam 2013 **Level IV**, n=19 [1 death] in 114 hospital presentations post-tramadol) (see Section 4.3.1.3) and children (following high doses of ≥7–10 mg/kg) (Stassinos 2019 **Level IV**, n=37 [36 ventilatory impairment, 1 death]; Moulis 2018 **Level IV**, n=5 [4 life threatening, 1 death]; Rodieux 2018 **Level IV**, n=18 [15 ventilatory impairment, 3 deaths] and a further 14 deaths [tramadol implicated but not as sole agent]; Tanne 2016 **Level IV**, n=7 [6 ventilatory impairment, 1 death]; Hassanian-Moghaddam 2015 **Level IV**, n=3 [ventilatory impairment]). The FDA investigation identified nine cases of ventilatory impairment following tramadol over 1969–2016 (overlapping with the above series; including three deaths of children under 6 y) (FDA 2017 **GL**). This is in the context of a single year's USA dispensing data for 167,000 prescriptions for children (<18 y) for 2014.

In the event of excess sedation or ventilatory impairment, naloxone has been used as a reversal agent (Tanne 2016 **Level IV**, n=3/7; Hassanian-Moghaddam 2015 **Level IV**, n=16/19 [apnoeic patients]; Tsutaoka 2015 **Level IV**, n=540 [naloxone use age unspecified]; Hassanian-Moghaddam 2013 **Level IV**, n=3/19 [apnoeic adult patients]; Marquardt 2005, **Level IV** n=2/51 young children; Grosek 2009 **CR**).

Seizures

Lowering of the seizure threshold and seizures are reported in adults (46.1% of adult presentations: Tsutaoka 2015 **Level IV**, n=5,491 [tramadol exposures >19 y]; Hassanian-Moghaddam 2013 **Level IV**, n=525; see also Section 4.3.1.3) and children with therapeutic and supratherapeutic dosing (Li 2012b **Level IV**, n=2) vs overdose >4.8 mg/kg with variable incidences of: nil (Hassanian-Moghaddam 2015 **Level IV**, n=20), 2.2% (Stassinos 2019 **Level IV**, n=24/1,115), 13.7 % (Marquardt 2005 **Level IV**, n=26/190; but 0/51 under 5y), 20% (Moulis 2018 **Level IV**, n=1/5 seizures), 71% (Tanne 2016 **Level IV**, n=7) and case series (Tsutaoka 2015 **Level IV**, n=3,051 [tramadol exposures <19 y; higher RR vs tapentadol]; Mazor 2008 **Level IV**, n=2), including in association with hypoglycaemia (Aliyu 2016 **CR**). In one report, naloxone administration is suggested to have terminated a recurrent seizure in a single toddler with tramadol overdose (Tanne 2016 **Level IV**, n=7).

Agitation and serotonin syndrome

Agitation occurs with therapeutic dosing and in adult and paediatric overdose in 0.7–14% of patients (Stassinos 2019 **Level IV**, n=51/7,334; Moulis 2018 **Level IV**, n=1/7; Marquardt 2005 **Level IV**, n=1/8 [children]). Drug-drug interactions are an important consideration. In adults, serotonin syndrome has been reported; it occurs more frequently with SSRIs sometimes in combination with tramadol. It has occurred with tramadol in isolation and has been reported in an infant following 28 mg/kg ingestion, but not older children (Marechal 2011 **CR**).

Fetal, neonatal and infant exposure with maternal use

Neonatal abstinence syndrome is described after chronic (maternal) exposure (Hartenstein 2010 **CR**; Willaschek 2009 **CR**). Infant exposure through breastmilk has been a literature focus subsequent to the FDA adding warning against tramadol by breastfeeding mothers (FDA 2017 **GL**). Exposure of infants was very low relative to maternal exposure and well below therapeutic dosing used in this age group (LactMed Database 2019 **NR**; Palmer 2018 **NR**).

Formulation issues and adverse outcome

A concentrated drop formulation (100 mg/mL) is available in many countries, licensed for adult palliative care (eg in Australia) but also in children (eg in France). Dosing error confusing the

number of drops with the number of mL is a concern in paediatrics (10 drops=25 mg=0.25 mL). Two children dosed at home with the concentrated oral tramadol drops post adenotonsillectomy had adverse outcomes. One aged 5 y with ultrarapid genotype experienced significant respiratory depression (Orliaguet 2015 **CR**). The single urine sample of M1 reported for this case was not accompanied by plasma concentrations of tramadol or M1. Thus, the accuracy of the stated single analgesic dose administered cannot be determined and dosing confusion was likely. The second child aged 2 y died due to tramadol toxicity with concentrated oral drops treatment. The TGA subsequently does not support the use of this concentrated oral formulation in children aged <12 y (TGA 2015 **GL**). New Zealand (NZ)'s Medicines and Medical Devices Safety Authority (Medsafe) has delisted the concentrated formulation (for all ages) and compounding pharmacists in NZ make a 10 mg/mL formulation (Medsafe 2017 **GL**; Pharmac 2016 **GL**). An Australian centre has described dispersing 50 mg in 5 mL (10 mg/mL) for administration to smaller children (Kluger 2016 **Level IV**, n=20 [dose preparations]). In France, following a further death with the concentrated formulation of a 3 y old boy of normal CYP2D6 metaboliser phenotype, the formulation has been retained with a revised dosing leaflet instruction (Moulis 2018 **CR**).

Impact of the FDA announcement for tramadol

Particularly following the FDA's contraindications for use of codeine and tramadol (in children and warning against use in breastfeeding mothers), further data is required to determine the role, optimum dose and safety of tramadol in children and the monitoring level required. Inadvertent overdose and formulation issues are likely of greater risk than CYP phenotypes resulting in variable drug metabolism; evidence for harm from this second mechanism is lacking (Anderson 2017b **NR**). Restriction of use of an effective analgesic and replacement with full agonist conventional opioids presents a similar or greater hazard in the at-risk population with SDB/OSA and post adenotonsillectomy.

10.4.4.13 | Tapentadol

Tapentadol is available in tablet IR and ER forms in Australia, but as of 2020 not in New Zealand. Both formulations are only indicated for adult use: IR for acute pain and ER for chronic pain. Evidence for tapentadol use in acute paediatric pain is limited in terms of number of studies and their sample size. There is drug company sponsored data for use of an oral solution in children postoperatively (studied for regulatory application in Europe: see below). See also Section 4.3.1.3 for summary of tapentadol in adults.

Pharmacokinetics and efficacy

Non-obese children received tapentadol 1 mg/kg oral solution postoperatively following dental or adenotonsillectomy (aged 2–18 y: Muse 2019 **Level IV PK**, n=66) and mixed surgery types (aged 6–18 y Finkel 2019 **Level IV PK**, n=44). Plasma concentrations of tapentadol were similar to adult data (following 50–100 mg) peaking at 1–1.5h (while the non-active metabolite tapentadol-O-glucuronide concentrations were lower or the same) (Muse 2019 **Level IV PK**). Pain scores decreased over 15 to 120 min post-dose in 2–18 y olds using developmentally-appropriate pain scales (Muse 2019 **Level IV**). Median times to rescue analgesia intake were 5 h (Finkel 2019 **Level IV**) and 6.3 h (Muse 2019 **Level IV**).

Adverse effects

Adverse events in the above studies included PON, POV, dizziness and headache (without placebo comparator nor provision of anaesthetic details including antiemetic prophylaxis).

USA toxicity data is available for single agent (mostly accidental) ingestion by children where 61% were aged ≤2 y (Borys 2015 **Level IV**, n=104). Most had no (59.6%) or minor (32.7%) ill effect;

5.8% had moderate and 2% major effects. Most common was drowsiness (29%), with other neurocognitive effects (in 6%) and nausea/vomiting, tachycardia and dizziness (each in 2 to 4%). The two patients with major effects were an infant who experienced coma with respiratory depression requiring naloxone (and was discharged) and a toddler with drowsiness and dyspnoea requiring oxygen and critical care monitoring. There were no deaths. No detail of formulation, dose or mg/kg was provided.

A further USA study analysed single agent exposures of tapentadol (n=217) vs tramadol (n=8,566) (Tsutaoka 2015 **Level IV**). The analysis included 31 tapentadol vs 1,785 tramadol accidental ingestions by children <6 y vs 9 and 1,266 accidental and intentional ingestions in older children (6–19 y). The children <6 y had greater risk of severe outcome from tapentadol exposure vs tramadol (formulation/ dose detail not provided). Neurological sequelae occurred in both groups: the tapentadol vs tramadol exposed more commonly experienced hallucinations, coma (RR 4.2; 95% CI 2.3-7.4), drowsiness, slurred speech, confusion and respiratory depression (RR 5.6; 95% CI 3.5 to 8.8), and use of naloxone (RR 3.8; 95% CI 3.0-4.9). Tramadol exposed more commonly experienced seizures (RR 7.9; 95% CI 3.0 to 21) and vomiting (RR 2.0; 95% CI 1.1 to 3.6). A cohort study assessing trends in selfpoisoning in children aged 5–19 y reported no adverse events related to tapentadol (2006–2016: Cairns 2019 **Level IV**, n=33,501).

See adult Section 4.3.1.3 for post-marketing surveillance ADR data, reports of serotonergic syndrome and mortality where tapentadol has been implicated (rarely as a single agent).

Potential for abuse

Intentional ingestions have been reported by adolescents (3 abuse, 3 suicide attempts and 2 other: Borys 2015 **Level IV**, n=104 [8 intentional]). There is no further data on abuse potential of tapentadol in adolescents. Reported nonmedical use in USA college students was low in comparison to conventional opioids and has decreased post initial launch (Dart 2014 **Level IV**); diversion rates and black market cost are low (Dart 2016 **Level IV**).

10.4.4.14 | Buprenorphine

Buprenorphine is used off-label in children for the treatment of acute pain including in cancer pain, palliative care (Vicencio-Rosas 2018 **NR**; Michel 2011 **Level IV SR**, 8 studies & 3 RCTs, n=274), opioid misuse disorders in teenagers (Borodovsky 2018 **NR**) and neonatal abstinence syndrome (NAS) (Kraft 2018 **NR**), with low level evidence support.

Pharmacokinetics and pharmacodynamics

With IV bolus 3 mcg/kg and infusion of 0.72 mcg/kg/hr, ex-preterm neonates have reduced clearance consistent with their immature CYP450 and glucuronidation (*UGTB27*) pathways and a prolonged half-life of 20–26 h. Following a single IV 3 mcg/kg dose, allometric scaling suggested clearance is higher in children (Michel 2011 **Level IV SR**, 8 studies & 3 RCTs, n=274). Combined PK-pharmacodynamic study is required to explore a possible paradoxical prolongation of effect.

See adult Sections 4.3.1.3 and 5.4.1.2, 5.5.2.2 and 5.5.3.1 for discussion of buprenorphine's PKs and PDs in adults (Butler 2013 **NR**).

A liquid formulation has been made for SL administration for NAS (Anagnostis 2011).

Efficacy

Buprenorphine via various routes (IV, SL, caudal usually 2.5–5 mcg/kg and transdermal [TD]) has been used in a few small studies of children having thoracotomy, orthopaedic, abdominal, hernia and genitourinary surgery (Michel 2011 **Level IV SR**, 8 studies & 3 RCTs, n=274):

Following inguinal herniorrhaphy or orchidopexy surgery,

- Caudal and IV buprenorphine 2.5 mcg/kg was added to and compared with caudal bupivacaine 0.5% 1 mL/kg alone with no difference in pain outcomes. The RCT ceased

recruitment with higher vomiting in both buprenorphine arms (80% caudal vs 50% IV vs 20% caudal bupivacaine alone) (Khan 2002 **Level II**, n=30, JS 5);
- Caudal buprenorphine 4 mcg/kg vs caudal bupivacaine 0.25% 0.5 mL/kg was equieffective on a 3 point Lickert scale, with longer duration following buprenorphine (Girotra 1990 **Level III-1**, n=40);
- Caudal buprenorphine 4 mcg/kg vs caudal morphine 50 mcg/kg was equieffective with longer duration (Girotra 1993b **Level II**, n=65, JS 5).

In orthopaedic surgery,
- IV buprenorphine 3 mcg/kg vs IV morphine 100 mcg/kg was transitioned to ward treatment with SL buprenorphine 6 mcg/kg vs IM morphine 150 mcg/kg with equianalegsic effect with self-report on a 4 point scale, similar side effect profile (for nausea and vomiting and urinary retention) and longer duration in the buprenorphine group (Maunuksela 1988a **Level II**, n=60, JS 4);
- Caudal buprenorphine 4 mcg/kg had a longer time to rescue analgesic request vs IM route (Girotra 1993a **Level III-1**, n=44).

Following thoracotomy, IV buprenorphine 1.5 or 3 mcg/kg vs IV morphine 50 or 100 mcg/kg was similarly effective (Sum of Pain Intensity Difference scores) (Maunuksela 1988b **Level II**, n=57, JS 4).

In a later systematic review of single and repeat IV dosing, IV buprenorphine 1.5–6mcg/kg was superior to IV morphine 50–150 mcg/kg in time to rescue analgesia (MD: 115 min; 95% CI 43 to 186) (Murray 2018 **Level I**, 4 RCTs, n=137) (2 RCT overlap with Michel 2011 above).

SL buprenorphine 50 mcg rescue use has been reported for acute pseudo-obstruction pain crises in children who had chronic abdominal pain managed with TD buprenorphine (Prapaitrakool 2012 **Level IV**, n=3). A small dose finding study (2.5–10 mcg/kg) suggests 5 mcg/kg SL 12 hly is effective in children with cancer pain (Massimo 1985 **Level IV**).

Adverse effects

In the past, it was suggested that buprenorphine had a ceiling effect for ventilatory impairment (Khanna 2015 **NR**); this is now under debate with increasing overdose presentations and reports of death (Michel 2011 **Level IV SR**, 8 studies and 3 RCTs, n=274; Butler 2013 **NR**). It has not been reassessed recently in the paediatric population (Vicencio-Rosas 2018 **NR**). Case series of accidental paediatric overdose (total n=150) document opioid adverse effects including ventilatory impairment requiring hospitalisation for young children (Toce 2017 **Level IV**, n=88; Vicencio-Rosas 2018 **NR**). Children <6 y have accounted for the majority of buprenorphine poisoning exposures in the USA (5,761 of 5,078; 88%) and of these, 51% were admitted to a health care facility (Allen 2017 **Level IV,** n=188,468 [opioid poisonings]). One series found no relationship between ventilatory impairment incidence and estimated ingested dose in the range of 0.03–7.62 mg/kg (Toce 2017 **Level IV**). Naloxone boluses of 0.04–0.2 mg/kg were administered to most paediatric patients in these series and some received continuous infusion. The resistance to naloxone reported in adult volunteer studies (Dahan 2010 **NR**) was not noted in these children.

Plasma vs cord concentrations are low at birth following maternal opioid replacement therapy, with NAS incidence similar to other opioids of 6/10 (60%) (Bartu 2012 **PK Level IV**). In infants born to buprenorphine vs methadone-treated mothers, the NAS incidence was similar between groups with 27/58 (47%) buprenorphine-exposed infants requiring therapy for NAS (Jones 2012 **Level II**, n=175, JS 4). In each of two further studies, 4/7 infants had NAS and 1/7 required therapy; breast milk penetration after maternal SL administration was assessed and resulted in a relative infant dose exposure of 0.18 to less than 1% (Ilett 2012 **PK**; Lindemalm 2009 **PK**).

See also subsection 9.1.1.1 opioids use as Medications used in pregnancy and subsection 9.8.9.2 of Pain in pregnant patients with an opioid use disorder.

10.4.4.15 | Nalbuphine

Nalbuphine is a mu antagonist and partial kappa agonist. It has been used in paediatrics and Cochrane reviewed (Schnabel 2014 **Level I** [Cochrane], 10 RCTs, n=658). The trials were old, heterogeneous and determined low quality. Nalbuphine reduces the number of patients in severe pain at 1 and 2 h (1 RCT) and requirement for rescue (1 RCT) vs placebo, was similar to morphine for patients in severe pain at 2 h (2 RCTs), was similar to tramadol at 2 h (1 RCT) and 12 h (1 RCT), and pethidine at 2 h and 24 h (1 RCT). PONV rates in PACU were similar vs placebo and morphine.

KEY MESSAGES

Opioids

1. Young and obese children with history of obstructive sleep apnoea/sleep-disordered breathing are at higher risk of developing serious opioid-induced ventilatory impairment and death (**U**) (**Level IV**).
2. Opioid-induced ventilatory impairment and death occur rarely with therapeutic dosing in children taking opioids at home (**N**) (**Level IV**).
3. Safe dosing of opioids requires consideration of the child's age, body weight, comorbidities and ethnicity (**U**) (**Level IV**).

Fentanyl

4. Intranasal fentanyl is an effective treatment for paediatric acute pain management, with an acceptable adverse effect profile and ease of delivery (**N**) (**Level I**).

Codeine

5. The efficacy of oral codeine in children is unpredictable due to genetic differences in the ability to generate the active metabolite morphine (**U**) (**Level II**), as are adverse effects and serious toxicity (**U**) (**Level IV**).
6. Codeine should not be used in children, especially after adenoidectomy or tonsillectomy, due to an increased risk of opioid-induced ventilatory impairment and death (**S**) (**Level IV**).

Tramadol

7. Tramadol provides superior analgesia to placebo and has similar efficacy to conventional opioids in children of all ages administered by various routes for multiple surgery types (**S**) (**Level I** [Cochrane]).
8. It is unclear if tramadol causes less ventilatory impairment than other opioids in children due to insufficient trial size (**N**) (**Level I** [Cochrane]).

Buprenorphine

9. Buprenorphine administered IV or caudally has similar efficacy to morphine or caudal local anaesthetic in children for different surgery types (**N**) (**Level II**).

Nalbuphine

10. Nalbuphine intravenously is effective for postoperative pain relief in children in several low quality heterogeneous trials (**N**) (**Level I** [Cochrane]).

The following tick boxes represent conclusions based on clinical experience and expert opinion:

- ☑ Careful titration of opioids is advised according to the individual child's response (analgesia and adverse effects) (**U**).
- ☑ Despite the regulatory response with boxed warning and upscheduling of codeine, prescription continues in at risk patients (with obstructive sleep apnoea/sleep-disordered breathing or post adenotonsillectomy) or has been replaced by prescription of potent conventional opioids such as oxycodone and hydrocodone which present similar or greater hazard (**N**).
- ☑ The practice of applying an occlusive dressing to the skin surface of a transdermal fentanyl delivery system does not limit dose delivery (**U**).
- ☑ Tramadol shares some adverse effects with the conventional opioid class in children, with similar or reduced rates of nausea and vomiting, sedation and fatigue but less constipation and pruritus (**U**). Sedation (not necessarily associated with miosis), seizures, ventilatory impairment and deaths have occurred (**N**).
- ☑ Naloxone has been used to treat tramadol overdose in children with effect (**N**).
- ☑ CYP2D6 phenotype has been the reason for codeine's black box warning, but the clinical significance in terms of tramadol/M1's analgesic efficacy and adverse-effect profile including safety is still unknown (S). Inadvertent overdose and formulation issues are likely of greater risk than CYP phenotypes resulting in variable drug metabolism; evidence for harm from this second mechanism is lacking (**N**).
- ☑ Tramadol 100mg/mL concentrated drops formulation use is potentially harmful in children with possible dosing confusion (drops with millilitres) and resultant overdose (**U**).
- ☑ In paediatric overdose, buprenorphine causes the spectrum of neurocognitive adverse events as seen with conventional opioids which may be reversible with naloxone (**N**).
- ☑ More studies are required to determine tapentadol's comparative efficacy in paediatric acute pain and if its adverse effect profile in children is improved versus placebo, conventional opioids or tramadol (**N**).
- ☑ In paediatric overdose, tapentadol causes the spectrum of neurocognitive adverse events seen with conventional opioids, which may be reversible with naloxone (**N**).

10.4.5 | Discharge opioid prescribing for children

USA survey data from 1996–2012 indicates that whilst opioid prescriptions for adults have more than doubled in this time, it has not increased for children <18 y (Groenewald 2016 **Level IV**, n=144,918 children). Despite this, the public health concerns surrounding discharge and community opioid prescribing have extended to children; there are relevant implications of current opioid prescribing practices and consumer use patterns in both adults (who are relatives of children and adolescents who may then have access to these medications) and children for postoperative, post-trauma and medical indications. The recent literature focus on community and discharge prescribing for the paediatric age group is presented below; the majority is North American data, with Australia and New Zealand data provided where available.

See also the relevant adult Section 8.13 Discharge opioid medications for acute pain management.

10.4.5.1 | Prescribers of opioids and types of opioid prescribed

A systematic review identifies the paucity in research on opioid prescription and usage in children and adolescents for at home pain management postoperatively or post trauma (Dautremont 2017 **Level IV SR** [PRISMA], 9 studies [5 adolescent], n unspecified). Post hospital discharge, prescribers are generally surgeons. Since the FDA investigation of children after (adeno)tonsillectomy, codeine use has reduced in the USA (Chua 2017b **Level III-2**, n=362,992). However, as of December 2015, 1 in 20 children undergoing these procedures were still prescribed codeine (by ear nose and throat surgeons), with high potency agents such as hydrocodone and oxycodone increasingly prescribed. In two USA audits of paediatric patients (surgical and medical) discharged from hospital, discharge opioids were mostly prescribed postoperatively by surgical teams, most commonly orthopaedic (Monitto 2017 **Level IV**, n=343 families; George 2016 **Level IV**, n=34,218). Long acting preparations were rarely prescribed. Oxycodone was the most frequently prescribed agent at both centres, with the larger audit revealing near cessation of codeine prescribing. In the smaller audit, over 80% of patients also utilised paracetamol and/or ibuprofen (Monitto 2017 **Level IV**, n=343). Nearly half (47%) of patients were discharged with diazepam, having had mostly orthopaedic (70%) or urological surgery (22%). Notably, the Society for Pediatric Anesthesia guidelines recommend that opioids should not be prescribed in combination with benzodiazepines in outpatient management of paediatric patients, adding the proviso 'unless there are specific indications, with parents being warned of the risk of sedation and respiratory depression' (Cravero 2019 **GL**). These guidelines also state there is insufficient evidence to guide whether prn or scheduled opioid dosing strategies are most appropriate for paediatric patients following surgery, with expert consensus tending toward prn dosing (Cravero 2019 **GL**).

10.4.5.2 | Opioid-related poisonings and deaths

In Australia between 2003 and 2013, prescription opioids were the commonest cause of poisoning death (accounting for 24%) in children (of which 59% were adolescents: 12–16 y) (Pilgrim 2017 **Level IV,** n=90 deaths). New Zealand paediatric poisoning data is not available.

From the USA's National Poison Data System review 2000–2015, poisoning exposures to prescription opioids (most often hydrocodone, oxycodone, codeine and tramadol) was common among children <6 y and teenagers (Allen 2017 **Level IV,** n=188,468; Tadros 2016 **Level IV,** n=21,928). Causes of opioid poisoning varied between age groups with unintentional or therapeutic error most common for children <6 y and intentional overdose most common for teenagers. Over 6% of children poisoned with opioids experienced serious medical outcomes (particularly with fentanyl exposure) with overall fatality of 0.1%. In a third USA series, the mortality rate of children and adolescents with opioid poisonings has increased nearly 3-fold over 18 years, where prescription opioids were implicated in over 70% of deaths (Gaither 2018 **Level IV**, n=8,986 deaths). In this latter series, one quarter of deaths in children <5 y were homicide, while most opioid-related deaths were adolescents aged 15–19 y (88%); most (80%) were unintentional (in contrast to the above series). Co-ingestion of one or more prescription or illicit substances was found in 38.5% of adolescent cases; in adolescents, synthetic opioids (eg illicitly manufactured fentanyl) was an increasing cause of death (Gaither 2018 **Level IV**, n=8,986 deaths). For a further USA cohort of opioid-naïve adolescents, prescription opioid overdose rate was 1 in 1,600 (0.06%) (Groenewald 2019b **Level IV**, n=725). In this cohort, a subanalysis revealed the risk for overdose in adolescents increased with increased number of dispensed tablets: ≥30 opioid tablets vs ≤18

tablets (HR 1.35; 95%CI 1.05 to 1.7). Tramadol was also associated with increased risk after controlling for sociodemographic level, pre-existing health conditions, pill quantity and dose (HR 2.7; 95%CI 1.9 to 3.8). Receipt of oxycodone, presence of comorbid mental health conditions or receiving multiple opioid prescriptions did not increase risk. Across the first three series, the majority of opioid-related deaths occurred outside a medical setting. The increase of accidental opioid overdoses in children and adolescents (Burghardt 2013 **Level IV**, n=62,416 [opioid-related overdoses]) and paediatric mortality rates for opioid poisonings follow similar temporal and drug use patterns to adults and the prescribing patterns for prescription opioids (Gaither 2018 **Level IV**, n=8,986 deaths).

From USA's outpatient prescription data, the most commonly prescribed opioids include hydrocodone, oxycodone, codeine, hydromorphone, pethidine (meperidine) and tramadol (included by some authors) (see Table 10.8). One of the series reported combined rates for paediatric opioid-related ED visit, hospitalisation or death of 1 in 2,611 opioid prescriptions for children, with three deaths overall (Chung 2018a **Level III-3**, n=1,362,503 [outpatient prescriptions]) and subsequently published their state's data with one death (Chung 2019 **Level III-3**, n=529,731 [opioid prescriptions]). A further USA series specific to opioid-related deaths demonstrated increase across all age groups between 2001 and 2016: from 0.4 to 1.5% of all-cause mortality (Gomes 2018 **Level III-3**, n=335,123 [opioid-related deaths]). The rates were 1.4 /1 million for children <15 y and higher at 92.3/1 million in 15–24 y olds, without stating if relating to overdose (intentional or accidental). Simultaneously (between 2004 and 2015), the rate of opioid-related paediatric hospitalisations (where 43% required intensive care) increased in the USA (Kane 2018 **Level IV**, n=3,647 [opioid-related] of 4,175,624 admissions [31 hospitals]). The majority were adolescents 12–17 y, but one-third were children <6 y; events were coded as accidental poisoning (1,658: 80% related to opioids other than methadone and heroin) and poisonings (1,989: 61% related to opioids other than opium, methadone and heroin). The number specific to therapeutic prescriptions was not stated in this series.

In a legal settled claims post-tonsillectomy series, opioids (most commonly codeine) were implicated in death (17 of 96 claims), respiratory depression (20 of 137) and hypoxic brain injury (20 of 137) (Subramanyam 2013 **Level IV**, n=233). The ultrarapid metabolism issue for codeine and published cases of serious adverse events (including deaths) led to the 2013 FDA restriction on codeine administration in this paediatric surgical population (see Section 10.4.4.5). Subsequently, a paediatric anaesthetist survey revealed 92 cases and closed claim report analysis a further 19 serious adverse events, including apnoea and subsequent death post tonsillectomy (and adenoidectomy); 57% of patients were determined to be at risk of OSA (Cote 2014 **Level IV**, n=111). Importantly 58% of the postoperative events occurred within 24 h and 48% occurred after hospital discharge.

10.4.5.3 | Opioid-related adverse events: out of hospital

National USA prescription data revealed opioid-related adverse events were increased in adolescents vs young children (12–17 y vs 2–5 y: incidence rate ratio [IRR] 2.22; 95%CI 1.67 to 2.96) and with higher opioid doses (>0.66 mg/kg/d MED vs ≤0.38: IRR 1.86; 95%CI 1.45 to 2.39) (Chung 2018a **Level III-3**, n=1,362,503 [outpatient prescriptions]). The most frequent prescribed opioid-related adverse drug events (ADEs) were gastrointestinal (31%), neuropsychiatric (28%), CNS depression (22%) and dermatological (23%). Respiratory depression was uncommon at 2.8%. Notably most ADEs (72%) were associated with therapeutic use of the prescribed regimen. The same author group published their state's data with the same ADEs and similar incidences (Chung 2019 **Level III-3**, n=529,731 [opioid prescriptions]) (see Table 10.8). In children prescribed opioids upon discharge from hospital, ADEs were also common: 48% of 218 responding parents reported that their child had ≥1 ADE; these were also dose-related (MD 0.05 MED mg/kg/d;

95%CI 0.02 to 0.08) (Voepel-Lewis 2015b **Level IV**, n=514 parents). Concerningly, only 14 of 38 parents who reported their child as experiencing over sedation changed their child's analgesic therapy in response to this ADE. Children who received an opioid prescription post laparoscopic appendicectomy vs those who did not had increased risk of ED presentation in one audit for constipation (overall 1%; with increasing RR related to duration of opioid use) but not for pain (Sonderman 2018 **Level III-2**, n=9,684) and in a second audit for both constipation and abdominal pain (OR 3.3; 95%CI 1.3 to 8.2) (Anderson 2018 **Level III-2**, n=590). Post paediatric tonsillectomy, less severe adverse effects in patients prescribed codeine after discharge included nausea, vomiting and light-headedness; pain scores and time (POD 0) predicted sedation, but not obstructive sleep apnoea or CYP2D6 phenotype (Prows 2014 **Level IV**, n=249).

Prescribing and dispensing error is a recognised source of harm with paediatric opioid prescription. For young children <3 y, excessive dose prescribing errors (>10%) were made in 2.7% of outpatient opioid prescriptions, with higher frequency in infants (8.9% 0–2 mth and 5.7% 2–5 mth) (Basco 2015 **Level IV**, n=59,536). While discharge opioid prescriptions for children written by trainees at one USA paediatric centre had errors in 82% (re weight, dispensing information or date) and 2.9% had the potential for serious harm if dispensed and administered as prescribed (Lee 2009 **Level IV**, n=314 prescriptions). Electronic prescribing, including weight-based dosing logic with alerts, may reduce the rate of errors in paediatric opioid prescribing (George 2016 **Level IV**, n=34,218).

See also Section 8.13.2.4 Impaired driving as relevant to adolescents who drive.

10.4.5.4 | Risk of inducing long term opioid use in adolescents

Unintended prolonged opioid use was identified as a significant concern following acute postoperative opioid prescribing (Harbaugh 2018b **Level III-2**, n=88,637 perioperative opioid prescription fills). Following various surgeries, 3–15% (4.8% overall) of previously opioid naïve adolescents were using opioids at 90–180 d. Factors that increased risk slightly included older age (OR 1.07; 95%CI 1.05 to 1.08), female sex (OR 1.22; 95%CI 1.14 to 1.31), substance use disorder (SUD) (OR 1.41; 95%CI 1.12 to 1.77), chronic pain diagnosis (OR 1.48; 95%CI 1.33 to 1.66), preoperative opioid use (OR 1.26; 95%CI 1.17 to 1.36) and cholecystectomy or colectomy surgeries. Following cleft palate related surgery in children >8 y, persistent opioid use was 4.4% at 90 to 180 d vs 0.1% of non-surgical controls (Bennett 2018 **Level III-2**, n=4,139). Distractor surgery increased risk (OR 5.34; 95%CI 2.00 to 14.24) and older age only slightly (OR 1.11; 95%CI 1.04 to 1.17). Following traumatic injury (46.2% major trauma), 7% of adolescents reported prescription opioid use prior and 12.5% of adolescents continued on opioids at 1 y, with increased risk in those with preinjury mixed substance use and higher baseline pain score, but not older age (Whiteside 2016 **Level IV**, n=120). Of adolescents treated at one USA major paediatric and one adult trauma hospital (where 10 % experienced major trauma), after discharge 20% had filled >2 opioid prescriptions at 1 y, while 13% had filled >8 prescriptions at 4 y (Bell 2019b **Level IV**, n=736). Concurrent mental health diagnoses were relatively uncommon compared with adults: anxiety 11 %, depression 6% and post-traumatic stress disorder (PTSD) 2.1%.

Following each new opioid prescription filled by adolescents in the USA, the incidence of long term opioid therapy (>90 days' supply within 6 mth) was estimated as 3 in 1,000 (95%CI 2.8 to 3.1) within 3 y (Quinn 2018 **Level III-2,** n=1,224,520 prescriptions). Adolescents with mental health conditions were more likely to be prescribed opioids than those without (OR 1.13; 95%CI 1.10 to 1.16). While, the risk of long term opioid therapy was increased with ADHD (HR 1.73; 95%CI 1.54 to 1.95), non-opioid SUD (HR 4.02; 95%CI 3.48 to 4.65) and prior opioid use disorder (OUD) (HR 8.90; 95%CI 5.85 to 13.54); a greater number of co-existing or pre-existing mental health conditions increased risk of long term opioid therapy.

10.4.5.5 | Misuse, abuse, overdose and diversion of prescription opioids in children

North American data

Between 1990 and 2014, the prevalence of past-year prescription opioid misuse in the USA had increased in young people aged 11–30 y by 0.4% each year (Jordan 2017 **Level IV** [PRISMA], 19 studies, n=503,845). The pooled prevalence in high-school/college settings was 7.4% (95%CI 5.8 to 8.9). In 2016, of the USA's 12–17 y olds, 3.6% reported opioid misuse (Groenewald 2019a **NR**). However, medical prescription without nonmedical use of prescribed opioids was not associated with OUD development reported at age 35 (McCabe 2016 **Level IV**, n=4,072). In an adolescent trauma series 5 y post-discharge from two USA centres (one paediatric and one adult), 11% required opioid antagonist injection, 14% had SUD diagnosis and 8% an overdose (Bell 2019b **Level IV**, n=736). Older age (>15 y), male sex, African ethnicity, penetrating injury and treatment at the adult hospital were associated with later overdose and SUD (the latter was also associated with positive alcohol/drug screen and non-blunt/non-penetrating injury). Injury severity score was not an association (where 10% experienced major trauma).

The most common reported motives for adolescents misusing medically prescribed opioids were to get high (sensation seekers) and to relieve pain (self treaters) (McCabe 2013b **Level III-3**, n=393). Medical opioid users are up to 10 times more likely to report lifetime and past-year nonmedical opioid use, however use is usually not consistent (Boyd 2006 **Level IV**, n=1,086). Most paediatric nonmedical opioid users obtain the medications from family or friends (SAMHSA 2019 **Level IV**; McCabe 2013a **Level IV**, n=8,888 [647 nonmedical use]; Brands 2010 **Level IV**, n=2,914; Boyd 2006 **Level IV**, n=1,086).

Opioid use disorder in the past-year is estimated to affect 0.4–0.6 % of adolescents (12–17 y) in the USA in 2015–2018 surveys (SAMHSA 2019 **Level IV**, n=104,000 [2018 data]). In 2018, approximately 310,000 adolescents (850 per day) in the USA misused prescription pain relievers for the first time in the past-year. Nearly all OUD (99%) reported in 2016 by USA adolescents was related to prescription opioids and OUD was a risk factor for opioid overdose (HR 3.1; 95%CI 2.3 to 3.4) (Groenewald 2019b **Level IV**, n=1,146,412 new prescriptions). Rates of opioid prescribing for children and adolescents with common, noncancer pain conditions (eg dental, postoperative and trauma indications) are high (Groenewald 2019b **NR**). Legitimate opioid use prior to high school graduation in the USA is independently associated with a 33% increase (from 1.7–3% to 3–5%) of nonmedical use of prescription opioids by age 23 (Miech 2015 **Level IV**, n=6,220). Importantly, these individuals report little to no history of drug use and have a baseline disapproval of drug use. In USA high school seniors with nonmedical use of prescription opioids, their most common pattern was initial use of medically prescribed opioids followed by subsequent nonmedical use (McCabe 2017 **Level III-3**, 40 cohorts [Monitoring the Future], n=2,181 to 3,791 per cohort).

In Canada, the nonmedical use of prescription opioids by adolescents (at least one occasion) is common (prevalence: 20%; 95%CI 18.9 to 22.3), but behind alcohol and cannabis (Brands 2010 **Level IV**, n=2,914). Of prescription drugs, opioids were the most frequently misused by 5.9% adolescents, particularly females (Currie 2012 **Level IV**, n=44,344 [Youth Smoking Survey]).

Medical use of prescription opioids without any history of nonmedical use in adolescence is not associated with SUD symptoms at age 35 (McCabe 2016 **Level III-3**, n=4,072 surveyed). Adults at age 35, who as adolescents used opioids with high misuse potential or more than one opioid, co-ingested them with other substances or used them nonmedically and/or progressed to later medical use, have increased odds of subsequent SUD symptoms compared with those who used prescription opioids medically or no opioids during adolescence (McCabe 2019 **Level III-2**, n=8,373). Compared to low prevalence of OUD in adolescents, past-year use and misuse of prescription opioids is common, and was highest for those not engaged in schooling (Schepis 2018 **Level IV**, n=13,585 adolescents & 14,553 young adults).

National USA data has shown correlation of increased opioids prescriptions with increased poison centre telephone calls by adolescents who had abused opioids (Sheridan 2016 **Level IV**, n=4,186). For each opioid prescription increase per 100 persons per year, the annual rate of calls increased by 1.8% (95%CI 0.9 to 2.8) or 4–5 calls per 1,000 teens annually.

In one USA state (Ohio), while overall opioid prescriptions for adolescents have decreased (7 per capita annually), adult prescriptions remained unchanged (100 per capita annually) over 2008–2012 (McKnight 2017 **Level IV**, n=50,030,820 doses for 12–20 y & 3,811,288,395 doses for adults >20 y). This provides a potential source for nonmedical access by adolescents.

Low parental monitoring and low adolescent perception of parental warmth predicted pro-substance attitudes and social ties, which in turn predicted higher levels of lifetime nonmedical prescription opioid use (Donaldson 2015 **Level III-3**, n=17,339).

Harm minimisation interventions for young people who use prescription opioids nonmedically, such as provision of and education on the use of naloxone, as well as harm reduction education in schools has been proposed to address the known risks associated with opioid misuse (Marshall 2016 **NR**).

New Zealand and Australian data

In New Zealand in 2017, national opioid prescriptions for children and young adults (0–24 y) remained low: most prescriptions per 1,000 population were for the 'weak opioids' codeine (24.8) and tramadol (18.7), and infrequently the 'strong' opioids: morphine (1.6), oxycodone (0.6) and fentanyl (0) (HQSC 2019 **Level IV**, n=3,327 [dispensed to ≤24 y]). Morphine prescriptions had increased from 0.8 per 1,000 in 2011 to 1.6 per 1,000 in 2017 in this age group. A small percent of morphine (4.1%) and oxycodone (5.9%) were prescribed for more than 6 wk; the division for cancer vs noncancer indications was not specified. The majority of prescriptions in this age group were in association with a hospital event (73%). New Zealand data for nonmedical use is not available.

In Australia between 2012 and 2017, the number of prescriptions of opioids has increased by 11% (AIHW 2019 **Level IV**, n=15,419,793 [dispensed in 2016–17] with n=232,588 to ≤24 y). The extent of pharmaceutical opioid consumption is lower per capita when compared to the USA, however has specifically risen in the population aged >14 y (Chan 2019b **Level IV**, n=23,233). The Australian National Drug Strategy Household Survey 2016 found 3.6% of the population >14 y old used prescription opioids nonmedically, 33% with other illicit substances. The latter were more likely to be younger (and possibly started nonmedical prescription opioid use opportunistically and for recreation). While Australia's Pharmaceutical Benefit Scheme's data, which captures community prescriptions only (and not over the counter, hospital or private purchase), revealed annual opioid dispensing to children decreased slightly by -2.2% (CI -3.5 to -0.8) between 2013–2017 (Bell 2019a **Level IV**, n=78,320 prescriptions to 50,730 children). In 2017, one in 74 Australian children (0–17 y) overall were dispensed an opioid, highest in the adolescent age group at one in 25. Like New Zealand, codeine and tramadol comprised most dispensed prescriptions (51 and 10% respectively); oxycodone was the most frequently dispensed 'strong' opioid (37%), with other opioids dispensed infrequently (4%). Strong opioid dispensing increased in all age groups, with the 1.5 fold increased oxycodone dispensing; codeine dispensing decreased in all age groups, except those <1 y. Long acting opioids were dispensed to 7.5% of children (1–12 y) and 9.5% of adolescents prescribed opioids. Noncancer vs cancer indication information was not provided. The majority of children (80%) were dispensed one prescription only. General practitioners prescribed 48%, medical specialists 28% and other prescribers 22%. General practitioners prescribed mostly codeine and tramadol, while specialists prescribed strong opioids.

The Australian national survey revealed low rates of nonmedical use of opioids (1.1%) and sleeping pills/tranquilisers (2.7%) by adolescents (14–19 y) in the previous 12 mth (AIHW 2019 **Level IV**).

10.4.5.6 | Consequences of excess prescribed opioids

Practice varied widely regarding doses and amount of opioid prescribed for children and adolescents <21 y following various surgery types eg arthrodesis, humeral supracondylar fracture repair and Nuss surgery (Harbaugh 2018b **Level III-3**, n=88,637) and laparoscopic appendicectomy (Anderson 2018 **Level III-2**, n=590). As a consequence, many children are prescribed and dispensed excessive amounts of opioid that remain at large in the community. Several audits have documented a mean or median duration of discharge opioid prescription: 4.8 d (± 2.9) prescribed for 63% post laparoscopic appendicectomy (Anderson 2018 **Level III-2**, n=590), 4 d (IQR 3–5 d) for 68% post laparoscopic appendicectomy (Sonderman 2018 **Level III-2**, n=9,684) and 4 d (IQR 1–8) for 100% post mixed surgery (Monitto 2017 **Level IV**, n=343). In the latter, 36% of patients were still taking opioids 7 d post discharge. Of concern, one prescription at times provided opioid for up to 30 and 65 d (Sonderman 2018 **Level III-2**, n=9,684; Anderson 2018 **Level III-2**, n=590) and in separate series, the number of dispensed opioid doses (median 43, IQR 30–85) (Monitto 2017 **Level IV**, n=343), liquid volumes (mean 106 mL ± 125) and tablets (mean 51 ± 51) (George 2016 **Level IV** n=34,218) were high. Another centre reported a low median of 10 doses (IQR 6-15) of discharge opioid prescribed for 22%; this audit included the 7 commonest (mostly day-stay) paediatric surgical procedures (Harbaugh 2019 **Level IV**, n=404). Postoperative intake of non-opioids with opioids was high (but could be improved upon): paracetamol 88% and/or ibuprofen 78% were taken for a median of 3 d (IQR 2–5 d), with opioids used for a median of 2 d (IQR 1–3 d) (Harbaugh 2019 **Level IV,** n=404); and both agents by 81% of patients at a second centre (Monitto 2017 **Level IV**, n=343).

Where opioid prescription exceeds use, leftover medications result. Parental surveys have documented high proportions (25–90%) of unused/leftover prescription opioid doses following paediatric surgeries (Groenewald 2019a **NR**; Hunsberger 2019 **Level IV**, n=115 interviewed; Monitto 2017 **Level IV**, n=343), where 14% (Voepel-Lewis 2015a **Level IV,** n=223) to 31% of parents report using none of the prescription and 37% less than half (Harbaugh 2019 **Level IV**, n=404 [78 prescribed opioid]). Various factors contribute to this such as age of the child (younger patients consumed fewer doses than patients >15 y), decrease in daily use with recovery (and appropriate cessation as pain is well controlled) or early cessation due to side effects (as reported by 18% of parents whose children had nausea, vomiting or sedation) (Monitto 2017 **Level IV**, n=343) versus early tapering and discontinuation of opioid medications by parents (Voepel-Lewis 2015a **Level IV**, n=223). However, for some surgery types such as Nuss and major orthopaedic surgery, the mismatch of dispensed vs use was large (Monitto 2017 **Level IV**, n=343). Leftover opioids represent a major source of nonmedical use of prescribed opioids in adolescents (McCabe 2013a **Level III-3**, n=647 [nonmedical use]) and leftover prescription opioids have been implicated in accidental opioid overdoses (Groenewald 2019b **NR**). The strongest predictor of the number of doses remaining was the number of doses dispensed (Monitto 2017 **Level IV**, n=343).

10.4.5.7 | Safe opioid storage and disposal

Opioids were kept in locked storage in the USA by only 28% parents whose children were discharged with opioids (Harbaugh 2019 **Level IV**, n=404) and 29% of adults who had past-year use of opioids and were living in households with children and adolescents (McDonald 2017 **Level IV**, n=681). The lack of childproof packaging for many commonly prescribed opioids has been recognised as an area for concern (Gaither 2018 **Level IV**, n=8,986 deaths). Young children commonly gain access to prescribed medications which are stored incorrectly, in plain sight or accessing

from an adult's purse or bag (Allen 2017 **Level IV,** n=188,468). Disposal of leftover opioids is widely variable: 85% of parents were unaware of how to manage leftover opioids and 33% planned to keep them for future use (Groenewald 2019a **NR**), 19% recalled being advised on how to dispose of opioids (Monitto 2017 **Level IV**, n=343) eg by return to a pharmacy, with only 4% and 11% appropriately disposing of the leftover opioids (Harbaugh 2019 **Level IV**, n=404; Monitto 2017 **Level IV**, n=343). Dual harm potential with unsafe storage and non-disposal of prescription opioids leads to a reservoir for nonmedical use by families and adolescents (including diversion) and accidental ingestion by young children. Parents may also be an important source of prescription opioids that are intentionally shared for medical (and nonmedical) use by children and adolescents.

10.4.5.8 | Education of prescribers, families and patients: pain trajectories and safe practices

Perceptions of the expected duration of pain following common surgical procedures vary significantly (Raney 2018 **NR**), although it is known that postoperative pain is commonly experienced by children at home, lasting for days to weeks. The adult Education Section 3.1 provides an overview of the impact of education on various clinical staff members, patients and carers assessed by different outcomes including postoperative pain, analgesic use and quality of life. The safe and practical prescribing sections in 8.13 Discharge analgesia (sections 8.13.2.5 and 8.13.5) have overlap with this paediatric section, which focuses on staff and family education pertaining to opioid prescription and additional safe practices relevant to children.

Barriers to adequate pain relief include various factors (Walker 2015b **GL**):

- Parental factors, eg tendency to underdose and not optimise therapy;
- Child factors, eg anxiety/distress, difficulty swallowing medication (or formulation) or refusal;
- Medication factors, eg incorrect dosing or lack of palatable paediatric formulation that permits appropriate dosing; and
- System factors, eg knowledge base, training, confidence and seniority of staff prescribing analgesia and provision of adequate information.

As highlighted above by the variability in practice, it is important to optimise discharge opioid prescription in the paediatric population (Monitto 2017 **Level IV**, n=343) and create guidelines for safe and responsible opioid prescribing (Groenewald 2019a **NR**; Cravero 2019 **GL**). Education interventions at a hospital level should focus on hospital prescribers, particularly surgical services who write the majority of postsurgical discharge prescriptions (George 2016 **Level IV**, n=34,218). This needs to be informed by research with focus on understanding the pain trajectories after common surgical procedures, to reduce leftover medications and educate the broader opioid prescribing and dispensing community and then carers (Raney 2018 **NR**). There is growth in web-based delivery of education programs for health professionals focussing on opioid prescribing. Online educational resources improve knowledge and skills, but not confidence and competence (Liossi 2018 **Level IV SR** [PRISMA], 32 studies [6 paediatric], n unspecified). Studies were heterogeneous, including paediatric and adult patients, and acute and chronic pain populations in various clinical settings (one specific to primary care and opioids); relevant health outcomes for patients were not assessed. The interventions were generally 1 h in duration and permitted multiple logins. A subsequent survey of clinicians who had completed an interactive online opioid prescription learning module determined that clinician knowledge, likelihood of adherence to prescription guidelines and perceived competence in opioid prescription improved following participation (Langford 2020 **Level III-3**, n=167 [clinical staff]). Quality improvement initiatives include review of postoperative opioid consumption eg post urological surgery where investigators found the median consumption was 2 (IQR 3–6) of the 10 doses prescribed, with subsequent revision of prescription to 5 dose maximum (Cardona-Grau 2019 **Level IV**, n=98). A rapid cycle audit initiative

in the paediatric palliative care setting (for consideration for postoperative patients) has increased use of a risk stratification tool for opioid misuse when seeing children in the clinic, with implications for ongoing prescribing and managing abuse or opioid diversion (Thienprayoon 2017 **Level IV**, n=17 [positive risk ≤18 y]).

It is important to target education of carers to set expectations and simultaneously address the barriers and concerns highlighted above. Web-based parental education and preoperative child preparation strategies have been recommended (Walker 2015b **GL**). A systematic review evaluating educational websites included only two RCTs with information on acute postoperative pain (Bender 2011 **Level I**, 17 RCTs, n=2,503). One was paediatric and assessed preparation of adolescents prior to tonsillectomy (O'Conner-Von 2008 **Level II**, n=69, JS 3). Improved satisfaction and knowledge were seen with internet (commonly viewed >1 time) vs standard face to face afterhours preparation program vs no treatment, with no difference in pain scores or anxiety (the latter were high normal at 34–37, but below the therapeutic cut off of 39/80). A written oxycodone information sheet supplement to verbal instruction was provided to parents after tonsillectomy in children with information regarding dose and timing vs verbal instruction alone (Bailey 2015 **Level II**, n=60, JS 5). The information sheet recipients had higher parental satisfaction and knowledge and some improvements in pain scores up to POD 7. Parental recall of instruction for "around the clock" opioid administration predicted greater opioid use (Voepel-Lewis 2015a **Level IV**, n=166 [prescribed opioids]). This could be positive or negative depending on the response of parents to subsequent adverse events such as sedation (Voepel-Lewis 2015b **Level IV**, n=514 parents). To reduce harm from opioid medications, interventions should also include education of adolescents, and carers (and adults in the home) on the risk of opioids, the importance of storage in a locked medicine cabinet and safe disposal (Cravero 2019 **GL**; Groenewald 2019a **NR**; Binswanger 2015 **NR**). Initiatives such as the Australian National Prescribing Service Choosing Wisely program permit dialogue between consumers and clinical staff with written take home information that addresses at home pain management and safe practices (NPS Medicinewise 2019b **GL**).

The use of state prescription drug monitoring programs is also recommended (Groenewald 2019a **NR**). Some USA states have seen a reduction in problematic opioid behaviours since the utilisation of prescription drug monitoring programs; however it is difficult to directly attribute this change to the use of these programs versus other social and regulatory changes.

KEY MESSAGES

1. Postoperative opioid therapy in children and adolescents may lead to long term opioid use and misuse in later life (**N**) (**Level III-2**); risk factors include type of surgery, psychological and social factors and other substance use (**N**) (**Level III-2**).
2. Long term opioid use following therapeutic medical prescription is uncommon in children and adolescents (**N**) (**Level IV**). However, prior diagnosis of chronic pain, substance use or mental health conditions are risk factors (**N**) (**Level IV**).
3. Misuse of prescription opioids is common amongst adolescents and young adults either as medical use (self-treatment) or nonmedical use (sensation seeking/recreational) (**N**) (**Level IV**).
4. Leftover prescribed opioids are a common source of nonmedical opioid use in adolescents, with most adolescents gaining access through family or friends (**N**) (**Level IV**).

5. Unsafe storage of prescription opioids in the home and non-disposal of leftover opioids is common (**N**) (**Level IV**).
6. Prescription opioids are a large source of opioid-related poisonings: usually accidental in young children and related to recreational use or with intentional overdose in adolescents (**N**) (**Level IV**).
7. Adverse drug events in children and adolescents sent home with prescription opioids are common (**N**) (**Level IV**).

The following tick boxes represent conclusions based on clinical experience and expert opinion:

☑ As for adults, a sensible approach should be used in the setting of prescribing discharge opioid medications for children and to adults with children at home (**N**).

☑ As for adults, prescribing discharge medications for children should be done with consideration of the child's anticipated opioid requirements. The tablet number and volume of opioid solution prescribed should be judicious and individualised (**N**).

☑ Understanding and education is required to determine procedure specific pain trajectories in children (**N**).

☑ Carer/parental, patient and clinical staff education is necessary about risks of opioids and how to safely dispose of unused medication by return to a pharmacy (**N**).

☑ Carer/parental and patient education in case of ongoing pain and analgesic issues is appropriate with follow-up by general practitioners or pain medicine services as indicated (**N**).

☑ Education and guidelines are desirable for adult and paediatric discharge and community opioid prescribers with focus on information provision for staff delivering the advice (ideally written and verbal combined) to carers and families (**N**).

10.4.6 | Opioid tolerance in children and adolescents

10.4.6.1 | Groups of opioid-tolerant children

Opioid tolerance is discussed in the adult section; for the definitions of tolerance and dependence see adult Section 9.7; see Table 9.8. Opioid-tolerant paediatric patients have been less well studied than opioid-tolerant adults.

Like adults, there are four main groups of opioid-tolerant children and adolescents:

1. *Chronic non-cancer pain (CNCP)*
   The prevalence of moderate to severe CNCP in children is suggested to be 1 in 20 (Brooks 2016 **NR**). An Australian dataset revealed opioid use by 15.7% of children at referral to paediatric chronic pain clinics (Lord 2019, **Level IV**, n=1,100) with data also for paediatric sickle cell patients chronically taking opioids (see 10.9.5), but not for other potentially opioid-tolerant paediatric groups with chronic pain (eg inflammatory bowel disease, inflammatory arthritis or pelvic pain). There is no RCT data available in this patient group (Cooper 2017a **Level I** [Cochrane], 0 RCTs).

2. *Paediatric cancer patients being treated with opioids*

   Many government prescription databases provide data that is not linked to a cancer diagnosis and so the prevalence of chronic opioid use in patients with active disease (undergoing treatment or in the palliative phase), in remission or survivors of childhood cancer is unknown. Prescription analgesic use was reported by 16.7% of survivors 16.5 y (mean) post cancer diagnosis vs 12.6% of their siblings (Lu 2011 **Level IV**, n=10,397). Many adolescents and young adults with cancer have at least one psychosocial risk factor for misuse and some have documented aberrant opioid-related behaviours (Ehrentraut 2014 **Level IV**, n=94 [opioid using]); survivors may be at increased risk of opioid use disorder in later life. This raises the ethical challenge of withholding analgesia on the basis of addiction risk – thus screening and subsequent monitoring and management of those found to have opioid misuse is recommended (Pinkerton 2017 **NR**). An initiative in paediatric palliative care increased use of a risk stratification tool for opioid misuse when seeing children in the clinic, with implications for ongoing prescribing and managing abuse or opioid diversion (Thienprayoon 2017 **Level IV**, n=17 [positive risk ≤18 y]).

3. *Nonmedical prescription opioid use (NMPOU)*

   This group are mostly adolescents. Nonmedical use is either long term prescription opioid use postoperatively (4.8 % of previously opioid naïve adolescents (13–21 y) continued use of opioids at 90–180 d) (Harbaugh 2018b **Level III-2**, n=88,637 perioperative opioid prescription fills) or illicit opioid misuse (non-prescription or prescription): 3.6% of USA adolescents (12–17 y) (Groenewald 2019a **NR**), 5.9% of Canadian high school students (Currie 2012 **Level IV**, n=44,344 [Youth Smoking Survey]) or 7.4% of adolescents/young adults (11–30 y) (Jordan 2017 **Level IV SR** [PRISMA], 19 studies, n=503,845) had addiction or SUD, including those on an opioid treatment program (see also Section 10.4.5.4, 10.4.5.5 and adult Section 9.7).

4. *Acute or subacute tolerance in children*

   Children and adolescents, like adults, are at risk of opioid-tolerance, dependence and withdrawal after opioid therapy during inpatient or paediatric intensive care unit (PICU) stay. Opioid tolerance and/or dependence may occur with 5–10 d of therapy with most opioids, particularly with synthetic opioids and/or at high cumulative doses (Best 2015 **Level IV SR** [PRISMA], 33 studies, n unspecified; Anand 2010 **NR**).

   i. Acute opioid tolerance

   Intraoperative remifentanil was associated with an increase in PCA morphine requirement in the 24 h post scoliosis surgery (Crawford 2006b **Level II**, n=30, JS 5), possibly due to acute opioid tolerance or opioid-induced hyperalgesia. In younger children having surgery of approximately 3h duration, patients who received intraoperative remifentanil 0.6-0.9 mcg/kg/min had higher postoperative fentanyl requirements for 24 h vs those who received 0.3 mcg/kg/min or saline (Kim 2013 **Level II**, n=60, JS 4). Intraoperative weaning strategies for remifentanil in children have not been explored (see adult Section 9.7.2).

   ii. Subacute opioid tolerance

   During and following fentanyl and morphine infusion, children, whilst in (Ibach 2017 **Level IV**, n=21/59) and post discharge from PICU and neonatal intensive care units (NICUs) have exhibited tolerance and experienced withdrawal symptoms (Anand 2013b **Level III-2**, n=419 [7 centres]; Anand 2010 **NR**; Birchley 2009 **NR**). Fentanyl administered as a prolonged IV infusion in the NICU and PICU has been associated with more rapid dose escalation and greater likelihood of doubling the daily dose than when the primary opioid is morphine

(Anand 2013b **Level III-2**, n=419 [7 centres]). This was also true for the subgroup admitted immediately postoperatively.

10.4.6.2 | Perioperative outcomes and management of opioid tolerance in children

There is no data on the influence of opioid-tolerance on paediatric perioperative outcomes. Recommendations for management have been primarily based upon extrapolation from multimodal management of opioid naïve patients with severe pain (see paediatric Sections 10.9.1 Management of pain due to trauma in children and 10.9.2 Management of acute burn injury in children) and the adult literature (See Sections 9.7.4.2 and 9.7.6).

Strategies include perioperative use of multimodal analgesia with adjuvant use of (Brooks 2016 **NR**; Geary 2012 **NR**):

- Ketamine (see paediatric Section NMDA Antagonists 10.4.7);
- Alpha-2 agonists (see paediatric Section 10.4.8);
- Alpha-2-delta ligands (see paediatric Section 10.4.9);
- Local anaesthesia – peripheral nerve blocks (see Section 10.6.1), regional (10.6.2 and 10.6.3) and systemic lidocaine infusion (see Section 10.4.11 and adult Section 4.4.1).

Opioid-related withdrawal syndromes in children and management

Recognition and management of opioid-related withdrawal is important to reduce physiological disturbance. This is particularly relevant for PICU patients receiving opioids for sedation, endotracheal tube tolerance and acute or postoperative pain (eg post cardiac surgery, major burns or trauma), where tolerance (particularly to shorter acting opioids eg fentanyl) is recognised (Anand 2013b **Level III-2**, n=419 [7 centres]; Gish 2011 **Level III-3**, n=31) including polytolerance eg to other sedatives such as benzodiazepines (Best 2015 **Level IV SR** (PRISMA), 33 studies (9 opioid only, 22 opioid/benzodiazepine, 2 benzodiazepine only), n unspecified). These patients may frequently experience withdrawal; reported by 63% of burns centres (Singleton 2015 **Level IV**, n=41 centres).

There are several paediatric withdrawal assessment scales such as the validated withdrawal assessment tool (WAT-1) and others (Fenn 2017 **Level IV SR**, 15 studies, n=567; Best 2015 **Level IV SR** [PRISMA], 33 studies, n unspecified; Whelan 2015 **NR**) (8 study overlap). Some paediatric institutions have weaning and concurrent observation guidelines (SickKids 2018 **GL;** Starship 2017 **GL**). Weaning 10–20% of the total opioid dose every 48 h is generally recommended (Galinkin 2014 **NR**; Anand 2013b **Level III-2**, n=419 [7 centres]). There is little evidence to recommend any particular withdrawal prevention or treatment regimen eg with methadone (Dervan 2017 **Level IV SR** [PRISMA], 12 studies, n=459) (7 and 8 study overlap with above SRs) or alpha-2 adrenergic agonist use including as 'bridging therapy' (Whelan 2015 **NR**). IV Ketamine infusion at anaesthetic doses has been used to facilitate opioid rotation for a median of 3 d in patients (median age 2.5 y) who had received opioid infusions for several days with clonidine/midazolam infusion in PICU (Neunhoeffer 2017 **Level IV**, n=32). Upon cessation, fentanyl requirements were reduced and COMFORT-B scores improved vs prior to commencement (See 10.4.7 ketamine use for opioid-induced hyperalgesia).

KEY MESSAGES

1. Iatrogenic withdrawal syndrome following prolonged inpatient intravenous opioid therapy in critically ill children is common (**N**) (**Level IV SR** [PRISMA]).

The following tick boxes represent conclusions based on clinical experience and expert opinion:

☑ There are groups of paediatric patients who are opioid-tolerant, as in adults. They require special consideration for inpatient pain management and perioperative care. In children with opioid tolerance, inadequate pain relief and withdrawal (if opioids are acutely ceased) are specific risks. Acute pain service input can assist with preadmission planning and use of various adjuvants beyond standard multimodal interventions (**N**).

☑ For assessment of withdrawal reactions, the use of a validated withdrawal tool in paediatric opioid-tolerant patients is recommended; management strategies vary and include opioid weaning, rotation and adjuvant use (**N**).

10.4.7 | Systemic NMDA-receptor antagonists

10.4.7.1 | Ketamine

This section covers the use of ketamine for acute pain management in children. Ketamine has been studied at varying doses, via various routes and regimens, for multiple paediatric surgery types, generally in small studies rendering interpretation of its effects challenging.

See also Section 10.7 for use in paediatric procedural sedation, Section 10.8 for use in paediatric cancer pain, and Section 10.6.3 for regional adjuvant use and peritonsillar infiltration in addition to those summarised in the various systematic reviews below. See also Adult ketamine Section 4.6.1.1, where neuraxial, adjuvant peripheral nerve use and topical administration are discussed in the one section.

Pharmacokinetics and pharmacodynamics of ketamine in children

Ketamine has a large volume of distribution at steady state (mean 3.3 L/kg ± 1.3) and a clearance that approximates liver blood flow in children above 1 y of age (Elkomy 2019 **PK**). Pharmacokinetic (PK) modelling reveals ketamine infusions of 0.2 mg/kg/h for 24 h will achieve a median steady-state plasma concentration of 0.15 mg/L (Herd 2007 **PK**). Median ketamine concentration is maintained >0.1 mg/L (assumed minimum analgesic serum concentration) for 0.5 h post cessation of infusion. The metabolite norketamine is thought to have one third the potency of ketamine. With this assumption, the combined "effective" concentration of ketamine/norketamine is >0.1 mg/L for 1.5 h post infusion cessation. After IV ketamine 2 mg/kg, norketamine plasma concentration peaks within 1 h, and may contribute to analgesia for up to 4 h. In an adult volunteer study an anti-analgesic effect of norketamine has also been proposed (Olofsen 2012 **EH**).

Ketamine is a racemic mixture. The isomeric formulation S(+) ketamine has twice the analgesic potency of the racemate, and is shorter acting with slightly less adverse cognitive effects in adults (Mion 2013 **NR**)**.**

For procedural sedation up to 20 min, PK modelling has suggested doses for IV ketamine of 2 mg/kg and for IM ketamine 6-8 mg/kg (Hornik 2018 **PK**). With IM ketamine, bioavailability was estimated at 41% and desired effect achieved at 10 min. Children on extracorporeal membrane

oxygenation (ECMO) had higher ketamine clearance, with a dose suggestion of >5 mg/kg IV for procedural sedation.

Oral ketamine has a high first-pass clearance (See adult Sections 4.6.1.1 Ketamine and 5.5.3.2 regarding sublingual ketamine). This results in high early norketamine concentrations vs IV administration. The peak ratio of norketamine/ketamine at 1 h is 2.8 after PO administration allowing an analgesic contribution from the metabolite at this time. This property has proved useful when racemic ketamine is given 1 h before burns dressings (Brunette 2011 **Level IV**). The PKs following SL and IN route administration have been studied in adults with respective bioavailabilities of 30 and 45% (Yanagihara 2003 **PK**). In adults, a ketamine lozenge (25 mg) had 24% bioavailability by both SL and PO routes (with peak plasma levels at 30 min and 120 min respectively, and high norketamine concentrations) (Chong 2009 **PK**); a SL wafer presentation (25 mg) had similar SL bioavailability of 29% (Rolan 2014 **PK**). For procedural analgesia, the bioavailability of IN racemic ketamine (0.5 mg/kg combined with sufentanil 0.5 mcg/kg) was 36%, with a T_{max} of 8.9 min in awake children (half the value reported in anaesthetised children) (Nielsen 2014 **Level IV**). The IN spray was acceptable to the majority of patients. IN S-ketamine 2 mg/kg has also been administered to anaesthetised children and its PKs assessed but data quantifying effect are not available (Weber 2004 **PK**).

Efficacy of ketamine

Perioperative use of ketamine

Four meta-analyses have assessed perioperative paediatric ketamine use by various routes for various surgery types (Michelet 2016 **Level I** [PRISMA], 11 RCTs, n=508; Cho 2014 **Level I** [PRISMA], 24 RCTs, n=1,257; Tong 2014a **Level I** (PRISMA), 10 RCTs, n=522; Dahmani 2011 **Level I** [QUORUM], 35 RCTs, n=1,925) (0-10 RCT overlap). Studied systemic dose regimens generally consist of a bolus ranging from 0.1 mg/kg to 0.5 mg/kg mostly, to as high as 6 mg/kg. Some incorporated intraoperative and postoperative ketamine infusions which have generally ranged between 0.08 and 0.25 mg/kg/h, with 2 RCTs using 1–1.4 mg/kg/h. Findings for all administration routes are generally positive, mainly for early analgesic outcomes.

Caudal ketamine for inguinal and urological surgery

Caudal ketamine increases the duration of sensory block (SMD 2.26; 95%CI 1.53 to 2.98) (10 RCTs, n=686) and reduces analgesic requirement in PACU (OR 0.26; 95%CI 0.10 to 0.66) (10 RCTs, n unspecified), but did not reduce pain intensity in PACU or in the first 6 h postoperatively (Dahmani 2011 **Level I** [QUORUM], 13 RCTs [caudal], n unspecified).

Systemic ketamine for various surgery types

In patients having adenotonsillectomy (13 RCTs), inguinal hernia repair and circumcisions (2 RCTs), appendicectomy (1 RCT), scoliosis surgery (1 RCT) and ambulatory surgery (1 RCT) (Dahmani 2011 **Level I** [QUORUM], 18 RCTs [systemic], n=985), systemic ketamine:

- Reduces pain intensity in PACU (SMD -0.45; 95%CI -0.73 to -0.16) (10 RCTs, n=647);
- Reduces analgesic requirement in PACU (OR 0.46; 95%CI 0.29 to 0.72) (7 RCTs, n unspecified);
- But not intensity or analgesic requirement later in the 6–24 h postoperative period; and
- Does not reduce opioid consumption in the first 24 h.

Peritonsillar and topical ketamine for adenotonsillectomy

Peritonsillar (2 RCTs) and topical ketamine (1 RCT):

- Reduces pain intensity in PACU (SMD -1.62; 95%CI -2.83 to -0.41) (3 RCTs, n=190) ;
- Reduces analgesic requirement in PACU (OR 0.09; 95%CI 0.03 to 0.27) (2 RCTS, n=90) (Dahmani 2011 **Level I** [QUORUM] 35 RCTs, n=1,925).

Systemic, peritonsillar and topical ketamine for tonsillectomy
Intraoperative ketamine by all three routes:

- Vs opioid, achieves similar pain scores at five time points over 0–24 h (Cho 2014 **Level I** [PRISMA], 9 RCTs [opioid], n=428);
- Vs placebo, reduces early pain intensity
    - at 0 h (SMD -1.7; 95%CI -3.17 to -0.24) (Cho 2014 **Level I** [PRISMA], 6 RCTs [placebo], n=290);
    - at 0.5–2 h (Tong 2014a **Level I** (PRISMA), 10 RCTs, n=522) (10 RCT overlap with Cho);
    - and 4 h (SMD -0.8; 95%CI -1.2 to -0.4) (Cho 2014 **Level I** [PRISMA], 14 RCTs [placebo], n=718), but not later at 6–24 h;
- Subgroup analysis reveals similar results for IV and peritonsillar administration with a stronger effect size for peritonsillar route, countered by higher heterogeneity of the studies. There is reduced need for (LogOR -1.2) and amount of analgesia required (SMD -1.3) and longer time to first rescue analgesic (SMD 0.96) (Cho 2014 **Level I** [PRISMA], 24 RCTs, n=1,257) (overlapping with the first SR by 8 RCTs [4 IV, 1 topical and 3 peritonsillar infiltration]);
- Adminstered as peritonsillar infiltration 2 mg/kg, PR 2 mg/kg or IV 0.5 mg/kg vs IV tramadol 2 mg/kg reduced pain scores similarly (Yenigun 2015 **Level III-1**, n=120).

Multidose perioperative ketamine
IN pump-pack administration of ketamine 1.5 mg/kg vs fentanyl 1.5 mcg/kg (at induction and then three times daily) reduced pain scores over 24 h similarly (Yenigun 2018 **Level III-1**, n=63). Both were superior but with more sedation vs IV paracetamol 10 mg/kg, with no difference in other adverse effects.

Systemic perioperative ketamine and postoperative opioid-sparing effect
For various surgeries (Michelet 2016 **Level I** [PRISMA], 11 RCTs, n=508) (with 7, 3 & 0 RCT overlap respectively with the above SRs), systemic ketamine vs placebo does not reduce:

- Opioid consumption in the first 24 h (primary outcome) (6 RCTs, n=278) or in PACU or in the first 48 h;
- Pain intensity (in PACU, or in the first 24 and 48 h);
- PONV or psychotomimetic symptoms in the first 24 h.

There was also no difference in subgroup analysis of postoperative ketamine infusions only (4 RCTs, n=179) and use in scoliosis surgery (3 RCTs, n=128) on opioid consumption to 24 h vs placebo. Overall, the authors calculated a sample size of 445 patients would adequately power an RCT to determine if ketamine is opioid-sparing.

- A single additional scoliosis surgery RCT conflicts with those included in the meta-analysis where IV ketamine (0.5 mg/kg bolus and 0.12 mg/kg/h for 48 h) reduced cumulative morphine consumption at 24 and 48 h vs placebo (Minoshima 2015 **Level II**, n=36, JS 5). There was no difference in pain intensity, sedation score or PONV incidence;
- In a further scoliosis RCT, intraoperative IV infusion of ketamine (0.2 mg/kg bolus and 0.15 mg/kg/h)/remifentanil/magnesium (50 mg/kg bolus and 8 mg/kg/h) vs ketamine/ remifentanil/placebo reduced 0-48 h PCA morphine requirements by 29.5% (Jabbour 2014 **Level II**, n=50, JS 5).

Postoperative combined PCA ketamine/opioid
Adding ketamine to opioid in the PCA pump improves pain at rest at 24 h (WMD -21.1/100 mm; 98%CI 21.8 to 20.4) (9 RCTs, n=595), reduces opioid consumption by 28% (7 RCTs, n=495) and PONV by 44% (7 RCTs, n=435) (Assouline 2016 **Level I** [PRISMA], 19 RCTs [2 paediatric], n=1,453). Respiratory depression (RR 0.31; 98%CI 0.06 to 1.51) (9 RCTs, n=871) and hallucinations (OR 1.16; 98%CI 0.47

to 2.79) (7 RCTs, n=690) are not increased. Both included paediatric studies involved Nuss surgery. Intraoperative ketamine bolus 0.3 mg/kg followed by PCA IV ketamine added to fentanyl (ratio per mL 0.15 mg/kg: 0.5 mcg/kg) vs fentanyl PCA alone resulted in a small but statistically significant decrease in mean pain scores at 6 h (2.5/10 vs 2.9), 24 h (1.4/10 vs 1.9) and 48 h (1.0/10 vs 1.6) and reduced cumulative fentanyl consumption at 24 and 48 h (Assouline 2016 **Level I** [PRISMA], 1 RCT: Cha 2012 **Level II**, n=60, JS 3). Combining ketamine with hydromorphone/ketorolac in a PCA (ratio per mL 0.15mg/kg: 3 mcg/kg: 0.05 mg/kg) reduced postoperative PCA use (50.8 ± 1.9 mL vs 57.8 mL ± 2.5) with no difference in other outcomes (Assouline 2016 **Level I** [PRISMA], 1 RCT: Min 2012 **Level II**, n=44, JS 4).

S(+) ketamine

The efficacy of S(+) ketamine has been investigated in a limited number of paediatric studies. Following major urological procedures, children treated with intraoperative low-dose IV S(+) ketamine (bolus 0.2 mg/kg and infusion 0.3 mg/kg/h) vs placebo had a longer time to first analgesic request, but similar pain scores and 72 h IV NCA morphine consumption (Becke 2005 **Level II**, n=30, JS 5).

Adjuvant caudal S(+)ketamine 0.5 mg/kg increases the duration of analgesia vs local anaesthetic alone (SMD 2.35; 95%CI 1.02 to 3.67) (4 RCTs) (Dahmani 2011 **Level I** [QUORUM], 35 RCTs, n=1,925). The duration was similar to that for adjuvant caudal racemic ketamine 0.25–0.5 mg/kg (9 RCTs).

Ketamine use by various routes in acute non-surgical pain

Ketamine has been used prehospital and in the ED for analgesia, commonly for severe pain (>6/10) following limb injury/fracture, burns, falls or road traffic accidents. Doses of 0.25–1 mg/kg have been used in children via IV, IM and IN routes (Yeaman 2013 **Level IV;** Bredmose 2009a **Level IV**; Bredmose 2009b **Level IV**; Reid 2011 **CR**), as well as higher doses IM (Svenson 2007 **Level IV**). IN Ketamine 1–1.5 mg/kg was similarly effective vs IN fentanyl 1.5–2 mcg/kg for children presenting to the ED with limb injuries, with reduced pain scores at 20–60 min (Frey 2019 **Level II**, n=90, JS 5; Reynolds 2017 **Level II**, n=87, JS 3; Graudins 2015 **Level II,** n=80, JS 5). (See also adult Sections 5.5.2.3 Ketamine via IN route and 8.6.5.2 for use in acute headaches).

Beneficial use of low-dose 0.1–0.2 mg/kg/h infusion in sickle cell crises is described in children in addition to (n=4) or to replace (n=1) IV opioid PCA (Zempsky 2010 **Level IV**). Bolus IV ketamine 1 mg/kg for sickle cell crisis resulted in similar mean maximum percentage change in pain score during a 2 h period vs bolus IV morphine 0.1 mg/kg (66.4% vs 61.3), but with a higher rate of minor adverse effects (37.5% vs 3.3: mainly nystagmus and dysphoria) (Lubega 2018 **Level II**, n=240, JS 5).

Nebulised ketamine 2 mg/kg vs dexmedetomidine 2 mcg/kg vs combination ketamine 1 mg/kg and dexmedetomidine 1 mcg/kg has been trialled for paediatric pre-medication 30 min prior to dental surgery and may contribute to improved postoperative analgesia (although the data on acceptance of the nebulised technique by the young children is not specified) (Zanaty 2015 **Level II**, n=60, JS 5).

When IV ketamine is used for procedural sedation, there is a steep concentration-response relationship (almost all or no response) with an EC_{50} for arousal of 0.56 mg/L (Herd 2008 **Level IV**). A dose finding study of rectal ketamine 4–8 mg/kg with midazolam 0.5 mg/kg achieved effective sedation and analgesia for burns dressing changes in young children; the higher dose of 8 mg/kg was associated with prolonged recovery time and adverse events (Grossmann 2019 **Level II**, n=90, JS 5). Similar doses were effective for botox injections in children with cerebral palsy (Nilsson 2017 **Level IV,** n=61 [128 procedures]).

Ketamine use in opioid-induced hyperalgesia (OIH)

Three RCTs have assessed the opioid-sparing effect of perioperative ketamine in adolescents receiving remifentanil based anaesthesia for scoliosis surgery (Perello 2017 **Level II**, n=48, JS 5; Pestieau 2014 **Level II**, n=54, JS 5; Engelhardt 2008 **Level II**, n=34, JS 4). They each found no difference in pain scores and opioid consumption up to 72 h. The validity of using opioid consumption as a surrogate for OIH has limitations; the 2017 RCT also assessed peri-incisional hyperalgesia at 72 h (using Von Frey hairs) but found no difference between groups. Additionally, there was no difference in the measured area of peri-incisional hyperalgesia in patients who had any vs no pain 6 mth later.

The paediatric data differs to the positive findings in adults: see the adult Section 4.6.1.1 Ketamine.

See also Section 10.4.6 for discussion of use of ketamine in opioid-tolerant children and adult Sections 9.7.2 and 9.7.6.4 for use in opioid-tolerant adults.

Adverse effects of ketamine

Generally, when analgesic (low dose) ketamine has been used perioperatively in children, increased incidence of adverse effects has not been reported. IV Ketamine (median dose 0.5 mg/kg) is not associated with PONV during the first 24 h, or psychomimetic manifestations such as hallucinations, dysphoria-euphoria and sedation (Dahmani 2011 **Level I** [QUORUM], 18 RCTs [systemic], n=985). Similar results were found in a more recent meta-analysis assessing PONV at 2 time points (7 RCTs) and psychomimetic effects (6 RCTs) (Michelet 2016 **Level I** [PRISMA], 11 RCTs, n=508) (7 RCT overlap). The odds ratios were similar for these outcomes in the topical/peritonsillar (4 RCTs) and caudal (13 RCTs) administration routes (Dahmani 2011 **Level I** [QUORUM], 35 RCTs, n=1,925).

After Nuss surgery, ketamine added to fentanyl PCA reduced nausea and vomiting incidence over 48 h when compared to fentanyl PCA alone (23 vs 53%) (Cha 2012 **Level II**, n=60, JS 3).

However, when used in the ED, minor adverse effects (mostly dizziness, bad taste in mouth and sleepiness) were more common with IN ketamine vs IN fentanyl: RR 2.5 (95%CI 1.5 to 4.0) (Frey 2019 **Level II**, n=90, JS 5); 100 vs 61% (Reynolds 2017 **Level II**, n=87, JS 3); and 78 vs 41% (Graudins 2015 **Level II**, n=80, JS 5).

In patients who received ketamine for procedural sedation in the ED, the following adverse effects were recorded: airway and respiratory events (3.9%), laryngospasm (0.3%), apnoea (0.8%), emesis (8.4%), any recovery agitation (7.6%), and clinically important recovery agitation (1.4%) (n=8,282) (Green 2009b **Level IV**; Green 2009c **Level IV**).

Neurotoxicity and ketamine

The possible neurodegenerative effect of ketamine (and other analgesic/anaesthetic agents) on the developing brain is under discussion (Davidson 2013 **NR**; Walker 2012c **NR**). Racemic ketamine (with its preservative benzethonium chloride) and S(+) ketamine have been associated with neuronal apoptosis in developmentally regulated cortical and subcortical areas in rodents and sensorineural consequence in animal models following high dose and/or long term IV and IT administration (Davidson 2013 **NR;** Walker 2012c **NR;** Walker 2010 **BS;** Green 2009a **NR**). Conversely, ketamine has demonstrated neuroprotective effects in the presence of noxious stimuli in animals (Cheung 2019 **NR**). Proposed mechanisms include inhibition of neuronal excitotoxicity, and anti-inflammatory effects. The translatability of these findings to humans is questioned and the impact of lower subanaesthetic doses (bolus and perioperative infusion) is uncertain.

See adult Section 4.6.2.1 ketamine regional administration and neurotoxicity issues.

Efficacy

Magnesium (Mg) administered by local infiltration or IV (bolus and/or infusion) has been studied in children having tonsillectomy (Cho 2018a **Level I** [PRISMA], 10 RCTs, n=615; Xie 2017a **Level I** [PRISMA], 10 RCTs, n=665) (9 RCT overlap). In the earlier systematic review, Mg sulphate (IV or local infiltration) vs control does not reduce pain scores (8 RCTs, n=555), but does reduce the number of patients receiving rescue analgesia (RR 0.53; 95%CI 0.31 to 0.91) (5 RCTs, n=305), having emergence agitation (OR 0.18; 95%CI 0.07 to 0.48) (2 RCTs, n=105) and laryngospasm (OR 0.36; 95% CI 0.13 to 0.96) (7 RCTs, n=500) (Xie 2017a **Level I** [PRISMA], 10 RCTs, n=665). The subsequent systematic review found overall Mg (IV or local infiltration) does not reduce early pain scores at ≤1 h but does reduce late pain scores at 24 h vs control (SMD -0.39; 95%CI -0.71 to -0.07) (6 RCTs, n=330), with sub-analysis revealing that local infiltration is effective (SMD -0.62; 95%CI -0.89 to -0.36) (4 RCTs, n=230) and IV route is not (2 RCTs, n=100) (Cho 2018a **Level I** [PRISMA], 10 RCTs, n=615). Mg vs control increases time to first analgesia (SMD 0.75; 95%CI 0.20 to 1.31) (3 RCTs), reduces rescue analgesia administration (SMD -0.39; 95%CI -0.71 to -0.07) (5 RCTs), postoperative agitation at 15 min (SMD -0.31) (3 RCTs) and 1 h (SMD -0.67) (2 RCTs), and laryngospasm (SMD -1.09; 95%CI -2.11 to -0.07) (8 RCTs), and did not alter bleeding risk (3 RCTs). The sample sizes for the subanalyses were not provided.

For scoliosis surgery, the addition of intraoperative Mg (50 mg/kg initial bolus and 8 mg/kg/h infusion) to ketamine (0.2 mg/kg initial bolus and 0.15 mg/kg/h infusion)/remifentanil reduced postoperative PCA-morphine requirements by 29.5% (over 0–48 h) (Jabbour 2014 **Level II**, n=50, JS 5). While, adding the same bolus and slightly higher dosing of intraoperative Mg (10 mg/kg/h) to remifentanil did not reduce 0–24 h hydromorphone requirement vs remifentanil alone (0.38 ± 0.10 mg/kg vs 0.34 ± 0.11 mg/kg), where IV methadone 0.1 mg/kg did (0.26 ± 0.10 mg/kg), with no difference in postoperative pain scores in the three groups (Martin 2018 **Level II**, n=60, JS 4).

For severe migraine, IV Mg bolus (max dose 1–2 g over 15–30 min) in the ED substantially reduced pain severity in 35-48% of paediatric patients (Orr 2018a **Level IV SR**, 21 studies [2 IV Mg], n [IV Mg]=57 [65 migraines]).

For tonsillectomy, the addition of peritonsillar Mg 2-5 mg/kg to local anaesthetic reduced pain scores (4 RCTs) and the number of analgesic requests (WMD -0.68; 95% CI -1.17 to -0.18) (3 RCTs, n=180) (Vlok 2017 **Level I**, 4 RCTs [Mg], n=230).

See also adult NMDA antagonists discussion of magnesium Section 4.6.1.3 and specific to adult Headache 8.6.5.1 , Migraine 8.6.5.2 and Paediatric Migraine 10.9.3.

KEY MESSAGES

Ketamine

1. Perioperative low-dose intravenous ketamine bolus is similarly effective to opioids and superior to placebo in reducing early pain scores and analgesic requirements in children (**U**) (**Level I** [PRISMA]).
2. Perioperative low-dose intravenous ketamine bolus does not increase the postoperative incidence of nausea and vomiting, sedation, agitation, dreams or hallucinations in children (**S**) (**Level I** [PRISMA]).
3. Peritonsillar infiltration and topical application of ketamine for paediatric tonsillectomy reduces early pain scores and analgesic requirements versus placebo (**S**) (**Level I** [PRISMA]).
4. When added to multimodal analgesia, perioperative ketamine (bolus with or without intra/postoperative infusion) in children is not opioid-sparing vs placebo (**S**), although low postoperative pain scores and small sample sizes mean the meta-analysis is underpowered (**Q**) (**Level I** [PRISMA]).
5. There is low level evidence that combination ketamine and opioid PCA improved pain scores and PCA use post Nuss surgery (**N**) (**Level II).**

Magnesium

6. Magnesium (intravenous or peritonsillar infiltration) in children for tonsillectomy reduces postoperative rescue medication use, and increases time to first analgesia versus control; magnesium also reduces risk of postoperative emergence agitation and laryngospasm (**N**) (**Level I** [PRISMA]).
7. Magnesium (locally infiltrated) in children reduces late (24 hour) but not early (<1 hour) pain scores post tonsillectomy versus control (**N**) (**Level I** [PRISMA]).

The following tick boxes represent conclusions based on clinical experience and expert opinion:

☑ High-dose long term ketamine is neurotoxic in animal models. The neurodevelopmental impact in children of subanaesthetic/analgesic doses of ketamine administered by bolus or postoperative infusion is unclear (**U**).

☑ The benefit of perioperative ketamine in preventing remifentanil induced hyperalgesia has not been adequately assessed in paediatric surgery (**U**).

10.4.8 | Alpha-2 agonists

The alpha-2 agonists, clonidine and dexmedetomidine, are attractive for paediatric use with their analgesic, sympatholytic (anxiolytic, haemodynamic modulation), antinausea/antiemetic and behavioural modification/sedative effects (Sottas 2017 NR). Administered as bolus and/or infusion via various routes, both agents have been used in various paediatric settings.

Perioperative use

- Preoperatively as premedication;
- Intraoperatively for controlled hypotension and to modify anaesthetic/perioperative opioid requirements; postoperative nausea and vomiting, shivering and emergence agitation; and
- As local anaesthetic adjuvants (see Section 10.6 and 10.6.3.3).

Use in paediatric and neonatal intensive care units (PICUs/NICUs)

Particularly in ventilated patients (Piotrowski 2015 **Level IV**, n=33 [12 postoperative]; Nemergut 2013 **NR**; Gupta 2012 **Level III-2**; Playfor 2006 **GL**):

- For sedation and analgesia;
- To modify distress or hypertensive response and escalating opioid requirements; and
- To prevent and treat opioid withdrawal symptoms (Honey 2009 **Level IV SR**, 9 studies, n=44; Oschman 2011 **NR**;) and facilitate opioid weaning.

Use in other settings

For similar indications, these agents are used in paediatric ward settings and also for procedural sedation and analgesia in the outpatient, ED and radiology settings (Ter Bruggen 2017 **Level I**, 5 RCTs [paediatric], n=372; Jooste 2017 **Level IV**, n=90; McMorrow 2012 **NR**).

See also the adult Section 4.9 Alpha-2 agonists.

10.4.8.1 | Clonidine

Pharmacokinetics

Bioavailability of clonidine after rectal and epidural administration is high (100%) (Potts 2007 **PK**), but is erratic after nasal drop administration in supine anaesthetised children (Almenrader 2009 **PK**, n=11). Oral bioavailability is lower in children than in adults at 55% when mixed with apple juice (which may influence intestinal transport); thus PO doses greater than 4 mcg/kg should be considered (Larsson 2011 **PK**, n=8); nasal administration has higher bioavailability than oral and Tmax occurs later (Blackburn 2014 **PK**, n=66). Clearance at birth is reduced and matures to achieve 82% of the adult rate at 1 y (Potts 2007 **PK**, n=72 [380 samples]).

The PKs of clonidine have also been assessed during sedation as an adjuvant to morphine and midazolam infusion during ECMO in children, with simulation aiming for a target concentration of 2 ng/mL, suggesting 3 boluses of 5 mcg/kg at 20 min intervals and infusion of 1 mcg/kg/h in children >12 y (Kleiber 2017 **PK**, n=22 [375 samples]). For mechanically ventilated patients, PK simulation suggested optimal clonidine dosing for a target of 2 ng/mL was 2 mcg/kg bolus and infusions up to 2 mcg/kg/h; this regimen should be halved in neonates (Hayden 2019 **PK**).

Efficacy

Clonidine has been used for the above indications for decades by various routes (Basker 2009 **NR;** Nishina 2002 **NR;** Eisenach 1996 **NR**).

Preoperative clonidine 2-4 mcg/kg administration (PO in 10 RCTs, rectal in 1 RCT) reduces postoperative pain scores, analgesic requirement and PONV vs midazolam and placebo, but not fentanyl (Lambert 2014 **Level I** [Cochrane], 11 RCTs [comparators: 6 midazolam, 4 placebo and 1 fentanyl], n=748). An earlier review draws similar conclusions (Dahmani 2010 **Level I**, 10 RCTs, n unspecified) (4 RCT overlap). It additionally reports superiority of clonidine vs midazolam for sedation at induction (OR 0.49; 95%CI 0.27 to 0.89) (2 RCTs) and superiority vs diazepam for PONV (OR 0.34; 95%CI 0.13 to 0.94) (2 RCTs). The same review reports reduced emergence agitation incidence (OR 0.25; 95%CI 0.11 to 0.58) (3 RCTs). This is also confirmed for intraoperative IV clonidine administration vs placebo (OR 0.5; 95%CI 0.26 to 0.95) (Pickard 2014 **Level I,** 2 RCTs [clonidine], n=170; Ydemann 2018 **Level II**, n=379, JS 5).

Typical bolus clonidine doses are 1–3 mcg/kg: IV, regionally, for nerve blocks and for infiltration (see Section 9.6).

Clonidine has been infused in cardiac surgery and intensive care at widely ranging rates: 0.18 to 1–3 mcg/kg/h (Lambert 2014 **Level I** [Cochrane], 1 RCT: Hunseler 2014 **Level II**, n=213, JS 5; Basker 2009 **NR**).

Aerosolised IN clonidine 3–8 mcg/kg has unreliable sedative efficacy and time to onset of effect (Larsson 2012 **Level II**, n=60, JS 5). This route has not been used for analgesic indications.

10.4.8.2 | Dexmedetomidine

Dexmedetomidine is more alpha-2 selective than clonidine. Its off licence use has increased in various paediatric settings (Sottas 2017 **NR**) (see below).

Pharmacokinetics

Dexmedetomidine PKs have been studied extensively in children. Population parameter estimates [and between subject variability] for a 2-compartment model were: clearance (CL) 42.1 L/h/70kg [31%], central volume of distribution (V1) 56.3 L/70kg [61%], inter-compartment clearance (Q) 78.3 L/h/70kg [37%] and peripheral volume of distribution (V2) 69.0 L/70kg [47%] (Potts 2009 **PK**, n=95 [730 observations]). Clearance matures with age and increases from 18.2 L/h/70kg at birth in a term neonate to reach 84.5% of the mature value by 1 y of age. Simulation of published infusion rates that provide adequate sedation for PICU patients found a target therapeutic concentration of between 0.4 and 0.8 mcg/L. This estimate has been reviewed and an EC_{50} of 0.9 mcg/L (95%CI 0.45 to 2.34) for sedation proposed by modelling PK-PD data (Li 2018a **Level II PK**, n=8 [3 way cross over study]). The equilibration half time between plasma and the effect compartment was 3.3 min (95%CI 1.8 to 4.7), indicating that slow onset of effect after enteral delivery is mostly due to slow absorption and not a delay between plasma concentration and effect site.

Subsequent IV dexmedetomidine PK studies in children post 1-2 mcg/kg for bronchoscopy, radiological imaging (Vilo 2008 **PK**, n=16), prior to (Liu 2017 **PK**, n=39), and during general surgery, following loading dose and infusion of 0.2–1.4 mcg/kg/h post liver transplantation (Weerink 2017 **NR PK**) are consistent with the earlier study (Potts 2009 **PK**, n=95). Hepatic function, assessed using INR, may alter clearance. Clearance after liver transplantation varied widely and was associated inversely with INR and not weight (Damian 2020 **Level IV PK**, n=20). Titration to clinical effect, rather than weight-based dosing, was suggested for this population, with attention to changes in INR.

Bioavailability in adults is 82% after intranasal and buccal administration (Weerink 2017 **NR PK**) with similar time to onset of 1 mcg/kg by atomiser (47.5 min; 95%CI 25 to 135) and drop administration (60 min; 95%CI 30 to 75) vs IV (15 min; 95%CI 15-20) (Li 2018a **Level II PK**, n=8). In children, after orogastric administration bioavailability was only 16% (Weerink 2017 **NR PK**); while after IN atomiser administration, bioavailability was 84% (95%CI 70 to 98%) (Miller 2018 **Level III-1 PK**, n=18) and lower with intranasal syringe administration (lying supine with head extended, where more pharyngeal run off possibly occurred) (Wang 2019a **PK**, n=13). Absorption half time was 18 to 20 min in both studies.

Efficacy

Several overlapping reviews have been performed with similar findings mostly in favour of dexmedetomidine. Data for emergence agitation is included here as severe pain in PACU may mimic this. Following various paediatric surgery types (mostly tonsillectomy, but also ear, laparoscopic appendectomy and genitourinary surgery), dexmedetomidine:

IV/IN bolus only 0.15–2 mcg/kg intraoperatively vs placebo reduces

- Postoperative pain (RR 0.51; 95%CI 0.32 to 0.81) (2 RCTs, n=138) (Schnabel 2013 **Level I** [PRISMA], 11 RCTs [10 IV, 1 IN], n=874) and pain in PACU (RR 0.41; 95%CI 0.25 to 0.65) (5 RCTs, n=356) (Zhang 2014 **Level I** [PRISMA], 12 RCTs, n=812) (5 RCT overlap);
- The need for rescue analgesia (OR 0.16; 95%CI 0.05 to 0.48) (3 RCTs, n=168) (Pickard 2014 **Level I**, 10 RCTs [dexmedetomidine], n=669) (7 RCT overlap) and for postoperative opioid rescue (RR 0.4; 95%CI 0.26 to 0.62) (4 RCTs, n=249), but does not reduce overall morphine requirement (2 RCTs, n=98) (Schnabel 2013 **Level I** [PRISMA] [10 IV, 1 IN], n=874);

- Emergence agitation (OR 0.22; 95%CI 0.14 to 0.33) (8 RCTs, n=499) (Pickard 2014 **Level I**, 10 RCTs [dexmedetomidine], n=669) (7 RCT overlap) (RR 0.35; 95%CI 0.26 to 0.45) (12 RCTs, n=812) (Zhang 2014 **Level I** [PRISMA], 12 RCTs, n=812) (5 RCT overlap).

IV bolus 0.15–2 mcg/kg with short term infusion 0.1–0.7 mcg/kg/h (in 8 RCTs) vs placebo reduces:

- Pain intensity in PACU (MD -1.18; 95%CI -1.88 to -0.48) (13 RCTs, n unspecified) and
- Postoperative opioid consumption in PACU (RR 0.31; 95%CI 0.17 to 0.59) (11 RCTs, n unspecified);
- But does not reduce PONV (RR 0.67; 95%CI 0.41 to 1.08) (3 RCTs, n=290) (Bellon 2016 **Level I** [PRISMA], 14 RCTs, n=1,463) (6 & 7 RCT overlap).

In tonsillectomy only, IV dexmedetomidine 0.15–2 mcg/kg (intraoperative bolus or over 10 min and in 5 RCTs by infusion: pre, during or post surgery) vs mixed comparators (4 opioid, 10 placebo, 1 no therapy) reduces:

- Postoperative pain scores in PACU (MD-1.82; 95%CI -2.5 to -1.13) (5 RCTs, n=480 [3 placebo, 1 opioid, 1 no therapy]);
- Analgesic requirement in PACU (OR -0.59; 95%CI -0.89 to -0.3) (7 RCTs, n=680);
- The need for rescue overall (OR 0.44; 95%CI 0.26 to 0.73) (11 RCTs, n=1,233); and
- Emergence agitation score in PACU (MD -1.4; 95%CI -2.1 to -0.7) and incidence of EA (OR 0.28; 95%CI 0.21 to 0.36) and severe EA (OR 0.22; 95%CI 0.12 to 0.38) (Cho 2018b **Level I**, 15 RCTs, n=1,552) (3 & 4 RCT overlap).

Compared to intraoperative opioids, IV dexmedetomidine 0.75–4 mcg/kg reduces

- Postoperative pain (RR 0.49; 95%CI 0.25 to 0.94) (3 RCTs, n=234);
- But does not reduce the need for postoperative opioids (RR 0.77; 95%CI 0.6 to 1.1) (4 RCTs, n=394) (Schnabel 2013 **Level I** [PRISMA], 11 RCTs [10 IV, 1 IN], n=874).

Subsequent RCTs or ones not included in the above reviews had similar findings. In tonsillectomy, IV dexmedetomidine 0.3 mcg/kg reduced EA vs propofol 1 mg/kg and both were effective given IV 5 min before surgery cessation vs saline placebo (Cho 2018b **Level I**, 1 RCT: Ali 2013 **Level II**, n=120, JS 5). While, IV dexmedetomidine 1 mcg/kg given 10 min preoperatively vs placebo had similar postoperative pain scores, reduced EA, with lower HR and stable mean blood pressure intraoperatively (10 mmHg lower at all time points) (Sharma 2019 **Level II**, n=60, JS 4).

For myringotomy in children (1–8 y), post induction administration of IN dexmedetomidine 1 mcg/kg vs IN fentanyl 2 mcg/kg, with and without midazolam premedication, achieved similar postoperative pain scores (Dewhirst 2014 **Level II**, n=100, JS 5) .

For strabismus surgery, intraoperative IV dexmedetomidine 1 mcg/kg bolus with 1 mcg/kg/h vs IV ketamine 1 mg/kg bolus with 1 mg/kg/h similarly reduced EA and pain scores on the ward (but not in PACU), with both superior to placebo (Chen 2013 **Level II**, n=84, JS 5).

For cardiac surgery, intraoperative dexmedetomidine infusion 0.5 mcg/kg/h reduced postoperative fentanyl and inflammatory markers of the post surgery stress response, with similar pain scores vs placebo (Sun 2017 **Level II**, n=50, JS 4).

Following scoliosis surgery, postoperative IV dexmedetomidine infusion 0.4 mcg/kg/h (for 24 h) in addition to IV morphine PCA had no effect on morphine consumption or adverse effects (Sadhasivam 2009 **Level III-2**). In ventilated scoliosis patients, IV dexmedetomidine 0.4 mcg/kg/h vs IV midazolam 0.1 mg/kg/h reduced pain scores and modestly reduced low 24 h fentanyl consumption (124 mcg $\pm$ 28 vs 165.8 $\pm$ 33) (Aydogan 2013 **Level II**, n=32, JS 4).

Postalveolar bone graft surgery in children, dexmedetomidine 0.2–0.4 mcg/kg/h was administered for <24 h as an alternative to opioid infusion (Lopez 2018 **Level III-3**, n=54). Adjuvant

infusion following craniosynostosis repair is also described (Kattail 2018 **Level IV**, n=4). For a 2 y old child with chemotherapy-induced enterocolitis, adjuvant dexmedetomidine 0.05–0.2 mcg/kg/h coadministration for 5 d improved pain control and allowed hydromorphone infusion reduction (Winton 2011 **CR**).

10.4.8.3 | Adverse effects of alpha-2 agonists

Haemodynamic effects

Hypotension and bradycardia are desirable effects with use of these agents for "controlled hypotension" or blunting of pressor response. Alpha-2 agonists have provided cardiac stability in the setting of paediatric cardiac surgery, intensive care patients (Gupta 2012 **Level III-2**; Sottas 2017 **NR**; Basker 2009 **NR**; Phan 2008 **NR**) and in supraventricular tachycardia eg in neonates and children requiring cardiac surgery (Tobias 2013b **NR**). The haemodynamic effects can be undesirable and are variably reported in RCTs and thus the reviews/meta-analyses.

For systemic clonidine:

- RCTs with clonidine 2–5 mcg/kg reported no difference overall in hypotension or bradycardia incidence but interpretation was complicated by the use of atropine pretreatment, with no comments made on the use of corrective interventions (Lambert 2014 **Level I** [Cochrane], 4 RCTs, n=279); two included trials of 2 vs 4 mcg/kg clonidine vs placebo were underpowered to detect a difference for hypotension and bradycardia – defined as a 20% decrease from baseline, which occurred in 10 of 60 clonidine-treated vs 0 of 30 placebo-treated (Mikawa 1996 **Level II**, n=90, JS 4) and hypotension defined as <70 mmHg and bradycardia defined as <60 beats/min occurred in 4 of 30 clonidine-treated and 0 of 15 midazolam-treated (Cao 2009 **Level II**, n=45, JS 3).

For dexmedetomidine, significant change that requires medical intervention occurs uncommonly:

- The two largest reviews of IV administration do not comment on bradycardia and hypotension (Cho 2018b **Level I**, 15 RCTs, n=1,552; Bellon 2016 **Level I** [PRISMA], 14 RCTs, n=1,463) (7 RCT overlap). Two earlier reviews stated no haemodynamic events were reported in the included RCTs (Zhang 2014 **Level I** [PRISMA], 12 RCTs, n=812; Pickard 2014 **Level I,** 10 RCTs [dexmedetomidine], n=669). One series documented bradycardia (>20% decrease from baseline) in 4% of children who received dexmedetomidine 3 mcg/kg for MRI sedation (Mason 2008 **Level III-2**, n=767 referenced in Pickard 2014 **Level I**, 10 RCTs [dexmedetomidine], n=669);
- One review documents 5 RCTs including haemodynamic outcomes (4 RCTs [placebo], n=180 & 1 RCT [opioid], n=60) where 3 dexmedetomidine recipients had >30% change requiring intervention: 1 received atropine for bradycardia and 2 saline bolus and isoflurane decrease for hypotension (1 RCT [placebo], n=26); while no patients needed rescue treatment for bradycardia in the RCT with opioid comparator (Schnabel 2013 **Level I** [PRISMA], 11 RCTs, n=874).

Sedation and delay to discharge

The sedative effect is often useful and therapeutic in children but may be undesirable if delaying discharge. Several small perioperative studies assessing the outcome of time spent in PACU or delay in discharge have been incorporated in the systematic reviews summarised below.

Clonidine RCTs conflict regarding time to discharge:

- With delay (WMD 10.8 min; 95%CI 4.2 to 17.5) and increased sedation frequency post discharge vs placebo (Pickard 2014 **Level I**, 1 RCT: Malviya 2006b **Level II**, n=120, JS 5);
- And slightly earlier discharge vs placebo (1 RCT, n=46), with no difference vs midazolam (2 RCTs, n=194) (Lambert 2014 **Level I** [Cochrane], 11 RCTs, n=748).

While following IV dexmedetomidine, minimal clinical impact is reported on:

- Time to extubation (WMD 0.6 min; 95%CI 0.28 to 0.96) (9 RCTs, n=555) and emergence (WMD 1 min; 95%CI 0.4 to 1.6) vs placebo (8 RCTs, n=548) (Zhang 2014 **Level I** [PRISMA], 12 RCTs, n=812);
- Duration of PACU stay in 3 reviews (1 and 2 RCTs overlap): WMD 4.6 min (95%CI -0.08 to 9.275) vs placebo (3 RCTs, n=256) (Zhang 2014 **Level I** [PRISMA], 12 RCTs, n=812), SMD -0.37 (95%CI -1.02 to 0.28) vs placebo or control (5 RCTs, n=792) (Cho 2018b **Level I**, 15 RCTs, n=1,552) and 3 min vs placebo (4 RCTs, n=275) (Pickard 2014 **Level I**, 10 RCTs [dexmedetomidine], n=669);
- Time to discharge (2 RCTs, n=92) (Pickard 2014 **Level I**, 10 RCTs [dexmedetomidine], n=669).

Respiratory events

No oxygen desaturation or postoperative respiratory depression was reported for dexmedetomidine treated patients, while 3 children in the placebo group had bronchospasm (Zhang 2014 **Level I** [PRISMA], 12 RCTs, n=812) and one placebo recipient required oxygen supplementation (5 RCTs, n=295) (Schnabel 2013 **Level I** [PRISMA], 11 RCTs, n=874);

Incidents of desaturation post tonsillectomy occurred less in dexmedetomidine treated vs placebo or control (OR 0.40; 95%CI 0.21 to 0.77) (6 RCTs, n=843) (Cho 2018b **Level I**, 15 RCTs, n=1,552).

Neurotoxicity

In contrast to most anaesthetic agents used, neuraxial clonidine has not been implicated in any reports or studies of neural toxicity/apoptosis and neither has epidural or intraperitoneal dexmedetomidine in animal models (Davidson 2013 **NR;** Walker 2012b **NR**). With dexmedetomidine, some changes are seen with direct neural application of high dose in animal studies. In rats who received a single injection brachial plexus block, the addition of dexmedetomidine 60 mcg/kg to ropivacaine 0.5% reduced inflammatory cytokine (TNF-α and IL-6) amounts in the nerves vs saline (n=15) (Kang 2018 **BS**, n=39). While administration of high dose dexmedetomidine 60 mcg/kg alone increased inflammatory cytokines (including caspase 3, an important apoptosis protease) in the nerves of d 5 rat pups (neonatal equivalent), while moderate dose 20 and 40 mcg/kg did not, in either d 5 or d 14 (child equivalent) rat pups (n=24). In rabbits who received a femoral nerve CPNC infusion (for 72 h), the addition of dexmedetomidine 3 mcg/mL to ropivacaine 0.25% was associated with myelin lamellar structure changes; not seen with 1-2 mcg/mL added to ropivacaine, ropivacaine alone or normal saline (Wang 2019b **BS**, n=30). Pre-emptive intraperitoneal administration of dexmedetomidine ameliorated the effect of intrathecal administration of toxic doses of 10% lidocaine in rats, an effect that was reversed by intraperitoneal injection of yohimbine or a specific protein kinase C inhibitor (Xu 2018a **BS**, n=64). The neuroprotective effect of dexmedetomidine in brain injury is not discussed here.

KEY MESSAGES

1. Preoperative oral clonidine reduces postoperative pain scores and analgesic requirement in children compared to placebo or midazolam but not fentanyl (**U**) (**Level I** [Cochrane Review]).
2. Preoperative oral clonidine reduces postoperative nausea and vomiting in children compared to placebo or midazolam (**U**) (**Level I** [Cochrane Review]).
3. Preoperative intranasal dexmedetomidine reduces postoperative pain scores, rescue analgesic requirements and emergence agitation with minimal adverse effects vs placebo (**N**) (**Level I** [PRISMA]) and mixed comparators (**N**) (**Level I**).
4. Intraoperative dexmedetomidine reduces postoperative pain scores (**U**) (**Level I** [PRISMA]) and need for postoperative rescue analgesia (**Q**) (**Level I**) including opioid (**U**) (**Level I** [PRISMA]) in children compared to placebo, with minimal impact on time to discharge (**N**) (**Level I** [PRISMA]) via intravenous (**S**) (**Level I** [PRISMA]) and intranasal routes (**S**) (**Level I**).

The following tick box represents conclusions based on clinical experience and expert opinion:

☑ Alpha-2 agonists offer benefits in addition to analgesia in children in the perioperative, intensive care and procedural settings. These benefits include anxiolysis, sedation (MAC sparing), behavioural modification, prevention or treatment of opioid withdrawal (facilitating opioid weaning) (**U**) and reduction of emergence agitation (**S**).

10.4.9 | Alpha-2-delta ligands (gabapentinoids)

There is increased off licence use of alpha-2-delta ligands in children following the adult experience in various pain states; paediatric data to support this is heterogeneous and limited (Egunsola 2019 **Level III-3 SR** [PRISMA], 7 RCTs, n=379). The meta-analysis includes the small studies quoted below. They demonstrate efficacy for multi-day perioperative but not single preoperative dosing.

Multi-segment scoliosis surgery

A single preoperative dose of gabapentin 600mg (≈11 mg/kg) did not reduce opioid consumption over 24 h vs placebo (Mayell 2014 **Level II**, n=35, JS 5).

Gabapentin over 5 d (15mg/kg preoperatively then 15mg/kg/d) reduced total morphine consumption in PACU, postoperative day (POD) 1 and 2 by 16-23% and pain scores in PACU and the first postoperative morning only, with no differences in other outcomes vs placebo (Rusy 2010 **Level II**, n=59, JS 3).

Gabapentin over 3 d (5–10mg/kg preoperatively then 7.5–22.5mg/kg/d [max 900 mg]/d) reduced:

- POD 1–3 pain scores and opioid use POD 1–2 (Trzcinski 2019 **Level III-2**, n=129);
- The time required to meet physical therapy goals, but not length of stay [LOS] (Thomas 2018b **Level III-3**, n=101); and
- POD 1 (but not day of surgery) PCA opioid consumption by 40%, alone and in combination with transdermal clonidine, with earlier PO intake, ambulation and for the combination slight clinical impact on LOS (Choudhry 2017 **Level III-3**, n=127).

Other surgery types and conditions

For tonsillectomy, preoperative gabapentin (dose 10-20 mg/kg in the 3 paediatric of 6 RCTs) and pregabalin (2 RCTs: 1 mixed, 1 adult) similarly reduce pain in the first 8 h, analgesic requirements in the first 24 h and PONV without increasing adverse effects (Hwang 2016a **Level I** [PRISMA], 8 RCTs [3 adult, 2 mixed, 3 paediatric], n=608).

In laparoscopic appendicectomy, varying doses of pre and postoperative gabapentin for 3 d (range 4.4–30.4 mg/kg/d) alone or with postoperative ketorolac reduced postoperative opioid consumption for simple and complicated appendicitis with no difference in time to pain score ≤3 or LOS (Baxter 2018 **Level III-2**, n=87).

For the Nuss procedure in adolescents, low dose gabapentin 100–200mg three times daily for 72 h has been used in combination with PCA hydromorphone, clonidine patch and local anaesthetic via wound catheter with similar pain scores to those in thoracic epidural recipients (ropivacaine 0.2% with hydromorphone 10 mcg/mL) (Choudhry 2016 **Level III-3**, n=32).

In children with severe cerebral palsy (Gross Motor Function Classification System [GMFCS] IV–V), gabapentin (7–18 mg/kg/dose or 900mg/d) improved pain (and dystonia) frequency and impact (in patients co-receiving baclofen, diazepam and botulinum injections) (Harvey 2018 **Level IV**, n=11 doctors, 57 patients; Liow 2016 **Level IV**, n=82).

In paediatric burns, in addition to or instead of antihistamines (in inpatient and outpatient settings), alpha-2-delta ligands reduced itch and pain: gabapentin 15 mg/kg/d (prescribed for 53% of patients) (Nieuwendijk 2018 **Level IV**, n=413) and 24–34 mg/kg/d (where 23 patients poorly responded to gabapentin had pregabalin 3.7–6.5 mg/kg/d added) (Kaul 2018 **Level IV**, n=136).

In paediatric oncology, preoperative and therapeutic gabapentin use 900 mg/d for 30 d reduced phantom limb pain incidence at 60 d (43 vs 77%) with similar reduction of early perioperative pain scores vs placebo (Wang 2018 **Level II**, n=45, JS 5). Gabapentin 20–40mg/kg/d for phantom limb pain is also described in 3 case series (DeMoss 2018 **NR**). Pregabalin 1.25–2.5 mg/kg/d, as part of a multimodal analgesic regimen, has been used in a 4 y old girl with a severe crush injury requiring foot amputation (Wossner 2017 **CR**).

In vincristine induced painful peripheral neuropathy (used for solid tumours and leukaemia), 8 weeks of pregabalin 150-300 mg (4–5.7 mg/kg)/d decreased mean pain score by 59% from baseline with dose dependent effect (Vondracek 2009 **Level IV**, n=30). Gabapentin 15–70 mg/kg/d pre-emptive and therapeutic use is described in a larger series of leukaemic patients (Anghelescu 2011b **Level IV**, n=112 [gabapentin-treated]).

In children with chronic pain from fibromyalgia and CRPS type 1, alpha-2-delta ligands have been used with some benefit (Cooper 2017c **Level I** [Cochrane], 2 RCTs, n=141) as well as in painful restless legs syndrome (Frenette 2011 **NR**).

The use of alpha-2-delta ligands in prevention of chronic postsurgical pain in children has not been studied.

For alpha-2-delta ligands use in adults, see Sections regarding efficacy in acute 4.8.1.1 and chronic pain 4.8.2.1, and Section 1.4.6.3 for prevention of chronic postsurgical pain.

KEY MESSAGES

1. Multi-day perioperative (but not single preoperative) gabapentin dosing reduces postoperative morphine consumption vs placebo following multilevel posterior spinal fusion for adolescents with idiopathic scoliosis (**N**) (**Level II**).
2. Multiday perioperative gabapentin reduces phantom limb pain incidence vs placebo in paediatric oncology amputation surgery (**N**) (**Level II**).
3. Preoperative gabapentin and likely pregabalin improve analgesia after tonsillectomy in children and reduce PONV without increasing adverse effects (**N**) (**Level I** [PRISMA]).

The following tick boxes represent conclusions based on clinical experience and expert opinion:

☑ Alpha-2 delta ligands use in children for acute (and chronic) pain conditions is expanding based mostly on expert opinion and case series. The pain indications are similar to those for adults with similar benefit and adverse event profiles (**N**).

☑ Gabapentin and pregabalin are used to manage pruritus and neuropathic pain following burn injury in children (**N**).

☑ The use of alpha-2 delta ligands for the prevention of chronic postsurgical pain in children has not been studied (**N**).

10.4.10 | Corticosteroids

Systemic corticosteroids

The impact of systemic corticosteroid use on various outcomes in children post-surgery or with acute pharyngitis has been assessed; for data on corticosteroid use in combination with local and regional techniques see paediatric Section 10.6.2.6. See also Section 4.12.1 for use of systemic corticosteroids in adults.

10.4.10.1 | Efficacy in painful medical conditions

Pharyngitis/Sore throat

For pharyngitis (proven bacterial or severe symptoms) presenting in the primary care or emergency department setting, PO dexamethasone 0.6 mg/kg (max 10 mg) achieved onset of analgesia 5–24 h earlier than placebo (measured with three different scoring systems), with a single dose as effective as a 3 d course (Sadeghirad 2017 **Level I**, 3 RCTs [paediatric], n=393) (see Section 8.6.7.5 for adult data which includes information on steroid, as well as antibiotic and topical treatments). Data is not available for systemic corticosteroid administration for post extubation sore throat in children.

Septic arthritis

In low quality RCTs, 4 d of dexamethasone 0.15–0.2mg/kg 6–8 h reduces the number of days of IV antibiotic treatment (MD -2.77; 95%CI -4.16 to -1.39) (Delgado-Noguera 2018 **Level I** [Cochrane], 2 RCTs, n=149). At 12 mth follow-up, dexamethasone may increase the proportion of patients without pain (RR 1.33; 95% CI 1.03 to 1.72) (1 RCT, n=49) and with normal function of the affected joint (RR 1.32; 95% CI 1.12 to 1.57) (1 RCT, n=100). Small study numbers limit the capacity to assess serious adverse effects.

Henoch-Schonlein Purpura and abdominal pain

In case series and retrospective analyses only of patients with Henoch-Schonlein Purpura [HSP] and abdominal pain, corticosteroids reduced pain, usually within 24 h (Haroon 2005 **NR**). In HSP associated pancreatitis, corticosteroid use (pulsed 2nd daily IV methylprednisolone 10–15 mg/kg/d, followed by PO prednisolone 1 mg/kg/d) for 2–3 wk reduced abdominal symptoms including pain (Zhang 2018 **Level IV**, n=13).

10.4.10.2 | Efficacy in postoperative pain

Dental surgery

Following paediatric dental surgery under general anaesthesia, single-dose IV dexamethasone 0.3 mg/kg (max 8 mg) did not improve pain scores or oral intake but reduced postoperative vomiting (McIntyre 2012 **Level II**, n=200, JS 5).

Strabismus surgery

The combination of single dose IV dexamethasone 0.15 mg/kg and intraoperative superhydration (30 mL/kg/h until oral intake) vs single therapy reduced PONV, pain scores and paracetamol use with increased time to first analgesic request (Sayed 2016 **Level II**, n=120, JS 5).

Knee arthroscopy

In teenagers receiving femoral nerve block, neither adjuvant IM or perineural dexamethasone further improved analgesia (Veneziano 2018 **Level II**, n=77, JS 5).

Adenotonsillectomy

Beneficial effects upon multiple outcomes are reported for single-dose dexamethasone in children 1 d following tonsillectomy (Steward 2011 **Level I** [Cochrane], 19 RCTs, n=1,756). Compared to placebo, IV dexamethasone 0.15–1.0 mg/kg (max 8–25 mg) improved postoperative pain scores (MD -1.1/10; 95%CI -1.7 to -0.4) (8 RCTs, n=652), reduced postoperative vomiting (RR 0.49; 95%CI 0.41 to 0.58) (15 RCTs, n=1,273) and resulted in an earlier return to soft diet (RR 1.45; 95%CI 1.15 to 1.83) (5 RCTs, n=452). A subanalysis to assess dose-dependent effect was not performed. A subsequent systematic review of adult and paediatric RCTs includes RCTs with lower dosing to 0.05 mg/kg and PO and local infiltration routes (see below) (Titirungruang 2019 **Level I**, 64 RCTs [42 paediatric], n=6,327) (16 RCT overlap). This meta-analysis has further comparisons of IV route with comparator arms. There were consistent findings with IV administration preoperatively or at time of induction (in mostly paediatric RCTs, some including adults) reducing pain scores across four time periods of <24 h (22 RCTs, n=1,868), 1 d (19 RCTs, n=1,520), 3 d (6 RCTs, n=346) and 7 d (5 RCTs, n=266) and PONV (OR 0.24; 95%CI 0.18 to 0.33) (35 RCTs, n=3,415).

An RCT (excluded from the 2011 Cochrane review due to early termination) compared dexamethasone 0.05, 0.15 and 0.5 mg/kg (max 20 mg) and demonstrated a dose-dependent effect for PONV (Czarnetzki 2008 **Level II**, n=215, JS 5). The reason for termination was a dose-dependent increase in bleeding in dexamethasone-treated patients (above those ibuprofen-treated) - see bleeding risk discussion below.

IV dexamethasone 0.5 mg/kg with IV ketamine 0.5 mg/kg reduced pain scores, analgesic requirement and vomiting vs single agent therapy and placebo (Safavi 2012 **Level II**, n=120, JS 4).

IV dexamethasone 0.5 mg/kg (max 16 mg) was compared with infiltration with 2–4 mL LIA (2% lidocaine with 1:400, 000 adrenaline [6 mL], 0.5% bupivacaine [3 mL], 25 mcg fentanyl, 50 mcg clonidine). The LIA group had a lower incidence of PONV, pain on jaw opening and swallowing and reduced analgesic use POD 1–5 (Naja 2017 **Level II**, n=129, JS 5).

Following paediatric tonsillectomy, multiday PO prednisolone 0.25–0.5mg/kg (max 10-20 mg/d) for 5–7 d did not reduce PONV, or pain at POD 3 or 7 (3 RCTs, n=441) (Titirungruang 2019 **Level I**, 3 RCTs [prednisolone], n=441).

In comparison with ibuprofen for 4 d (where patients co-received paracetamol for 7 d), adjunctive PO prednisolone for 7d was inferior in pain relief, rescue analgesic use, PONV, sleep and oral intake (Aveline 2015 **Level III-3**, n=1,231). Alternate day therapy with PO dexamethasone in addition to ibuprofen and paracetamol reduced phone calls regarding pain and haemorrhage (Redmann 2018 **Level III-3**, n=1,200).

10.4.10.3 | Bleeding risk post-tonsillectomy

Five systematic reviews of dexamethasone have included the above early terminated RCT and have qualified the issue of bleeding (Titirungruang 2019 **Level I**, 64 RCTs [42 paediatric], n=6,327; Plante 2012 **Level I**, 29 RCTs [19 paediatric], n=2,674; Shargorodsky 2012 **Level I**, 12 RCTs [paediatric], n=1,180; Geva 2011 **Level I**, 14 RCTs [11 paediatric], n=1,429; Bellis 2014 **Level III-1 SR**, 15 RCTs, n=1,693 and 3 studies, n=2,088) (4 to 14 RCTs overlap). The included studies assess haemorrhage as primary or secondary, requiring readmission, transfusion or reoperation and with 6 h to 14 d follow-up. The largest review of RCTs reports an overall bleeding rate of 4.4% (Plante 2012 **Level I**, 29 RCTs [19 paediatric], n=2,674). Dexamethasone does not increase the overall risk of bleeding post tonsillectomy (OR 0.96; 95%CI 0.66 to 1.40 for pooled adult and paediatric data, results comparable regardless of age). However, reoperation for bleeding is increased in children (OR 3.43; 95%CI 1.29 to 9.13) (8 RCTs, n=679), but not in adults (4 RCTs, n=499). The most recent meta-analysis reports no increased odds for either primary (15 RCTs, n=1,740) or secondary haemorrhage (23 RCTs, n=2, 440) (Titirungruang 2019 **Level I**, 64 RCTs [42 paediatric], n=6,327). A retrospective US paediatric cohort study found statistical, but minimal clinical difference in revisits for bleeding in 30 d postoperatively in dexamethasone vs non-dexamethasone treated (3.1 % vs 2.7, difference 0.4 %; 95% CI 0.13 to 0.67) with a small increase risk seen across three age strata (Mahant 2014 **Level III-2**, n=139,715 [97,242 dexamethasone treated]). A subsequent retrospective review with a prevalence of 2.8% secondary haemorrhage did not find a relationship of haemorrhage to dexamethasone (assessed with linear and quintile dose models) (Yiu 2017 **Level IV**, n=9,843). Older age (OR 1.08) and a primary haemorrhage (OR 2.89) were predictors (See Section 10.4.2 Nonselective NSAIDs where age and chronic tonsillitis as the indication for surgery are predictors).

10.4.10.4 | Non-systemic corticosteroids

See Sections 10.6.2.6 for adjuvant use including infiltration, 10.6.5 for topical application and 10.6.6 for comparator use in nerve blocks for tonsillectomy.

KEY MESSAGES

1. Single dose intravenous dexamethasone reduces pain post tonsillectomy, postoperative vomiting and time to soft diet commencement in children (**U**) (**Level I** [Cochrane Review]).
2. Intavenous dexamethasone does not increase the overall risk of bleeding post tonsillectomy but increases the risk of reoperation for bleeding in children (S) (**Level I**).
3. Oral dexamethasone (given in addition to antibiotics) shortens the time to onset of pain relief in pharyngitis in children (**U**) (**Level I**).
4. Oral prednisolone multiday course post tonsillectomy does not reduce pain outcomes at day 3 or day 7 or postoperative nausea and vomiting (**N**) (**Level I**).

10.4.11 | Systemic lidocaine infusions

Systemic lidocaine infusions are used in the paediatric setting for patients experiencing severe refractory pain. As per many analgesic interventions, this has been extrapolated from practice in adults (See Section 4.4.1.1). Paediatric hospital guidelines have been created based upon adult dosing (RCH 2017 **GL**)

In young children <6 y having laparoscopic inguinal hernia repair, intraoperative IV lidocaine 1.5mg/kg and 1 mg/kg/h (17 mcg/kg/min) reduced PACU pain scores vs placebo (Lee 2019 **Level II**, n=66, JS 5).

In young children <6 y having abdominal surgery, IV lidocaine (initial 1.5mg/kg and infusion 1.5mg/kg/h (25mcg/kg/min) for <6 h) vs placebo reduced postoperative fentanyl requirement on POD 1 and 2, time to return of bowel function 19 vs 23 h and hospital stay by 2 d (El-Deeb 2013 **Level II**, n=80, JS 5). Plasma concentrations at 0.5 and 4 h were ≈3 mcg/mL.

For various surgeries (including spinal fusion, Nuss surgery and nephrectomy) in older children (median age 14 y), perioperative IV lidocaine infusion ≈0.86 mg/kg/h (14.4 mcg/kg/min) for 31 ± 22 h has been used (Lemming 2019 **Level IV**, n=50). This case series did not provide detail of the patients' multimodal analgesic therapy; adverse events were experienced by 22% of patients (at various rates of 0.53−1.26 mg/kg/h (8.8−21 mcg/kg/min)), with discontinuation in 9% and dose reduction in 4%.

See also Sections 10.8.1, 10.9.3 and 10.9.5 where similar and higher dosing have been used in paediatric cancer pain, migraine and sickle cell disease respectively.

KEY MESSAGES

1. Perioperative intravenous lidocaine infusion in abdominal surgery in children improved various pain and non-pain related postoperative outcomes (**N**) (**Level II**).

The following tick box represents conclusions based on clinical experience and expert opinion:

☑ Dosing of perioperative lidocaine infusions have been extrapolated from use in adults and pharmacokinetic study is warranted to determine safe dosing practices in children (**N**).

10.5 | Opioid infusions and Patient Controlled Analgesia (PCA) in children

This section incorporates the techniques of parenteral administration of opioids to children via continuous infusion and patient controlled analgesia (PCA) devices, including a subsection on nurse-controlled and parental proxy. As intermittent intramuscular (IM) injections are distressing for children, parenteral administration via the intravenous (IV) route is preferred; if peripheral perfusion is normal, the subcutaneous (SC) route can be used (McNicol 1993 **Level IV**) with similar safety and efficacy to the IV route (Doyle 1994a **Level II**, n=60, JS 3). Procedure-specific dose recommendations and evidence for the use of these parenteral techniques have been published (APAGBI 2012 **GL**). Large-scale audits (of >10,000 children) provide data for serious clinical incidents and adverse effects associated with the use of these parenteral opioid techniques (see individual subsections and Section 10.5.5 Overall safety at the end of this section).

10.5.1 | Opioid infusions

10.5.1.1 | Pharmacokinetics of opioid infusions

Pharmacokinetic data has provided support for age-adjusted weight-based initial dosing recommendations for morphine infusion for postoperative pain: 10 mcg/kg/h in neonates, 15 mcg/kg/h in toddlers and 25 mcg/kg/h in children >5 y (Taylor 2013 **Level IV PK**); 10–40 mcg/kg/h are standard postoperative ward order parameters (APAGBI 2012 **GL**). Titration and observation of effect is the key as there is wide between subject variability with further impact of critical illness (Anderson 2014b **NR PK**). In ventilated children after cardiac surgery, PKs of morphine have been assessed (Valkenburg 2016 **Level III-2 PK**, n=38). Requirements were similar in children with and without Down's syndrome: 32 mcg/kg/h guided by COMFORT B and observer-NRS scoring. Body weight was the most predictive covariate; while Down's syndrome was not.

10.5.1.2 | Efficacy of opioid infusions

Differences between intermittent bolus doses and continuous infusion of opioid relate more to the total dose than to the administration method (Lynn 2000 **Level III-2**). Comparison in neonates and young infants of the same total dose of morphine given via infusion (10 mcg/kg/h) or bolus (30 mcg/kg every 3 h) found no difference in pain scores (COMFORT and observer VAS) (Bouwmeester 2003a **Level II**, n=68, JS 3; van Dijk 2002 **Level II**, n=181, JS 4) or stress response to surgery (Bouwmeester 2001 **Level II**, n=204, JS 4). However, these doses were inadequate in children aged 1–3 y, in whom additional bolus doses were required and the 3 h interval was less effective (possibly due to more rapid clearance) (van Dijk 2002 **Level II**, n=181, JS 4).

In ventilated postsurgical neonates, various morphine infusion regimens have been used ranging from 2.5–5 mcg/kg/h (Ceelie 2013 **Level II**, n=71, JS 5) to 10–30 mcg/kg/h (Olischar 2014 **Level II**, n=71, JS 5; Anand 2008 **Level II**, n=1,773, JS 5). Fentanyl has been increasingly used in PICUs; seven centres varied widely in terms of initial opioid choice (fentanyl 64% vs morphine 36%) and dosing with peak infusion rates of 0.1–16 mcg/kg/h over a 14 d study period (converting morphine rates to fentanyl equivalents using 1:80 dose ratio) (Anand 2013b **Level IV**, n=419 [half postsurgical]). For control of acute procedural pain in ventilated neonates, continuous opioid infusions have limited efficacy (Anand 2008 **Level II**, n=1,773, JS 5). Bolus opioid administration (eg

fentanyl) (Ancora 2013 **Level II**, n=131, JS 5) and other analgesic interventions are recommended (APAGBI 2012 **GL**) (see also Section 10.4.1).

Following ureteroneocystostomy, fentanyl loading of 1 mcg/kg and then infusion 0.17 mcg/kg/h was effective, although patients who received continuous ketorolac infusion experienced less frequent bladder spasms (Jo 2011 **Level II**, n=52, JS 5).

10.5.1.3 | Adverse effects, complications and outcomes of opioid infusions

Major adverse events

A prospective multicentre audit has reported use of opioid infusions in children (Morton 2010 **Level IV**, n=1,955 [infusions]). This audit reports only two cases of respiratory depression in association with continuous opioid infusion, one requiring naloxone. Sedation scores, oxygen saturations and oxygen administration data were not collected. Programming or prescription errors were the most common reported incidents with continuous opioid infusions (n=9), none of which led to patient harm (see also Section 10.5.2.3 for errors with PCAs).

Opioid infusions in neonates and later neurodevelopmental impact

The impact of the routine use of morphine infusion in ventilated neonates on neurodevelopmental and other outcomes has been studied and remains of concern (Anand 2004 **Level II**, n=898, JS 4). A meta-analysis found no differences in mortality, duration of ventilation, or improvements in short or long term neurological outcomes; but the analysed outcomes were assessed by small, heterogeneous and usually single trials of low quality including 3 RCTs that enrolled preterm and term neonates (Bellu 2008 **Level I** [Cochrane], 13 RCTs, n=1,505).

Detrimental effects of prolonged sedation and/or analgesia on preterm neonates have also been a research focus (Anand 2004 **Level II**, n=898, JS 4; Anand 1999 **Level II**, n=67, JS 5). A 5 y follow-up of very preterm neonates found morphine and sedative exposure for >7 d was associated with poor neurodevelopmental outcome; this association was abolished once adjusted for gestational age and propensity scores (Roze 2008 **Level III-2**, n=1,572). A second author group assessed long term outcomes of expreterm infants who were ventilated and participants in a dual centre RCT comparing continuous morphine infusion 10 mg/kg/h for <7 d vs placebo (Simons 2003 **Level II**, n=150, JS 4). At 5 y follow-up, they suggested a negative association with morphine use and the "visual analysis" intelligence quotient subtest, after adjusting for propensity scores (de Graaf 2011 **Level II**, n=90, JS 4). While at 8 y follow-up, no overall harm was found with positive effects of low-dose infusion 10 mcg/kg/h on higher executive function (WISC-III; de Graaf 2013 **Level II**, n=89, JS 4) and no adverse effects on thermal detection or pain thresholds (assessed with quantitative sensory testing (QST); vs 28 contemporary controls), chronic pain incidence or overall neurological functioning (assessed by physical examination) (Valkenburg 2015 **Level II**, n=89 JS 4). At 2 y follow-up, expreterm toddlers, who as neonates were mechanically ventilated (mostly for lung indications) and received fentanyl infusion 1 mcg/kg/h (and boluses), had worse hand eye coordination vs placebo infusion and fentanyl boluses (Ancora 2017 **Level II**, n=78, JS 5).

As studies vary in the degree and manner of correction for confounding factors, follow-up at a later age focusing on higher-order neurocognitive function is necessary, ideally in a larger cohort.

Subacute opioid tolerance

Administration of parenteral opioids for as little as 5–7 d can produce opioid tolerance/dependence. See Section 10.4.6 for discussion of opioid dependence, tolerance and withdrawal in children, Section 10.4.7 for use of ketamine and 10.4.8 for use of alpha-2 agonists for use in withdrawal, as well as the relevant adult Section 9.7.

10.5.2 | Patient-controlled analgesia (PCA)

PCA can provide safe and effective analgesia for children aged as young as 5–6 y and compares favourably with continuous morphine infusion (Morton 2010 **Level IV** n=5,605 [PCA] & 1,955 [infusion]). PCA (and NCA) have been used for 2 decades in children (in 2016 at a single centre: most commonly morphine 72%, hydromorphone 28% and rarely fentanyl 1% postoperatively) (Donado 2019 **Level IV**, n=32,338 [22 y]).

Patient selection is important and depends on the ability of the child and carers to understand the concepts of PCA and the availability of suitable equipment and trained staff.

10.5.2.1 | Efficacy of PCA

Compared with continuous IV opioid infusions, opioid PCA provided greater dosing flexibility, and similar analgesia. PCA has been associated with higher opioid consumption but the incidence of adverse effects has varied, depending on the PCA dosing parameters (Peters 1999 **Level II**, n=47, JS 3; Bray 1996 **Level III-2**). PCA vs non-PCA techniques result in lower pain scores 9–10/100 over 24–48 h, higher opioid consumption (7 mg ME) and pruritus, with similar incidence of other adverse events (McNicol 2015 **Level I** [Cochrane], 49 RCTs [1 paediatric], n=3,412). The only paediatric study compared PCA bolus alone vs PCA bolus with background 15 mcg/kg/h for orthopaedic surgery found equal efficacy but greater acceptability vs IM morphine (McNicol 2015 **Level I** [Cochrane], 1 RCT: Berde 1991 **Level II**, n=99, JS 3).

PCA can be particularly useful in children with altered opioid requirements. In children with sickle cell disease, postoperative PCA morphine requirements were almost double those of non-sickle children (Crawford 2006a **Level III-3**). Morphine PCA with bolus and background (mean rate 20 mcg/kg/h) has been used for paediatric sickle cell patients (Jacob 2008 **Level IV**). Opioid PCAs have been used by children with cancer including during their terminal phase and at home (Anghelescu 2015b **Level IV**, n=45 [69 PCAs]; Anghelescu 2015c **Level IV**, n=28 [44 PCAs]; Mherekumombe 2015 **Level IV**, n=33); see also sections 10.8.1.2 and 10.8.3.1 re pain management in children with cancer.

Following scoliosis surgery, morphine and hydromorphone by PCA have been used (McDonnell 2012 **Level III-3**; Ravish 2012 **Level III-3**; Milbrandt 2009 **Level III-3**; Matava 2014 **Level IV**). A high early PCA demand ratio predicts higher pain scores, 24 h morphine consumption (Matava 2014 **Level IV**) and the need to rotate to hydromorphone (McDonnell 2012 **Level III-3**). Intraoperative remifentanil was associated with an increase in PCA morphine requirement in the 24 h post scoliosis surgery (Crawford 2006b **Level II**, n=30, JS 5), possibly due to acute opioid tolerance or opioid-induced hyperalgesia.

Following pectus excavatum surgery, PCA morphine and hydromorphone have been compared to epidural analgesia with minimal advantage of epidural analgesia with regard to pain scores and no other differences (Stroud 2014 **Level III-3 SR**, 6 studies, n=403) (see also Section 10.6.2). PCA morphine with ketoprofen vs placebo has been trialled (Rugyte 2007 **Level II**, n=31, JS 5) and morphine by PCA was similarly effective to morphine by continuous infusion (Rugyte 2010 **Level III-3**). In addition to thoracic epidural infusion, paracetamol and ibuprofen, PCA (mostly morphine; rotated to fentanyl in 7.4% of patients for side effects of PONV and pruritus) has been used for a mean of 3 d with low POD 1 pain scores at rest (median 2 [IQR 2–3]) (Frawley 2016 **Level IV**, n=217).

Post tonsillectomy, PCA morphine 20 mcg/kg vs tramadol 0.2 mg/kg bolus were similarly effective for 24 h (Ozalevli 2005 **Level III-1**).

For ureteroneocystostomy or pyeloplasty, PCA (and NCA) opioid has been compared with intrathecal (IT) morphine (mean dose 4.4 mcg/kg) ± bupivacaine (Putnam 2015 **Level III-2**, n=128). Overall pain scores were low; PCA/NCA patients required earlier and more systemic opioids with less pruritus and constipation. In the IT group, the technique failed in 7 patients and 2 patients required naloxone, with one requiring ICU admission.

Post appendicectomy, PCA opioid was used for laparoscopic (49%) and open operations; pain was improved by combination with diclofenac (Ousley 2016 **Level IV**, n=649 [552 PCA]).

Post neurosurgery in children aged 7–12 y, PCA fentanyl, morphine and tramadol were effective with similarly low pain scores and less ibuprofen and morphine rescue vs placebo PCA (Xing 2019 **Level II**, n=320 [195 PCA], JS 5).

Fentanyl is a useful alternative opioid via PCA, particularly for patients with renal impairment or those experiencing morphine-related adverse effects (Tobias 1992a **Level IV**). Fentanyl PCA has been used safely and effectively following neurosurgery (Chiaretti 2008 **Level IV**), pectus excavatum surgery (Butkovic 2007 **Level IV**) and for acute cancer-related pain (Ruggiero 2007 **Level IV**) (see also Section 10.8).

Oxycodone PCA use in children is not reported to date; although paediatric centres are including prescription recommendations in their pain management guidelines (CHW 2019 **GL**; CHI 2019 **GL**).

As in adults, the use of pethidine should be discouraged in the paediatric setting (Benner 2011 **NR**). Pethidine does not have any advantage over other opioids and neurotoxicity from norpethidine (normeperidine) accumulation has been reported in a healthy adolescent (Kussman 1998 **CR**) (see also Section 4.3.1.2).

See also Section 10.4.7.1 for the paediatric literature of ketamine addition to PCA opioid.

10.5.2.2 | PCA prescription

A survey of paediatric anaesthetists in the USA found significant variation in standard prescribing practices for PCA (Nelson 2010 **Level IV**, n=294). Worldwide, morphine is the medicine used most frequently in paediatric PCA. A bolus dose of morphine 20 mcg/kg is a suitable starting dose (APAGBI 2012 **GL**) and is associated with improved pain scores during movement vs 10 mcg/kg (Doyle 1994b **Level II**, n=40, JS 3).

The addition of a background infusion is more common in children than adults, tends to be reserved for more painful surgeries or conditions such as scoliosis and mucositis, and may be time limited postoperatively eg first 12–48 h or to night-time only. Morphine 0–4 mcg/kg/h is recommended (APAGBI 2012 **GL**). Higher background rates are also prescribed (Nelson 2010 **Level IV**, n=294 [surveyed anaesthetists]). Although use of a background infusion was associated with increased sleep disturbance in one audit (calculated from the number of hours PCA presses were required; OR 0.19), numbers were too small to fully investigate the contribution of the kind of surgery (Kelly 2006 **Level IV**, n=126). Background infusions added to PCA of morphine 4–20 mcg/kg/h in children aged 5–20 y showed no difference in pain scores at 12 and 24 h after surgery (5 RCTs, n=203), total opioid consumption (WMD 2.58; 95% CI −2.77 to 7.93) (7 RCTs, n=338) and improved sleep duration (3 RCTs, n=165), with no difference in the number of night-time awakenings (median of 3 per night in both bolus only vs bolus and background 20 mcg/kg/h groups) (1 RCT, n=42) (Hayes 2016 **Level I SR**, 7 RCTs, n=338).

Morphine PCA 20 mcg/kg bolus with 5–20 mcg/kg/h background infusion has been used for children >7 y having laparoscopic appendectomy (Liu 2013 **Level IV**).

Surveyed anaesthetists reported fentanyl bolus prescriptions of 0.2–0.4 mcg/kg and hydromorphone of 1–3 mcg/kg (with similar background infusion rates) (Nelson 2010 **Level IV**, n=294).

Hydromorphone was dosed in a paediatric series as IV PCA 3 mcg/kg boluses and had similar efficacy and adverse effect profile to morphine 15 mcg/kg boluses (Karl 2012 **Level III-1**). IV Hydromorphone PCA 2 mcg/kg bolus with 2 mcg/kg/h background has been compared with PCEA bupivacaine/hydromorphone in scoliosis surgery (Gauger 2009 **Level II**, n=38, JS 3).

10.5.2.3 | Adverse effects, complications and outcomes of PCA

Recognition of potential complications of PCA use was enhanced by providing set instructions for monitoring and by APS support (Wrona 2007 **Level III-2**). Audit and administrative analysis has provided outcome data for this specialised technique (outlined below and also see Section 10.5.5).

PCA preparation, programming errors and device problems

Some adult hospitals have moved to pre-prepared syringe purchase for infusion and PCA administration. While in paediatric centres, clinical staff generally remain responsible for preparation of weight-based dosing in fixed syringe sizes, where 1–2 mL is then the standard bolus size. An evaluation of syringe preparation in a single centre revealed excess syringe volumes and deviations from stated label strength: usually in excess, with 21% of deviations >20% (Rashed 2016 **Level IV**, n=153 [syringe preparations]).

Programming error data (from a referenced tertiary adult centre report) has highlighted the contribution of human factors such as nursing task interruption (Ocay 2018 **NR**). Errors occurred infrequently: human programming 0.74% and device related 0.19%. Pump misprogramming had serious consequences such as respiratory depression, over sedation or poorly treated pain. The above Canadian paediatric centre has moved to staged implementation of standardised morphine PCA (and NCA) concentrations based on weights of 3 mg (≤3.9 kg), 10 mg (4 to 19.9 kg) and 50 mg (≥20–25 kg) in 50 mL and found this has eliminated preparation errors and reduced setup time (preparation and pump programming) and changed the PCA incidents from confusion with or wrong dose to expiry date issues (Rashed 2019 **Level III-2**, n=175 syringes [157 children]).

Impact of background infusion addition to PCA in children

A meta-analysis reports that the addition of a background infusion increases the odds for respiratory depression in adults (see Section 6.4.3), but not in children (George 2010 **Level I**, 14 RCTS, n=796 [3 paediatric, n=122]). A subsequent meta-analysis of low quality RCTs of mostly children (5–20 y) comparing PCA alone vs PCA with background infusion showed no difference in adverse effects of PONV (18.8% vs 27.6: RR 1.2; 95% CI 0.8 to 1.8) (5 RCTs, n=239) or sedation (0 vs 8.5%: RR 3.5; 95% CI 0.4 to 29.3) (2 RCTs, n=81) (Hayes 2016 **Level I**, 7 RCTs, n=338) (3 RCT overlap).

Major adverse events

A large UK audit has included prospective data for PCA (Morton 2010 **Level IV**, n=5,605 [PCA]). No incident of permanent harm occurred, with a very low incidence (approximately 1 in 500) of "harm with full recovery", including respiratory depression requiring naloxone (n=1), urinary retention (n=4), nausea/vomiting (n=5) and itch (n=3). Sedation scores were not collected. These adverse effects were defined by "requiring cessation of or change in technique", which explains why rates were lower than reported in case-control series and RCTs. Seven programming and prescribing errors that did not lead to harm were also reported.

Administrative data analysis of morphine recipients for non-surgical and surgical indications in 42 USA hospitals demonstrated a low incidence of interventions for PCA patients (Faerber 2017 **Level III-2**, n=62,959 [PCA]); see below for detail of matched comparison with IV morphine recipients).

Nausea and vomiting

Nausea and vomiting occurs in 30–45% of children using morphine PCA and can be reduced by prophylactic antiemetics (Carr 2009 **GL**). Adding antiemetics directly to PCA solutions for children was not effective (Munro 2002 **Level II**, n=60, JS 5).

Pruritus

Addition of a low-dose naloxone infusion 0.25 mcg/kg/h did not impair analgesia but decreased pruritus and nausea in postoperative children treated with PCA (Maxwell 2005 **Level II**, n=46, JS 5). Naloxone 1 mcg/kg/h more effectively decreased pruritus than 0.25 mcg/kg/h in children requiring morphine infusions during a sickle cell crisis (Koch 2008 **Level IV**). The suggested optimal dose of IV naloxone by continuous infusion (determined by up titration from 0.05 to 1.65 mcg/kg/h) is ≈1 mcg/kg/h (Monitto 2011 **Level IV**, n=59). Addition of naloxone to morphine PCA with background infusion (ratio 12 mcg: 1 mg) did not reduce pruritus incidence vs morphine PCA alone (22% vs 36: difference -15%; 95% CI -33 to 4) (West 2015 **Level II**, n=92, JS 5).

Escalation of PCA use as a sign of compartment syndrome

Compartment syndrome in children occurs infrequently (1.3–3%), usually diagnosed at a mean of 19 h (range 1.5–65 h) post fracture or surgery of the limb (Ferlic 2012 **Level IV**, n=1,028). Pain as one of the "5 P hallmarks" can be further qualified as pain escalation at rest as well as with passive movement, unrelieved by plaster splitting and with increased analgesic request. Escalation in PCA demands may occur, as reported in two paediatric patients (Yang 2010 **Level IV**). See also later discussion regarding compartment sydrome and regional use in children 10.6.1.3.

10.5.3 | Nurse-controlled analgesia

In younger children and infants, "PCA" devices have been used by nurses to administer intermittent bolus doses (with or without a background infusion), a technique termed "nurse-controlled analgesia" (NCA). This technique may increase ease of administration particularly prior to movement or procedural interventions, increase dose flexibility and improve parent and nurse satisfaction. Dose recommendations for morphine are generally 5–40 mcg/kg/h with 10–20 mcg/kg nurse-initiated boluses (Howard 2010 **Level IV**, n=10,000). NCA has also been used in older children in intensive care who are unable to activate a conventional PCA device.

10.5.3.1 | Efficacy of NCA

Adequate analgesia comparable to PCA was reported but efficacy was dependent on accurate nurse assessment of pain (Weldon 1993 **Level III-2**). The technique has been used in open vs laparoscopic Nissen fundoplication surgery (McHoney 2011 **Level II**, n=39, JS 5) and for fast-track cardiac surgical patients (Iodice 2011 **Level IV**). In intubated patients post cardiac surgery, tramadol NCA in comparison to morphine NCA provided minor improvements in time to extubation (Chu 2006 **Level II**, n=40, JS 4). In intubated children post cardiac surgery, fentanyl NCA and remifentanil NCA (both with background) achieved similar pain and sedation scores, with less side effects but greater bolus requirement in the remifentanil treated (Xiang 2014 **Level III-1**, n=60). Post neurosurgery, NCA fentanyl, morphine and tramadol were effective with similarly low pain scores and less ibuprofen and morphine rescue required vs placebo NCA in children aged 1–6 y (Xing 2019 **Level II**, n=320 [192 NCA], JS 5).

In young children (<2 y) post ureteroneocystostomy, fentanyl NCA with paracetamol (or placebo) has been used (Hong 2010 **Level II**, n=63, JS 5).

10.5.3.2 | Adverse effects, complications and outcomes of NCA

Major adverse events

The incidence of adverse effects was similar in children self-administering conventional PCA and those receiving NCA (Voepel-Lewis 2008 **Level III-2**, n=302; Morton 2010 **Level IV**, n=3,706 [NCA]). Rescue events (requiring naloxone, airway management or admission to high dependency/ICU) were more common in the NCA (and parental proxy) group but this group was also younger and had a higher prevalence of comorbidities (Voepel-Lewis 2008 **Level III-2**). Cognitive impairment and high opioid dose requirements on d 1 were associated with increased adverse effects. Two large prospective audits in institutions with APS oversight affirm NCA use (mostly morphine) as safe and effective for postoperative analgesia in children (Howard 2010 **Level IV**, n=10,000; Morton 2010 **Level IV**, n=3,706 [NCA]). The multicentre 2007–2008 UK audit reports one incident of harm overall, which was with the NCA technique (cardiac arrest in a 2.5 kg neonate), and eleven respiratory depression events (0.3%) with "harm but full recovery", six requiring naloxone (Morton 2010 **Level IV**, n=3,706 [NCA]). The single centre 1996–2008 audit reports no deaths but a similar rate of 0.4% for serious potentially life-threatening events of oversedation or respiratory depression requiring active resuscitation and naloxone (Howard 2010 **Level IV**, n=10,000). This audit provided rates for respiratory depression and sedation at 4.5% (with 91% improving with temporary cessation or adjustment of technique), PONV 25% (severe for 14%) and pruritus 9.4% (severe for 4%). The incidences varied with age, morphine dose and type of surgery. Notably both audits report higher incidences of serious adverse effects with NCA in neonates than children aged >1 mth: 0.8% vs 0.4 (Morton 2010 **Level IV**, n=3,706 [NCA]) and 2.5% vs 0.27% (Howard 2010 **Level IV**, n=10,000).

10.5.4 | PCA by proxy

Administration by a nurse trained in pain assessment, rather than parents, is recommended in most centres (Howard 2010 **Level IV**, n=10,000). Confusingly the term "PCA by proxy" has been used to describe administration by both nurses and/or parents. The Joint Commission on Accreditation of Healthcare Organisations issued a sentinel alert cautioning against the practice of parental proxy in 2004. In response, some US centres ceased using parental proxy technique (reported by 11% of surveyed anaesthetists) (Nelson 2010 **Level IV**, n=294). However, many centres continue this practice and, as for the conventional PCA technique, selection criteria, education and guidelines should be followed (Chidambaran 2012 **NR**). In a prospective series of PCA by proxy (parents or health care providers), effective analgesia was achieved in 81–95% of children <6 y of age; 25% required supplemental oxygen and 4% required naloxone for respiratory depression (Monitto 2000 **Level IV**). In a retrospective series, PCA by proxy resulted in low pain scores, while somnolence or respiratory depression requiring naloxone occurred in 2.8% of children with developmental delay (Czarnecki 2008 **Level IV**) and 1.9% of infants and preschoolers (Czarnecki 2011 **Level IV**). PCA by proxy vs conventional PCA in children with cancer pain was associated with comparable (Anghelescu 2005 **Level III-3**) and lower complication rates in a follow-on series (Anghelescu 2012 **Level IV**). In children with developmental delay, no differences in outcomes were seen when comparing postoperative use of parental/nurse controlled analgesia vs nurse administered IV opioids (Czarnecki 2018 **Level II**, n=81, JS 2).

Comparison of morphine and hydromorphone via PCA, NCA and PCA by proxy (70% with a background infusion) has been described (Voepel-Lewis 2008 **Level III-3**, n=302). Fentanyl PCA was administered by parental proxy (initial settings 0.075 mcg/kg bolus and background 0.3 mcg/kg/h) for toddlers for 48 h post cleft palate repair to establish an $ED_{50–95}$ of 0.63–0.83 mcg/kg/h (Choi 2008 **Level IV**).

10.5.5 | Overall safety of parenteral opioid use in children

Overall, parenteral opioid techniques are safe in children as long as administered in appropriate settings. Of surveyed paediatric anaesthetists (representing 252 USA institutions with 51% having APS oversight), 8 recalled deaths (in the preceding 5 y) in association with these techniques and 42 recalled cardiorespiratory events requiring naloxone (in the year prior; denominator unknown) (Nelson 2010 **Level IV**, n=294). The incidence rates of respiratory depression in the various paediatric studies will vary depending upon how it is defined; degree of desaturation, requirement for supplemental oxygen, suspension/cessation of opioids, requirement for naloxone or respiratory intervention including ventilation. The studies done to date are generally underpowered to detect differences in the incidence of respiratory depression. The large UK prospective audit of parenteral opioids delivered by the above techniques reports an overall 1 in 10,000 incidence of serious harm and 0.13% incidence of respiratory depression (requiring intervention with respiratory support, naloxone or opioid cessation) (Morton 2010 **Level IV**, n=10,726). Importantly, these low rates occurred in UK centres with 100% oversight by a paediatric APS and with institutional guidelines in place. Safety can be improved through avoidance of concurrent sedatives or opioids by other routes, awareness of comorbidities posing extra risk and by careful dosing, with heightened monitoring in infants. Opioid prescription and pump programming errors were an issue (1 in 631 infusions or 0.16%) and can be minimised through adherence to guidelines and careful cross-checking (Morton 2010 **Level IV**, n=10,726).

Administrative data assessment from 42 USA hospitals revealed morphine by PCA vs morphine by IV route was not associated with an increased risk of requirement for CPR or mechanical ventilation (Faerber 2017 **Level III-2**, n=108,956 [PCA surgical n=11,220 & PCA non-surgical n=6,030; each matched with an IV morphine group]); in the matched cohorts on day 1 of IV morphine use, CPR events occurred in 0.89% of non-surgical and 0.45% of surgical patients. PCA exposure had lower risk of requiring CPR in surgical (OR 0.56; 95%CI 0.45 to 0.70) and non-surgical recipients (OR 0.80; 95%CI 0.76 to 0.85).

A single institution reported use of PCA and NCA over 14 y as associated with 146 errors (1%), of which two resulted in severe and preventable adverse events (Donado 2019 **Level IV**, n=16,806 [PCA or NCA administrations with error reporting]).

KEY MESSAGES

1. Addition of a low-dose background infusion to patient controlled analgesia (PCA) bolus results in similar pain scores and total opioid consumption and improves sleep duration in children; numbers are inadequate to assess safety of adding a background (**N**) (**Level I**).
2. In ventilated preterm neonates, routine use of morphine infusions does not affect mortality, duration of ventilation or neurological outcomes (**U**) (**Level I** [Cochrane Review]), including when followed up as older children (**S**) (**Level II**).
3. Postoperative intravenous opioid requirements vary with age in neonates, infants and children (**U**) (**Level II**).
4. Intermittent intramuscular injections are distressing for children and are less effective for pain control than intravenous infusions (**U**) (**Level III-1**).
5. Patient-controlled analgesia (PCA) can provide safe and effective analgesia for children as young as 5 years old (**S**) (**Level III-3**).
6. Intravenous opioids via continuous infusion, nurse-controlled analgesia and parental proxy use of patient controlled analgesia (PCA) devices can be used effectively (**U**) (**Level III-2**) and safely (**N**) (**Level IV**) in children of all ages.
7. Nurse-controlled analgesia (**U**) (**Level III-2**) and parental proxy use of patient controlled analgesia (PCA) devices in children (**U**) (**Level III-3**) may require more rescue interventions (such as naloxone, airway management or intensive care) than PCA, but this may reflect the younger patient population where this technique is offered.
8. Morphine by patient controlled analgesia (PCA) is at least as safe as intermittent nurse administered intravenous morphine (**N**) (**Level IV**).

The following tick boxes represent conclusions based on clinical experience and expert opinion:

☑ Initial doses of opioid should be based on the age, weight and clinical status of the child and then titrated against the individual's response (**U**).

☑ Effective patient controlled analgesia (PCA) prescription in children incorporates a bolus that is adequate for control of movement-related pain (**U**).

10.6 | Paediatric Regional Analgesia

Paediatric regional analgesia (PRA) incorporates peripheral nerve or neuraxial blocks and catheter techniques. The efficacy of various PRA techniques for common paediatric surgical conditions is described below. Differences between groups in RCTs can be difficult to detect with small sample sizes or when outcome measures are relatively insensitive (eg supplemental analgesic requirements following procedures with low ongoing pain). This and the heterogeneity of studies and outcomes leads to systematic reviews with conclusions based often on single RCTs (eg Kendall 2018 **Level I** [PRISMA], 40 RCTs, n=2,408). Previous prospective multicentre French and UK audits (Ecoffey 2010 **Level IV**, n=29,870 PRA with GA & 1,262 PRA alone; Llewellyn 2007 **Level IV**, n=10,633 [epidural]) and retrospective single centre Italian audit (Vicchio 2015 **Level IV**, n=18,279 PNBs) have been superseded by larger scale population safety data provided by the USA's Paediatric Regional Anaesthesia Network (PRAN) with more than 20 children's hospitals participating (Walker 2018 **Level IV**, n=104,393 blocks in 91,701 children). Data collection and publication by PRAN is ongoing and informs our practices and information we can provide to families during the consent process.

PRA safety under general anaesthesia, practice advisory and adjuvant use

PRA is typically performed in children under general anaesthesia. The safety of this has been demonstrated in the PRAN audits and is comparable to placing blocks in awake adults (Walker 2018 **Level IV**, n=104,393 [97,825 under GA]; Walker 2018 **Level IV**, n=2,017; Suresh 2018a **Level IV**, n=40,121).

The European Society of Regional Anaesthesia and Pain Therapy (ESRA) and The American Society of Regional Anaesthesia and Pain Medicine (ASRA) joint committee practice advisory group has published recommendations (Ivani 2015 **GL**):

1. Support for the performance of regional nerve blocks under deep sedation or GA;
2. Discretionary use of an adrenaline (epinephrine) containing test dose (as false negatives occur);
3. Detection of epidural space with loss of resistance to either air or normal saline (or both) in small volumes;
4. Regional anaesthesia does not obscure or delay diagnosis of compartment syndrome.

This practice advisory has since been reaffirmed with dosing recommendations for neuraxial blocks (Lonnqvist 2017 **GL**).

The addition of adjuvant medications to local anaesthetic agent can improve block quality and duration (Forestier 2017 **NR**). Adjuvant agent addition to the regional or peripheral nerve injectate should demonstrate a viable local mechanism of action beyond systemic administration, be safe, tolerable and non-toxic via this route. See later sections 10.6.2.6 and 10.6.3.3.

10.6.1 | Peripheral nerve blocks and catheters

10.6.1.1 | Single injection peripheral nerve blocks (PNBs)

Single injection peripheral nerve blocks (PNBs) are effective and safe adjuncts for the management of procedural, perioperative and injury related acute pain (PNBs: Walker 2018 **Level IV**, n=45,324; Ecoffey 2010 **Level IV**, n=20,576; Giaufre 1996 **Level IV**, n=4,090) (See also Section 5.8). The use of US-guidance for PNBs in children has grown significantly over the last decade, including in the ambulatory setting (Walker 2018 **Level IV**, n=45,324; : Suresh 2018a **Level IV**, n=40,121;

Kendall 2018 **Level I** [PRISMA], 40 RCTs, n=2,408; 1 RCT overlap with Lam 2016 **Level IV SR** [PRISMA], 23 studies [PNBs: including 10 RCTs], n=1,280). PRAN data have shown increase in the proportion of PNB relative to neuraxial blocks: from 43.4 to 52.5% (Walker 2018 **Level IV**, n=86,328 [single injection]; Polaner 2012 **Level IV**, n=10,622).

Dosing

PRAN audit reveals PNB dosing practices vary 5−10 fold with volumes of 0.16 to 2.4 mL/kg and doses of bupivacaine (means 0.5−1.25 mg/kg) or ropivacaine (means 0.42−1.42 mg/kg) (where the upper 95%CI limit is less than the per kg max dose recommendations) (Suresh 2018a **Level IV**, n=40,121).

10.6.1.2 | Continuous peripheral nerve catheters

Continuous peripheral nerve catheters (CPNCs) for continuous local anaesthetic infusion have been used in all age groups (CPNCs: Walker 2018 **Level IV**, n=4,945; Walker 2015a **Level IV**, n=2,074; Ecoffey 2010 **Level IV**, n=1,098). Within the PRAN dataset, the numbers of CPNCs inserted increased gradually, and since 2012 have been stable relative to the more commonly inserted neuraxial catheters (Walker 2018 **Level IV**, n=4,945 [CPNCs] vs 13,120 [neuraxial]). The majority of CPNCs were inserted in older children >10 y; with ultrasound for the majority of catheter placements (Walker 2015a **Level IV**, n=2,074).

Efficacy in hospital and post discharge

Case series report CPNC use in hospital and on discharge as an ambulatory option with elastomeric pumps (discharged home on POD 0–3 (Walker 2015a **Level IV**, n=2,074 [n discharged unspecified]; Gurnaney 2014 **Level IV**, n=1,954 CPNCs in 1,700 patients [1,285 discharged]; Visoiu 2014b **Level IV**, n=410 CPNCs in 403 patients [all discharged]; Ganesh 2007 **Level IV**, n=226 CNPCs in 217 patients [108 discharged]). High efficacy (as an adjuvant to oral analgesia including opioids) has been reported in the above case series (balanced with low complication and failure rates per below). Success rates were 93 to 98% when assessed by numerical rating (NRS) of pain control satisfaction (parent, patient and nurse), pain scores in PACU vs at home and analgesic consumption (Visoiu 2014b **Level IV**, n=403 [discharged]; Gurnaney 2014 **Level IV**, n=1,285 [discharged]; Visoiu 2014a **Level IV**, n=5 [paravertebral]). In PACU, 37% of patients with CPNCs in situ required no opioid (Visoiu 2014b **Level IV**, n=403). Most patients required opioid at home: ≥1 dose for 96% (Visoiu 2014b **Level IV**, n=403), as needed by 64% vs regularly by 15% or 8% as needed which then moved to regular (Gurnaney 2014 **Level IV**, n=1,285).

CPNC dosing

Usual reported CPNC dosing were of plain ropivacaine 0.1−0.2% or bupivacaine 0.1−0.125% at rates of 2−10 mL/h for 2 to 10 d (Walker 2015a **Level IV**, n=2,074; Gurnaney 2014 **Level IV**, n=1,954 [CPNCs]; Visoiu 2014b **Level IV**, n=410 [CPNCs]; Ganesh 2007 **Level IV**, n=226 [CPNCs]). The joint practice advisory committees recommend CPNC local anaesthetic dosing based upon the above audit data practices (with no PK-PD study) for peripheral nerve and fascial planes of 0.1−0.3 mg/kg/h for racemic bupivacaine, levobupivacaine or ropivacaine (ESRA-Suresh 2018a **GL**; ASRA-Lonnqvist 2017 **GL**). Lower dosing is suggested for neonates and younger children (with their differing PK profiles to ≈6 y) reflecting greater risk for local anaesthetic systemic toxicity (LAST) with higher free non protein-bound drug fractions and immature CYP3A4/7 enzyme systems (Suresh 2018a **GL**; Johr 2015 **NR**). Some children have received higher than recommended local anaesthetic dosing without adverse events (Walker 2015a **Level IV**, n=2,074; Moriceau 2015 **CR**).

Safety

Safety of PNB (PNBs: Walker 2018 **Level IV**, n=45,324; Ecoffey 2010 **Level IV,** n=20,576; Giaufre 1996 **Level IV,** n=4,090) are described below and in Section 10.6.2.4 under the individual block headings.

In the largest series, a low overall failure rate for PRA (PNB, CPNC and neuraxial single injection and catheters) of 1% was reported (Walker 2018 **Level IV**, n=104,393). For two PNBs (1 penile and 1 superficial cervical plexus block) broken needles required surgical retrieval and one wrong-sided femoral PNB was performed (Walker 2018 **Level IV**, n=45,324). One wrong-sided block has been reported in an Australian paediatric centre's series (Drake-Brockman 2016 **Level IV**, n=148 [PNBs]). Adoption of the 'Stop Before You Block' checklist (Clebone 2017 **GL**; ANZCA 2015) as an anaesthesia time out (pre or post-induction of GA but preblock, ie before surgical time out) practice in paediatric centres world-wide is unknown. Some paediatric institutions have developed additional local procedures to reduce this error (eg scrub nurses hand the anaesthetist the block needle after the anaesthesia time out) with focus on correct patient identification, site marking, patient weight and safe drug dosing.

Safety of CPNC use has been confirmed by retrospective (CPNCs: Gurnaney 2014 **Level IV**, n=1,954; Visoiu 2014b **Level IV**, n=410; Dadure 2009 **Level IV**, n=339; Ganesh 2007 **Level IV**, n=226 CNPCs) and subsequent prospective PRAN audits (Walker 2015a **Level IV**, n=2,074 case overlap with Walker 2018 **Level IV**, n=4,945) and is described further below.

Complications related to CPNC technique

Primary failure rates of CPNC insertion were reported in the earlier audits (generally ≤2%; higher for upper limb 7.6%).

Recognised vascular puncture rates vary between 2−3% (CPNCs: Gurnaney 2014 **Level IV**, n=1,954; Dadure 2009 **Level IV**, n=339; Ganesh 2007 **Level IV**, n=226 CNPCs) and lower in prospective data of 0.9% (95%CI 0.5 to 1.4) (Walker 2015a **Level IV**, n=2,074).

The most common adverse event for CPNC in all series were secondary failures of the catheter (dislodgement, occlusion or disconnection) or of the delivery system.

In the PRAN audit, the secondary failure rate was 1.3% (95%CI 0.8 to 1.7); while catheters were removed because of various complications on POD 0 to 2 in 6.1% patients; overall 7.3% (95%CI 6.2 to 8.5) (Walker 2015a **Level IV**, n=2,074).This was independent of insertion while under GA, sedated vs when awake, insertion site or patient age. An earlier series reported similar rates of secondary failure (1.9%) and excessive catheter leak in 1% (Gurnaney 2014 **Level IV**, n=1,492 CPNCs). Another series reported catheter problems (6.9%) including elastomeric pump delivery failure and leak (Visoiu 2014b **Level IV**, n=410).

Post discharge, CPNC related problems at home include motor block and difficult removal. The families received education in catheter clamping in the event of adverse effects. With low concentration and low infusion rates (see above), reported rates of motor block were 10% (Ganesh 2007 **Level IV**) to 20% (Dadure 2009 **Level IV**), resolving within 3 h of catheter clamping (Gurnaney 2014 **Level IV**, n=1,492). Most series reported difficult removal in a few patients only (Walker 2015a **Level IV**, n=2,074 [2 difficult–1 attended ED]; Gurnaney 2014 **Level IV**, n=1,492 [2 difficult]; Visoiu 2014b **Level IV**, n=410 [1 difficult, 2 refusals by the patient]).

Anticoagulation and PNB/ CPNCs

Children rarely receive thromboprophylaxis after major surgery. There is no paediatric literature pertaining to anticoagulation and PNBs; practice for paediatric patients receiving anticoagulants generally follows adult recommendations. See discussion in adult Section 5.9.2 (and specific to epidural haematoma and epidural catheters in adults in 5.9.1 and in children in 10.6.3.5).

Infection in CPNCs

Local cutaneous infections related to CPNC use was lower (26/10,000; 95%CI 15 to 45) than with neuraxial catheters (60/10, 000; 95%CI 48 to 75) independent of insertion site (Walker 2018 **Level IV**, n=4,945 [CPNCs] vs 13,120 [neuraxial]). An earlier overlapping series of CPNCs documented superficial infection incidence of 0.9% (95%CI 0.5 to 1.4) associated with longer CPNC duration 4.5 d (range 3 to 7) vs 3 (1 to 3); 3 further catheters were removed in patients with fever only (and no superficial infection) and no deep infections, abscesses or sepsis events were documented (Walker 2015a **Level IV**, n=2,074). Retrospective studies report site infection requiring antibiotics of ≤0.5−0.9% (Gurnaney 2014 **Level IV**, n=1,954; Dadure 2009 **Level IV**, n=339; Ganesh 2007 **Level IV**, n=226 CNPCs).

Local Anaesthetic Systemic Toxicity (LAST) with PNBs/CPNCs

The incidence of Local Anaesthetic Systemic toxicity (LAST) with PNBs has not changed over time (OR 1.08; 95%CI 0.21 to 5.43) (Walker 2018 **Level IV**, n=45,324 PNBs). One severe LAST event (seizure) occurred in a teenager who received an infraclavicular PNB and was treated with lipid emulsion with seizure resolution. While in a femoral fracture ED series of fascia iliaca compartment blocks (FICNB) landmark technique with ropivacaine 0.5% 0.5–0.75 mL/kg (max 30 mL), two patients had a seizure, one treated with intralipid and one (with known subarachnoid haemorrhage) with benzodiazepine (Neubrand 2014 **Level IV**, n=158 [FICNB]).

With CPNCs, LAST incidence in the earlier series was ≤0.3/10,000 (Gurnaney 2014 **Level IV**, n=1,954; Dadure 2009 **Level IV,** n=339; Ganesh 2007 **Level IV**, n=226 CNPCs) and 4/10,000 (95% CI 0.6 to 30) (Vecchione 2016 **Level IV**, n=625 CPNC [468 patients]). Early symptoms of LAST (ringing in the ears or metallic taste) occurred in 0.5/10,000 (Suresh 2018a **Level IV**, n=40,121 PNBs; Visoiu 2014b **Level IV**, n=410 CPNCs) and 0.2/10,000 which resolved with clamping and CPNC removal (Gurnaney 2014 **Level IV**, n=1,492 children). One infant had LAST with a self-resolving seizure related to paravertebral CPNC and chloroprocaine bolus: 0.8/10,000 (95%CI 0 to 4.8) (Walker 2018 **Level IV**, n=2,074).

Postoperative Neurological Symptoms (PONS) and PNBs/CPNCs

Prospective audit reports the incidence of neurological complication with PNBs has decreased over time (OR 0.60; 95%CI 0.38 to 0.90) (Walker 2018 **Level IV**, n=45,324). No permanent neurological deficits (95%CI 0 to 0.4/10,000) and low risk of transient neurologic deficit of 2.4/10,000 (95%CI 1.6 to 3.6) were reported (Walker 2018 **Level IV**, n=104,393 blocks in 91,701 children). There was no difference in neurologic complication rate when comparing peripheral vs neuraxial blocks, CPNCs vs single injection (OR 0.63; 95%CI 0.21 to 2.74) or local anaesthetic type (bupivacaine vs ropivacaine).

Case reports have described prolonged neurological deficit (Drake-Brockman 2016 **Level IV**, n=148 PNBs) and permanent injury (Walker 2018 **NR**; Ivani 2015 **GL**).

Acute compartment syndrome and PNB or CPNC

Acute compartment syndrome (ACS) associated with PNBs/CPNBs was not specifically reported in the PRAN audit. There are reports where PNBs have masked ACS in adults with others where PNB/CPNC did not, including three adolescents (Klucka 2017 **Level IV** [PRISMA], 15 studies, n=20; Ivani 2015 **GL**; Munk-Andersen 2013 **CR;** Walker 2012a **CR**; Cometa 2011 **CR**). This highlights the need for frequent clinical monitoring and early review following high-risk injury or surgery (eg diaphysis of long bones, particularly tibia, and comminuted fracture) in the event of breakthrough pain (particularly where analgesia including PRA has been previously effective).

In those deemed at risk, the Joint ASRA-ESRA Practice Advisory has suggested limiting the drug dosing regimens to low concentrations/low volumes and avoiding adjuvants in PNBs, neuraxial blocks and CPNCs (Lonnqvist 2017 **GL**).

10.6.1.4 | Ultrasound guidance impact on safety and success of PNBS and CPNCs

PRAN has documented high use of ultrasound (US) guidance for CPNC placement: 78–90% (Walker 2015a **Level IV**, n=2,074) and increased use for PNB placement from ≈30% in 2007 to ≈90% in 2015, with concomitant decrease in peripheral nerve stimulator use as sole assisting device (Walker 2018 **Level IV**, n=45,324 [PNBs]; Suresh 2018a **Level IV**, n=40,121). The joint committee practice advisory groups suggest lower dosing is required when using US-guidance (Suresh 2018b **GL**; Lonnqvist 2017 **GL**). Although neurologic complications with PRA have decreased over time, US-guidance has not impacted this: with 0/10,000 (95%CI 0 to 4.2) events with US use overlapping with 3.6/10,000 (95%CI 2.1 to 6.0) without US (Walker 2018 **Level IV**, n=45,324 [PNBs]). Neither has US use affected LAST incidence (95%CI −1.6 to 1.0/10,000), despite use being associated with documented smaller local anaesthetic volumes.

A systematic review has summarised several heterogeneous RCTs without meta-analysis showing similar or greater success rates vs nerve stimulation (1 RCT [axillary], n=40; 1 RCT [infraclavicular], n=50; 1 RCT [femoral], n=60) and landmark technique (2 RCTs [penile block], n=106), with variable effects on speed of block performance (vs landmark: faster (1 RCT [axillary], n=40) and slower (1 RCT [penile], n=40) and postoperative outcomes including pain scores and opioid requirements (equivocal for transversus abdominus plane block (1 RCT [lap. appendicectomy], n=30) and rectus sheath block (1 RCT [umbilical hernia], n=52) vs positive vs wound infiltration for ilioinguinal/iliohypogastric nerve block (2 RCTs [inguinal hernia], n=109)) (Lam 2016 **Level IV SR** [PRISMA], 23 studies [peripheral: including 10 RCTs], n=1,280). The earlier review by the same authors summarised two earlier RCTs with similar findings: where US-guided ilioinguinal/iliohypogastric block reduced the local anaesthetic dose given and PACU rescue paracetamol requirements vs landmark technique (Tsui 2010 **Level IV SR** [PRISMA], 1 RCT: Willschke 2005 Level II n=100 JS 3) and reduced block onset time for infraclavicular block vs nerve stimulator use (Tsui 2010 **Level IV SR** [PRISMA], 1 RCT: Marhofer 2004 **Level II**, n=40, JS 3).

See sections 10.6.2.1 and 10.6.2.2 for discussion of US use in caudal and epidural insertion respectively.

10.6.2 | Specific peripheral nerve blocks and catheters

10.6.2.1 | Lower limb blocks in children

Lumbar plexus (or psoas compartment) block

For lower limb/hip surgery, lumbar plexus (or psoas compartment) single injection block (Gurkan 2017 **Level IV**, n=75; Walker 2011 **Level IV**, n=305) or CPNC (Walker 2018 **Level IV**, n=274 PNBs & 722 CPNCs) may be useful alternatives to neuraxial techniques (Omar 2011 **Level II**, n=40, JS 3; Villalobos 2019 **Level III-2**, n=61).

Lateral femoral cutaneous or femoral PNB or CPNC alone or in PNB combinations

For lateral thigh skin donor sites in burns surgery, an US-guided single injection lateral femoral cutaneous nerve (LFCN) PNB and US-guided fascia iliaca compartment nerve block (FICNB) with CPNC reduced postoperative pain scores vs local anaesthesia infiltration (Shank 2016 **Level II**, n=19, JS 3). For femoral fracture or surgery, FICNB by landmark technique reduced pain scores (Paut 2001 **Level IV**, n=20) and rescue analgesic use vs IV opioid (Suresh 2014 **Level I** [PRISMA], 1 RCT: Kim 2011 **Level II**, n=64, JS 3; Wathen 2007 **Level II**, n=55, JS 3; Neubrand 2014 **Level III-2**, n=259 [158 FICNB]). For knee reconstructive surgery, FICNB vs femoral PNB were equivalent for postoperative analgesia (Suresh 2014 **Level I** [PRISMA], 1 RCT: Farid 2010 **Level II**, n=23, JS 3) and femoral PNB (alone or via CPNC) was effective vs IV opioid (Micalizzi 2014 **Level III-2**, n=93).

For femoral fracture and traction application, landmark and US-guided (Turner 2014 **Level III-2**, n=81) single injection femoral nerve blocks and CPNCs have been used effectively, including in an infant (Frenkel 2012 **CR**) and PICU patients (Tobias 1994 **Level IV**, n=4; Johnson 1994 **Level IV**, n=23). In the latter, plasma concentrations during bupivacaine 0.125% infusion of 0.3 mL/kg/h at 10–92 h were 0.67–0.93 mg/L.

Three-in-one blocks have been used in iliac bone graft harvest in comparison with wound infiltration and a wound catheter (Kumar Raja 2014 **Level II**, n=60, JS 5).

Following knee arthroscopic surgery, US-guided femoral and obturator blocks reduced pain scores and analgesia requirements vs no block (Kendall 2018 **Level I** [PRISMA], 1 RCT: Marinkovic 2016 **Level II**, n=60 JS 2). In adolescents with skeletal dysplasia having arthroscopic knee surgery, femoral, femoral/sciatic or femoral/sciatic/obturator blocks were effective (Eiszner 2016 **Level IV**, n=10 [PNB]). Combined femoral-sciatic nerve block offered better analgesia with fewer adverse effects than IA infiltration with bupivacaine/clonidine/morphine in children undergoing anterior cruciate ligament reconstruction (Tran 2005 **Level II**, n=36, JS 2).

Popliteal PNB and CPNC

For lower limb contracture surgery in cerebral palsy patients, US-guided popliteal vs sham block reduced pain scores for 0–12 h (Kendall 2018 **Level I SR** [PRISMA], 1 RCT: Ozkan 2017 **Level II**, n=54, JS 5). Following major foot and ankle surgery, popliteal CPNC with ropivacaine 0.2% 0.1 mL/kg/h achieved comparable analgesia with fewer adverse effects (PONV, urinary retention, early discontinuation) vs continuous epidural infusion 0.2% 0.2 mL/kg/h (Dadure 2006 **Level II**, n=52, JS 3).

10.6.2.2 | Upper limb blocks in children

Brachial plexus blocks

Traditionally the axillary approach to the brachial plexus was preferred in paediatric patients with its relative safety when using the landmark technique. US-guidance has led to new approaches in children for brachial plexus regional analgesia (Walker 2018 **Level IV**, n=5,636 [brachial plexus PNBs/CPNCs]; Marhofer 2004 **Level II**, n=36, JS 3; De Jose Maria 2008 **Level III-1**, n=80; Dadure 2009 **Level IV**, n=31 [upper limb CPNCs]); Ergonenc 2017 **CR**).

Supraclavicular approach: single injection and CPNC

PRAN audit has documented increased use of this approach in children (Walker 2018 **Level IV**, n=2,860 PNBs & 93 CPNCs [supraclavicular]). Following a single injection supraclavicular block, one 2 y old developed a pneumothorax which was managed conservatively.

For percutaneous fixation of supracondylar fractures, US-guided supraclavicular block reduced the mean and peak pain score only in PACU vs IV opioids (Glover 2015 **Level III-2**, n=230 [36 PNB]).

Infraclavicular approach: single injection and CPNC

Infraclavicular nerve block (ICNB) has been described in paediatrics with nerve stimulator (NS) (Ponde 2008 **Level IV**) and/or US-guidance (Walker 2018 **Level IV**, n=811 PNBs & 133 CPNCs [infraclavicular]). This approach is as safe as other brachial plexus approaches, with more reliable musculocutaneous nerve block/less tourniquet pain vs the axillary approach (Chin 2013 **Level I** [Cochrane], 3 RCTs [paediatric], n=156). For arm, forearm and hand surgery, US-guided low-volume 0.25 mL/kg vs standard volume 0.5 mL/kg bupivacaine 0.25%/lidocaine 1% infraclavicular block achieved similar sensory with shorter motor block duration (Kendall 2018 **Level I** [PRISMA], 1 RCT: Ince 2017 **Level II**, n=60, JS 5).

Axillary approach: single injection and CPNC

For forearm and hand surgery, axillary brachial plexus block provided satisfactory analgesia in 75−94% of cases (Gurnaney 2014 **Level IV**, n=2 [axillary]; Dadure 2009 **Level IV**, n=15 [axillary]; Fisher 1999 **Level IV**, n=185 [250 procedures]). US has assisted insertion of axillary catheters in children (Walker 2018 **Level IV**, n=981 PNBs & 9 CPNCs [axillary]) and single injection block for hand surgery in severe epidermolysis bullosa (van den Heuvel 2016 **Level IV**, n=9 [19 procedures]). Two fractionated nerve stimulator-guided axillary brachial plexus injections in children produced similar sensory and motor block quality at 30 min to a single injection (Carre 2000 **Level II**, n=70, JS 2), unlike in adults (Chin 2016 **Level I** [Cochrane], 22 RCTs [adult], n=2,193). Selective block of the musculocutaneous nerve is recommended when a surgical procedure takes place in its territory.

Interscalene approach: single injection and CPNC

Interscalene single injection blocks and CPNCs use in children is documented in the PRAN audit (Walker 2018 **Level IV**, n=984 PNBs & 103 CPNCs). An earlier PRAN series assessed the safety of the technique where 88% were performed in teenagers (10−18 y) and usually under GA (75%) (Taenzer 2014a **Level IV**, n=518 [472 PNB & 46 CPNCs]). US-guidance in 88%, nerve stimulation with US 11%, nerve stimulation alone 2.5% and rarely fluoroscopy assisted placement. One vascular puncture and one superficial infection were documented and no other serious events (LAST, neurological, cardiovascular or dural puncture) (95%CI 0 to 7.7/1,000). For forequarter amputation, direct surgical placement and infusions via epineural CPNCs in the 3 brachial plexus trunks (for 5 to 14 d) as part of a multi-modal regimen has been described (Kaddoum 2013 **Level IV**, n=4).

Wrist blocks

For distal hand surgery in anaesthetised young children, wrist block vs intraoperative alfentanil reduced postoperative pain scores, PONV and recovery time (De Windt 2010 **Level II**, n=60, JS 3). For trigger thumb release, US-guidance increased median nerve block success rates vs landmark technique (100 vs 74%) (Liu 2018 **Level II**, n=100, JS 3).

10.6.2.3 | Truncal blocks in children

Paravertebral block PVB and CPNC

Paravertebral block (PVB) or PV CPNC infusion has been reported in PRAN audit (Walker 2018 **Level IV**, n=535 PVB & 550 PV CPNC). With US uptake and the advent of newer truncal plane blocks, the role and risk profile of the PVB technique is of interest, but the paediatric evidence base lacks comparative trials. Of note, infant cadaveric studies suggested a single US-guided PVB 0.2−0.3 mL/kg at T12/L1 provides dose dependent coverage of T10 to L1 segments (Albokrinov 2014 **Level III-2**, n=20). Dosing in children for single and multi-injection reported in mg/kg ropivacaine equivalents (not in mL/kg) was higher for infants at a mean of 1.47 and 2 respectively vs 1.25 and 1.75 for older children (Vecchione 2016 **Level IV**, n=2,390 in 871 children [1765 PVBs & 625 CPNCs]). No complications were reported with single injection PVBs. While with PVB CPNC, 2 major complications occurred: one was a LAST event in an infant relating to chloroprocaine 3% 1 mL/kg bolus and one teenager with bilateral PV CPNCs developed a large paravertebral haematoma with epidural extension that was conservatively managed (event rate for paravertebral CPNC: 18.2/10,000; 95%CI 0 to 113) (Walker 2018 **Level IV**, n=535 PVB & 550 PV CPNC). Minor complications for PVB CPNCs recipients included: catheter dislodgement 4.9%, occlusion 1.5%, leakage 5.9%, skin irritation 2.9% and minor bleeding in 1% (Vecchione 2016 **Level IV**, n=625).

Paravertebral block: single injection

Single injection PVB has provided effective analgesia following thoracoabdominal surgery in children.

In a systematic review of heterogeneous paediatric trials, single and multi-injection PVB reduced pain scores at 4−6 h (SMD 0.85; 95%CI 0.12 to 1.58) and 24 h (4 RCTs, n=282) and supplemental analgesia requirement (3 RCTs [inguinal; comparators no block, ilioinguinal block and caudal] n=199) (OR 0.17; 95%CI 0.08 to 0.34) (Page 2017 **Level I** [PRISMA], 6 RCTs [PVB], n=358). PVBs have also been effective for several hours (median 10 h to mean 22 h) following cardiac surgery for aortic coarctation (Saleh 2018 **Level II**, n=50, JS 4; Turkoz 2013 **Level IV**, n=15) and PDA ligation (Chalam 2015 **Level II**, n=100, JS 4), Nuss procedure (vs no block; Kendall 2018 **Level I** [PRISMA], 1 RCT: Qi 2014 **Level II**, n=30, JS 2), infant pyloromyotomy (Mata-Gomez 2015 **Level IV**, n=3) and renal surgery (vs caudal Narasimhan 2019 **Level II**, n=50, JS 5; vs IV paracetamol Akinci 2019 **Level II**, n=40, JS 4; Berta 2008 **Level IV**, n=24).

Paravertebral block: CPNC

Compared with thoracic epidural catheter infusion, PVB CPNC infusion (US-guided; bilateral) provided equivalent analgesia for cardiac surgery via thoracotomy (nerve stimulator guided) with higher insertion success and less adverse events (El-Morsy 2012 **Level II**, n=60, JS 5) and was equivalent for the Nuss procedure (Muhly 2019 **Level III-2**, n=331 [56 paravertebral, 114 epidural]; Hall Burton 2014 **Level III-2**, n=20) or with higher pain scores and opioid use postoperatively (as with intercostal nerve catheters) but shortest LOS (mean 2.0 vs 4.0 d vs 4.9) (Loftus 2016 **Level III-2**, n=137).

Surgically placed paravertebral CPNCs have been effective post-thoracotomy in children for empyema decortication (bupivacaine 0.1% 0.3 mg/kg/h) (Murphy 2016b **Level IV**, n=83), in infants for congenital pulmonary malformations (ropivacaine 0.125% 0.2 mg/kg/h) (Di Pede 2014 **Level III-3**, n=40) and neonates for tracheo-oesophageal fistula (TOF) surgery (levo-/bupivacaine 0.0625% ≈0.25 mg/kg/h for 43 h median) (Palmer 2012 **Level IV**, n=37).

Unilateral PVB CPNC ropivacaine infusion for 2 d provided equivalent analgesia vs single injection caudal ropivacaine/morphine for upper abdominal surgery in infants (Sato 2017 **Level III-2**, n=21). Bilateral and unilateral US-guided PVB CPNCs have been used for various thoracoabdominal procedures for 1−5 d (Boretsky 2013 **Level IV**, n=22) including including following TOF repair (ropivacaine 0.08% 0.2 mg/kg/h for 4−5 d) (Thompson 2015 **Level IV**, n=2). Following iliac crest bone graft harvest, paravertebral L2 CPNCs with elastomeric pump reservoir (ropivacaine 0.2%, 0.06–0.2 mL/kg/h) were effective for outpatient analgesia (Visoiu 2014a **Level IV**, n=5).

Erector spinae plane block (ESPB)

It is debated whether the erector spinae plane block (ESPB) is a paravertebral variant with neuraxial spread (Tsui 2019 **Level IV**, n=242 [23 children]) vs a myofascial plane block: see the discussion in adult Section 5.8.5.3. A median volume of 3.4 mL per dermatomal level is suggested for ESPB dermatomal spread in adults (De Cassai 2018 **NR**); with no paediatric dosing recommendation data specific to this block.

Erector spinae plane block: single injection

US-guided single injection ESPB has been described in various paediatric surgeries in children (6 mth to 16 y): at T1 for posterior chest wall surgery (Hernandez 2018b **CR**), T5−8 for thoracic surgery (Ueshima 2018 **Level IV**, n=2; Adhikary 2018 **CR**; Munoz 2017 **CR**), T7 for laparoscopic cholecystectomy (Aksu 2019b **Level IV**, n=3; Thomas 2018a **CR**), T12 for nephrectomy for Wilm's tumour (Aksu 2018b **Level IV**, n=2), and at L1 for laparoscopic or open lower abdominal surgeries (Aksu 2019a **Level II**, n=60, JS 4; Aksu 2019c **Level IV**, n=2) and inguinal hernia repair (Aksu 2018a

Level IV, n=10), including in an ex-preterm infant (Hernandez 2018a **CR**). Post inguinal surgery, ESPB at L1 vs quadratus lumborum block (transmuscular approach) reduced pain scores similarly (0−6 h) with similar times to first analgesic rescue (Aksu 2019c **Level II**, n=60, JS 4).

Erector spinae plane block: continuous infusion

ESPB CPNC infusion is reported as used following thoracotomy (De la Cuadra-Fontaine 2018 **CR**), video assisted thoracoscopic surgery (VATS) (Adhikary 2018 **CR)** and pyeloplasty (Munshey 2018 **CR**).

Intercostal nerve block single injection and CPNC

For ear reconstruction cartilage graft site pain, a surgically placed intercostal CPNC was superior to IV analgesia in reducing pain scores at rest and on coughing (Woo 2016 **Level II**, n=66, JS 3). While a single injection intercostal block was inferior to a wound catheter infusion (Niiyama 2016 **Level II**, n=48, JS 2).

Pectoralis nerves and serratus anterior plane PNBs

Ultrasound-guided pectoralis nerve (PECS) blocks and serratus anterior plane (SAP) blocks are regional analgesia techniques of the thorax (for technique description see also adult Section 5.8.5.4). Following paediatric cardiac surgery via thoracotomy, PECS II and SAP block recipients had clinically modest 0.5−0.9/10 difference in pain scores from 4−10 h with reduced fentanyl requirement (by 0.5 and 0.6 mcg/kg) vs ICN block recipients (Kaushal 2019 **Level II**, n=108, JS 3).

Sternal bed block single injections

In paediatric cardiac surgical patients having a median sternotomy, parasternal 2nd to 6th intercostal space injections of ropivacaine 0.5% 0.5−2 mL per level (total dose <5 mg/kg) reduced pain scores (MD 2.6/10) and postoperative fentanyl requirement (MD 3 mcg/kg) vs placebo (Chaudhary 2012 **Level II**, n=30, JS 4).

Quadratus lumborum block (QLB) single injection and CPNC

US-guided quadratus lumborum block (QLB) is performed by four approaches: Type 1 (lateral), Type 2 (posterior), transmuscular (TM or anterior) (NYSORA 2020 **GL**) and intramuscular (IM). Use has been described for various lower abdominal surgeries in the T12−L1 dermatomal distribution. The PRAN data set provides no specific data for this block (presumed included in 'other truncal') reflecting the low frequency of use in children (Walker 2018 **Level IV**, n=256 [single injection other truncal] & 20 [other truncal CPNCs]).

In children undergoing lower abdominal surgery, TM QLB reduced pain scores (0−24 h) and analgesic requirements vs IM QLB (18.5 vs 48.1%), but with more quadriceps weakness (29.6 vs 3.7%) (Hussein 2018 **Level II**, n=54, JS 3). Post ureteral reimplantation, US-guided Type 2 QLB recipients had similar pain scores and similar vomiting incidence to US-confirmed caudal ropivacaine 0.2% 1 mL/kg/morphine 30 mcg/kg block (Sato 2019 **Level II**, n=47, JS 5). Post inguinal surgery, TM QLB vs ESPB at L1 were similarly effective (0-6h) (Aksu 2019c **Level II**, n=60, JS 4) and type 2 QLB achieved statistically lower but clinically similar pain scores vs transversus abdominis plane block (TAPB) (means <1 vs 2/10 for 0−24h), with reduced rescue requirement (12% vs 40) (Oksuz 2017 **Level II**, n=50, JS 5). TM QLB had utility in young children having day case inguinal surgery (Aksu 2018c **Level IV**, n=10) and was used for congenital hip dislocation surgery (Ahiskalioglu 2018b **Level IV**, n=2).

The use in children of QLB CPNC infusion of levobupivacaine 0.1% 5 mL/h following radical nephrectomy (Chakraborty 2015 **CR**) and ropivacaine 0.2% 5 mL/h following colostomy closure is described (Visoiu 2013 **CR**).

Transversus abdominis plane block (TAPB)

Paediatric RCT data is limited (see below), surpassed by increasing numbers in the PRAN audit, where no complications specific to TAPB were described (Walker 2018 **Level IV**, n=5,630 [TAPB] & n=199 [TAPB CPNCs]). An earlier PRAN TAPB subgroup analysis (95% US-guided) documented a low incidence of complications 0.1% (95%CI 0.02 to 0.3%): including one vascular aspiration and one peritoneal puncture without sequelae (Long 2014 **Level IV**, n=1,994). Notably, bupivacaine dosing varied widely (mean 1 mg/kg; range 0.47 to 2.29) with 7% of patients receiving potentially toxic doses (2 mg/kg) usually younger in age; this highlights the need to dose according to weight. No LAST events were reported. US-guided TAPB in children provides abdominal wall sensory block below T10 with 0.4 mL/kg local anaesthetic injection (Palmer 2011 **Level IV**, n=27 [38 TAPB]).

Transversus abdominis plane block: single injection

In a systematic review of heterogeneous RCTs, TAPB is superior to wound infiltration for pain scores at rest at 8 h (7 RCTs, n=416) and 24 h (7 RCTs [2 paediatric], n=425) (Guo 2015 **Level I** [PRISMA], 9 RCTs [3 paediatric], n=500 [176 children]). In the paediatric RCTs, TAPBs vs wound infiltration reduced paracetamol rescue use (1 RCT [inguinal], n=57), with no overall difference in morphine requirements following open pyeloplasty (1 RCT [n=32) or laparoscopic appendicectomy where more TAPB recipients had complicated appendicitis (31 vs 11%) (1 RCT, n=87). In contrast, ipsilateral TAPB reduced morphine requirements vs saline block in open appendicectomy, where perforation and positive histopathology rates were similar (Hamill 2016 **Level I** [PRISMA], 1 RCT: Carney 2010 **Level II**, n=40 JS 4). Several subsequent studies are mostly positive:

- Post laparoscopy, TAPB was superior to surgical site infiltration (Karnik 2019 **Level II**, n=92, JS 4);
- Post mixed abdominal surgery, TAPB was effective and more so with higher dose bupivacaine 0.25% vs 0.125% (with adrenaline/epinephrine 5mcg/mL) 1 mL/kg (Suresh 2015b **Level II**, n=36, JS 5);
- Following ureteral reimplantation, TAPB was effective (0.5 mL/kg) vs caudal block with less morphine (although higher initial PACU pain scores) (Baeriswyl 2018 **Level I** [PRISMA], 10 RCTs, n=505 [4 paediatric, n=195], 1 RCT: Bryskin 2015 **Level II**, n=45, JS 3);
- Following colorectal procedures, TAPB was effective where 90% of infants had pain scores of 0/7 for 24 h (Chen 2015 **Level IV**, n=10);
- Following inguinal surgery, US-guided TAPB bupivacaine 0.25% 0.4 mL/kg vs no block attenuated the surgical stress response (Abu Elyazed 2016 **Level II**, n=60, JS 2). TAPB was more effective than surgical site infiltration (Kendigelen 2016 **Level II**, n=40, JS 2), similarly effective vs caudal block (Baeriswyl 2018 **Level I** [PRISMA], 1 RCT: Sethi 2016 **Level II**, n=80, JS 3) and both TAPB and caudal were more effective vs ilioinguinal-iliohypogastric nerve block (II/IHNB) (Sahin 2017 **Level II**, n=90, JS 3). In contrast, low volume US-guided TAPB 0.3 mL/kg was inferior to US-guided ilioinguinal block in early rescue analgesic requirement (Fredrickson 2010 **Level II**, n=41, JS 3); and
- Post robot assisted laparoscopic renal/urological procedures, neither TAPB nor caudal provided additional benefit vs no block (Faasse 2015 **Level III-2**, n=120).

Transversus abdominis plane block: CPNCs

US-guidance is used for TAPB CPNC insertion (97% US-guided) (Walker 2015a **Level IV**, n=58 [TAP CPNCs]). TAPB CPNC infusions have been employed in small children (weighing ≤10 kg) where epidural use was contraindicated or refused (Bakshi 2017 **Level IV**, n=2; Visoiu 2012 **Level IV**, n=6).

Rectus sheath block (RSB)

Rectus sheath block (RSB) provides analgesia for midline abdominal procedures with block of the 7th to 11th intercostal nerve terminal branches (Visoiu 2015 **NR**). There has been wide variation in

the dose and volume of local anaesthetic used for RSB: mean bupivacaine dose 0.72 mg/kg (95%CI 0.23 to 2.30) and ropivacaine 1.19 mg/kg (95%CI 0.39 to 2.43) (Suresh 2018a **Level IV**, n=2,331 [RSB]).

Compared to systemic analgesia, RSB has longer time to first morphine rescue (MD 19 min; 95%CI 6 to 33) (3 RCTs [RSB], n=222) and reduces early postoperative morphine consumption at 6–8 h (MD -20 mcg/kg; 95%CI -30 to -10) (4 RCTs [RSB], n=235) (Hamill 2016 **Level I** [PRISMA], 5 RCTs [RSB 4 umbilical & 1 laparoscopic appendicectomy], n=287; Suresh 2014 **Level I** [PRISMA]: 2 RCTs [RSB], n=65) (2 RCT overlap).

Subsequent RCTs show US-guided RSB is similarly effective vs surgical site infiltration for laparoscopic assisted inguinal hernia repair (Uchinami 2017 **Level II**, n=34, JS 3) and for umbilical surgery vs both caudal and pre-incision surgical site infiltration (Relland 2017 **Level II**, n=39, JS 5), independent of whether surgically or US-placed (Litz 2017 **Level II**, n=58, JS 3).

Ilioinguinal/iliohypogastric nerve block (II/IHNB)

The ilioinguinal/iliohypogastric nerve block (II/IHNB) is used for pain relief following inguinal surgery in children. Dosing is variable per PRAN audit data where mean dose for bupivacaine was 0.68 mg/kg (95%CI 0.23 to 1.66) and for ropivacaine 0.95 mg/kg (95%CI 0.29 to 2.48) (Suresh 2018a **Level IV**, n=3,892 [II/IHNB]). Of note, after II/IHNB landmark technique, weak hip flexion (inadvertent FNB) occurred in 8.8% (95%CI 5.1-13.9%) (Lipp 2004 **Level IV**, n=182). Bowel puncture has been described with resultant subserosal haematoma noted during appendicectomy without consequence (Frigon 2006 **CR**), persistent superficial infection with skin flora (Johr 1999 **CR**) and development of intestinal obstruction resulting in laparotomy and bowel resection (Amory 2003 **CR**).

Single vs double injection II/IHNB landmark techniques have similar success rates of 72% (1 RCT, n=87), with similar efficacy of different needle insertion sites (1 cm inferomedial to ASIS; 1 to 2 cm medial to ASIS; 2 cm superomedial to ASIS) (1 RCT, n=132) (Suresh 2014 **Level I** [PRISMA], 15 RCTs [II/IHNB], n=1,046). US-guidance improves the success rate of II/IHNB to 94% with smaller volumes of local anaesthetic administered (2 RCTs, n=166). With US study post landmark technique demonstrating intramuscular injection was common (82%: iliac 18%, transversus 26%, internal oblique 29% or external oblique 9%) and intraperitoneal uncommon (2%) (Weintraud 2008 **Level III-2**, n=62). The overall clinical block success rate was 61%: 100% success when injectate was deposited in the correct plane vs 45% when injected into surrounding tissues.

For II/IHNB, the same dose at two concentrations/volumes was similarly effective (1 RCT, n=72) and higher doses were effective for longer (1 RCT, n=60) (Suresh 2014 **Level I**, [PRISMA], 2 RCTs [II/IHNB dose], n=132). Similar analgesic efficacy following inguinal hernia repair has been found with wound infiltration, II/IHNB or caudal analgesia (Baird 2013 **Level III-1 SR,** 1 RCT: Machotta 2003 **Level II**, n=58, JS 4; Splinter 1995 **Level II**, n=200, JS 5).

After US-guided II/IHNB, plasma ropivacaine concentrations were higher and peaked earlier by ≈5 min at 1.78 mcg/mL (range 0.56-2.97) vs 1.23 mcg/mL with landmark technique (Suresh 2014 **Level I SR**, [PRISMA], 1 RCT: Weintraud 2009 **Level II**, n=66, JS 3).

10.6.2.4 | Superficial head and neck blocks

Scalp blocks

Blocks of scalp branches of the frontal (supraorbital, supratrochlear), maxillary (zygomaticotemporal) and auriculotemporal nerves as well as branches of the superficial cervical plexus (greater auricular and occipital nerves) have been used in a small number of children, as an adjunct to postoperative opioids, following craniosynostosis repair (Rothera 2014 **Level III-2**, n=78; Pardey Bracho 2014 **Level IV**, n=32) and neurosurgery (Pardey 2008 **Level IV**, n=3) including in a 700 gm neonate (Suresh 2004b **CR**). See also Section 8.1.8.

Infraorbital nerve block

In addition to use in cleft lip repair (Suresh 2012 **NR**) (see Section 10.6.6 below), infraorbital block has described applications for endoscopic maxillary sinus surgery (Higashizawa 2001 **Level II**, n=50, JS 3) and trans-sphenoidal hypophysectomy (McAdam 2005 **Level IV**). Use of bilateral infraorbital blocks with block of the external nasal branch of the anterior ethmoidal nerve has been used as an alternative option for intra and postoperative pain management of nasal fracture repair (Cok 2015 **CR**).

Superficial cervical plexus block

Superficial cervical plexus block has provided relief in paediatric patients for internal jugular haemodialysis catheter insertion (Ciftci 2014 **Level IV**), thyroplasty in an awake patient (Suresh 2004c **CR**) and cochlear implant (Merdad 2012 **Level III-3**, n=91), though there was association with postoperative fever in the latter.

Blocks for ear surgery

Greater auricular nerve block (GANB) provided near equivalent analgesia with reduced PONV vs IV morphine following tympanomastoid surgery (Suresh 2002 **Level II**, n=40, JS 4). Pre-incision GANB vs placebo in addition to GANB performed at surgery completion did not affect postoperative pain scores, analgesia requirements, time to rescue analgesia or PONV (Suresh 2004a **Level II**, n=40, JS 4). For otoplasty, GANB with lesser occipital nerve block provided equivalent analgesia to surgical site infiltration (Cregg 1996 **Level II**, n=43, JS 2) and local anaesthetic infiltration alone had reduced PONV vs in local/general anaesthesia recipients (Lancaster 2003 **Level III-3**, n=85).

Following bilateral myringotomy and tube insertion, postoperative pain scores or PONV did not differ with auricular (vagal nerve branch) block vs IN fentanyl (Voronov 2008 **Level II**, n=200, JS 4).

10.6.2.5 | Continuous local anaesthetic wound catheter infusions

The evidence for use of wound catheter infusions in children is limited (See adult Section 5.8.8). One RCT was negative where, in children undergoing median sternotomy for ASD closure (with mediastinal drain), wound catheter ropivacaine 0.2% infusion ≈0.35 mg/kg/h vs placebo infusion did not benefit pain scores, opioid consumption (0-72 h), PONV nor time to mobilisation (Mattila 2016 **Level II**, n=49, JS 5). The remaining RCTs have been positive:

- Continuous wound catheter recipients had lower postoperative pain scores (2.5/10 vs 3.5) (with 4-fold lower morphine use) after open appendicectomy vs systemic analgesia and after laparotomy vs epidural analgesia (2.5/10 vs 3.0) (and 1.75 fold lower morphine use) (Machoki 2015 **Level II**, n=71, JS 5). Wound catheter recipients mobilised earlier with no difference in surgical site complications;
- For ear reconstruction cartilage graft site pain, a surgically placed para-rectus 72 h wound catheter infusion ropivacaine 0.2% 2−4 mL/h had extended analgesic benefits vs single injection ICNB ropivacaine 0.75% (Niiyama 2016 **Level II**, n=48, JS 2). Mean plasma concentrations of ropivacaine were low at 0.9 mg/L at 2 and 24 h and 0.7 at 48 h;
- In children with spina bifida undergoing open urinary tract surgery, a wound catheter infusion vs an opioid infusion or PCA (in conjunction with multimodal analgesia) achieved similar pain scores with reduced morphine equivalent use by two thirds and reduced antiemetic requirement (Chalmers 2015 **Level III-2**, n=36);
- For Nuss surgery, wound catheter recipients (who also received hydromorphone PCA, low dose gabapentin 100-200 mg three times daily and clonidine patch 50 mcg/d) had similar pain scores to thoracic epidural infusion recipients (ropivacaine 0.2%/hydromorphone 10 mcg/mL) (Choudhry 2016 **Level III-3**, n=32). While in a study exploring the addition of

preoperative self-hypnosis training, wound catheter recipients had higher pain scores but lower PCA opioid requirement vs thoracic epidural recipients (Manworren 2018 **Level III-3**, n=53). In a further study, wound catheter (ropivacaine 0.2%) recipients also had higher mean postoperative pain scores vs thoracic epidural (bupivacaine 0.1%) recipients (3.8/10 vs 2.9) (Thaker 2019 **Level III-3**, n=124). In all three studies, wound catheter recipients had shorter mean LOS: 2.9 d vs 4.1 (Choudhry 2016 **Level III-3**, n=32), 4.4 d vs 5.1 (Manworren 2018 **Level III-3**, n=53) and 4.9 d vs 5.6 (Thaker 2019 **Level III-3**, n=124);

- In neonates following major thoraco-abdominal surgery, wound catheters infusing levobupivacaine 0.125% 0.16mL/kg/h (0.2 mg/kg/h) were used in addition to paracetamol and IV clonidine (Krylborn 2015 **Level IV**, n=20). Median plasma levobupivacaine concentrations over 12−72 h were low [free 0.018 mg/L; total 1.305 mg/L], with 90% of free concentration values remaining below 0.05 mg/L for the duration of the infusion.

10.6.2.6 | Adjuvants in PNBs

Multiple studies have been performed assessing the addition of various adjuvants in PNBs, usually without systemic comparator, and are summarised below. See also adult Section 4.9.2.

Alpha-2 agonist adjuvant use in PNBs

Results of RCTs for adjuvant use of alpha-2 agonists are contradictory with small sample sizes, variation in dosing and operation type (major vs minor). To date they have lacked a systemic comparator arm.

Two overlapping SRs are contradictory. The first concludes alpha-2 agonists increase single injection PNB duration with longer time to first rescue analgesic administration based on predetermined pain score change (Lundblad 2016 **Level I**, 3 RCTs & 2 unpublished RCTs' abstracts [4 clonidine, 1 dexmedetomidine], n=283). The time until 25% of patients needed rescue analgesia was ≈6 h longer with alpha-2 agonist/local anaesthetic vs local anaesthetic alone (HR 1.7; 95%CI 1.1 to 2.4) with no complications reported. The prolongation occurred across all the heterogeneous PNBs assessed (Lundblad 2016 **Level I**, 3 RCTs & 2 unpublished RCTs' abstracts, n=283). This finding was also reported in an earlier study (Cucchiaro 2007 **Level III-2**, n=435) where motor block duration was shorter for blocks without adjuvant clonidine (OR 0.33; 95%CI 0.16–0.69).

The second systematic review was negative: concluding clonidine 1−2 mcg/kg added to local anaesthetic does not confer any additional benefit in postoperative pain outcomes for caudal or II/IHNB for inguinal surgery or axillary block for arm surgery (Suresh 2014 **Level I** [PRISMA], 2 RCTs [inguinal], n=160 & 1 RCT [axillary]: Trifa 2012 **Level II**, n=60, JS 5) (2 RCT overlap). A third non-overlapping systematic review of paediatric tonsillectomy concludes no benefit with fixed dose clonidine 25mcg added to peritonsillar local anaesthetic infiltration (Vlok 2017 **Level I**, 2 RCTs [clonidine], n=123).

Subsequent studies are positive with increased duration of analgesia with adjuvant clonidine 1 mcg/kg added to:

- Local anaesthetic DPNB (Anouar 2016 **Level II**, n=40 JS 3) and to nerve stimulator-guided pudendal nerve block for penile surgery (Naja 2013 **Level II**, n=80, JS 5); and
- Bilateral infraorbital nerve blocks for cleft lip surgery (Feriani 2016 **Level I** [Cochrane], 1 RCT: Jindal 2011 **Level II**, n=50, JS 5);

And adjuvant dexmedetomidine 1-2 mcg/kg added to:

- Greater palatine nerve blocks for cleft palate repair (time to first analgesia mean 22h vs 14.2) with no side effects (Obayah 2010 **Level II**, n=30, JS 3);
- II/IH block where the addition doubled the time to first analgesic request following inguinal surgery (Arirachakaran 2018 **Level II**, n=60 JS 5);

- TAPB reduced postoperative morphine requirements and reduced the ED_{min} for bupivacaine from 0.08% to 0.06% (assessed by haemodynamic changes to skin incision at 15 min) for inguinal surgery (Raof 2017 **Level II**, n=60, JS 5).

Adrenaline

Adrenaline as an additive has been used in various PNBs as described in this section; but has not been analysed as an adjuvant comparator in PNBs.

Opioids

Opioids are used frequently as part of multimodal analgesia and rescue therapy in patients receiving PNBs. There are 2 RCTs where the addition of adjuvant opioids to the local anaesthetic for infraorbital nerve block have been positive with increase in analgesia duration, without systemic route comparator (see cleft lip Section 10.6.6).

Systemic and perineural steroids – dexamethasone

For tonsillectomy, a Cochrane review is positive for multiple outcomes (see Section 10.4.10 for systemically administered dexamethasone). The below RCTs assess dexamethasone of varying doses 0.1−0.5 mg/kg as an adjuvant to local anaesthesia in PVBs, by perineural and systemic routes.

The adjuvant use of dexamethasone:

- IV 0.5 mg/kg (max unspecified) vs placebo added to DPNB reduced pain scores with longer time to rescue following hypospadias repair (Shirazi 2016 **Level II**, n=42, JS 3);
- IV 0.15 mg/kg (max 8mg) added to glossopharyngeal nerve block provided superior postoperative analgesia to either in isolation (Mohamed 2009 **Level II**, n=150, JS 3). However, glossopharyngeal nerve block in 2 children has been associated with postoperative airway obstruction (Bean-Lijewski 1997 **Level III-3**, n=8);
- Added to local anaesthetic for peritonsillar infiltration reduced analgesic use and PONV incidence (RR 0.56; 95% CI 0.35 to 0.89) following tonsillectomy (2 RCTs, n=299) (Vlok 2017 **Level I**, 3 RCTs [dexamethasone: 2 paediatric], n=361 [309 children]). Infiltration of 0.5 mg/kg (max 8 mg) added to local anaesthetic reduced early and later (>12 h) pain scores vs bupivacaine alone and placebo, where all patients received IV dexamethasone 0.5mg/kg (max 16 mg) (Kilinc 2019 **Level II**, n=120, JS 5);
- In US-guided PVB, expedited extubation by ≈5 h and reduced pain scores at 12 and 24 h following coarctation repair in infants (Saleh 2018 **Level II**, n=50, JS 4);
- While adding perineural or IM dexamethasone to FNB did not further improve analgesia following knee arthroscopy in teenagers (Martin 2018 **Level II**, n=77, JS 5).

Ketamine

Adding IV ketamine 0.5 mg/kg to peritonsillar bupivacaine 0.25% was more effective than IV placebo/peritonsillar bupivacaine infiltration, and IV placebo/placebo infiltration with lower pain scores (1−24 h) and longer time to first analgesia (Inanoglu 2009 **Level II**, n=90, JS 5).

See Section 10.4.7.1 for summary of 3 overlapping systematic reviews assessing peritonsillar ketamine administration as a comparator vs placebo and one RCT of peritonsillar administration vs other systemic routes.

Magnesium

The addition of peritonsillar magnesium 2-5 mg/kg (max unspecified) to local anaesthetic reduced pain scores (4 RCTs, n=230) and the number of analgesic requests (WMD −0.68; 95% CI −1.17 to −0.18) (3 RCTs, n=180) (Vlok 2017 **Level I**, 4 RCTs [Mg], n=230).

Tramadol

Tramadol has been assessed as a comparator arm in various RCTs by systemic administration and infiltration and nerve block summarised in Section 10.4.4.12. See also below 10.6.6 for an RCT of peritonsillar infiltration of tramadol as an adjuvant.

Midazolam

Midazolam has not been assessed as an adjuvant for PNBs.

10.6.3 | Neuraxial blocks

Central neuraxial blocks are used in paediatric patients to provide postoperative analgesia and to supplement intraoperative anaesthesia. Patient selection, technique, choice of medicines, availability of experienced staff for performing blocks, an APS or outpatient resources and adequacy of follow-up vary between centres (Williams 2003 **NR**).

10.6.3.1 | Epidural analgesia

As the epidural space is relatively large with loosely packed fat in neonates, catheters can be threaded from the sacral hiatus to lumbar and thoracic levels (Tsui 2004 **Level IV**). Accuracy of caudal-epidural catheter placement in young infants (2 d to 5 mth) to the desired vertebral level was improved with US-guidance vs external measurement in one study (Ponde 2017 **Level IV**, n=25). In older infants, various techniques have been suggested to improve correct placement including US, nerve stimulation and ECG guidance (Willschke 2006 **Level IV**, n=64; Tsui 2004 **Level IV**, n=10; Tsui 2002 **Level IV**). US provides visibility of the dura mater and ligamentum flavum, especially in infants and younger children.

Insertion of epidural catheters at the segmental level required for surgery was more reliable in older children and has been shown to be safe in experienced hands with appropriately sized equipment (Walker 2018 **Level IV**, n=13,120 [epidural catheters] & 854 single injection epidurals (not including caudal); Llewellyn 2007 **Level IV**, n=10,633 [epidural]; Giaufre 1996 **Level IV**, n=2,396 [epidural]). Cephalad or caudad migration (assessed by x-ray) of caudal-thoracic epidural catheters occurred in 64% of patients (1 d to 10 mth old); however >1 level of migration occurred only in infants ≤6 kg (Simpao 2019 **Level IV**, n=85). In older children with a thoracic epidural catheter, catheter migration was also related to patient size: 1.1 level change in those <40 kg and less change of 0.3 level in those ≥40 kg (where catheters fell out in 10% of patients) (Strandness 2015 **Level IV**, n=59).

MRI anatomical studies have shown the largest dura to spinal cord distance is mid thoracic at T5/6 and the smallest at the L2/3 region (Wani 2018 **Level IV**, n=88 patients). A formula for the mean skin to epidural space distance at L3/4 in ≤6 y olds based on MRI data (9 + 0.62 x weight kg=depth in mm) may be more accurate than previously reported formulas based on depth of needle insertion (Franklin 2015 **Level IV**, n=70).

Furthermore, MRI has shown spinal cerebrospinal fluid (CSF) volumes per kg are less in children (0–18 y) than previously predicted (Jang 2019 **Level IV**, n=500 [248 thoracolumbar]). Thoracolumbar CSF volume (T1 to end of dural sac) reduced with increasing age (r 0.66: <1 y mean 1.95 mL/kg vs >12 y 0.99), height (r 0.72), and weight (r 0.73). In young children 0–3 y, MRI study demonstrated the median epidural space volume per vertebral segment: the lumbar value was 1.18 mL/kg (95%CI 0.94 to 1.43) and the thoracic value was half that at 0.60 mL/kg (95%CI 0.38 to 0.75) (Forestier 2017 **Level IV**, n=20).

Ultrasound can identify normal and abnormal spinal anatomy in children (6–12 y) post myelomeningocoele repair, facilitating selection of the optimal intervertebral space for epidural catheter placement (Ponde 2018 **Level IV**, n=12).

Ultrasound is a reliable predictor of depth to loss of resistance (or depth of epidural space), offers visibility of the needle and catheter, and may reduce bone contacts (Guay 2019a **Level I** [Cochrane], 1 RCT overlap with Tsui 2010 **Level IV SR** [PRISMA], 1 RCT: Tachibana 2012 **Level II**, n=20 JS 1). US prescanning vs landmark technique in children (mean age 10 y) having a Nuss procedure decreased the time to insert a thoracic epidural catheter (by ≈1 min: median 1.67 min vs 2.75) (not including pre-scanning time). Whilst continuous US scanning in neonates to 6 y olds reduced epidural lumbar or thoracic catheter insertion time (mean 2.7 min vs 3.9) (Guay 2019a **Level I** [Cochrane], 1 RCT: Willschke 2006 **Level II**, n=64 JS 1).

Local anaesthetics

Continuous epidural infusions of bupivacaine are effective and safe in children (Walker 2018 **Level IV**, n=13,120 [epidural catheters]; Wong 2013a **Level IV**, n=3,152 [epidurals]; Ecoffey 2010 **Level IV**, n=10,098; Llewellyn 2007 **Level IV**, n=10,633). In children <4 y having abdominal surgery, bupivacaine 0.25% epidural infusion (0.1 mL/kg/h) vs morphine infusion were similarly effective (Wolf 1993 **Level II**, n=32, JS 3). In children aged 7–12 y having lower extremity major orthopaedic surgery, patient-controlled epidural analgesia (PCEA) ropivacaine 0.2% vs continuous infusion both achieved low pain scores (≤1/10) in the first 48 h postoperatively (Antok 2003 **Level II**, n=48, JS 2). Total ropivacaine dose was reduced with PCEA (0.2 mg/kg/h vs 0.4 mg/kg/h) but no differences in adverse effects were detected.

In neonates, due to reduced clearance and the potential for accumulation of bupivacaine, the hourly dose should be reduced, and the duration of therapy limited to 24–48 h (Larsson 1997 **Level IV**; Ivani 2015 **GL**). Postnatal age and weight influence the pharmacokinetic profile of levobupivacaine, with slower absorption and clearance in neonates and infants (Chalkiadis 2006 **Level IV**, n=86). Total plasma levobupivacaine concentrations after caudal epidural bolus in 3–6 mth old infants peaked at 1 h post 2 mg/kg at 0.30 mg/L (range: 0.20–0.70) (Vashisht 2019 **Level IV PK**, n=8). During subsequent infusion of 47 h duration, the total plasma level increased (with rising alpha-1 acid glycoprotein); however free plasma concentrations plateaued at steady state early, remained low at 0.03 mg/L and were cleared rapidly over ≈12 h post cessation. In infants >6 mth, although plasma levobupivacaine concentrations increased, they remained low after 24 h of epidural infusion (Lerman 2003 **Level II**, n=120, JS 5). Epidural infusions of ropivacaine were effective and safe in neonates (Bosenberg 2005 **Level IV**) and children (Berde 2008 **Level IV**) with minimal drug accumulation.

Postoperative continuous epidural infusion with chloroprocaine 1% (0.4–3 mL/h) or 1.5% (0.25–1.5 mL/kg/h) for 7–118 h has been used in neonates, infants and children having various surgeries, (Veneziano 2016 **Level IV**, n=21 [15 ≤6 mth]; Ross 2015 **Level IV**, n=18 [≤6 mth]; Kamata 2014 **CR**), and was similarly effective to ropivacaine 0.1% in infants (≤6 mth) post-thoracotomy (Muhly 2015 **Level III-2**, n=54). No serious adverse events related to epidural analgesia were reported in any of the three studies. As an ester local anaesthetic which is rapidly metabolised in plasma at all ages including neonates, chloroprocaine may have a lower risk of accumulation and LAST than amide local anaesthetics in neonates and young infants with immature hepatic enzymes (Veneziano 2017 **NR**).

For infants (median age 59 d) having a Kasai portoenterostomy, epidural local anaesthetic (with various adjuvants: fentanyl or hydromorphone with clonidine in 56%) vs no epidural had lower pain scores from 6–30 h (highest median score 0.2/10 vs 2.1), were more likely to be extubated in theatre (88% vs 59%) and had shorter LOS (median 6 d vs 8) (Phelps 2019 **Level III-2**, n=47).

In children (5 mth to 12 y) having ureteric reimplantation surgery, patients with a caudal epidural catheter threaded 5–7cm vs lumbar epidural catheters (bupivacaine 0.125%/fentanyl 2 mcg/mL infusions at 0.1–0.3 mL/kg/h) had less interventions for bladder spasms (mean

1.8/patient vs 8) and wound pain (mean 8.8/patient vs 11.4) (Sommerfield 2016 **Level III-2**, n=135 [catheter]).

In infants (<12 mth) having a laparotomy, epidural analgesia vs systemic analgesia resulted in similar opioid administration 0–48 h and similarly adequate pain scores for 0–72 h postoperatively but with less sedation (13% vs 30%) (Martin 2019 **Level III-2**, n=82).

Epidural opioids alone

Epidural opioids alone have a limited role. Epidural morphine provided prolonged analgesia but no improvement in the quality of analgesia vs systemic opioids (Bozkurt 2004 **Level II**, n=32, JS 1). Without a systemic or epidural local anaesthetic comparator, epidural morphine 0.1 mg/kg vs epidural tramadol 2 mg/kg had similar pain scores and time to first rescue analgesic but with higher rates of adverse effects (Demiraran 2005 **Level II**, n=80, JS 3). Epidural fentanyl 1 mcg/mL alone was less effective than both levobupivacaine 0.0625% and 0.125% alone and levobupivacaine/fentanyl combined (Lerman 2003 **Level II**, n=114, JS 5). Bolus doses of epidural morphine 20–30 mcg/kg were less effective than epidural infusions of fentanyl 1–2 mcg/mL and local anaesthetic (Reinoso-Barbero 2002 **Level II**, n=30, JS 1; Kart 1997 **Level II**, n=30, JS 5). IV Ketoprofen improved analgesia vs saline when given in conjunction with epidural sufentanil (Kokki 1999 **Level II**, n=54, JS 5).

10.6.3.2 | Caudal analgesia

Despite innovation and increasing use of PNB, caudal analgesia remains a commonly performed regional technique (comprising 27–40% of audited blocks), especially in the smaller paediatric patient (Ecoffey 2010 **Level IV**, n=8,493 [caudal]; Walker 2018 **Level IV**, n=38,116 single injection caudal and 2,016 lumbosacral caudal catheters), although single injection caudal block has been used effectively in older children weighing 30 to 50 kg (Keplinger 2016 **Level IV**, n=20). Single injection caudal block provides intra and postoperative analgesia and is generally used for surgery on the lower abdomen, perineum and lower limbs (see Table 10.9 and for comparison with PNBs Section 10.6.2.1). Large series have reported a high success rate (particularly in children aged <7 y) and a low incidence of serious complications (Walker 2018 **Level IV**, n=40,132 [PRAN]; Suresh 2015a **Level IV**, n=18,650 [PRAN]; Ecoffey 2010 **Level IV**, n=8,493; Giaufre 1996 **Level IV**, n=12,111). The complication rate for single injection caudal blocks was 1.9% (95%CI 1.7% to2.1): most commonly these were failure 1% (95%CI 0.8 to 1.1), blood aspiration 0.6% (95%CI 0.5 to 0.8) and a positive test dose indicating intravascular injection 0.1% (95%CI 0.1 to 0.2) (Suresh 2015a **Level IV**, n=18,650). There was one seizure (in a 1 mth old) and one cardiac arrest (in a 36 mth old), and no complications that led to long term sequelae. Total plasma concentrations have been documented post administration of ropivacaine 3.1 mg/kg in larger children (30-50 kg) and were low, 1.16 mg/L (range 0.65 to 2.61), peaking at 1 h (95%CI 0.5 to 1.5) (Keplinger 2016 **Level IV**, n=20).

Caudal bupivacaine, levobupivacaine and ropivacaine produced similar times to onset of block and quality of postoperative analgesia (Sharma 2018 **Level II**, n=90, JS 3; Praveen 2017 **Level II**, n=60, JS 4; Cinar 2015 **Level II**, n=80, JS 2; Ingelmo 2006 **Level II**, n=86, JS 5; Frawley 2006 **Level II**, n=310, JS 5; Ivani 2005 **Level II**, n=60, JS 5; Breschan 2005 **Level II**, n=182, JS 3).

Concentration-dependent differences have been noted for individual agents. Ropivacaine 0.175% was superior to lower concentrations and was as effective as a 0.2% solution but produced less motor block (Khalil 2006 **Level II**, n=74, JS 5). In children aged 1–3 y having inguinal surgery, six concentrations of levobupivacaine were administered (0.08–0.18%, 1 mL/kg) (Yao 2009 **Level II**, n=60, JS 5); for caudal analgesia, this study established the EC_{50} as 0.109% (95%CI 0.098 to 0.120) and the EC95 as 0.151% (95%CI 0.135 to 0.193).

The PRAN data provides information of large variation in local anaesthetic dosing practices for caudal blocks (IQR, 1.23 to 1.98 mg bupivacaine/kg) (Suresh 2015a **Level IV**, n=17,867 [dosing known]). This was not explained by weight differences (r 0.5; 95%CI 0.48 to 0.52). This may in part

reflect the desire for differential block heights. Importantly, 25% recipients received doses >2 mg/kg of bupivacaine equivalents and 5.4% received >2.5 mg/kg that could be potentially unsafe.

The volume administered directly influences the height of block achieved. The spread of caudal block has been measured clinically (assessing dermatomes and myotomes) and the vertebral height measured by US, contrast and MRI studies (see Table 10.9). Dosing in volume based on weight is practical. For effective caudal analgesia, volumes of 0.5–0.7 mL/kg are used for sacral dermatome surgery and 0.8–1 mL/kg for lumbar and lower abdominal dermatome surgery. Higher volume 1.2–1.5 mL/kg blocks are effective for abdominal and thoracic surgery; spread above the T12 dermatome occurs most reliably in neonates and infants.

Table 10.9 | Block height following caudal injection in children using different formulae

Surgery type Patient number and age	**Local anaesthetic agent (%) and additives**	**Volume used vs suggested formula**	**Block height achieved**
Clinical			
Study	McGown 1982 **Level IV**, n=500		
Upper abdominal; lower abdominal; lumbosacral; sacral Height assessed in n=360 aged 6 mth–10 y	Lidocaine 1% (with adrenaline 5 mcg/mL)	1.65 mL/kg 1.1 mL/kg 0.55 mL/kg	Range: T2–T8 T8–T12 L1–S3
Outcome/conclusion	Volume/weight calculation successful for 430 (86%)		
Study	Satoyoshi 1984 **Level IV**		
Abdominal Paediatric cadaver radio-opaque contrast study: n=16 Clinical: n=21 aged 1 mth–11 y	Bupivacaine 0.25–0.375% or Mepivacaine 0.75–1.5%	1 mL/kg or Spiegel formula (x1–1.5) Developed new formula: mL=[(cm in distance from C7 to sacral hiatus) – 13]	New formula achieved T4–5 height: assessed by response to painful stimulus
Outcome/conclusion	Reduced thoraco-abdominal musculature movement; abdominal surgery successfully completed		
Study	Coad 1989 **Level II**, n=60, JS 3		
Inguinal n=48 (including 2 failures); mean age 2 ± 1 y	Bupivacaine 0.25% Bupivacaine 0.25% Bupivacaine 0.5%	1 mL/kg vs formula ([Age in years]+2)mL	
Outcome/conclusion	No difference found for weight- vs formula-based dosing with similar postoperative pain scores.		

Surgery type Patient number and age	Local anaesthetic agent (%) and additives	Volume used vs suggested formula	Block height achieved
Study	Verghese 2002 **Level II**, n=50, JS 4		
Orchidopexy aged <6 y	Bupivacaine 0.25% vs Bupivacaine 0.2% (both with adrenaline 5 mcg/mL and sodium bicarbonate 8.4% 0.1 mL/10 mL)	0.8 mL/kg vs 1 mL/kg	35% to T 10 vs 70% to T10 (assessed with spermatic cord traction test)
Outcome/conclusion	Higher volume lower concentration had less response to spermatic cord traction. The sample was too small to detect a difference in postoperative rescue analgesia (fentanyl 7 vs 17% p=0.4; paracetamol 59 vs 74% p=0.37).		
Ultrasound			
Study	Lundblad 2011 **Level IV,** n=50		
Subumbilical surgery: urogenital, anal, foot, and inguinal aged 0–4 y	Ropivacaine 0.2%	All received 1.5 mL/kg with volume/kg noted once T12 reached: Formula generated by US was lower than studies with dermatomal testing: mL per spinal segment =(0.154 x kg) minus 0.094	Block ≥T12 vertebral level on US in 93% neonates, 73% infants and 25% young children.
Outcome/conclusion	Inverse relationship with age (r 0.8) and weight (r 1.0).		
Study	Brenner 2011 **Level II**, n=75, JS 5		
Anal, penile and inguinal median age 21–32 mth	Ropivacaine 0.2% if <12 mth 0.35% if >12 mth	0.7 mL/kg 1.0 mL/kg 1.3 mL/kg	Median vertebral height L2; same for age <12 or >12 mth.
Outcome/conclusion	Weak inverse correlation with weight, height, BMI.		
X-ray contrast study			
Study	Hong 2009 **Level II**, n=73, JS 4		
Orchidopexy aged 1–5 y	Ropivacaine 0.225% vs Ropivacaine 0.15%	1 mL/kg 1.5 mL/kg	Median height (range) T6 (T3–11) T11 (T8–L2);
Outcome/conclusion	No difference in recovery times, postoperative pain scores or adverse effects Higher volume/lower concentration had longer time to acetaminophen rescue (9.2 vs 6.1 h; p<001) and reduced requirement (50 vs 76%; p=0.03).		

Surgery type Patient number and age	**Local anaesthetic agent (%) and additives**	**Volume used vs suggested formula**	**Block height achieved**
Study	Koo 2010 **Level III-2**, n=87		
Perineal, inguinal, orchidopexy n=83 had caudal aged 6 mth–4.5 y	Ropivacaine 0.2%	 0.5 mL/kg 1 mL/kg 1.25 mL/kg	Median height (range) L2 (L4–T12) T12 (L1–T8) T10 (L2–T7)
Outcome/conclusion	More segments were covered per mL administered with younger age: mean number of segments (SD) of 1.3 (0.4) for <1 y, 1.1 (0.3) for 1–3 y and 0.8 (0.4) for >3 y. Dosed according to surgical type; effective for surgery in 100%, with low median postoperative pain scores (>2 h), 4% required analgesic rescue.		
Study	Thomas 2010 **Level III-2**, n=45		
Perineal/lower limb, inguinal, abdominal aged 1–7 y	Bupivacaine 0.25%	 0.5 mL/kg 0.75 mL/kg 1 mL/kg	Median height ±SEM L2 ± 0.44 L1 ± 0.32 T12 ±0.43
Outcome/conclusion	Contrast study 1 mL/kg of caudal injectate reliably achieved one vertebral level higher than 0.5 mL/kg (L2 vs L3 for 93% of patients)		
Study	Forestier 2017 **Level IV**, n=20		
Normal MRIs of spine and sacrum assessed to measure: volume of spinal canal/ caudal space, dural sac, and spinal cord. From this data volume of epidural space and cerebrospinal fluid was calculated.	N/A	Median epidural volume by weight 1.30 mL/kg 1.57 mL/kg 1.78 mL/kg Median epidural volume by height 0.146 mL/cm 0.172 mL/cm 0.204 mL/cm	Predicted height L1 T10 T6 L1 T10 T6
Outcome/conclusion	The epidural space volume showed a linear relationship to both height (r 0.83) and weight (r 0.82)		

Anatomical variations

Commonly used anatomical landmarks (posterior superior iliac spines and sacral hiatus) when scanned by US do not form an equilateral triangle in children ≤7 y old (Abukawa 2015 **Level IV**, n=282) and infants (<9mth) (Mirjalili 2015 **Level IV**, n=26); the latter reported the sacral cornua were identifiable by US in all 26 infants, but could not be palpated in 4 (15%).

In an MRI study of children (<12 y), the distance between the sacro-coccygeal ligament and the dural sac correlated with weight (r 0.77), height (r 0.77), age (r 0.76) and most strongly with body surface area (r 0.80) (Lee 2017b **Level IV**, n=141). From this data, a formula to calculate the sacro-coccygeal ligament to dural sac distance (95%CI lower limit) based on BSA was developed: 25 x BSA (mm). In a neonatal cadaveric study, the mean distance from the sacral hiatus apex to the dural sac was 10.5 mm (range 4.9 to 26.2); there was a correlation between neonatal length and distance from apex of sacral hiatus to dural sac (r 0.39) such that for every 1 cm increase in neonate length, the distance increased by 3.3% (van Schoor 2018 **Level IV**, n=39). In a further series of anaesthetised children, the dural sac ended below S2/3 in 7.6% of patients (Shin 2009 **Level IV**, n=317).

Ultrasound guidance

US allows the real-time visualization of local anaesthetic spread during caudal injection (Lam 2016 **Level IV SR** [PRISMA], 11 studies [caudal], n=1,101]). Continuous US scanning vs landmark technique reduced time to perform a caudal (mean 2.42 min vs 2.73) (Lam 2016 **Level IV SR** [PRISMA], 1 RCT: Wang 2013 **Level II**, n=140 JS 3). Two subsequent RCTs in children (1–12 y) found continuous US-guided caudal injection vs landmark technique resulted in higher success on first puncture (80–93% vs 63–66%) and lower rates of vascular puncture (0–1.5% vs 11–12%) and subcutaneous bulging (0% vs 8–12%), but with a similar success rate (no movement, HR and RR change ≤20%) and mean time to perform caudal (Karaca 2019 **Level II**, n=266, JS 3; Ahiskalioglu 2018a **Level II**, n=134 JS 3).

For the use of US and other techniques to facilitate caudal epidural catheter placement, see Section 10.6.3.1 above.

10.6.3.3 | Adjuvants for epidural and caudal

Opioid and nonopioid adjuvants have been added to caudal local anaesthetic with the aim of improving the efficacy or duration of analgesia. The neurotoxicity of nonopioid spinal additives has not been systematically evaluated in neonates and children (Walker 2012c **NR**). Preservative-free morphine and clonidine are registered drugs for use in the epidural space; the remaining drugs listed below are used off label (Suresh 2018b **GL**). However, these recommendations by the European/American Society of Regional Anaesthesia endorse clonidine, dexmedetomidine, preservative-free morphine and ketamine as neuraxial adjuvants.

Epidural adjuvants

Opioids

A combination of local anaesthetic and opioid is frequently used in epidural infusions but there are limited data available to assess the relative merits of different regimens. Fentanyl 1–2 mcg/mL addition to local anaesthetic infusions had both improved analgesia (less IV opioid rescue) (Lovstad 2001 **Level III-2**) and similar analgesic effect (Lerman 2003 **Level II**, n=114, JS 5) but increased nausea and vomiting (Cho 2009 **Level II**, n=108, JS 5; Lovstad 2001 **Level III-2**). Addition of fentanyl 5 mcg/mL to bupivacaine 0.1% provided similar analgesia but increased adverse effects vs clonidine 1.2 mcg/mL with bupivacaine 0.1% (Cucchiaro 2006 **Level II**, n=47, JS 3). In children with cerebral palsy (mean age 11 y) having single event multi-level surgery (SEMLS), epidural bupivacaine 0.125% (0.25 mL/kg/h initial rate) with fentanyl 2 mcg/mL vs clonidine 2.5 mcg/mL was similarly effective over 72 h in terms of diazepam use, frequency and severity of muscle

spasm, pain scores and epidural bolus requirement (Chalkiadis 2016 **Level II**, n=50, JS 4). Vomiting, antiemetic use and oxygen desaturations were more common with epidural fentanyl, whilst blood pressure and heart rate were lower in epidural clonidine recipients. For children (3–12 y old) (86% with cerebral palsy) having lower limb orthopaedic surgery, an intraoperative epidural dose of dexmedetomidine 1 mcg/kg vs fentanyl 1 mcg/kg in addition to ropivacaine 0.2% PCEA achieved lower pain scores at 6 h (median 0/10 vs 1) but not at 12–48 h (Park 2017b **Level II**, n=60, JS 5). Total ropivacaine dose, and the incidence of minor adverse effects (eg emergence agitation and nausea and vomiting) were similar. In cerebral palsy patients (3–17y) having SEMLS, adding baclofen (3 mcg/kg bolus followed by 0.5 mcg/kg/h) to 0.1% bupivacaine (with clonidine in 26–40% and fentanyl in 8–11% of patients) for continuous epidural infusion did not reduce supplemental opioid or benzodiazepine administration, pain scores or length of stay (Nemeth 2015 **Level III-2**, n=44).

Following a postoperative epidural infusion of ropivacaine 0.2% 0.15 mL/kg/h with fentanyl 0.375 mcg/kg/h (for median 38 h), fentanyl plasma levels reached a secondary peak 3–6 h post cessation, and remained detectable for longer in infants and toddlers (3 mth – 3y) than in older children (3–12 y) (mean residence time: 22.9 h vs 11.5) (Karas-Trzeciak 2015 **Level IV PK**, n=43). There was marked variability in post-infusion fentanyl PKs, which was greater in infants and toddlers than older children.

Epidural infusion of sufentanil (0.015 mcg/kg/mL)/ropivacaine 0.15% achieved similar pain scores following paediatric urological surgery with reduced rescue analgesic use but with more pruritus vs fentanyl (0.1 mcg/kg/mL)/ropivacaine 0.15% (Cho 2008 **Level II**, n=64, JS 4).

The addition of morphine 10 mcg/mL to an epidural local anaesthetic infusion was more effective than clonidine 0.6 mcg/mL (Cucchiaro 2003 **Level II**, n=26, JS 5), but higher doses of clonidine improved analgesia when added to epidural ropivacaine infusion (De Negri 2001 **Level II**, n=60, JS 4).

Tramadol 2 mg/kg has been added to ropivacaine 0.2% via the epidural route and was superior to ropivacaine alone (Inanoglu 2010 **Level II**, n=44, JS 5).

For the use of epidural morphine and hydromorphone in scoliosis surgery and pectus excavatum repair, see Section 10.6.6.

Caudal adjuvants

Opioids

Addition of morphine to caudal local anaesthetic prolonged analgesia but dose-related adverse effects were relatively common (Cesur 2007 **Level II**, n=135, JS 5; Bozkurt 1997 **Level IV**). Morphine 7.5 mcg/kg added to 0.125% levobupivacaine resulted in a lower incidence of vomiting than higher morphine doses and provided effective postoperative analgesia (Dostbil 2014 **Level II**, n=240, JS 5). Morphine 20 mcg/kg added to bupivacaine 0.166% (with adrenaline 1:600,000) 1 mL/kg was more effective (lower pain scores and fewer patients requiring rescue analgesics) than bupivacaine/adrenaline alone or with clonidine 1 mcg/kg, although with higher rates of PONV (Fernandes 2012 **Level II**, n=80, JS 5). Single injection caudal with bupivacaine 0.25% (1 mL/kg) and morphine (30–50 mcg/kg) vs IV fentanyl for infants and children (0.5–12 y) having laparoscopic surgery prolonged time to first rescue analgesia, and halved postoperative fentanyl consumption (mean 24 h cumulative dose 1.1 mcg/kg vs 2.3) (Kundu 2015 **Level III-2**, n=65).

Clinically significant respiratory depression has been reported, particularly with higher morphine doses and in younger patients (de Beer 2003 **NR**). Adverse effects are potentially fewer with lipid soluble opioids but, while fentanyl may prolong caudal analgesia (Constant 1998 **Level II**, n=59, JS 5), other RCTs have shown no benefit (Kawaraguchi 2006 **Level II**, n=35, JS 3; Baris 2003 **Level II**, n=75, JS 3; Joshi 1999 **Level II**, n=56, JS 2).

Adrenaline (epinephrine)

Adding adrenaline (epinephrine) to bupivacaine has minimal effect on the duration of analgesia, particularly in older children (Ansermino 2003 **Level I**, 3 RCTs, n=407). The influences of caudal adrenaline and/or clonidine on the absorption characteristics of caudal levobupivacaine has been evaluated (Chalkiadis 2013 **Level IV**, n=240). Adrenaline (5 mcg/mL) decreased the rate of levobupivacaine systemic absorption, reducing peak concentration by half but with minimal impact on levobupivacaine's time-concentration profile. Adrenaline (2.5 mcg/mL) addition to caudal ropivacaine slowed the T_{max}, and reduced the peak ropivacaine concentration by 35% (Van Obbergh 2003 **PK**).

Alpha-2 agonists

Addition of clonidine 1–2 mcg/kg to caudal local anaesthetic, as assessed by two systematic reviews, prolongs analgesia (MD 3.7 h; 95%CI 2.7 to 4.7 and MD 4 h; 95%CI 2.8 to 5.1), with fewer patients requiring rescue analgesics (RR 0.72; 95%CI 0.57 to 0.90 and OR 0.22; 95%CI 0.13 to 0.37) (Schnabel 2011b **Level I** [PRISMA], 20 RCTs, n=993; Engelman 2013 **Level I** [PRISMA], 18 RCTs, n=782) (14 RCT overlap). In assessing the sedative effects of clonidine as a caudal additive, these systematic reviews conflict; one finding positive association (OR 2.48; 95%CI 1.63 to 3.69) (Engelman 2012 **Level I** [PRISMA], 3 RCTs [sedation], n unspecified) and the other none (RR 4.76; 95% CI 0.24 to 93.19) (Schnabel 2011b **Level I** [PRISMA], 4 RCTs [sedation], n=142). Both found no reduction of PONV.

Subsequent studies of infraumbilical surgery in 1–12 y olds have similar findings for caudal clonidine where:

- 1, 2 and 3 mcg/kg dose dependently spared levobupivacaine: from 0.2% to ED50s of 0.11, 0.08 and 0.04% respectively (Disma 2011 **Level II**, n=120, JS 4). The optimal dose was 2 mcg/kg with longer time to first analgesic rescue, reduced rescue analgesic requirement and less emergence agitation vs 1 mcg/kg, with more sedation in 3 mcg/kg recipients (30% vs 10 vs 0);
- 2 mcg/kg vs fentanyl 1 mcg/kg added to ropivacaine were similarly effective, with more adverse events (POV, desaturation and bradycardia) in fentanyl treated (Shukla 2011 **Level II**, n=90, JS 4). 1mcg/kg combined with fentanyl 1 mcg/kg was superior to caudal fentanyl 1 mcg/kg (added to local anaesthetic) with prolonged analgesia duration and reduced pain scores from 1–12 h (by 0.5–1.8/13) (Jarraya 2016 **Level II**, n=40, JS 2);
- 1 mcg/kg was superior to caudal midazolam 30 mcg/kg, with both superior to bupivacaine alone with ≈2 fold increase in analgesic duration (12.1 h vs 10.1 vs 4.9) and less use of 3 rescue medications (4% vs 28 vs 60) (Sanwatsarkar 2017 **Level II**, n=75, JS 5). Intraoperative haemodynamic changes and postoperative sedation were similar between groups, however all received midazolam premedication;
- In addition to caudal local anaesthetic, caudal clonidine 1 mcg/kg was superior to IV clonidine and placebo in prolonging duration of analgesia (16.7 h vs 9.4 vs 4.2) and reducing the number of patients requiring rescue analgesia (0–24 h) (80% vs 96 vs 100%), with no difference in sedation (Potti 2017 **Level II**, n=75, JS 4);
- While clonidine (2 mcg/mL) differed from adrenaline with faster systemic absorption of levobupivacaine; but both agents had minimal impact upon levobupivacaine's time-concentration profile overall (Chalkiadis 2013 **PK**).

Three overlapping systematic reviews document similar positive benefit of caudal dexmedetomidine 1–2 mcg/kg as an adjuvant to local anaesthetic in children aged 0.5–12 y having various surgeries:

- The duration of postoperative analgesia vs local anaesthetic alone is prolonged (WMD 8.2 h; 95%CI 5.0 to 11.4) (5 RCTs, n=270) (Trifa 2018 **Level I** [PRISMA], 21 RCTs, n=1,590; Tong

2014b **Level I** [PRISMA], 6 RCTs, n=328) (6 RCT overlap) and (SMD 3.19; 95%CI: 2.16 to 4.22) (Tu 2019 **Level I** [PRISMA], 10 RCTs, n=691) (overlap 3 & 8 RCTs respectively). Subanalysis reveals no difference between 1 mcg/kg (SMD 3.76; 95%CI 2.16 to 5.37) and 2 mcg/kg dose (SMD 1.73; 95%CI 1.73 to 2.89). Dexmedetomidine addition also reduces the need for rescue analgesia vs bupivacaine alone at 6 h (RR 0.09; 95%CI 0.05 to 0.17), 12 h (RR 0.50; 95%CI 0.32 to 0.79) and 24 h (0.66; 95%CI 0.51 to 0.85), with no difference in PONV.

- A dose related increase in emergence time and sedation scores is consistently reported, without increased risk of respiratory depression (Trifa 2018 **Level I** [PRISMA], 21 RCTs, n=1,590). Compared to other caudal adjuvants, dexmedetomidine provides similar analgesia to clonidine (2 RCTs) and dexamethasone (1 RCT), and is superior to opioids (fentanyl 4 RCTs; morphine 1 RCT) with longer duration of analgesia, lower use of rescue analgesia and lower pain scores.

For unilateral inguinal hernia repair, the addition of dexmedetomidine 1 mcg/kg by caudal or IV route to levobupivacaine was similarly effective vs placebo in doubling the median time to first rescue analgesia (14.2 h vs 12.4 vs 6.0), reducing the number of patients requiring rescue analgesia (63% vs 70% vs 93%) and reducing the incidence of emergence agitation (3% vs 3% vs 27%) (Yao 2018 **Level II**, n=90, JS 5). Emergence time was mildly delayed (by 6 and 7 min) vs placebo, with no difference in PACU LOS; no bradycardia, hypotension or motor block was observed.

For hypospadias repair, caudal combinations of bupivacaine 0.25%/dexmedetomidine 1 mcg/kg/dexamethasone 0.1 mg/kg vs bupivacaine/dexmedetomidine 1 mcg/kg vs bupivacaine/dexamethasone 0.1 mg/kg increased the mean duration of analgesia (11.5 h vs 7.4 vs 4.5), lowered pain scores from 0.5 to 6 h, but with increased sedation in both dexmedetomidine groups from 0.5 to 12 h postoperatively (Hassan 2018 **Level II**, n=63, JS 5).

Dexamethasone

Three systematic reviews have concluded that adjuvant dexamethasone caudally (0.1–0.2 mg/kg) or IV (mostly 0.5 mg/kg with one study 1.5 mg/kg) vs placebo prolongs the time to first rescue analgesia following a single injection caudal block in children (mostly ≤10 y) having lower abdominal/perineal or lower limb orthopaedic surgery (Zhu 2018a **Level I** [PRISMA], 7 RCTs, n=647; Chong 2018 **Level I** [PRISMA], 14 RCTs, n=1,315; Kawakami 2017 **Level I** [PRISMA], 6 RCTs [IV only] n=424) (6 & 4 RCT overlap). The largest review found prolongation with both caudal (WMD 5.4 h; 95%CI 3.5 to 7.3 9 RCTs) and IV routes (WMD 5.5 h; 95%CI 3.6 to 7.5) (5 RCTs) (Chong 2018 **Level I** [PRISMA], 14 RCTs, n=1,315). Dexamethasone reduces pain scores postoperatively at 6 h (WMD -1.31; 95%CI -2.07 to -0.54) (6 RCTs) and 24 h (WMD -0.80; 95%CI -1.37 to -0.24) (5 RCTs), but not at PACU, 12 h, or 48 h. It reduces the number of patients needing rescue analgesia in PACU (RR 0.30; 95%CI 0.18 to 0.51) (5 RCTs) and post PACU (RR 0.46; 95%CI 0.23 to 0.92) (9 RCTs), and reduces PONV (RR 0.47; 95%CI 0.30 to 0.73). No increased risk of adverse effects with dexamethasone were reported in these reviews. Subsequent RCTs have similar results for 0.1 mg/kg via caudal (Parameswari 2017 **Level II**, n=130, JS 3) and 0.25 mg/kg by IV route (Salami 2017 **Level II**, n=94, JS 5). While a further RCT was positive for 0.1 mg/kg caudal over IV route (Dongare 2018 **Level II**, n=60, JS 1).

Magnesium

Adding magnesium (Mg) 50 mg caudally vs control reduces the number of patients requiring rescue analgesia postoperatively (RR 0.45; 95%CI 0.24 to 0.86) (Kawakami 2018 **Level I** [PRISMA], 6 RCTs [Mg], n=371). Duration of analgesia is prolonged with caudal magnesium (3/5 RCTs), with a mixed effect on postoperative pain scores (6 RCTs); there were no serious adverse events reported, with a similar rate of minor adverse events (eg shivering, sedation, motor block). In a

further RCT, the combination of caudal Mg 50 mg/ dexmedetomidine 1 mcg/kg increased time to first analgesic request vs Mg 50 mg alone vs dexmedetomidine alone which were also superior to no adjuvant (Sayed 2018b **Level II**, n=120, JS 3). Dexmedetomidine recipients in both arms had more sedation for 1–1.5 h.

Ketamine

The addition of caudal ketamine 0.25–0.5 mg/kg to local anaesthetic prolongs time to first analgesic request vs local anaesthetic alone (MD 5.6 h; 95%CI: 5.45 to 5.76) without prolonging motor block (Schnabel 2011a **Level I** [PRISMA], 13 RCTs [paediatric], n=584), increases duration of block (with ketamine 0.5 mg/kg: SMD 2.25; 95%CI 1.53 to 3) and reduces postoperative analgesic requirements (OR 0.26; 95%CI 0.1 to 0.7) (Dahmani 2011 **Level I** [QUORUM], 10 RCTs [caudal], n=686) (6 RCT overlap). Some adverse effects were more frequent in the ketamine group (eg sedation) but not significantly different to placebo for PONV (OR 1.17; 95%CI 0.7 to 2) (Schnabel 2011a **Level I** [PRISMA], 13 RCTs [paediatric], n=584) or psychomimetic effects (OR 1.72; 95%CI 0.7 to 4.3) (Dahmani 2011 **Level I** [QUORUM], 10 RCTs [paediatric], n=686). A subanalysis of S-ketamine added to caudal anaesthesia was performed showing similar prolongation of block vs racemic ketamine (Dahmani 2011 **Level I** [QUORUM], 4 RCTs [S-ketamine], n unspecified). A subsequent RCT found similar results (Aliena 2018 **Level II**, n=58, JS 4). A significant concern that continues to limit the use of neuraxial ketamine is local neurotoxicity *in vitro* (Walker 2012c **NR;** Werdehausen 2011 **BS**).

Tramadol, neostigmine and midazolam

Caudal tramadol 1–2 mg/kg added to local anaesthetic prolongs the time to first rescue analgesic (4.5 h: 95%CI 2.8 to 6.1) at the expense of increased vomiting (OR 2.5; 95%CI 1.3 to 4.6) with no IV comparator (Engelman 2012 **Level I** [PRISMA], 9 RCTs [tramadol], n=258). Caudal tramadol 2 mg/kg added to bupivacaine and levobupivacaine was similarly effective for inguinoscrotal surgery (Sezen 2014 **Level II**, n=68, JS 5).

Caudal tramadol 1 mg/kg added to bupivacaine vs bupivacaine 0.25% alone prolonged duration of analgesia (9.6 h vs 7.2), reduced the amount of rescue paracetamol used to 24 h and had lower rise of IL-6, CRP and cortisol over 24 to 72 h postoperatively (Sayed 2018a **Level II**, n=60, JS 5).

Tramadol 2mg/kg/bupivacaine 0.25% vs fentanyl 2 mcg/kg/bupivacaine 0.25% prolonged duration of analgesia (10–18 h vs 7–11 h) with lower pain scores from 4–10 h, but more PONV (8 vs 0%) (Solanki 2016 **Level II**, n=100, JS 2).

Neostigmine added in doses of 1–4 mcg/kg extends the time to first analgesic rescue request by 2.5 times that of clonidine (MD 10 h; 95%CI 7.8 to 12.2) without any dose-dependent effect evident. This is at the expense of increased vomiting (OR 1.8; 95%CI 1.1 to 2.8) (Engelman 2012 **Level I**, 7 RCTs [neostigmine], n=533). Neostigmine (administered with adrenaline 5 mcg/mL) without local anaesthetic demonstrated analgesic efficacy for 20–50 mcg/kg (but not 10 mcg/kg), with a dose-dependent increase in PONV (Batra 2003 **Level II**, n=120, JS 2). Adding neostigmine 2 mcg/kg, midazolam 50 mcg/kg or ketamine 0.5 mg/kg to bupivacaine 0.25% (1 mL/kg) for a single injection caudal all prolonged duration of analgesia (21 h vs 18.3 vs 12.8 vs 7.2), and reduced postoperative pain scores (mean 2.6/10 vs 3.1 vs 4.4 vs 5.6), but with increased vomiting with neostigmine and ketamine (25% vs 15% vs 5% vs 5%) (Shirmohammadie 2019 **Level II**, n=80, JS 3).

Caudal midazolam 50 mcg/kg/bupivacaine vs caudal fentanyl 1 mcg/kg/bupivacaine vs bupivacaine alone had similar 0–24 h analgesic requirement, with higher sedation scores over the initial 1.5 h (Baris 2003 **Level II**, n=75, JS 3). This dose added to bupivacaine prolonged time to first rescue analgesic (similar to neostigmine 2 mcg/kg and ketamine 0.5 mg/kg) with no difference in sedation scores over 24 h vs plain bupivacaine (Kumar 2005 **Level II**, n=80, JS 4). Compared to plain bupivacaine, midazolam 50 mcg/kg vs morphine 50 mcg/kg added to bupivacaine prolonged the duration of analgesia (mean duration: 8 h vs 21 vs 15 respectively) with similar prolongation of sedation to 12 h (Gulec 1998 **Level II**, n=60, JS 1).

10.6.3.4 | Other outcomes of Paediatric Regional Analgesia

Stress response

Perioperative regional analgesia modifies the stress response to surgery in children (Nasr 2013 **Level II**, n=40, JS 3; Humphreys 2005 **Level II**, n=59, JS 2; Wolf 1998 **Level II**, n=26, JS 1). Suppression of the stress response may necessitate a local anaesthetic block that is more intense or extensive than required for analgesia, and therefore the risks of increased adverse effects or toxicity must be balanced against any potential benefit (Wolf 1998 **Level II**, n=26, JS 1). Use of caudal opioids alone (morphine 30 mcg/kg) was less effective than plain bupivacaine 0.25% in attenuating cortisol and glucose responses following hypospadias surgery (Teyin 2006 **Level II**, n=28, JS 3). Sufentanil added to bupivacaine modified the stress response to cardiac surgery (Sendasgupta 2009 **Level II**, n=30, JS 3).

Respiratory outcomes including apnoea

Improvements in respiratory outcome with regional analgesia have not been established in controlled comparative trials. Reductions in respiratory rate and oxygen saturation were less marked during epidural analgesia vs with systemic opioids but the degree of difference was of limited clinical significance (Wolf 1993 **Level II**, n=32, JS 2). Case series report improvements in respiratory function and/or a reduced need for mechanical ventilation with regional analgesia techniques (Raghavan 2008 **Level IV**; Aspirot 2008 **Level IV;** Hodgson 2000 **Level IV;** McNeely 1997 **Level IV**). A review summarises the use of awake caudal or combined spinal epidural vs epidural as a supplement to general anaesthesia in 560 neonates having multiple surgery types with multiple outcomes (surgical efficacy, postoperative respiratory events, other) (Maitra 2014 **NR**). A meta-analysis of PRA (spinal, caudal or epidural) vs general anaesthesia for inguinal herniorrhaphy in ex-premature infants reported a reduction in postoperative apnoea with PRA when infants having preoperative sedation were excluded (RR 0.53; 95%CI 0.34 to 0.82) (4 studies n=129); the groups did not differ in the need for postoperative ventilation (3 RCTs, n=98) (Jones 2015 **Level I** [Cochrane], 7 RCTs, n=203). A subsequent multicentre RCT assessing PRA (spinal, caudal, or combined spinal and caudal) vs general anaesthesia (sevoflurane <1 h) for infants (≤60 wk post-menstrual age) having hernia repair qualifies these findings (Davidson 2015 **Level II**, n=722, JS 3). Prematurity was the strongest predictor of apnoea (OR 22; 95%CI 4 to 109), and PRA reduced early (0 to 0.5 h) (1 vs 3%) (OR 0.20; 95%CI 0.05 to 0.91) but not late apnoea (0.5 to 12 h). Neurodevelopmental outcomes did not differ between the regional anaesthesia and general anaesthesia groups at 2 y (Davidson 2015 **Level II**, n=532, JS 3) and 5 y of age (McCann 2019 **Level II**, n=447, JS 3).

10.6.3.5 | Safety and complications of Paediatric Regional Analgesia

Performance of PRA under general anaesthesia vs awake

The safety of performing paediatric regional anaesthesia (PRA) under general anaesthesia or deep sedation has been demonstrated in six large prospective multi-regional audits (Walker 2018 **Level IV**, n=104,393; Taenzer 2014a **Level IV**, n=53,564; Wong 2013a **Level IV**, n=3,152; Polaner 2012 **Level IV**, n=14,917; Ecoffey 2010 **Level IV**, n=31,142; Llewellyn 2007 **Level IV**, n=10,633; Giaufre 1996 **Level IV,** n=24,409) (see Table 10.10). Placement of regional anaesthesia/analgesia under general anaesthesia is confirmed to be as safe as placement in sedated and awake children (Walker 2018 **Level IV**, n=104,393 in 91,701 children). The combined incidence for major adverse events (LAST and neurological deficit together) was 2.2/10,000 (95%CI 1.5 to 3.4) for blocks placed under GA and 15.2/10,000 (95%CI 7.8 to 28.4) for blocks placed when awake or sedated.

Overall complications

The earlier audits reported rates of overall complications for regional analgesia of 0.09% (Giaufre 1996 **Level IV**, n=24,409), 0.12 % (95%CI 0.09 to 0.17) (Ecoffey 2010 **Level IV**, n=31,142) and in PRAN audits: 0.2% (Polaner 2012 **Level IV**, n=14,917) to 1.2% (95%CI 1.1 to 1.3) (Taenzer 2014b **Level IV**, n=53,564); with the most recent providing specific adverse effect and not overall complication incidence (Walker 2018 **Level IV**, n=104,393).

Younger age is associated with higher incidence of complications: neonates and infants vs older children (OR 2.9; 95%CI 1.2 to 7.0) (Wong 2013a **Level III-2**, n=3,152); 1.13% for neonates vs 0.3–0.8% older children, particularly dosing error (0.3% <12 mth vs 0.07% >12 mth) (Llewellyn 2007 **Level IV**, n=10,633); and 0.4% for infants <6 mth vs 0.1% >6 mth of age (Ecoffey 2010 **Level IV**, n=3,860 [infant] vs 27,272 [older]). A higher incidence of complications with neuraxial catheters (inclusive of catheter malfunction, catheter contamination and vascular puncture) of 13.3% (95%CI 9.8 to 17.4%) was reported in neonates in a USA multicentre safety analysis (Long 2016 **Level IV**, n=307). No complications resulted in long term sequelae, and the risk of a serious complication was estimated as 0.3/10,000 (95%CI 0.08 to 1.8). In young children having a laparotomy and epidural ropivacaine/sufentanil for postoperative analgesia, the epidural catheter was removed early in 35%, the most common reasons being inadequate analgesia and technical failure; further adverse effects were documented in 16 patients (18%) (Bravenboer-Monster 2019 **Level IV**, n=90).

Table 10.10 | Incidence of adverse effects in large-scale audits of paediatric regional analgesia

Study	Walker 2018 **Level IV**		
Denominator	104,393 blocks; 41,004 neuraxial GA 94%,	Years audited	PRAN Apr 2007 – Sept 2015
Adverse effects type and incidence			
LAST	LAST 0.76/10,000: 3 seizures; 4 cardiac arrests	Dural tap, PDPH	rates of dural tap: 86/10,000 lumbar 66/10,000 thoracic and 10/10,000 for caudal approach; 7/11 patients with PDPH had an epidural blood patch
PONS	Permanent neurological deficits: 0/10,000 (95%CI 0 to 0.4) Transient neurological deficits (primarily sensory): 2.4/10,000 (95%CI 1.6 to 3.6); 92% resolving by 3 mth	Drug error	NS

Death, cardio-respiratory event/ arrest	NS	Pressure sore	NS
Bleeding	0/10,000 haematomas associated with neuraxial catheters (95%CI 0 to 3.5); 1 epidural haematoma with a paravertebral catheter	Compartment syndrome	NS
Infection	29/92 catheter associated infections treated with antibiotics		
Study	Wong 2013a **Level III-2**		
Denominator	3,152 epidurals	Years audited	Jan 1997–Dec 2011
Adverse effects type and incidence			
LAST	0 (1 intravascular catheter; unrecognised)	Dural tap, PDPH, intrathecal placement	1 PDPH; blood patch NS; 1 IT placement-unrecognised
PONS	1/3,152 permanent with residual left sided 3–4/5 weakness of L5–S1 (blood staining of dural sac)	Drug error	3
Death, cardio-respiratory event/arrest	1 fatal cardiac arrest; 1 respiratory depression	Pressure sore	3
Bleeding	NS (bar that in patient with PONS above)	Compartment syndrome	1
Infection	11 local of skin: 5 required antibiotics		
Study	Ecoffey 2010 **Level IV**		
Denominator	31,142 blocks; 11,418 neuraxial GA 96%	Years audited	(ADARPEF II) Nov 2005–Oct 2006
Adverse effects type and incidence			
LAST	5.1/10,000 (95%CI 3 to 8): 1 convulsion; 15 cardiac: 2 ECG change, 13 arrhythmia; (134 reports of positive test doses excluded from adverse event assessment)	Dural tap, PDPH, total spinal anaesthesia	10 dural taps 0 PDPH 1 total spinal anaesthesia
PONS	5 of short duration (18 h–3 wk); 0 permanent	Drug error	1 leading to LAST in infant

Death, cardio-respiratory event/arrest	0 deaths/cardiac arrests; 1 total and 2 high spinals: requiring short term ventilation <12 h	Pressure sore	NS
Bleeding	NS	Compartment syndrome	NS
Infection	1 local		
Study	Llewellyn 2007 **Level IV**		
Denominator	10,633 epidurals	Years audited	Mar 2001–Dec 2005
Adverse effects type and incidence			
LAST	1 seizure post 2 boluses; 1 seizure/LAST at 24 h high end dosing	Dural tap, PDPH, blood patch	5 PDPH, 1 blood patch
PONS	1 permanent (peripheral nerve); 1 cauda equina; 5 resolved over 4–10 mth (2 concurrent spinal cord insult: 1 haematoma with rods, 1 impaired blood supply)	Drug error	13
Death, cardio-respiratory event/ arrest	0 deaths/cardiac arrests; 2 respiratory arrests 1 total spinal and 1 with opioid and epidural bolus; ventilated <24 h	Pressure sore	33
Bleeding	(1 possible haematoma mentioned in PONS above in patient with 2 epidural catheters attributed to rod placement in scoliosis surgery)	Compartment syndrome	4 (not masked by epidural)
Infection	2 epidural abscesses; 1 meningism; 25 local		
Study	Giaufre 1996 **Level IV**		
Denominator	24,409 blocks; 15,013 neuraxial	Years audited	May 1993–April 1994 (ADARPEF I)
Adverse effects type and incidence			
LAST	7 LAST: 2 convulsions; 1 arrhythmia; 2 delayed arrhythmia (with overdose); 2 “subclinical”	Dural tap, PDPH	2 dural puncture; 2 PDPH; 4 total spinal
PONS	2 transient <8 h	Drug error	NS
Death, cardio-respiratory event/ arrest	1 apnoea secondary to excess epidural morphine	Pressure sore	NS

Bleeding	NS	Compartment syndrome	NS
Infection	1 local burn from skin preparation solution/heated mattress; 1 rectal puncture (with caudal) without sequelae		

Table 10.10 legend

ADARPEF = French-Language Society of Paediatric Anaesthesiologists; IT: intrathecal; LAST: local anaesthetic systemic toxicity; NS: none specified; PDPH: postdural puncture headache; PONS: postoperative neurological symptoms; PRAN: Paediatric Regional Anesthesia Network.

Local anaesthetic systemic toxicity

Accidental intravascular injection and LAST remain high-risk complications of caudal and epidural analgesia. It is reported to occur rarely: 0.76 to 5 in 10,000 (see Table 10.10) and may be less common in paediatric populations than in adults (Neal 2018 **GL**). As the sacrum is largely cartilaginous during infancy and early childhood, vascular puncture can occur (38 in 6,011) (Polaner 2012 **Level IV**) and there is an increased risk of injecting local anaesthetic into the highly vascular medullary space of the sacrum (Veyckemans 1992 **Level IV**). Sevoflurane attenuated cardiovascular responses to adrenaline 0.5 mcg/kg IV less than halothane and may be a better agent to facilitate detection (Kozek-Langenecker 2000 **Level III-2**). Changes in T-wave amplitude can be observed in 91% of patients within 1 min of IV injection of 0.1 mL/kg of lidocaine 1%/adrenaline 5 mcg/mL (and >25% change measured in 94%) (Varghese 2009 **Level II**, n=68, JS 4); this is a sensitive way of detecting intravascular injection. Almost all regional blocks are performed under general anaesthesia in children but there is no clear evidence that this obscures early signs of LAST (Taenzer 2014b **Level IV;** Bernards 2008 **Level IV**). In the PRAN audit, 5 of 7 LAST events occurred in association with neuraxial block (see Section 10.6.1.3 for detail of the peripheral block associated events): 3 caudal single injections, 1 subarachnoid block and 1 thoracic epidural (Walker 2018 **Level IV**, n=59,069 [neuraxial]). Four were infants resulting in a greater risk of severe LAST for <6mth vs >6 mth of OR 7.4 (95%CI 1.3 to 39.3).

Paediatric patients with LAST (neonates to 18 y) have been successfully resuscitated with 20% lipid emulsion (Presley 2013 **Level IV SR** [14 case reports]; Gitman 2019 **NR**). In conjunction with advanced life support resuscitation, it is recommended as an early intervention (Neal 2018 **GL;** AAGBI 2010 **GL**) (see also Section 4.4.3). Dosing recommendations are the same as for adults: if <70 kg, 1.5 mL/kg bolus (can be repeated twice every 5 min for persistent cardiovascular collapse) and infusion 0.25 mL/kg/min (increased to 0.5 mL/kg/min if hypotension persists), continuing for 10 min after attaining circulatory stability; the maximum cumulative recommended dose is 12 mL/kg. Adverse effects when higher doses of 20% lipid emulsion were used to treat LAST have been reported: hypoxia and V/Q mismatch occurred in a 3 y old child (dose 15.5 mL/kg) (Shenoy 2014 **CR**), and severe hyperlipidaemia, metabolic acidosis and raised lactate associated with hypersomnolence, tachypnoea and tachycardia occurred in an 11 y old girl (dose 66 mL/kg) (Corwin 2017 **CR**); both patients made full recoveries.

Postoperative neurological symptoms

Neurological damage attributable to paediatric regional analgesia is rare (see Table 10.10). PRAN publication has reported an overall event rate of no permanent neurological deficits (95%CI 0 to 0.4/10,000), and very low incidence of transient neurological deficits of 2.4/10,000, with similar risk for neuraxial and peripheral blocks (Walker 2018 **Level IV**, n=104,393). The risk of transient

neurological deficits or LAST combined was lower in patients having their blocks under general anaesthesia vs awake/sedated, including when adjusted for age (OR 2.93; 95% CI 1.34 to 5.52) (Walker 2018 **Level IV**, n=104,393).

The prior UK audit reports a similar incidence of postoperative neurological symptoms (PONS) to PRAN audits, with two events with residual symptoms at 12 mth: one cauda equina syndrome resulting from a drug volume error and one peripheral nerve injury (Llewellyn 2007 **Level IV**, n=10,633). Five other cases of peripheral or nerve root damage were of short duration: three resolved spontaneously, two required chronic pain referral and gabapentin but resolved by 10 mth. The two previous French audits report only transient PONS events (Ecoffey 2010 **Level IV**, n=31,142; Giaufre 1996 **Level IV,** n=24,509); a single centre audit reports one permanent PONS event likely related to epidural insertion (Wong 2013b **Level IV**, n=3,152) and a survey reports two permanent events in two infants (Flandin-Blety 1995 **Level IV**, n=2).

Care of insensate body regions is important post PRA as prolonged block/immobility may result in nerve compression, accompanied by neurological deficit or neuropathic pain (Symons 2008 **CR**).

Infection

Local skin infection is variably reported (see Table 10.10), with *Staphylococcus aureus* the most commonly identified organism (Llewellyn 2007 **Level IV**, n=10,633 [paediatric epidurals]). This UK audit reported three serious infections: two epidural abscesses and one meningism. The PRAN audit reported one epidural abscess (in a 2 mth old with a lumbar epidural catheter removed on POD 4 that required surgical intervention and fully recovered) and 92 cases of local cutaneous infection (53/10,000; 95%CI 43 to 64) (Walker 2018 **Level IV**, n=18,065 [catheters]). Most were treated with catheter removal only; 29 were treated with antibiotics. Risk of infection was higher with neuraxial vs peripheral catheters (60 vs 26/10,000) and increased by 6.7% per catheter day: the median catheter duration for cases of infection vs no infection was 4 d vs 2. There were no infections reported with single injection blocks. Additional cases of epidural abscesses associated with epidural catheters in children ≤2 y old that responded to antibiotics are reported from the UK (Desai 2016b **Level IV**, n=2) and USA (Suchar 2016 **CR**).

Bacterial colonisation of catheters was more commonly associated with caudal than lumbar catheters (Kost-Byerly 1998 **Level IV**), however, no difference was found in odds of superficial infection for caudal vs lumbar epidural catheters, or caudal vs thoracic epidural catheters (Walker 2018 **Level IV**, n=18,065 [catheters]).

Acute compartment syndrome and pressure sores

There have been reports of acute compartment syndrome (ACS) in adult epidural recipients; in 4 of 8, the epidural was not felt to have masked the ACS (Klucka 2017 **Level IV** [PRISMA], 15 studies, n=20). In children, 6 events have been reported felt to not have been masked by the single injection caudal (Klucka 2017 **Level IV** [PRISMA], 15 studies, n=20 [1 caudal epidural]) or epidural infusion (Wong 2013b **Level IV**, n=3,152 [1 ACS]) and (Llewellyn 2007 **Level IV**, n=10,633) with no events in the PRAN database (see Table 10.10). Avoiding unnecessarily dense sensory/motor block allows full assessment and may prevent delay in diagnosis of compartment syndrome (Johnson 2009 **Level IV**).

Appropriate staff education regarding pressure care and vigilant monitoring for pressure areas to prevent sores is essential for patients receiving continuous regional analgesia (Llewellyn 2007 **Level IV**).

Dural puncture and post-dural puncture headache (PDPH)

The audits report variably on dural puncture and resultant total spinal or post-dural puncture headache (PDPH) and the need for respiratory or blood patch intervention (see Table 10.10). The

PRAN audit reported the risk of unintentional dural tap with an epidural needle for the different approaches as 86/10,000 (95%CI 66 to 112) for lumbar, 66/10,000 (95%CI 46 to 95) for thoracic and a low incidence 10/10,000 (95%CI 7 to 14/10,000) for caudal (Walker 2018 **Level IV**, n=54,124 [single injection & catheters]). Eleven (7%) patients with an unintentional dural tap reported PDPH, of which 7 had an epidural blood patch. An 11 mth old who required three attempts for an epidural insertion developed a CSF cutaneous fistula following removal of the epidural catheter on POD 3; this resolved following a sterile skin suture and occlusive dressing (Rusy 2018 **CR**).

Bleeding/epidural haematoma

Vascular puncture is reported in association with PRA, generally without consequence, and epidural haematomas are rare. One audit included removal of an epidural catheter in a coagulopathic patient without comment on the consequence (Wong 2013a **Level IV**). Two audits report on epidural/dural sac blood with neurological sequelae; the former related to surgical rod placement (Llewellyn 2007 **Level IV**) and the latter attributed to epidural placement (Wong 2013a **Level IV**). The PRAN audit has reported no epidural haematoma related to epidural catheter insertion/infusion (Walker 2018 **Level IV**, n=18,065 [epidural]). Two reports of bleeding complications and motor deficit with neuraxial blocks have required surgical intervention: an anterior spinal artery arteriovenous fistula/pseudoaneurysm related to an epidural needle and spinal cord trauma was reported in a 5 y old (who fully recovered over 20 mth) (Alnaami 2013 **CR**); and an epidural haematoma in a 12 y old with sickle cell disease, choledocholithiasis and mildly deranged coagulation with a thoracic epidural catheter (who fully recovered by 6 mth) (Sathyamoorthy 2017 **CR**). Otherwise, epidural haematoma in children occurs more commonly spontaneously (40–50%), associated with anticoagulants (25–30%) and rarely in association with trauma (usually falls) (Sim 2010 **CR**) (see also Section 5.6.5).

Deaths associated with epidural use

One survey (Flandin-Blety 1995 **Level IV**, n=24,005) and one retrospective audit (Wong 2013a **Level IV**, n=3,152) have reported deaths in association with neuraxial block insertions: three infants – one related to LAST, one possibly due to cerebral air embolism, one due to spinal cord ischaemia – and one child aged 6 y with cerebral palsy and carnitine deficiency, who had cardiac arrest with intravascular catheter migration of an epidural catheter and presumed bupivacaine toxicity (Wong 2010 **CR**). No deaths have been reported in the large scale audits (see Table 10.10).

Physiological effects of caudal injection

Following caudal injection of local anaesthetic with adrenaline (1 mL/kg, max 20 mL injected over 1 min) in infants and children (2.3 mth to 8.6 y), there was a transient rise in epidural pressure that returned to baseline within 60 s (Goeller 2016 **Level IV**, n=31). Caudal injection under general anaesthetic of both 1 mL/kg and 1.5 mL/kg of ropivacaine 0.15% increased optic nerve sheath diameter (a surrogate for intracranial pressure) with a similar peak of 14% and 19% respectively 10 min following injection, normalising at 30 min (Lee 2017a **Level II**, n=80, JS 5).

Complications of caudal analgesia

An attempted US-guided caudal block in a 1 mth old infant having an inguinal hernia repair failed in the context of an ongoing cerebrospinal spinal fluid leak presumably secondary to a lumbar puncture on d 13 of life (Bruce 2015 **CR**). Rectal puncture is a risk of caudal injection that may be increased by the presence of faecal loading and rectal distension (Sathianathan 2015 **CR**).

10.6.4 | Intrathecal opioids

Following cardiac surgery, IT morphine 20 mcg/kg prolonged time to first analgesia and decreased postoperative morphine requirements but did not alter time to discharge from

intensive care (Suominen 2004 **Level II**, n=80, JS 5). Addition of IT tetracaine and morphine to IV remifentanil decreased pain scores and analgesic requirements after early extubation (Golianu 2005 **Level II**, n=45, JS 3). Spinal morphine 2 mcg/kg vs placebo added to bupivacaine increased time to first rescue analgesic (12 h ± 3.2 vs 8 ± 3.5) and reduced need for supplementary analgesia (17 vs 60%) following hypospadias repair (Apiliogullari 2009 **Level II**, n=54, JS 5). In 3–17 y olds having ureteroneocystostomy or pyeloplasty, IT morphine (mean 4.4 mcg/kg) vs opioid via PCA/NCA resulted in less patients receiving rescue opioid 0–16 h postoperatively (0–8 h: 14% vs 96 and 8–16 h: 33% vs 92), less rescue opioid (oral morphine equivalents: 5 mcg/kg/h vs 10), and similar adverse event rates (eg nausea and vomiting, pruritus: 75% vs 67%) including hypoxia (as a surrogate for respiratory depression: 9% vs 8%) (Putnam 2015 **Level III-3**, n=128). In children and adolescents (0.5 to 20 y) having laparoscopic urological surgery, IT morphine (4–5 mcg/kg) vs bupivacaine infiltration of port sites resulted in similar perioperative systemic opioid requirement (Srinivasan 2016 **Level III-3**, n=130). Early postoperative opioid requirements, adverse effects and LOS were not reported.

In infants undergoing lower abdominal and urological surgery, addition of fentanyl 1 mcg/kg (but not lower doses) to IT local anaesthetic prolonged the duration of analgesia and reduced supplemental analgesic requirements (Batra 2008 **Level II**, n=58, JS 5). Fentanyl 0.2 mcg/kg added to local anaesthetic prolonged block duration and reduced analgesic requirements after hernia repair in infants (Duman 2010 **Level II**, n=50, JS 4).

Dose-responsiveness for IT opioids is not evident in adults; studies are too few to assess this in children.

For the use of IT morphine in scoliosis surgery, see Section 10.6.6.

10.6.5 | Topical therapies

As is the case for addition of adjuvant to injectate, topical application can lead to systemic absorption. Thus for effective comparison, a systemic comparator arm is desirable but rarely employed in the below summarised RCTs.

Studies relevant to photobiomodulation use in paediatric dental, cleft and tonsillectomy are not discussed here but are included in the adult Section 7.4.

10.6.5.1 | Tonsillectomy

Following tonsillectomy, topical application of bupivacaine and ropivacaine reduces pain scores at 4–6 h vs saline (-1.3/10; 95%CI -1.67 to -0.9) (Grainger 2008 **Level I**, 2 RCTs [paediatric], n=71). Regular dosing with lidocaine spray (1 RCT, n=40) vs saline improves pain scores post tonsillectomy in children until the third postoperative day (Fedorowicz 2013 **Level I [**Cochrane], 6 RCTs [1 adult, 1 mixed, 4 paediatric], n=593 [397 children]).

No benefit was seen following single topical application of tramadol 5% over 0–24 h, but thereafter pain scores were reduced for 7 d (Akbay 2010 **Level II**, n=40, JS 5). Single tonsillar applications of tramadol 40 mg vs ketamine 20 mg were superior to placebo (artificial saliva), with similar pain scores and rescue analgesic requirements (0–24 h) (Tekelioglu 2013 **Level II**, n=60, JS 5). Tonsillar application of ketamine 20 mg vs morphine 20 mg alone and in combination were superior to placebo (artificial saliva) with reduced rescue paracetamol use (0–24 h), but pain scores were only reduced in PACU (Canbay 2008 **Level II**, n=60, JS 5).

Cryotherapy (ice lollipop) over 4 h reduced pain post-tonsillectomy in children 2–12 y at 0.5 and 1 hr (Keefe 2018 **Level I** [PRISMA], 1 RCT**:** Sylvester 2011 **Level II**, n=87, JS 3).

10.6.5.2 | Acute otitis media

Acute otitis media is common in children. Topical local anaesthetic drops (benzocaine/ antipyrine or lidocaine) used in acute otitis media, in addition to PO analgesia, are effective vs saline at 10 min (RR 2.13; 95%CI 1.19 to 3.80) and 30 min after instillation (RR 1.43; 95% CI 1.12 to 1.81) (2 RCTs, n=117) (Foxlee 2011 **Level I** [Cochrane], 5 RCTs, n=391). Superiority of local anaesthetic (amethocaine/ antipyrine) vs naturopathic drops (3–4 herbal extracts in olive oil) is not established in three RCTs (in addition to paracetamol in one RCT and amoxicillin in one RCT) (3 RCTs, n=274 [analysed]).

10.6.5.3 | Acute mouth ulceration

In painful acute mouth ulceration in children, topical viscous lidocaine 2% did not improve oral intake, with similar requirement for rescue analgesic at 1 h vs placebo (Hopper 2014 **Level II**, n=100, JS 5). Lidocaine 2% gel was massaged onto mouth ulcers and reduced pain by 19.7/100 (±18.3) at 3 min vs placebo in children prior to dental work (Coudert 2014 **Level II**, n=64, JS 5).

Topical therapies (commonly Maalox®: lidocaine, aluminium hydroxide combined with diphenhydramine syrup) are used 2nd line (to paracetamol and/or ibuprofen) by 42% of USA paediatric emergency physicians at 15 centres (MacLellan 2017 **Level IV**, n=150 [surveyed]).

10.6.3.4 | Nasogastric tube insertion

For efficacy of sweet solutions in nasogastric tube insertion in neonates see Section 10.7.1.5. For evidence of efficacy of topical and nebulised local anaesthetic and IN ketamine in children see Section 10.7.2.6.

10.6.3.5 | Circumcision

Ring block is more effective (across all operative stages) than DPNB and both are more effective than EMLA® which is more effective than placebo in awake infant circumcision (1 RCT, n=54) (Suresh 2014 **Level I** [PRISMA], 5 RCTs [EMLA®], n=266). EMLA® has shorter time to analgesic rescue vs DPNB (4 RCTs, n=212); including in older children who received general anaesthesia (Salgado Filho 2013 **Level II**, n=41, JS 4). EMLA®/sucrose 25% 2 mL /lidocaine ring block was more effective vs EMLA®/sucrose/DPNB and EMLA®/sucrose (Sharara-Chami 2017 **Level II**, n=70, JS 5).

One study measured methaemoglobin plasma concentrations after EMLA® 2 gm application for 90 min; these were elevated at 6 h but did not require treatment (Suresh 2014 **Level I** [PRISMA], 1 RCT: Lander 1997 **Level II**, n=54, JS 1). Of note, a neonate who developed acquired methaemoglobinaemia following circumcision with topical EMLA® cream (and lidocaine infiltration) was successfully treated with methylene blue (Kuiper-Prins 2016 **CR**).

10.6.6 | Use of Paediatric Regional Analgesia (PRA) in Specific Paediatric Surgical Procedures

There are numerous small observational and interventional studies of variable quality assessing various PRA techniques for many surgeries as outlined below. Despite this body of work, heterogeneity in interventional and control arms (in PRA technique, medication combinations and dosing) makes comparison of studies and performing meta-analyses difficult. Two qualitative systematic reviews by the same author group concluded that more evidence is needed to establish the effects of PRA techniques, on the postoperative pain outcomes for

specific procedures (Kendall 2018 **Level I** [PRISMA], 40 RCTs, n=2,408; Suresh 2014 **Level I** [PRISMA], 73 RCTs, n=5,125).

Penile surgery: circumcision and hypospadias repair

Policy statements from the Royal Australasian College of Physicians (RACP 2010 **GL**), the British Association of Paediatric Urologists (BAPU 2007 **GL**) and the American Academy of Pediatrics (American Academy of Pediatrics Task Force on Circumcision 2012 **GL**) emphasise the need for effective analgesia for neonatal circumcision.

In boys (infants to adolescent) who also received a general anaesthetic, a dorsal penile nerve block (DPNB) provides similar analgesia to a caudal block with similar need for rescue analgesia (RR 1.25; 95%CI 0.64 to 2.44) (4 RCTs, n=336) (Cyna 2008 **Level I** [Cochrane], 10 RCTs [5 RCTs DPNB], n=721; Canakci 2017 **Level II**, n=60 JS 1), and is as or more effective with a longer duration than post EMLA® cream application (Suresh 2014 **Level I** [PRISMA], 5 RCTs [EMLA®], n=266). PONV rates are also similar (RR 1.88; 95%CI 0.70 to 5.04) (4 RCTs, n=336) with more leg weakness in caudal recipients (RR 10.7; 95%CI 1.3 to 86.1) (2 RCTs, n=110) (Cyna 2008 **(Level I** [Cochrane], 10 RCTs, n=721). However in a single (PRAN participant) institution, DPNBs (landmark technique; surgically inserted at cessation) were inferior to caudal blocks (often containing clonidine) with higher pain scores (OR 2.7; 95%CI 1.7 to 4.4) and perioperative opioid requirement (OR 5.2; 95%CI 3.3 to 8.1) (Chan 2018 **Level III-2**, n=738). Caudal block vs parenteral analgesia does not reduce PONV (RR 0.61; 95%CI 0.36 to 1.05) or the need for early or later rescue analgesia (RR 0.41; 95%CI 0.12 to 1.43) (Cyna 2008 **Level I** [Cochrane], 4 RCTs [parenteral], n=235). There is no clear analgesic intervention recommendation; the clinical decision is influenced by perceived failure rates, risk/benefit of parenteral analgesia and side effects especially leg weakness in children old enough to walk (Suresh 2014 **Level I** [PRISMA], 13 RCTs [circumcision]; Cyna 2008 **Level I** [Cochrane], 10 RCTs [caudal], n=721; Brady-Fryer 2004 **Level I** [Cochrane], 35 RCTs [14 DPNB], n=1,984; Bellieni 2013 **NR** 14 RCTs [9 DPNB], n=1,192) (2-3 RCT overlap).

Landmark technique DPNB has a failure rate of 10% (Faraoni 2010 **Level II**, n=40, JS 3) to 30% (O'Sullivan 2011 **Level II**, n=66, JS 5; Chan 2018 **Level III-2**). For US-guided DPNB there are at least two described techniques (Qian 2015; Sandeman 2007). Compared to landmark technique, US-guided DPNB reduced postoperative pain scores and increased time to first analgesic 9.5 h vs 1 (Faraoni 2010 **Level II**, n=40, JS 3), reduced postoperative analgesic requirements (6 vs 38%), with improved success rates (eg to 97%: O'Sullivan 2011 **Level II**, n=66, JS 5; Qian 2015) and reported increase in procedure time (Sandeman 2011 **Level III-2**, n=216 [101 DPNB]) by ≈10 min (Faraoni 2010 **Level II**, n=40, JS 3).

There are insufficient controlled trials (DPNB vs placebo or sham, topical local anaesthetic or ring block; local anaesthetic vs placebo or ring block; ring block vs no treatment) to rank the efficacy of local anaesthetic techniques for circumcision in awake neonates (Brady-Fryer 2004 **Level I** [Cochrane], 35 RCTs, n=1,984; Bellieni 2013 **NR**) (2 RCT overlap). As topical local anaesthetic cream only partially attenuates the pain response to circumcision, more effective analgesic techniques are recommended. In one further RCT, EMLA® cream/PO sucrose 25% 2 mL/ lidocaine ring block was more effective than EMLA®/PO sucrose/lidocaine DPNB (surgically inserted) and EMLA®/sucrose (Sharara-Chami 2017 **Level II**, n=70, JS 5).

For circumcision, nerve stimulator-guided pudendal nerve block vs DPNB had lower pain scores, reduced analgesic requirement and provided longer duration of analgesia (Naja 2011 **Level II**, n=60, JS 3) up to 18 h (Tutuncu 2018 **Level II**, n=85, JS 5). For hypospadias repair, nerve stimulator-guided pudendal nerve block vs caudal block had lower pain scores, reduced analgesic requirement and provided longer duration of analgesia vs local anaesthetic alone (Kendigelen 2016 **Level II**, n=81 JS 5) and with clonidine 1 mcg/kg (Naja 2013 **Level II**, n=80, JS 5). Studies conflict in their results for DPNB vs caudal block for this surgery: a high success rate with both blocks was

reported (DPNB 93% vs caudal 98%), with higher postoperative analgesic requirements for DPNB vs caudal (70% vs 44%) (Seyedhejazi 2011 **Level II**, n=85, JS 2); while a second RCT had longer time to first rescue analgesia for DPNB vs caudal (5 h vs 3.7) and reduced morphine requirement 0–48 h (Kundra 2012 **Level II**, n=54, JS 4).

An association has been suggested between caudal analgesia and postoperative complications including urethrocutaneous fistula or glanular dehiscence in hypospadias: 19% vs 0 DPNB recipients (Kundra 2012 **Level II**, n=54, JS4); aOR 13.4 (95%CI 1.8 to 101.8) (Taicher 2017 **Level III-2**, n=326 [230 caudal]); OR 2.1 (95% CI 1.14 to 3.8) for postoperative complications overall, but similar fistula incidence (Kim 2016 **Level III-2**, n=342 [216 caudal]) countered by OR 0.75 (95%CI 0.33 to 1.68) (Zaidi 2015 **Level III-2**, n=135 [45 fistulae]) and similar complication rates in hypospadias surgical patients who received caudal vs DPNB (OR 2.4; 95%CI 0.9 to 6.4) (Braga 2017 **Level III-2**, n=518 [367 caudal]) including vs GA alone (Splinter 2019 **Level III-2**, n=764 [825 procedures; 87% caudal]). The latter studies proposed additional factors that were positively associated in the univariate analysis such as hypospadias type (eg proximal meatus), surgery type and duration. Caution must be exercised in interpreting these retrospective observational studies assessing association for clinical significance, and the outcome scrutinised for biological plausibility.

Inguinal surgery

Inguinal surgery includes inguinal hernia repair, hydrocoele and testicular operations. All abdominal wall truncal blocks and caudals have been used for this surgery (see earlier individual sections for II/IHNB, PVB, ESPB, TAPB, TMQLB comparisons eg with surgical site infiltration and see also Section 10.6.3.2 for caudal).

Two systematic reviews of inguinal surgery conflict in their conclusions on the analgesic efficacy of single injection caudal block vs II/IH nerve block and/or wound infiltration. The first found single injection caudal block with local anaesthetic reduces the number of patients requiring rescue analgesia early 0–4 h (RR 0.81; 95%CI 0.66 to 0.99) (13 RCTs, n=789) and late 4–24 h (RR 0.81; 95%CI 0.69 to 0.96) (9 RCTs, n=532) on POD 0 (Shanthanna 2014 **Level I** [PRISMA], 17 RCTs, n unspecified). In this setting, caudal block increases motor block (RR 2.59; 95%CI 1.29 to 5.20) (6 RCTs, n=469) and urinary retention (RR 2.23; 95%CI 1.27 to 3.91) (5 RCTs, n=429). The parallel lower quality systematic review found no difference in pain intensity at 1 h, or use of rescue analgesia (Baird 2013 **Level III-2 SR**, 13 studies n=733) (9 RCT overlap). The efficacy of different volumes of caudal local anaesthetic has been assessed for inguinal surgery. One RCT found 0.75 mL/kg was more effective than 0.5 mL/kg (Akpoduado 2017 **Level II**, n=56, JS 3); while another found no difference between 0.6 vs 0.8 and 1 mL/kg (Marjanovic 2017 **Level II**, n=40, JS 2).

Failure rates for II/IHNB are variable (as they are for caudal see Section 10.6.3.2), reported as 30–39% for landmark technique (Lim 2002 **Level II**, n=90, JS 3; Weintraud 2008 **Level III-2**, n=62). While US-guidance may reduce failure rates for II/IHNB (eg to 6%: Weintraud 2009 **Level II**, n=66, JS 3; Willschke 2005 **Level II**, n=100, JS 3) and possibly improve safety over the landmark technique (Suresh 2014 **Level I** [PRISMA], 15 [II/IHNB], n=1,046).

The effect of the addition of clonidine 1–2 mcg/kg to blocks for this surgery has not been adequately assessed (Suresh 2014 **Level I** [PRISMA], 22 RCTs [inguinal: 2 clonidine], n=1,598; Seyedhejazi 2014 **Level II**, n=66, JS 2). See also PNB Adjuvant Section 10.6.2.6 and Neuraxial adjuvant Section 10.6.3.3.

Umbilical hernia repair

Analgesia for this common paediatric surgery is covered in the rectus sheath block (RSB) section (see 10.6.2.3), with no data specific to TAPB for this surgery to date.

Pectus excavatum repair

Pectus excavatum repair (including minimally invasive repair of pectus excavatum, Nuss and Ravitch procedures) is painful surgery typically performed in adolescents. Thoracic epidural has been shown to be effective (Frawley 2016 **Level IV**, n=217 [all epidural]), and similar or superior to systemic analgesia. Epidural analgesia (bupivacaine or ropivacaine with fentanyl or hydromorphone) vs PCA (morphine, fentanyl or hydromorphone) for Nuss surgery reduced postoperative pain scores at 12 h (WMD -1.12/10; 95%CI -1.61 to -0.62) (4 studies, n=196) and 48 h (WMD -0.85; 95%CI -1.62 to -0.07) (6 studies, n=365) but not at other times; with no differences between secondary outcomes (eg rescue analgesia, adverse events, LOS) (Stroud 2014 **Level III-3 SR**, 6 studies, n=430). While three epidural infusion regimens have been compared: bupivacaine 0.125%/fentanyl 5 mcg/mL was least effective with higher pain scores by ≈0.9/10 vs bupivacaine 0.125%/hydromorphone 10 mcg/mL vs ropivacaine 0.1%/hydromorphone 20 mcg/mL on POD 1, but not later (Siddiqui 2016 **Level III-2**, n=72).

With the expansion of available regional analgesic techniques, there is no consensus on postoperative pain management for pectus excavatum repair: 91% of respondents in an international survey (North America, Europe, Asia and Australia) reported thoracic epidural as the primary analgesic modality for minimally invasive pectus excavatum repair or Nuss procedure, with 27% concomitantly using PCA opioid (Muhly 2014 **Level IV**, n=58). While USA registry data reported less frequent use of epidurals (34%); pain scores and postoperative opioid consumption were lower with an epidural catheter vs no regional analgesic technique or a wound catheter, and achieved similar analgesia to paravertebral catheters (Muhly 2019 **Level III-2**, n=331 [114 epidural]; Stroud 2014 **Level III-2**, n=331). Epidural recipients had longer time to ambulation (vs PVB CPNCs), higher rates of urinary catheterisation and longer LOS (median 4 d vs 3). While LOS was similar vs PCA only in a low quality RCT, where epidural failure rate was 22%, PCA was used during transition from epidural to orals for 19% and no detail of infusion adjuvant or opioid use for either arm was provided (Desai 2016a **Level II**, n=110, JS 1). Longer LOS for epidural recipients by 1–3 d is consistently reported in small and retrospective pectus excavatum surgery studies below.

Pain outcomes were mixed where thoracic epidural infusion:

- Provided equivalent analgesia vs PVB CPNC infusions (US-guided; bilateral) (Muhly 2019 **Level III-2**, n=331 [56 paravertebral, 114 epidural] Hall Burton 2014 **Level III-2**, n=20);
- Resulted in lower pain scores and opioid use postoperatively vs PVB CPNCs and intercostal nerve catheters, but LOS was shortest with PVB CPNCs (mean 2.0 d vs 4.0 vs 4.9) (Loftus 2016 **Level III-2**, n=137);
- (With adjuvant hydromorphone 10 mcg/mL) achieved similar pain scores vs wound catheter recipients (who also received hydromorphone PCA, low dose gabapentin 100–200 mg three times daily and clonidine patch 50 mcg/d) (Choudhry 2016 **Level III-3**, n=32);
- Achieved lower pain scores vs wound catheter recipients (Kabagambe 2018 **Level III-2**, n=31; Thaker 2019 **Level III-3**, n=124) but higher PCA requirements in a study exploring the addition of preoperative self-hypnosis training (Manworren 2018 **Level III-2**, n=53);
- (With adjuvant hydromorphone) had higher (Keller 2016 **Level III-2**, n=52) or similar postoperative opioid use and pain scores vs intercostal nerve cryoablation (Harbaugh 2018a **Level III-2**, n=32);
- Had similar pain scores vs single injection intercostal nerve block (0.25% bupivacaine) and/or PCA (Schlatter 2019 **Level III-2**, n=173);
- Resulted in higher pain scores from POD 2–5 vs IV parecoxib 1 mg/kg (max 40 mg) BD (Yang 2015 **Level III-2**, n=120 [14 parecoxib]);

- (With adjuvant clonidine 0.6 mcg/mL)/ketorolac/PCA had similar pain scores but greater opioid use vs multimodal analgesia with no regional analgesia (paracetamol, NSAID, PCA, gabapentin, clonidine patch, diazepam) (Man 2017 **Level III-3**, n=50); and
- Resulted in greater postoperative opioid requirement and more minutes in severe pain (≥7/10) vs multimodal analgesia (including some receiving intraoperative methadone [0.1 mg/kg max 7.5 mg]) (Singhal 2016 **Level III-3**, n=124). There was no difference in adverse effects, although respiratory depression was not reported.

While two non-epidural studies show benefit for PRA in addition to PCA opioid, where US-guided bilateral intercostal nerve blocks reduced early pain scores (0–6 h) and opioid requirements in PACU and 0–24 h vs saline blocks (Luo 2017 **Level II**, n=62, JS 4) and US-guided bilateral single injection thoracic PVB reduced pain scores by >2.5/10 vs PCA opioid alone at all time points with lower PCA opioid use 0–48 h postoperatively (Qi 2014 **Level II**, n=30, JS 2).

Scoliosis surgery

Intrathecal and epidural opioids in posterior spinal fusion for idiopathic scoliosis

Studies of IT opioid dosing in children and adolescents having scoliosis surgery have used larger doses on a per kg basis than adult studies. Doses of ≥9 mcg/kg are associated with respiratory complications and PICU admission.

IT opioids given preoperatively reduced blood loss and provided good analgesia in the immediate perioperative period: morphine 5–15 mcg/kg and/or sufentanil 1 mcg/kg (Eschertzhuber 2008 **Level II**, n=46, JS 5) and morphine 12 mcg/kg (Lesniak 2013 **Level III-3**, n=256). IT morphine (7.5 mcg/kg) vs extended release epidural morphine (150 mcg/kg) had similar time to first PCA use and postoperative IV PCA morphine use 0–48 h (Cohen 2017 **Level II**, n=71, JS 4). Pain scores differed relating to the kinetics of the epidural preparation and were lower with IT morphine from 0–4 h, similar from 8–24 h, and lower with extended release epidural morphine from 28–36 h.

IT morphine prolonged time to first IV morphine: 22.9 h for ≥20 mcg/kg (mean 24) vs 16.7 h for 9–19 mcg/kg (mean 14) vs 6.6 h with no IT morphine (Tripi 2008 **Level III-2**, n=407). This was at the expense of respiratory depression (15.2% vs 2.7 vs 1.5) and PICU admission (17.4% vs 2 vs 0). Pruritus (4–9%) and PONV incidence (25–30%) was similar. IT morphine (3–7 mcg/kg) combined with 2–5 d epidural infusion of ropivacaine and/or fentanyl (Ravish 2012 **Level III-3**, n=146) or bupivacaine/hydromorphone epidural infusion (Milbrandt 2009 **Level III-2**, n=138) provided superior analgesia vs IV PCA opioid alone.

Continuous epidural infusion with hydromorphone only 5 mcg/mL at 60–80 mcg/h (with 10 mcg bolus q30 min prn) achieved adequate analgesia in 95% of adolescents (Hong 2016 **Level IV**, n=56). No serious adverse effects were reported but subsequently, the same group compared IT morphine vs a lower dose epidural hydromorphone infusion (40–60 mcg/h and 5 mcg bolus q30 min prn), where 9 mcg/kg IT (Li 2018b **Level III-3**, n=56) reduced pain scores on POD 0, while 12 mcg/kg IT (Hong 2017 **Level III-2**, n=40) only lowered PACU pain scores. In both studies, the IT group had shorter time to ambulation and urinary catheter removal. Two serious adverse events occurred in the IT 9 mcg/kg group: one respiratory depression and one with severe hypotension/bradycardia and both required ICU admission (Li 2018b **Level III-3**, n=56).

Epidural local anaesthetic and or opioid in mixed scoliosis surgery

In children and adolescents having thoracolumbar spinal surgery (9 RCTs posterior spinal fusion [PSF] & 1 RCT anterior surgery for idiopathic scoliosis; 1 RCT of selective dorsal rhizotomy in cerebral palsy patients), epidural analgesia (local anaesthetic, opioid or both) vs systemic analgesia reduces pain scores at 72 h at rest (MDs -0.65/10 to -1.32) (5 RCTs, n=157) and on movement (MDs -1.07/10 to

-1.51) (2 RCTs [1 anterior; 1 posterior approach], n=60), with more patients opening their bowels within 48 h (RR 11.5; 95%CI 2.4 to 56.3) (2 RCTs, n=60) (Guay 2019b **Level I** [Cochrane], 11 RCTs, n=559). There was no difference in POV (0–48 h), time to ambulation or hospital LOS.

Dual epidural catheter techniques have been effective after anterior (Guay 2019b **Level I** [Cochrane], 1 RCT: Blumenthal 2006 **Level II**, n=30, JS 3), and posterior (Guay 2019b **Level I** [Cochrane], 1 RCT: Blumenthal 2005 **Level II**, n=30, JS 3; Lavelle 2010 **Level III-2**, n=55) spinal fusion with improved dermatomal spread after combined surgical approach (Ekatodramis 2002 **Level IV**, n=23). PCEA has been effective with a high level of patient satisfaction in selected cases (Saudan 2008 **Level IV**, n=98). There is however a significant epidural failure rate within 24 h of 8.5–37% due to incorrect placement, patency issues and the long wound length (Guay 2019b **Level I** [Cochrane], 1 RCT: Gauger 2009 **Level II**, n=38, JS 3; Ravish 2012 **Level III-3**, n=146).

In a comparison of two epidural morphine administration techniques for PSF for idiopathic scoliosis, patient-controlled intermittent epidural bolus (PCIEB) (50 mcg/kg initial bolus and q1 h prn) vs PCEA (20 mcg/kg initial bolus then 10 mcg/kg/h with 5 mcg/kg q30 min prn) had no difference in pain scores with less morphine in 24 h (median 5 mg vs 12.5), PON (16% vs 50%), POV (8% vs 35%) and pruritus (17% vs 40%) (Erdogan 2017 **Level II**, n=44, JS 5).

In patients with neuromuscular disorders and restrictive lung disease having PSF, epidural analgesia with ropivacaine 0.2% (4–6 mL/h) and systemic analgesia vs systemic analgesia alone (NSAIDs and pentazocine) reduced pain scores and frequency of rescue analgesia use in the first 3 d postoperatively (Saito 2015 **Level III-3**, n=10).

Wound catheter use in scoliosis surgery

Continuous bupivacaine infusion via a wound catheter reduced basal morphine use in idiopathic scoliosis surgery (Ross 2011 **Level III-3**, n=244 [129 wound catheter]).

Cardiothoracic surgery

In paediatric cardiac surgery, caudal injection of various medications and combinations reduced intraoperative and postoperative analgesia vs control in 9 studies and pain scores in three of five studies (Maharramova 2019 **Level IV SR** [PRISMA], 17 studies, n=2,159). In two of three studies caudal/general anaesthesia vs general anaesthesia alone reduced the perioperative stress response (cortisol, blood glucose or IL-6 levels), and caudal vs control reduced LOS in four of four studies; the authors concluded the data quality was too poor to make any recommendations for caudal analgesia use in this surgery.

Tonsillectomy

The assessment and comparison of efficacy of analgesia in tonsillectomy trials is challenged by the variation in surgical technique both within and between trials. Due to the proximity of significant vascular structures and nerves, peritonsillar infiltration and nerve block have inherent risks which can result in severe complications (Kang 2001 **Level IV**, n=2; Weksler 2001 **CR**). RCTs of infiltration with agents that are effective systemically should have a systemic arm for comparison that permits assessment of additive risk vs analgesic benefit.

For discussion of topical local anaesthetic and topical ketamine in children see Section 10.6.5 and adult Section 8.6.7.3

Local anaesthetic infiltration or application

Various local anaesthetics by infiltration (5 RCTs) or topical application (2 RCTs) produced modest reductions in pain (SMD 7–19/100 mm) vs placebo following tonsillectomy; this is a pooled value with no subgroup analyses for paediatric patients (Grainger 2008 **Level I**, 13 RCTs [7 RCTs paediatric, n≈356]) (see also adult Section 8.6.7.3). Infiltration with local anaesthetic solutions containing adrenaline may reduce blood loss (Johr 2015 **NR**). Compared to placebo, bupivacaine 0.25–0.5% infiltration alone (3 RCTs) and with adrenaline (3 RCTs) results in fewer children requiring

additional analgesia across 0–4 h postoperatively (RR 0.62; 95%CI 0.48 to 0.80) (4 RCTs, n=163) and lower pain scores at 12–48 h (5 RCTs, n=204), but with no difference in PONV (3 RCTS, n=121) (Sun 2010 **Level I**, 7 RCTs, n=286) (2 RCT overlap). However, patients who received infiltration with bupivacaine 0.25% 5 mL vs pre-emptive administration of IV tramadol 3 mg/kg had higher postoperative pain scores by 0.83/10 (95% CI 0.47 to 1.2) and required more postoperative rescue analgesia (81% vs 57), with no difference in PONV (Teunkens 2019 **Level II**, n=200, JS 4).

Systemic or peritonsillar infiltration of dexamethasone

Peritonsillar infiltration pre-incision of dexamethasone as a comparator arm (and not as an adjuvant) (in single doses of 0.3 to 1 mg/kg, with 0.5 mg/kg the most studied dose) was superior to or equivalent to various active therapies, with all superior to placebo (Titirungruang 2019 **Level I**, 7 RCTs [dexamethasone infiltration], n=728). In these heterogeneous RCTs, dexamethasone infiltration vs placebo reduced postoperative pain at 0–24 h (OR -0.77; 95 %CI -1.02 to -0.53) (6 RCTs, n=528) and on POD 1 (OR -1.06; 95%CI -1.6 to -0.52) (7 RCTs, n=676) and reduced PONV (OR 0.56; 95%CI 0.36 to 0.87) (7 RCTs, n=728).

Details of the active therapies in these RCTs reveals dexamethasone infiltration pre-incision:

- Resulted in lower pain intensity vs IV 0.5 mg/kg (max 24 mg) with both routes superior to placebo (Gao 2015 **Level II**, n=240, JS 4);
- Was similar to bupivacaine 0.25% (3–5 mL) infiltration and postoperative topical lidocaine spray (applied four times daily) with all treatment arms superior to placebo (Kaygusuz 2003 **Level II**, n=40, JS 2);
- Lowered pain scores over 1 wk vs levobupivacaine infiltration 0.25% (with 5mcg/mL epinephrine/adrenaline) with both superior to placebo; both active therapies increased time to first analgesia similarly (Aysenur 2014 **Level II**, n=60, JS 4);
- 0.3 mg/kg (max dose unspecified) was superior to placebo in lowering pain scores but inferior to tramadol infiltration 0.1 mg/kg (with no systemic comparator) (Topal 2017 **Level II**, n=60, JS 2).

An earlier systematic review with 1 RCT overlap drew the same conclusions (Vlok 2017 **Level I**, 3 RCTs [2 paediatric, n=309]).

In contrast to the Cochrane review of systemic use of dexamethasone presented in 10.4.10, IV dexamethasone 0.5 mg/kg (max 16 mg)/saline block (a comparator arm) was less effective than pre-emptive local anaesthetic infiltration/IV placebo which reduced pain scores and analgesia requirements 0–24 h and PONV in PACU (3.1% vs 15.6%) and 24 h (9.2% vs 26.6%) (Naja 2017 **Level II**, n=129, JS 5). The combination of glossopharyngeal nerve block with IV dexamethasone 0.15 mg/kg (max 8 mg) for tonsillectomy provided superior postoperative analgesia to either in isolation (Mohamed 2009 **Level II**, n=150, JS 3). However, glossopharyngeal nerve block in 2 children has been associated with postoperative airway obstruction (which terminated the proposed RCT) (Bean-Lijewski 1997 **Level III-3**, n=8).

Peritonsillar infiltration or systemic NMDA antagonists

Three systematic reviews of peritonsillar infiltration of ketamine for tonsillectomy (see Section 10.4.7.1) summarise between 3 and 10 RCTs with 2 to 10 RCT overlap. The effect for peritonsillar infiltration is positive vs placebo for pain scores at 60 min (WMD -1.71/10; 95% CI -2.12 to -0.22) and reduced analgesic rescue (RR 0.51; 95%CI 0.26 to 0.9), with no systemic arm for comparison (Tong 2014a **Level I**, 10 RCTs, n=522). Adding IV ketamine 0.5 mg/kg to peritonsillar bupivacaine 0.25% was more effective than IV placebo/peritonsillar bupivacaine infiltration, and IV placebo/placebo infiltration with significantly lower pain scores from 1–24 h, and longer time to first analgesia (Inanoglu 2009 **Level II**, n=90, JS 5). A subsequent study compared peritonsillar

ketamine administration vs PR and IV routes vs IV tramadol with similar pain scores in all four treatment arms (Yenigun 2015 **Level III-1**, n=120).

The addition of peritonsillar magnesium 2–5mg/kg to local anaesthetic reduced pain scores (4 RCTs, n=230) and the number of analgesic requests (WMD −0.68; 95% CI −1.17 to −0.18) (3 RCTs, n=180) (Vlok 2017 **Level I**, 4 RCTs [Mg], n=230).

Peritonsillar tramadol and pethidine

Adjuvant use of peritonsillar infiltration of tramadol added to local anaesthetic was beneficial to pain scores (0.25–24 h), with no difference in PONV (Vlok 2017 **Level I**, 1 RCT: Honarmand 2015 **Level II**, n=120, JS 5). Adjuvant use of peritonsillar infiltration of pethidine added to local anaesthetic reduced pain scores (at 3 h) and increased time to first analgesic use (Vlok 2017 **Level I**, 1 RCT: Elhakim 1997 **Level II**, n=80, JS 4).

Ophthalmological surgery

Peribulbar block

Compared to intraoperative opioids, pre-emptive peribulbar block reduced the occurrence of intraoperative oculocardiac reflex and PONV during strabismus (Chhabra 2005 **Level II**, n=109, JS3) and other paediatric ophthalmic surgery with lower postoperative pain scores from 0.5–6 h (Subramaniam 2003 **Level II**, n=85, JS 3; Deb 2001 **Level II**, n=50, JS 1). A peribulbar block may eliminate the need for opioid in children down to 5 wk of age undergoing vitreoretinal surgery (Patel 2012 **Level IV**, n=6).

Sub Tenon block

For vitreoretinal surgery, a sub Tenon block vs intraoperative opioids reduced the occurrence of the oculocardiac reflex with longer time to first rescue analgesic vs IV fentanyl (Chhabra 2009 **Level II**, n=196, JS 5); with benefit (Ramachandran 2014 **Level II**, n=67, JS 3; Kachko 2010 **Level II**, n=79, JS 1; Gupta 2007 **Level II**, n=45, JS 2; Steib 2005 **Level II**, n=40, JS 5) and no benefit to the reflex and PONV for strabismus surgery (Tuzcu 2015 **Level II**, n=40, JS 3).

For strabismus surgery, a sub Tenon block yielded a small clinical improvement in early postoperative pain scores at 30 min only (and not from 1–2 h) vs no block (Tuzcu 2015 **Level II**, n=40, JS 3); with reduced postoperative analgesic requirements vs placebo (Steib 2005 **Level II**, n=40, JS 5). Pain scores after sub Tenon block with bupivacaine did not differ vs topical lidocaine 3.5% gel or placebo (Enyedi 2017 **Level II**, n=50, JS 5). Sub Tenon block reduced emergence agitation post strabismus surgery vs placebo (10.4% vs 27.2%) independent of anaesthesia maintenance type (sevoflurane vs propofol/remifentanil) (Seo 2011 **Level II**, n=250, JS 5).

For paediatric cataract surgery, sub Tenon blocks were superior to IV opioid with reduced oculocardiac reflex, lower pain scores and longer time to first analgesic (median 16 h [range 2–13] vs 4 [0.5–8.5]) (Ghai 2009 **Level II**, n=114, JS 5).

The relative risks of the different eye block approaches have not been fully evaluated and a meta-analyses for the various techniques has not yet been performed.

Cleft lip and palate repair

Infraorbital nerve block for cleft lip repair

For paediatric cleft lip repair, there is low quality evidence that an infraorbital nerve block with lidocaine or bupivacaine may reduce postoperative pain vs placebo (SMD -3.54; 95%CI -6.13 to -0.95) and vs IV analgesia (SMD -1.50; 95%CI -2.40 to -0.60) (Feriani 2016 **Level I** (Cochrane], 8 RCTs, n=353). An infra-orbital nerve block vs surgical site infiltration reduces supplemental analgesia requirements (RR 0.05; 95%CI 0.01 to 0.18) and prolongs analgesia duration (MD 8.26 h; 95%CI 5.41 to 11.11). The addition of clonidine 1 mcg/kg to bupivacaine in a bilateral infraorbital nerve block prolonged duration of analgesia (11.1 h vs 9.3); with no systemic comparator (Feriani 2016 **Level I** [Cochrane], 1 RCT: Jindal 2011 **Level II**, n=50, JS 5). Adding opioids to bupivacaine infraorbital

nerve block (with no systemic comparators) increases duration of analgesia from 18 to 24 h for fentanyl and from 29 to 35 h for pethidine (Feriani 2016 **Level I** [Cochrane], 2 RCTs: Mane 2011 **Level II**, n=45, JS 5; Jonnavithula 2007 **Level II**, n=40, JS 2). Infraorbital nerve block reduces postoperative opioid requirement and emergence agitation but not pain scores vs placebo (Kendall 2018 **Level I** [PRISMA] 1 RCT: Wang 2015 **Level II**, n=100, JS 4). Future studies should standardise the observation time and the instruments used to measure outcomes, have larger sample sizes and stratify children by age group (Feriani 2016 **Level I** [Cochrane], 8 RCTs, n=353).

Bilateral suprazygomatic maxillary nerve block and palatal block

For cleft palate repair, bilateral suprazygomatic maxillary nerve block (SZMNB) with ropivacaine vs saline reduced postoperative opioid requirements (Mesnil 2010 **Level III-3**, n=33), halved the 48 h IV morphine (mean 104 mcg/kg; 95%CI 69 to 140 vs 205 mcg/kg; 95%CI 131 to 280) and reduced the need for morphine infusion postoperatively (3.6% vs 31) (Chiono 2014 **Level II**, n=57, JS 4). Minor adverse events related to the SZMNB have been reported: bleeding at the puncture site, localised swelling (Mostafa 2018 **Level II**, n=60, JS 4) and an infrazygomatic cheek haematoma which appeared on POD 1 and resolved by POD 5 (Chiono 2014 **Level II**, n=57, JS 4). US-guidance permitted confirmation of needle location and assessed local anaesthetic spread (Sola 2012 **Level IV**, n=25 [50 blocks]). Levobupivacaine 0.2% and bupivacaine 0.2% SZMNBs provide equivalent postoperative analgesia (Mostafa 2018 **Level II**, n=60, JS 4).

Palatal block (combined nasopalatine, greater and lesser palatine nerve block) vs no block reduced pain scores following cleft palate repair, and delayed time to first analgesia (18 h vs 6) with less demands for rescue analgesia (Jonnavithula 2010 **Level II**, n=45, JS 3). The addition of dexmedetomidine 1 mcg/kg to bupivacaine 0.25% for greater palatine nerve blocks reduced pain scores across 0–24 h vs bupivacaine 0.25% alone and prolonged time to first analgesia (mean 22 h vs 14.2) with no side effects (Obayah 2010 **Level II**, n=30, JS 3).

Bilateral SZMNB vs bilateral infraorbital nerve block for cleft lip and vs palatal block for cleft palate surgery achieved similar postoperative pain scores, opioid consumption, complication and failure rates (Echaniz 2019 **Level II**, n=120 [102 children], JS 4).

Interventions for the iliac bone graft donor site for cleft palate repair are described in Section 10.6.2.1 lower limb blocks.

Dental procedures

Outpatient dental procedures

Topical anaesthetics should be used prior to local anaesthetic injection to minimise discomfort with needle penetration and injection (Kuhnisch 2017 **GL**). Local anaesthetic infiltration reduced pain following dental extractions (Anand 2005 **Level III-2**); adding morphine 25 mcg/kg to the local anaesthetic did not improve the quality or duration of analgesia (Bhananker 2008 **Level II**, n=42, JS 3). There is low quality evidence suggesting similar efficacy for local anaesthetics during routine dental treatments with articaine achieving slightly more pain score reduction than lidocaine post procedure (SMD 0.37) (4 RCTs, n=397) (Tong 2018 **Level I** [PRISMA], 6 RCTs, n=541); while inferior alveolar nerve block was superior to buccal infiltration for mandibular molar extraction (1 RCT, n=113) (Klingberg 2017 **Level I** [PRISMA], 8 RCTs, n unspecified) (3 RCT overlap). Use of local anaesthesia for dental work is documented in children with rare medical diseases (Dougall 2017 **Level IV SR** [PRISMA], 3 studies, n=83).

The use of a computer assisted injection devices delivery device vs conventional infiltration was not painful, with high success rates (Giannetti 2018 **Level IV**, n=66; Sixou 2015 **Level IV**, n=278 [421 procedures]) and similar onset of effect for submucosal and buccal injection for 1st permanent molar work (Kandiah 2012 **Level II**, n=30, JS 3) and less painful for buccopalatal injection (Feda 2010 **Level II**, n=40 JS 1). A vibrating device did not reduce pain scores during local anaesthetic injection (Raslan 2018 **Level II**, n=40, JS 2; Roeber 2011 **Level II**, n=90, JS 4). A needleless jet system was inferior

to standard local anaesthetic infiltration, as it required more local anaesthetic supplementation and more patients reported post procedure pain (Arapostathis 2010 **Level III-2**, n=87 [174 procedures-split mouth design]).

Eutectic Mixture of Local Anaesthetics (EMLA®) with audiovisual aid distraction reduced pain scores during needle insertion and was superior to EMLA® alone, or topical benzocaine (20%) with and without audiovisual aid distraction (mean 4.7/10 vs 5.7 vs 5.9 vs 7.4) (Agarwal 2017 **Level II**, n=120, JS 1). Acupuncture at L14 improved pain levels with local anaesthetic injection (buccal infiltration, intraligament injection and block analgesia): mean 2.3/10 (95%CI 1.5 to 3.1) vs 3.9 (95%CI 3.0 to 4.7) (Usichenko 2016 **Level II**, n=49, JS 4). A Cochrane review did not find positive benefit for hypnosis (Al-Harasi 2010 **Level I** [Cochrane], 3 RCTs, n=69). The addition of preoperative systemic analgesic prior to orthodontic separator placement (without general anaesthesia) is likely of benefit (Ashley 2016 **Level I** [Cochrane], 5 RCTs, n=190).

See also adult Section 8.6.7.2 Acute postoperative dental pain.

Dental procedures under general anaesthesia

RCTs of local anaesthetic for children undergoing dental work with a general anaesthetic were heterogeneous regarding injection site (intra-ligamental vs surgical site infiltration vs topical) and varied in supplemental analgesics and follow-up (Parekh 2014 **Level I** [Cochrane], 14 RCTs, n=1,152). This precluded pooling of results, with a suggestion for further good quality RCTs. The addition of local anaesthetic to IV ketorolac in dental restoration or extraction under general anaesthetic does not improve quality of recovery vs IV ketorolac alone and young children may bite or chew the anaesthetic cheek or lip (Townsend 2009 **Level II**, n=27, JS 5). 'Best Clinical Practice Guidelines' by the European Academy of Paediatric Dentistry recommend the routine use of local anaesthetic agents with vasoconstrictors to slow systemic absorption, prolong analgesic effect and provide additional haemostasis (Kuhnisch 2017 **GL**).

KEY MESSAGES

1. Topical local anaesthetic does not adequately control pain associated with circumcision in awake neonates (**U**) (**Level I** [Cochrane Review]).
2. Caudal local anaesthetic, dorsal penile nerve block (**U**) (**Level I** [Cochrane Review]) and ring block (**N**) (**Level II**) provide effective perioperative analgesia for circumcision in infants to adolescents.
3. Caudal local anaesthetic in addition to general anaesthesia for circumcision does not reduce postoperative nausea and vomiting or the need for early rescue or other analgesia in children (infants to adolescents) when compared to parenteral analgesia (**U**) (**Level I** [Cochrane Review]).
4. In acute otitis media, topical local anaesthetic drops are effective in children compared to placebo and equivalent to naturopathic drops (**S**) (**Level I** [Cochrane Review]).
5. For paediatric cleft lip repair, infraorbital nerve block with lidocaine or bupivacaine may reduce postoperative pain versus placebo; duration is increased when opioids are added (with no systemic comparator) (**N**) (**Level I** [Cochrane Review]).
6. Epidural analgesia compared to systemic analgesia after spinal surgery in children improves pain up to 72 hours postoperatively (N) (Level I[Cochrane Review]).
7. Local anaesthetics (by infiltration or nerve block) reduce pain scores post dental procedures (**N**) (**Level I** [PRISMA]).

8. Ketamine added to caudal local anaesthetic for paediatric day-stay surgery prolongs analgesia but not motor block (**U**) (**Level I** [PRISMA]); however concerns regarding neurotoxicity remain.
9. Dexamethasone (caudal, perineural or IV) prolongs the duration of analgesia of local anaesthetic caudal (**N**) (**Level I** [PRISMA]) and peripheral nerve blocks (**N**) (**Level II**).
10. Magnesium added to caudal local anaesthetic blocks improves analgesia in children (**N**) (**Level I** [PRISMA]).
11. Clonidine (**U**) and dexmedetomidine (**N**) improve analgesia in children when added to local anaesthetic caudal blocks, epidural infusions (**Level I** [PRISMA]) and peripheral nerve blocks (**N**) (**Level II**).
12. Peritonsillar dexamethasone or peritonsillar ketamine may reduce pain scores following paediatric tonsillectomy compared to placebo (in trials with no systemic comparator arms) (**N**) (**Level I**).
13. Ultrasound guidance for epidural catheter insertion is a reliable predictor of depth to loss of resistance (or of epidural space), offers visibility of the needle and catheter and may reduce bone contacts (**N**) (**Level IV SR**).
14. In children having cardiac surgery, caudal injections with various medication combinations vs control reduces postoperative analgesia requirements and pain scores (**N**) (**Level IV SR** [PRISMA]).
15. In children having scoliosis surgery, the addition of epidural local anaesthetic infusion to intravenous PCA morphine improves pain scores and patient satisfaction (**U**) (**Level I**) and decreases postoperative nausea (**U**) (**Level II**).
16. Peripheral nerve blocks (**S**) (**Level I** [PRISMA]), wound infiltration and caudal local anaesthetic provide effective analgesia after day-stay paediatric inguinal surgery (**S**) (**Level II**).
17. Epidural infusions of local anaesthetic in children provide similar levels of analgesia compared to systemic opioid infusion (**U**) (**Level II**) and intravenous PCA (**U**) (**Level III-3 SR**).
18. Epidural opioids alone are less effective than epidural local anaesthetic or combinations of local anaesthetic and opioid in children (**U**) (**Level II**).
19. Intrathecal opioids provide prolonged analgesia after surgery in children and reduce blood loss during paediatric spinal fusion (**U**) (**Level II**). High doses of intrathecal morphine in children have been associated with respiratory failure and intensive care admission (**N**) (**Level III-2**).
20. Paediatric regional analgesia (peripheral nerve and neuraxial blocks as single injections and continuous catheters) are effective (**Level II**) and safe analgesic techniques in children (**S**) (**Level IV**); continous peripheral nerve catheters have been used in hospital and following discharge, with low secondary failure rates (**N**) (**Level IV**).
21. Ultrasound guidance to assist peripheral block and catheter placement has increased block success (**Level II**) but not impacted the incidence of local anaesthetic systemic toxicity or neurological complications in children; the latter having decreased independently over time (**N**) (**Level IV**).

22. Continuous wound catheter infusions of local anaesthetic are effective (**N**) (**Level II**) and safe analgesic techniques (**N**) (**Level IV**).
23. Caudal local anaesthetic blocks provide effective analgesia for lower abdominal, perineal and lower limb surgery (**Level II**) and have a low incidence of serious complications (**S**) (**Level IV**).
24. Continuous ultrasound-guided caudal injection versus landmark technique increases success of first puncture and lowers risk of vascular puncture and inadvertent subcutaneous injection (**N**) (**Level II**); while permitting real-time visualisation of injectate spread (**N**) (**Level IV**).
25. Sub Tenon block for paediatric ocular surgery achieved longer time to first analgesic administration versus placebo or intravenous opioid (**N**) (**Level II**).
26. Complications of epidural infusions are rare; the rates are slightly higher in neonates and infants versus older children (S) (**Level III-2**).
27. Continuous epidural infusions provide effective postoperative analgesia in children of all ages (**U**) (**Level III-2**).
28. Continuous epidural infusions are safe in children of all ages (**S**) (**Level III-2**) if appropriate doses and equipment are used by experienced practitioners, with adequate monitoring and management of complications (**U**) (**Level IV**).
29. Thoracic epidural, paravertebral catheters, wound catheters and intercostal nerve blocks all provide effective analgesia for pectus excavatum repair surgery, with longer hospital stays in thoracic epidural recipients (**N**) (**Level III-3**).
30. Placement of paediatric regional analgesia (peripheral nerve and neuraxial blocks as single injections and catheters) in children under general anaesthesia is not associated with an increased rate of complications (**S**) (**Level IV**).

The following tick boxes represents conclusions based on clinical experience and expert opinion:

☑ An association between urethral fistula formation complicating hypospadias repair and caudal block has not been consistently reported; variation in anatomical presentation and surgical technique are more biologically plausible risk factors (**N**).

☑ Lipid emulsion (20%) has been used in successful resuscitation of paediatric patients (neonates to 18 years) with local anaesthetic systemic toxicity; dosing recommendations are the same as for adults and higher doses have led to adverse effects (**N**).

☑ Dosing practices for peripheral nerve blocks vary and concerningly doses sometimes approach or exceed the accepted safe dose limit; this occurs more commonly in younger children (**N**).

10.7 | Management of procedural pain in children

Procedure-related pain is a frequent and distressing component of medical care for children, their families and hospital staff (Atkinson 2009 **NR**; Kennedy 2008 **NR**). Repeated interventions are often required and the level of pain and memory of the first procedure affect the pain (Taddio 2009 **Level II**, n=240, JS 5; Noel 2012 **Level IV**), fear (de Vos 2012 **Level IV**) and distress (Chen 2000 **NR**) associated with subsequent procedures (Kennedy 2008 **NR**). Poorly managed procedural pain may also result in greater anxiety, pain and avoidance of health care as adults (Young 2005 **NR**). Studies suggest that minor procedures are still undertaken in children, particularly neonates and infants, in the elective and emergency hospital setting without evidence-supported pain management interventions (Bueno 2017 **Level IV SR,** 68 videos; Cruz 2016 **Level IV SR,** 18 studies, n=3,156; Ali 2014 **Level IV**; Codipietro 2011 **Level IV**; Losacco 2011 **Level IV**; Hoyle 2011 **Level IV**; MacLean 2007 **Level IV**).

The aim of procedural pain management is to minimise physical discomfort, pain, movement and psychological disturbance without compromising patient safety. Management may include analgesic agents via different routes of administration, concurrent sedation or general anaesthesia and nonpharmacological methods. The choice of technique will depend on the age and previous experience of the child, the type of procedure, the expected intensity and duration of pain, the treatment environment and available resources (Atkinson 2009 **NR**; Murat 2003 **GL**). Sedation alone must not be seen as an alternative to appropriate analgesia, particularly when pain is expected after completion of the procedure. Further information is available from evidence based guidelines produced by various anaesthetic, paediatric and emergency physician associations (Green 2019b **GL**; Lago 2017 **GL;** Cote 2016 **GL;** Mace 2008 **GL;** RACP 2005 **GL**).

10.7.1 | Procedural pain in the neonate

10.7.1.1 | Blood sampling, skin puncture and intravenous cannulation

Effective pain management is a desirable standard of care for preterm and term neonates and may improve their clinical and neurodevelopmental outcomes (Hall 2014 **NR**). Multiple interventions have been assessed and their use is strongly supported; combining interventions appears to be more effective and is recommended (Lago 2017 **GL**). Neonates in NICUs require frequent painful procedures (mean 7.5–17.3 per day) (6 studies); however pain management strategies in these studies are inconsistently applied (Cruz 2016 **Level IV**, 18 studies, n=3,156). Many studies continue to be published on interventions such as breastfeeding, sweet solutions, non-nutritive sucking (NNS) and kangaroo care (ventral skin to skin contact with an adult); where these studies do not alter the conclusions of published systematic reviews, they have not been referenced.

Different techniques of blood sampling

In term neonates, venipuncture is less painful than heel lance (HL) (SMD -0.76; 95%CI -1.00 to -0.52) (5 RCTs, n=288), including when a sweet solution is administered (SMD -0.38; 95%CI -0.69 to -0.07) (3 RCTs, n=170) with less pain behaviour exhibited during and after the procedure and fewer attempts required (SMD 0.34; 95% CI -0.43 to -0.25) (4 RCTs, n=254) (Shah 2011b **Level I** [Cochrane], 6 RCTs, n=478). Spring-loaded automated devices for HL reduced the pain behaviour exhibited vs manual lance (Shah 2003 **Level II**, n=80, JS 5).

Topical local anaesthesia

Evidence-based recommendations could not be made regarding the use of topical local anaesthetics for the prevention of needle related procedural pain in newborns (Foster 2017 **Level I** [Cochrane], 8 RCTs, n=506). This includes for venipuncture, IV cannulation, arterial puncture, arterial cannulation, HL, lumbar puncture (LP), supra-pubic aspiration of urine, peripherally inserted central catheter (PICC) placement and intramuscular injection. Subsequently, for infants (<3 mth), EMLA® vs placebo, sucrose or breastfeeding did not reduce pain during (6 RCTs, n=742) or at the end (4 RCTs, n=226) of venipuncture (Shahid 2019 **Level I** [PRISMA], 10 RCTs, n=907) (1 RCT overlap). None of the RCTs reported clinical symptoms of methaemoglobinaemia; in two RCTs (n=134) methaemoglobin levels were <5%. However, acquired methaemoglobinaemia in a neonate following circumcision with EMLA® (dose unknown) and lidocaine infiltration, which was successfully treated with methylene blue has been reported (Kuiper-Prins 2016 **CR**).

Breastfeeding, supplemental breastmilk and sweet solutions

Breastfeeding

In term neonates, breastfeeding reduces pain scores, behavioural (cry), and physiological (heart rate) responses to skin puncture procedures when compared to positioning (swaddling and placement in a crib), holding by the mother, maternal kangaroo care, no intervention, placebo, pacifier use and PO sucrose or both, topical local anaesthetics and music therapy (Benoit 2017a **Level I** [PRISMA], 21 RCTs, n=1,764; Shah 2012 **Level III-1 SR** [Cochrane], 10 RCTs [breastfeeding], n=1,076) (0 RCT overlap). The effect in preterm neonates is not clear; studies are of limited number, and preterm neonates often cannot breastfeed and are more likely to receive repeated painful procedures.

Supplemental breastmilk

Studies of supplemental/expressed breast milk report mixed effects vs sweet tasting solutions (5 RCTs), placebo (6 RCTs) and no intervention (3 RCTs), and inferiority to pacifier use and rocking (1 RCT each) (Benoit 2017a **Level I** [PRISMA], 21 RCTs, n=1,764; Shah 2012 **Level III-1 SR** [Cochrane], 10 studies [supplemental breast milk], n=1,002) (0 study overlap).

Sweet solutions

A systematic review pooled data for meta-analysis on all sweet solutions (sucrose 106 studies, glucose 62 studies, non-sucrose sweetener 2 studies, honey and fructose 1 study each) for procedural pain in neonates (Harrison 2017 **Level III-1 SR** [PRISMA], 168 studies, n unspecified). Sweet solutions overall vs placebo reduced composite pain scores (SMD -0.90; 95%CI -1.09 to -0.70) (50 studies, n=3,341) and cry duration (SMD -23.18 s; 95%CI -28.89 to -17.47) (29 studies, n=1,775).

The most frequently studied intervention for managing procedural pain in preterm and term infants is sucrose with or without NNS. Studies vary in concentration and volume of sucrose administered, comparison group intervention and outcomes measured, meaning meta-analysis for each research question typically only combines a few studies or pool heterogeneous data.

Studies specific to sucrose mostly support an analgesic effect at higher concentrations (>20%) for HL (39 RCTs), venipuncture (10 RCTs), and intramuscular (IM) injection (4 RCTs); this effect may be greater when combined with other interventions (eg NNS, swaddling) (Stevens 2016 **Level I** [Cochrane], 74 RCTs, n=7,049). There is high quality evidence in this review for the following:

- For HL, 24% sucrose (0.5–2 mL) with NNS or sucrose 0.5 mL orally vs placebo in preterm and term infants reduces pain score at 30 s (WMD -1.70/21; 95%CI -2.13 to -1.26) (3 RCTs, n=278) and 60 s post procedure (WMD -2.14/21; 95%CI -3.34 to -0.94) (2 RCTs, n=164);
- 24% sucrose (2 mL) vs placebo for term neonates reduces pain score during venipuncture (WMD -2.79/21; 95%CI -3.76 to -1.83) (1 RCT, n=213);

- 24% sucrose (2mL) vs placebo for term neonates reduces pain score during IM injection (WMD -1.05/21; 95%CI -1.98 to -0.12) (1 RCT, n=232);
- Evidence for effectiveness of sucrose for arterial puncture (1 RCT) and SC injection (2 RCTs) is inconclusive.

Debate continues as to the optimal dose and administration of sucrose with one RCT documenting a minimum effective dose of 0.1 mL of 24% sucrose (Stevens 2018 **Level II**, n=248, JS 3).

A separate review focussing on the efficacy and safety of *repeated* sucrose over multiple procedures in neonates found limited evidence supporting its use to reduce pain scores and behaviours (cry), with no adverse effects reported; no meta-analysis was possible (Gao 2016 **Level I** [PRISMA], 8 RCTs, n=782).

Sweet non-sucrose solutions via dropper, syringe or pacifier have shown efficacy for procedural pain in preterm and term infants (Bueno 2013 **Level I** [PRISMA], 38 RCTs [35 glucose; artificial sweetener, fructose, glycine, honey, maltitol, 1 RCT each; 36 skin puncture], n=3,785):

- Glucose 10–50% (0.2–2mL) vs no intervention or water reduces pain scores during and/or after HL (6 RCTs, n=322; no meta-analysis);
- Glucose 20–30% (1–2 mL) vs water for HL reduces pain scores (WMD −3.61/21; 95%CI -4.58 to -2.63) (2 RCTs, n=124);
- Artificial sweetener, maltitol or fructose vs water or no intervention for HL reduces pain scores (1 RCT each);
- Maltitol, artificial sweetener or honey vs water for HL reduces cry duration (1 RCT each);
- Glucose 25–30% (1–2mL) vs glucose 10%, water, no intervention or EMLA® reduces pain scores for venipuncture (11 RCTs, n=1,250, no meta-analysis);
- Glucose 25–50% (1–2 mL) vs water for venipuncture reduces cry response (RR 0.80; 95%CI 0.66 to 0.96: NNT 6; 95%CI 3 to 20) (3 RCTs, n=130).

A further systematic review of Chinese studies on all sweet solutions for neonatal procedural pain found similar results to the above reviews (Huang 2019 **Level III-1 SR** [PRISMA], 31 studies, n=4,999) (0 study overlap).

Paracetamol

Paracetamol given 30–60 min prior vs placebo does not reduce pain with HL (3 RCTs), and findings are conflicting for eye examination (2 RCTs) (for further discussion, see 10.7.1.4); no meta-analysis was possible due to study heterogeneity (Ohlsson 2016 **Level I** [Cochrane], 9 RCTs, n=728). A subsequent RCT found paracetamol was not more effective than sucrose 24% for managing pain during PICC placement in preterm neonates (Roofthooft 2017 **Level II**, n=60, JS 4).

Opioids

Background morphine infusions in ventilated neonates had limited efficacy for acute procedural interventions in intensive care (Bellu 2008 **Level I** [Cochrane], 2 RCTs [procedures], n=965). An RCT of PO morphine (100 mcg/kg) vs placebo in non-ventilated premature infants for HL or eye examination was stopped early due to a high rate of respiratory depression requiring resuscitation (20% vs 0%) (Monk 2019 **Level II**, n=31, JS 5). IN Fentanyl (mean dose 1.3 mcg/kg) has been used in neonates in NICU having painful procedures (78% PICC insertion); respiratory depression occurred in 26% (McNair 2018 **Level IV**, n=23).

Combination intervention in neonates: pharmacological

In preterm neonates, topical local anaesthesia EMLA® combined with PO sucrose 30% was more effective than sucrose alone in reducing venipuncture-related pain (Biran 2011 **Level II**, n=76, JS 3). In term neonates, the addition of liposomal lidocaine for venipuncture to sucrose did not confer additional benefit (Taddio 2011 **Level II**, n=330, JS 5).

For PICC placement, IV morphine bolus with topical amethocaine provided more effective analgesia than morphine or amethocaine alone in preterm neonates (Taddio 2006 **Level II**, n=132, JS 5). In ventilated term and preterm neonates pre-treated with EMLA®, a glucose 30% pacifier combination was inferior to sevoflurane (Bueno 2013 **Level I** [PRISMA], 1 RCT [sevoflurane]: Michel 2010 **Level II**, n=59, JS 2).

Nonpharmacological intervention alone and in combination

Many nonpharmacological interventions have been studied for procedural pain in preterm and term neonates including NNS, swaddling/tucking, rocking/holding and kangaroo care. However, study designs are heterogeneous and prone to bias due to difficulty blinding interventions; caution interpreting results is required. A systematic review assessed the efficacy of nonpharmacological interventions on pain reactivity (behavioural responses within 30 s of painful procedure) and immediate pain regulation (behavioural response >30 s after painful procedure) (Pillai Riddell 2015c **Level III-I SR** [Cochrane], 63 studies [32 HL, 17 vaccination, 8 venipuncture], n=4,905). It found:

- NNS vs control reduces pain reactivity in term neonates (SMD -1.20; 95%CI -2.01 to -0.38) (5 studies, n=270) and improves immediate pain regulation in preterm (SMD -0.43; 95%CI -0.63 to -0.23) (5 studies, n=260) and term neonates (SMD -0.90; 95%CI -1.54 to -0.25) (7 studies, n=325);
- Swaddling/facilitated tucking vs control reduced pain reactivity in preterm neonates (SMD -0.89; 95%CI -1.37 to -0.40) (8 studies, n=331);
- Rocking and holding vs control improved immediate pain regulation in term neonates (SMD -0.75; 95%CI -1.20 to -0.30) (2 studies, n=81);
- NNS with pacifier/sucrose appeared superior to NNS alone (1 study, n=24), and facilitated tucking appeared to have an additive effect to NNS in preterm neonates (1 study n=45);
- There were smaller benefits for the following interventions: environmental modification (eg low noise and lighting, clustering procedures) and touch/massage interventions in preterm infants; swaddling/facilitated tucking and familiar odours (familiarisation with vanilla 24 h prior to procedure) in term infants;
- Subsequent to this review, olfactory stimulation from lavender, breast milk and amniotic fluid vs control for HL reduced pain scores (2.91/7 vs 3.31 vs 3.90 vs 5.20) (Akcan 2016 **Level II**, n=102, JS 2).

For vaccination, individual studies report NNS to be inferior to PO sucrose 20% (Liaw 2011 **Level II**, n=165, JS 3) and glucose 25% (Lima 2017 **Level II**, n=78, JS 2), whilst external warming was superior to NNS alone and PO sucrose 25% alone (Gray 2012 **Level II**, n=47, JS 3).

Two RCTs combined interventions for repeated HL in preterm infants. NNS/PO sucrose provides better pain relief than NNS or PO sucrose alone (Gao 2018 **Level II**, n=91, JS 3), whilst PO sucrose 20% is superior to facilitated tucking, but facilitated tucking/sucrose does not confer additional benefit to sucrose alone (Cignacco 2012 **Level II**, n=71, JS 5).

Kangaroo care appeared to be safe and reduce pain response to HL, venipuncture, and IM injections; however, the degree of benefit was difficult to estimate and may not be large (Johnston 2017 **Level III-I SR** [Cochrane], 25 studies, n=2,001). For all procedures on preterm neonates, kangaroo care vs standard care reduced pain score at 30 s (MD -3.21/21; 95%CI -3.94 to -2.47) (6 studies, n=267) and 60 s (MD -1.64/21; 95%CI -2.86 to -0.43) (4 studies, n=156). No difference was seen between mothers and alternative kangaroo care providers in preterm neonates. Single studies in this review comparing kangaroo care with other active interventions demonstrated similar efficacy to breastfeeding but superiority to PO dextrose and glucose solutions. Kangaroo care combined with breastfeeding, or PO sucrose/dextrose solutions was superior to kangaroo

care alone. A subsequent RCT found kangaroo care remained efficacious across three procedures (HL) with similar efficacy to PO sucrose 24% (Campbell-Yeo 2019 **Level II**, n=242, JS 3).

For HL, passive music therapy (played lullaby) was superior to no music for preterm neonates and, combined with NNS, was superior vs either alone, with lower pain and stress scores in both preterm and term neonates (Wright 2013 **Level I**, 2 RCTs [heel lance], n=87).

Acupuncture (invasive or non-invasive) for preterm and term neonates receiving HL did not reduce pain intensity (Stadler 2019 **Level I** [PRISMA], 5 RCTs, n=265). Distress during acupuncture itself was not reported. A subsequent RCT found auricular non-invasive magnetic acupuncture vs placebo reduced pain scores during (mean 5.9/21 vs 8.3) but not after HL in preterm and term neonates (Chen 2017a **Level II**, n=26, JS 3).

Applying mechanical vibration (5 s of 100 Hz) to the foot prior to HL, in addition to use of a pacifier with sucrose and heel warming, did not impact upon pain scores vs pacifier and sucrose alone (Baba 2010 **Level II**, n=20, JS 3).

For venipuncture, pre-recorded maternal voice was an effective intervention for reducing term neonates' physiological response to pain (Azarmnejad 2017 **Level III-1**, n=60).

10.7.1.2 | Lumbar puncture

For infant lumbar puncture (LP), surveyed clinicians working in paediatric EDs at five USA centres reported frequent use of NNS (67%), with low use of other interventions (<30% for sucrose, topical and injectable lidocaine) (Hoyle 2011 **Level IV**, n=156). A further USA centre audited local anaesthetic use for LP in children aged 0–24 mth with 0% use in neonates, 54% in infants but 99% in toddlers (Gorchynski 2011 **Level IV**, n=223). A Canadian ED survey revealed minimal use of PO sucrose in infants, and low use of topical local anaesthetic, across the paediatric age range (Ali 2014 **Level IV**, n=72 [EDs]). The poor translation of evidence into practice is disappointing with the data known regarding the consequences of poor analgesia (Kennedy 2008 **NR**) and the suggested positive association of local anaesthetic use with increased first pass success and atraumatic taps (Kennedy 2014 **NR**).

EMLA® reduced the physiological and behavioural response with needle insertion for LP in preterm and term neonates (Foster 2017 **Level I** [Cochrane], 1 RCT: Kaur 2003 **Level II**, n=60, JS 5).

10.7.1.3 | Urine sampling

EMLA® reduced pain scores in neonates and young infants undergoing suprapubic aspiration (Nahum 2007 **Level II**, n=52, JS 5). Oral sucrose 24% vs water reduced cry incidence (29 vs 78%) and pain scores during transurethral catheterisation in neonates (Stevens 2016 **Level I** [Cochrane], 1 RCT [catheterisation]: Rogers 2006 **Level II**, n=80, JS 5).

Four RCTs have compared pain from transurethral catheterisation to suprapubic aspiration. Transurethral catheterisation after urethral application of lidocaine 2% was less painful than suprapubic aspiration after skin application of EMLA® (Kozer 2006 **Level II**, n=58, JS 3). Transurethral catheterisation with lubrication only was less painful than suprapubic aspiration without topical local anaesthesia in preterm neonates (Badiee 2014 **Level II**, n=80 [uncircumcised males only], JS 2; El-Naggar 2010 **Level II**, n=48, JS 3) but not when compared to suprapubic aspiration with EMLA® in preterm and term neonates (Ghaffari 2014 **Level II**, n=90, JS 3).

10.7.1.4 | Ocular examination for retinopathy of prematurity

Screening for retinopathy of prematurity (ROP) causes pain in neonates (Belda 2004 **Level IV**). Topical local anaesthetic reduces pain scores (Dempsey 2011 **Level III-1 SR** [Cochrane], 2 studies,

n=168). A systematic review on the efficacy of sucrose found mixed results for eye examination (Stevens 2016 **Level I** [Cochrane], 7 RCTs [ROP], n=259):

- Oral sucrose 24–33%/NNS is more effective than sterile water/NNS in reducing pain scores (WMD -2.47/21; 95%CI -3.27 to -1.66) (3 RCTs, n=114);
- Sucrose did not affect cry (2 RCTs) or HR (2 RCTs);
- Two RCTs report short-lived reduction in oxygen saturation in PO sucrose treated infants, during but not persisting after eye examination.

A review including lower level evidence concluded that topical local anaesthetic/sweet tasting solution and a nonpharmaocological (adjunct) intervention was superior to topical local anaesthetic alone (MD -3.67/21; 95%CI -5.86 to -1.47) (17 studies) (Disher 2018 **Level III-1** [NMA], 29 studies, n=1,487) (2 & 7 study overlap with above). A fourth review included two RCTs comparing paracetamol to placebo for eye examination which have conflicting results whilst a third RCT reported higher pain scores for paracetamol vs sucrose 24% (Ohlsson 2016 **Level I** [Cochrane], 3 RCTs [ROP], n=213) (overlap 0, 0 & 3 RCTs).

10.7.1.5 | Nasogastric tube insertion

The evidence for efficacy of PO sucrose reducing pain from nasogastric/orogastric insertion is inconclusive (Stevens 2016 **Level I** [Cochrane], 3 RCTs [nasogastric], n=164). The highest quality evidence is for sucrose 24% vs sterile water lowering mean pain score 30 s post orogastric tube insertion (WMD -1.30/21; 95%CI -2.31 to -0.29) (1 RCT) but not during or 1 min post procedure (Pandey 2013 **Level II**, n=105, JS 5). A subsequent review that included lower level evidence concluded sweet solutions (sucrose 24 to 30% or glucose 25%) vs no intervention or placebo reduced pain score during or immediately after gastric tube insertion (MD -2.18/21; 95% CI -3.86 to -0.51) (4 studies, n=344) (Chen 2017b **Level III-1 SR**, 6 studies, n=441 [630 insertions]) (3 RCT overlap).

10.7.1.6 | Nasal CPAP prong insertion

Topical lidocaine 2% vs control did not reduce pain intensity or cortisol levels for preterm neonates having nasal CPAP prongs inserted (Soliman 2016 **Level II**, n=60, JS 3).

10.7.2 | Procedural pain in infants and older children

10.7.2.1 | Venipuncture and intravenous cannulation

Venipuncture causes significant distress in many children (Kennedy 2008 **NR**). Both pharmacological and nonpharmacological interventions have supportive evidence.

Hospital initiatives

In a large children's hospital, a system-wide initiative implemented a new standard of care for needle procedures that required staff to consistently offer 4 strategies: topical anaesthetics; PO sucrose or breastfeeding for infants 0–12 mth old; age-appropriate comfort positioning; and age-appropriate distraction (Friedrichsdorf 2018 **Level III-3**, n=20,758). This reduced wait times for services and increased patient satisfaction. Staff concerns about implementation (such as wait times) were allayed by the results. Using a similar multidisciplinary approach for venipuncture (including universal offering of EMLA®, child preparation, carer education, comfort positioning and age-appropriate distraction), the majority of carers were satisfied (91%) with the process and 82% reported the procedure eliminated the fear of needle-related procedures in their children (Yamamoto-Hanada 2015 **Level IV**, n=132).

Topical local anaesthesia

Topical local anaesthesia (via cream/gel, patch, iontophoresis and needleless compression device delivery) reduces pain associated with venipuncture and IV cannulation in all age groups (Zempsky 2008 **Level I**, 52 RCTs, n unspecified).

Amethocaine (tetracaine) gel is more effective than EMLA® cream (RR 0.78; 95%CI 0.62 to 0.98) with more rapid onset (Lander 2006 **Level I** [Cochrane], 6 RCTs, n=634), although does not improve first time cannulation success rate (Pywell 2015 **Level I** [PRISMA], 3 RCTs, n=922) (1 RCT overlap). A heated lidocaine/tetracaine patch was superior to both placebo (2 RCTs, n=109) and EMLA® (1 RCT, n=200) (Croxtall 2010 **Level I**, 3 RCTs [paediatric], n=309) and associated with a higher first-time venipuncture/cannulation success rate than EMLA® (Cozzi 2017 **Level II**, n=356, JS 3). Application of a heat pack after EMLA® does not increase first time success rate (Schreiber 2018 **Level II**, n=400, JS 3). EMLA® was more effective than a Valsalva manoeuvre in children (5–12y), both being more effective than control (1/10 vs 2.15 vs 2.55) (Akdas 2014 **Level II**, n=60, JS 2).

Iontophoresis of lidocaine 1–4% is superior to placebo (4 RCTs, n=420) and is equivalent to or superior to EMLA® (2 RCTs, n=144) with a time to onset of 10 min (Zempsky 2008 **Level I**, 52 RCTs, n unspecified). Liposomal lidocaine 4% cream was similar with only 15 min application to placebo (Brenner 2013 **Level II**, n=120, JS 5), but after 30 min was both similar to amethocaine 4% (Poonai 2012 **Level II**, n=60, JS 5) and superior to placebo (1 RCT, n=142) (Zempsky 2008 **Level I**, 52 RCTs, n unspecified). It had a more rapid onset, was as effective as EMLA® (3 RCTs, n=240) and was as effective as buffered lidocaine (1 RCT, n=69) (Zempsky 2008 **Level I**, 52 RCTs, n unspecified). Sonophoresis prior to application of liposomal lidocaine accelerated the onset time from 30 to 5 min (1 RCT, n=60) and sonophoresis/liposomal lidocaine was superior to sonophoresis/placebo cream (1 RCT, n=77).

Intradermal delivery of powdered lidocaine (0.5–1 mg) under high pressure (20 bar) via a needleless device (CO_2 or helium driven) was effective within 3 min and produced more effective skin anaesthesia than EMLA® in one RCT (Jimenez 2006 **Level II**, n=116, JS 3), but was less effective than EMLA® in another (Stoltz 2017, **Level II**, n=150, JS 3). Powdered lidocaine 0.5 mg was more effective than 0.25 mg (1 RCT, n=307) and placebo (2 RCTs, n=452) (Zempsky 2008 **Level I**, 52 RCTs, n unspecified; Schmitz 2015 **Level II**, n=517, JS 5), and associated with infrequent mild adverse events such as erythema and petechiae (Schmitz 2015 **Level II**, n=517, JS 5). In children (1–6 y) intradermal needleless pressure-injected lidocaine was more effective than vapocoolant spray and placebo (Lunoe 2015 **Level II**, n=205, JS 3). A cooling and rapidly vibrating device (Buzzy®) combined with intradermal needleless pressure-injected lidocaine provided no benefit vs intradermal needleless pressure-injected lidocaine alone, both for the administration of lidocaine and venipuncture (Kearl 2015 **Level III-2**, n=356).

Nitrous oxide (N_2O)

N_2O at 20–75% reduced pain and anxiety associated with venipuncture/IV cannulation and, in one study, shortened time to achieve access with fewer attempts (Tobias 2013a **Level IV SR**, 5 studies [venipuncture/cannulation], n unspecified). N_2O 70% for 3 and 5 min reduced pain scores by >50% (Furuya 2009 **Level II**, n=73, JS 5). The combination of N_2O 40–50% and topical EMLA® for IV cannulation is more effective in reducing pain scores and increased satisfaction vs either method alone (Pedersen 2013 **Level I** [PRISMA], 3 RCTs [IV cannulation], n=233). This systematic review also included five large case series of N_2O use in mixed minor procedures, supporting the safety of N_2O 50–70% administration in children. Minor adverse events were reported in 4–8% of patients and serious or potentially serious adverse events were reported in less than 0.5% of patients. (Pedersen 2013 **Level IV SR** [PRISMA], 5 studies, n=53,108).

Dexmedetomidine

IN Dexmedetomidine (2 mcg/kg) 30 min prior reduced pain scores during venous cannulation when given via mucosal atomisation device (MAD) vs dropper administration (Xie 2017b **Level II**, n=106, JS 3).

Sweet-tasting solutions in older children

For school aged children, chewing sweetened gum before needle-related painful procedures (2 RCTs, n=111) or during the procedure (2 RCTs, n=103) did not reduce pain scores during the procedure (Harrison 2015 **Level I** [Cochrane], 8 RCTs, n=808). In toddlers/preschool children (6 RCTs, n=520) there was insufficient evidence of an analgesic effect for sweet tasting solutions or substances during acutely painful procedures.

Combination pharmacological intervention

The combination of EMLA® and N_2O 50% reduced procedure duration with more successful IV placements than EMLA®/low-dose PO midazolam 0.3 mg/kg (max 15 mg) 40 min prior (Ekbom 2011 **Level II**, n=90, JS 4). Notably, the usual PO midazolam dose is 0.5 mg/kg and, at 40 min, offset of effect is relevant.

Nonpharmacological intervention

Skin cooling techniques

Evidence on the use of skin cooling techniques in children is conflicting. Vapocoolant sprays did not reduce pain from venipuncture or IV cannulation in children vs placebo or no treatment (3 studies, n=387) (Hogan 2014 **Level III-1 SR** [PRISMA], 12 studies, n=1,266 [4 paediatric, n=509]). Pain or discomfort from application of vapocoolant spray was not assessed in children. Two subsequent meta-analyses of the same 2 paediatric RCTs (n=165, both RCTs included in the above review) similarly reported no pain reduction with vapocoolant sprays vs placebo (Zhu 2018b **Level I**, 11 RCTs, n=1,410; Griffith 2016 **Level I** [Cochrane], 9 RCTs, n=1,070). In two separate RCTs, a vapocoolant spray (5-fluoropropane/4-fluoroethane: Painease®) applied 10 s prior to IV cannulation was similarly effective to 3 min application of ice in older children (9–18 y) (Waterhouse 2013 **Level II**, n=95, JS 4) and vapocoolant spray was superior to control but inferior to EMLA® (Dalvandi 2017 **Level II**, n=40, JS 3). Ice application (0° C) for 3 min has previously been reported to improve pain-related behaviours in children aged 6–12 y undergoing venipuncture (Movahedi 2006 **Level III-2**). With use of a metal applicator (Coolsense®: refrigerated to -2°C requiring 10 s application time), 94% of children aged 6–18 y rated their pain score during cannulation <3/10; patient and carer satisfaction with the device was high (Ragg 2017 **Level IV**, n=100).

Vibration alone or combined with cooling

The efficacy of the Buzzy® device (vibration alone or combined with cooling) vs no intervention for children (3–18y) having needle-related procedures has been assessed (Ballard 2019 **Level I** [PRISMA], 9 RCTs [7 IV cannulation/venipuncture, 2 vaccine injection], n=1,138). Buzzy® reduces:

- Self-reported pain intensity (SMD -1.12; 95%CI -1.53 to -0.71) (6 RCTs, n=609);
- Parent-reported pain intensity (SMD -0.94; 95%CI -1.62 to -0.27) (5 RCTs, n=398);
- Observer-reported pain intensity (SMD -1.19; 95%CI -1.90 to -0.47) (4 RCTs, n=329).

Smaller meta-analyses suggest a beneficial effect on parent and observer-reported anxiety, but not success of procedure on first attempt, or adverse effects. Additionally, Buzzy® vs distraction cards (1 RCT, n=110) and Buzzy®/topical anaesthesia vs vapocoolant spray/topical anaesthesia (1 RCT, n=81) improve self and parent-reported pain intensity, whilst Buzzy®/comfort plan is not superior to topical anaesthetic /comfort plan for IV cannulation (1 RCT, n=224).

The following RCTs with mixed results were not included in the above review where Buzzy®:

- Added to distraction cards for venipuncture was more effective than the hypnoanalgesic *'Magic Glove'* technique in 3–10 y olds (mean pain score 3.65/10 vs 4.67) (Susam 2018 **Level II**, n=64, JS 3);
- Vs a handheld computer game for venipuncture resulted in similar median pain scores in 4–12 y olds (3/10 vs 2) (Cozzi 2018 **Level II**, n=200, JS 3);
- Vs virtual reality (VR) for venipuncture resulted in similar pain scores in 7–12 y olds (mean 2.0/10 vs 1.5) (Gerceker 2018 **Level II**, n=121, JS 3);
- Alone or combined with animated cartoons vs control for 5–12 y olds having venipuncture did not reduce pain scores (Bergomi 2018 **Level II**, n=150, JS 3);
- Was not as effective as EMLA® patch in reducing pain intensity for children (18 mth to 16 y) having IV cannulation (mean 8.5/18 vs 7.2) (Bourdier 2019 **Level II**, n=607, JS 3);
- Resulted in lower pain scores than ShotBlocker®, bubble blowing or control in children aged 5–10 y receiving IM injection in the ED (mean 3.87/10 vs 4.14 vs 4.75 vs 6.72) (Yilmaz 2019 **Level II**, n=160, JS 3).

A second review included lower level evidence and evaluated vibratory stimulation *by any method* to reduce needle related procedure pain in children (0–18 y) (Ueki 2019 **Level III-1**, 21 studies, n=1,727) (7 RCT overlap). It found vibratory stimulation vs control reduced self-rated pain intensity (SMD -0.55; 95%CI -0.92 to -0.18) (13 studies, n=1,589), observer-rated pain intensity (SMD -0.47; 95%CI -0.76 to -0.18) (16 studies, n=1,721) and observer-rated anxiety (SMD -1.03; 95%CI -1.85 to -0.20) (4 studies, n=624). There was no difference in success of procedure on first attempt or adverse effects.

Distraction

A customised multimodal distraction device (Ditto®) designed for children aged 3–12 y provides procedural preparation stories and distraction content. Compared to standard distraction, combined Ditto® procedural preparation and distraction significantly reduced nursing staff and carer reported pain and distress (Miller 2016 **Level II**, n=98, JS 3). Carers also reported combined Ditto® procedural preparation and distraction as more effective than either in isolation.

Immersive virtual reality (Sony Snow World®) use in children aged 7–17 y significantly reduced time spent thinking about pain, pain unpleasantness and worst pain; patients reported more fun than controls (Atzori 2018 **Level III-2**, n=15). Patients aged 10–21 y used Bear Blast® with VR goggles during venipuncture and experienced less pain and anxiety than controls (Gold 2018 **Level II**, n=143, JS 3). Secondary analysis revealed patients with a high anxiety sensitivity experienced less anxiety with VR vs control, while patients with low anxiety sensitivity did not. For further discussion of distraction techniques including virtual reality see Section 10.7.5 Nonpharmacological Strategies in Adolescents and Children.

Other techniques

For older infants up to 36 mth having needle procedures, NNS improved immediate pain regulation (behavioural response >30 s post procedure: SMD -1.34; 95%CI -2.14 to -0.54) (2 studies, n=151) (Pillai Riddell 2015c **Level III-2 SR** [Cochrane], 63 studies, n=4,905). Touch/massage-related strategies and structured non-parent involvement also improved immediate pain regulation.

For pain during venipuncture in 6–12 y olds, acupressure and EMLA® reduced FLACC scores similarly with both better than routine care (mean 2.65/10 vs 2.75 vs 7.75) (Pour 2017 **Level II**, n=120, JS 3). Medical clowning (also termed clown care by therapeutic clowns or "clown doctors") for children aged 2–10 y reduced mean crying duration vs control (1.3 min vs 3.8) (Meiri 2016 **Level III-1**, n=100). Clowning also lowered parental assessment of child's anxiety about future blood tests assessed the following day vs both control and EMLA®, but did not reduce pain

scores. In a further venipuncture study, medical clowning vs standard care reduced pain scores in older 7–15 y old children (1.5/10 vs 2.7), but not in younger 4–6 y olds (Kristensen 2018 **Level III-2**, n=111).

Therapeutic dog presence for venipuncture in 4–11 y olds reduced observer-reported distress and patients' cortisol levels, but not pain scores during the procedure or parental anxiety (Vagnoli 2015 **Level II**, n=50, JS 2).

Children with an intellectual disability having venipuncture or IV cannulation experienced more pain and anxiety despite receiving more pain and anxiety interventions (eg EMLA®, distraction, physical or verbal comforting) (Pascolo 2018 **Level III-2**, n=141).

10.7.2.2 | Lumbar puncture and bone marrow aspiration

Numerous techniques are used to alleviate the pain and distress occurring in children undergoing lumbar puncture (LP) alone or combined with bone marrow aspiration (BMA) in the ED and oncology settings (Kennedy 2014 **NR**). Interventions have usually been assessed in isolation. Despite positive benefits, use of analgesic intervention in EDs has penetrated poorly (Ali 2014 **Level IV**). Combining techniques is recommended best practice: topical local anaesthesia, local anaesthesia infiltration by slow injection, and PO sucrose with NNS in infants; and, for older children, adding distraction (see Section 10.4.5) and anxiolysis with midazolam and/or further analgesia with N_2O (Kennedy 2014 **NR**). Deeper sedation techniques and general anaesthesia are also used. The choice of intervention is best determined by the setting, the local resources and skills, and assessment of the individual child.

Topical local anaesthesia and nitrous oxide (N_2O) (alone or in combination)

Several RCTs and case series have reported on the safety of N_2O 50–70% for mixed minor procedures in children (see Section 10.7.2.1). Nitrous oxide is often co-administered with other agents or strategies. For LP:

- In infants <3 mth, needle-free jet injection of lidocaine vs saline resulted in lower pain scores (mean 4.1/10 vs 4.8) and slightly reduced cry duration (by 10 s) (Ferayorni 2012 **Level II**, n=55, JS 5);
- In infants <4 mth, needle free injection of lidocaine was of similar efficacy to EMLA® in reducing pain intensity during needle insertion (Caltagirone 2018 **Level II**, n=58, JS 5);
- For 3–21 y olds, topical local anaesthesia with EMLA® vs placebo reduced median propofol requirements 4 mg/kg (95%CI 3.5 to 4.4) vs 4.9 mg/kg (95%CI 4.3 to 5.6), decreased movement at skin puncture (8% vs 84%) and reduced heart rate change (mean 1 bpm vs 8.3) (Whitlow 2015 **Level III-2**, n=25);
- In 5–14y old children with leukaemia, self-administered N_2O/oxygen mixture (ratio unspecified) reduced self-reported pain intensity vs control (mean 1.05/10 vs 8) (Liu 2019 **Level II**, n=114, JS 5);
- In an oncology LP clinic (2–29 y olds), N_2O 40–70% with or without topical local anaesthesia was 98% successful, with minimal sedation (Livingston 2017 **Level IV**, n=78 [LPs n=350]).

For LP and BMA:

- Coadministration of local anaesthesia and sedative/anxiolytic has been used both infrequently (18% and 8.2%) (Onody 2006 **Level IV**, n=3,964) and frequently (98.7% and 64.5%) (Annequin 2000 **Level IV**, n=286 [LPs] & n=231 [BMAs]). The latter study described low pain scores during LP and BMA (respective median procedural pain scores – patient 5/100 and 12.5; nurse 0/10 and 2) with a low need overall for restraint, 18.2% initially and 6% during the procedure.

Fentanyl alone

Oral transmucosal fentanyl is not licensed for paediatric use but 10–15 mcg/kg reduced pain scores vs placebo dosette for LP/BMA (Schechter 1995 **Level II**, n=48, JS 4). As yet, IN use is unreported for this procedural indication.

Single or double agent sedation vs general anaesthesia

For oncology LP/BMA, general anaesthesia is considered by some to be best practice (eg with propofol/fentanyl) (Ghasemi 2013 **Level IV**), while volatile-based general anaesthesia (sevoflurane/N_2O) was preferred to sedation, with less distress and pain for children requiring multiple procedures (Crock 2003 **Level III-3**). Propofol has been used by an ED physician-led sedation team for these procedures (Lamond 2010 **Level IV SR**, 1 study [ED physician], n=87 [291 procedures]). In two small cross-over trials of children with leukaemia undergoing LPs/BMAs, adding IV fentanyl 1 mcg/kg to propofol sedation improved satisfaction, recovery time by 10 min (Cechvala 2008 **Level II**, n=22, JS 5) and analgesia (Nagel 2008 **Level II**, n=25, JS 5). The addition of fentanyl 0.5–1 mcg/kg was propofol sparing with less movement during the procedure and shorter recovery times but no difference in post LP/BMA pain scores (Anghelescu 2013 **Level II**, n=162, JS 5).

Oral or IV ketamine was effective and associated with less distress vs placebo or IV midazolam during LP and/or BMA in children with cancer (Rayala 2019 **Level II**, n=52, JS 2; Tobias 1992b **Level III-3;** Evans 2005 **Level IV**). In the ED setting, IV ketamine 1 mg/kg alone vs with IV midazolam 0.1 mg/kg was similarly effective (Dilli 2008 **Level II**, n=99, JS 3), whilst for oncology patients, IV ketamine 1mg/kg/midazolam 0.1mg/kg vs IV pethidine 1mg/kg/midazolam 0.1mg/kg resulted in lower median pain scores at the beginning of BMA/biopsy (3/10 vs 7) (Abdolkarimi 2016 **Level II**, n=57, JS 4). Adding ketamine 0.5 mg/kg to propofol (administered by non-anaesthetists) vs propofol alone was propofol sparing, resulted in better observer scored intraprocedural pain scores and reduced recovery time (Chiaretti 2011 **Level II**, n=121, JS 3). In an outpatient oncology unit, thiamylal/pentazocine vs ketamine/midazolam (routes unspecified) for LP/BMA was used by paediatricians with similar efficacy, but with increased transient desaturation (36 vs 22%) and oxygen supplementation (82 vs 36%) (Nakagawa 2018 **Level III-2**, n=35 [268 procedures]). Protocolised administration by non-anaesthetists of propofol sedation vs ketamine/midazolam resulted in a higher sedation failure rate (12 vs 0%), but a lower rate of emergence symptoms (9.2 vs 50%) (Chayapathi 2018 **Level II**, n=152, JS 3). Pain outcomes were not assessed. A study of a standardised sedation procedure with IV midazolam and S(+) ketamine for BMA reported 2% prevalence of hypoxia requiring intervention and 3% prevalence of minor complications (Sauer 2019 **Level IV**, n=107). The qualifications of the practitioner administering sedation were not specified.

Nonpharmacological intervention

See also Section 10.7.5 for nonpharmacological techniques.

Child distress during a course of consecutive LPs/BMAs increased over time and was positively related with parental distress (Caes 2014a **Level IV**, n=28 [242 procedures]). Additionally, parental distress about LPs/BMAs decreased over time with low-catastrophising parents but remained high with high-catastrophising parents. In another study by the same group, parental catastrophic thinking contributed to increased parental distress during, but less pain attending behaviour before LP/BMA (Caes 2014b **Level IV**, n=46).

Massage therapy just prior to IT chemotherapy or BMA was associated with greater reduction in children's pain and anxiety vs control when evaluated prior to treatment and 20 min after (Celebioglu 2015 **Level III-2**, n=25). IV sedation was also given to both groups; however the amount of hypnoanalgesia administered was not reported.

Authors concluded that all youth with cancer having invasive medical procedures should receive preparatory information to reduce distress and increase coping and compliance (low quality evidence, strong recommendation), and psychological interventions such as distraction, hypnosis, and combined cognitive behavioural therapy (CBT) interventions to reduce pain and distress (high quality evidence, strong recommendation) (Flowers 2015 **GL**). Psychosocial intervention (preparation and CBT) was associated with less mean anticipatory and total behavioural distress ratings (OSBD-R) in patients receiving BMA or LP. Reduced behavioural distress ratings from one procedure to the next were observed when psychosocial interventions (preparation and CBT) with a child-life specialist were given for the second procedure (Hsiao 2019 **Level III-3**, n=18).

Reduction of post-dural puncture headache (PDPH) incidence

Risk of PDPH after LP was higher with traumatic vs atraumatic needles (RR 2.14; 95%CI 1.72 to 2.67) (36 RCTs, n=9,378); however the paediatric sub-analysis revealed no difference (2 RCTs, n=315) (Arevalo-Rodriguez 2017 **Level I** [Cochrane], 66 RCTs, n=17,067 [3 paediatric, n= 475]). With the exception of one adult RCT, there was no difference with different gauge traumatic needles (multiple sub-analyses, 10 RCTs [1 paediatric], n=2,288) or different gauge atraumatic needles (multiple sub-analyses, 13 RCTs, n=3,134 [paediatric unspecified]). Subsequently, a lower risk of PDPH was confirmed with atraumatic vs traumatic needles (RR 0.40; 95%CI 0.34 to 0.47) (n=24,901) but again, no difference in the paediatric sub-analysis (2 RCTs, n=782) (Nath 2018 **Level I** [PRISMA], 110 RCTs [2 paediatric, unspecified number of mixed adult/paediatric], n=31,412 [1,065 paediatric]) (39 RCTs overlap [2 paediatric]).

Lower level evidence have mixed findings. Following diagnostic LP in children, less PDPH resulted with use of a 27-guage atraumatic vs 26-g traumatic needle (0.4% vs 4.5%) (Apiliogullari 2010 **Level III-2**, n=414). In children having IT chemotherapy, the incidence of PDPH with a 22-g traumatic vs 25-g atraumatic needle was similar (11 vs 7%) (Lowery 2008 **Level III-2**). With guideline change from 22-g spinal needles to 25-g (type unspecified) for diagnostic LPs/chemotherapy administration and 27-g for spinal anaesthesia, epidural blood patch rates decreased from 0.8% (5 y data) to 0.2–0.3% (10 y data) (Kokki 2012b **Level III-3**). Injected mean blood volumes of 0.27 mL/kg (range 0.16–0.53 mL/kg) for epidural blood patch achieved complete persistent resolution of headache in 83% of 42 patients (see also Section 8.6.5).

The use of atraumatic needles for LP is strongly recommended in patients (including children) of all ages (Rochwerg 2018 **GL**).

10.7.2.3 | Botulinum toxin (intramuscular) or steroid (intra-articular) injection

IM botulinum toxin for spasticity and intra-articular steroid injections are acutely painful procedures, and general anaesthesia should be considered for these procedures, especially when multiple injections are performed.

Nitrous oxide (N_2O)

Use of N_2O 70% in isolation reduced patient, parent and nurse-reported pain scores vs PR midazolam 0.35–0.5 mg/kg (Zier 2008 **Level II**, n=50, JS 4). Using topical EMLA® and N_2O 50% in children reduced pain in only 50% of the 51 procedures (n=39) with the remainder experiencing severe pain intensity (≥9/13) (Brochard 2009 **Level IV**). N_2O 50%/oxygen treatment for botox or joint injections was superior to inhaled nitrogen 50%/oxygen mix, with lower pain scores (by 50%) and fewer patients requiring rescue with propofol or sevoflurane (18 vs 55%) (Reinoso-Barbero 2011 **Level II**, n=100, JS 4). Use of N_2O 50–70% in a small series of children having joint injection achieved adequate analgesia in most (89%) children (Cleary 2002 **Level IV**, n=55).

Local anaesthetic

Girls had lower post procedural pain scores with topical local anaesthesia (EMLA® or Numby®) plus subcutaneous buffered lidocaine vs topical local anaesthesia alone for corticosteroid knee joint injections, but boys did not (Weiss 2015 **Level II**, n=63, JS 2).

The use of vapocoolant spray (used in 89%) or topical local anaesthetic (used in 2%), as well as younger age, and body region injected (leg, thigh, hand) was associated with increased pain with botulinum toxin injection for spasticity (Fisher 2018b **Level IV**, n=249 [563 procedures]).

Other sedative agents

IV ketamine with or without midazolam in addition to topical local anaesthesia was successfully used for botulinum toxin injection to treat spasticity with a low prevalence of minor adverse effects (Chow 2016 **Level IV**, n=87 [152 procedures]). PR midazolam and ketamine in addition to topical local anaesthesia has also been used successfully for botulinum toxin injection (Nilsson 2017 **Level IV**, n=61 [128 procedures]).

Impact of localisation techniques

For botulinum toxin injection, US-guidance may help localise muscles more accurately (Py 2009 **Level IV**) and reduce procedure related pain vs use of electrical stimulation with/ without US-guidance (Bayon-Mottu 2014 **Level III-2**, n=107 [155 procedures]).

Nonpharmacological intervention

Medical clowning has been used for intra-articular steroid injections (Weintraub 2014 **Level IV)**. For botulinum toxin injections, results are mixed; medical clowning vs standard care was associated with lower pain scores in one study (Ben-Pazi 2017 **Level III-2**, n=45) but not in another (Houx 2019 **Level III-2**, n=88). Virtual reality has been used for botulinum toxin injection (Chau 2018 **Level IV**, n=14).

10.7.2.4 | Urethral catheterisation and micturating (voiding) cystourethrogram

Children with stronger medical fears were more anxious during the micturating cystourethrogram (MCUG) as reported by their parents and examining technologists and demonstrated more procedural distress as measured by their vocalisations (Fox 2016 **Level IV**, n=34).

Local anaesthesia — topical and installation

Lidocaine 2% gel is no better than non-anaesthetic gel in reducing pain from transurethral bladder catheterisation (Chua 2017c **Level I** [PRISMA], 5 RCTs, n=369). A subsequent RCT similarly reported lidocaine 2% gel was not better than usual care with high reported median pain scores (8/10 vs 9) and the authors thus emphasised that analgesia for this procedure needs to improve (Uspal 2018 **Level II**, n=73, JS 3); however high pain scores are not universally reported (Chua 2017c **Level I** [PRISMA], 5 RCTs, n=369).

Nitrous oxide (N_2O)

N_2O use is associated with low pain and distress scores in children undergoing urethral catheterisation and/or MCUG (Pedersen 2013 **Level IV SR** [PRISMA], 2 studies [catheterisation], n≈5,000).

Intranasal fentanyl alone

IN fentanyl 2 mcg/kg, administered slowly by dropper 10 min prior to catheterisation for MCUG, with no distraction, resulted in similarly low pain scores vs water (mean 2.6/10 vs 2.9) (Chung 2010 **Level II**, n=69, JS 5). Nasal irritation was reported by 6 and 14% respectively.

Midazolam

Midazolam administered PO or IN vs no treatment for urinary catheterisation in 4–24 mth olds was associated with lower parent and nurse-reported pain/distress (mean 33.6/100 vs 71.7) and shorter cry duration (median 0 s vs 240) (Weiser 2014 **Level III-2**, n=51).

Sucrose

Sucrose 75% 4 mL vs water for children (3 mth–3 y) did not reduce pain intensity with transurethral bladder catheterisation (London 2019 **Level II**, n=40, JS 5).

Other

Pain scores were not different when olive oil/calcium hydroxide (oleocalcareous) liniment vs a dry compress was used to aid removal of a urine collection bag (Lamy 2019 **Level II**, n=135, JS 3).

Nonpharmacological intervention

Preparing the child for the MCUG using a story booklet alone or with play preparation reduced distress (Phillips 1998 **Level III-2**). Hypnosis was superior to play preparation, with reduced distress and procedure duration (Butler 2005 **Level II**, n=44, JS 3).

10.7.2.5 | Chest drain and intercostal catheter insertion and removal for thoracic surgery or pneumothorax management

Chest drains and intercostal catheters are inserted for a variety of reasons perioperatively and for management of pneumothorax.

The incidence of paediatric spontaneous pneumothorax is low; it can be primary [PSP] or secondary [SSP] due to asthma, cystic fibrosis and congenital cystic adenomatoid malformations. Pain is commonly present (along with dyspnoea); overall hospital admission rates for PSP and SSP (reported by the British Thoracic Society) are 5.8 and 16.7/100 000 for women and men (respectively), without paediatric subgroup data (MacDuff 2010 **GL**). Most paediatric patients are admitted (81% of 219 presentations) and have non-surgical management with oxygen, needle aspiration (PSP 27% and SSP 9%) and/or intercostal catheter (ICC) insertion (PSP 48% and SSP 67%), with 38% PSP and 47% SSP requiring surgery (Robinson 2015 **Level IV**, n=162 children [120 with PSP]).

Pain service involvement in patients with PSP/SSP in the acute phase of care has decreased – likely related to the use of less painful small bore or micro/pig tail catheters; duration of care postoperatively has also shortened with change in surgical technique from open to limited axillary (LATS) or video-assisted thoracic surgery (VATS) procedures. VATS had lower analgesic requirement and shorter period of follow-up vs LATS (Butterworth 2007 **Level III-3**, n=31). Analgesic intervention follows stepwise escalation with paracetamol, nsNSAID and opioids PO or IV including by PCA. Following antibiotic or talc pleurodesis, nsNSAIDs are generally avoided (with no positive or negative data to support this practice) but are used post-bleb or apical pleural abrasion or resection.

Removal of chest drains/ICCs can cause significant pain and distress. For chest drain/ICC removal (inserted for various indications), IV morphine, topical anaesthesia with EMLA® and N_2O reduced pain but did not provide adequate analgesia in children (and adults) (Bruce 2006a **Level III-2**; Bruce 2006b **Level IV SR**, 14 studies, n=758 [1 study, 1 RCT, paediatric n=144]). For children aged <7 y having chest drain removal post cardiothoracic surgery, pain scores were similarly high during the procedure (7/10) with EMLA® applied 3 h prior and IV placebo vs placebo cream and IV morphine 0.1 mg/kg 30 mins prior (Rosen 2000 **Level II**, n=120, JS 2). IN Ketamine 0.5 mg/kg combined with IN sufentanil 0.5 mcg/kg has been used in children for drain removal (Nielsen 2014 **Level IV**).

Following paediatric cardiac surgery, a nursing education program improved timely use of periprocedural intervention including analgesic and nonpharmacological therapies for ICC removal (Ring 2017 **Level IV**, n= 68 staff surveyed & 21 charts reviewed). Similarly, introduction of a procedural treatment protocol (play therapist, topical local anaesthetic and targeted pharmacological intervention based on the tool's estimate of risk) reduced the number of patients that were inconsolable after chest drain and pacing wire removal (Craske 2013 **Level III-3**, n=163).

10.7.2.6 | Nasogastric tube insertion

Nasogastric tube (NGT) insertion causes pain and distress particularly in children (Juhl 2005 **Level IV**).

Topical local anaesthesia

In adults, topical gel and/or nebulised anaesthesia of the nose and pharynx reduces pain associated with NGT insertion (OR 0.42; 95%CI 0.20 to 0.88) (Kuo 2010 **Level I**, 5 RCTs, n=212; Uri 2011 **Level II**, n=62, JS 5) and reduced NGT insertion time (Chan 2010 **Level II**, n=206, JS 5). Lidocaine/phenylephrine spray (10 mg/1mg for 6–12 kg, 20 mg/2 mg for >12 kg) was not superior to saline spray in infants and young children (6 mth–5 y) (median 9/10 vs 9) (Craig 2019 **Level II**, n=107, JS 5). An RCT in children aged 1–5 y of nebulised lidocaine was terminated early due to the distress associated with nebulisation; this may outweigh its potential benefit (Babl 2009 **Level II,** n=36, JS 5).

Ketamine

In adults, IN ketamine 50 mg reduced pain scores vs placebo for NGT insertion (Nejati 2010 **Level II**, n=72, JS 5). In mostly preschool aged children having NGT insertion (for repeat gastric aspirates), IN ketamine 2 mg/kg and IN midazolam 0.5 mg/kg (max 10 mg) vs placebo achieved sedation for 71 min (95%CI 64 to 80) and reduced pain scores and the need for physical restraint (4% vs 100), with low post-procedure agitation rates (11% of procedures) (Buonsenso 2014 **Level II**, n=36 [108 procedures], JS 5).

10.7.2.7 | Dental procedures

For pharmacological interventions see the various analgesic subsections in 10.4 and for local anaesthetic interventions see Section 10.6.6

Nonpharmacological interventions for dental procedures

In children <18 y having dental procedures, distraction techniques including music, virtual reality, magic tricks, exposure to positive dental images and relaxation training have been studied with mixed results for pain, anxiety and behaviour outcomes (Goettems 2017 **Level I**, 13 RCTs, n unspecified) including during local anaesthetic infiltration (Sridhar 2019 **Level II**, n=66, JS 3) and pulpotomy (Shetty 2019 **Level III-1**, n=120). Acupuncture (at the LI 4 meridian point bilaterally) in children and adolescents (4–18 y) reduced self-reported pain intensity (2.3/10 vs 3.9) during local anaesthetic injection for dental treatment (Usichenko 2016 **Level II**, n=49 [98 injections], JS 3).

10.7.2.8 | Intraosseous pin removal

Topical local anaesthetic vs placebo in children (3–16 y) having interosseous pin removal did not reduce pain intensity (Dulai 2016 **Level II**, n=281, JS 5).

Children who have sustained burns injuries often require repeated, painful and distressing dressing changes (see also Section 8.5). Considerable interindividual variation occurs and analgesia needs to be titrated to effect as requirements differ according to the surface area involved, the location, the stage of healing and need for grafts, and the child's previous experiences (Palmer 2014 **NR**). It is important to consider significant coexistent post-traumatic stress symptoms or disorder (Stoddard 2011 **Level III-1;** Stoddard 2006 **Level IV**) and anxiety and depression (van Baar 2011 **Level III-2**). Additionally, parental post-traumatic stress symptoms and parental guilt predict more child distress, and parental general anxiety/depression predict less child coping (Brown 2019 **Level IV**, n=87). Long term post-traumatic stress symptoms may be reduced by adequate early opioid administration (Sheridan 2014b **Level IV**). In the early phases, general anaesthesia may be preferred for dressing changes, stepping down to procedural interventions on the ward and then as outpatients (Palmer 2014 **NR**).

Burn dressing types

Numerous dressings for superficial and partial thickness burns have been assessed and the optimal choice is unclear (Wasiak 2013 **Level I** [Cochrane], 6 RCTs [paediatric], n=364). In paediatric patients, biosynthetic dressings are superior to silver sulphadiazine in reducing daily opioid requirements (1 RCT, n=20), the time to healing, number of dressing changes and hospital stay (2 RCTs, n=109) but were similar to hydrocolloid dressing (Duoderm®) in terms of pain scores and time to healing (1 RCT, n=72).

Pharmacological interventions for burn dressing

Opioids

Opioids are frequently required and prescribed for burns dressing changes, with little published data. Compared to placebo, oral transmucosal fentanyl (≈10 mcg/kg) compared favourably with PO morphine (Robert 2003 **Level II**, n=8, JS 4), PO hydromorphone 60 mcg/kg (Sharar 1998 **Level II**, n=14, JS 4) and PO oxycodone 0.2 mg/kg in reduction of pain associated with dressing changes (Sharar 2002 **Level III-2**). IN fentanyl 1.4 mcg/kg reduced pain scores similarly with similar recovery time vs PO morphine 1 mg/kg in paediatric burns dressing change (Borland 2005 **Level II**, n=28, JS 4).

Ketamine

IN Ketamine 0.5 mg/kg combined with IN sufentanil 0.5 mcg/kg has been used in children for burn dressing change (Nielsen 2014 **Level IV**, n=7). IV Ketamine administration by non-anaesthetists was audited, where doses of 6–800 mg were given to children weighing 3–111 kg for procedures of 1–105 min duration (Owens 2006 **Level IV**, n=347). Ten events occurred that required intervention (2.9% incidence): eight were airway related and responded to repositioning, supplemental oxygen or bag-mask ventilation and two hypotensive events responded to fluid administration.

For burns dressing changes in children aged 1–5 y, PO ketamine 5 mg/kg with midazolam 0.5 mg/kg vs combination PO midazolam 0.5 mg/kg/paracetamol 10 mg/kg/codeine 1 mg/kg may provide superior analgesia: mean pain scores 7.4/13 (95%CI 4 to 12) vs 8.9 (95%CI 4 to 13) (Norambuena 2013 **Level II**, n=60, JS 4).

Dexmedetomidine

IN dexmedetomidine 2 mcg/kg has been used as premedication prior to burns reconstructive surgery (Talon 2009 **Level II**, n=50, JS 3) but no conclusion can be drawn as to the impact upon pain outcomes. Use in deep sedation is described below.

Deep sedation/analgesia

Three doses of PR ketamine (4, 6 and 8 mg/kg) with PR midazolam 0.5mg/kg for burns wound care sedated children with low pain scores (median 0 vs 0 vs 0) and a dose dependent effect on recovery (mean 25 vs 27 vs 36 min) (Grossmann 2019 **Level II**, n=201, JS 4). Propofol 2mg/kg/ketamine 1mg/kg was comparable to propofol 2mg/kg/remifentanil bolus 0.1 mcg/kg and infusion 0.05 mcg/kg/min for burns dressing changes, but with longer recovery time (median 22.5 min (IQR 20.3–25) vs 10.3 (IQR 9.1–11.5)); pain outcomes were not reported (Seol 2015 **Level II**, n=50, JS 5). IV Ketamine 0.8–2 mg/kg with propofol 0.8–2.5 mg/kg or dexmedetomidine 0.4–1.2 mcg/kg has also been used for short duration (10 min) dressing change (Canpolat 2012 **Level III-1**).

Nonpharmacological interventions for burn dressing

Nonpharmacological strategies such as distraction, virtual reality (VR), preparation, parental presence and hypnosis may be effective (see also Section 10.7.5). Studies vary substantially in the specifics of interventions and comparison groups and are difficult to blind.

Child life therapy

Child life (previously termed educational play) therapy (preparation, education and distraction delivered by a therapist) for pain and anxiety management vs standard care for initial burn dressing change reduced a combined scaled pain and anxiety score (mean 1.7/20 vs 2.9) and pain scores alone (median 5.3/13 vs 6.0), but not anxiety scores alone (Children's Fear Scale); nor did it improve wound outcomes or reduce need for grafting (Hyland 2015 **Level II**, n=100, JS 3). In a cohort of patients with low procedural pain scores, directed medical play vs standard preparation reduced maximum pain score during burns dressing change (median 2/10 vs 3) (Moore 2015 **Level III-1**, n=21).

Distraction

The use of therapeutic clowning increased compliance with dressing change vs standard care assessed by behavioural response (mean 4.8/15 vs 11.0) (Yildirim 2019 **Level II**, n=50, JS 3).

Child life therapists using computer tablet distraction vs their standard intervention during hydrotherapy for burns dressing changes in 4–12 y olds did not reduce self-reported pain scores, but reduced nurse-reported pain and emotional response during and after the procedure (Burns-Nader 2017 **Level II**, n=30, JS 3).

Multimodal procedural preparation (video shown on screen device: "Bobby got a burn") and multimodal distraction (screen device using games: "touch and find" stories with multisensory visual, auditory, and vibratory feedback: Ditto®) lowered pain scores (child by 20–27%, parent by 29–37% and nursing staff by 16–34%) vs a hand-held video game device or standard distraction (varied use of TV, video games, stories, toys, nursing staff soothing and care giver support) (Miller 2010 **Level II**, n=80, JS 3). Across three procedures, multimodal distraction reduced pain scores, while multimodal procedural preparation, video or standard distraction did not. Ditto™ vs standard distraction (in addition to varying pharmacological agents) did not impact significantly on pain or anxiety ratings during the first three dressing changes (Brown 2014b **Level II**, n=117, JS 3).

Adding animated cartoon watching to PO ibuprofen vs ibuprofen alone was not associated with improved pain scores during burns dressing change (Feng 2018 **Level III-2**, n=54).

A multidisciplinary group of clinicians identified barriers to routine iPad® use for distraction during burns dressing change including competing demands of clinicians, differing views on the relevance of distraction, and lack of experience and confidence with iPad® use (Green 2018 **Level IV**, n=15). The authors suggested that effective use of iPads in this context required training and guidelines for clinicians.

Immersive VR gaming vs standard distraction reduced nurse observer-rated pain scores (mean 2.9/10 vs 4.7) and rescue use of N_2O (15 vs 43%) (Kipping 2012 **Level II**, n=41, JS 3). Augmented reality gaming achieved lower patient pain scores vs basic cognitive therapy intervention (2.9/10 vs 5.4) (Mott 2008 **Level III-1**). When immersive VR games were added to routine analgesia, patient pain scores with burn dressing changes decreased (Das 2005 **Level IV**, n=7).

Other nonpharmacological interventions

Pain scores with burn dressing changes reduced with music ("active alternate engagement") (Klassen 2008 **Level III-2 SR**, 1 RCT [paediatric burn dressing change], n=14; Fratianne 2001 **Level II**, n=24, JS 3) and massage therapy (O'Flaherty 2012 **Level IV**; Hernandez-Reif 2001 **Level IV**). Twice weekly massage for 15–20 min for 5 wk lowered heart and respiratory rate, with a positive response (becoming relaxed or falling asleep in 93%, verbally requesting more in 20%) (O'Flaherty 2012 **Level IV**) and decreased pain and anxiety by 58% vs no change in patients receiving standard care (Parlak Gurol 2010 **Level III-1**).

Hypnosis had no effect on pain and wound healing for burn dressing changes, but reduced preprocedural anxiety on the second of three burns dressing changes (MD -0.8/10; 95%CI -1.5 to -0.1) (Chester 2018 **Level II**, n=62, JS 3).

Nonpharmacological interventions for physiotherapy in burns rehabilitation

Use of PlayStation II EyeToy™ to facilitate body movement vs standard therapy in 5–18 y olds did not increase range of motion gains; as rehabilitation progressed, standard therapy did increase pain scores while EyeToy™ did not (r 0.18 vs 0.05) (Parry 2015 **Level II**, n=17 [31 limbs], JS 1). Xbox Kinect™ plus standard physiotherapy in 5–12 y olds achieved greater improvements in active range of motion between discharge and follow-up vs standard physiotherapy and had higher fun and enjoyment scores; pain outcomes were not reported (Lozano 2018 **Level III-2**, n=66).

In adult and paediatric burn patients having physiotherapy, immersive VR SnowWorld® reduced mean worst pain intensity by 20% (54/100 ± 3 vs 44 ± 4), pain unpleasantness by 26% (41/100 ± 4 vs 30 ± 3), and time spent thinking about pain by 37% (47/100 ± 4 vs 30 ± 3) (Sharar 2007 **Level II**, n=88 [66 children], JS 3). Repeated use of SnowWorld® in addition to pharmacotherapy by children with burns having physiotherapy reduced cognitive, sensory and affective pain scores (by 44, 27 and 32%) with patients experiencing three-fold more fun than when no immersive VR was used, although there was no difference in the maximum range of motion achieved (Schmitt 2011 **Level II**, n=54, JS 3).

Distraction through purposeful activity with play and games vs "exercise by rote" modulated the pain experience and improved range of motion achieved during physiotherapy for hand burns in children (Omar 2012 **Level II**, n=30, JS 2).

10.7.3 | Vaccine injection pain in infants and children

Vaccine injections are the most commonly performed medical procedures worldwide, and concern about pain caused by vaccine injection is a barrier to future vaccine uptake; managing vaccine injection pain therefore has immediate and long term implications for the health and wellbeing of individuals and populations (Taddio 2015a **NR**). There is supportive evidence for various interventions. Most studies focus on assessing the effects of a single intervention in an RCT or quasi-randomised study design, and control groups often include active treatments. Outcomes assessed depend on stage of development and include patient distress (using behavioural pain/distress scales, cry duration and/or physiological variables), by carer, health professional or researcher, and self-reported pain and fear at different time points, typically prior to injection, in the acute phase (usually within 1 min of injection) and recovery phase (usually

1–3 min post injection). Translation of evidence to practice is slow but can be improved with a (telephone-based) educational outreach program (Schechter 2010 **Level IV**), assessment of lay and medical perceptions and practice (Harrison 2014 **Level IV**) and then use of innovative techniques to effect change eg social media (Center for Pediatric Pain Research **NR**). Guidelines for evidence-based recommendations across the lifespan are available (McMurtry 2016 **GL;** Taddio 2015c **GL**; WHO 2015 **GL**). Work is also being done to develop painless modes of vaccine delivery (eg IN, PO, transdermal) (Garg 2018 **NR**).

10.7.3.1 | Procedural modifications

Procedural modifications were assessed in a systematic review with the following findings (Taddio 2015d **Level III-1 SR**, 31 studies, n unspecified):

- IM injection without aspiration vs with aspiration reduces acute distress in infants (18 mth) (SMD -0.82; 95%CI -1.18 to -0.46) (2 studies, n=313);
- Simultaneous vs sequential injections reduces acute distress in infants (<1 y) (SMD -0.56; 95%CI -0.87 to -0.25) (2 studies, n=172);
- Injecting the most painful vaccine last reduces acute distress in infants (≤6 mth) (SMD -0.69; 95%CI -0.98 to -0.40) (2 studies, n=196);
- Vastus lateralis vs deltoid injection reduces acute and recovery phase distress in infants (<1 y) (SMD -0.7; 95%CI -1.0 to -0.4) (1 study, n=185);
- Subsequently, term infants (<4 mth) who received HBV vaccine first vs DTwP vaccine first had lower pain scores (MD -4.13/7; 95%CI -1.9 to -6.4) and HR, and higher oxygen saturation (Kumar 2016 **Level II**, n=130, JS 4).

A wider (23-guage 25 mm vs 25-g 25 mm) needle reduces pain intensity (MBPS: MD 0.70/15; 95%CI 0.39 to 1.01) and cry duration (MD 8s; 95%CI 2.86 s to 13.14) in infants (<6 mth) receiving DTwP vaccines in the thigh; however this effect is probably not clinically relevant, and the generalisability of this result is uncertain (Beirne 2018 **Level I** [Cochrane], 1 RCT: Bharti 2010 **Level II**, n=320, JS 3). Longer needles of 25 mm (23 or 25-g) vs 16 mm (25-g) resulted in both fewer severe (NNT=25) and non-severe (NNT=5-6) reactions (Beirne 2018 **Level I** [Cochrane], 1 RCT: Diggle 2006 **Level II**, n=458, JS 3). Applying pressure has a positive effect in adults and may be of use in children (Schechter 2007 **NR**, 1 negative RCT, 2 positive unpublished RCTs, n unspecified). In an additional RCT, fast injection vs slow injection in infants (2-6 mth) receiving DTaP-IPV-Hib (0.5 mL) reduced mean pain scores (MBPS: 6/15 vs 7.4) but not cry duration or parent-reported pain (Taddio 2016 **Level II**, n=120, JS 3).

Evidence based guidelines strongly recommend not aspirating on vaccine injection and injecting the most painful vaccine last for all children (18 y); weaker recommendations include simultaneous injection for ≤1 y but not 1-3 y olds, and vastus lateralis (rather than deltoid) injection site for ≤11 mth (Taddio 2015c **GL**).

10.7.3.2 | Topical local anaesthesia

Topical local anaesthesia for infants and children (0-12 y) is recommended (Taddio 2015c **GL**). For infants (age unspecified), topical local anaesthesia (EMLA® in 12 of 13 studies) vs control (placebo in 6 of 13 studies) reduced acute distress from vaccine injection (SMD -0.91; 95%CI -1.36 to -0.47) (13 studies, n=1,424), but not for children (4-12 y), although this finding was qualified by a positive result if one study (n=39) at high risk of bias was removed from the meta-analysis (SMD -0.47; 95%CI -0.73 to -0.21) (2 studies, n=230) (Shah 2015 **Level III-1 SR**, 55 studies, n unspecified). Meta-analyses for adolescents (≥12 y) was not possible; two included studies had conflicting results. Despite this, selective use of topical local anaesthesia has been recommended in older

children (Taddio 2015c **GL;** Schechter 2007 **NR**). Topical local anaesthesia vs placebo in infants and children did not affect immune response to vaccines (MMR, DTaP-IPV-Hib HBV, BCG vaccines) as measured by antibody response (4 studies, n=833) (Shah 2015 **Level III-1 SR**, 55 studies, n unspecified).

10.7.3.3 | Sweet solutions

Two systematic reviews (14 study overlap) support efficacy of sweet solutions for vaccination injection in infants <2 y old:

- For 1–12 mth olds, PO sucrose (12–75%) and glucose (30–40%) 1-2 mL vs water, saline or no treatment reduces incidence of cry and crying duration (MD -13.5; 95%CI -16.8 to -10.2) (Kassab 2019 **Level III-1 SR** [Cochrane], 14 studies, n=1,551);
- PO sucrose vs control for <2 y olds was associated with lower acute distress (SMD -0.37; 95%CI -0.67 to -0.06) (18 studies, n=881) and acute and recovery distress (SMD -0.76; 95%CI -1.19 to -0.34) (18 studies, n=2,071); PO sucrose 2 mL was typically given (15 of 18 studies) 2 min prior to injection (15 of 18 studies) and was effective in concentrations of 20-33% (9/18 studies) but not 12% (Shah 2015 **Level III-1 SR**, 55 studies, n unspecified);
- PO glucose 1–2 mL (25–50%) vs control for <1 y olds reduces acute + recovery distress (SMD -0.69; 95%CI -1.03 to -0.35) (6 studies, n=818) (Shah 2015 **Level III-1 SR**, 55 studies, n unspecified);
- Sweet solutions combined with NNS (1 study) or breastfeeding (1 study) in infants <3 mth was not superior to either intervention alone (Shah 2015 **Level III-1 SR**, 55 studies, n unspecified).

In further individual studies not included or subsequent to the above reviews:

- PO glucose 25% 2 mL vs NNS in neonates receiving HBV vaccine reduced pain score (mean 3.3/7 vs 5.6) and crying time (mean 10.9 s vs 33.9), however increased HR (147 vs 137) (Lima 2017 **Level II**, n=78, JS 2);
- Infants (2–4 mth old) who received oral rotavirus vaccine (contains 71.5% sucrose) vs sucrose 24% prior to vaccine injection had no difference in observer-reported pain scores (mean 7.4/15 vs 7.7), parent or clinician reported pain scores, or cry duration (Taddio 2015b **Level II**, n=120, JS 5);
- For 2–6 mth old, high-dose PO sucrose 50–75% (2 mL) was equivalent to water in terms of pain scores and crying time (Curry 2012 **Level II**, n=113, JS 5);
- For older infants (15 mth MMR vaccination) sucrose 30% vs water reduced cry duration (mean 18 s vs 33) (Despriee 2016 **Level II**, n=114, JS 3).

Sweet solutions (sucrose or glucose) are strongly recommended for infants (≤2 y) receiving vaccines, with weaker recommendations to combine with NNS or breastfeeding (Taddio 2015c **GL**). In older children, there is insufficient evidence to support the use of sweet solutions (sucrose) in 1–4 y olds (6 studies, n=520), and no evidence of analgesic effect of sweet solutions (sweetened chewing gum) in school aged children (2 studies, n=111) (Harrison 2015 **Level III-1 SR**, 8 studies, n=808 [n vaccination unspecified]).

10.7.3.4 | Nonpharmacological intervention for vaccine injection

Preparation and education

A systematic review found supportive evidence for the following nonpharmacological interventions (Pillai Riddell 2015b **Level III-1 SR**, 13 studies, n=972 [children] & 53 [nurses] & 197 [expectant parents]):

- Educating nurses administering vaccines improved use of pain management interventions (SMD 0.66; 95%CI 0.47 to 0.85) (1 study: Chan 2013 **Level III-1**, n=53 [459 procedures]);
- Parental presence reduced pre-vaccine injection distress in infants and children (1–7 y) (SMD -0.85; 95%CI -1.35 to -0.35) (3 studies, n=67);
- Parental education *before vaccination day* improved use of interventions pre-vaccination (RR 2.08; 95%CI 1.51 to 2.86) (2 studies, n=300) and reduced acute distress (SMD -0.35; 95%CI -0.57 to -0.13) (3 studies, n=350) in infants ≤2 y old;
- Parental education *on vaccination day* improved use of interventions (SMD 1.02; 95%CI 0.22 to 1.83) (4 studies, n=183), (RR 2.42; 95%CI 1.47 to 3.99) (4 studies, n=239) and reduced periprocedural distress (SMD -0.48; 95%CI -0.82 to -0.15) (4 studies, n=262) in infants and children ≤6 y old.

The effect of information provision has been assessed in further RCTs:

- Information provision to new mothers prior to leaving hospital on vaccine pain management given by factsheet vs control (baby general health information) did not improve knowledge scores or utilisation of pain management interventions 2 mth later (Taddio 2014 **Level II**, n=120, JS 3);
- Post-natal education for parents with a pain pamphlet and/or pain video vs general vaccine information increased the use of pain management interventions (breastfeeding, sucrose, topical local anaesthesia) at infant (≤6 mth) vaccination (pain pamphlet + pain video 63%, pain pamphlet only 61%, general vaccine information 53%) (Taddio 2018 **Level II**, n=2,549, JS 3);
- Excluding toddler (18 mth) pain scores during the regulatory phase of vaccine injection, parental psychological distress (assessed by BSI-18) had no moderating effect on the impact of a parent education video (ABCDs of pain management) when assessing various outcomes (parental soothing behaviours, parental worry, infant (6 mth) and toddler reactivity and regulatory phase pain scores) (Gennis 2018 **Level II**, n=128, JS 5);
- For parents of older children (4–6y), automated parent-training via a 10 min interactive computer program + distraction, vs distraction only vs no treatment did not reduce child distress or pain. However, it did improve parental knowledge, parents' behaviours during vaccination, and children's engagement in distraction and deep breathing during vaccination (Cohen 2015 **Level II**, n=90, JS 3).

Parents who were educated on pain management strategies for an RCT most commonly used strategies such as acting calm, holding the child and distraction, whilst strategies such as PO sucrose, topical local anaesthetic cream and pacifier use were uncommon; reasons cited for this included parents thinking these strategies were unnecessary, forgot to use strategy, or they were not easily accessible at the vaccine clinic (McNair 2017 **Level IV**, n=130).

In a review of YouTube videos of children receiving vaccination injections, 73% of infants (<12 mth) received at least one pain management strategy during injection, with distraction (66%) the most common strategy; no videos showed breastfeeding or the use of a sweet solution (Harrison 2014 **Level IV SR**, n=142 [videos]).

Feeding interventions

Two systematic reviews found supportive evidence for breastfeeding in infants <12 mth old (Shah 2015 **Level III-1 SR**, 55 studies, n unspecified) and beyond the neonatal period (Harrison 2016 **Level III-1 SR** [Cochrane], 10 studies, n=1,066) (6 study overlap):

- For infants <12 mth, breastfeeding during vaccination injection vs control reduces acute phase distress (SMD -1.78; 95%CI -2.35 to -1.22) (8 studies, n=792), and acute and recovery phase distress (SMD -1.89; 95%CI -3.19 to -0.59) (n=424) (Shah 2015 **Level III-1 SR**, 55 studies, n unspecified);

- For infants <12 mth, breastfeeding before vaccination injection (if not used during) vs control reduces acute phase distress (SMD -1.43; 95%CI -2.14 to -0.72) (2 studies, n=100) and acute and recovery phase distress (SMD -1.47; 95%CI -2.05 to -0.90) (Shah 2015 **Level III-1 SR**, 55 studies, n unspecified);
- Beyond the neonatal period (mostly 1–6 mth old), breastfeeding vs water or no treatment reduces cry time (MD -38 s; 95%CI -50 to -26) (6 studies, n=547), and pain scores (SMD -1.7; 95%CI -2.2 to -1.3) (5 studies, n=310) but not HR (2 studies, n=186) (Harrison 2016 **Level III-1 SR** [Cochrane], 10 studies, n=1,066);
- Additionally, there was supportive evidence for breastfeeding reducing cry time and pain scores vs massage and cuddling, PO glucose 25%, topical local anaesthesia (EMLA®) and vapocoolant spray (1 study each) (Harrison 2016 **Level III-1 SR** [Cochrane], 10 studies, n=1,066).

Subsequent RCTs continue to support a beneficial effect of breastfeeding (Dar 2019 **Level II**, n=60, JS 3; Gad 2019 **Level II**, n=120, JS 2; Fallah 2017 **Level II**, n=120, JS 3; Hashemi 2016 **Level II**, n=131, JS 2). Additionally, formula feeding of infants (4–10 wk) during vaccine injection vs no treatment reduced cry duration (MD -32.9 s; 95%CI -58.0 to -7.8) and recovery phase pain scores (MD -3.78/7; 95%CI -2.52 to -5.05) (Bos-Veneman 2018 **Level II**, n=48, JS 2).

Physical interventions

Various physical interventions have been assessed in a systematic review (Taddio 2015d **Level III-1 SR**, 31 studies, n unspecified):

- In neonates, kangaroo care vs lying supine reduces acute and recovery phase distress (SMD -0.65; 95%CI -1.05 to -0.25 and SMD -0.89; 95%CI -1.26 to -0.52 respectively) (3 studies, n=736);
- Excluding one high risk bias study, for infants (6 wk–6 mth) holding by parent during vaccination vs lying supine and not being held reduces acute distress (SMD -1.25; 95%CI -2.05 to -0.46) (2 studies, n=181);
- For infants (0–4 mth) holding by parent after vaccination (if not held during) reduced acute and recovery distress (SMD -0.65; 95%CI -1.08 to -0.22) (2 studies, n=417);
- For infants (0–4 mth), NNS reduces acute distress (SMD -1.88; 95%CI -2.57 to -1.18) (2 studies, n=186);
- Manual tactile stimulation (pressure, rubbing/stroking, tapping) vs no treatment does not reduce acute distress in infants (3 studies, n=301), or self-reported pain in older children and adults (3 studies, n=893);
- For children (4–6 y), sitting upright vs lying supine reduces fear (SMD -0.39; 95%CI -0.77 to -0.01) (1 RCT: Lacey 2008 **Level II**, n=107, JS 2) but not pain;
- For children (4–7 y) vibrating device with cold reduces pain (SMD -1.23; 95%CI -1.58 to -0.87) (2 studies, n=145) but not fear;
- For vaccination for older children (≥7 y) and adults, a muscle tension intervention reduces risk of fainting during injection (RR 0.11; 95%CI 0.02 to 0.79) (2 studies, n=38).

Application of cold and vibration (using the Buzzy® device) vs no treatment reduced self-reported pain scores in paediatric patients receiving vaccination (3–18y) (SMD -0.76; 95%CI -1.09 to -0.43) (2 RCTs, n=144) (Ballard 2019 **Level I** [PRISMA], 9 RCTs, n=1,138) (1 RCT overlap), whilst vapocoolant sprays were not effective in reducing pain for infants (3 mth old) (1 study, n=74) or older children (3–17 y) (4 studies, n=228) (Shah 2015 **Level III-1 SR**, 6 studies [vapocoolant in children], n unspecified).

Further studies to the above reviews have been published on physical interventions:

- Facilitated tucking vs holding in supine position in term neonates receiving HBV vaccine reduces pain score (mean 2.83/7 vs 6.47) but not HR, RR or oxygen saturation (Kucukoglu 2015 **Level II**, n=60, JS 2);
- White noise vs no intervention for premature neonates (born at 28–32 wk) receiving their 2nd dose of HBV vaccine reduced pain scores (mean 8.14/21 vs 14.35) and peak HR (mean 154/min vs 166) and RR (mean 50/min vs 61) (Kucukoglu 2016 **Level III-1**, n=75**);**
- ShotBlocker™/swaddling vs swaddling alone for healthy term neonates receiving HBV vaccine reduces pain scores during (mean 1.64/7 vs 2.96) and 3 min after (mean 0.74/7 vs 1.42) injection, but not HR or RR (Caglar 2017 **Level II**, n=100, JS 3);
- Maternal kangaroo care vs swaddling for infants (ex-term and preterm) reduces pain scores at 1 min (median 2.5/7 vs 5) and 5 min (0/7 vs 4) post vaccine injection, as well as cry duration (median 42.5 s vs 135) (Pandita 2018 **Level II**, n=61, JS 3);
- Holding infants (6–12 wk post-natal age) in the supine vs upright position reduced crying (52 vs 70%), irritability (43 vs 58%) and distressed facial expression (46 vs 60%) 30 s after vaccine injection (Yin 2017 **Level III-2**, n=282);
- There was no difference in pain scores, and cry duration between infants (4–6 mth) receiving 10 s manual pressure, rapid injection without aspiration, or both; all study groups were superior to standard care (GoI 2017 **Level II**, n=128, JS 3);
- In older children (4–12 y) ShotBlocker™ vs placebo and typical care was not found to be more effective in reducing self-reported or observer-reported pain scores, distress behaviours (crying, screaming or requiring adult restraint) or observer-reported distress (Cobb 2009 **Level II**, n=89, JS 2).

Physical interventions that are strongly recommended include kangaroo care for ≤1 mth old, breastfeeding during vaccination injection for ≤2y old, holding for ≤3 y old, and sitting up for 3–18y olds; weaker recommendations include to use NNS during vaccination injection for ≤2 y olds, vibrating device with cold for 3–18 y olds, and muscle tension for 7–18 y olds, and recommend against manual tactile stimulation and warming the vaccine for all ages (Taddio 2015c **GL**).

Psychological interventions

Parental responses during injection such as excessive reassurance, criticism or apology increase distress, whereas humour and distraction tend to decrease distress (Schechter 2007 **NR**, 4 studies, n unspecified). Parental stress promoting behaviours had a stronger relationship than soothing behaviours and emotional availability with infant reactivity (immediate response) and regulation (non-immediate response), suggesting that teaching parents what not to do may be at least as important as teaching parents what to do (Badovinac 2018 **Level IV**, n=220). Furthermore, care-giver behaviour and poorer pain regulation at 12 mth vaccination predicted forward to pre-school vaccination coping, and care-giver behaviour also showed relationships to broader child cognitive behavioural abilities (Campbell 2018 **Level IV**, n=760). Healthcare staff can also influence a child's vaccination experience, and should purposefully use coping promoting strategies (Pedro 2016 **Level IV**, n=220 [4–7y]).

Three systematic reviews have assessed psychological interventions for vaccine injection:

- For 0–3 y olds, directed video distraction vs control reduces acute and recovery phase distress (SMD -0.68; 95%CI -1.04 to -0.32) (4 studies, n=126) and pre-vaccination distress (SMD -0.49; 95%CI -7.6 to -0.22) (4 studies, n=216) (Pillai Riddell 2015a **Level III-1 SR**, 10 studies, n=1,259);

- Directed toy distraction vs control for 0–3 y olds reduces peri-vaccination distress (SMD -0.47; 95%CI -0.91 to -0.02) (1 study, n=81), whilst non-directed toy distraction vs control does not reduce acute distress as the confidence interval includes zero (SMD -0.93; 95%CI -1.86 to 0.00) (4 studies, n=290) (Pillai Riddell 2015a **Level III-1 SR**, 10 studies, n=1,259);
- Verbal distraction vs control reduces distress in children (3–7 y) (SMD -1.22; 95%CI -1.87 to -0.58) (2 studies, n=46) but not pain (Birnie 2015 **Level III-1 SR**, 22 studies, n 1,717);
- Breathing with a toy reduces pain in children (3–9 y) (SMD -0.49; 95%CI -0.85 to -0.13) (6 studies, n=368) but not fear (Birnie 2015 **Level III-1 SR**, 22 studies, n=1,717);
- Video distraction vs control reduces distress in children (2–12 y) (SMD -1.22; 95%CI -1.87 to -0.58) (5 studies, n=328) but not pain (Birnie 2015 **Level III-1 SR**, 22 studies, n=1,717);
- Music distraction vs control reduces pain in children (3–7 y) (SMD -0.45; 95%CI -0.71 to -0.18) (4 studies, n=417) but not in adolescents (1 study n=118) (Birnie 2015 **Level III-1 SR**, 22 studies, n=1,717);
- There is no benefit for breathing techniques without a toy for pain or fear in children (3–7 y olds) (2 studies, n=136), coughing with injection for pain in 4–5 y olds (1 study n=136), false suggestion for pain or distress in 4–7 y olds (2 studies, n=240) or repeated reassurance for pain, distress or fear in 3–7y olds (2 studies, n=82) (Birnie 2015 **Level III-1 SR**, 22 studies, n=1,717);
- Psychological interventions for needle-related procedural pain in older children and adolescents (2–19 y) are effective (11 unique RCTs studying immunisation or injection: distraction 7 RCTs, combined CBT 6 RCTs, suggestion 1 RCT), but a sub-group analysis on vaccine injection was not done (Birnie 2018 **Level I** [Cochrane], 59 RCTs, n=5,550) (0 & 10 RCT overlap).

Further studies published on psychological interventions for vaccine injection pain found:

- Parent participation to deliver distraction during vaccination in 4–6 y olds vs medical assistant delivered distraction did not change self-reported pain or satisfaction scores, parent-reported pain or satisfaction scores, or observer-reported pain scores (Franck 2015 **Level II**, n=76, JS 3);
- Music therapy for children (4–6 y) vs no treatment did not reduce parent ratings of child's pain but did reduce child distress behaviours during and after vaccination and parent distress promoting behaviours before, during and after vaccination (Yinger 2016 **Level II**, n=58, JS 2);
- Relaxation therapy and guided imagery had similar effects on cortisol reactivity, self-reported stress, pain intensity and pain unpleasantness in females (11–12 y) receiving the HPV vaccine (Nilsson 2015 **Level III-2**, n=37).

There is no data for needle phobia interventions alone; *in vivo* exposure based therapy for children (7–17y) with other phobias reduced specific fear (SMD -1.71; 95%CI -2.72 to -0.70) (4 studies, n=235), whilst imagined exposure based therapy in children (7–17y) reduced specific fear post-treatment (SMD -0.88; 95%CI -1.7 to -0.05) (2 studies, n=41) and at 3 mth (SMD -0.89; 95%CI -1.73 to -0.04) (1 study, n=24) (McMurtry 2015 **Level III-1 SR**, 11 studies, n=620).

The following psychological interventions are recommended: verbal signal of impending procedure, suggestion and reassurance for all children (0–17 y); directed video distraction, directed or non-directed toy distraction for ≤3 y; verbal, video or music distraction and breathing with a toy for 3–12 y olds; and recommend against a planned cough during injection for 3–17 y olds (Taddio 2015c **GL**). For patients with high levels of needle fear *in vivo* exposure-based therapy, and if this is not used, non-*in vivo* (imagined) exposure-based therapy is strongly recommended for children 7–17 y old (McMurtry 2016 **GL**).

Combination intervention

Various combinations of interventions have been studied in vaccine injection pain. Further reviews and studies are summarised here:

- In infants <3 mth, topical anaesthesia with breastfeeding vs topical anaesthesia alone reduced acute and recovery phase distress (SMD -0.83; 95%CI -1.36 to -0.30) (Gupta 2013 **Level II**, n=90, JS 3), whilst there was no benefit for sweet tasting solutions with NNS vs either alone (1 study), or breastfeeding and sweet tasting solutions vs either alone (1 study) (Shah 2015 **Level III-1 SR**, 55 studies, n unspecified);
- PO sucrose, oral tactile stimulation (with a pacifier or a bottle) and parental holding reduced the duration of crying in infants (2 mth) receiving multiple immunisations (Reis 2003 **Level II**, n=116, JS 5);
- EMLA® combined with N_2O 50% was superior to either alone for observed pain in infants (<24 mth) during and post vaccination injection (Carbajal 2008 **Level II**, n=55, JS 5);
- EMLA® and breastfeeding was similarly effective to vapocoolant spray and breastfeeding, and both combinations were superior to breastfeeding alone in terms of cry duration (36 s vs 33 s vs 68 s) and pain intensity at 1 min (mean 1.4/6 vs 1.8 vs 3.2) and 3 min (mean 0.9/6 vs 0.6 vs 2.3) post vaccine injection (Gupta 2017 **Level II**, n=90, JS 3);
- Combination of video/ sucrose/topical lidocaine administered to infants at each of their vaccinations up to 12 mth old reduced pain scores during vaccine injection vs video/sucrose, video alone and placebo (mean 6.3/15 vs 6.7 vs 6. 7 vs 6.7 respectively) suggesting benefit from this combination of interventions was derived from topical lidocaine only (Taddio 2017b **Level II**, n=352, JS 5);
- The same four groups all received video/sucrose/topical lidocaine for vaccinations at 15 mth old, and there was no difference in pain scores across groups before, during and after vaccination injection, suggesting consistency in vaccine pain management interventions in the first year of life does not confer benefit at 15 mth (Taddio 2017a **Level II**, n=352, JS 5).

10.7.4 | Procedural pain management in the emergency department

Clinical guidelines from various bodies have been developed for procedural pain management in the ED. The American College of Emergency Physicians has published a guideline for unscheduled procedural sedation in children and adults; it focusses on safety of delivering sedation in this context rather than on individual drug efficacy, and is applicable to the use of various sedatives (Green 2019b **GL**).

10.7.4.1 | Laceration repair

All oral agents as specified in Sections 10.4.1 to 10.4.3 have been used in children having laceration repair, usually to supplement topical or injected local anaesthetic. IN fentanyl use is not yet specifically reported for laceration repair.

Topical local anaesthesia

Topical local anaesthetic application for wound closure can avoid the distress caused by intradermal injection; importantly cocaine-containing preparations are no longer recommended (Tayeb 2017 **Level III-1 SR** [Cochrane], 25 RCTs [2 paediatric, 19 mixed paediatric/adult], n=3,278 [paediatric unspecified]). Numerous topical local anaesthetic agents have been assessed. Only a descriptive analysis is possible as studies have high risk of bias, mostly involve only single comparisons and only 15 of 25 RCTs report pain scores. The most widely used topical agent applied to paediatric wounds is lidocaine-adrenaline-amethocaine (tetracaine) preparation (abbreviated to ALA in Australia and LAT or LET in the USA). This combination appears as effective as tetracaine-

adrenaline-cocaine (3 RCTs, n=341), buffered lidocaine-adrenaline infiltration (1 RCT, n≈66), infiltrated lidocaine (1 RCT, n=40) and as a gel or solution with no other comparator (1 RCT, n=194).

Topical ALA solution applied to wounds at triage reduced treatment time by 31 min vs controls (Priestley 2003 **Level II**, n=161, JS 4) and pain associated with subsequent intradermal injection of lidocaine (Singer 2000 **Level II**, n=43, JS 5).

Local anaesthesia infiltration

In mainly adult patients, pain on injection of local anaesthesia is reduced by warming (to 37–43°C) (Hogan 2011 **Level I** [PRISMA], 1 RCT [paediatric], n=44) or buffering with sodium bicarbonate (increasing the pH of lidocaine to ≥7.35) (Cepeda 2010 **Level I** [Cochrane], 2 RCTs [mixed age], n=165 and 1 RCT [paediatric], n=7) (see also Section 4.4.2).

Alternatives to suturing: tissue adhesives and hair apposition

Tissue adhesives vs suturing for simple lacerations produce similar cosmetic results (9 RCTs, n=889), and less parent-reported pain (WMD -13.4/100; 95%CI -20 to -6.9) (5 RCTs, n=434) with shorter procedure time (WMD -4.7 min; 95%CI -7.2 to -2.1) (6 RCTs, n=584) and may be more acceptable to children (Farion 2003 **Level I** [Cochrane], 13 RCTs [paediatric], n unspecified). The risk of dehiscence is increased slightly with tissue adhesive vs standard wound care (NNH 40; 95%CI 20 to 1,168) but it is offered to parents as a preferred initial intervention. Hair apposition was as effective as suturing for simple scalp lacerations (Hock 2002 **Level II**, n=189, JS 3), and can be performed effectively by doctors and nurses (Ong 2008 **Level II**, n=164, JS 3).

Children who received topical local anaesthetic (ALA) prior to tissue adhesive application were more likely to have a pain-free procedure vs placebo by self or observer report (RR 0.54; 95%CI 0.37 to 0.80) (Harman 2013 **Level II**, n=221, JS 5).

Midazolam

Midazolam is a useful adjunct in the procedural sedation pharmacotherapy armamentarium for laceration repair in younger or noncooperative children. IN administration stings and the PO route is generally preferred, although efficacy may be more variable (influenced by first-pass metabolism and duration of fasting). Compared to PO route or aerosolised buccal delivery prior to laceration repair in young children (0.5–7 y), aerosolised delivery IN had faster onset and achieved adequate sedation, at the expense of nasal irritation and being less readily accepted than the PO route (Klein 2011 **Level II**, n=169, JS 5). PO midazolam 0.7 mg/kg vs PO ketamine 5 mg/kg for children (1–10 y) having laceration repair resulted in similar parent-reported pain scores (3.7/10 vs 5.1) (Rubinstein 2016 **Level II**, n=68, JS 5).

Nitrous oxide (N_2O) and ketamine alone or in comparison

Inhaled N_2O 50–70% (with oxygen) is commonly used for laceration repair and minor surgery in children and reduces pain and anxiety, with large case series affirming the utility and safety of the technique for this and other indications (Tobias 2013a **Level I SR**, 1 RCT [laceration], n=30; Pedersen 2013 **Level IV SR** [PRISMA], 1 RCT [laceration], n=204 & multiple studies [laceration], n unspecified; Heinrich 2015 **Level IV**, n=210; Babl 2010 **Level IV**, n=504). Ketamine is also commonly used as dissociative sedation and analgesia for laceration repair. Common doses used as sole agent in the ED are 0.5–1 mg/kg IV and 3–5 mg/kg IM; coadministration of atropine or benzodiazepine is no longer recommended (Green 2011 **GL**). PO and IN routes are also used (see below).

For facial laceration repair in the ED by a plastic surgeon, in children and adolescents (1–16 y; 60% unfasted), N_2O 50% with lidocaine infiltration vs lidocaine infiltration alone reduced pain scores during lidocaine infiltration (mean 1.9 /10 vs 9.7) and suturing (2/10 vs 8.8); in controls forceful restraint was applied in 100% vs patients receiving N_2O where only 15% required mild restraint (Bar-Meir 2006 **Level III-2**, n=60). Minor adverse effects (mostly nausea) occurred in 29%

of patients receiving N_2O. N_2O 50–70% and IV ketamine 2 mg/kg had similar analgesic efficacy, with deeper sedation and longer median duration by 13.5 min in those ketamine treated (Lee 2012 **Level II**, n=32, JS 3). The addition of PO ketamine 5 mg/kg to PO midazolam 0.5 mg/kg vs midazolam alone for laceration repair, resulted in similar pain scores during local anaesthetic injection (parent and researcher: 4/10), with increased sedation and time to discharge for the combination group (MD 65 min; 95%CI 22 to 107) (Barkan 2014 **Level II**, n=60, JS 5). IN Ketamine 9 mg/kg achieved adequate sedation for laceration repair in young children, whilst doses of 3mg/kg and 6 mg/kg did not (Tsze 2012 **Level II**, n=12, JS 2).

The safety of ketamine has been documented in a large paediatric ED series (n=8,282) with low rates of emergence reactions (clinically important 1.4 vs "any" 7.6%), vomiting 8.4% and respiratory events 3.9% (Green 2009c **Level IV**). Variables independently associated with increased risk of respiratory effects included age <2 y (OR 2.00; 95%CI 1.47 to 2.72) and ≥13 y (OR 2.72; 95%CI 1.97 to 3.75), high IV dosing (initial dose ≥2.5 mg/kg or total dose ≥5.0 mg/kg) (OR 2.18; 95%CI 1.59 to 2.99) and co-administered anticholinergic (OR 1.82; 95%CI 1.36 to 2.42) or benzodiazepine (OR 1.39; 95%CI 1.08 to 1.78). Oropharyngeal procedures, ASA class ≥3 and use of IV vs IM route were not associated with increased risk.

10.7.4.2 | Closed fracture reduction

Closed fracture reduction is a major procedure, which may be performed in EDs with a variety of analgesic techniques including N_2O (Pedersen 2013 **Level IV SR** [PRISMA], 4 studies, total n=45,120), ketamine IV or IM (Babl 2010 **Level IV**, n=2,002 [1,622 N_2O & 340 ketamine]), opioids (IV morphine, IN or IV fentanyl and IV alfentanil), propofol or combinations of these agents (Migita 2006 **Level I SR**, 5 RCTs, n=526; Hoeffe 2017 **Level IV,** n=90; Schofield 2013 **Level IV**). The majority of studies assess procedural pain scores and not postprocedural impact. Paediatric guidelines for procedural sedation have been produced by the American College of Emergency Physicians (Green 2019b **GL).** Different regimens may result in no or mild sedation through to heavy sedation or even anaesthesia. Comparison of specific regimens studied are summarised below:

Ketamine

- With PO oxycodone 0.2 mg/kg pre-treatment, IV ketamine 1 mg/kg with IV midazolam 0.1 mg/kg vs N_2O 50% and haematoma block (1% buffered lidocaine 2.5 mg/kg) had similar parental and child pain scores, but later readiness for discharge (mean 83 min vs 16); minor adverse effects were frequent in both groups (vomiting 24% vs 26; headache 11% vs 13) with the ketamine/midazolam group reporting more ataxia (24% vs 9) nightmares (20% vs 7) and hallucinations (29% vs 4) (Luhmann 2006 **Level II**, n=102, JS 3);
- IV Ketamine/midazolam vs IV etomidate/fentanyl achieved lower observer pain scores, similar amnesia and greater parental satisfaction, despite longer recovery time (Lee-Jayaram 2010 **Level II**, n=23, JS 5);
- In children (3–14 y) receiving IV midazolam 0.2 mg/kg (max 10 mg), IV morphine 0.1 mg/kg and 0.05 mg/kg prn (max 5 mg) vs IV ketamine 2mg/kg (max 70 mg) resulted in similar pain scores following the procedure (median 2/10 vs 2); sedation scores were not reported (Barcelos 2015 **Level II**, n=25, JS 3);
- An ED dose finding study for IV ketamine for procedural sedation/anaesthesia in 3–18 y olds (71% fracture/dislocation reduction) suggested similar median sedation depth (Ramsay sedation scores 5.5–6/6) and duration (23–24.5 min) with an initial dose of 1.5 or 2 mg/kg vs 1 mg/kg, but greater need for redosing with 1 mg/kg (16% vs 3% with 1.5mg/kg and 5% with 2 mg/kg) (Kannikeswaran 2016 **Level II**, n=125, JS 5);

- In another dose finding sedation study, the ED_{95} dose for bolus IV ketamine for closed forearm fracture reduction was estimated at 0.7 mg/kg for 2–5 y olds and 6–11 y olds, with 0.8 mg/kg for 12–17 y olds (Chinta 2015 **Level IV**, n=60);
- Following ED intervention for fracture reduction, laceration repair and other painful procedures (where procedural pain scores were not assessed), ketamine mostly single agent (or combined with midazolam) vs fentanyl/midazolam had similar vomiting rates (20% vs 14), low incidence of emergence reaction (1% vs 0) and lower incidence of post-hospital behavioural disturbance (McQueen 2009 **Level III-3**, n=554 [294 fracture reductions]).

Intranasal and inhaled analgesia

- IN fentanyl 1.5 mcg/kg added to N_2O 70% did not improve analgesia over N_2O alone in children (2–16 y) with low procedural pain scores and short procedure duration (mean 3.62 min; 84% fracture manipulation) (Seiler 2019 **Level II**, n=402, JS 5);
- IN diamorphine 0.1 mg/kg with N_2O 50% has been used successfully for closed fracture reduction in the ED (Kurien 2016 **Level IV**, n=100);
- Inhaled N_2O for closed fracture reduction in children and adolescents is safe but its efficacy is reported to be mixed (Pedersen 2013 **Level IV SR** [PRISMA], 6 studies, n=54,127 [closed fracture reduction unspecified]; Babl 2010, n=2,002 [393 closed fracture reduction]; Hennrikus 1995 **Level IV**, n=100; Hennrikus 1994 **Level IV**, n=54);
- Methoxyflurane via Penthrox® inhaler in children (5–13 y) requiring mostly upper extremity fracture reduction was an effective analgesic with rapid onset (<30 s), but variable effectiveness for procedural sedation; minor adverse events (eg cough, agitation, blurry vision) occurred in 5 of 14 patients (Babl 2007 **Level IV**, n=14);
- Dexmedetomidine IN or IV use is not yet reported for this indication (McMorrow 2012 **NR**).

For children and adolescents (≤21 y old) with a forearm or lower extremity fracture, the use of procedural sedation (23% vs 18) by paediatric and general ED physicians was similar. Paediatric ED physicians were more likely to use fentanyl (62% vs 19), the IV route (91% vs 67), and a combination of agents (90% vs 44) (Cimpello 2004 **Level III-2**, n=718). Patient age and characteristics of a displaced fracture (but not ethnicity: African-American or Caucasian) were predictors of use of conscious sedation (midazolam and fentanyl, or ketamine) for closed forearm fracture reduction in children and adolescents (≤18 y) presenting to a paediatric ED (VanderBeek 2006 **Level IV**, n=503).

Opioid/propofol and ketamine/propofol combinations

Opioid/propofol or ketamine/propofol (ketofol) combinations for deeper procedural sedation are increasingly used in paediatric EDs. In various paediatric procedural sedation settings, adverse effects of propofol use (of 0.5–2mg/kg and higher) have been reported at rates of: cardiovascular (hypotension 15.4% and bradycardia 0.1%); respiratory (desaturation 9.3%, apnoea 1.9%, assisted ventilation 1.4%, unplanned intubation 0.02%, laryngospasm 0.1%); and post-procedure vomiting (0.14%) (Lamond 2010 **Level IV SR**, 60 studies, n=17,066). Of the seven included ED studies, six were for fracture reduction (2 RCTs, n=204; 4 case series, n≈610) with coadministration of opioid (morphine or fentanyl) and supplemental oxygen. Desaturation rates varied from 5–31%, with lower rates of airway intervention (such as jaw manoeuvres and bag-mask assistance) and no intubations. Ketofol has been compared to propofol only (with and without opioid pre-treatment) for fracture reduction with focus upon satisfaction with procedural sedation, and respiratory (9–28% depending how defined) and other adverse effects (Weisz 2017 **Level II**, n=183, JS 3; Shah 2011a **Level II**, n=140, JS 5; David 2011 **Level II**, n=220, JS 5). Pharmacokinetic modelling has been done for ketofol with dosing recommendations for longer duration procedures (Coulter 2014 **PK**).

Regional anaesthesia/analgesia

Haematoma blocks and Bier's block (or IV regional anaesthesia/block [IVRA/IVRB]) are used for closed forearm fracture reduction in the ED. A survey of orthopaedic surgeons and paediatric ED physicians found 78% of respondents had used a local anaesthetic technique for closed reduction of a forearm fracture but only 17% reported frequent use; of respondents who had used local anaesthetic techniques, haematoma blocks (93%) and Bier's blocks (20%) were the most common (Constantine 2007 **Level IV**, n=85). A subsequent survey of paediatric ED physicians found that 35% of respondents had used a Bier's block and 4% a haematoma block (Schofield 2013 **Level IV**, n=111). Local anaesthetic IVRB is highly effective and safe (Migita 2006 **Level I SR**, 3 RCTs [IVRB], n=560; Murat 2003 **Level III-3 SR**, 5 studies, n=1,178; Chua 2017a **Level IV**, n=1,788) but data on optimal dosing, safety and comparisons of efficacy are limited, and serious complications may arise with faulty equipment, inappropriate local anaesthetic use, or inadequate monitoring and training of staff.

Trans-arterial axillary brachial plexus block (1% lidocaine with adrenaline 0.7 mL/kg) achieved similar procedural pain scores to ketamine/midazolam deep sedation in children (>8 y) having closed reduction of a forearm fracture in the ED (mean 6.4 /13 vs 7.5); 11/20 blocks were assessed as incomplete (residual motor block) (Kriwanek 2006 **Level II**, n=43, JS 2).

Ultrasound (US)-guided ulnar, radial, and median nerve blocks in the forearm for hand injuries managed procedurally in the ED (fractures, dislocations, crush injuries, complex lacerations) have been used successfully in children and adolescents (7–17 y old) (Mori 2019 **Level IV**, n=6; Frenkel 2015 **Level IV**, n=10). US-guided intra-articular lidocaine injection to the glenohumeral joint has been used successfully for analgesia to reduce an anterior shoulder dislocation in a 17 y old male (Breslin 2014 **CR**).

10.7.4.3 | Psychological interventions

In addition to pharmacological interventions, procedural planning for children in the ED should include age-appropriate psychological interventions, such as distraction techniques (see below Section 10.7.5).

10.7.5 | Nonpharmacological strategies in children and adolescents

For further information on nonpharmacological strategies for specific procedures, see sections 10.7.1–4 above.

Distraction

Distraction can be passive (eg listening to music, being read a book, watching a screen, kaleidoscope, distraction boxes) or active (eg guided imagery, handheld video games, non-immersive or immersive virtual reality). Distraction reduces self-reported needle-related procedure pain (SMD -0.56; 95% CI -0.78 to -0.33) (30 RCTs, n=2,802), and self-reported needle-related distress (SMD -0.82; 95%CI -1.45 to -0.18) (4 RCTs, n=426) (Birnie 2018 **Level I** [Cochrane], 59 RCTs, n=5,550). Further reviews including lower level evidence generally support distraction techniques for various needle procedures, laceration repair and bone marrow aspiration (Bukola 2017 **Level III-I SR**, 7 studies, n=312; Wente 2013 **Level III-2 SR**, 10 studies, n=1,164; Koller 2012 **Level III-2 SR**, 37 studies, n=1,575; Landier 2010 **Level III-2 SR**, 26 studies, n=1,675).

A systematic review assessed immersive virtual reality for ≤21 y olds undergoing medical procedures (Eijlers 2019 **Level III-1 SR** [PRISMA], 17 studies, n=859). It found immersive VR vs usual care reduced:

- Self-reported pain scores (SMD -1.30; 95%CI -0.68 to -1.91) (14 studies);
- Self-reported anxiety (SMD -1.32; 95%CI -0.21 to -2.44) (7 studies);

- Carer (SMD -0.47; 95%CI -0.22 to -0.72) (4 studies), and professional-reported pain scores (SMD -0.82; 95%CI -0.48 to -1.15) (3 studies);
- Self-reported pain scores in burns care (SMD -0.66; 95%CI -0.40 to -0.91) (5 studies) and venous access (SMD -0.32; 95%CI -0.01 to -0.62) (2 studies) but not oncological care (3 studies).

Subsequently, VR vs standard of care reduced pain scores in 4–11 y having venipuncture in the ED (Chan 2019a **Level II**, n=123, JS 3) and pathology (Chan 2019a **Level II**, n=131, JS 3), whilst, immersive VR was not superior to nurse led distraction in 7–16 y olds for venous cannulation but had higher satisfaction (100% vs 85) (Walther-Larsen 2019 **Level II**, n=64, JS 3).

A retrospective series analysed three comfort measures (distraction, positioning and medication) and used number of attempts to complete a procedure (IV cannulation, gastrointestinal tube placement, incisional procedures, urinary catheterisation) as a measure of efficacy in minimising distress (Dastgheyb 2018 **Level IV**, n=74,276). Higher success rates occurred with distraction in younger children, particularly <1 y, whilst in older children (>4 y) higher success rates occurred with positioning; however, differences between comfort measures for each procedure and age group were generally small.

Hypnosis

Hypnosis requires the skills of a trained health professional and time for the child to learn the technique. Hypnosis vs control for needle-related procedural pain reduces pain scores (SMD -1.4; 95%CI -2.32 to -0.48) (5 RCTs, n=176), distress scores (SMD-2.53; 95%CI -3.93 to -1.12) (5 RCTs, n=176) and behavioural measures of distress (SMD -1.15; 95%CI -1.76 to -0.53) (6 RCTs, n=193) (Birnie 2018 **Level I** [Cochrane], 59 RCTs, n=5,550). For children undergoing cancer-related procedures, hypnosis is an effective pain-control technique (Tome-Pires 2012 **Level I SR**, 10 RCTs [cancer procedural pain], n=394) (5 RCT overlap). A subsequent review of oncology patients found hypnosis reduced pain scores vs usual treatment (pooled effect size Cohen's d 2.16; 95%CI 1.41 to 2.92) and controls having attention focus (Cohen's d 2.24; 95%CI 1.66 to 2.82) but not vs active control groups (eg music, play, audiobooks) (Nunns 2018 **Level I** [PRISMA], 15 RCTs, n=585 [8 hypnosis, n=337]) (6 RCT overlap with above reviews).

Cognitive behavioral therapies (CBT)

Combined CBT (defined as combining at least one cognitive strategy with at least one behavioral strategy) may include parent coaching, parent positioning, child distraction and suggestion (Birnie 2018 **Level I** [Cochrane], 59 RCTs, n=5,550):

- Reduces observer-reported pain (SMD -0.52; 95%CI -0.73 to -0.30) (4 RCTs, n=385) and behavioral distress (SMD -0.40; 95%CI 0.67 to -0.14) (11 RCTs, n=1,105);
- Does not reduce self-reported pain (14 RCTs, n=1,359), self-reported distress (6 RCTs, n=234) observer-reported distress (6 RCTs, n=765) or behavioral measures of pain (2 RCTs, n=95);
- The same review found breathing interventions reduced self-reported pain (SMD -1.04; 95%CI -1.86 to -0.22) (4 RCTs, n=298), however preparation and information (4 RCTs, n=313), and suggestion (3 RCTs, n=218) showed no effect for any pain or distress outcome. No conclusion could be made on memory alteration (1 RCT, n=15).

A second systematic review further explored memory reframing interventions in children (3–18 y) (Noel 2018 **Level III-1 SR**, 3 studies, n=158). It found a memory reframing intervention vs control on the day of a subsequent needle procedure did improve memory of fear (SMD -0.60; 95%CI -1.05 to -0.15) but did not improve memory of pain, anticipatory fear or acute fear (2 studies, n=50 [oncology LP] & 45 [dental injection]); memory reframing intervention following a needle procedure (immediately and at follow-up) did improve memory of pain (SMD -0.53;

95%CI -1.03 to -0.02) (1 study, n=63 [vaccination]); outcomes regarding subsequent procedures were not assessed.

Relaxation and biofeedback vs control for 12 y olds receiving venipuncture did not lower pain intensity during the procedure (Forsner 2014 **Level III-2**, n=109).

In children (8–14 y) having cancer-related procedures, a 4-session intervention of preprocedural relaxation plus biofeedback was associated with progressively reduced state anxiety across the sessions, and improvement in heart rate variability; 81% of participants reported the combination of relaxation and biofeedback helped them feel in control of their bodies prior to the procedure (Shockey 2013 **Level IV**, n=12). Of patients (7–18 y) undergoing needle-related procedures (venipuncture, IV cannula insertion and Botox injection), 83.3% of those who used 'Brighthearts' (a biofeedback assisted relaxation application) reported the app was helpful and would use it again, 100% of parents and 96% of healthcare providers indicated they would use it again, and 64% of the healthcare providers perceived that it assisted with ease of procedure performance (Burton 2018 **Level IV**, n=107 [30 patients 27 parents 50 health professionals]).

Music therapy

Music therapy includes passive listening to recorded or played music and active participation of the patient with music. In children aged 1 mth–20 y, music therapy has a positive impact on pain (8 RCTs, n=882) and anxiety (6 RCTs, n=324) or both (5 RCTs, n=279) with various procedures (venipuncture/IV cannulation, bone marrow aspiration, dental/oral and other surgery) (Klassen 2008 **Level I**, 19 RCTs [5 active, 14 passive], n=1,513). On meta-analysis, music therapy reduces pain (SMD -0.39; 95%CI -0.66 to -0.11) (5 RCTs, n=465) and anxiety (SMD -0.39; 95%CI -0.76 to -0.03) (5 RCTs, n=284). A further RCT on IV cannulation in the ED shows the addition of passive music therapy to standard care (topical local anaesthetic, nurse explanation and reassurance) achieves lower pain and anxiety scores vs standard care alone (Hartling 2013 **Level II**, n=42, JS 3).

Other nonpharmacological interventions

Inviting parental presence for procedures (with and without sedation) is common practice. A child being positioned vertically and held by a parent vs being restrained by staff supine on an exam table reduced distress during IV cannulation (Sparks 2007 **Level II**, n=118, JS 4). During venipuncture, fearful parental expression and being reassured uninformatively (told "don't worry") increased children's fear, while informative reassurance and distraction use decreased it (McMurtry 2010 **Level IV**, n=100). Preprocedural preparation of the parent and child in a developmentally appropriate way is considered best practice and is being incorporated within hospital and national guidelines (Duff 2012 **GL**), as is staff and parent training in the use of nonprocedural talk (RACP 2005 **GL**) and use of child-friendly language for preparation/explanation (Stock 2012 **GL**). Nurse or play therapist coaches or hospital employed "child life interventionists" are also being employed to educate, distract and plan procedural intervention strategies for children and their parents informally and formally (LeBlanc 2014 **NR**).

KEY MESSAGES

Neonates

1. In term neonates, venipuncture is less painful than heel lance (**N**) (**Level I** [Cochrane Review]).
2. Sucrose (**S**) (**Level I** [Cochrane Review]) and non-sucrose sweet solutions (mostly glucose) (**N**) (**Level I** [PRISMA]) reduce pain scores and behavioural response for skin-breaking procedures in neonates.
3. Providing physical comfort measures, including kangaroo care (maternal or alternative skin to skin provider), non-nutritive sucking (alone or combined with sweet-tasting solutions), facilitated tucking (swaddling) or rocking and holding (**N**) reduces pain experienced by term and preterm neonates having skin-breaking procedures (**S**) (**Level I** [Cochrane Review]).
4. Pain from ocular examination for retinopathy of prematurity is reduced by sucrose and non-nutritive sucking (**N**) (**Level I** [Cochrane Review]) and topical local anaesthetic (**N**) (**Level III-1 SR** [Cochrane Review]).
5. Kangaroo care (or skin to skin contact) in neonates reduces the distress of vaccine injection (**N**) (**Level III-1 SR**).
6. Sucrose reduces distress after gastric tube placement in neonates (**N**) (**Level III-1 SR**).

Infants and children

7. Breastfeeding (<2 years of age) reduces pain intensity and crying duration for skin-breaking procedures including vaccine injection compared to positioning, holding by mother, maternal skin to skin contact (<1 months), topical anaesthetics, music therapy, pacifier use (<4 months), placebo, no intervention and/or oral sucrose (**S**) (**Level I** [Cochrane Review]).
8. Non-nutritive sucking reduces pain after needle-related procedures in infants and young children (<3 years) (**N**) (**Level I** [Cochrane Review]).
9. Oral sucrose and glucose reduce cry incidence and duration (**U**) (**Level III-1 SR** [Cochrane Review]**)** and distress (**N**) (**Level III-1 SR**) of vaccine injection in infants.
10. Distraction in infants and young children (<3 years) reduces vaccine injection pain (**N**) (**Level III-1 SR**).
11. Procedural modifications reduced distress of vaccine injection including injection without aspiration (≤18 months), simultaneous injection of multiple vaccines (≤12 months) and injection of most painful vaccine last (≤6 months) (**N**) (**Level III-1 SR**).
12. Topical local anaesthetic reduces distress of vaccine injection in infants (**N**) (**Level III-1 SR**).
13. Parental presence reduces prevaccine injection distress in infants and children (**N**) (**Level III-1 SR**).
14. Parental education before or on vaccination day increases use of evidence-based pain management strategies and reduces distress in infants and children (**N**) (**Level III-1 SR**).
15. Physical interventions including holding by parent (during or after) and non-nutritive sucking in infants (0–4 months) reduces the distress of vaccine injection (**N**) (**Level III-1 SR**).
16. The efficacy of supplemental/expressed breast milk for procedural pain management is unclear (**N**) (**Level III-1 SR**).
17. Needle-free pressure injected lidocaine is quick in onset and reduces pain from subsequent needle-related procedures in infants and children (**N**) (**Level II**).

Children and adolescents

18. EMLA® is an effective topical local anaesthetic for children but amethocaine is superior for reducing needle-insertion pain (**U**) (**Level I** [Cochrane Review]).
19. Topical local anaesthetic application (**U**) **(Level I** [Cochrane Review]), inhalation of nitrous oxide 50–70% or the combination of both (**U**) (**Level I** [PRISMA]) provides effective and safe analgesia for minor procedures in children.
20. Distraction (including with video, toys, music or stories) and hypnosis reduces needle related pain (**S**) and distress (**N**) in children and adolescents (**Level I** [Cochrane Review]).
21. Buzzy® (which combines vibration and cold) (**N**) (**Level I** [PRISMA]) and vibration by other methods (**S**) (**Level III-1 SR**) reduces needle-related procedure pain, including vaccine injection in children.
22. Active and passive music therapy reduces pain and anxiety associated with various needle-related procedures in children (**U**) (**Level I**).
23. Immersive virtual reality reduces pain of medical procedures including wound dressing care and venipuncture (**N**) (**Level III-1 SR** [PRISMA]).
24. Immersive virtual reality for medical procedures in children reduces self-reported pain and anxiety (**N**) (**Level III-1 SR**).
25. Ketamine is effective for paediatric procedural pain management (**Q**) (**Level IV**).
26. Hospital wide initiatives to implement evidence-based standards of care for needle related procedures can improve service delivery and patient satisfaction (**N**) (**Level IV**).

The following tick boxes represent conclusions based on clinical experience and expert opinion:

☑ Using combinations of evidence-supported single pain management strategies for painful procedures is strongly recommended (**N**). Non-pharmacological intervention should always be incorporated (**N**).

☑ It is of concern that minor procedures are still undertaken in children, particularly neonates and infants, in the elective and emergency hospital setting with minimal or no pain management intervention (**N**).

☑ Inadequate monitoring, lack of adequate resuscitation skills and equipment, and the use of multiple medicine combinations has been associated with major adverse outcomes during paediatric procedural analgesia and sedation (**U**).

☑ Pain caused by injection is a barrier to vaccine uptake; thus managing vaccine injection pain has immediate and long term implications for the wellbeing and health of individuals and society (**N**).

☑ Based on data from other specific phobias, exposure-based therapy (*in vivo* or imagined) is recommended for children and adolescents (7–17 years) with needle phobia receiving vaccine injections (**N**).

☑ Hypnosis requires teaching by a trained professional, but distraction can be readily provided by staff or parents and should be routinely offered in the paediatric setting (**U**).

☑ For children and adolescents, sitting upright may reduce procedural pain and distress (**N**).

10.8 | Acute pain in children with cancer

Acute pain in children with cancer may be due to tissue destruction from the cancer itself, its consequences (eg infection), or from its treatment (eg chemotherapy, radiotherapy, painful procedures, surgery), and may be primarily nociceptive or neuropathic. It is a common symptom in children with cancer (Ye 2019 **Level IV**, n=205; Tutelman 2018 **Level IV**, n=230; Friedrichsdorf 2014 **NR**; Fortier 2014 **Level IV**, n=45) and may be more common in children from low-income households (64% vs 42) (Ilowite 2018 **Level IV**, n=78). It is associated with significant fear and distress (Ljungman 1999 **Level IV**), and difficulty in pursuing and achieving personal goals (Schwartz 2017 **Level III-2**, n=199). Self-reported pain scores by children with cancer have been of higher intensity than nurse-reported pain scores (2 studies), whilst agreement with parent/carer-reported pain scores varied (9 studies) (Cheng 2018 **Level III-2 SR**, 33 studies, n=3,063 [children paired with parents/nurses]). Use of symptom self-report wherever possible is recommended.

Compared with adults (see Section 8.9), the pattern and sources of acute pain differ significantly in children with cancer. The WHO guideline *Pharmacological Treatment of Persisting Pain in Children with Medical Illnesses* (WHO 2012 **GL**) addresses pain in cancer and other medical conditions (such as HIV/AIDS, sickle cell disease, burns, trauma and phantom limb pain). It recommends a two-step analgesic management approach, abolishing the middle step that previously contained codeine. In 2019, this guideline was withdrawn by the WHO, however it remains endorsed by organisations in Australia, New Zealand and internationally until it is replaced.

10.8.1 | Cancer-related pain

10.8.1.1 | Tumour-related pain

Pain due to tumour is present at diagnosis in the majority of children (Miser 1987 **Level IV**) and often resolves with initial disease modifying therapy. Systematic reviews for cancer pain management have not identified any paediatric RCTs of paracetamol (Wiffen 2017b **Level I** [Cochrane], 3 RCTs [0 RCTs in children]), NSAIDs (Cooper 2017b **Level I** [Cochrane], 0 RCTs), opioids (Wiffen 2017a **Level I** [Cochrane], 0 RCTs) and pharmacological interventions (Eccleston 2019 **Level I**, 0 RCTs [cancer]) and pharmacokinetic, pharmacodynamic and pharmacogenomic data on commonly used drugs in children with cancer is limited (Constance 2017 **NR**). Thus, recommendations for their use are based on low quality evidence, extrapolation from different populations, and expert opinion.

Breakthrough pain

Breakthrough cancer pain in children is usually of sudden onset, severe and of short duration (Friedrichsdorf 2014 **NR**; WHO 2012 **GL**). For incident and breakthrough pain treatment, IR opioids are recommended at 10–15% of total daily dose. Commonly PO or IV morphine is used but all other opioids have been administered including via more rapid onset routes eg fentanyl transmucosally, SL or IN (Triarico 2019 **NR**; Coombes 2017 **Level IV**, n=26). “End of dose” pain is managed with escalation of background dosing, as in adults.

Background pain

For background pain, morphine is the most commonly used opioid; hydromorphone IR and oxycodone IR and controlled or extended release use starting at typical initial doses has also been described (Snaman 2016 **NR**). Transdermal buprenorphine has been used in 2–17 y olds with suggested weight-based doses starting at 8.75 mcg/h (<15 kg), 17.5 mcg/h (15–30 kg) and 35

mcg/h (>30 kg), titrated up to a maximum of 70 mcg/h (Ruggiero 2013 **Level IV**, n=16; Michel 2011 **Level IV SR**, 2 studies [cancer pain], n=4). Use of SL buprenorphine (2.5–10 mcg/k 12 hly) has also been described (Michel 2011 **Level IV SR**, 1 study, n=13).

Transdermal fentanyl has been used for cancer-related pain in previously opioid-tolerant children (2–19 y old in and outpatients) receiving a minimum of 30 mg/day PO morphine for a variable time period prior (Finkel 2005 **Level IV**, n=199 [132 cancer]; Hunt 2001 **Level IV**, n=41; Noyes 2001 **Level IV**, n=13; Collins 1999 **Level IV PK**, n=13). Opioid naïve cancer patients with pain (not controlled by paracetamol/ibuprofen) were admitted for TD fentanyl uptitration (Othman 2016 **Level IV**, n=64). They commenced 12 mcg/h (if <15 kg) or 25 mcg/h (if >30 kg or 15–30 kg with severe pain) with IV morphine rescue administration 50–100 mcg/kg; 16% required up titration within 15 d (max dose reached 50 mcg/h) (Othman 2016 **Level IV**, n=64). Transdermal fentanyl mean clearance and volume of distribution were similar to adults in older children (7–18 y) (Collins 1999 **Level IV PK**, n=13).

Opioid rotation/switch (mostly from morphine, hydrocodone or hydromorphone) to methadone has been described in children and adolescents (1–18 y) as both inpatients and outpatients (Madden 2018 **Level IV**, n=52; Mott 2018 **Level IV**, n=16; Davies 2008 **Level IV**, n=17). Inpatient rotation/switch is usually done in more opioid-tolerant patients and with more aggressive dosing. Initial dose calculations include 0.1 mg/kg/dose or using conversion ratios (usually 10 to 25:1) dependent on the context (eg pain intensity, inpatient vs outpatient and morphine equivalent daily dose). Methadone has also been used as an adjunct opioid (typical initial dose 1 mg nocte) (Mott 2018 **Level IV**, n=16). QT_c prolongation in small case series without complication has been reported; the clinical significance is unclear (Madden 2019 **Level IV**, n=42; Madden 2017 **Level IV**, n=25; Anghelescu 2016 **Level IV**, n=37). There are single case reports of hypoglycaemia (Gjedsted 2015 **CR**) and central sleep apnoea (Amos 2013 **CR**) in children with cancer on methadone. For further discussion re methadone also adult Section 4.3.1.

IV bisphosphonates (mostly zoledronate) have been used for pain related to bone metastases and primary bone malignancies (Anghelescu 2019a **Level IV**, n=35).

Lidocaine infusions can be considered in patients with cancer pain that is refractory to opioid escalation (Berde 2016 **NR**). However it has a narrow therapeutic range and is not titratable to pain intensity; infusion rates >2 mg/kg/h (33 mcg/kg/min) or plasma concentrations >6 mcg/mL are likely to carry a substantial risk of seizures, and many factors (eg hepatic or renal dysfunction) may confer risk at lower infusion rates or plasma concentrations (see also 10.4.11 Systemic lidocaine infusions).

Epidural and subarachnoid infusions (mostly opioid, local anaesthetic and/or baclofen), through a tunnelled indwelling catheter connected to an external pump, are the most commonly reported regional techniques for invasive tumour pain, where systemic analgesia has become ineffective or intolerable (Rork 2013 **NR**). Fully implantable systems have been used in adolescents (Rork 2013 **NR**; Bengali 2014 **CR**). Other reported regional techniques include local anaesthetic delivered by tunnelled femoral nerve and brachial plexus catheters (Rork 2013 **NR**). Neuro-destructive techniques, such as coeliac plexus or splanchnic nerves blocks with neurolytic agents (Rork 2013 **NR)**, surgical cordotomy (Steel 2017 **CR**) and stereotactic mesencephalotomy (Ivanishvili 2016 **CR**) have been reported.

Neuropathic pain

Neuropathic pain in children is often treatment-related (see below); cancer-related neuropathic pain usually occurs with invasion or compression of nerves, plexus or spinal cord (by sarcomas) or following limb-sparing surgery (Collins 1995 **NR**). It requires multimodal and adjuvant therapy (alpha-2-delta ligands, antidepressants and opioids; see respective sections in adult Section 4 and paediatric 10.4.4 and 10.4.9) including nonpharmacological approaches (see Section 10.7.5)

with physiotherapy and psychology (Friedrichsdorf 2014 **NR**; Anghelescu 2014 **Level IV**). Methadone has been used in the acute setting for new onset neuropathic pain, to assist weaning and postoperatively (Anghelescu 2011a **Level IV**).

Nonpharmacological interventions

Various nonpharmacological therapies have been studied in children and adolescents with cancer pain including creative art therapy (1 RCT), aromatherapy (1 study), physical activity (1 study), massage and touch therapy (3 studies) (Jibb 2015 **Level IV SR**, 32 studies [6 cancer pain], n=1,171 [n=143 cancer pain]) and scrambler (TENS-like) therapy (Park 2017a **CR**) with mixed results.

A web-based intervention (C-TIPS) delivering information to carers of children with cancer in their home focussed on pharmacological and nonpharmacological pain management and coping strategies (Chung 2018b **Level IV**, n=30). An electronic tablet device in 8–18 y olds (Fortier 2016 **Level IV**, n=12) and a smart phone application in 12–18 y olds (Jibb 2017 **Level IV**, n=40) aimed at children and adolescents with cancer-related pain have been developed to provide real-time pain self-management support.

10.8.1.2 | Pain in the terminal stages

In the terminal stages of cancer, pain is common (Wolfe 2015 **Level IV**, n=104; Goldman 2006 **Level IV**, n=185; Wolfe 2000 **Level IV**, n=103) and poorly managed pain is associated with higher levels of long term parental grief (van der Geest 2014 **Level IV**, n=89; Kreicbergs 2005 **Level IV**, n=449). Feeding back to patients, families, and health providers of self- and carer-reported child symptoms and health-related quality of life did not improve child distress or health-related quality of life (Wolfe 2014 **Level II**, n=90, JS 3).

Opioid requirements may escalate (Hewitt 2008 **Level IV**, n=185; Sirkia 1998 **Level IV**, n=100), and benefit has been reported with the use of PCA opioids to allow rapid dose titration (Anghelescu 2015b **Level IV**, n=159; Schiessl 2008 **Level IV**), with the addition of low dose IV ketamine infusion (Taylor 2015 **Level IV**, n=14; Finkel 2007 **Level IV**, n=11) and intervention with continuous nerve catheter infusions (Anghelescu 2010 **Level IV**, n=10) (see Sections 10.4.5, 10.5 and 10.6). Outpatient PCA opioids have also been administered (using the Computerised Ambulatory Drug Delivery device CADD®), enabling children to stay at home during the terminal stages of their illness (Mherekumombe 2015 **Level IV**, n=37 [33 cancer]; Anghelescu 2015c **Level IV**, n=45). Methadone has been used in small series of children/young adults with cancer for terminal care and pain unresponsive to escalation of other opioids (Mott 2018 **Level IV**, n=16; Anghelescu 2011a **Level IV**; Davies 2008 **Level IV**).

10.8.2 | Procedure-related pain

Children, their parents, physicians and nurses all rate procedural interventions and treatment as a significant source of pain (Ljungman 1999 **Level IV**; Ljungman 1996 **Level IV**). Multiple diagnostic and therapeutic interventions are required during the course of treatment and require pain management matched to the procedure type and needs of the child.

10.8.2.1 | Lumbar punctures, bone marrow aspirations, blood sampling

See Sections 10.7.2 for pharmacological intervention and 10.7.5 for nonpharmacological intervention used in paediatric oncology care.

10.8.2.2 | Central venous port access

For pain relief during central venous port access in children with cancer, EMLA® was evaluated as superior to placebo (Miser 1994 **Level II**, n=47, JS 5). When added to topical anaesthesia with EMLA® for port access, neither PO morphine 0.25 mg/kg (Heden 2011 **Level II**, n=50, JS 5) nor PO paracetamol 40 mg/kg (maximum 2 g) (Heden 2014 **Level II**, n=51, JS 5) impacted upon pain, fear and distress scores, which were equally low in placebo treated patients. Outcomes for second and subsequent procedures were improved if adequate analgesia was provided for the first procedure (Weisman 1998 **Level III-2**). Individual studies suggest various modes of distraction (eg virtual reality, bubble blowing, book reading) are equivalent or superior to active controls for port access (4 studies [age 2–19 y]) (Jibb 2015 **Level IV SR**, 32 studies, n=1,171).

Parents showed increased non-verbal caring behaviours with repeated port access procedures (Bai 2018 **Level IV**, n=43 [105 procedures]), which can reduce child distress during the procedure (Bai 2017 **Level IV**, n=43).

10.8.3 | Treatment-related pain

Pain during active treatment is common (Levine 2017 **Level IV**, n=258), worse than post-treatment pain (Tutelman 2018 **Level IV**, n=230), and a source of high distress and suffering to children with cancer (Levine 2017 **Level IV**, n=258; Ljungman 2000 **Level IV**; Collins 2000 **Level IV**). Parental acceptance of pain has been shown to predict decreased child distress, and an instrument to measure parental acceptance of pain during their child's treatment has been developed (Thorsell Cederberg 2017 **Level IV**, n=243). Parental trait anxiety predicts a higher frequency of parent-reported pain episodes, lower child health-related quality of life and increased parental solicitous behaviours (Link 2016 **Level IV**, n=353 [parents] & n=137 [children]).

10.8.3.1 | Mucositis

Oral mucositis is a common painful condition occurring in 52–80% of children receiving chemotherapy (Mazhari 2019 **Level III-3 SR** [PRISMA], 9 studies, n=504; He 2018 **Level III-3 SR** [PRISMA], 8 studies, n=373). It can be difficult to assess (Tomlinson 2008 **NR**), and is a frequent indication for IV opioid therapy. Opioid requirements are often high and escalate with the severity of mucositis (Coda 1997 **Level II**, n=119, JS 5; Dunbar 1995 **Level IV**).

Opioids

A systematic review concludes that morphine by PCA or continuous infusion provides similar analgesia (no difference in pain scores), and PCA use results in reduced hourly and overall morphine intake and duration of pain by 1.9 d (95%CI 0.25 to 3.5) with a stated concern of bias due to drop out rates in these studies (Clarkson 2010 **Level I** [Cochrane], 3 RCTs [1 paediatric], n=184). PCA morphine and pethidine (Oudot 2011 **Level II**, n=29, JS 5) and PCA morphine and hydromorphone had similar efficacy (Collins 1996 **Level II**, n=10, JS 4) but PCA sufentanil was less effective than PCA morphine or hydromorphone (Coda 1997 **Level II**, n=199, JS 5). Prolonged administration is often required (6–74 d) (Dunbar 1995 **Level IV**). If excessive or dose-limiting adverse effects occur, rotation to another opioid (morphine to fentanyl or fentanyl to hydromorphone) can produce improvement in the majority of patients, without loss of pain control (Drake 2004 **Level IV**).

Ketamine

Ketamine 20–40 mcg/kg/mL improved pain scores when added to PCA/NCA morphine (James 2010 **Level IV**) and also decreased morphine consumption when patients were requiring ≈1 mg/kg of morphine per day (White 2011 **Level III-3**). In a small case series of children with mucositis,

topical morphine 0.025–0.4 mg/kg was used in a dose-response study and reduced pain scores by ≥36% in six of seven children (Nielsen 2012 **Level IV**). Plasma levels were low, suggesting minimal systemic absorption.

Laser and photodynamic therapy

Low level laser therapy for oral mucositis, both as a prophylactic and therapeutic intervention in children and adolescents (<18 y) has been shown to be effective, however its effect on pain from oral mucositis is variably reported and unclear (Mazhari 2019 **Level III-3 SR** [PRISMA], 4 studies [low level laser therapy], n=504 [n=244]; He 2018 **Level III-3 SR** [PRISMA], 8 studies, n=373) (8 study overlap). Photodynamic therapy (methylene blue + low level laser therapy) was not superior to low level laser therapy alone in children (<18 y) (Ribeiro da Silva 2018 **Level II**, n=29, JS 3).

Honey

Honey was not superior to control for moderate to severe mucositis in teenagers, despite showing benefit in adults (Yang 2019 **Level I** [PRISMA] [NMA], 17 RCTs [5 paediatric], n=1,265 [276 paediatric]).

Cryotherapy, cytokines and growth factors

Systematic reviews on the use of cryotherapy (Riley 2015 **Level I** [Cochrane], 14 RCTs [1 mixed adult and children], n=1,280) and cytokines and growth factors (Riley 2017 **Level I** [Cochrane], 35 studies [4 paediatric], n=3,102) for the prevention of mucositis found insufficient evidence to support their use in children and adolescents.

Other therapies

Palifermin (IV keratinocyte growth factor) reduced the incidence (OR 4.1; 95%CI 2.4 to 7.0) (5 studies) and severity (SMD 0.64; 95%CI 0.30 to 0.97) (3 studies) of oral mucositis in children (<18 y) (Mazhari 2019 **Level III-3 SR** [PRISMA], 9 studies [5 palifermin], n=504 [n=260]) and one RCT found that Mucosyte® mouthwash (verbascoside, polyvinylpyrrolidone, sodium hyaluronidate) vs placebo reduced pain intensity (D 3 median 1/10 vs 2; D 8 median 0/10 vs 1) and analgesic requirements in 5–18 y olds with mild to moderate oral mucositis (Bardellini 2016 **Level II**, n=56, JS 3).

There is limited evidence in children that topical vs ingested vitamin E improved mucositis (1 RCT, n=40), while debridement in addition to standard care reduced severity and days to resolution (1 RCT, n=80) (Clarkson 2010 **Level I** [Cochrane], 32 RCTs [4 paediatric], n=1,505 [n=176]).

For further reading, see adult section 8.9.8.2 regarding acute mucositis pain.

10.8.3.2 | Neuropathic pain

Neuropathic pain during treatment can occur acutely secondary to chemotherapy, where it may be dose limiting (eg vincristine) or after surgery (Anghelescu 2019b **NR**). It may be more common than expected and poorly documented. In an adolescent and young adult cohort (13–39 y, median 18 y) screened for neuropathic pain, 26% of patients receiving treatment and 11% post treatment had neuropathic pain, and only 26% had the diagnosis documented in their medical record (Acquazzino 2017 **Level IV**, n=78). Of patients undergoing definitive surgery (amputation or limb sparing, mostly lower limb) for osteosarcoma, 81% were diagnosed with neuropathic pain (based on pain descriptors eg tingling, burning, shooting and pins and needles); mean duration of documented neuropathic pain was 6.5 wk (Anghelescu 2017 **Level IV**, n=37).

Gabapentin (reported doses ≈10–45 mg/kg/d) and amitriptyline or nortriptyline (reported doses ≈0.3–0.45 mg/kg/d) are the recommended first line agents for neuropathic pain in children with cancer; reported doses are typically lower than in adults (on a per kg basis) (Anghelescu 2019b **NR**). Opioids (Windsor 2019 **NR**) including methadone, ketamine infusions and lidocaine (patch or infusion) (Anghelescu 2019b **NR**) have also been used, as have multimodal interventions including

pharmacological (mostly with an opioid and gabapentin) and nonpharmacological therapy (Anghelescu 2014 **Level IV**, n=66).

Anti-glycolipid disialoganglioside (GD)-2 agents (typically given over 10–20 h/d for several days) have improved outcomes in patients with high-risk neuroblastoma. However, neuropathic pain (thought to be due to complement activation) during infusion can be severe and dose limiting. Morphine by NCA/PCA (Ari 2018 **Level IV**, n=16) and hydromorphone/dexmedetomidine infusions (Gorges 2015 **Level IV**, n=6) have been used in a ward environment to manage this neuropathic pain. Anti-GD2 therapy with Hu14.18K322A monoclonal antibody that causes less complement activation resulted in lower opioid requirements over 4 d (IV morphine equivalent, median 1.57 mg/kg vs 2.41) (Anghelescu 2015a **Level III-3**, n=28).

10.8.3.3 | Postoperative pain

Postoperative pain related to surgical procedures for diagnostic biopsies, insertion of long term IV access devices and tumour resection is also a frequent source of treatment-related pain. Analgesic intervention using all modalities including preoperative gabapentin and postoperative wound and CPNC local anaesthetic infusions have been described for limb salvage surgery (Anghelescu 2010 **Level IV,** n=150) and for upper limb forequarter amputation (Kaddoum 2013 **Level IV**, n=4). Subsequently, in children and adolescents (10–17 y) having a lower limb amputation for osteosarcoma, perioperative gabapentin (300 mg three times daily for 30 d) (as part of a multimodal analgesic regimen) vs placebo resulted in similar reduction of early perioperative pain scores, and reduced the incidence of phantom limb pain at 60 d postoperatively (43% vs 77%) (Wang 2018 **Level II**, n=45, JS 5). (See also adult Section phantom limb pain 8.1.5)

In children with cancer requiring morphine infusions, the highest rate of breakthrough pain was found in postoperative cases, of which 92% had solid tumours (Flogegard 2003 **Level IV**). In children with thoracic, abdominal or lower limb cancer, supplemental IV opioid boluses (either nurse-administered or via PCA) were safely combined with epidural bupivacaine and fentanyl infusion to control postoperative pain. Of 117 patients, 1 developed respiratory depression (due to a dosing error) but patients were closely monitored and had pre-existing tolerance to opioids (Anghelescu 2008 **Level IV**).

10.8.3.4 | Vertebral compression fracture

Balloon kyphoplasty has been used to manage intractable pain in teenagers from vertebral compression fractures secondary to chemotherapy and steroid-induced osteoporosis/ osteopaenia (Hoashi 2017 **Level IV**, n=3). For further reading, see adult Section 8.9.7.6.

KEY MESSAGES

1. PCA and continuous opioid infusions are equally effective in the treatment of pain in mucositis in children, but opioid consumption and duration of pain is less with PCA (**U**) (**Level I** [Cochrane Review]).
2. Topical local anaesthetic application for children having central venous port access is effective and analgesia is not further improved by oral analgesics (morphine or paracetamol) (**U**) (**Level II**).
3. Self-reported pain scores by children with cancer were higher in intensity compared with nurse-reported pain scores, with variable agreement with parent/carer-reported pain scores (**N**) (**Level III-2 SR**).
4. There is limited evidence that low-level laser therapy reduces the severity of mucositis in children (**U**) (**Level III-2 SR** [PRISMA]).
5. QT interval prolongation with methadone in children with cancer has been reported without complication; the clinical significance is not clear (**N**) (**Level IV**).
6. Poorly managed pain in children during the terminal stages of cancer is associated with higher levels of long term parental grief (**N**) (**Level IV**).
7. Outpatient intravenous PCA opioid has been used to help children in the terminal stages of cancer stay at home (**N**) (**Level IV**).
8. Transdermal fentanyl patch use may be appropriate in opioid tolerant children with cancer (**N**) (**Level IV**).

The following tick boxes represent conclusions based on clinical experience and expert opinion:

☑ In paediatric cancer pain management, the same therapeutic approaches as in adults are used, although evidence is limited (**U**).

☑ The World Health Organization has removed codeine from the management approach to paediatric cancer pain reducing the number of tiers from three to two: with tier one including nonopioid analgesics and adjuvants and tier two including strong opioids; in 2019 the WHO withdrew the reference document, but it remains endorsed by organisations throughout Australia, New Zealand and internationally until it is replaced (**Q**).

☑ Caution must be taken during uptitration of transdermal systems due to the pharmacokinetic profile of transdermal delivery that has slow penetration and delayed uptake from the stratum corneum (**N**).

10.9 | Other acute pain conditions in children

10.9.1 | Management of pain due to trauma and burns in children

10.9.1.1 | Early and prehospital trauma pain

Prehospital care of paediatric patients suffering moderate to severe trauma is administered by a range of people with varying levels of healthcare expertise including parents, carers or family members, childcare or school staff, and emergency medical services. The provision of first aid is an important component of pain management. Administration of analgesics (and sedatives) by emergency medical services is strongly recommended (ACEP 2016 **GL**; Gausche-Hill 2014 **GL**). Despite this, and evidence that it is effective, administration of analgesia for moderate to severe trauma in the prehospital setting is reported to be low. In a systematic review on the efficacy and safety of analgesics used for injured children and adolescents (<18 y) in the prehospital setting only a descriptive review was possible (Samuel 2015 **Level IV SR**, 19 studies [13 paediatric, 6 mixed adult/paediatric], n>67,287). The authors made the following conclusions:

- Overall rates of analgesic administration were low;
- Fentanyl 1-3 mcg/kg (route unspecified) had an accepted efficacy, and although other analgesics have a documented benefit (eg morphine, methoxyflurane, nitrous oxide), no comparisons could be made;
- Rates of reported adverse effects in studies and large case series are low, but there is insufficient evidence to assess the safety profile of analgesics in this setting.

Further studies report variable documentation of pain assessment (18-81%) and consistently low administration rates of any analgesics (6.4-45%), despite a high prevalence of moderate to severe pain intensity (up to 74%) when it is documented (Browne 2016a **Level III-3**, n=7,340; Hewes 2018 **Level IV**, n=276,925; Schauer 2018 **Level IV**, n=3,439; Lord 2016 **Level IV**, n=38,167; Murphy 2016a **Level IV**, n=6,371; Rutkowska 2015 **Level IV**, n=1493; Johnson 2014 **Level IV**, n=5,057). There were two exceptions, where an ambulance service gave an analgesic agent to 79−92% of children (<15 y) who reported pain (Jennings 2015 **Level IV**, n=15,016; Galinski 2011 **Level IV**, n=433). Younger age (Hewes 2018 **Level IV**, n=276,925; Lord 2016 **Level IV**, n=38,167; Murphy 2016a **Level IV,** n=6,371; Johnson 2014 **Level IV**, n=5,057; Watkins 2006 **Level IV**, n=45), and in two USA studies, non-white ethnicity (Hewes 2018 **Level IV**, n=276,925; Johnson 2014 **Level IV**, n=5,057) were associated with less pain score documentation and provision of analgesics.

Children (≤17 y old) compared to adults were less likely to have their pain assessed (OR 0.80; 95%CI 0.76 to 0.85) (Ramgopal 2018 **Level III-2**, n=371,746) and be administered opioid analgesia by an ambulance service (Bendall 2011b **Level III-2**, n=97,705; Hennes 2005 **Level III-2**, n=5,383). A further study found factors associated with opioid administration in children were vascular access (OR 11.89; 95%CI 7.33 to 19.29), longer patient transport time (OR 1.07; 95%CI 1.04 to 1.11) and pain score documentation (OR 2.23; 95%CI 1.40 to 3.55) (Browne 2016b **Level IV**, n=1,368).

Barriers to managing acute pain in children identified by paramedics include concern/difficulty administering analgesia (by IV, PO or inhalational route) to a distressed and uncooperative child, difficulty assessing pain in children, limited education, training, and experience managing children, as well as risk of adverse reactions with analgesics (Whitley 2017 **Level IV**, n=127; Rahman 2015 **Level IV**, n=191; Murphy 2014a **Level IV**, n=16; Williams 2012 **Level IV**, n=16; Watkins 2006 **Level IV**, n=52 [surveyed]).

Self-reported self-efficacy scores in ambulance officers for assessing pain in toddlers and children improved immediately following the implementation of a pain management protocol (self-report pain scale and analgesic dosing guide) in one RCT, with some improvement

maintained 13 mth later (Jaeger 2017 **Level II**, n=264, JS 2). Education combined with protocol implementation was not superior to protocol implementation alone. However, an attempt to improve the assessment of pain and provision of analgesia by implementing prehospital pain management protocols (use of age appropriate pain scales, decreased minimum age for opioid administration and updated fentanyl dosing) was unsuccessful in another study (Browne 2016a **Level III-3**, n=7,340).

The most commonly reported analgesics used by Australian prehospital emergency medical services for children and adolescents with acute pain were inhaled methoxyflurane, IN fentanyl and IV morphine; all have been found to be effective analgesics in this setting (Bendall 2011a **Level III-2**, n=3,312; Murphy 2017 **Level IV**, n=94; Lord 2016 **Level IV**, n=38,167; Jennings 2015 **Level IV**, n=15,016; Babl 2006 **Level IV**, n=105). The most frequently administered analgesic was methoxyflurane with one study reporting no serious adverse effects with its use; mild adverse effects occurred in 36% (mostly drowsiness) with deep sedation occurring in 33% of patients under 5 y (Babl 2006 **Level IV**, n=105). Ketamine has also been used with doses of 0.25−1 mg/kg via IV and IN routes and a higher IM dose of 5 mg/kg (Schauer 2018 **Level IV**, n=3,439; Bredmose 2009a **Level IV**, n=164). IN S-ketamine 0.45−1.25 mg/kg has been used in 7−17 y olds (Johansson 2013 **Level IV**, n=6 [paediatric]).

In children with acute pain (mostly from limb injury) presenting to the ED, the majority of parents and carers (72-78%) reported trying to manage their child's pain, but only 28-56% administered an analgesic (Conrad 2019 **Level IV**, n=338; Whiston 2018 **Level IV**, n=743; Rogovik 2007a **Level III-2**, n=310; Maimon 2007 **Level IV**, n=214). Reasons reported for not giving analgesics included concern about masking signs and symptoms, the child not showing signs of pain, not wanting to delay being seen by a physician, no analgesics available and did not have time (Conrad 2019 **Level IV**, n=338; Whiston 2018 **Level IV**, n=743; Maimon 2007 **Level IV**, n=214).

10.9.1.2 | Trauma pain in hospital

The majority of literature on hospital management of paediatric trauma focuses on ED management of isolated limb injuries; literature on multi-trauma pain management is limited. This section is on management of pain from a traumatic injury; for management of procedural pain with closed fracture reduction or laceration repair see Section 10.7.4.

Multi-trauma

In children and adolescents (<18 y) with severe trauma (injury severity score [ISS] ≥12/75), only 32% received analgesia during resuscitation in the ED (mostly opioids; 67% during primary survey) (Anantha 2014 **Level III-2**, n=203). Patients who received analgesia vs those who did not were more likely to be in a car accident (58% vs 42), and have parents present during resuscitation (17% vs 6), had a higher median ISS (22/75 vs 17), shorter duration in the ED (141 min vs 195) and longer ICU (median 3 d vs 1) and hospital stay (median 6 d vs 4).

Isolated limb injuries

For children with suspected fractures presenting to the ED, fast-tracking is occurring to facilitate rapid analgesic administration and direct referral for X-ray from triage. To avoid the distress associated with IV access or IM injection, alternative administration routes for analgesics are being increasingly used in this setting. Despite this, reported analgesic administration is variable. In children and adolescents (3–18 y) with a limb or clavicle area injury (62% fractures), analgesic administration rate was low (29%) and sufficient analgesia (assessed as adherence to protocol for paediatric ED analgesia) was only prescribed in 16.4% of patients; the median time to initiation of an analgesic medication after arrival in the ED was 2 h (Rogovik 2007a **Level III-2**, n=310). In children and adolescents (<18 y) with a closed long bone fracture, mean time to first analgesia was 70 min, and severity of pain assessed at triage did not influence the provision of

analgesia (Weng 2010 **Level IV**, n=211). In a cohort of children and adolescents (<18 y, 90% with extremity fracture) presenting to USA EDs, 72% received analgesia, and 55% of these patients received opioids; younger age (<3 y) and children who were admitted to hospital were less likely to receive analgesics in the ED (Yackey 2018 **Level IV**, n=1,341). Further evidence suggests younger children may be at increased risk of poorly managed pain: when presenting to the ED with an isolated painful injury (82% long bone fracture), infants (6–24 mth) vs school age children (6–10 y) were more likely to receive no analgesia (65% vs 48) and less likely to receive opioid analgesia (17 vs 44%) (Alexander 2003 **Level III-2**, n=180).

Ethnicity, and its association with pain and its management in the ED has been assessed. In children (mean age 7.6 y) with a long bone fracture presenting to two USA EDs, mean initial pain scores were not statistically different across ethnic groups (4.7–7/10), except for patients who identified as Somali, who reported lower pain scores (4/10) (Ortega 2012 **Level IV**, n=880). In the same cohort, patients were less likely to receive a discharge prescription for an opioid analgesic if they identified as biracial (RR 0.45), African-American/non-Hispanic (RR 0.59) or Hispanic/Latino (RR 0.61) vs patients who identified as white/non-Hispanic (Ortega 2013b **Level IV**, n=878). In Northern Israel, Arabic and Jewish patients (3–15 y olds) presenting to a paediatric ED with severe pain (≥7/10) from a fracture or dislocation received opioid analgesia at similar rates (99%, mostly PO oxycodone) through a nurse driven pain protocol; ethnicity of the nurse did not influence opioid administration (Shavit 2016 **Level III-2**, n=3,782).

In an ED, 91% of carers consented to their child (4–17 y; 70% musculoskeletal injury) receiving an analgesic (Whiston 2018 **Level IV**, n=743). Of those who refused, the most common reason was that their child refused the medication. Thus, carer refusal was not thought to be a major barrier to children's pain management in this context.

System interventions to improve pain management have been studied with mixed results:

- A physician pain reminder (pain scale form added to chart) did not enhance the prescription of analgesics to children and adolescents (3–18 y) with a limb or clavicle area injury (62% fractures, mean pain score on arrival: 4.4/10) (Rogovik 2007b **Level III-2**, n=310);
- In children (mean age 6 y) presenting to the ED with a supracondylar fracture, implementation of a medical directive to triage nursing staff (to assess and document pain scores and administer paracetamol or ibuprofen for pain ≤7/10) increased rate of analgesic administration within 60 min of presentation from 15 to 54% and reduced median time to analgesic administration from 72.5 min to 11 min; rate of opioid administration was not reported (Porter 2015 **Level III-3**, n=184). Increasing awareness of splinting through posters aimed at medical staff in the ED did not increase the rate of back slab application before X-ray (29% vs 33);
- A computerised reminder triggered with X-ray ordering increased splint application prior to X-ray (from 22% to 49) in patients (<16 y) with a forearm fracture requiring manipulation (Mills 2016 **Level III-3**, n=298). However, this did not change analgesia provision within the first hour of presentation;
- Implementation of a pain protocol for triage nurses to assess pain, document intensity and administer paracetamol for suspected long bone fractures reduced median time to first analgesia from 71.5 to 26 min; the initial analgesic was paracetamol in 52% (median time to paracetamol 20 min) and an opioid in 47% (77% IN fentanyl) (median time to opioid analgesia 29 min) (Schuman 2018 **Level III-3**, n=1,011).

Various combinations of opioids (PO, IN, or IV), sedatives, NSAIDs and paracetamol for fracture pain management in the ED have been studied; these studies are summarised below. Also see Section 10.4.4 Conventional and Atypical opioids.

Intranasal fentanyl

IN Fentanyl for fracture pain has been studied to assess its analgesic efficacy and speed of onset, whilst the effects of introducing an IN fentanyl protocol to the ED on quality of care has also been assessed:

- Following limb fracture, IN fentanyl 1–2 mcg/kg effectively reduces pain in the ED (Murphy 2014b **Level I** [Cochrane], 3 RCTs, n=313; Setlur 2018 **Level IV SR** [PRISMA], 6 studies [limb injury], n=2081; Mudd 2011 **Level IV SR**, 3 studies [limb injury], n=150) (2 & 2 study overlap). It is effective in the usual concentration 50 mcg/mL vs high concentration 300 mcg/mL (lower volumes required) (1 RCT, n=189), and is equivalent to IV (1 RCT, n=65) and IM morphine (1 RCT, n=45) with more rapid onset;
- IN Fentanyl 1.5–2 mcg/kg achieves similar pain score reduction to IN ketamine 1–2 mg/kg at 15–30 min; minor adverse effects (eg dizziness, bad taste) were less common with IN fentanyl (41–61% vs 78–100%)(Frey 2019 **Level II**, n=90, JS 5; Reynolds 2017 **Level II**, n=87, JS 3; Graudins 2015 **Level II**, n=80, JS 5).
- Introduction of an IN fentanyl protocol for suspected fracture pain reduced time to opioid analgesia vs IV morphine by 8.5–29 min (Schoolman-Anderson 2018 **Level III-3**, n=132; Schacherer 2015 **Level III-3**, n=94; Holdgate 2010 **Level III-3**, n=181; Borland 2008 **Level III-3**, n=617). Reduced rates of unnecessary IV cannulation (Schoolman-Anderson 2018 **Level III-3**) and length of ED stay (Schacherer 2015 **Level III-3**, n=94) were also reported;
- In a paediatric ED with an IN fentanyl pain pathway for children and adolescents (3–21 y) with a long bone fracture, where the pathway could have been utilised, 41% did not receive IN fentanyl, with consequences including unnecessary IV cannulation for IV morphine administration (Arnautovic 2018 **Level IV**, n=1,374).

Transmucosal/nebulised fentanyl

- Transmucosal (transbuccal) fentanyl 10–15 mcg/kg was equi-efficacious vs IV morphine 0.1 mg/kg over 15–75 min (Mahar 2007 **Level II**, n=95, JS 3);
- Nebulised fentanyl 3–4 mcg/kg was similarly effective vs IV fentanyl 1.5 mcg/kg (Miner 2007 **Level II**, n=41, JS 3) and vs IV morphine 0.1 mg/kg (Furyk 2009 **Level II**, n=77, JS 4) (both RCTs in Thompson 2016 **Level I** [PRISMA], 7 RCTs [2 paediatric limb injury], n=475 [n=118]).

Paracetamol, NSAIDs and oral opioids

- Ibuprofen for fracture pain in the ED was superior (Clark 2007 **Level** II, n=300, JS 3) or similar to (Friday 2009 **Level II**, n=68, JS 3) paracetamol/codeine and similarly effective to ibuprofen/codeine (Le May 2013 **Level II**, n=81, JS 5), oxycodone and oxycodone/ibuprofen (Koller 2007 **Level II**, n=66, JS 5);
- In a further study, children and adolescents (6–17 y) presenting to ED with a musculoskeletal injury (38% fracture) analgesia with PO morphine 0.2 mg/kg/ibuprofen 10 mg/kg vs morphine/placebo vs ibuprofen/placebo did not provide adequate analgesia in 70% of patients (Le May 2017 **Level II**, n=456, JS 5);
- PO oxycodone was more effective and produced less itching than codeine but early administration at triage was required as having X-rays, rather than examination or casting, was identified as the most painful period (Charney 2008 **Level II**, n=107, JS 5);
- PO morphine 0.5 mg/kg alone and combined with SL midazolam 0.2 mg/kg for displaced long bone fractures reduced pain scores similarly, but at the expense of increased sedation for 59% patients with combination treatment vs 23% with morphine alone (Wille-Ledon 2011 **Level II**, n=58, JS 5);

- SL Ketorolac 0.5 mg/kg vs SL tramadol 2 mg/kg were both effective for moderate to severe fracture pain; the lack of comparison with other analgesics limits the usefulness of this study (Neri 2013 **Level II**, n=131, JS 5).

See also paediatric Section 10.4.2 and adult Section 4.2.1 on NSAIDs, including effects on bone healing.

Diamorphine and hydromorphone

IN Diamorphine 0.1 mg/kg drops and spray provide rapid effective analgesia for fracture pain (Regan 2013 **Level III-3**, n=297; Kendall 2015 **Level IV**, n=226) with similar efficacy but more rapid onset vs IM morphine 0.2 mg/kg (Kendall 2001 **Level II**, n=404, JS 3). A pharmacokinetic study has been done of IV vs IN diamorphine in children with fractures (Kidd 2009 **PK**, n=24).

IN Hydromorphone 0.03–0.06 mg/kg has been used to treat acute pain (49% limb fracture requiring closed or open reduction) in the ED (Tsze 2019b **Level IV**, n=35)

Ketamine

IN Ketamine 1–2 mg/kg achieves similar pain reduction to IN fentanyl 1.5–2 mcg/kg but with more frequent minor adverse effects (see fentanyl section above) (Frey 2019 **Level II**, n=90, JS 5; Reynolds 2017 **Level II**, n=87, JS 3; Graudins 2015 **Level II**, n=80, JS 5). In children (3–13 y) with an isolated limb injury (75% fractures) and moderate to severe pain intensity at triage, IN ketamine (mean total dose 1 mg/kg) reduced pain scores from baseline to 30 min post ketamine (median 74.5/100 vs 30) which was maintained at 60 min (median 25/100) (Yeaman 2013 **Level IV**, n=28). All patients were rated as awake or mildly sedated (University of Michigan Sedation Scale 0–1), and minor side effects were common (dizziness 36%, bad taste 29%, dysphoria 14%).

Methoxyflurane (Penthrane®)

Although no longer used as an anaesthetic agent (Brown 2012 **NR**), methoxyflurane is available as a self-administered Penthrox® inhaler which dispenses 0.2–0.4% methoxyflurane (Medical Developments International 2001). In adolescents who presented with minor trauma and moderate pain to the ED, methoxyflurane was effective vs placebo (Coffey 2014 **Level II**, n=300 [90 adolescents], JS 5). In smaller series, methoxyflurane reduced pain scores associated with extremity injuries by 2.5–4.7/10 with high satisfaction, but did not provide analgesia for subsequent fracture manipulation (Grindlay 2009 **Level IV SR**, 6 studies, n=293) (see also Section 4.5.2).

Regional analgesia

The following studies have reported on the efficacy of regional analgesia for limb injuries in the ED and during hospital admission:

- Children and adolescents (15 mth−18 y) who received a fascia iliaca block with ropivacaine 0.5% (0.5–0.75 mL/kg) vs IV morphine 0.1 mg/kg for femoral fracture in the ED had a lower rate of failure of analgesia (failure to achieve pain score <4/10) 30 min post intervention, lower combined pain scores to 6 h (difference 15%; 95%CI 6 to 24%), and longer duration of analgesia (median time to next analgesic administration 313 min vs 60) (Black 2013 **Level II SR** [Cochrane], 1 RCT: Wathen 2007 **Level II**, n=55, JS 3);
- In patients (15 mth–22 y) presenting to a paediatric ED with a femoral fracture, 61% received a fascia iliaca compartment nerve block (FICNB; landmark technique) for pain management (Neubrand 2014 **Level III-2**, n=259). Those who received a FICNB/systemic analgesia vs systemic analgesia alone were older (median age 8.0 y vs 5.3), and in the 6 h post-intervention had lower pain scores (median 1/10 vs 2.5) and parenteral medication use (median doses 1 vs 2). There was no difference in the prevalence of adverse events, however, two patients receiving FICNB had seizures: one patient had an intracranial haemorrhage; the other resolved with intralipid;

- In patients presenting to ED with an isolated femoral fracture, single shot US-guided femoral nerve block vs systemic analgesia resulted in longer time to next analgesic dose (6.1 h vs 2.2), lower subsequent analgesic dose frequency (0.15 vs 0.30/h), and lower morphine requirements (6.5 vs 14.8 mcg/kg/h, route unspecified) (Turner 2014 **Level III-3**, n=81);
- A single shot femoral nerve block has been used for femoral fracture management in infants as young as 3 mth old (Frenkel 2012 **CR**);
- Continuous femoral nerve blockade in children (15 mth–14 y) with femoral fractures for up to 6 d has been used successfully (Johnson 1994 **Level IV**, n=23; Tobias 1994 **Level IV**, n=4).

Alpha-2-delta ligands

Pregabalin 1.25–2.5 mg/kg/d, as part of a multimodal analgesic regimen, has been used in a 4 y old girl with a severe crush injury requiring foot amputation (Wossner 2017 **CR**).

See also paediatric alpha-2-delta ligands Section 10.4.9.

10.9.1.3 | Trauma pain post-discharge

Nearly 60% of patients (mean age 7.6 y) presenting to two USA EDs with a long bone fracture were given an opioid prescription on discharge (Ortega 2018 **Level IV**, n=873). Socioeconomic status (measured by household income) did not influence this; however, the rate of over the counter analgesic (paracetamol and ibuprofen) prescription decreased as household income increased. In a similar cohort from the same centre, fracture severity and opioid discharge prescription provision were lower in younger children (<4 y), but in children requiring closed reduction of their fracture in the ED, analgesic discharge prescription did not differ with age (Ortega 2013a **Level IV**, n=877).

For fracture pain management post discharge from the ED, ibuprofen (either regularly or as needed) was similarly effective to paracetamol (Shepherd 2009 **Level II**, n=72, JS 3), paracetamol/codeine (Drendel 2009 **Leve II**, n=336, JS 5) and PO morphine (Poonai 2014 **Level II**, n=134, JS 5) with less minor adverse effects (eg nausea, vomiting, drowsiness) than codeine (30% vs 51) and morphine (31% vs 56).

Carer administered analgesia

For children (5–10 y) treated in the ED with an extremity or clavicle fracture, parent administered analgesia in the first two days post-discharge was low (65% received ≤1 dose/d) (Zisk 2008 **Level IV**, n=50). Analgesia administration correlated with parental postoperative pain scores on d 1 (r 0.41) and d 2 (r 0.23) and child pain report only on day 2 (r 0.22). However, active and loud behaviour tool items correlated more strongly with analgesia administration than the quiet withdrawn behaviours items suggestive of pain.

Both a web-based module and an online video were superior to standard of care (verbal instructions) in improving caregiver knowledge about pain management of a child's fracture but did not improve functional outcomes (eg number of school or carer work days missed) (Golden-Plotnik 2018 **Level IV**, n=311).

10.9.2 | Management of acute burn injury in children

Following the initial injury, burn patients experience both background and procedural pain; itch is also a significant symptom (Nelson 2019 **NR**). Higher acute pain intensity is associated with delayed re-epithelialisation (Brown 2014a **NR**) and may influence psychological outcomes. Some children require treatment throughout the rehabilitation phase including reconstructive

surgeries, and physical and occupational therapies for months or years, and may experience pain with these treatments (Nelson 2019 **NR**).

Children who sustain a burns injury in early childhood can have long term changes in somatosensory and pain processing, including reduced stress-induced activation of endogenous pain inhibitory mechanisms (Pardesi 2017 **NR**). Furthermore, on quantitative sensory testing, 9–16 y olds who had sustained a moderate burn injury (5–10% total body surface area, mostly 2nd degree) in infancy (6–24 mth) had altered responses to mechanical (increased detection threshold, lowered pain threshold, greater perceptual sensitisation), but not thermal (warm) stimuli. In contrast, severe burn injury (>10% total body surface area, mostly 2nd or 3rd degree) only showed perceptual sensitisation to a tonic heat stimulus and no difference in response to mechanical stimuli (Wollgarten-Hadamek 2009 **Level III-2**, n=72).

See also the adult Section 8.5.

10.9.2.1 | Early and prehospital burn pain

First aid measures reduce pain from burn injury in the initial stages (Varley 2016 **NR;** ANZBA 2014 **GL**). Placing the burnt area under cool running water for ≥20 min should be performed (up to 3 h post initial burn) with application of longitudinally (not circumferentially) placed thin film plastic "cling" wrap (or clean sheets, if unavailable). Additionally, analgesic medication is recommended as part of the initial resuscitation management of severe burns (ANZBA 2014 **GL**). In children and adolescents (0–15 y) admitted to a burns centre within 24 h of injury, pre-burn centre analgesic administration (paracetamol, NSAID and/or opioid) increased over time (68 to 79% from 2002–2004 to 2007–2008); flame burns and more extensive burns were predictors of receiving pre-burn centre analgesics, whilst transfer/referral by ambulance services or general practitioners were predictors of not receiving pre-burn centre analgesics (Baartmans 2016 **Level III-3**, n=622). In children (0–4 y) with burns, median pain scores reduced with treatment by an ambulance service (initial 6.5/10 vs final 1/10); in addition to nonpharmacological measures, 49% were administered analgesics (paracetamol, ibuprofen, methoxyflurane or morphine) by PO, IM, IV or inhaled routes (Fein 2014 **Level IV**, n=117). Most patients (83%) received no analgesia prior to ambulance arrival.

10.9.2.2 | Background burn pain

Psychological impact

The full impact of children and adolescents' acute pain experience whilst recovering from a burn injury is unknown, but it may influence psychosocial function both immediately and long term (Nelson 2019 **NR**). Burn injured children (8–17 y) who use internalisation as a pain coping strategy may be more vulnerable to the development of a long term anxiety disorder (Rimmer 2015 **Level IV**, n=187). Girls were more likely than boys to use internalisation or seeking social support as coping strategies, whilst children whose burn injury occurred at ≥10 y old were more likely to use information seeking and positive self-statements vs <5 y olds. Post-traumatic stress symptoms and post-traumatic stress disorder are common in youth following burn injury (18–25% prevalence) and can be observed in children as young as 12 mth (Nelson 2019 **NR**). In children and adolescents admitted to hospital with burn injuries, higher morphine doses during admission correlated with a reduction in post-traumatic stress symptoms over 3–6 mth in young children (age 1–4 y: r -0.32) (Stoddard 2009 **Level IV**, n=11), 6 mth in older children (age 6–16 y: r -0.44) (Saxe 2001 **Level IV**, n=24) and 4 y (age range 1.5–17.1 y; survival curves stratified according to number of opioid units and size of burn) (Sheridan 2014b **Level IV**, n=147). Separation anxiety, but not pain intensity, may be a mediator between increased morphine doses during admission and a reduction in post-traumatic stress symptoms 3 mth post burn injury (age 6–18 y) (Saxe 2006 **Level IV**, n=61).

Patterns of pain and analgesic prescribing practices

In 0–4 y olds with a small mean total body surface area burn (6.3%), observer-reported mean background pain scores were low. However, 21–28% of morning and afternoon pain scores were moderate for background pain and 25% had moderate and 66% severe procedural pain scores (de Jong 2014 **Level IV**, n=168).

A survey of burn centres treating children and adolescents (18y) found the most commonly used analgesics for inpatient background and breakthrough pain were: IV morphine (49–65%), paracetamol with codeine (41–52%) and paracetamol alone (29–49%); for outpatient pain management, paracetamol with codeine and paracetamol alone were most commonly used (Martin-Herz 2003 **Level IV**, n=111). Sustained release opioids were used in school age children and adolescents by 27% and 46% of respondents respectively, whilst antipruritics (mostly antihistamines) and anxiolytics were used in 53–66% and 17–40% of respondents across all age groups. Distraction was the most common nonpharmacological strategy used (36–67% of respondents), with other strategies including music/art therapy (27–29%), relaxation (13–42%) and massage (7–11%). In a survey of centres that care for critically ill paediatric burns patients, the most common sedatives and analgesics used were midazolam, fentanyl, morphine, ketamine and diphenhydramine; routine use of scoring systems to assess pain and sedation were common (90%), but only 63% of centres had a sedation policy, and only 54% of respondents reported noticing withdrawal signs and symptoms in their patient population (Singleton 2015 **Level IV**, n=41 [centres]).

Children and adolescents (mean age 5.3 y, range 0.5–16) with severe burns (mean total body surface area [TBSA] burned: 48.3%, range 10–95%) and ventilated in intensive care (mean duration 25 d, range 8–112) received morphine and midazolam infusions for background pain and anxiety which reached mean peaks of 0.40 mg/kg/h and 0.15 mg/kg/h respectively, on average 14 d after admission; at extubation, mean morphine and midazolam infusion rates were 0.22 mg/kg/h and 0.10 mg/kg/h respectively (Sheridan 2001 **Level IV**, n=28). Ketamine infusion (40–200 mcg/kg/h) as part of a multimodal analgesic regimen has been used for 37 d in a 9 y old with severe burns (White 2007 **CR**). IV clonidine has been used in an 11 y old burns patient as part of a multimodal analgesic regimen (Lyons 1996 **CR**).

Development and implementation of a paediatric pain and anxiety guideline resulted in adequate background and procedural pain and anxiety scores with no complications related to overmedication of patients (Sheridan 1997 **Level IV**, n=125).

Perioperative analgesia

Tumescent local anaesthesia (high volume/low concentration 0.05%–0.1% lidocaine: 7 mg/kg max) for surgical acute burn management resulted in all patients requiring no opioid or ketamine (0–24 h) postoperatively, and 80% of patients required no analgesia at all (Bussolin 2003 **Level III-3**, n=60). For burns contracture release surgery with lateral thigh donor sites, a single injection lateral femoral cutaneous nerve (LFCN) US-guided peripheral nerve block (PNB) and US-guided fascia iliaca compartment nerve block (FICNB) with continuous infusion reduced postoperative pain scores vs local anaesthesia infiltration in 6–9 y olds (Shank 2016 **Level II**, n=19, JS 3). Dual peripheral nerve catheters (axillary and sciatic) successfully managed postoperative pain for toe to hand transfer reconstructive surgery following severe burns in a 3 y old (Dadure 2004 **CR**). The combined bupivacaine maintenance infusion dose was 5 mg/kg/d for 48 h and serial plasma bupivacaine levels remained below toxic levels.

Procedural interventions

See Section 10.7.2.9

Subacute interventions

There was no difference in observer-rated pain scores in patients (5 wk–13 y) admitted to a burns unit having massage sessions with a carrier oil or aromatherapy oil vs standard nursing care (van Dijk 2018 **Level II**, n=284, JS 3).

Regular massage therapy (15 min twice a wk) vs standard treatment reduced the severity of pain, itch and less so state anxiety in adolescents (12–18 y) post burn over a 5 wk period (Parlak Gurol 2010 **Level III-2**, n=63).

Similar to previously published prevalence rates in paediatric non-burn populations, phantom limb pain following amputation for burn injury occurred in 38% of patients, where amitriptyline was commonly used (Thomas 2003 **Level IV**, n=34). See also adult Section 8.1.5.

10.9.2.3 | Pruritus

Pruritus is a common symptom following burn injury in children that often presents in the acute phase of recovery. A behavioural post-burn pruritus scale (Toronto Pediatric Itch Scale) has been developed for infants and children ≤5 y old (Everett 2015 **Level IV EH**, n=30 patients [3 raters]). A self-report tool (Itch man scale) has been validated in children ≥6 y old (Morris 2012 **Level IV**, n=45). In a cohort of paediatric burn survivors (mean age 7.8 y; mean TBSA 41%), pruritus was present in 93% at discharge with a mean intensity of 5.7/10, decreasing to 63% and 2.5/10 respectively at 2 y follow-up (Schneider 2015 **Level IV**, n=430). In a subsequent cohort, 72% of patients (≤13 y) reported itch following burns injury, predictors of itch included time since burn, depth of injury, TBSA burned and skin grafting (Nieuwendijk 2018 **Level IV**, n=413). In preschool children with minor burns (mean age 1.6 y; mean TBSA burn 4%) assessed within 32 d of injury, parents reported pruritus in 47%, with the majority (78%) being mild; weak correlations were found between pruritus and ethnic minorities (Black, Latino/Hispanic, Asian or other), greater TBSA of burn, and more days elapsed since burn (Stewart 2019 **Level IV**, n=256). Significant improvements in multiple outcomes following burn injury including itch and pain have been observed in children (mean age 7 y) over 2 y (Wurzer 2017 **Level IV**, n=167) and preschool children (<5 y) up to 4 y, with the greatest rate of recovery occurring in the first 6 mth (Kazis 2016 **Level IV**, n=456).

In addition to, or instead of antihistamines in paediatric burns (inpatient and outpatient settings), alpha-2-delta ligands reduced itch and pain: gabapentin 15 mg/kg/d (prescribed for 53% of patients) (Nieuwendijk 2018 **Level IV**, n=413) and 24–34 mg/kg/d (where 23 patients poorly responding to gabapentin had pregabalin 3.7–6.5 mg/kg/d added) (Kaul 2018 **Level IV**, n=136).

Evidence based guidelines for post-burn pruritus recommend cetirizine and cimetidine as first line and loratadine as second line peripherally acting agents, gabapentin as a first line centrally acting agent, and laser therapy and pressure garments as possible nonpharmacological interventions (Goutos 2010 **GL**). Combination therapy is commonly used and should be implemented in a judicious stepwise fashion that includes peripherally acting, centrally acting and nonpharmacological interventions early.

KEY MESSAGES

1. For paediatric trauma patients in the prehospital setting, frequency of administration of analgesics is low (**N**) (**Level IV SR**) and documentation of pain assessment is variable (**N**) (**Level IV**).
2. Intranasal fentanyl is equivalent to intravenous or intramuscular morphine in reducing pain associated with paediatric fracture presenting to the emergency department (**U**) (**Level II**).
3. Intranasal ketamine (1–2 mg/kg) achieves similar pain reduction to intranasal fentanyl (1.5–2 mcg/kg) for isolated limb fracture pain, but with an increased frequency of minor side effects (eg dizziness, bad taste) (**N**) (**Level II**).
4. The introduction of an intranasal fentanyl protocol for limb injury can reduce the time to first analgesia in the emergency department, compared to intravenous morphine (**N**) (**Level III-3**).
5. Single shot fascia iliaca compartment block is effective in managing femoral fracture pain (**N**) (**Level III-3**).
6. Methoxyflurane, intranasal or intravenous fentanyl and intravenous morphine are effective and commonly used prehospital to manage pain from trauma (**N**) (**Level IV**); intravenous or intranasal ketamine is also an effective analgesic in the prehospital setting (**U**) (**Level IV**).
7. Younger children (<3 years) with an isolated limb injury receive less analgesia in the emergency department than older children (**N**) (**Level IV**).
8. In children and adolescents admitted to hospital with burns, higher morphine doses during admission predict reduced post-traumatic stress symptoms (**N**) (**Level IV**).
9. Pruritus following burn injury in children is common; predictors for pruritus include greater total body surface area of burn and greater number of days since burn injury (**N**) (**Level IV**).

The following tick boxes represent conclusions based on clinical experience and expert opinion:

☑ Administration of analgesia by emergency medical services and emergency departments for trauma patients (including those with burns) is strongly recommended as part of the initial resuscitation along with first aid measures such as cooling and dressings for burns and splint application for trauma (**N**).

☑ Gabapentin and pregabalin are used to manage pruritus and neuropathic pain following burn injury in children (**N**).

10.9.3 | Paediatric migraine

Migraine is common in children: 9.1% over all age ranges, more prevalent in girls (10.5%) vs boys (7.6%); with increased prevalence in both female and male adolescents (aged >14 y) by 2.7% and 1.3% respectively (IHS 2018 **GL**; Wober-Bingol 2013 **Level IV**, n=210,524). However, headache is an infrequent presentation to the paediatric ED (1%) (Orr 2018c **NR**; Sheridan 2014a **NR)**. Of paediatric ED headache presentations, primary headache makes up 27–40%, and migraine accounts 34–74% of primary headaches (Hsiao 2014 **Level IV,** n=43,913; Conicella 2008 **Level IV**, n=55,273). Of migraineurs presenting to the ED, 85% of children and adolescents were discharged home; with low re-presentation rates: 5.5% return within 3 d (Bachur 2015 **Level IV**, n=32,124). Paediatric vs adult migraine may be shorter in duration (2–72 h vs 4–72 h), bilateral and typically frontotemporal (IHS 2018 **GL**; Sheridan 2014a **NR**). The general management principles of acute paediatric migraine are the same as for adults (see Section 8.6.5): environmental modification and nonpharmacological/psychological intervention should be considered (see below 10.9.3.3 and Section 10.7.5).

Guidelines for the treatment of migraine in children and adolescents acknowledge the lack of large paediatric efficacy and safety studies, summarise the same trials and make similar recommendations (Oskoui 2019 **GL**; Gelfand 2018 **GL**; Rastogi 2018 **GL**; NICE 2015 **GL**; Alfonzo 2015 **GL**; Sheridan 2014a **NR**). Triptan trials in children and adolescents have led to licensed use ≥6 y for rizatriptan in the USA and ≥12 y for the other triptans in the USA, Canada and Europe (Faber 2017 **NR**). The New Zealand and Australian product information statements (Medsafe and Australian Register of Therapeutic Goods) for the various triptans state there is inadequate data for children <18 y, without specifying a licensing age cut off.

The challenges in assessing efficacy of various agents include the high placebo response rate (eg 28–58% for pain freedom at 2 h), trials using different enrichment strategies (longer time since migraine diagnosed, longer duration of untreated headache [eg 4 h] and placebo administration with exclusion of placebo responders) and the use of different outcomes: headache relief vs pain freedom or if recurs vs relief of other symptoms (see below and also Section 8.6.5.2 for definitions of outcomes used in the below studies).

10.9.3.1 | Oral and Intranasal therapies

The evidence available for the standard of care first line abortive therapy using simple PO analgesia for acute paediatric migraine is limited. Trial data for triptans is of better quality; triptans (with NNT 6 for adolescents and NNT 13 for children) are recommended in most guidelines as either first line, in combination or second line abortive therapy.

A Cochrane review of acute migraine treatments in children (<12 y) and adolescents (12–17 y) assessing the primary outcome of pain freedom at 2 h post intervention is summarised below according to child vs adolescent age groups (Richer 2016 **Level I** [Cochrane], 27 RCTs, n=9,158):

Children (<12 y)

- Paracetamol 15 mg/kg is not superior to placebo (RR 1.40; 95%CI 0.75 to 2.58); there is no difference in headache relief, rescue medication use, headache recurrence or adverse events (1 RCT, n=88);
- Ibuprofen 7.5–10 mg/kg is superior to placebo (RR 1.87; 95%CI 1.15 to 3.04: NNT 4) (2 RCTs, n=172). It also improves headache relief (RR 1.49; 95%CI 1.11 to 2.00) (2 RCTs, n=125), but not rescue medication use (2 RCTs, n=164) or headache recurrence (1 RCT, n=38);
- Triptans are superior to placebo (RR 1.67; 95%CI 1.06 to 2.62: NNT 13) (3 RCTs, n=345). However, there was no difference in secondary outcomes of headache relief (3 RCTs,

n=345), rescue medication use (2 RCTs, n=145), nausea (3 RCTs, n=345), vomiting (3 RCTs, n=345) or adverse events (3 RCTs, n=420).

Adolescents (12–17 y)

- Ibuprofen has not been adequately assessed. One RCT found it is not superior to placebo for pain freedom at 2 h, headache recurrence, rescue medication or adverse events, but does achieve superior headache relief (RR 2.5; 95%CI 1.02 to 6.10) (1 RCT, n=32);
- Triptans are superior to placebo for pain freedom at 2 h (RR 1.32; 95%CI 1.19 to 1.47: NNT 6) (21 RCTs, n=6,761), but with increased minor adverse events (risk difference 0.13; 95% CI 0.08 to 0.18: NNH 8) (21 RCTs, n=7,876);
- Triptans are also superior to placebo for headache relief (RR 1.14; 95%CI 1.04 to 1.24) (20 RCTs, n=6,182), rescue medication use (RR 0.79; 95%CI 0.72 to 0.87) (18 RCTs, n=5,066) and headache recurrence (RR 0.79; 95%CI 0.68 to 0.93) (15 RCTs, n=2,463); there is no difference in nausea (RR 0.94; 95%CI 0.79 to 1.12) (17 RCTs, n=4,975) or vomiting (RR 0.73; 95%CI 0.48 to 1.12) (14 RCTs, n=4,037);
- Subgroup analysis reveals individual triptans are superior to placebo in achieving pain freedom at 2 h
    - PO Rizatriptan 5 mg (RR 1.34; 95%CI 1.13 to 1.60) (4 RCTs, n=1,438);
    - Sumatriptan PO 25, 50, 100 mg and IN 5, 10, 20 mg (RR 1.27; 95%CI 1.10 to 1.48) (10 RCTs, n=2,299);
    - Zolmitriptan PO 2.5, 5 , 10 mg and IN 0.5, 2.5, 5 mg (RR 1.66; 95%CI 1.16 to 2.38) (4 RCTs, n=1,480);
    - Whilst PO almotriptan (1 RCT), eletriptan (1 RCT) and naratriptan (1 RCT) have not demonstrated superiority to placebo;

The authors concluded it is not possible to recommend one triptan over another.

Subsequent to the above Cochrane review, in adolescents (12–17 y) IN zolmitriptan 5 mg vs placebo achieved pain-freedom at 2 h (30% vs 17), headache relief at 2 h (51% vs 39) and reduced rescue medication use up to 24 h post-treatment (20.3% vs 31.6) (Winner 2016 **Level II**, n=798, JS 4). Mild to moderate adverse events were more common with zolmitriptan (25.5% vs 9.9%); most commonly disturbed taste.

Three dose combinations of sumatriptan/naproxen (10/60, 30/180 and 85/500 mg) in adolescents (12–17 y) achieved pain freedom at 2 h for 29, 27 and 24% vs 10% of placebo treated patients (Derosier 2012 **Level II**, n=589, JS 5). The higher 85/500 mg dose has shown efficacy in two subsequent repeated use studies of adolescents (12–17 y) with recurrent migraine. When instructed to take early (within 1 h) vs placebo, pain freedom at 2 h was higher (37% vs 18); there was no difference in sustained pain-free response up to 24 h (86% vs 78), but more adverse effects (eg neck spasm/tightness, drowsiness, throat tightness) with sumatriptan/naproxen (10.8% vs 3) (Winner 2015 **Level II**, n=94 [347 migraines], JS 4). While in a case series, 42% achieved pain freedom at 2 h (McDonald 2011 **Level IV**, n=622 adolescents [12,957 exposures]).

Pharmacokinetics of triptans in adolescents

Iontophoretic sumatriptan patch (6.5 mg delivered over 4 h to upper arm or thigh skin) in adolescents (12–17 y) resulted in similar systemic exposure vs adults (Gutman 2016 **Level III-3 PK**, n=37). IN zolmitriptan (5 mg) in adolescents (12–17 y) and adults resulted in similar plasma concentrations of zolmitriptan and its active metabolite (Zhou 2017 **Level IV PK**, n=30). The authors used a simulation model to predict dosing in young children, but absorption kinetics from the smaller nasal mucosa is unknown making the model's clinical application questionable.

10.9.3.2 | Intravenous (IV) therapies

Intravenous (IV) therapies for acute childhood migraine are administered in the ED, outpatient infusion clinics or during inpatient admission. In practice, they are usually second or third line interventions in varying combinations given to patients who have not responded adequately to PO/IN intervention. Various medications and combinations have been reported as mostly level III and IV evidence making assessment of efficacy difficult.

Second line single and combination IV therapies

In 5–17 y olds, IV fluid bolus 10 mL/kg (0.9% sodium chloride) alone or with nurse administered placebo reduced migraine intensity 30 min post bolus (-12.5/100; 95%CI -17.2 to -7.8); expectation of additional drug treatment did not influence the effectiveness of IV fluid bolus (Richer 2014 **Level II**, n=47, JS 3). After failing at home treatments, IV prochlorperazine 0.15 mg/kg (max 10 mg) was superior to IV ketorolac 0.5 mg/kg (max 30 mg) in 5–18 y olds with complete resolution within 1 h in 85% vs 55% (SMD 30%; 95%CI 8 to 52%) (Brousseau 2004 **Level II**, n=62, JS 5).

When used in the ED for children and adolescents (<19 y) with ketorolac and usually diphenhydramine (given to 65–89%), treatment failure (defined as subsequent opioid administration) occurred less following IV prochlorperazine vs IV metoclopramide vs IV promethazine (8.7% vs 25 vs 43) (Sheridan 2018b **Level III-2**, n=67).

For paediatric patients, a standardised IV regimen including fluid bolus 20 mL/kg (0.9% sodium chloride: max 1 L)/ketorolac 0.5 mg/kg (max 30 mg)/prochlorperazine or metoclopramide 0.15 mg/kg (max 10 mg) or diphenhydramine 1 mg/kg (max 50 mg) vs a combination of various other regimens reduced pain scores (by 6.9/10 vs 5.3), ED LOS (4.4 h vs 5.3) and hospital admission rate (3% vs 32) without changes in ED return rate (Leung 2013 **Level III-3**, n=252). In 12–21 y olds who received an IV fluid bolus 20 mL/kg (± ketorolac), the addition of IV prochlorperazine (dose unspecified) vs IV chlorpromazine 0.1 mg/kg (max unspecified) had lower treatment failure (15% vs 40), hospital admission (4.7% vs 16) and rescue medication use (9.9% vs 29.3) (Kanis 2014 **Level III-3**, n=349).

In children, adolescents and young adults (mean age 15 y) attending an outpatient infusion centre, headache resolution was achieved 30 min post combination IV therapy with fluid bolus/ketorolac/metoclopramide or prochlorperazine and/or dexamethasone in 79% of visits; treatment success was less likely in those with increasing frequency of migraine headaches and medication overuse headache (Orr 2018b **Level IV**, n=543 [837 visits]). For severe migraine in <18 y olds, IV prochlorperazine 0.15 mg/kg (max 10 mg) and IV diphenhydramine 0.5 mg/kg (max 25 mg) administered in the ED resulted in a 14 and 21% treatment failure rate (further rescue therapy, hospitalisation or return visit to the ED within 48 h) (Trottier 2012 **Level IV**, n=79; Trottier 2010 **Level IV**, n=92). For 6–18 y olds with a step-up protocol dependent on medications taken prior, ED discharge rates were higher after intervention with combination IV ketorolac /IV antiemetic (prochlorperazine or ondansetron) (77% of 300 visits) vs IV ketorolac alone (56% of 39 visits) vs IV antiemetic alone (58% of 50 visits) vs PO or IN therapies (47% of 285 visits) (Aravamuthan 2017 **Level IV**, n=700 visits).

Third line IV therapies for refractory or status migrainosus

IV dihydroergotamine 0.1–1.0 mg/kg 6–8 hly and IV antiemetic (prochlorperazine, metoclopramide or ondansetron) administered to inpatients (<18 y) achieved complete or near complete headache resolution in 21–80% in 3 case series (Nelson 2017 **Level IV**, n=124 [145 admissions]; Kabbouche 2009 **Level IV**, n=32; Linder 1994 **Level IV**, n=30). Minor adverse effects were common (34–91%), including nausea and vomiting despite coadministered antiemetic therapy.

Mean length of stay was 3–3.7 d; one series reported mean admission cost of $US 7,569 (Nelson 2017 **Level IV**, n=145 [admissions]).

IV magnesium bolus 1–2 g max over 15–30 min administered in the ED substantially reduced pain severity in 35–48% of paediatric patients with severe migraine (Orr 2018 **Level IV SR**, 21 studies [2 magnesium IV, n=65]). See adult sections for NMDA antagonists Section 4.6.1.3 and Headache 8.6.5.1 and Migraine 8.6.5.2.

IV sodium valproate has been used in three case series: IV bolus 500–1000 mg in children and adolescents (<19 y) in the ED (Sheridan 2015 **Level IV**, n=12; Reiter 2005 **Level IV**, n=58) and IV bolus 20 mg/kg and infusion 1 mg/kg/h for 24 h in admitted children and adolescents (<18 y) (Zafar 2018 **Level IV**, n=83). In the first two series, pain scores reduced by a mean of 36 and 40% with low prevalence of minor adverse events (0 and 14%) eg dizziness and nausea. The third series reported complete resolution of migraine in 66% of patients, with nausea (8.4%) and vomiting (2.4%) the only adverse effects.

IV lidocaine (mean bolus 2.9 mg/kg and mean maximum infusion 1.6 mg/kg/h) administered in PICU for status migrainosus in children and adolescents (10–19 y) achieved 50% reduction in migraine pain intensity at 16.3 h (mean) with resolution at 19.3 h (mean) (Ayulo 2018 **Level IV**, n=31). Complete resolution occurred in 90.3% with one non-serious event (self-resolving chest pain and anxiety) and no serious side effects (see also Section 10.4.11 Systemic lidocaine infusions).

Low dose bolus IV propofol 0.25 mg/kg (1–5 doses) added to IV fluid bolus 20 mL/kg vs standard IV combination therapy of IV fluid bolus/ ketorolac 0.5 mg/kg (max 30 mg)/ diphenhydramine 1 mg/kg (max 50 mg)/metoclopramide 0.1 mg/kg (max 10 mg) in 7–19 y olds in the ED achieved similar pain reduction (51% vs 59) with less rebound headache at 24 h (7% vs 25) (Sheridan 2018a **Level II**, n=74, JS 2). This study was limited by the 5 minutely titration of propofol to a pain score of <4/10 and does not specify sedation scores or the mean dose or range given vs the fixed dosing of standard therapy.

10.9.3.3 | Nonpharmacological interventions for headache

Stress is considered a common trigger for headaches in children and adolescents (Bougea 2018 **NR**). Various preventive stress management strategies have been studied including yoga, relaxation therapy, biofeedback, hypnosis, massage therapy and acupuncture. Although many of these studies have positive results, their design is limited by small sample sizes, absence of controls and lack of follow-up. Whilst these strategies can be used for acute migraine management, many require skills that need to be developed with time and there is a literature gap on their use in this context.

Psychological interventions are effective as a preventive strategy for headache (Trautmann 2006 **Level I**, 23 RCTs [10 migraine/12 migraine & tension type/1 tension type only], n=999). Individual and group relaxation training, including progressive muscle relaxation (16 RCTs with 4 including stress/pain management strategies), biofeedback (7 RCTs) and cognitive behavioural therapy (10 RCTs) reduce the intensity of headache by ≥50% in 70% of adolescents vs 30% of waitlist controls. Treatment success is maintained for at least 1 y, although comparative efficacy with pharmacological treatments has not been investigated. An overlapping Cochrane review draws a similar conclusion for reduced headache frequency (RR 2.4; 95%CI 1.7 to 3.3) (15 RCTs, n=644) (Fisher 2018a **Level I** [Cochrane], 47 RCTs [23 headache], n=2,884) (14 RCT overlap). No impact on disability is demonstrated (6 RCTs, n=446). A meta-analysis on biofeedback only for prevention in paediatric (<18 y) migraine has been performed (Stubberud 2016 **Level I**, 5 RCTs, n=137) (1 & 3 RCT overlap). Biofeedback (EMG, peripheral skin temperature and blood-volume pulse biofeedback) vs waitlist control reduces migraine frequency (MD -1.97; 95%CI -2.72 to -1.21) (3 RCTs, n=72), attack duration (MD -3.94; 95%CI -5.57 to -2.31) (2 RCTs, n=48) and headache intensity (MD -

1.77/10; 95%CI -2.42 to -1.11) (2 RCTs, n=52), but is not superior to active treatment arms or effective as an adjuvant therapy.

Use of mind body techniques of transcendental meditation and hypnotherapy vs progressive muscle relaxation had similar reduction in headache frequency at 3 (37–44%) and 9 mth (42–53%) (Jong 2019 **Level II**, n=131, JS 3).

Following insertion of gold auricular acupuncture needles in 8–18 y olds presenting to the ED with severe migraine, mean pain scores reduced (from 7.63/10 to 0.55) only at 15 min, with 4 patients refusing treatment and 2 withdrawing post treatment initiation (Graff 2018 **Level IV**, n=19).

KEY MESSAGES

1. In children (<12 years), effective acute migraine treatments include ibuprofen and triptans (**Q**) (**Level I** [Cochrane]), however there is a significant placebo response rate in this setting.
2. In adolescents (12–17 years), triptans are effective acute migraine treatments, however there is a significant placebo response rate in this setting. One triptan cannot be recommended over another (**Q**) (**Level I** [Cochrane]).
3. Nonpharmacological preventive therapies including relaxation training and cognitive behavioural therapy reduce the frequency and intensity of headache in adolescents for 1 year (**S**) (**Level I** [Cochrane]). Biofeedback also reduces migraine attack duration (**S**) (**Level I**).

The following tick boxes represent conclusions based on clinical experience and expert opinion:

☑ Guidelines for the treatment of migraine in children and adolescents recommend environment modification, paracetamol, ibuprofen, naproxen (or other nonselective NSAIDs), dopamine antagonists (if nausea prominent), fluid therapy and triptans (**U**).

☑ Evidence is limited for standard of care second line therapies (single and multiple IV therapies including fluids and antiemetics) and third line therapies (such as IV dihydroergotamine, magnesium, sodium valproate, lidocaine or propofol) for acute childhood migraine (**N**).

☑ The use of psychological interventions and stress management strategies have not been assessed in acute migraine episodes; it must be recognised that many of these skills need to be developed over time (**N**).

10.9.4 | Acute abdominal pain in children

All medical causes of acute abdominal conditions are discussed in adult Section 8.6.1 (including renal and ureteral stones, biliary colic and acute pancreatitis, dysmenorrhoea, irritable bowel syndrome and colic). These also affect children and teenagers but are not reviewed separately here. The data for recurrent abdominal pain is presented below.

As for adults, early pain relief (usually in the form of opioids) does not interfere with the diagnostic process in acute abdominal pain in children (Green 2005 **Level II**, n=108, JS 5; Kim 2002 **Level II**, n=60, JS 5).

For abdominal pain associated with Henoch-Schonlein Purpura, see 10.4.10.1; and for the principles of management of abdomincal pain associated with haematological disorders see 10.9.5.

For CAMT interventions for infantile colic see Section 10.11.4.

10.9.4.1 | Recurrent abdominal pain (abdominal migraine)

Recurrent abdominal pain (RAP) or abdominal migraine presents to primary care and EDs and is functional and a diagnosis of exclusion (Brusaferro 2018 **NR**). It occurs usually in male school-aged children, sometimes adolescents, rarely in adults. RAP is characterised by recurrent attacks of acute abdominal pain, nausea, vomiting and often headaches.

There is currently no good evidence for the efficacy of any pharmacological treatment (tricyclic antidepressants, antibiotics, 5-HT4 receptor agonists, antispasmodics, antihistamines, H2 receptor antagonists, serotonin antagonists, selective serotonin re-uptake inhibitors, dopamine receptor antagonists, and hormones) in RAP in children (Martin 2017 **Level I** [Cochrane], 16 RCTs, n=1,024).

Probiotics are effective in improving pain in children with RAP vs placebo (NNT 8) (7 RCTs, n=722), however, based on moderate quality evidence (Newlove-Delgado 2017 **Level I** [Cochrane] 19 RCTs, n= 1,453). There is no convincing evidence that fibre-based interventions improve pain in children with RAP.

Cognitive Behavioural Therapy (CBT) (4 RCTs, n=175) and hypnotherapy/guided imagery (4 RCTs, n=146) reduce pain (in part or fully) in the short term (immediately to 1 or 3 mth) in children and adolescents presenting with RAP (Abbott 2017 **Level I** [Cochrane], 18 RCTs [10 CBT, 4 hypnosis], n=928).

KEY MESSAGES

1. Probiotics improve pain in children with recurrent abdominal pain versus placebo (**N**) (**Level I** [Cochrane Review]) with no good evidence for positive effect of various pharmacological treatments (**N**) (**Level I** [Cochrane Review]).
2. Cognitive behavioural therapy (CBT) and hypnotherapy reduce pain short term (over 1 to 3 months) in children and adolescents with recurrent abdominal pain (**N**) (**Level I** [Cochrane Review]).

10.9.5 | Acute pain associated with haematological disorders in children

10.9.5.1 | Sickle Cell Disease (SCD) in Children

Sickle cell disease (SCD) affects all age groups. Neonatal sceening is routinely available in resource rich countries with moderate prevalence, with some impact on global disease burden. Highest prevalence countries do not have the funds to screen. As is the case for adults, there is interindividual variability in the impact of SCD upon paediatric patients. Hydroxyurea prophylaxis, transcranial doppler and red cell exchange transfusion programs have had positive benefit, reducing vaso-occlusive crises (VOC) and emergency department (ED) presentation frequency and mortality (Lovett 2017 **NR**; Yawn 2015 **GL**), with subsequent reduced need for in hospital pain service input. The majority of ED visits and hospital admissions for patients with SCD are pain related (Glassberg 2017 **GL**).

The principles of care are the same as for adults and involve individual care plans and step-up analgesic administration for at home and in hospital analgesic escalation, combined with simultaneous treatment of the precipitants of infection, dehydration and hypoxia (Glassberg 2017 **GL**; Yawn 2015 **GL**; NICE 2012 **GL**). Paediatric centres have developed clinical care pathways eg those from www.chop.edu/clinical-pathway/sickle-cell-disease-with-pain-clinical-pathway and (Kavanagh 2015 **Level III-2**, n=289 [ED visits for VOC]). With clinical pathway introduction in an urban paediatric centre, time to first analgesic medication, time to first opioid and use of IV ketorolac improved (Ender 2014 **Level III-2**, n=68). Early achievement of maximum opioid analgesia improved hospitalisation outcomes in children (Payne 2018 **Level III-3**, n=108 [236 admissions]).

See adult Section 8.6.4 Acute pain associated with haematological disorders.

Pharmacogenomics relevant to SCD

There is increased prevalence of poor CYP2D6 metaboliser phenotype in populations of African descent. Children with sickle cell disease have had CYP2D6 geno-phenotyping where 44% had intermediate and 5.3% poor phenotype (Yee 2013 **Level IV**, n=75). This is an important consideration when choosing analgesic therapies for this patient group, where 27% of children ≤17 y with SCD have received codeine (Han 2018 **Level IV**, n=581 ≤ 19 y [opioid recipients]).

NSAIDs and opioid use in children with SCD

The use of an oral at home opioid protocol reduced the number of ED visits, time spent in the ED and hospital admissions over 12 mth for sickle cell pain (Conti 1996 **Level IV**, n=9; Friedman 1986 **Level IV**, n=15). Admission rates were lower following an initial paediatric ED intervention with nsNSAID/opioid combination vs opioid only (33% vs 64) (Cacciotti 2017 **Level III-3**, n=176). A paediatric ED treatment protocol administering PO paracetamol 15 mg/kg/ibuprofen 10 mg/kg/morphine 0.3 mg/kg for pain scores >5/10 reduced the number of patients requiring subsequent IV insertion for parenteral therapy, length of stay in the ED and hospital admission (Paquin 2019 **Level IV**, n=97 [147 visits]). Sustained-release PO morphine for children admitted with VOC was as effective as a continuous IV morphine infusion (Jacobson 1997 **Level II**, n=56, JS 5). However, in children treated with PO morphine vs IV morphine infusion, incidence of acute sickle chest syndrome and plasma concentrations of morphine and morphine-6-glucuronide (M6G) were significantly higher (Kopecky 2004 **Level II**, n=50, JS 4).

IV morphine PCA with bolus and background (mean 20 mcg/kg/h) has been used for children admitted with VOCs (Jacob 2008 **Level IV**, n=10 [48 admissions]). Postoperative PCA morphine requirements in children with SCD were almost double those of nonsickle children (Crawford 2006a **Level III-3**, n=22 [12 SCD]).

Acute kidney injury in SCD

Children with VOC with acute kidney injury had longer LOS; the risk of developing AKI increased for every additional day of ketorolac treatment (OR 1.63; 95%CI 1.08 to 2.47) (Baddam 2017 **Level III-3**, n=33 AKI patient events vs 164 without AKI).

Pruritus management related to opioid infusions

For children receiving morphine infusions for sickle cell crises, naloxone 1 mcg/kg/h more effectively decreased pruritus than 0.25 mcg/kg/h (Koch 2008 **Level IV**, n=16).

Intranasal opioid analgesia in SCD

IN fentanyl has been incorporated into clinical practice guidelines for VOC paediatric ED presentations (Carden 2018 **Level IV**, n=60; Kavanagh 2015 **Level III-2**, n=289 visits). IN fentanyl was a suitable alternative with reduced time to initiation of opioid analgesia (Kelly 2018 **Level III-2**, n=105 [487 visits]; Kavanagh 2015 **Level III-2**, n=128 [289 visits]). IN fentanyl vs placebo decreased pain scores at 20 min only (and not at 10 or 30) (Fein 2017 **Level II**, n=49, JS 5). IN fentanyl use increased the

proportion of patients discharged from the ED and reduced time to initiation of subsequent IV opioid including by PCA (Kavanagh 2015 **Level III-2**, n=289 visits); however in another study it did not reduce the need for IV opioid analgesia (Kelly 2018 **Level III-2**, n=487 visits).

IN diamorphine has been used for sickle cell crises and was effective in reducing pain scores (Telfer 2009 **Level IV**, n=21). It was introduced in an ED protocol as initial therapy 0.1 mg/kg (with optional IV morphine 100 mcg/kg). Subsequently the protocol was revised to coadministration with PO morphine 0.4 mg/kg (which could be repeated at 1 h) to reduce need for IV insertion.

Chronic opioid use in SCD including methadone

Over a 5 y period, children with SCD aged 0–9 y had a low prevalence of opioid use 8.5% vs teenagers 46.3% and vs adults 48.7 to 58.3% (Han 2018 **Level IV**, n=3,882 [2,123 ≤19 y]). Most patients (87% of children and 55% of adults) used <5 mg PO MED, but some used >30 mg PO MED (3% paediatric and 23% of adults). A subgroup of patients experience frequent painful VOCs with subsequent increased ED presentations and hospital admissions with pain recurrence that may require daily opioids. Adolescents with frequent recurrent (chronic) pain related to SCD were treated for several months with methadone (commenced at 12.5 mg, uptitrated to 30 mg/d max), with reduced hospitalisations from 0.35± 0.19 to 0.19 ± 0.17/mth (LeBlanc 2018 **Level IV**, n=16).

Corticosteroid use in SCD

In children, a 2 d course of IV methylprednisolone 15 mg/kg/d vs placebo decreased the duration of severe pain associated with acute VOCs; but patients who received methylprednisolone had more rebound attacks after therapy was discontinued (Dunlop 2006 **Level I** [Cochrane], 1 RCT (paediatric): Griffin 1994 **Level II**, n=36 [116 VOCs], JS 5).

Ketamine infusion in SCD

Beneficial use of low-dose IV ketamine infusion 0.05–0.4 mg/kg/h is described for children and adolescents with VOC usually in addition to or to replace opioid IV PCA (Puri 2019 **Level IV**, n=4; Sheehy 2015 **Level IV**, n=7; Zempsky 2010 **Level IV**, n=5) with reduction in pain scores and opioid requirement (Nobrega 2018 **Level IV**, n=80 [181 infusions]). A single dose given over 10 min of IV ketamine 1 mg/kg was non-inferior to IV morphine 0.1 mg/kg for VOC pain in children (Lubega 2018 **Level II**, n=240, JS 5). Both therapies impacted similarly on change in maximal pain scores by 66.4% vs 61.3; the reduction was achieved earlier for ketamine (at 20 min vs 34), but was shorter in duration (60 min vs 120) with increased transient side effects (37.5% vs 3.3).

Dexmedetomidine infusion in SCD

In children with refractory pain due to VOC despite nsNSAID/IV opioid/ketamine 0.1–0.3 mg/kg/h infusion, dexmedetomidine infusion 0.2–0.4 mcg/kg/h for up to 6 d duration has been used (Sheehy 2015 **Level IV**, n=3).

Inhaled nitric oxide

Nitric oxide deficiency or defective nitric oxide-dependent mechanisms may underlie many of the processes leading to vaso-occlusion. An early paediatric study suggested inhaled nitric oxide may be of benefit in painful acute VOC (Weiner 2003 **Level II**, n=25, JS 4); however, in young adults admitted with VOC, there was no difference between inhlaed nitric oxide vs nitrogen placebo in time to VOC resolution or LOS (Gladwin 2011 **Level II**, n=150, JS 5).

Inhlaed nitrous oxide (N_2O)

Despite the frequency of use of inhaled N_2O in paediatrics, there is no current data on the use of this agent specifically in VOC in children.

Rehydration

Hydration supplementation of patients with VOC is commonly practiced. Most children (84%) with VOC in the ED received fluids; a subanalysis of those who received normal saline bolus revealed less pain score improvements (Carden 2019 **Level IV**, n=400 [261 bolus]).

Oxygen

Oxygen supplementation is a standard of care despite old trials not supporting efficacy (see adult Section 8.6.4.1). Nocturnal oxygen desaturation was associated with a higher rate of painful VOC in children (Hargrave 2003 **Level IV**). Comorbid obstructive sleep apnoea (OSA) in children is associated with serious complications of SCD (Katz 2018 **Level III-3**, n=272 SCD [136 OSA]); a 6 wk pilot trial reports no rebound pain on CPAP cessation (Marshall 2009 **Level II**, n=24, JS 3).

Magnesium

Magnesium IV or PO therapy has no effect on reducing pain or LOS in adults or children with VOC (Than 2019 **Level I** [Cochrane], 5 RCTs [3 paediatric & 2 mixed], n=386).

Lidocaine infusion

IV lidocaine 1–2 mg/kg/h (17-33 mcg/kg/min) for 2 d has been used for VOC (resistant to PCA morphine) with analgesic benefit (Puri 2019 **Level IV**, n=2 [3 occasions]).

Vitamin D supplementation

Vitamin D deficiency has been associated with vaso-occlusive crises and acute pain in children and adolescents (1–20 y) with sickle cell disease (Adegoke 2017 **Level IV**, n=123; Lee 2015 **Level IV**, n=95). Vitamin D supplementation for acute pain management in this population has not been studied.

Nonpharmacological interventions

Psychological therapies such as relaxation, hypnosis and cognitive behavioural therapy (CBT) reduce pain immediately after treatment for other recurrent acute pain presentations; but 2–4 sessions of CBT in patients with SCD focusing on coping skills (1 RCT), pain management (1 RCT) or a family intervention (1 RCT) were not beneficial at 1–12 mth follow-up (Fisher 2018a **Level I** [Cochrane], 3 RCTs [SCD], n=174). In a further Cochrane review, CBT for adolescents with SCD did not reduce pain frequency (1 RCT, n=53) or health care utilisation (2 RCTs, n=68) (Anie 2015 **Level I** [Cochrane], 5 RCTs [adolescents & young adults], n=260) (2 RCT overlap). Internet delivered CBT was feasible and the impact on pain burden vs control (internet delivered pain education) can be assessed (Palermo 2018 **Level II**, n=25, JS 3). Although adherence to use of a smart phone app to guide CBT was low (12%), if the app was used on a day of high pain, next-day pain was reduced vs waitlist controls (Schatz 2015 **Level II**, n=46, JS 3).

Massage therapy in youth with SCD improved function and reduced pain, depression and anxiety (Lemanek 2009 **Level II**, n=34, JS 1). However, the parents (who performed the massage therapy) had higher levels of anxiety and depression following the intervention. In children admitted with VOC, yoga vs listening to relaxing music reduced pain but not anxiety scores with the first but not subsequent sessions (Moody 2017 **Level II**, n=73, JS 2).

Prevention of painful VOC in children

Hydroxyurea (or hydroxycarbamide) 15–25 mg/kg for 10–24 mth vs placebo improved pain outcomes: pain scores (1 RCT n=193) with reduced frequency of pain crises (4 RCTs, n=577), acute chest syndrome (RR 0.43; 95% CI 0.29 to 0.63) (2 RCTs, n=492) and hospitalisations (1 RCT, n=60) (Nevitt 2017 **Level I** [Cochrane], 8 RCTs [6 paediatric only & 2 mixed], n=899). Hydroxyurea improves only fetal haemoglobin level vs control (observation: 1 RCT [paediatric], n=22) or when added to

magnesium therapy (1 RCT [mixed], n=44). Guidelines based upon this data as to when to institute hydroxyurea therapy in children (and adults) are available (Qureshi 2018 **GL**).

Zinc supplementation reduces the incidence of painful VOC in children and adults (Nagalla 2018 **Level I** [Cochrane], 1 RCT [zinc], n=145). While the evidence in children for piracetam is insufficient to support its use (Al Hajeri 2016 **Level I** [Cochrane], 3 RCTs, n=169) and is negative for prasugrel (Heeney 2016 **Level II**, n=341, JS 5).

10.9.5.2 | Haemophilia

As in adults, pain in children with haemophilia A (Factor VII) and B (Factor IX deficiency) is either recurrent acute, related to spontaneous or injury-related bleeding into joints, muscles (and rarely viscera), or chronic with secondary painful arthropathies. Preventative use of recombinant factor concentrates has had greater positive impact on pain management in affected children vs acute 'on demand' treatment (Usuba 2019, **Level III-3**, n=401).

There is no data or evidence base specifically for haemophilia but guidelines as referenced in the adult Section (See 8.6.4.2) are available (Holstein 2012 **Level IV**, n=1,678 children & 5,103 adults). The principles involve rest, ice, compression and elevation, paracetamol and escalated therapy at home or in hospital including adjuvants and nonpharmacological intervention. The use of analgesic medication needs to be encouraged (Rambod 2016 **Level IV**, n=154), possibly through education of parents of young affected children and guideline creation by haematologists in conjunction with primary care and pain specialists.

KEY MESSAGES

Sickle cell disease

1. Hydroxyurea decreases the frequency of acute vaso-occlusive crises, life-threatening complications and hospitalisations in children with sickle cell disease (**S**) (**Level I** [Cochrane Review]).
2. Intravneous or oral magnesium does not reduce pain of vaso-occlusive crises associated with sickle cell crises or length of hospital stay (**N**) (**Level I** [Cochrane Review]).
3. Attention must be paid to acute kidney injury risk in sicker inpatients with sickle cell disease receiving multiple doses of nsNSAID (**N**) (**Level III-3**).
4. Parenteral corticosteroids reduced the duration of severe pain in children with vaso-occlusive crises in sickle cell disease at the expense of more rebound attacks post cessation (**Q**) (**Level II**).

The following tick boxes represent conclusions based on clinical experience and expert opinion:

☑ It is standard of care for oral and IV paracetamol, nsNSAIDs and opioids to form part of an individual at home or hospital care plan for children with vaso-occlusive crises. Upon admission this is escalated to parenteral nsNSAID and opioid therapy (**N**).

☑ There is no evidence that fluid replacement therapy reduces pain in children with VOC, although it is common practice (**N**).

☑ The impact on painful vaso-occlusive crises of oxygen supplementation in patients with and without obstructive sleep apnoea and CPAP in patients with obstructive sleep apnoea requires assessment (**N**).

☑ Most children with sickle cell disease are not on opioids for chronic or frequent recurrent pain (while adolescents are, at similar rates to affected adults). In patients with sickle cell disease, postoperative opioid requirements may be higher (**N**).

☑ Adjunctive low-dose ketamine and IV lidocaine infusions reduce pain intensity and opioid requirements in refractory pain of acute vaso-occlusive crisis in children with sickle cell disease (**N**).

Haemophilia

☑ In children with haemophilia, on demand and preventative use of recombinant factor concentrates has improved pain-related quality of life measures. Otherwise the principles of pain management in acute bleeds in affected children and adults involve rest, ice, compression and elevation and stepwise escalation of analgesia. Parents of young affected children need education regarding analgesic medication (**N**).

10.10 | The overweight or obese child or adolescent

10.10.1 | Definitions of obesity

Obesity in childhood has been defined in various ways. The ideal definition based on percentage body fat is not practical for epidemiological use (Cole 2000 **Level IV**, n=192,727). Body mass index [BMI] is widely used but has limitations. In children, it varies substantially with age and sex (Chidambaran 2018 **NR**), does not discriminate between lean and fat mass, provides poor height standardisation for weight, and is not a consistent marker of body fat across ethnic groups (Hudda 2019 **Level IV**). Internationally, BMI cut-offs used for overweight and obesity vary. Both Australia (ABS 2018 **Level IV**) and New Zealand (NZ MoH 2018 **Level IV**) use the International Obesity Taskforce cut-offs developed for children aged 2–18 y (Cole 2000 **Level IV**, n=192,727). These are linked to adult BMI cut-offs at 18 y which have been related to health risk. The WHO defines cut-offs for overweight and obesity in SD: for 0-5 y, using the WHO median growth standard weight for length/height (overweight ≥ 2 SD; obese ≥ 3 SD) (de Onis 2010 **Level III-3**); for 5-19 y, using the WHO median growth reference of BMI for age (overweight ≥ 1 SD; obese ≥ 2 SD) (de Onis 2007 **Level IV**, n=30,018).

10.10.2 | Prevalence of childhood obesity

Global age standardised obesity prevalence increased in girls and boys respectively from 0.7 and 0.9% in 1975 to 5.6 and 7.8% in 2016 (NCD-RisC 2017 **Level IV**). The latter equates to 50 million obese girls and 74 million obese boys worldwide. In several countries, the prevalence of obesity was ≥20% such as the Middle East, North Africa, the Caribbean and Polynesian region and >30% in the Pacific Islands. The trends in mean BMI have accelerated in South East Asia, with flattening for North Western Europe and the high income English speaking countries.

In the USA, childhood (2–19 y) obesity prevalence increased from 5.5% (1976–1980) to 17.1% (2003–04) and 18.5% (2015–16) (National Center for Health Statistics 2019 **Level IV**). In Australia and New Zealand, the increase in obesity has been less marked. In Australia, obesity prevalence in 5–17 y olds increased from 5% (1995) to 8% (2007–08) (ABS 2009 **NR**); when combined with those overweight, the prevalence rates were 22% in 1995 increasing to 25% in 2007–08 and have remained stable since (ABS 2018 **Level IV**). In New Zealand, the prevalence of obesity in 2–14 y olds has increased from 8.4% (2006–07) to 12.4% (2017–18); when combined with those overweight the total prevalence was 21% in 2006–07, increasing to 31.9% in 2017–18 (NZ MoH 2018 **Level IV**).

10.10.3 | Morbidity associated with paediatric obesity

Obesity is a risk factor for morbidity in children including: sleep-disordered breathing [SDB] incorporating obstructive sleep apnoea [OSA], dyslipidaemia, hypertension, atherosclerosis, left ventricular hypertrophy, impaired glucose tolerance and type 2 diabetes mellitus, metabolic syndrome, non-alcoholic fatty liver disease and non-alcoholic steatohepatitis (Chidambaran 2018 **NR**). The most immediately relevant condition to acute pain management is SDB/OSA, and the increased risk of ventilatory impairment with opioids and other sedative/hypnotics. The prevalence of OSA varied from 13–36% in obese children and adolescents, and was 24–77% in obese children and adolescents with symptoms of SDB (Baker 2017 **Level IV**, n=224 [148 obese]; Verhulst 2008 **NR**, 6 case series, n=269).

See also Section 10.4.4.5 for information regarding mortality in obese children related to codeine and for adults see sections 9.4 and 9.5.

10.10.4 | Medication dosing in paediatric obesity

When dosing a medication, its volume of distribution (Vd), clearance (CL) and pharmacodynamics should be considered (Anderson 1997 **NR**); however this can be challenging to apply in practice. Furthermore, obesity can influence pharmacokinetics (PKs) through its effects on body size, body composition and organ function, as well as being a risk factor for comorbid disease. Its influence is unpredictable and can place the patient at risk of both underdosing and overdosing of medication (Samuels 2016 **NR**). For example, the Vd for lipophilic drugs may be increased, unchanged or reduced, and for hydrophilic drugs may be unchanged or reduced (Chidambaran 2018 **NR**). In paediatrics, the influence of maturation and growth on Vd, CL and pharmacodynamics must also be considered.

Barriers to appropriate drug dosing in overweight and obese children include: a paucity of paediatric bariatric pharmacokinetic data (Chidambaran 2018 **NR**); the range of doses calculated for a given drug from the many size descriptors that have been proposed (Chidambaran 2018 **NR**); a requirement to use different size descriptors for initial dosing and maintenance dosing for some drugs (Anderson 2017a **NR PK**); and cumbersome dosing calculations that may lead to temptation for arbitrary or "educated guess" dose adjustment in the clinical setting (Callaghan 2015 **Level III-2**). Given the barriers to accurate dosing in overweight and obese children, authors have emphasised the importance of judicious dosing and titration to effect wherever possible (Baines 2011 **NR**; Samuels 2006 **NR**).

Lean body mass (LBM) and ideal body weight (IBW) have been recommended for dosing many drugs in overweight and obese patients. A nomogram (https://onlinelibrary.wiley.com/doi/full/10.1111/anae.12860) developed from UK data of children >5 y was created to facilitate calculations of LBM and IBW in a perioperative setting or urgent drug dose calculation scenario (Callaghan 2015 **Level III-2**). It was quicker to use, with less mistakes and similar accuracy compared to calculations using equations. Other proposed size descriptors for various drugs have included: total body weight, dosing weight, adjusted body weight, predicted body weight, PK mass, fat free mass, normal fat mass, body surface area and BMI (Anderson 2017a **NR**). For some medications, LBM may work eg for maintenance dosing of remifentanil or dexmedetomidine and for others ideal body weight may fit eg for benzodiazepines, while for further medications (eg paracetamol) neither may be appropriate.

Total body mass can be partitioned into fat and fat-free components. The relative influence of fat mass compared with fat free mass on a drug's pharmacokinetics differs for each drug. The size descriptor "normal fat mass" is based on allometric theory and accounts for the relative influence of fat mass. It calculates a drug and PK parameter specific mass that can range from fat free mass to total body weight (Anderson 2017a **NR PK**). Calculating normal fat mass for drug dosing has been proposed as a principle-based approach that accounts for size and body composition effects on PKs of all drugs in children and adults of all sizes.

Concerns have been raised about increased risk of toxicity in obese patients when weight-based dosing exceeds the recommended maximum dose. An important example is paracetamol, where CYP2E1, the enzyme responsible for metabolising paracetamol to its toxic metabolite N-acetyl-p-benzoquinone-imine (NAPBQI), may be induced in obesity with potentially increased NAPBQI production (Hakim 2019 **Level IV PK**), although this concern remains poorly documented. Available data suggest uncompromised clearance and low plasma concentrations of paracetamol were achieved in obese adolescents when given routine doses (1 g 6 hly) (Hakim 2019 **Level IV PK**). There are few paediatric data available, despite one unpublished coroner reported death due to

hepatic failure of an obese child who received paracetamol dosed per kg without allometric scaling. The influence of obesity on paracetamol toxicity, if any, is unknown.

Obesity has been described as a chronic inflammatory state and associated with other changes in the enzyme activity of metabolic and elimination pathways (Brill 2012 **NR**). However, the clinical relevance of many of these changes is questionable. In the absence of data, dosing by IBW for age is considered reasonably safe, but capping at usual adult maximums will likely result in underdosing. Pharmacokinetic and pharmacodynamic study for individual drugs is required to establish whether this provides effective analgesia in the overweight and obese.

10.10.5 | Weight/mass adjusted dosing for individual drugs

The terms weight and mass are used interchangeably in the literature (eg ideal body mass = ideal body weight). Due to limited data in overweight and obese children and adolescents, suggestions are typically based on studies of obese adults and normal weight children (See Table 10.11).

Table 10.11 | Dosing suggestions for common analgesics relevant to body weight

Analgesic	Initial dosing	Maintenance dosing	Dosing not specified as initial or maintenance	References
Morphine	Ideal BW	Ideal BW		Mortensen 2011
			Ideal BW	Chidambaran 2018
Fentanyl	Total BW	Lean BW		Mortensen 2011
			Lean body mass/PK mass	Chidambaran 2018
Alfentanil	Total BW	Lean BW		Mortensen 2011
			Lean BW/Total BW	Chidambaran 2018
Sufentanil	Total BW	Total BW		Mortensen 2011
			Total BW	Chidambaran 2018
Remifentanil	Lean BW	Lean BW		Mortensen 2011
			Lean body mass/Ideal BW	Chidambaran 2018
Ketamine	Nil data	Nil data		
Lidocaine	Total BW	Ideal BW		Chidambaran 2018
Paracetamol			Total BW with allometric scaling (single dose only)	Hakim 2019
Ibuprofen			Total BW with allometric scaling (multidose)	Anderson 2019

BW=body weight

KEY MESSAGES

The following tick boxes represent conclusions based on clinical experience and expert opinion:

☑ When dosing medication in the overweight or obese child or adolescent, age of the patient, each individual drug and the dose type (initial or maintenance) must be considered (**N**).

☑ Given the barriers to accurate dosing in overweight and obese children, judicious dosing and titration to effect wherever possible is recommended. This requires consideration of both pharmacokinetic and pharmacodynamic factors (**N**).

☑ Young and obese children with history of obstructive sleep apnoea syndrome/sleep-disordered breathing are at higher risk of developing serious opioid-induced ventilatory impairment and death (**U**) (**Level IV**).

10.11 | Complementary and alternative medicines and therapies in children

Complementary medicines and therapies are defined as evidence-based health care approaches developed outside of conventional Western medicine; they are used in conjunction with conventional care (McClafferty 2017 **NR**). Alternative medicines and therapies are used in place of conventional care. Complementary and alternative medicines and therapies (CAMTs) are commonly used in communities. Increasingly, complementary medicines and therapies are used as part of integrative approaches to hospital-based healthcare in the paediatric population. Therefore, there is a need for health care professionals managing acute pain to be informed about CAMTs and, where relevant, their potential drug interactions. The evidence for CAMTs is limited by the large degree of heterogeneity of the various interventions and small sample sizes resulting in low level power to detect differences.

See also adult Section on CAMs 4.14. Studies relevant to photobiomodulation use in paediatric dental, cleft and tonsillectomy are not discussed here but are included in the adult Section 7.4.

10.11.1 | Natural products

Aromatherapy

Studies on aromatherapy for paediatric acute pain show mixed results (Dimitriou 2017 **Level I** [PRISMA], 9 RCTs [2 paediatric], n=644 [112]; Lakhan 2016 **Level III-3** [PRISMA], 12 studies [3 paediatric], n=1,019) (2 study overlap):

- In 6–12 y olds post-tonsillectomy, lavender essential oil (in addition to paracetamol every 6 h) rubbed onto the palms and inhaled 6 h prn did not reduce pain intensity, but did reduce paracetamol use (1 RCT: Soltani 2013 **Level II**, n=48, JS 2);
- In infants (3–36 mth) following craniofacial surgery, massage with mandarin oil vs massage with a carrier oil did not reduce pain scores, HR or mean arterial pressure (1 RCT: de Jong 2012 **Level II**, n=60, JS 3);
- In 3–6 y olds having various surgery types (mostly thoraco-abdominal), *rosa damascena* essential oil vs sweet almond oil (placed on a small pad, adjacent to the head) postoperatively every 3 h for 12 h reduced mean pain scores 3–12 h postoperatively (1 RCT: Marofi 2015 **Level II**, n=64, JS2).

Melatonin

Melatonin is a neurohormone synthesised endogenously by the pineal gland from the amino acid tryptophan. Antinociceptive effects of melatonin have been demonstrated in animal models and, in addition to acting on melatonin receptors (MT1/MT2), other proposed analgesic mechanisms include modulation of opioid, benzodiazepine, alpha adrenergic, serotonergic and cholinergic receptors (Srinivasan 2012 **NR**). Although exogenous melatonin is commonly used in paediatrics, clinical studies on its use as an analgesic in children are lacking (Marseglia 2015a **NR**). In children 1–14 y, PO melatonin 0.5 mg/kg (max 5 mg) vs placebo 30 min prior to venipuncture reduced preprocedural anxiety (mean 1.3/5 vs 2.2) and pain scores during venipuncture (for ≤3 y olds, mean 2.5/10 vs 3.2; and for >3 y olds, mean 1.2/10 vs 2.1) (Marseglia 2015b **Level II**, n=60, JS 5).

Honey

Honey in children vs placebo reduces pain and analgesic use for up to 5–10 d post-tonsillectomy; regimens of honey administered varied substantially in volume (4–15 mL), frequency (daily to

hourly) and duration (1–10 d) (Lal 2017 **Level I** [QUOROM], 8 RCTs, n=545; Hwang 2016b **Level I** [PRISMA], 4 RCTs, n=264) (4 RCTs overlap). The analgesic medication regimens used in included studies was not clear. An RCT not included in the meta-analyses found that onset to pain relief was faster, pain severity was lower and the need for rescue analgesia was less in the honey recipients vs controls (Mohebbi 2014 **Level II**, n=80, JS 2).

For neonates having a heel lance, honey vs water reduced cry duration (Bueno 2013 **Level III-1** [PRISMA], 1 study: Ramenghi 2001 **Level III-1**, n=15).

See Section 10.7.1–2 for use of sweet solutions in procedural pain in children.

Turmeric and Ginger (Zingiberaceae)

Zingiberaceae include *Curcuma longa* (turmeric), *Zingiber officinale* (ginger), *Curcuma zanthorrhiza* (Javanese ginger) and *Alpinia galanga* (galangal). Curcumin (diferuloyl methane) is the principal curcuminoid of the Indian spice turmeric, while the anti-inflammatory components of ginger are gingerol and zingerone. The available systematic reviews have assessed efficacy for pain in adults. There have been no peer reviewed publications in children regarding analgesic efficacy, although conference abstracts reflect growing interest for use of turmeric in juvenile arthritis. Efficacy of ginger in nausea and vomiting is not presented here.

Supplements and vitamins

Fish oil (500 mg/d) and vitamin B1 (100 mg/d) alone or in combination vs placebo improved pain intensity and reduced duration of pain in 13–18 y old girls with dysmenorrhoea; comparisons between active arms were not reported (Hosseinlou 2014 **Level II**, n=240, JS 3). In adolescents with dysmenorrhoea, zinc 50 mg/d during menstruation reduced the mean duration of pain in 3 menstrual cycles, and mean pain scores in two of three menstrual cycles (Zekavat 2015 **Level II**, n=120, JS 5).

Perioperative enteral docosahexaenoic acid (DHEA) 37.5 mg/kg two times daily vs sunflower oil in neonates (>34/40 wk gestational age) having cardiovascular surgery (without cardiopulmonary bypass eg Blalock-Taussig shunt or aortoplasty) reduced postoperative IV buprenorphine requirements (14.6 mcg/kg vs 25.2) and duration (2 d vs 4.5) (Bernabe-Garcia 2016 **Level II**, n=35, JS 4).

Vitamin D supplementation for acute pain management in children has not been studied (see paediatric sickle cell disease Section 10.9.5.1 for comment on Vitamin D deficiency in sickle cell disease).

10.11.2 | Acupuncture

Acupuncture (invasive [skin breaking] or non-invasive eg pressure, laser or transcutaneous electrical) for preterm and term neonates receiving heel lance does not reduce pain intensity (Stadler 2019 **Level I** [PRISMA], 5 RCTs, n=265). Individual RCTs found mixed results: two RCTs showed reduced pain scores with acupuncture, one RCT showed no difference vs control, and two RCTs showed increased pain with acupuncture. A subsequent RCT found auricular non-invasive magnetic acupuncture vs placebo reduced pain scores during (mean 5.9/21 vs 8.3) but not after heel lance in preterm and term neonates (Chen 2017a **Level II**, n=26, JS 3).

Perioperative acupuncture (including electroacupuncture) vs control in children and adolescents (<18 y) having tonsillectomy reduces pain intensity (4–48 h) (4 RCTs, n=234 [3 paediatric, n=201]) and analgesic consumption postoperatively (4 RCTs, n=232 [3 paediatric, n=199]) (Cho 2016 **Level I** [PRISMA], 12 RCTs, n=1,025 [11 paediatric, n=910]). Similar results are reported by an overlapping systematic review of RCTs and non-RCTs (Pouy 2019 **Level IV SR**, 9 RCTs and 3 studies, n=910 children) (9 RCT overlap).

For bilateral myringotomy and tympanostomy tube insertion, intraoperative acupuncture vs control in 1–6 y olds reduced postoperative pain, agitation and analgesic use, with increased time to first analgesic request (Lin 2009 **Level II**, n=60, JS 3).

For percutaneous kidney biopsy in 7–26 y olds, there was no difference in pain scores between laser acupuncture vs placebo groups (during or after the procedure) where all pain scores were low (<2/10) (Oates 2017 **Level II**, n=66, JS 5). Change in self-reported pain scores from during the procedure to after the procedure were mildly greater with laser (-0.8/10 vs -0.5).

For dental treatment, acupuncture (at the LI4 point bilaterally) in children and adolescents 4–18 y reduced self-reported pain intensity (2.3/10 vs 3.9) during local anaesthetic injection (Usichenko 2016 **Level II**, n=49 [98 injections], JS 3).

For 8–18 y olds presenting to the ED with severe migraine, pain scores reduced (mean from 7.63/10 to 0.55) at 15 min following insertion of gold auricular acupuncture needles, with 4 patients refusing treatment and 2 withdrawing post treatment initiation (Graff 2018 **Level IV**, n=23).

Acupuncture has been used in postoperative patients 0.5–18 y admitted to intensive care (Wu 2009 **Level IV**, n=20) and in 10–17 y olds with appendicitis in the ED (Nager 2015 **Level IV**, n=6); however efficacy was not adequately assessed.

For further discussion of acupuncture for acute pain in adults see Section 7.3.

10.11.3 | Mind-body practices

10.11.3.1 | Hypnosis

Hypnosis encompasses a variety of interventions (eg self-hypnosis, hypnotic guided imagery), and requires the skills of a trained health professional and time for the child to learn the technique. It has been studied mostly for procedural pain management. Hypnosis vs control for needle-related procedural pain reduces pain intensity (SMD: -1.4; 95%CI -2.32 to -0.48) (5 RCTs, n=176), distress (SMD: -2.53; 95%CI -3.93 to -1.12) (5 RCTs, n=176) and behavioural measures of distress (SMD: -1.15; 95%CI -1.76 to -0.53) (6 RCTs, n=193) (Birnie 2018 **Level I** [Cochrane], 59 RCTs, n=5,550). For children undergoing cancer-related procedures hypnosis is an effective pain-control technique (Tome-Pires 2012 **Level I**, 10 RCTs [cancer procedural pain], n=394) (5 RCT overlap). A subsequent review of oncology patients found hypnosis reduces pain scores vs treatment as usual (Cohen's d 2.16; 95%CI 1.41 to 2.92) and vs controls having attention focus (Cohen's d 2.24; 95%CI 1.66 to 2.82) but not vs active control groups (eg music, play, audiobooks) (Nunns 2018 **Level I** [PRISMA], 15 RCTs [8 hypnosis], n=585 [337]) (6 & 6 RCT overlap).

Hypnosis had no effect on pain and wound healing for burn dressing changes but reduced preprocedural anxiety on the second of three burns dressing changes (MD -0.8/10; 95%CI -1.5 to -0.1) (Chester 2018 **Level II**, n=62, JS 3).

Hypnosis interventions have been studied for postoperative pain (including Nuss procedure, spinal fusion, tonsillectomy) with mixed results, and no conclusions on its efficacy can be drawn in this setting (Accardi 2009 **Level III-3 SR**, 13 studies [3 postoperative], n=528; Duparc-Alegria 2018 **Level II**, n=120, JS 2; Manworren 2018 **Level III-2**, n=53). See also adult section 7.1.4 Hypnosis.

10.11.3.2 | Mindfulness-based interventions (attention and meditation)

Mindful attention vs guided imagery helped children 10–14 y focus their attention on experimental pain (cold pressor) without increasing pain intensity or decreasing tolerance (Petter 2013 **Level II EH**, n=82, JS 2). While in adolescents 13–18 y, mindful attention vs guided imagery prior to experiencing experimental pain (cold pressor) did not change pain intensity or tolerance overall; however in the subgroup who meditated regularly, mindful attention did reduce pain intensity (Petter 2014 **Level II EH**, n=198, JS 2).

Instructor taught Mantram meditation (commenced prior to infusion commencement) has been used successfully by children 3–14 y with high risk neuroblastoma experiencing pain from anti-glycolipid disialoganglioside (GD)-2 monoclonal antibody infusions (Ahmed 2014 **Level IV**, n=34). See also adult sections 7.1.3 Mindfulness-based interventions and 7.1.5 Attentional techniques.

10.11.3.3 | Guided imagery, relaxation and biofeedback

Postoperative guided imagery (at least 3 times a week)/standard care vs standard care alone reduced pain intensity following spinal fusion surgery for scoliosis in 11–20 y olds (Charette 2015 **Level II**, n=40, JS 3). Preoperative relaxation-guided imagery vs control in 6–12 y olds (having inguinal hernia repair, phimosis repair or endoscopy) reduced mean pain scores 2 h postoperatively (4.5/10 vs 7.7) (Vagnoli 2019 **Level II**, n=60, JS 3).

Relaxation and biofeedback vs control for 12 y olds receiving venipuncture did not lower pain intensity during the procedure (Forsner 2014 **Level III-2**, n=109). Relaxation therapy and guided imagery had similar effects on cortisol reactivity, self-reported stress, pain intensity and pain unpleasantness in females 11–12 y receiving the HPV vaccine (Nilsson 2015 **Level III-2**, n=37).

In children 8–14 y having cancer-related procedures, a 4-session intervention of preprocedural relaxation plus biofeedback progressively reduced state anxiety across the sessions, with improvement in heart rate variability; 81% of participants reported the combination of relaxation and biofeedback helped them feel in control of their bodies prior to the procedure (Shockey 2013 **Level IV**, n=12). In patients 7–18 y undergoing needle-related procedures and using 'Brighthearts' (a biofeedback assisted relaxation application), 83% reported the app was helpful and would use it again, 100% of parents and 96% of healthcare providers indicated they would use it again, and 64% of the healthcare providers perceived that it assisted with the ease of performing a procedure (Burton 2018 **Level IV**, n=107 [30 patients, 27 parents, 50 health providers]).

10.11.3.1 | Physical and other complementary therapies

Other complementary therapies have been assessed for acute pain management with studies reporting mixed results: massage therapy (Staveski 2018 **Level II**, n=60, JS 3; de Jong 2012 **Level II**, n=60, JS 3), Therapeutic Touch (Johnston 2013 **Level II**, n=55, JS 2), Reiki (Kundu 2014 **Level II**, n=38, JS 5), yoga (Moody 2017 **Level II**, n=70, JS 3), reflexology (Koc 2015 **Level II**, n=60, JS 2) and Korean hand therapy (Ochi 2015 **Level IV**, n=29). Conclusions on their effectiveness cannot be made due to small samples and study designs prone to bias.

See also adult sections regarding massage and yoga in 7.5 Physical therapies.

10.11.4 | Infantile colic

Infantile colic can be defined as excessive crying in the first few months of life; the most cited clinical diagnostic criteria is the rule of 3s: crying for longer than 3 h/d for ≥3 d/wk for at least 3 wk (Biagioli 2016 **Level III-1 SR** [Cochrane], 18 RCTs, n=1,014). In mothers who had used complementary medicine (mostly homeopathic remedies, probiotics or herbal medicines) to treat their infant's colic where 73% was alongside conventional medicine treatments, 66% felt it was effective and 47% reported no side effects (Di Gaspero 2019 **Level IV**, n=152).

Oral herbal, antifoaming, sweet solution or anticholinergic agents

Various pain-relieving agents to treat colic have been studied: herbal agents (defined as plant derived remedies), (6 studies, n=427), simethicone (4 studies, n=166), sweet solution [sucrose or

glucose] (3 studies, n=120), dicyclomine (5 studies, n=137) and cimetropium bromide (2 studies, n=126) (Biagioli 2016 **Level III-1** [Cochrane], 18 RCTs, n=1,014). Although some of these studies found positive results, reported benefits are inconsistent, and study designs are prone to bias, with the authors concluding that none of these agents could be recommended. Additionally, a subsequent systematic review of systematic reviews found supporting evidence specifically for fennel extract, but methodological issues with studies call this result into question (Perry 2019 **Level I** [PRISMA], 16 SRs [5 herbal medicine SRs], n RCTs unspecified).

Probiotics

Three systematic reviews have reported on the efficacy of probiotics for infantile colic. These draw the same conclusion: *Lactobacillus reuteri* (10^8 colony forming units daily for 21 or 28 d) is effective at reducing cry/fuss time >50%: RR 2.34 (95%CI unspecified) (5 RCTs, n=317) (Schreck Bird 2017 **Level I** [PRISMA], 5 RCTs, n=388); RR 1.67 (95%CI 1.10 to 2.81) (6 RCTs, n=391) (Dryl 2018 **Level I** [PRISMA], 7 RCTs, n=471); RR 1.71 (95%CI 1.35 to 2.15) (4 RCTs, n=293) (Sung 2018 **Level I** [PRISMA], 4 RCTs, n=345) (4 RCT overlap). Most infants included in these RCTs were breastfed (although not all exclusively). There is insufficient evidence for probiotics in formula fed infants (Sung 2018 **Level I** [PRISMA], 1 RCT [formula fed], n=66 (21 d)]. A systematic review of systematic reviews identified a further 4 older reviews that drew similar conclusions (Perry 2019 **Level I** [PRISMA], 16 SRs [7 probiotic], n RCTs unspecified). A Cochrane review assessed probiotics for prevention of colic in infants (<1 mth old at recruitment) where probiotics vs placebo did not reduce the number of new cases of infantile colic (3 RCTs, n=1,148), but did reduce the duration of crying (MD -32.6 min/d; 95%CI -55.6 to -9.54) (3 RCTs, n=707); there was no difference in the incidence of serious adverse effects (6 RCTs, n=1,851) (Ong 2019 **Level I** [Cochrane], 6 RCTs, n=1,886) (0 RCT overlap).

Dietary modifications

Various dietary modifications for infantile colic have been studied including maternal low allergen diets for breastfed infants (2 studies), lactase enzyme supplementation (3 studies), and hydrolysed formula (6 studies) (Gordon 2018 **Level III-1** [Cochrane], 15 studies, n=1,121). The authors concluded that reported benefits for hydrolysed formula were inconsistent, and overall, due to small samples and high risk of bias, no intervention was able to be recommended.

Skeletal manipulation

Individual studies report positive outcomes for skeletal manipulative therapies to treat infantile colic. However, studies were small and methodologically biased and these flaws make the results inconclusive; only one study assessed for adverse effects and reported none (Perry 2019 **Level I** [PRISMA], 16 SRs [6 manipulation]; Dobson 2012 **Level I** [Cochrane], 6 RCTs, n=325).

Acupuncture

There is no conclusive evidence to support the safety and efficacy of acupuncture to treat colic in infants (1–25 wk old) (Skjeie 2018 **Level I** [PRISMA], 3 RCTs, n=307; Lee 2018 **Level I**, 4 RCTs, n=357) (3 RCT overlap).

KEY MESSAGES

1. Hypnosis for needle-related procedural pain (including for cancer-related procedures) reduces pain intensity (**S**) and distress (**N**) versus control (**Level I** [Cochrane Review]).
2. Preventive use of probiotics does not reduce infantile colic incidence, but does reduce crying duration versus placebo (**N**) (**Level I** [Cochrane Review]).
3. The probiotic *Lactobacillus reuteri* reduces cry/fuss time in breastfed infants with colic; there is insufficient evidence in formula fed infants (**N**) (**Level I** [PRISMA]).
4. Oral administration of honey versus control in children reduces pain and analgesic use after tonsillectomy (**N**) (**Level I** [PRISMA]).
5. Perioperative acupuncture (including electroacupuncture) versus control in children having tonsillectomy reduces postoperative pain intensity (in the first 48 h) and analgesic consumption (**N**) (**Level I** [PRISMA]).
6. Acupuncture (invasive or non-invasive) versus control for preterm and term neonates receiving heel lance does not reduce pain intensity (**N**) (**Level I** [PRISMA]).

The following tick boxes represent conclusions based on clinical experience and expert opinion:

☑ Complementary and alternative medicines and therapies encompass a wide variety of interventions with common use in the community; complementary medicines and therapies are increasingly used as part of integrative approaches to hospital-based healthcare in the paediatric population (**N**).

☑ The evidence on complementary and alternative medicines and therapies is characterised by small sample sizes and study designs prone to bias and caution is urged in interpreting results. Additionally, the safety and potential drug interactions of many complementary and alternative medicines and therapies have not been adequately assessed (**N**).

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Appendix B: Process report

This is the fifth edition of the book *Acute Pain Management: Scientific Evidence*. The first edition was written by a multidisciplinary committee headed by Professor Michael Cousins and published by the National Health and Medical Research Council (NHMRC) in 1999.

The second and third editions were written by multiple contributors and a working group chaired by Professor Pam Macintyre. The editions were approved by the NHMRC and published by the Australian and New Zealand College of Anaesthetists (ANZCA) and its Faculty of Pain Medicine (FPM) in 2005 and 2010. They were also endorsed by other major organisations worldwide.

As guidelines and key sources of information should be revised as further evidence accumulates (ideally every 5 years), a fourth edition was written by multiple contributors and a working group chaired by Professor Stephan Schug and published by ANZCA and its FPM in 2015. In view of the NHMRC changing its criteria, this edition was not submitted for NHMRC approval, but it was widely endorsed by many significant national and international organisations - the International Association for the Study of Pain (IASP), the Royal College of Anaesthetists and its Faculty of Pain Medicine, the American Academy of Pain Medicine, the Australian Pain Society, Australasian College of Sport and Exercise Physicians, the Australasian Faculty of Rehabilitation Medicine, the College of Anaesthesiologists of the Academies of Medicine of Malaysia and Singapore, the College of Intensive Care Medicine of Australia and New Zealand, the European Society of Regional Anaesthesia and Pain Therapy (ESRA), the Faculty of Pain Medicine of the College of Anaesthetists of Ireland, the Hong Kong College of Anaesthesiologists, the Hong Kong Pain Society, the Malaysian Association for the Study of Pain, the New Zealand Pain Society, the Pain Association of Singapore, PainSA (South Africa), PROSPECT (Procedure Specific Postoperative Pain Management), the Royal Australasian College of Physicians, the Royal Australian and New Zealand College of Psychiatrists, the Royal Australasian College of Surgeons and the South African Society of Anaesthesiologists.

Since the fourth edition was published in 2015, a sizeable amount of new evidence relating to the management of acute pain has been published. The aim of this fifth edition is, as with the first four editions, to combine a review of the best available evidence for acute pain management with current clinical and expert practice, rather than to formulate specific clinical practice recommendations. Accordingly, the document aims to summarise, in a concise, accessible, and easily readable form, the substantial amount of evidence currently available for the management of acute pain in a wide range of patients and acute pain settings using a variety of treatment modalities. It aims to assist those involved in the management of acute pain with the best current (up to at least August 2019) evidence-based information.

It is recognised that while knowledge of current best evidence is important, it plays only a part in the management of acute pain for any individual patient and many factors in addition to scientific evidence should be considered if such treatment is to be effective.

Evidence-based medicine has been defined as “the conscientious, explicit and judicious use of current best evidence in making decisions about the care of individual patients” and that must “integrate research evidence, clinical expertise and patient values” (Sackett 1995 **NR**). Therefore evidence, clinical expertise and, importantly, patient participation (ie including the patient as part of the treating and decision-making team, taking into account their values, concerns and expectations) are required if each patient is to get the best treatment. The information provided in this document is not intended to over-ride the clinical expertise of health professionals. There is no substitute for the skilled assessment of each individual patient’s health status, circumstances and perspectives, which health professionals will then use to help select the treatments that are relevant and appropriate to that patient.

This report provides examples of the decision-making processes that were put in place to deal with the plethora of available evidence under consideration.

Development process

An editorial working group was convened to coordinate and oversee the development process, to edit the reference and also contribute updates to some sections – members were Prof Stephan Schug, A/Prof Greta Palmer, Prof David Scott, Dr Mark Alcock, Dr Richard Halliwell, and Dr Jeff Mott. While all members of the working group contributed to the whole document, A/Prof Greta Palmer and Dr Mark Alcock provided specific input and expertise to the paediatric section. This section will remain as Chapter 10 in the PDF of the book, but In view of the largely increased amount of information in the paediatric section, it will be published as a separate volume II of the hardcopy of the book.

The editorial working group was assisted by an editorial advisory group comprising Dr Mark Rockett, nominated by the Faculty of Pain Medicine, Royal College of Anaesthetists in the United Kingdom, and Dr Clara Sze Ming Wong, nominated by the Hong Kong College of Anaesthesiologists.

A large panel of contributors was enlisted to draft sections of the document and a multidisciplinary consultative committee was chosen to review late drafts and contribute more broadly as required. A list of panel members is attached in Appendix A, together with a list of contributing authors and editorial working group members.

Structures and processes for the revised edition were developed, and within these frameworks, contributors were invited to review the evidence and submit content for specific sections according to their area of expertise. All contributors were given specific instructions about the process of the literature search and the requirements for submission of their section, were referred to the website of the NHMRC document *How to Use the Evidence: Assessment and Application of Scientific Evidence* (NHMRC 2000 **GL**), received an electronic copy of the respective contribution in the fourth edition and were directed to the ANZCA website for copies of the full fourth edition of the document.

Members of the editorial working group were responsible for the initial editing of each section, the evaluation of the literature submitted with the contributions and checking for further relevant references. In a series of meetings, the editorial working party compiled and edited an initial draft. Once the draft of a section had been prepared, it was returned to the respective contributor for comment before being redrafted for public consultation as well as review by members of the multidisciplinary panel. To ensure general applicability, there was a very wide range of experts on the contributor and multidisciplinary committee, including medical, nursing, allied health and complementary medicine clinicians and consumers (see Appendix A).

Acute Pain Management: Scientific Evidence 5th Edition (Volumes I and II) is based on the NHMRC's recommendations for guideline development. That is, this review of the best available evidence for acute-pain management focuses on improving patient outcomes, includes statements concerning the strength of levels of evidence underpinning recommendations and uses a multidisciplinary approach involving all stakeholders (including consumers).

Competing interests

Conflicts of interest were managed by the members of the working party responsible for writing the content of the document by completing an International Committee of Medical Journal Editors *Uniform Disclosure Form for Potential Conflicts of Interest*. A list of conflicts of interest is provided below:

Member	Conflicts of interest
Prof Stephan A. Schug (Chair)	Emeritus Professor and Honorary Senior Research Fellow in Anaesthesiology and Pain Medicine, Medical School, University of Western Australia, Perth Previous Chair of Anaesthesiology at University of Western Australia (retired October 2019); previous Director of Pain Medicine at Royal Perth Hospital (retired October 2019). Previous Member of Board of FPMANZCA and various committees of ANZCA and FPMANZCA (retired May 2020). Vice Chair of SIG Acute Pain of IASP and previous Chair of SIG Acute Pain of ACECC (retired May 2020). Member of Advisory Board of PROSPECT group, of Faculty of 1000 (F1000), of IASP Taskforce for ICD-11 (Pain), previous Executive Secretary and member of Board of AOSRA (retired May 2020). Current recipient of competitive research funding from ANZCA and NHMRC. The Anaesthesiology Unit of the University of Western Australia chaired by Prof Schug has received research and travel funding and speaking and consulting honoraria until October 2019, from then on Prof Schug personally, from Aspen, bioCSL, Bionomics, Biogen, Emerge, ESA, Foundry, Gruenenthal, HealthEd, iX Biopharma, Indivior, Janssen Pharmaceuticals, Luye Pharma, Mundipharma, Pfizer, Seqirus, Socratec, Therapeutic Guidelines and Xgene over the last 5 years.
A/Prof Greta M. Palmer	Paediatric and Adult Specialist Pain Medicine Physician and Specialist Anaesthetist, Royal Children's and Royal Melbourne Hospitals; Deputy Head of the Children's Pain Management Service, Royal Children's Hospital; Research Associate, Murdoch Childrens Research Institute; Associate Professor, University of Melbourne, Melbourne. Travel funding and consultation honorarium from Gruenenthal for attendance at an international tapentadol paediatric research advisory meeting. No further industry support has been received in the last 5 years.
Prof David A. Scott	Professor, University of Melbourne; Director of the Department of Anaesthesia and Acute Pain Medicine, St. Vincent's Hospital Melbourne; Elected Councilor (honorary) to May 2020. Chair ANZCA Research Committee. No industry support or funding, either directly or indirectly, has been received in the last 5 years. Current recipient of competitive research funding from ANZCA and the NHMRC.
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No disclosures of interests were requested from contributors. Contributors conducted searches and summarised the new literature and had no influence on the content or the decisions about inclusion or exclusion of material.

Review of the evidence

This document is an extensive revision of the fourth edition of *Acute Pain Management: Scientific Evidence* published in 2015. Therefore, most of the new evidence included in this fourth edition has been published from August 2014 onwards, which was the cut-off date of literature inclusion in the fourth edition. Literature was considered when published between this date and the cut-off date for this fifth edition (August 2019). However, in rare circumstances, references published after this cut-off were considered but only if of high relevance and encountered in the editorial process. These were identified by team members. High-quality evidence-based guidelines had been published independently by a number of organisations in the areas of acute back and musculoskeletal pain and recommendations relevant to the management of acute pain were drawn directly from these.

Search strategies

Searches of the electronic databases Medline or PubMed, Embase and Cochrane were conducted for each of the main topics included in the review, from August 2014 until August 2019. Searches were limited to articles concerning humans and basic science literature for some subsections. Included literature was required to be full text, written in English language.

The initial searches were inevitably broad, given the very wide scope of the topic. “Pain”, “acute pain”, “postoperative pain” or “analgesia” was searched with the key headings of the various sections and subsections of the document such as “neuropathic”, “patient-controlled”, “epidural”, “paracetamol” and so on. For drugs and techniques, a search was also made for “efficacy”, “complications” and “adverse effects”. Hand searches were also conducted of a large range of relevant journals from August 2014 onwards and bibliographies of relevant papers were checked to identify references that may not have been identified from database search.

Levels of evidence

Levels of evidence were documented according to the NHMRC designation (NHMRC 1999 **GL**) and, as for the second and third edition of this document, clinical practice points have been added.

Levels of evidence	
I	Evidence obtained from a systematic review of all relevant randomised controlled trials.
II	Evidence obtained from at least one properly designed randomised controlled trial
III-1	Evidence obtained from well-designed pseudo-randomised controlled trials (alternate allocation or some other method)
III-2	Evidence obtained from comparative studies with concurrent controls and allocation not randomised (cohort studies), case-controlled studies or interrupted time series with a control group
III-3	Evidence obtained from comparative studies with historical control, 2 or more single-arm studies, or interrupted time series without a parallel control group
IV	Evidence obtained from case series, either post-test or pre-test and post-test
Clinical practice points	
☑	Recommended best practice based on clinical experience and expert opinion

Foreign language evidence

Where new systematic reviews or meta-analyses were identified with an English abstract, but written substantially in another language, these were considered for inclusion if there was enough information in the abstract to establish it as valid NHMRC Level I evidence. In this instance, these were included and then classified as Level I evidence for this review. Similarly, where relevant, studies with lower hierarchies in a foreign language were also considered, if there was enough information in the English abstract to establish study validity (eg critical appraisal score and relevant findings). If there was insufficient information in the abstract to establish its validity then such references were excluded. Where available in the review team, speakers of the language would be engaged for translation.

Preferred evidence

A review of acute pain management requires a broad focus on a range of topics (eg postoperative pain, musculoskeletal pain, migraine, pain associated with spinal cord injury etc). This broad focus inevitably produces a very large number of research publications. In order to provide the best information to inform practice, it was important to concentrate on the highest ranked, highest quality evidence where available (eg Cochrane review).

Secondary evidence: High-quality systematic reviews of RCTs (NHMRC Level I) were the preferred evidence source. Reference lists of such designated Level I evidence were then scanned for the included RCTs. If these RCTs had also been identified in the literature search, they were excluded from subsequent analysis as their findings had already been accounted for in the Level I evidence. Relevant RCTs identified in the search, which had not been included in the systematic reviews or meta-analyses and relevant RCTs published since the cut-off date for literature inclusion in the systematic reviews or meta-analyses, were included in the update, to provide additional primary evidence. In case of multiple systematic reviews or meta-analyses published in parallel, or a lower-ranked meta-analysis published after a previous higher-ranked one (eg an older Cochrane Review), their results were considered after identification of the number of overlapping studies. Cochrane Reviews, which had been withdrawn due to age and lack of an update, were considered in conjunction with subsequently published Level I evidence.

Systematic reviews or meta-analyses that included non-randomised controlled studies were assigned the level of evidence of their lowest level component studies, as outlined in the NHMRC designation of evidence levels (NHMRC 1999) and identified by SR following the level of evidence eg (Roberto 2014 **Level III-2 SR**).

Primary evidence: Where Level I reviews were not available, the next preferred level of evidence was RCTs (NHMRC Level II). Where these were not available, other experimental evidence or case series were accepted as the best available evidence by the guideline developers (reflecting NHMRC Level III and Level IV). According to NHMRC guidelines, Level IV evidence is obtained from case series, either post-test or pretest and post-test; these levels refer to evidence about interventions (NHMRC 1999 **GL**). Publications describing results of audits or surveys were also included as Level IV evidence in the absence of any other higher-level evidence.

Expert opinion: In the few instances where no relevant published evidence was available, expert opinion was included as the best available information. Narrative reviews containing such evidence are identified by NR following the reference eg (Graham 2013 **NR**). Where no opinion-based reviews were available, the guideline writing team (working group) provided expert input.

Other evidence types*:* Not all evidence relating to the management of acute pain is intervention-based. In a number of instances, best practice has been derived from studies such as record audit, quality processes or single case reports, pharmacokinetic studies, human experimental data and basic science or animal data. These studies were included where relevant and identified by a research identifier following the reference. Thus readers will find CR (for case report) eg (Madadi 2010 **CR**), GL for clinical practice guidelines eg (Kowalski 2011 **GL**), BS if presenting basic science or animal data eg (LaCrois-Fralish 2011 **BS**), PK if presenting pharmacokinetic studies eg (Holford 2012 **PK**) and EH if presenting human experimental data eg (Saxena 2013 **EH**). The latter two were also assigned an evidence level in line with NHMRC hierarchy if suitable eg (Williams 2002 **Level II PK**, n=96, JS 4).

Quality scoring

S*ystematic reviews and meta-analyses:* These studies were not directly assessed for quality using a critical appraisal instrument by the guideline development team. The quality assessment was based on the quality criteria that were reported to underpin the review. These were rated and reported in the following manner, on the assumption that if the study was reported as having been conducted along the lines of a specific quality approach, then the methodological quality of the study could be assumed.

- Reviews performed by the Cochrane Collaboration are identified as [Cochrane] in the text eg (Derry 2013 **Level I** [Cochrane]);
- Reviews that overtly state that the review conformed with an evidence-based minimum set of items for reporting referred to as Preferred Reporting Items for Systematic Reviews

and Meta-Analyses (PRISMA) (Liberati 2009) are identified as PRISMA eg (Moore 2014 **Level I** [PRISMA]);

- Reviews that overtly state that the review conformed with standards previously published as Quality of Reporting of Meta-analyses (QUOROM) (Moher 1999), a precursor of PRISMA, are identified as QUOROM eg (Macedo 2006 **Level I** [QUOROM]);
- Non-Cochrane meta-analyses that did not provide evidence of using PRISMA or QUOROM quality and reporting methods are only labelled Level I eg (Thorlund 2014 **Level I**).
- Network meta-analyses are identified as [NMA] eg (Martinez 2017 **Level I** (NMA), 135 RCTs, n=13,287).

For all systematic reviews and meta-analyses, the number of RCTs for Level I and the number of studies for all other levels is reported as well as the number of subjects included in these, if reported or immediately obvious eg (Rabbie 2013 **Level I** [Cochrane], 9 RCTs, n=4,473); if this is not the case, the term unspecified is used eg (Hughes 2011 **Level IV SR**, 5 studies, n unspecified).

Randomised controlled trials: The Jadad scoring instrument was used to score the quality of all RCTs (Jadad 1996).

Item	Maximum points	Description	Examples
Randomization	2	1 point if randomization is mentioned	"The patients were randomly assigned into two groups"
		1 additional point if the method of randomization is appropriate	The randomization was accomplished using a computer-generated random number list, coin toss or well-shuffled envelopes
		Deduct 1 point if the method of randomization is inappropriate (minimum 0)	The group assignment was accomplished by alternate assignment, by birthday, hospital number or day of the week
Blinding	2	1 point if blinding is mentioned	"The trial was conducted in a double-blind fashion"
		1 additional point if the method of blinding is appropriate	Use of identical tablets or injectables, identical vials Use of tablets with similar looks but different taste
		Deduct 1 point if the method of blinding is inappropriate (minimum 0)	Incomplete masking
An account of all patients	1	The fate of all patients in the trial is known. If there are no data the reason is stated	"There were 40 patients randomized but the data from 1 patient in the treatment group and 2 in the control were eliminated because of a break in protocol"

Considering the reporting of dropouts throughout trials, a Jadad score point was withheld if the numbers randomised were greater than the numbers analysed and insufficient explanation was provided. No dropouts were assumed if the text did not state this, but the descriptive reporting was comprehensive (ie 60 started, 60 finished, 60 analysed, therefore assume no dropouts). If there were obvious dropouts (i.e. 60 in, 56 completed), reviewers sought information on the percentage completing the study, and the analysis approach, which was taken to account for the dropouts.

In addition to the Jadad score, the number of patients randomised (prior to dropouts) is reported for all Level II references eg (Chan 2010 **Level II**, n=4,484, JS 5).

No quality evaluation was undertaken for lower ranked evidence (Level III and Level IV), when this was the highest available level of evidence. However, the number of patients or events included is reported if obvious in the publication and the size of the study subtracts from, or adds to, the quality of the evidence eg (Morton 2010 **Level IV**, n=5,065).

Thus, this document is underpinned by the highest level, highest methodological quality evidence available for each review question.

Conflicting evidence

If evidence was consistent, the most recent, highest hierarchy and highest quality references were used. If evidence was conflicting, the same approach was taken (identifying highest level, highest quality evidence), however examples were given of differences within the literature so that readers could appreciate the ongoing debate. In some instances, particularly in acute pain management in various patient populations, evidence was limited to case reports only, which was made clear in the document as the best available evidence in this instance.

Cost analyses

The area of acute-pain management remains remarkably deficient in research on costs and health economics, one obvious example is the costs associated with the adverse effects of treatment. Where available, relevant health economic information was reported to assist clinicians to better manage both pain and some of the adverse effects of treatment, as well as better individualise treatment for each patient, and to minimise overall expenditure. This is again noted as an area warranting further research.

Key messages

These levels of evidence were also used for the key messages, which are presented in order of level of evidence from the highest to the lowest. Key messages referring to information extracted from Cochrane meta-analyses or systematic reviews were marked “Level I [Cochrane Review]”, and these were listed first, followed by those marked “Level I [PRISMA]” and “Level I [QUOROM]”. The listing of key messages continued then with those derived from systematic reviews not adhering to these standards, which were marked “Level I” and then followed by key messages in descending level of evidence. At each level, key messages based on systematic reviews or meta-analyses are listed before those based on studies at this level, eg key messages based on “Level III-2 SR” were listed before those based on “Level III-2” studies.

Updating the evidence base from the fourth edition of the guidelines

There is no standard approach to updating wording or strength of evidence of existing guideline recommendations (Vernooij 2014 **GL**). The system used by Johnston et al, as applied to the updating process in the fourth edition of these guidelines, was again used in this update to reflect the implications of new evidence on clinical recommendations when reviewed and changed as required (Johnston 2003). The guideline team found this approach to be simple and straightforward when considering the implications of new research, layered onto existing recommendations. To indicate New, Unchanged, Strengthened, Weakened, Qualified and Reversed in the key messages, the bolded letters N, U, S, W, Q and R respectively were used — see table below for examples.

Review and revision of key messages	
New	New evidence leads to new key message(s).
Unchanged	The new evidence is consistent with the data used to formulate the original key message. The key message in the original report remains unchanged.
Strengthened	The new evidence is consistent with the data used to formulate the original key message. The key message in the original report remains unchanged or expanded. The level of evidence and/or content of the key message in the original report has been strengthened to reflect this additional evidence.
Weakened	The new evidence is inconsistent with the data used to inform the original key message(s). However, the new evidence does not alter the key message but weakens the level of evidence.
Qualified	The new evidence is consistent with the data used to formulate the original key message. The key message in the original report remains unchanged but applicability may be limited to specific patient groups/ circumstances.
Reversed	The new evidence is inconsistent with the data used to inform the original key message(s). The strength of the new evidence reverses the conclusions of the original document.
Note	*Clinical and scientific judgment informed the choices made by the Working Party members; there was no mandatory threshold of new evidence (eg number of studies, types of studies, magnitude of statistical findings) that had to be met before classification of categories occurred.* *The first letter of each of the words (**N** for **N**ew, **U** for **U**nchanged etc) was used to denote the classification, and changes (if any) from the last edition of this document.*

An example of the use of this system is taken from the key messages in Section 4.2.3.

KEY MESSAGES

1. Topical NSAIDs are effective in treating acute strains, sprains or sports injuries with systemic adverse effects comparable to placebo; gel formulations show superior efficacy over creams (**S**) (**Level I** [Cochrane Review]).
2. Topical NSAIDs are of limited analgesic efficacy for traumatic corneal abrasions, but reduce rescue analgesia requirements (**W**) (**Level I** [Cochrane Review]).
3. Topical NSAIDs reduce anterior chamber inflammation and thereby pain after cataract surgery (**N**) (**Level I** [PRISMA]).
4. The efficacy of NSAIDs for peri- or intra-articular injection as a component of local infiltration analgesia compared with systemic administration remains unclear (**U**) (**Level I** [PRISMA]).

Where the new evidence led to reversal of a conclusion and key message, this was noted in a green text box and labelled R in the key message. For example, this appears in the text:

Note: reversal of conclusion
This reverses the Level I key message in the previous edition of this document; a preceding meta-analysis had described no effect of hypnosis on postoperative pain scores.

and the related key message reads:

3. Hypnosis may reduce … postoperative pain (**R**) (**Level I**) …. .

Drug names

This document uses the generic names of drugs that apply in Australia and New Zealand (Australian Approved Names [AAN]); the Therapeutics Goods Administration (TGA) has updated medicine ingredient names in 2015 and where applicable, the new names in accordance with this update have been used (TGA 2015 **GL**). Where this name differs from the International Nonproprietary Name (INN) or the United States Adopted Name (USAN), these are given in brackets on first use within each of the chapters.

Bibliographic citations

Citations and bibliographic style are based on a modified Harvard (Author-Date) style. In-text citations use the format "First Author" then "Year of Publication" eg (Madden 2012). A decision was made to omit "et al" for in-text citations that had more than one author, for brevity and improved readability. Multiple references supporting one statement are listed in order of level of evidence and within each level from newest to oldest eg (Chan 2011 **Level II**, n=423, JS 5; Wylde 2011 **Level IV**, n=1,334; Haroutiunian 2013 **NR**; Macrae 2008 **NR**; Kehlet 2006 **NR**).

Small letters further qualify multiple publications by the same first author in the same year in in-text citations eg (Anderson 2014a) (Anderson 2014b) as in the reference lists eg

Anderson BJ & Dare T (2014b) We need to confirm, not relearn old information. *Paediatr Anaesth* **24**(6): 549–52.

Web pages are shown with their uniform resource locator (URL) and the date assessed by a member of the Working Group.

Public consultation

Following finalisation of the draft its availability was advertised through ANZCA and FPMANZCA by direct e-mail to all fellows and through college and faculty publications and social media.

The public consultation period was from 16 September 2020 to 16 October 2020. The draft was made available on a website (https://www.anzca.edu.au/news/top-news/acute-pain-management-scientific-evidence-5th-edit) and Colleges of many of the contributors and multidisciplinary consultative committee members were notified of the availability of the draft and asked to disseminate this information to their members.

Submissions and comments were received from the following 18 individuals, some of them representing organisations:

Name	Affiliation
Dr Caroline Ariaens	Specialist Anaesthetist, Waikato Hospital Hamilton, New Zealand
Dr Richard Barnes	Melbourne, Victoria
Dr Kirsty Belfrage	Bendigo, Victoria
Dr Michael Clifford	Consultant Anaesthetist & Paediatric Intensivist Department(s) of Paediatric Intensive Care, Anaesthesia and Pain Management, The Royal Children's Hospital Melbourne, Victoria
Michele Cree	Pharmacist Lead – Critical Care Queensland Children's Hospital South Brisbane, Queensland
Dr Suran Dhanapala	Pain Specialist, Ballarat Hospital Ballarat, Victoria
Dr Darren Emerick	VMP, Sunshine Coast Hospitals Queensland
Dr Sarah Flint	Medical Lead, Critical Care and Perioperative Services The Queen Elizabeth Hospital Adelaide, South Australia
Dr Mike Foss	Specialist Anaesthetist and Pain Physician, Waikato Hospital Hamilton, New Zealand
Dr Chris Hattingh	
Dr Kim Hattingh	Pain Physician, Bendigo Health Bendigo, Victoria
Dr Christine Huxtable	Consultant Anaesthetist Acting Head, APS, Royal Adelaide Hospital, South Australia
Dr Anju Tessa James	Consultant in Pain Medicine, The Townsville Hospital, Townsville, Queensland

Prof Pam Macintyre	Professor of Anaesthesia and Pain Medicine, University of Adelaide, Consultant in Anaesthesia and Pain Medicine, Royal Adelaide Hospital, Adelaide, South Australia
Claire Morgan	Associate Director, Medical Affairs Seqirus (Australia) Pty Ltd Melbourne, Victoria
Prof Michael Paech	Emeritus Professor of Obstetric Anaesthesia, University of Western Australia Perth, Western Australia
Dr Alette Roux	
Michael Sargent	AFT Pharmaceuticals Takapuna, New Zealand

Topics raised

The main topics raised in these submissions and comments related to:

- Additional websites with information about breastfeeding;
- Additional information re paediatric dosing and use of units;
- Additional information on changed medication names;
- Correction of typographical errors and suggestions for improved layout;
- Improvement of information and inclusion of additional references on perioperative methadone;
- Effects of NASAIDs on healing;
- Information on TGA regulated Good Manufacturing Practice compounded solutions available in Australia under Schedule 5a;
- Neurotoxicity and IT use of clonidine in labour analgesia;
- Combinations of paracetamol and NSAIDs;
- Use of slow release opioids in acute pain including suggestions of additional references;
- Toxicity of alpha-2-delta agonists including suggestions of additional references.

These submissions and comments and additional submissions and comments by the members of the multidisciplinary advisory committee (see listing in Appendix A) were considered by the editorial working group and resulted in changes to the document presented for public consultation if appropriate and necessary before finalising this edition.

Implementation, dissemination and revision

The Australian and New Zealand College of Anaesthetists (ANZCA) and its Faculty of Pain Medicine (FPM) will be responsible for the dissemination, implementation, and updating of this document. The document will be initially available on the internet via the ANZCA website (formatted to allow for downloading and printing as a PDF) as well as later in hard copy.

ANZCA will also notify other Colleges and professional groups and organisations of the availability of the document and ask them to disseminate the information to their members. In addition, information will be sent to relevant national and international organisations with the request to endorse this document and to distribution this information to their members. This is further expected to heighten awareness of the availability of this document. It will also be promoted at relevant professional meetings and conferences and by editorials in professional journals.

References

Jadad AR, Moore RA, Carroll D et al (1996) Assessing the quality of reports of randomized clinical trials: is blinding necessary? *Control Clin Trials* **17**(1): 1–12.

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Moher D, Cook DJ, Eastwood S et al (1999) Improving the quality of reports of meta-analyses of randomised controlled trials: the QUOROM statement. Quality of Reporting of Meta-analyses. *Lancet* **354**(9193): 1896–900.

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Vernooij RW, Sanabria AJ, Sola I et al (2014) Guidance for updating clinical practice guidelines: a systematic review of methodological handbooks. *Implement Sci* **9**: 3.

Acronyms and abbreviations

5-HT	5-hydroxytriptamine (serotonin)
AA	auricular acupuncture
AAN	Australian Approved Names
AAP	American Academy of Paediatrics
AAPD	American Academy of Paediatric Dentistry
AAPM	American Academy of Pain Medicine
ACB	adductor canal block
ACE	angiotensin-converting enzyme
ACT	acceptance and commitment therapy
ACTH	adrenocorticotrophic hormone
ADH	antidiuretic hormone
ADHD	attention deficit hyperactivity disorder
AHI	apnoea-hypopnoea index
AIDS	acquired immunodeficiency syndrome
AKI	acute kidney injury
ALA	adrenaline, lignocaine, amethocaine
AMPA	α-amino-3-hydroxyl-5-methyl-4-isoxazole-propionate
ANZCA	Australia and New Zealand College of Anaesthetists
APS	acute pain service
ASA	American Society of Anesthesiologists
ASIC	acid-sensing ion channel
ASRA	American Society of Regional Anesthesia and Pain Medicine
ATP	adenosine triphosphate
bd	twice daily dosing
BDNF	brain-derived neurotrophic factor
BIS	Bispectral Index (depth of anaesthesia)
BK	bradykinin
BMI	body mass index
BPS	Behavioural Pain Scale
CABG	coronary artery bypass graft
CAGE	“cut-annoyed-guilty-eye” screening questionnaire for problematic alcohol use
CAIP	channelopathy-associated insensitivity to pain
CaLD	culturally and linguistically diverse
CAM	complementary and alternative medicine
CB_1	cannabinoid type 1
CB_2	cannabinoid type 2
CBT	cognitive behavioural therapy

CCK	cholecystokinin
CCL3	chemokine (C-C motif) ligand 3
CGRP	calcitonin gene-related peptide
CHEOPS	Children's Hospital of Eastern Ontario Pain Scale
CIPA	congenital insensitivity to pain with anhydrosis
CIPN	chemotherapy-induced peripheral neuropathy
CKD	chronic kidney disease
C_{max}	maximum serum concentration
CNCP	chronic non-cancer related pain
CNS	central nervous system
CO_2	carbon dioxide
COMT	catechol-O-methyltransferase
COPD	chronic obstructive pulmonary disease
COX-2	cyclooxygenase-2
CPAP	continuous positive airway pressure
CPM	continuous passive movement
CPNB	continuous peripheral nerve block
CPNC	continuous peripheral nerve catheters
CPOT	Critical-Care Pain Observation Tool
CPSP	chronic postsurgical pain
CR	controlled-release
CRIES	Cries, Requires oxygen, Increased vital signs, Expression, Sleeplessness
CRPS	chronic regional pain syndrome
CSE	combined spinal epidural
CSF	cerebrospinal fluid
CSI	central sensitisation inventory
CT	computer tomography
CTG	cardiotocograph
d	day
DALY	disability-adjusted life years
DAMP	damage-associated molecular pattern
DHE	dihydroergotamine
DIS	daily interruption of sedation
DLF	dorsolateral funiculus
DN 4	Douleur Neuropathique 4
dNCR	delayed neurocognitive recovery
DNIC	diffuse noxious inhibitory control
DRG	dorsal root ganglia
DRt	dorsal reticular nucleus

EA	Electro acupuncture (in paediatrics: Emergence agitation)
EBP	epidural blood patch
EC_{50}	Half maximal effective concentration
ECF	extracellular fluid
ECG	electrocardiogram
ED	emergency department
EDIN	Échelle Douleur Inconfort Nouveau-Né
EEG	electroencephalogram
eg	for example (*exempli gratia*)
EMA	European Medicines Agency
EMG	electromyelograph
ERAS	enhanced recovery after surgery
ERCP	endoscopic retrograde cholangiopancreatography
ERD	erosive reflux disease
EREM	extended-release epidural morphine
ES	effect size
ESA	European Society of Anaesthesiology
ESI	epidural steroid injection
ESPB	erector spinae plane block
ESRA	European Society of Regional Anaesthesia and Pain Medicine
EVENDOL	Evaluation ENfant DOuLeur
FANS	Faceless Acute Neonatal Pain Scale
FAS	Functional Activity Scale
FBSF	fentanyl buccal soluble film
FBT	fentanyl buccal tablets
FDA	Food and Drugs Administration (USA)
FLACC	Faces, Legs, Activity, Cry and Consolability
fMRI	functional magnetic resonance imaging
FNB	femoral nerve block
FPM	Faculty of Pain Medicine
FPS	Faces Pain Scale
FPS-R	Faces Pain Scale-Revised
g	gram
G	Gauge
G-CSF	granulocyte-colony stimulating factor
GABA	gamma-amino butyric acid
GANB	greater auricular nerve block
GDNF	glial-derived neurotrophic factor
GFR	glomerular filtration rate

GM-CSF	granulocyte macrophage-colony stimulating factor
H3G	hydromorphone-3-glucuronide
h	hour
HIV	human immunodeficiency virus
HL	heel lance
HRV	heart rate variability
HSAN	hereditary sensory and autonomic neuropathy
IA	intra articular
IASP	International Association for the Study of Pain
IC	intercostal
ICB	intercostal block
ICD	International Classification of Diseases
ICF	intracellular fluid
ICU	intensive care unit
ICV	intracerebroventricular
ID	intellectual disability
ie	that is (*id est*)
IL	interleukin
IM	intramuscular(ly)
IN	intranasal(ly)
INN	International Nonproprietary Name
INR	International Normalised Ratio
INRS	Individualised Numeric Rating Scale
IR	immediate-release
IT	intrathecal(ly)
IV	intravenous(ly)
IVRA	intravenous regional anaesthesia
JIA	juvenile idiopathic arthritis
LANSS	Leeds Assessment of Neuropathic Symptoms and Signs
LAST	local anaesthetic systemic toxicity
LBP	low back pain
LEA	lumbar epidural analgesia
LIA	local infiltration analgesia
LLLT	low-level laser therapy
LMWH	low molecular weight heparin
LTP	long-term potentiation
M1	O-desmethyltramadol
M3G	morphine-3-glucuronide
M6G	morphine-6-glucuronide

MAM	monoacetylmorphine
MBI	mindfulness-based interventions
mcg	microgram (*Note: In handwritten scripts microg or microgram should be used to avoid errors in line with NSQHS standards)*
MDMA	N-Methyl-3,4-methylenedioxyamphetamine (ecstasy)
MDR	multidrug resistance protein
MED	morphine equivalent dose
min	minute
mg	milligram
mGluR	metabotropic glutamate receptor
MHRA	Medicines and Healthcare Products Regulatory Agency (UK)
mL	millilitre
MLAC	minimum local anaesthetic concentration
mm	millimetre
MME	morphine mg equivalents
MPQ	McGill Pain Questionnaire
MRI	magnetic resonance imaging
MS	multiple sclerosis
N-PASS	Neonatal Pain, Agitation and Sedation Scale
mth	month
N_2O	nitrous oxide
NAC	N-acetylcysteine
NAPBQI	*N*-acetyl-*p*-benzoquinone imine
NAS	neonatal abstinence syndrome
NCA	nurse-controlled analgesia
NCAPC	Non-Communicating Adult Pain Checklist
NCCPC-PV	Non-Communicating Children's Pain Checklist — postoperative version
NCCPC-R	Non-Communicating Children's Pain Checklist
NFCS	Neonatal Facial Coding Scale
ng	nanogram
NGF	nerve growth factor
NHMRC	National Health and Medical Research Council
NICU	neonatal intensive care unit
NIPS	Neonatal Infant Pain Scale
NIRS	near infrared spectroscopy
NK1	neurokinin-1
NMDA	N-methyl-D-aspartate
NNH	number needed to harm
NNS	non-nutritional sucking

NNT	number needed to treat
NOAC	new oral anticoagulant
NPQ	Neuropathic Pain Questionnaire
NRS	numerical rating scale
NSAID	nonsteroidal anti-inflammatory drug
NSAID-ERD	NSAID-exacerbated respiratory disease
nsNSAID	nonselective non-steroidal anti-inflammatory drug
OCT1	organic cation transporter
ODI	Oswestry Disability Index
ODT	orally disintegrating tablet
OHS	obesity hypoventilation syndrome
OIH	opioid-induced hyperalgesia
OIVI	opioid-induced ventilatory impairment
ONJ	osteonecrosis of the jaw
OPRM1	opioid receptor mu-1
ORT	opioid risk tool
OSA	obstructive sleep apnoea
OST	opioid substitution therapy
OTFC	oral transmucosal fentanyl citrate
OUD	opioid use disorder
P_2X_3	purinergic receptor subtype
$PaCO_2$	Partial pressure of carbon dioxide in arterial blood
PACU	postanaesthesia care unit
PAG	periaqueductal grey
PaO_2	Partial pressure of oxygen in arterial blood
PAR	proteinase-activated receptor
PBM	photobiomodulation
PCA	patient-controlled analgesia
PCC	percutaneous cervical cordotomy
PCEA	patient-controlled epidural analgesia
PCINA	patient-controlled intranasal analgesia
PCS	Pain Catastrophising Scale
PDA	patent ductus arteriosus
PDMP	Prescription Drug Monitoring Program
PDPH	postdural puncture headache
PET	positive emission tomography
PGB	pelvic girdle pain
PGE_2	prostaglandin E2
PGI_2	prostacyclin

PICC	peripherally inserted central catheter
PICU	paediatric intensive care unit
PIEB	programmed intermittent boluses
PIPP	Premature Infant Pain Profile
PMA	postmenstrual age
PNB	peripheral nerve block
PND	perioperative neurocognitive disorders
PNS	peripheral nerve stimulation
PO	per ora (oral route)
POCD	postoperative cognitive dysfunction
POD	postoperative day
PON	postoperative nausea
PONS	postoperative neurological symptoms
PONV	postoperative nausea and vomiting
POV	postoperative vomiting
PPDA	postoperative pain days averted
PPI	proton pump inhibitor
PPP	Paediatric Pain Profile
PPPM	Parents Postoperative Pain Measure
PR	per rectum (rectal route)
prn	*pro re nata* (as needed)
PROSPECT	PROcedure-SPECific postoperative pain management
PSF	posterior spinal fusion
PTA	Polymyxin E, tobramycin and amphotericin B
PTSD	post-traumatic stress disorder
PVB	paravertebral block
QALY	quality-adjusted life years
QI	quality improvement
qid	four times daily dosing
QoL	quality of life
QoR	quality of recovery
QST	quantitative sensory testing
RANKL	receptor activator of nuclear factor kappa-B ligand
RAP	recurrent abdominal pain
RASS	Richmond Agitation-Sedation Scale
RCT	randomised controlled trial
REMS	Risk Evaluation and Mitigation Strategy
RFID	radiofrequency identification
RID	relative infant dose

ROP	retinopathy of prematurity
RSB	rectus sheath block
rTMS	repetitive transcranial magnetic stimulation
RVM	rostroventromedial medulla
s	second
SACD	subacute combined degeneration
SAS	Sedation-Agitation Scale
SC	subcutaneous(ly)
SCC	spinal cord compression
SCD	sickle cell disease
SCI	spinal cord injury
SDB	sleep-disordered breathing
SF-36	Short Form 36 of Medical Outcomes Study
SF-MPQ	Short Form of McGill Pain Questionnaire
SHORE	Social and Health Outcomes Research and Evaluation
SIADH	Syndrome of inappropriate antidiuretic hormone secretion
SIP	Sickness Impact Profile
SL	sublingual(ly)
SNP	single-nucleotide polymorphism
SNRI	serotonin–norepinephrine-reuptake inhibitors
SOAPP-R	Screener and Opioid Assessment for Patients with Pain-Revised
SPID	summed pain intensity difference
SR	slow-release
SRE	skeletal related events
SRW	standardised regression weights
SSRI	selective serotonin-reuptake inhibitor
SSTS	sublingual sufentanil tablet system
SUD	substance use disorder
SUNCT	Short-lasting Unilateral Neuralgiform headache attacks with Conjunctival injection and Tearing
$t_{1/2keo}$	time taken to achieve 50% effect-site concentration (with plasma concentrations at steady state) or defined in paediatrics as the equilibration halftime between plasma and effect compartment
TAPB	transversus abdominis plane block
TBSA	total body surface area
TCA	tricyclic antidepressant
TD	transdermal(ly)
TdP	Torsades de Pointes
tds	three times daily dosing (ter die sumendum)
TEA	thoracic epidural analgesia

TEAS	transcutaneous electrical acupoint stimulation
TENS	transcutaneous electrical nerve stimulation
TGA	Therapeutic Goods Administration
THA	total hip arthroplasty
THC	tetrahydrocannabinol
TIRF	transmucosal immediate-release fentanyl medicines
TKA	total knee arthroplasty
T_{max}	time to reach maximum serum concentration
TMD	temperomandibular disorder
TMJ	temporomandibular joint
TNF	tumour necrosis factor
TNS	transient neurological symptoms
TOTPAR	total pain relief
TrkA	tyrosine kinase receptor
TRP	transient receptor potential
TRPV1	transient receptor potential vanilloid 1
TTH	tension-type headache
URL	uniform resource locator
US	ultrasound
USA	Unites States of America
US$	USA dollar
USAN	United States Adopted Name
VATS	video-assisted thoracic surgery
VAS	visual analogue scale
Vd	volume of distribution
VDS	verbal descriptor scale
VIGOR	Vioxx Gastrointestinal Outcomes Research
VNRS	verbal numerical rating scale
VOC	vaso-occlusive crisis
VPL	ventral posterolateral nucleus of the thalamus
VPM	ventral posteromedial nucleus of the thalamus
VR	virtual reality
VZV	varicella-zoster virus
WBFPRS	Wong-Baker Faces Pain Rating Scale
WHO	World Health Organization
WISP	withdrawal-associated injury site pain
wk	week
WOMAC	Western Ontario and McMaster Universities Osteoarthritis Index
y	year

Methodological and statistical terms

aHR	adjusted hazard ratio
aOR	adjusted odds ratio
aRR	adjusted relative risk
BS	basic science or animal data
CCT	case-controlled trial
CI	confidence interval
CPG	clinical practice guideline
CR	case report
EH	experimental human studies
GL	clinical practice guideline
HR	hazard ratio
IRR	incidence rate issue
JS	Jadad Score
MD	mean difference
NMA	network meta-analysis
NNH	number-needed-to-harm
NNT	number-needed-to-treat
NR	narrative review
OR	odds ratio
PK	pharmacokinetic study
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
QUOROM	Quality of Reporting of Meta-analyses
r	correlation coefficient
RCT	randomised controlled trial
RD	risk difference
RR	relative risk
SMD	standardised mean difference
SR	systematic review
SRW	standardised regression weights
WMD	weighted mean difference

ANZCA

FPM