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Evidence-informed management of chronic low back pain with opioid analgesics

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Abstract **EDITORS' PREFACE:** The management of chronic low back pain (CLBP) has proven to be very challenging in North America, as evidenced by its mounting socioeconomic burden. Choosing among available nonsurgical therapies can be overwhelming for many stakeholders, including patients, health providers, policy makers, and third-party payers. Although all parties share a common goal and wish to use limited health-care resources to support interventions most likely to result in clinically meaningful improvements, there is often uncertainty about the most appropriate intervention for a particular patient. To help understand and evaluate the various commonly used nonsurgical approaches to CLBP, the North American Spine Society has sponsored this special focus issue of *The Spine Journal*, titled Evidence-Informed Management of Chronic Low Back Pain Without Surgery. Articles in this special focus issue were contributed by leading spine practitioners and researchers, who were invited to summarize the best available evidence for a particular intervention and encouraged to make this information accessible to nonexperts. Each of the articles contains five sections (description, theory, evidence of efficacy, harms, and summary) with common subheadings to facilitate comparison across the 24 different interventions profiled in this special focus issue, blending narrative and systematic review methodology as deemed appropriate by the authors. It is hoped that articles in this special focus issue will be informative and aid in decision making for the many stakeholders evaluating nonsurgical interventions for CLBP.

Keywords: Chronic low back pain; Opioid analgesics; Pharmacological treatment

Description

The medical treatment of patients with chronic low back pain (CLBP) is most often directed toward decreasing pain and increasing function rather than curing the condition. Treatment is usually multimodal and might include rehabilitation, spinal injections, surgery, or medications. In turn, the choice of medication depends on the severity, duration, and type of pain, as well as each patient's values, responses, and circumstances. Pharmacological treatment should be just one part of a comprehensive program to improve pain and function. This paper will review the role of opioid analgesics for CLBP.

Terminology

The preferred terms for this class of medications are opioid or opioid analgesic rather than narcotic [1]. Opioids most suitable for long-term use can be divided into two categories: sustained-release opioids (SROs) and immediate-release opioids (IROs). SROs release medication continuously from the gastrointestinal tract or transdermally via a reservoir and are variously termed continuous release (CR), sustained release (SR), or extended release (ER). Examples include morphine-ER, oxycodone-CR, oxymorphone-ER, and transdermal fentanyl (TDF). IRO formulations such as oxycodone-IR, hydrocodone, and morphine sulfate-IR have a rapid onset of analgesia, are short acting, and preferred for severe episodes of pain not controlled by

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usual pain medication (termed ''breakthrough'' pain). The other category of opioids is termed long acting (LA) and includes methadone and levorphanol.

History

In patients with pain because of cancer, opioids have been the standard of care for years despite the lack of high levels of evidence proving efficacy or safety with long-term use. On the other hand, there has been bias against the use of long-term opioids (LTOs) for chronic pain that is not because of cancer, a bias that does not appear to be grounded on solid evidence. This nihilistic position began to change two decades ago and by 1999, case series suggested opioids were safe and effective in well-selected patients with CLBP [2,3]. In many spine centers, LTO therapy has become an integral part of care for well-selected patients with moderate to severe and otherwise refractory CLBP [2,4,5].

Frequency of use

Opioid analgesics have become an integral part of the sophisticated management of patients. In 2001, a large insurance plan reported that 55% of patients with low back pain received analgesics, 38% of whom received opioids [6]. Of those receiving opioids, 9% received more than a 180-day supply. In specialty spine practices, opioids were part of the plan after a single visit for 3.4% of more than 25,000 patients, 75% of whom had pain for longer than 3 months [5]. In a university orthopedic spine clinic, opioids were prescribed for 66% of patients and 25% received LTO treatment [4].

Subtypes

There are several opioid analgesics readily available for long-term use (Table 1).

Morphine

Morphine remains the gold standard against which other analgesics are compared and has been shown to be safe and efficacious for many patients with CLBP at an average final dose of 105 mg (range 6–780 mg daily) [7,8]. The various SR morphine can provide analgesia for 8 to 24 hours, depending on the formulation and individual patient factors (eg, rate of absorption and drug metabolism). There are many dose sizes available, which makes dose titration convenient. The dose can be titrated upward once or twice weekly until there is good pain control or significant side effects. For breakthrough pain, morphine-IR, 15 or 30 mg every 4 to 6 hours is preferred.

Transdermal fentanyl

TDF has been shown to be effective in the treatment of CLBP in opioid-naïve patients at a mean dose of 57 μg per hour (range of 12.5 to 250 mg) [8–10]. TDF can be more convenient than oral formulations because in most patients the patch needs to be changed only every 2 to 3 days, and there may be less constipation with the transdermal route of administration.

Oxycodone

Oxycodone is an effective analgesic for CLBP at an average dose of 60 to 55 mg per day, with a wide range [7,10–14]. Drawbacks to this otherwise good analgesic are a high cost and higher prevalence of abuse and diversion compared with other opioids.

Table 1
Opioid analgesics most useful for chronic pain

Opioid	Brand names	Duration of analgesia (h)	Comments
Morphine	MS-Contin Oramorph Kadian Avinza	8 to 12 to 24, depending on product and patient factors	Multiple dose sizes Convenient Gold standard
Fentanyl	Duramorph	72	Transdermal Five dose sizes Less constipating
Methadone	Dolophine	8	Very inexpensive Initially more complicated to use
Oxycodone	Oxycontin	8 to 12	Multiple dose sizes Convenient Very expensive ??Higher abuse potential
Levorphanol	Levodromoran	6 to 8	Only 2 mg dose
Oxymorphone	Opana-ER	12	Multiple dose sizes Convenient Newest Perhaps best data
Tramadol	Ultram Ultracet	6 (immediate release) to 24 (extended release)	Very good data Less potent

Oxymorphone

Oxymorphone is the newest opioid and perhaps the best studied specifically for the treatment of CLBP at an average dose of 39 to 79 mg per day [11,15]. It is typically administered twice daily, and oxymorphone-IR is available for breakthrough pain.

Methadone

Methadone has gained in popularity as an analgesic because it is highly effective, has high biological availability, no known active metabolites, no known neurotoxicity, is inexpensive, and may have less opioid-induced hyperalgesia (OIH) than alternatives [16–18]. On the other hand, methadone has a high number of potential drug interactions, and it is more difficult to initiate therapy. It is important to note that because of the unique pharmacokinetics, the dose of methadone should not be increased more frequently than once every 5 to 7 days. Once a steady state is reached, analgesia usually lasts about 8 hours.

Levorphanol

Levorphanol is a LA opioid that has been shown to be effective in both nociceptive and neuropathic pain states [19]. However, shortages have occurred in the last few years as the manufacturer was not able to produce sufficient quantities of the drug, and the 2-mg pill size makes it inconvenient. Many patients need up to 8 to 12 mg every 6 to 8 hours.

Tramadol

Tramadol is a semisynthetic opioid available alone or combined with acetaminophen (APAP), and is also available in an ER formulation. It has been shown to be effective in patients with CLBP at an average dose of 158 mg per day; the maximum safe daily dose is 400 mg [7,20–22].

Meperidine

Meperidine (Demerol) should not be used as an LTO as it is poorly absorbed, does not provide reliable analgesia, and its primary metabolite, normeperidine, can accumulate over days to weeks and cause generalized hyperexcitability and even seizures [23].

General description

There are two ways to dose opioid analgesics: pain contingent or time contingent. Pain-contingent dosing is defined as medication taken when pain occurs (''as needed''), whereas time-contingent dosing is defined as medication taken on a regular schedule based on the duration of analgesia rather than intensity of symptoms at that time (''by the clock''). It is generally believed that time-contingent dosing provides better pain control, fewer side effects, and better compliance and therefore is usually preferred for chronic pain, including CLBP. Most often SROs or LA formulations are used for time-contingent treatment. The duration of action of SRO and LA opioids is somewhat variable, and depends on rates of absorption, distribution, metabolism, and excretion. Many patients require dosing intervals shorter than the manufacturers' original recommendations [10,24].

A short-acting opioid is usually prescribed for breakthrough pain. An occasional patient may experience better pain control with an IRO administered on a time-contingent basis than with an SRO or LA opioid. It is not uncommon for the physician to have to try several different opioids to identify which one is best for a particular patient. An individual patient's response is at least in part based on a genetic predisposition [25]; some CLBP patients may not respond to opioids. There is also no universally correct dose of opioid; dose and dosing must be titrated in each patient according to analgesic efficacy and side effects. Opioids do not have a true ceiling effect, so in theory, there is no maximum dose. The general guidelines for the use of opioid analgesics are summarized in Table 2.

Practitioner, setting, and availability

A physician is required for this intervention because these medications are only available by prescription. Although any licensed physician can prescribe opioids, pain management specialists will generally be more comfortable monitoring patients who require this type of therapy than general practitioners, and are more experienced at titrating dose and other medication requirements. Patients may consult physicians for this therapy in a variety of settings (outpatient pain centers, private pain clinics, private physician offices) and locations. This treatment is widely available across the United States, though specialty spine pain clinics tend to be located in larger cities.

Table 2
Guidelines for the treatment of chronic pain with opioid analgesics

Recommendation	Components
A careful evaluation of the patient includes	History Physical examination Review of imaging Review of medical records
A treatment plan that states the goals of therapy	
Informed consent (verbal or written)	Potential benefits Potential risks Probable and possible side effects Consequences of abuse, diversion, or illicit use of opioids
Therapeutic trial	If good response with acceptable side effects, continued treatment
Regular follow-up visits to assess and document	Efficacy Side effects Signs of abuse or diversion
Consultation when necessary with specialists in	Psychology/psychiatry Chemical dependence
The maintenance of good medical records	

Reimbursement

This treatment is generally reimbursed by most insurers, though it may be required to demonstrate that generic opioids are not effective before obtaining approval for brand name products.

Regulatory status

Opioids are approved by the FDA for similar indications, though not specifically CLBP.

Theory

Mechanism of action

Opioids exert their primary effect by binding to opioid receptors in the central nervous system (CNS), which inhibits transmission of nociceptive input from the periphery to the spinal cord, activate descending pathways that modulate and inhibit transmission in the spinal cord, and alter brain activity [26].

Diagnostic testing required

All patients should undergo a thorough medical history and physical examination in an attempt to determine the specific structural cause of the pain and rule out the possibility of more serious pathology. All patients with CLBP should have a course of active rehabilitation that emphasizes functional improvement and correction of fear-avoidance behavior before considering opioids. If there is a specific structural cause of the CLBP, the patient and physician must weigh the risks versus benefits of surgery or other corrective treatment versus a trial of palliative opioid or other analgesic therapy. If the underlying cause of pain is not directly treatable, the pain is severe and refractory, and a patient does not have overt psychological pathology, a trial of opioid analgesics is warranted.

Indications and contraindications

LTO analgesic therapy is indicated for patients with moderate to severe refractory CLBP who are psychologically healthy and have failed to respond to other forms of care. The only absolute contraindication to opioid therapy is allergy to that specific opioid. Patients with a history of addictive disease are at risk for relapse with exposure to therapeutic opioids; they can usually be managed successfully by collaborative care that includes an addiction specialist. Greater care is necessary in the elderly and in patients with other chronic illnesses.

It has been suggested that patients with chronic pain can be separated into three psychological categories: adaptive copers, dysfunctional persons, and interpersonally distressed [27]. Adaptive copers are the patients most likely to benefit from LTOs as they have pain that is appropriate to the structural pathology, function consistent with the pain and structural pathology, mood appropriate to their pain and impairment, no history of addictive disease, and reasonable goals and expectations. On the other hand, patients who are dysfunctional and interpersonally distressed tend to do poorly with opioid analgesics and, in fact, most other treatments. Their pain and disability appear out of proportion to the structural pathology, they may be significantly depressed, have a character disorder, or a prior history of addictive disease. Such patients may also have a history of doctor shopping and can appear unreasonable or overly demanding.

Evidence of efficacy

Systematic reviews

Recently Martell et al. published a systematic review of opioid analgesics for CLBP [28]. Despite the fact that the authors did not include several randomized controlled trials (RCTs) that showed both efficacy and safety of opioids for CLBP, they still concluded that opioids ‘‘may be efficacious for short-term pain relief,’’ though ‘‘long-term efficacy is unclear’’ [8,15,21,22]. Authors of this review did not include the study with the longest duration of 13 months [8] and gave less weight to other long-term studies that are lower quality but provided the best available evidence [2,4].

Randomized controlled trials

Placebo control

Katz et al. performed a 12-week RCT to compare pain relief of oxymorphone-ER with placebo in 325 opioid-naïve patients with CLBP [15]. Function related to low back pain was not addressed. During the titration period, 120 patients (37%) discontinued treatment because of adverse events, lack of efficacy, or other reasons. In the 205 remaining patients who obtained adequate analgesia and tolerable side effects during titration, pain intensity measured by visual analog scale (VAS) decreased from 69 to 23 mm. These patients were subsequently randomized to continue oxymorphone-ER or changed to placebo. After 12 weeks, there were clinically better outcomes in the oxymorphone-ER group in both numerical pain rating scores (NPRS) and patient satisfaction scales. There were 34 patients in the oxymorphone group who discontinued treatment because of lack of efficacy, adverse events, or other reasons, compared with 53 in the placebo group. The authors concluded that oxymorphone-ER was safe and effective for opioid-naïve patients with CLBP.

Hale et al. performed a 12-week RCT to compare pain relief of oxymorphone-ER with placebo in 250 opioid-experienced patients with CLBP [29]. During the titration period, 108 patients (43%) discontinued treatment because of adverse events, lack of efficacy, or other reasons. In the

143 remaining patients who obtained adequate analgesia and tolerable side effects during titration, there were statistically significant decreases in pain. These patients were subsequently randomized to oxymorphone-ER or placebo. After 12 weeks, there were clinically better outcomes in the oxymorphone-ER group in both NPRS and patient satisfaction scales. There were 20 additional patients in the oxymorphone group who discontinued treatment because of lack of efficacy, adverse events, or other reasons, compared with 55 in the placebo group. The authors concluded that oxymorphone-ER was safe and effective for opioid-experienced patients with CLBP.

Peloso et al. performed a 91-day RCT comparing the efficacy and safety of flexible dose tramadol 37.5 mg plus APAP 325 mg to placebo in 338 patients with CLBP [20]. The active treatment group had statistically and clinically significantly better improvements in pain (VAS) and function (Roland Morris Disability Questionnaire) compared with placebo patients. About 49% of the active treatment patients had greater than or equal to 30% reduction in pain and 49% had greater than or equal to 50% relief. The number needed to treat was four for greater than or equal to 30% relief and five for greater than or equal to 50% relief.

Schnitzer et al. reported a 4-week RCT that compared tramadol with placebo in 254 patients with CLBP who had had been shown to be tramadol responders in the open-label phase of the study [21]. The tramadol group had significantly greater improvements in pain (VAS) and function (Roland Morris Disability Questionnaire) compared with the control group.

Ruoff et al. reported a 91-day RCT that compared tramadol plus APAP with placebo in patients with CLBP [22]. The active treatment group had significantly better pain (VAS) and function compared with placebo.

Placebo and opioid controls

Hale et al. performed an 18-day multicenter RCT comparing oxymorphone-ER, oxycodone-CR, and placebo in 213 patients with CLBP [11]. The mean change in pain intensity was statistically significantly greater in both opioid groups compared with placebo, and there were no differences between opioids. Results measured by categorical pain ratings were most impressive, as about 35% of the opioid-treated groups described their pain as absent or mild, versus 12% in the placebo group. Sixty-one percent of the opioid groups reported moderate to complete pain relief versus 28% of the placebo group. Conversely 45% of the placebo group described their pain as severe versus 14% in the opioid groups. There were statistically significant improvements in general activity, mood, normal work, and enjoyment of life, but not walking ability. During the titration phase, about 15% of opioid-treated patients withdrew because of side effects and 4% because of lack of efficacy. In the treatment phase, 25% to 33% of the opioid groups withdrew because of adverse effects. In the titration phase, 57% of the placebo group withdrew because of lack of efficacy and 1% because of side effects. There were no instances of addictive behavior during the short study follow-up period. Side effects were common, but only sedation and constipation were more frequent in the opioid groups compared with controls.

Rauck et al. performed an 8-week multicenter RCT comparing the effectiveness and safety of a once-a-day morphine sulfate-SR (Avinza) with twice daily oxycodone-CR (Oxycontin) in 392 patients with moderate to severe CLBP [7]. Both groups had statistically and clinically significant reductions in pain. Although there were slightly better outcomes in the morphine group, the authors recognize that the study protocol mandated 12-hour dosing of the oxycodone-CR rather than the 8-hour dosing that is more often necessary, which may have biased the results slightly in favor of the morphine group. NPRS decreased from 6.5 to 3.7. The morphine-SR group had somewhat smoother pain control. About 32% to 43% of patients withdrew, most often because of side effects, but also because of inadequate pain relief. There were four instances of abuse or diversion in the oxycodone-CR group.

Allan et al. performed a 13-month unblinded RCT to compare doses of TDF with MS-ER titrated according to patient response in 680 patients with CLBP [8]. The TDF and MS-ER produced similar results. Depending on level of activity, 50% to 65% of patients described themselves as improved, and 37% to 53% of patients had greater than 50% reduction in pain. There were significant improvements in mean short-form 36 scores for physical functioning, bodily pain, role-physical, vitality, social function, and role-emotional; 31% to 37% of patients withdrew the because of adverse events. Over the 13 months of the study, opioid doses increased only slightly, usually early in the treatment to achieve the optimal dose rather than tolerance. There were no reported instances of addiction or abuse behavior.

Hale et al. performed a 10-day RCT to compare the efficacy and safety of titrated doses of oxycodone-CR and oxycodone-IR in 47 CLBP patients [12]. There were equal and significant improvements with both formulations. Pain intensity decreased from moderate to severe at baseline, to slight at the end of titration with both oxycodone formulations. Eleven patients (23%) withdrew because of side effects.

Jamison et al. performed a 16-week RCT to compare naproxen, fixed dose oxycodone, and a titrated dose of oxycodone plus morphine-ER in 36 patients [13]. All three groups had improvement in pain, activity level, and emotional distress. The titrated dose opioid group did best with less pain and less emotional distress than the other two groups. Both opioid groups were better than the naproxen group. There were 86% who found opioids beneficial. Three patients in the opioid groups withdrew because of side effects and one patient had a study medication abuse problem.

Observational studies

Simpson et al. found statistically significant improvement in pain in 50 patients changed to TDF compared with their prior regimens of pain-contingent oral opioids for CLBP [9]. Gammaitoni et al. prospectively studied 33 patients with CLBP treated with titrated doses of oxycodone-IR plus APAP three times daily for 4 weeks [14]. Three patients were not able to tolerate the oxycodone and two others withdrew for other reasons. The mean NPRS was reduced from 6.4 to 4.4 and worst NPRS from 7.7 to 5.6. There were also significant improvements in general activities, mood, walking tolerance, and sleep. Side effects were common, but there were no serious adverse effects. There were no instances of addictive behavior or other abuse.

Schofferman reported a prospective case series of 33 patients with refractory CLBP who were selected by response during the trial titration phase and subsequently treated with opioids for 1 year [2]. Five (15%) patients withdrew because of side effects. In the remaining 28, there were statistically and clinically significant improvements in pain and function at 1 year. The mean NPRS improved from 8.6 to 5.9 and mean Oswestry Low Back Disability Index from 64 to 54. There was a biphasic response. In 21 patients, there was an improvement of NPRS from 8.45 to 4.9, whereas 7 others had no change. Overall, of the 33 patients who started the study, opioids were beneficial in 21 (64%).

Mahowald et al. retrospectively evaluated opioid use over a period of 3 years in an orthopedic spine clinic [4]. Opioids were prescribed for 152 patients (58 of whom received them long term), with follow-up data available in 117. Pain was reduced from a mean of 8.3 to 4.5. It is noteworthy that there was no significant dose increase over time and the authors stated that they did not see tolerance in their patients. Side effects were common but well tolerated by most patients. There was a low prevalence of abuse. The authors concluded that there was clinical evidence to support treating CLBP patients with opioids.

Mixed populations

There are multiple studies and systematic reviews that examined the efficacy and safety of opioid analgesics for the treatment of chronic musculoskeletal pain, all of which included, but were not limited to, patients with CLBP. Furlan et al.'s meta-analysis of opioids for chronic pain concluded that opioids were more effective than placebo for pain and functional outcomes in patients with nociceptive pain, including CLBP [30]. With respect to side effects, only nausea and constipation were clinically and statistically significantly greater in the opioid groups. Study withdrawal rates averaged 33% in opioid groups and 38% in placebo groups.

Markenson et al. performed a 90-day RCT comparing oxycodone-CR with placebo in 107 patients with moderate to severe osteoarthritis, 40% to 50% of whom had CLBP [31]. There were statistically significant differences favoring oxycodone-CR group versus controls in pain intensity, pain-induced interference with general activity, walking, work, mood, sleep, and enjoyment in life. The improvements in pain were only modest. The discontinuation rate was similar between groups, either because of inadequate pain control or side effects.

Harms

Concerns regarding the long-term use of opioids include organ toxicity, tolerance, addiction and dependence, and fear of disciplinary action by medical licensing boards for the prescribing physicians. Each is briefly discussed below.

Organ toxicity resulting from opioids is rare, and there is no evidence that opioids are toxic to the liver, kidneys, brain, or other organs. Respiratory depression is rare except in persons with significant pulmonary disease, sleep-apnea syndrome, or other serious medical conditions. Although side effects are common, most are usually manageable with adjunctive medications [32,33]. There is a potential for endocrine changes. Clinically, the most common problem in men is androgen deficiency because of suppression of pulsatile gonadotropoin-releasing hormone by the hypothalamus which presents as low libido, erectile difficulties, low energy, easy fatigue, and depressed mood [34,35]. In women, there may also be decreased libido and changes in menstrual cycle. Testosterone replacement is usually very effective for such side effects [35]. There may also be instances of osteoporosis, and broader hypothalamic-pituitary suppression, but the clinical significance of these findings is not yet clear.

Tolerance is the need for progressively higher doses of an analgesic to produce the same degree of pain relief. True tolerance is a biological process that occurs at the cellular level and differs from addiction. There is no evidence that opioid tolerance is a significant clinical problem in the treatment of CLBP, and no evidence that opioids lose effectiveness over time unless there is disease progression [2,4]. Mahowald et al. reported dose escalations occurred in 29% of patients treated with LTOs, and 95% of the time it was because of disease progression, complications of spine surgery, or unrelated medical problems [28], rather than tolerance.

Another explanation for opioid dose increase is greater pain because of increased function. This usually occurs early in opioid treatment and perhaps should be called ''pseudo tolerance'' (Fig. 1) as this implies that the opioid is working, not failing. When pain is initially controlled with an opioid, it is expected that function will increase in parallel. This increased function may cause increased pain, which makes it necessary to raise the dose to the point of optimal balance between pain, activity level, and side effects.

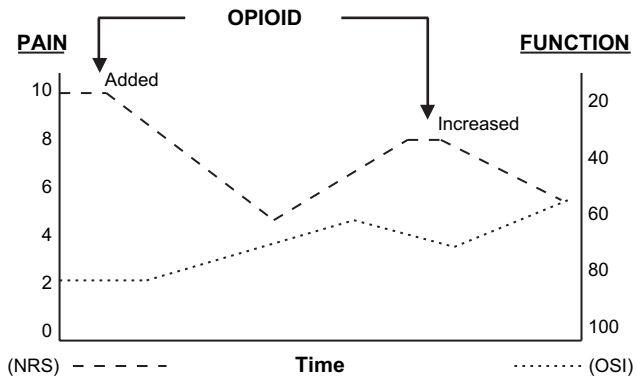

Fig. 1. Pseudo tolerance. NRS is numerical rating score for pain. A lower score indicates less pain. OSI is Oswestry Disability Index for function. A lower score indicates better function.

Addiction and dependence may be confusing. Addiction is a neurobiological disease with genetic, psychosocial, and environmental factors characterized by behaviors that include the compulsive use of a psychoactive substance despite biological, psychological, or social harm [36]. There is loss of control and craving. The prevalence of addiction in patients treated with opioids for pain appears to be about the same as it is in the general population (6%–10%). Addictive behavior, particularly drug seeking, should be distinguished from "pseudo addiction," a scenario in which patients seek medication because their pain relief is not adequate.

The most common aberrant behaviors in patients treated with opioids for pain include diversion, negative urine screen for the prescribed opioid, positive urine screen for unprescribed opioids or other controlled or illegal substances, obtaining opioids from multiple prescribers, and prescription forgery [37]. Neither patient demographics nor intensity of pain are predictive of aberrant drug-related behavior [37,38]. However, some of the potential predictors for higher risk of opioid misuse include past alcohol or other substance abuse; a prior DUI, drug conviction, or other significant problems with the law; and a family history of substance abuse or significant mental health problems [37–39].

Dependence is a state of physiological adaptation induced by the chronic use of a psychoactive substance, which would include alcohol and opioids, among others. There is an abstinence syndrome when the drug is suddenly stopped or the dose is reduced rapidly [36]. Dependence is very common in patients treated with opioids, but is rarely a clinical problem.

Fear of disciplinary action by medical boards, specialty societies, or law enforcement agencies is another concern related to the use of opioids. The treatment of pain is recognized as a priority by several states and their medical boards have issued statements describing the proper use of opioids for pain management [40]. It is generally considered appropriate medical practice to prescribe long-term opioids for chronic pain that cannot otherwise be managed effectively with simple analgesics, and physicians who prescribe opioids for appropriate clinical indications are acting well within the scope of good medical practice. However, it is necessary for physicians to maintain adequate documentation to support their decision to prescribe opioids. There should be discussion of efficacy of analgesia, level of function, mood, and inquiry regarding aberrant drug-related behaviors such as the "four Cs" of addiction—adverse consequences, impaired control, compulsive use, and craving—should be sought [37–39]. With appropriate documentation, fear of regulatory sanction should not constitute a barrier to the use of opioid analgesics in carefully selected appropriate patients with structural spinal pain.

Side effects are common with opioid treatment (Table 3). A recent review found 59% of patients treated with opioids for less than 3 months experienced an adverse effect [28]. Adverse effects were even more common with treatment longer than 3 months, occurring in 73% to 90% of patients, and up to one-third of patients discontinued treatment because of side effects. However, it must be noted that in most studies, about the same number of patients discontinued placebo because of lack of efficacy.

Gastrointestinal side effects are among the most common [41]. Constipation occurs as a result of decreased peristaltic propulsive contractions, increased small and large bowel tone, and decreased biliary, pancreatic, and intestinal secretions. Unlike most other adverse effects, tolerance does not develop to opioid-induced constipation. Patients beginning opioid treatment should begin a prophylactic bowel regimen including regular use of both a stool softener and a laxative. Senna is often useful. Some patients require regular use of polyethylene glycol powder (MiraLax). Nausea and vomiting occur as a direct central effect of opioids on the medullary chemoreceptor trigger zone. Tolerance to nausea may develop after several days but some patients require an antiemetic. Haloperidol or metoclopramide may be helpful in managing opioid-induced nausea.

Sedation and drowsiness are the most common CNS adverse effects of opioid therapy though a wide range of other neurological symptoms may occur including confusion, hallucinations, nightmares, myoclonus, and dysphoria

Table 3
Most common adverse effects of opioid treatment

Symptom	Prevalence (%)
Anorexia	8–11
Constipation	52–65
Dizziness	24–25
Dry mouth	9–18
Myoclonus	2.7–87
Nausea	50–54
Pruritis	15–20
Somnolence	27–30
Sweating	16–26
Urinary retention	9–15
Vomiting	26–29

[42]. Tolerance typically occurs to the sedating effects of opioids within the first week of treatment. In those patients who continue to feel sedated, modafinil 100 to 300 mg daily may help [43].

Opioids can be CNS depressants, raising concern that important tasks requiring alertness, manual dexterity, and reflex responses might be adversely impacted by the drugs. Interestingly, studies suggest chronic pain itself impairs performance on psychomotor testing, and opioid-treated patients who experience pain relief actually demonstrate test results similar to controls [44–46]. In fact, patients with CLBP on LTO treatment demonstrate improved performance on tests of psychomotor function with reduction in pain and distress. Even in elderly nursing home residents, chronic opioid use may not increase risk of mood disorders or cognitive abnormality [47]. Finally, a recent systematic review of studies addressing whether opioid-treated patients are driving impaired concluded that there was ''generally consistent evidence for no impairment of psychomotor abilities of opioid-maintained patients,'' including immediately after a dose of drug [48]. Most studies found opioid therapy did not impair driving ability.

There are adverse effects unique to two particular opioid agents, tramadol and meperidine. Because tramadol is an inhibitor of both serotonin and norepinephrine reuptake, concomitant administration with antidepressants of the selective serotonin reuptake inhibitor class risks development of a ''serotonin syndrome'' [49]. Symptoms of the serotonin syndrome include agitation, hyperreflexia, mental status change, myoclonus, tremor, seizures, fever, and even death. Meperidine is an opioid analgesic with a half-life of approximately 3 hours. Hepatic metabolism of meperidine results in an inactive metabolite, normeperidine, which has a much longer half-life of approximately 20 hours. Repeated, frequent administration of meperidine for analgesic effect may result in toxic accumulation of this long-lived metabolite, particularly in persons with hepatic or renal insufficiency, and the elderly [23,50]. Toxic levels of normeperidine have been associated with seizures, tremor, and hallucinations. Meperidine should not be used for long-term management of CLBP.

There is animal, human, and in vitro laboratory evidence that opioids can affect immune function adversely. The mechanism is not fully understood but may be partly mediated by neuroendocrine interactions, and direct effects on cells affecting immunity [51,52]. It is not clear whether this effect is clinically important [52].

Another concern is the potential for OIH [53]. In a systematic review, Angst et al. found case reports of patients who developed allodynia and hyperalgesia, especially with high-dose opioids and rapid dose escalation. However, at least in the experimental setting, OIH can occur in as little as 1 month [54]. Distinct from tolerance, OIH refers to an increased sensitivity to painful stimuli. The clinical picture is that of a patient who had been doing well with opioids, but then develops increased pain in the absence of disease progression. Often there is also unexplained expansion and generalization of pain. Pain improves in some patients with alternative analgesics (possibly a different opioid) or complete weaning from opioids.

Major negative outcomes for LTO treatment include aberrant opioid-related behavior and, arguably more importantly, treatment failure because of lack of efficacy or side effects. There has been a great deal of effort to find ways to predict aberrant behavior, summarized recently by Katz et al. [55]. However, there is only minimal literature focused on ways to accurately predict positive and negative outcomes. One recent and seemingly promising attempt to predict efficacy, risk, and compliance, rated patients in four domains (diagnosis, intractability, risk, and efficacy) [56]. Scores correlated moderately with efficacy and strongly with compliance. As previously noted, patients who are adaptive copers appear most likely to benefit from LTOs whereas those who are dysfunctional or interpersonally distressed appear to do worse in all domains.

Summary

There is sufficient evidence to suggest that opioid analgesics are safe and effective for the treatment of patients with CLBP, at least in the short term. In all high-quality studies, there are clinically and statistically significant improvements in pain, and the results are uniformly better for opioids than placebo. There is sufficient but less robust evidence to state that opioids retain their effectiveness over the longer term, and no reported loss of efficacy over time. It should be noted that the withdrawal rates reported in RCTs of opioids were generally high (20%–40%) because of side effects. Among the remaining patients who are able to tolerate opioids, one-third are excellent responders, one-third fair responders, and one-third nonresponders. The evidence for improvement of function with opioids is more limited than for improvement of pain. There is no evidence of superiority among the different opioids. Opioids are generally safe and serious toxicity is rare. The incidence of diversion, addictive behavior, or other social problems is acceptably low. Side effects are common, but are manageable in patients who can tolerate this type of medication. LTO analgesics appears to be a reasonable treatment option for patients with moderate to severe CLBP that has proven to be refractory to general rehabilitation, injections, nonopioid analgesic medications, or is not directly treatable because of either the structural disorder or patient preference. Opioids can also be used in conjunction with functional restoration [57], which is discussed elsewhere in this special focus issue.

Katz identified several consistent methodological problems in most studies to date, and made useful suggestions for improving future studies [58]. The research that would provide the most valid and clinically useful data regarding safety and efficacy of opioid analgesics would ideally use

dose titration, opioid rotation to find the best opioid for each patient, flexible dosing with a sufficiently high permitted maximum dose, minimal use of rescue medications, homogeneous patient samples, and fewer study sites [58].

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