Evidence-informed management of chronic low back pain with nonsteroidal anti-inflammatory drugs, muscle relaxants, and simple 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 amongst 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.   © 2008 Elsevier Inc. All rights reserved.

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Description

"The art of medicine consists of amusing the patient while nature cures the disease." Voltaire.

Terminology

Nonsteroidal anti-inflammatory drugs (NSAIDs) are medications that provide anti-inflammatory and analgesic effects and which include common products such as ibuprofen and naproxen. Older NSAIDs are sometimes termed nonselective NSAIDs because they inhibit both the cyclooxygenase (COX)-1 and COX-2 enzymes. Newer NSAIDs are commonly known as selective NSAIDs, coxibs, or COX-2 inhibitors because they block only the COX-2 isoenzyme involved in inflammation. Muscle relaxants are drugs used to relax skeletal muscle, usually for the purpose of analgesia when related to chronic low back pain (CLBP). The term analgesics is quite vague and can encompass

a number of drug classes if used to relieve pain. For the purposes of this review, analgesics will refer to simple nonopioid analgesics (eg, acetaminophen/paracetamol, tramadol). The use of opioid analgesics and adjunctive analgesics for CLBP is discussed elsewhere in this special focus issue.

Frequency of use

NSAIDs are the world's most frequently prescribed medications [1,2]. A 2000 US Medical Expectations Panel Survey [3] found that 44 million prescriptions (Rx) were written for 24.5 million patients with low back pain (LBP), both acute and chronic. Of these, 16.3% were for nonselective NSAIDs, 10.0% were for COX-2 inhibitors, and 18.5% were for muscle relaxants. Most (60%) NSAIDs Rx were for ibuprofen and naproxen, and most (67%) muscle relaxants Rx were for cyclobenzaprine, carisoprodol, and methocarbamol. A longitudinal study by Cherkin et al. [4] found that 69% of patients with LBP in the primary care setting were prescribed NSAIDs, 35% received muscle relaxants, 4% acetaminophen, and only 20% were not prescribed medications. A review of the University of Pittsburgh Healthcare System in 2001 [5] found that 53.1% of men and 57.4% of women presenting with LBP were prescribed an NSAID; more severe pain tended to be treated with opioids and/or muscle relaxants. A study in Sweden on 302 patients with CLBP reported that they took an average of two different medications for that condition [6]. The most common class of drug consumed for CLBP was analgesics (59% of sample), followed by NSAIDs (51%), muscle relaxants/anxiolytics (11%), and COX-2 inhibitors (5%). A study of health-care utilization in patients with mechanical LBP enrolled in Kaiser Permanente Colorado indicated that 31% of patients had a claim for NSAIDs [7].

Subtypes

There are multiple subclasses of NSAIDs including salicylates (eg, aspirin, diflusinal, salsalate), phenylacetics (eg, diclofenac), indoleacetic acids (eg, etodolac, indomethacin, sulindac, tolmetin), oxicams (eg, piroxicam, meloxicam), propionic acids (eg, ibuprofen, naproxen, ketorolac, oxaprozin), naphthylkanones (eg, nabumetone), and coxibs (eg, celecoxib, rofecoxib, valdecoxib, and etoricoxib). Muscle relaxants are a heterogeneous group of medications divided into antispasmodics and antispasticity medications [8]. Antispasmodic muscle relaxants include two main categories, benzodiazepines and nonbenzodiazepines. Benzodiazepine antispasmodics have many properties and are used as skeletal muscle relaxants, sedatives, hypnotics, anticonvulsants, and anxiolytics. Nonbenzodiazepine antispasmodics act at the brain or spinal cord level to decrease muscle spasm associated with LBP and include products such as cyclobenzaprine, tizanidine, flupirtin, and tolperisone. Antispasticity muscle relaxants reduce spasticity

associated with upper motor neuron (UMN) disorders and include products such as dantrolene and baclofen. Simple analgesics include commonly used products such as acetaminophen and tramadol.

General description

Treatment with these medications usually consists of following a prescribed pattern of use with initial visits to titrate the dosage and follow-up visits to monitor response to therapy and potential adverse events.

Practitioner, setting, and availability

Any licensed physician may prescribe these classes of drugs, which are available in a variety of settings, including private practices and hospitals. This intervention is widely available in the United States. Many lower doses of NSAIDs and analgesics are available as over-the-counter medications, though higher doses and specific medications in these drug classes are only available by Rx.

Reimbursement

Individual insurance carriers vary in their formulary coverage of newer medications. Some may require prior authorization with a failure of a cheaper medication, or medical justification for using a more expensive medication within the same class or category. In general, these medications are widely reimbursed by third-party payers.

Over-the-counter medications are generally inexpensive, whereas Rx medications vary greatly in price. Average US wholesale costs in 2005 for one tablet of aspirin was $0.03, naproxen was $0.15, whereas celecoxib was $2.43 [9]. In Canada, during 2003, the daily cost of ibuprofen 800 mg three times daily (TID) was $0.22CAD; acetaminophen 1,000 mg four times daily (QID) was $0.37CAD; naproxen 500 mg twice daily (BID) was $0.42CAD; and celecoxib 100 mg BID was $1.25CAD [10].

The costs of side effects associated with these drugs should also be considered. A Canadian study [11] using the Quebec provincial public health-care database found that for each dollar spent on nonselective NSAIDs an extra $0.66 was used on their side effects. Another Canadian study [10] found that rofecoxib or celecoxib were cost effective in patients with rheumatoid and osteoarthritis patients compared with nonspecific NSAIDs plus proton pump inhibitor (PPI). However, this was only the case when patients were over 76 years old (rofecoxib) or 81 years old (celecoxib). When assuming that the risk of gastrointestinal (GI) complications was 50% lower with COX-2 inhibitors, the ages at which they became cost effective dropped to 56 and 67 years, respectively. A 2005 study [9] considered GI and cardiovascular events comparing nonselective NSAID, NSAID plus PPI, and coxibs. For low-risk patients, a nonselective NSAID was the most cost effective. In patients with

high risk, an NSAID plus PPI seemed to be the most cost effective strategy.

Theory

Mechanism of action

Nonsteroidal anti-inflammatory drugs

NSAIDs function through various degrees of reversible blockade of COX isoenzymes, thus blocking the inflammatory cascade of arachidonic acid to prostaglandins, which mediate inflammation and sensitize peripheral nociceptors [12]. Aspirin is a salicylic NSAID with irreversible COX blockade. Another NSAID mechanism is inhibition of neutrophil function and phospholipase C activity, which increases intracellular calcium levels and production of arachidonic acid metabolites such as prostaglandins. These blockade mechanisms account for the anti-inflammatory and analgesic properties of NSAIDs.

Muscle relaxants

This heterogeneous group of medications generally acts by inhibiting central polysynaptic neuronal events, which indirectly acts on skeletal muscle [13]. Antispasticity medications act on the central nervous system (CNS) to decrease UMN spasticity pathways. Baclofen is thought to act as a gamma-butyric acid (GABA) analog at GABA-B receptors thus inhibiting presynaptic calcium influx and excitatory neurotransmitters. Tizanidine acts as an α-2 adrenergic agonist that is thought to inhibit presynaptic motor neurons. The muscle relaxing effect of diazepam is unknown, but is thought to act on postsynaptic spinal cord GABA transmission. Antispasmodic medications also act centrally by unknown mechanisms. Cyclobenzaprine is thought to act on the brainstem, whereas metaxalone may work by generalized CNS depression.

Simple analgesics

Acetaminophen possesses analgesic and antipyretic properties. It is a para-aminophen derivative that weakly inhibits COX isoenzymes to inhibit prostaglandin synthesis without inhibiting neutrophils. The antipyretic effects are from action at the hypothalamic heat-regulating center [12]. Although tramadol is chemically unrelated to opioids, it acts by weakly binding μ- and δ-opioid receptors. It also interferes with serotonin and norepinephrine reuptake in descending inhibitory pathways [5]. Tramadol is only partially affected by the opiate antagonist naloxone [14].

Diagnostic testing required

A careful medical history and physical examination are required to assess the underlying disease process and rule out the risk factors associated with serious pathology (eg, cauda equina syndrome, fever of 38 °C for more than 48 hours unrelenting rest or night pain, progressive neurological deficit, significant trauma, suspicion of cancer, ankylosing spondylitis, or osteoporosis, chronic corticosteroid use, immunosuppressed state, drug or alcohol abuse). The medical history should also note prior hypersensitivity/allergy or adverse events with similar drugs, and evaluate risk factors for these types of drugs (eg, prior history of GI bleeding).

Indications and contraindications

Nonsteroidal anti-inflammatory drugs

Indications for NSAIDs include muscle aches and pains, backaches, and arthritis [13].

Muscle relaxants

Cyclobenzaprine, metaxolone, methocarbamol, and carisoprodol are indicated for acute painful musculoskeletal conditions [12]. Baclofen and tizanidine are indicated for spasticity associated with UMN disorders, but are frequently used off-label for painful musculoskeletal conditions. Diazepam is indicated for UMN muscle spasticity and local painful musculoskeletal spasm, as well as anxiety. Because the true mechanism of action on muscle spasm is unknown, the sedating side effects are often used for the benefit of improved sleep.

Simple analgesics

Acetaminophen is indicated for first-line treatment of mild muscular aches, backaches, and arthritis; tramadol is recommended for moderate to moderately severe chronic pain [13].

General contraindications for all medications include prior allergy or hypersensitivity; the most common specific contraindications for each drug are summarized below.

Nonsteroidal anti-inflammatory drugs

Naproxen is typical of nonselective NSAIDs and is contraindicated for use in the last 3 months of pregnancy, during the perioperative period for cardiac surgery, and in patients with high risk of bleeding [13]. As the only remaining COX-2 inhibitor in the US market as of date [15], celecoxib is contraindicated in sulfonamide hypersensitivity and should be used with extra caution in cardiac disease and hypertension. NSAIDs should not be used in any patient with peptic ulcer disease or congestive heart failure [5], and should be monitored closely in patients with known renal disease.

Muscle relaxants

Because of sedation, all muscle relaxants should first be taken in safe situations, where poor mental clarity would not be detrimental. Benzodiazepines such as diazepam are contraindicated in narrow angle glaucoma [13]. Cyclobenzaprine carries the same contraindications as tricyclic antidepressants, should not be used within 14 days of monoamine oxidase inhibitors, or with cardiac arrhythmias,

coronary artery disease, or hyperthyroidism. Metaxalone is not recommended with significantly reduced renal or hepatic function. Dantrolene is contraindicated for skeletal spasm because of potential liver toxicity.

Simple analgesics

Acetaminophen should be used with care in the presence of hepatic disease. The Physician's Desk Reference warns against using acetaminophen when a patient has liver disease or consumes more than three alcoholic beverages daily [13]. Careful review of concurrent medications and seizure risk must be completed before initiating tramadol because of an increased risk of seizure activity that may be accentuated with use of antidepressants, anticonvulsants, or opioids [13]. Increased suicidal risk has been reported with tramadol.

An individual patient's response to any particular medication is not predictable. Patients most likely to experience improvements with these drugs are those without any contraindications or sensitivities to a specific medication and without psychological dysfunction, financial disincentives, or poor social support systems. Given that most of these medications are used only to address symptoms and do not effect any structural changes to the lumbosacral area, they are perhaps best used during acute exacerbations of CLBP rather than on an ongoing basis. The ideal CLBP patient for this type of intervention should also be willing to engage in an active intervention such as exercise to address possible physical contributors to their condition.

Evidence of efficacy

Clinical guidelines

Guidelines and protocols for primary management of CLBP typically advocate the initial appropriate use of medications and noninvasive therapies, though recommendations differ and often do not carry adequate evidence-based explanations for their conclusion [4,16]. A number of CLBP guidelines reviewed NSAIDs and simple analgesics, but there was no consensus on their use. The World Health Organization advocates using the "pain ladder" where simple analgesics and NSAIDs occupy the first rung followed by mild opiates and stronger opioids [8,16–19]. European guidelines for management of nonspecific CLBP were published in 2006 from the efforts of the COST B13 Working Group on LBP [8]. The evidence they uncovered is summarized below by study design and is supplemented with other systematic reviews and randomized controlled trials (RCTs) identified independently.

Systematic reviews

Nonsteroidal anti-inflammatory drugs

Two systematic reviews [1,20] uncovered 51 RCTs for the European guidelines [8,18] though only 5 RCTs

[21–25] reported exclusively on CLBP. The only "high-quality" trial (n=30) [22] reported better pain relief with diflusinal compared with placebo. An additional systematic review from Schnitzer et al. [26] found that NSAIDs were effective in short-term relief of CLBP.

Muscle relaxants

One systematic review [27] uncovered six RCTs, including four "high-quality" trials [28–31], and two "low-quality" trials [32,33]. Two trials [30,31] (n=222) demonstrated that tetrazepam 50 mg TID improved pain, global improvement, and muscle spasm in the short term at both 5 to 7 days and 10 to 14 days follow-up. Basmajian [32] demonstrated no difference (n=76) between diazepam or cyclobenzaprine and placebo for muscle spasm. Flupirtin was shown better than placebo at 7 days for pain relief, but not muscle spasm [29]. Another trial found tolperisone better than placebo in global improvement at 21 days, but not in decreasing pain or muscle spasm [28]. Studies did not provide evidence for long-term use of muscle relaxants in CLBP.

Simple analgesics

A number of different simple analgesics were considered for CLBP in the European guidelines [8]. Topical treatment of CLBP with capsaicin plaster was analyzed from one systematic review [34], which included one trial (n=154) [35], and one additional RCT [36] of 301 patients versus placebo. Keitel et al. [35] found significant improvement in nonspecific CLBP with a 60.8% positive response rate to capsaicin over 3 weeks. The same group repeated the results with a 67% positive response rate, compared with 49% with placebo plasters [36]. However, the review [34] included other trials in musculoskeletal pain and concluded that capsaicin had moderate to poor efficacy as in only one of eight patients pain decreased by 50%.

The above systematic reviews are summarized in Table 1.

Randomized controlled trials

Nonsteroidal anti-inflammatory drugs

Only five RCTs [21–25] were uncovered on CLBP in the European guidelines, and five additional papers using COX-2 selective inhibitors [37–41] and another trial [42] comparing rofecoxib with a proprietary extract of *Harpagophytum* were also included. The only "high-quality" trial (n=30) [22] reported better pain relief with diflusinal compared with placebo. A "lower quality" study (n=37) [21] showed naproxen improved global pain better than placebo, whereas diflusinal was equal to placebo. Four-week trials comparing rofecoxib 25 mg (n=228), 50 mg (n=233), and placebo (n=229) in three studies [38–40] found significantly decreased pain and disability scores at 1 week equally in both dose categories. Birbara et al. (n=319) [37] compared etoricoxib (a newer COX inhibitor) 60 mg or 90 mg with placebo and demonstrated decreased pain

Table 1
Systematic reviews

Reference	Type	Inclusion/exclusion	Studies uncovered	Outcomes	Results	Comments
[1]	NSAIDs	Inclusion: Random, controlled, Dbl-bl, CLBP ± radiation; Exclusion: specific dz	51 total RCTs, only 5 RCTs for CLBP	Pain	NSAID>placebo (1 RCT) NSAID>acetaminophen (limited) NSAID=NSAID (4 RCTs) NSAID+Vitamin B; not better	Few studies of only CLBP, insufficient evidence to make strong recommendations
[20]	NSAIDs	Inclusion: RCT LBP, chronic (>12 wk), English; Exclusion: neck pain, post-op	6 RCTs	Pain, function, overall improvement	NSAIDs > placebo (1 RCT) NSAID=NSAID	Moderate evidence NSAIDs effective for CLBP; strong evidence NSAIDs equal within class
[26]	NSAIDs	Inclusion: CLBP, age 18–89 y, English, Spanish, French, German, 1980–2002	4 RCTs	Pain, function	NSAID>placebo (1 RCT) NSAID effective compared with active tx	NSAIDs effective in short-term CLBP; few trials
[27]	Muscle relaxants	Inclusion: RCT, controlled, dbl-bl trials, compared with reference tx or combination; Exclusion: mixed musculoskeletal pains	6 RCTs	Pain, function, global improvement	Benzodiazepine>placebo for pain and overall, but conflicting on spasm, Nonbenzos>placebo for pain, NOT spasm	Strong evidence benzodiazepines improve short-term pain and overall; moderate evidence nonbenzos decrease pain, NOT spasm; no trials with antispasticity agents
[62]	Muscle relaxants	Inclusion: Only LBP, non-English; Exclusion: no placebo	7 RCTs	Pain, function	Norepinephrine reuptake inhibition, improved pain in 4/5 Mixed function results Non-NERI agents no improvement	Tricyclic and tetracyclic improve pain; SSRIs do not
[34]	Capsaicin plasters	Inclusion: RCT, multiple applications, musculoskeletal and neuropathic pain	1 RCT for LBP/total 16 RCTs (n=1,556, age 20–95 y)	Reduced pain by 50%	4 wk—musculoskeletal capsaicin 38% versus placebo 25% better NNT 8.1 neuropathic capsaicin 57% versus placebo 42% better	Small significant improvement with capsaicin, high placebo effect, local side effects 54% capsaicin versus 15% placebo

NSAIDs=nonsteroidal anti-inflammatory drugs; LBP=low back pain; RCT=randomized controlled trials; CLBP=chronic low back pain; ADL=activities of daily living; Dbl-bl=Double blind; dz=diagnoses; EMG=elcetromyography; ESR=erthrocyte sedimentation rate; f/u=follow up; IM=intra muscular; Incr Alk Phos=increased Alkaline Phosphatate; meds=medications; NERI=norepinephrine re-uptake inhibitor; NNT=number needed to treat; OMT=osteopathic manipulation treatment; PO=per oral; prox=proximal; psych=psychology; PT=physical therapy; SSRI=selective serotinin re-uptake inhibitor; wk=week.

and improved functioning at 12 weeks. These results were repeated by Palley et al. (n=325) [41]. A trial published in 2005 [43] showed that etoricoxib 60 mg QID was comparable with diclofenac 50 mg TID in pain relief. A study [24] compared indomethacin 25 mg TID with piroxicam 20 mg daily (with two placebo doses), and found no differences in pain or function at 6 weeks. One study of 256 patients [23] showed better pain relief with vitamin B plus diclofenac than diclofenac alone. A multiarmed study [25] comparing diclofenac, spinal manipulation, physical therapy, back school, and bed rest showed no significant difference in the small groups. A study [42] comparing a low dose of rofecoxib with an herbal extract of *Harpagophytum* found no difference in pain relief.

Muscle relaxants

There were six RCTs uncovered, including four "high-quality" trials [28–31] and two "low-quality" trials [32,33] for CLBP. Two trials (n=222)[30,31] demonstrated that tetrazepam 50 mg TID improved pain, global improvement, and muscle spasm in the short term at both 5 to 7 days and 10 to 14 days follow-up. Basmajian [32] demonstrated no difference (n=76) between diazepam or cyclobenzaprine and placebo for muscle spasm. Flupirtin was shown better than placebo at 7 days for pain relief, but not muscle spasm [29]. Another trial found tolperisone better than placebo in global improvement at 21 days, but not in decreasing pain or muscle spasm [28]. Studies did not provide evidence for long-term use of muscle relaxants in chronic back pain.

Simple analgesics

A number of different simple analgesics were considered for CLBP in the European guidelines. There were two RCTs on capsaicin plaster for CLBP [35,36]. Keitel et al. [35] found significant improvement in nonspecific CLBP with a 60.8% positive response rate to capsaicin over 3 weeks. The same group repeated the results with a 67% positive response rate, compared with 49% with placebo plasters [36]. Lidocaine patches have shown promise to reduce pain in observational pilots studies [44,45] for LBP, and other musculoskeletal pain [46]. However, there were no RCTs identified to date. A small study by Hickey et al. [22] compared acetaminophen 1,000 mg QID to

diflunisal 500 mg BID over 4 weeks in CLBP. They found more patients reported good to excellent improvement with diflunisal, but there was no significant difference in pain relief. Tramadol 200 to 400 mg daily was found to be effective in reducing pain and disability [47]. The combination of tramadol and acetaminophen was also shown to improve CLBP and disability compared with placebo [48,49], but it was not compared with other treatments.

The above RCTs are summarized in Tables 2–5.

Harms

Nonsteroidal anti-inflammatory drugs

The blockade of COX enzymes, neutrophil function, and phospholipase activity by NSAIDs account for related renal, GI, and potential cardiovascular side effects. It is notable that sulindac may be relatively renal sparing, whereas naproxen may be relatively cardioprotective. The risk of GI, renal, and hepatic complications in patients taking nonselective NSAIDs is well known [12,13,50]. The Celebrex Long-term Arthritis Safety Study (CLASS) demonstrated this where celecoxib 400 mg BID was compared with ibuprofen 800 mg TID and diclofenac 75 mg BID [50]. Incidence rates for GI complications were 0.44% with Celebrex compared with 1.27% with the other NSAIDs in a large cohort of 8,059 patients. The Vioxx Gastrointestinal Outcomes Research (VIGOR) trial compared rofecoxib with naproxen, and found fewer GI complications with rofecoxib [51]. However, there was a fivefold increase in myocardial infarctions in the rofecoxib group. This effect was thought to be because of a cardioprotective effect from naproxen, but the Adematous Polyp Prevention on Vioxx trial found similar cardiac trends in the rofecoxib group [15]. The pharmaceutical manufacturer pulled rofecoxib from the market in 2004.

The observed increase in cardiovascular risk with COX-2 inhibitors is theorized to be from the disruption of the normal balance between pro- and antithrombotic prostaglandins [12]. Thromboxane A2 is a platelet activator and aggregator that is mediated by prostaglandin products of the COX-1 isomer pathways. Prostaglandin PGI2 vasodilates and inhibits platelet aggregation when the COX-2 isomer is activated. Thrombotic cardiac events may follow when thromboxane A2 predominates over PGI2. However, a retrospective study of more than 70,000 Canadian elderly patients given celecoxib, rofecoxib, naprosyn, other NSAIDs, or control found no increased cardiac risk when use was less than a year [52]. A meta-analysis by Mukherjee et al. [53] of the VIGOR, CLASS, and two smaller studies found that allowing low-dose aspirin therapy provided cardioprotection compared with the VIGOR trial. Unfortunately, allowing aspirin therapy in the CLASS trial increased the incidence of GI events from 0.44% to 2.01%, compared with 1.27% in nonselective NSAIDs [50]. A meta-analysis [54] found that ibuprofen and diclofenac

Table 2
RCTs of NSAIDs for LBP

Reference	Intervention	Inclusion/exclusion	Participants	Outcomes	Results	Follow-up	Comments
[22]	Diflunisal 500 mg BID versus Acetaminophen 1,000 mg QID	Inclusion: axial LBP>6 mo; Exclusion: steroids, psych, contraindication	30 patients—16 diflunisal/14 acetaminophen (13% M, mean age 42.9 y)	Pain scale, functional DA, spine flexion/extension, overall improvement	10/16 diflunisal versus 4/14 acetaminophen groups "good or excellent" results, both improved in all categories	2 and 4 wk	Acetaminophen and diflunisal both comparably effective, small sample
[21]	A. Naproxen 550 mg BID, B. diflunisal 500 mg BID, C. placebo	Inclusion: LBP>3 mo; Exclusion: known cause, Incr Alk Phos/ESR	37 patients (mean age 55 y, 35% M)	Pain VAS, night/standing/movement pain scores	A and B better than C, A better than B only for pain VAS	2 wk	Naproxen comparable with diflunisal, only better pain VAS
[25]	Diclofenac versus PT/bed rest/back school/OMT versus placebo	Inclusion: acute and CLBP	459 patients—81 patients in NSAID group	Pain, DA, back flexion score	Diclofenac not significantly different than other active therapies	3 wk, 2 and 6 mo	Diclofenac not better than PT, bed rest, back school or manipulation
[23]	A. Diclofenac 50 mg TID versus B. Diclofenac 50 mg+Vitamin B TID	Inclusion: CLBP; Exclusion: not known (German)	252 patients—126 each (mean age A. 47 y, B. 50 y; 55% M)	Pain intensity	Pain intensity improvement 7 d—A. 19%, B. 29%, 14 d—A. 29%, B. 33%, better	3, 7, 14 d	No significant difference, trend for faster improvement with Vitamin B
[24]	A. Indomethacin 25 mg TID versus B. Piroxicam 20 mg Q day	Inclusion: severe CLBP, known causes; Exclusion: contraindications, wk comp claims, pregnancy	28 patients (mean age 45 y, 61% M)	Pain, ADLs, rescue meds, lumbar flexion	A and B improved pain equally, similar improvement in secondary outcomes	2, 4, 6 wk	Indomethacin and piroxicam provide comparable pain and functional improvements

RCT=randomized controlled trials; NSAIDs=nonsteroidal anti-inflammatory drugs; LBP=low back pain; DA=disability index; BID=twice daily; QID=four times daily; VAS=visual analogue scale; TID=three times daily.

Table 3
RCTs of COX-2 inhibitors for LBP

Reference	Intervention	Inclusion/exclusion	Participants	Outcomes	Results	Follow-up	Comments
[37]	Etoricoxib 60 mg versus 90 mg versus placebo Q day	Inclusion: LBP>3 mo, VAS>40 mm, worse in wash out; Exclusion: known dx, steroids, depression, back surgery	319 patients (mean age 52 y, 40% M)	Pain decrease at 4 wk, global improvement	Both etoricoxib doses decrease pain equally>placebo	4 and 12 wk	Etoricoxib analgesia better than placebo; no other comparisons
[39]	Rofecoxib A. 25 mg, B. 50 mg, or C. placebo Q day	Inclusion: CLBP; Exclusion: not specified	380 patients A. 126, B. 126, C. 128 (mean age 52.5 y, 36.8% M)	Pain VAS, DA, global scores	Rofecoxib decreases pain>placebo, doses equal; all measures better with rofecoxib	4 wk	Rofecoxib effective and well tolerated versus placebo
[38]	Rofecoxib A. 25 mg, B. 50 mg, or C. placebo	Inclusion: LBP>3 mo, VAS>40 mm, worse in wash out; Exclusion: known causes, steroids, depression	690 patients A. 233, B. 229, C. 228; duration 12.1 y (mean age 53.4 y, 37.7% M)	Pain intensity, bothersome scale, global effect, DA, rescue meds	Both doses equally decrease pain intensity, and all secondary outcomes	1, 2, 4 wk	Rofecoxib better pain relief than placebo; fewer SE with 25 mg (same cohort as [50])
[40]	Rofecoxib A. 25 mg, B. 50 mg, or C. placebo	Inclusion: LBP>3 mo, VAS>40 mm, worse in wash out; Exclusion: known causes, steroids, depression	690 patients A. 233, B. 229, C. 228; duration 12.1 y (mean age 53.4 y, 37.7% M)	Time to effect (50% reduced pain), bothersome scale, global, effect, DA	Perceptible pain relief at 2 h, meaningful pain relief at 1 d (placebo 2 d); rofecoxib better in all outcomes	0.5, 1, 2, 3, 4 h, first night, first AM; 1, 2, 4 wk	Rofecoxib earlier perceived and meaningful pain relief than placebo; equal dose responses; same cohort as [48]
[41]	Etoricoxib A. 60 mg, B. 90 mg, or C. placebo	Inclusion: LBP>3 mo, requiring NSAIDs or acetaminophen; Exclusion: known cause, depression, steroids, opiates	325 patients A. 109, B. 106, C. 110 (mean age 52.8 y, 37.5% M)	Pain VAS, DA, global, bothersome score, depression scale	Doses equally decrease pain>placebo, all secondary outcomes improved	1, 2, 4, 8, 12 wk	Etoricoxib was equally effective at both doses, and well tolerated
[42]	A. Rofecoxib 12.5 mg versus B. *Harpagophytum* extract 60 mg; tramadol for rescue	Inclusion: CLBP, radiating symptoms allowed; Exclusion: contraindications	88 patients—44 each (mean age 61.5 y, A. 32% M, B. 23% M)	Responders (5 d in week 6 without rescue meds)	A. 11.4% responded versus B. 22.7% responded	1, 2, 3, 4, 5, 6 wk	No significant difference, but only A. 29.5% versus B. 47.7% needed rescue medicines during the trial
[43]	A. Etoricoxib 60 mg Q day versus B. Diclofenac 50 mg TID	Inclusion: CLBP, worse in wash out; Exclusion: pain VAS > 80 mm	446 patients—A. 224, B. 222 (mean age 51.9 y, 28.3% M, mean duration 8.3 y)	Change in pain intensity, DA, global, bothersome scores	Change in pain, and secondary outcomes all comparable; both treatments effective	1, 2, 3 d; 1, 2, 4 wk	Comparable effectiveness and tolerability between etoricoxib 60 mg and diclofenac 50 mg TID

RCT=randomized controlled trials; COX-2=cyclooxygenase-2; LBP=low back pain; VAS=visual analogue scale; NSAIDs=nonsteroidal anti-inflammatory drugs; CLBP=chronic low back pain.

Table 4
RCTs of muscle relaxants for LBP

Reference	Intervention	Inclusion/exclusion	Participants	Outcomes	Results	Follow-up	Comments
[30]	Tetrazepam 150 mg versus placebo	Inclusion: subacute/CLBP; Exclusion: poor compliance, contraindications, placebo responders	50 patients—25 each (age 18–80 y, gender% unknown)	Pain, muscle spasm, lumbar flexion	Improved pain, spasm, not flexion	3, 7, 14 d	Tetrazepam improves short-term pain, less difference from placebo at 14 d
[32]	A. Cyclobenzaprine versus B. diazepam versus C. placebo	Inclusion: spasm>30 d; Exclusion: not specified	105 patients A. 34, B. 36, C. 35 (age/gender not specified)	Muscle spasm, ADLs, EMG activity	No difference in ADLs at 2 wk, better EMG scores with cyclobenzaprine, not others	1 and 2 wk	No difference in ADLs, decreased spasm (EMG activity) with cyclobenzaprine
[33]	Pridinol mesilate versus thiocolchiside IM×3 days, then PO×4 d	Inclusion: CLBP, >20 y; Exclusion: neurological disorders	120 patients (age range 20–77 y, 42.5% M)	Walking speed, climbing rate, lumbar flexion, pain	No difference in improvement walking/climbing, pridinol better flexion	3 and 7 d	Comparable improvement in CLBP; did not define CLBP; pridinol slightly better tolerated
[28]	A. Tolperisone 300 mg versus B. placebo; allowed PT	Inclusion: back and prox musculoskeletal spasm, PPT<2 kg/cm^3; Exclusion: contraindications, inflammation, pregnancy	137 patients (mean age 49.3 y, 27.7% M)	PPT, overall improvement	A. Better PPT, overall at 10 and 21 d; Increase in effect with PT and pain<1 y	4, 7, 14, 21 d	PPT improved with tolperisone and increase in effect with PT
[31]	A. Tetrazepam 150 mg BID versus B. placebo	Inclusion: CLBP, failed PT, musculoskeletal spasm, decrease in lumbar flexion; Exclusion: contraindications, improve with placebo at 2 d	152 patients (mean age 45.3 y, A. 58.2% M, B. 60.3% M)	Pain, movement, lumbar flexion	Pain, movement, flexion better at 7 and 14 d, but no change over 2 wk	3, 7, 14 d	Pain and movement better with tetrazepam; intension to treat not used and high exclusion rate

RCT=randomized controlled trials; LBP=low back pain; PPT=pain pressure threshold; CLBP=chronic low back pain.

Table 5
RCTs of simple analgesics for LBP

Reference	Intervention	Inclusion/exclusion	Participants	Outcomes	Results	Follow-up	Comments
[22]	A. APAP 1,000 mg QID versus B. diflunisal 500 mg BID	Inclusion: axial LBP>6 mo; Exclusion: steroids, psych, contraindications	30 patients—A. 14, B. 16 (mean age 42.9 y, 13% M)	Pain scale, functional DA, spine flexion/extension, overall improvement	10/16 diflunisal versus 4/14 acetaminophen groups "good or excellent" results, both improved in all categories	2 and 4 wk	Acetaminophen and diflunisal both effective, small sample
[48]	Tramadol 37.5 mg/APAP 325 mg versus placebo, maximum 8/day	Inclusion: LBP>3 mo, pain VAS>40 mm, >18 y; Exclusion: pregnant, other pain meds	338 patients (mean age 57.5 y, 37.5% M)	Pain VAS, Pain, DA	Initial pain VAS 67.8, final VAS med 47.4 versus placebo 62.9, improved pain DA Questionnaire	1, 14, 28, 56, 91 d	Tramadol/APAP effective in pain relief, and perceived DA; nearly same protocol as Ruoff [49]
[49]	Tramadol 37.5 mg/APAP 325 mg versus placebo, maximum 8/day	Inclusion: LBP>3 mo, pain, age 25–75 y; Exclusion: pregnancy, previous tx with tramadol, other prescription pain meds	318 patients (mean age 53.9 y, 36.8% M)	Pain VAS, pain, DA	Initial pain VAS med 71.1 versus placebo 68.4—final VAS med 44.4 versus placebo 52.3, improved pain and DA Questionnaire	1, 14, 28, 56, 91 d	Tramadol/APAP effective pain relief, more side effects; nearly same protocol as Peloso [48]
[47]	Tramadol 200–400 mg versus placebo	Inclusion: CLBP; Exclusion: recent back surgery	254 patients (age range 21–79 y)	Therapeutic failures during trial, VAS pain after 4 wk	20.7% tramadol failed versus 51.3% placebo; VAS tramadol 3.5 versus placebo 5.1	4 wk	Tramadol was effective compared with placebo for CLBP
[35]	Capsaicin plaster daily versus placebo	Inclusion: LBP>3 mo, pain VAS>5; Exclusion: specific LBP disorder	154 patients, 150 f/u (78 M/72 F)	Arhus LB rating (pain>30% better), pain, mobility, DA	Arhus responders capsaicin 60.8% versus placebo 42.1%; individual pain, DA, mobility not sign improved	1 and 3 wk	Local adverse effects, but similar drop out capsaicin and placebo
[36]	Capsaicin plaster daily versus placebo	Inclusion: LBP>3 mo, pain VAS>5; Exclusion: specific LBP disorder	319 patients (age range 18–75 y, 137 M/182 F)	Arhus LB rating, mobility, DA	Arhus responders capsaicin 67% versus placebo 49%, reduced pain score 42% versus placebo 31%, improved mobility and DA versus placebo	1 and 3 wk	Statistically significant difference in improvement with capsaicin versus placebo

RCT=randomized controlled trials; LBP=low back pain; QID=four times daily; BID=twice daily; DA=disability index; APAP=acetaminophen; VAS=visual analogue scale; CLBP=chronic low back pain; LB rating=low back rating.

had the lowest GI complication rates among nonselective NSAIDs because of the low doses used in practice.

Muscle relaxants

Muscle relaxants demonstrated more CNS side effects compared with placebo in nearly all trials [55,33]. Most common adverse reactions are dizziness and sedation. There are also concerns for dependency with some muscle relaxants, most notably carisoprodol, which is listed as a controlled substance in some states [56]. Withdrawal from some muscle relaxants is also a concern. Sudden discontinued chronic use of benzodiazepines is associated with delirium tremens, whereas abruptly discontinuing baclofen may result in seizures [13].

Simple analgesics

Fatalities from acetaminophen-induced liver toxicity are rare when the exposure is less than 7.5 to 10 g over 8 hours [13] but the recommended dose is 4 g or less in 24 hours. Capsaicin plaster often produces local skin irritation and unpleasant sensations.

Summary

Based on the best available evidence, Mens [57] advocates the use of an analgesic, antidepressant, or both for CLBP. When starting a new medication, patients should be educated as to why a medication is chosen and its expected risks and benefits. Patient preferences concerning medications should also be considered. A small trial dose is given for 3 to 4 days to test response to NSAIDs or muscle relaxants. Occasionally, there are patients who are also resistant to multiple therapeutic approaches and require individualized therapy combinations including other adjunctive analgesics. Although pooled data from large groups of patients show that no one medication in any drug class is better than another, it is unpredictable which patient will respond best to which medication within that class. Trial and error is unavoidable. In addition to the classical model of patient treatment, a biopsychosocial approach may help empower patients to take a more active role in their improvement reducing fears and possibly reliance on medications.

Trials with greater numbers and longer follow-up are needed for better evidence comparing classes of medications [58] such as NSAIDs, muscle relaxants, and simple analgesics. No trials were available comparing antispasticity drugs and placebo or other treatments, or acetaminophen with placebo in CLBP. Combination therapy trials are also needed after there is more evidence to support or refute use of individual therapies. The various classes of medications should also be studied in the postoperative CLBP population.

Despite concern for adverse effects using COX-2 inhibitors, their potential advantages and effectiveness makes continued safety and efficacy research with newer versions worthwhile. Currently, etoricoxib is approved for use in several countries, but the US Food and Drug Administration required further safety data before issuing approval [59]. Recent research suggests that other points in the prostaglandin cascade may be targeted for novel blockade including microsomal prostaglandin E synthase [60]. If this enzyme were blocked, production of pain and inflammation associated prostaglandin E2 could theoretically be decreased while cardioprotective prostacyclin would be unaffected. This could bypass a theorized COX-2 inhibitor decrease in prostacyclin production. Such a drug is yet to be reported.

Additional medications provide interesting potential treatments, but lack rigorous trials to support their usefulness. Curatolo and Bogduk [61] suggest that development of N-methyl-D-aspartic acid antagonists could theoretically block central hypersensitivity that occurs after persistent nociceptive input from chronic pain conditions. They also note that cannabinoids have shown useful properties in animal models, which include decreasing inflammation-induced allodynia, blocking hyperalgesia, and enhancing morphine-induced antinociception. Despite being forbidden in most countries, cannabinoids could potentially play a role in the management of CLBP that is refractory to other approaches. The potential usefulness of these and many other medications in the treatment of chronic low back pain will require proper research before they can be recommended.

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