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Pharmacotherapy for Chronic Low Back Pain

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1. Introduction

Chronic low back pain is a common, debilitating, and costly health problem (Centers for Disease Control and Prevention, 2001; Collins et al., 2005; Mapel et al., 2004; Vogt et al., 2005). The prevalence of chronic low back pain is higher in women and in whites versus blacks (Andersson, 1999; Mapel et al., 2004). Although the risk of chronic low back pain increases with age (Mapel et al., 2004), back pain remains the most common cause of disability in adults aged <45 years (Andersson, 1999).

Treatment guidelines issued in the United States (Chou et al., 2007) and Europe (Airaksinen et al, 2006) both state that back pain becomes chronic if it persists for ≥12 weeks. United States guidelines also distinguish between acute (<4 weeks) and subacute (4–<12 weeks) back pain (Chou et al., 2007). The 12-week threshold for classifying back pain as chronic makes sense given data suggesting that 80% to 95% of patients with disabling back pain can return to normal activities within 12 weeks, with less certain outcomes thereafter (Andersson, 1999).

Treatments for chronic low back pain include nonpharmacologic therapies (eg, exercise, lifestyle modification), which are discussed elsewhere in this book. First-line pharmacotherapies include acetaminophen, nonsteroidal anti-inflammatory drugs (NSAIDs), weak opioids, and strong opioids. Each of these therapies, including opioids, may be initiated during the acute phase of back pain, depending on the severity of pain (Chou et al., 2007). However, the course of chronic low back pain may be protracted (Andersson, 1999), meaning patients may require treatment over years or decades. It is therefore important that pharmacological treatments be effective and as safe as possible both in the short term and in patients requiring long-term treatment. Acetaminophen is a well-tolerated first-line pharmacotherapy but has limited efficacy (Zhang et al., 2010) and high-dose, long-term use is associated with hepatic toxicity (Watkins et al., 2006). NSAIDs have better efficacy than acetaminophen but have well-known risks of gastrointestinal (Boers et al., 2007; Gabriel et al., 1991; Hippisley-Cox et al., 2005), cardiovascular (Antman et al., 2007; Caldwell et al., 2006; Hippisley-Cox & Coupland, 2005; Kearney et al., 2006; Motsko et al., 2006), and other systemic adverse effects that increase with age, dose, and duration of use.

The serotonin norepinephrine reuptake inhibitor (SNRI) duloxetine has received US Food and Drug Administration (FDA) approval for the treatment of musculoskeletal pain such as chronic low back pain (Cymbalta® Delayed-Release Capsules, 2010). Duloxetine has only modest efficacy (Skljarevski et al., 2010a; Skljarevski et al., 2009), is associated with

systematic adverse events (Skljarevski et al., 2010a; Skljarevski et al., 2009), and may also interact with other analgesics, most notably certain opioids (Smith, 2009).

Opioids have the greatest efficacy of any oral therapy for relieving pain but also have significant risk of adverse events and potential for pharmacokinetic drug interactions (Malhotra et al., 2001; Tulner et al., 2008) and carry a substantial risk of addiction and abuse. Chronic opioid therapy requires long-term monitoring for treatment compliance.

This chapter will review guideline recommendations and clinical evidence for pharmacotherapies available for the management of chronic low back pain.

2. Review of guidelines for chronic low back pain and clinical evidence for pharmacotherapies

2.1 Multimodal approach to therapy

United States guidelines for the management of chronic low back pain recommend that effective pharmacotherapy be administered in conjunction with self-care options (eg, application of heat, continued activity, adoption of physical fitness regimens, use of a medium-firm mattress, lifestyle modifications) (Airaksinen et al., 2006; Chou et al., 2007). Nonpharmacologic therapies are discussed in detail elsewhere in this book. For patients not responding to medication and self-care, clinicians should employ other nonpharmacologic options, including intensive interdisciplinary rehabilitation, exercise therapy, acupuncture, massage therapy, spinal manipulation, yoga, cognitive behavioral therapy, and progressive relaxation (Airaksinen et al., 2006; Chou et al., 2007).

2.2 Acetaminophen

United States Guidelines for the management of chronic low back pain recommend acetaminophen as a first-line therapy for mild to moderate pain (Chou et al., 2007); the recommendations are based on modest efficacy and overall favorable tolerability in patients with osteoarthritis. European guidelines do not recommend acetaminophen (Airaksinen et al., 2006).

Randomized controlled trials of acetaminophen for chronic low back pain are lacking. Both US and European guidelines acknowledge that acetaminophen has been less effective than oral NSAIDs for osteoarthritis pain (Airaksinen et al., 2006; Chou et al., 2007), and effect sizes for acetaminophen calculated by the Osteoarthritis Research Society International are below the threshold for a clinically meaningful analgesia (Zhang et al., 2010). Acetaminophen is not as safe as it was once believed to be, particularly for a chronic condition such as chronic low back pain that may require treatment for many years and may also require dose escalation as the disease progresses over time. At doses >4 g/d, acetaminophen is known to cause liver enzyme increases >3-fold greater than the upper limit of normal in healthy volunteers (Watkins et al., 2006). The FDA is currently considering lowering the maximum recommended dose to 3.25 g/day (Kuehn, 2009). In the United States, acetaminophen is the leading cause of acute liver failure (Chun et al., 2009).

Overdose of acetaminophen may be accidental (Camidge et al., 2003; Larson et al., 2005), resulting from patients taking too much without realizing there is a dosage ceiling, or from

patients taking a product that combines a narcotic with acetaminophen and then augmenting it with additional acetaminophen (Larson et al., 2005). Overdose may also be deliberate (Camidge et al., 2003; Larson et al., 2005). Despite its reputation as a safe drug, acetaminophen is among the drugs implicated most frequently in suicide attempts (Camidge et al., 2003; Larson et al., 2005). Also, thought not typically believed to carry substantial potential for pharmacokinetic interactions, acetaminophen-associated liver failure is significantly associated with alcohol abuse and antidepressant use (Larson et al., 2005).

2.3 Nonsteroidal anti-inflammatory drugs

A Cochrane review of 65 randomized controlled trials found evidence that NSAIDs are effective for the management of chronic low back pain pain, but effect sizes were indicative of only a small treatment effect (Roelofs et al., 2008). The evidence presented in this Cochrane review suggested that different NSAIDs, including cyclooxygenase–2 inhibitors, show similar efficacy in patients with chronic low back pain.

Evidence from meta-analyses provide evidence that NSAIDs are moderately more effective than acetaminophen (Lee et al., 2004; Roelofs et al., 2008), and chronic low back pain guidelines also state that NSAIDs are more effective (Airaksinen et al., 2006; Chou et al., 2007). In patients with osteoarthritis, effect sizes for NSAIDs are substantially higher than with acetaminophen but nonetheless correspond to a small treatment effect (Zhang et al., 2010).

Nonsteroidal anti-inflammatory drugs are associated with well-known risks of gastrointestinal (Boers et al., 2007; Gabriel et al., 1991; Hippisley-Cox et al., 2005), cardiovascular (Antman et al., 2007; Caldwell et al., 2006; Hippisley-Cox & Coupland, 2005; Juni et al., 2004; Kearney et al., 2006; Motsko et al., 2006), and renal (Barkin & Buvanendran, 2004; Evans et al., 1995) adverse events. Hepatic adverse events have been reported infrequently (Rostom et al., 2005; Rubenstein & Laine, 2004), and are certainly less common than with acetaminophen. NSAIDs have been associated with potentially clinically meaningful increases in blood pressure (Forman et al., 2005; Johnson et al., 1994; Pavlicevic et al., 2008), probably both through direct effects (Forman et al., 2005; Johnson et al., 1994) and adverse pharmacokinetic interactions with diuretics and angiotensin-converting enzyme inhibitors (Pavlicevic et al., 2008). Drug interactions of NSAIDs with antihypertensives (angiotensin-converting enzyme inhibitors, diuretics), selective serotonin reuptake inhibitors (SSRIs), and corticosteroids (American Geriatrics Society, 2009; Malhotra et al., 2001; Tulner et al., 2008) are common. Ibuprofen can nullify the cardioprotective effects of aspirin (Gengo et al., 2008). Gastrointestinal bleeding events may occur in patients receiving an NSAID with warfarin (Cheetham et al., 2009), an SSRI, or a corticosteroid (American Geriatrics Society, 2009). Proton pump inhibitors administered as gastroprotection in NSAID-treated patients can block the cardioprotective effects of clopidogrel (Ho et al., 2009; Juurlink et al., 2009).

Cyclooxygenase-2 inhibitors have been associated with fewer adverse events than nonselective agents (Roelofs et al., 2008), and in particular have shown improved gastrointestinal tolerability (Singh et al., 2006). In a 12-week, 13,000 patient trial, the occurrence of abdominal pain, dyspepsia, diarrhea, headache, and nausea was reported in

2% to 5% of patients treated with celecoxib and 3% to 6% of those treated with naproxen or diclofenac (Singh et al., 2006). Confirmed gastrointestinal bleeding events were also less frequent with celecoxib compared with nonselective agents, but occurred in 1% of patients compared with 2.1% treated with the nonselective agents.

Given their risk/benefit ratio, guidelines for the treatment of chronic low back pain (Airaksinen et al., 2006; Chou et al., 2007) and osteoarthritis (Zhang et al., 2007; Zhang et al., 2008) recommend that oral NSAIDs be administered for the shortest period possible at the lowest effective dose. Guidelines for the management of chronic pain in the elderly suggest that regular oral NSAID use should be avoided if possible (American Geriatrics Society, 2009).

2.4 Topical therapies

United States guidelines for the management of chronic low back pain do not recommend topical therapies. European guidelines recommend only capsaicin plaster for short-term therapy (<3 wk) in patients with chronic low back pain (Airaksinen et al., 2006).

2.4.1 The lidocaine 5% patch

The lidocaine 5% patch has US approval only for the management of postherpetic neuralgia (LIDODERM®, 2010), particularly with allodynia (Attal et al., 2010). However, the lidocaine 5% patch has also shown efficacy in patients with chronic lower back pain (Galer et al., 2004; Gimbel et al., 2005). In a 6-week open-label trial, 71 patients with acute/subacute (n=11), short-term chronic (n=17), or long-term chronic (n=43) nonradicular back pain applied up to 4 patches to the maximal area of pain (Galer et al., 2004). All patient subgroups reported significant improvements in scores on the Neuropathic Pain Scale. In a second 6-week open-label study, 131 patients with subacute (n=21), short-term chronic (n=33), and long-term chronic (n=77) back pain reported significant mean improvements in scores on the Brief Pain Inventory (Gimbel et al., 2005) and significant improvements in the Brief Pain Inventory item for interference with quality of life. Beck Depression Inventory scores also improved significantly. Approximately two thirds of patients and investigators reported being Satisfied or Very Satisfied with treatment.

Application of up to 4 lidocaine 5% patches daily results in peak systemic lidocaine concentrations <200 ng/mL, or >7-fold less than the concentration of >1500 ng/mL required to produce cardiac effects and 20-fold less than the threshold concentration for toxic effects (Gammaitoni et al., 2003). Consistent with low systemic exposure, the most common adverse events reported in a trial of the lidocaine 5% patch in patients with chronic low back pain were mild to moderate skin and subcutaneous tissue reactions (eg, rash, pruritus, dermatitis, erythema, edema). Treatment-related systemic adverse events were relatively uncommon and included dizziness (4%), headache (2%), and nausea (2%–3%) (Gammaitoni et al., 2003).

2.4.2 The capsaicin 8% patch

In a double-blind, randomized trial, 320 patients with chronic low back pain were assigned to apply the capsaicin 8% patch or placebo patch once daily for 3 weeks (Frerick et al., 2003).

The capsaicin 8% patch was associated with a 42% reduction in pain assessed using the Arhus low back rating scale versus a 31% reduction with placebo. Sixty-seven percent of the capsaicin 8% patch group and 49% of the placebo group met response criteria, defined as a ≥30% reduction in pain. Though statistically significant, these differences compared with placebo are very modest. These results were similar to those obtained with a similar capsaicin 8% patch in a similarly designed trial (Keitel et al., 2001). The most common adverse events were application site warmth or itching, although inflammatory contact eczema, urticaria, small hemorrhagic spots, vesiculation, and dermatitis have been reported in a small number of patients (Frerick et al., 2003; Keitel et al., 2001). Given modest efficacy and generally good tolerability, the capsaicin 8% patch may only be useful as adjunctive therapy or as monotherapy in a small subgroup of patients.

2.4.3 Topical nonsteroidal anti-inflammatory drugs

Topical NSAIDs produce dramatically lower systemic NSAID concentrations compared with oral NSAIDs (Kienzler et al., 2010) and are recommended as a first-line therapy in patients with osteoarthritis of the knees or hands (Zhang et al., 2007; Zhang et al., 2008), particularly the elderly (American Geriatrics Society, 2009). However, no chronic low back pain guidelines recommend topical NSAIDs and chronic low back pain is not an approved indication for either of the two topical NSAID formulations used in the United States: diclofenac sodium 1% gel (Voltaren® Gel 1%, 2007) and diclofenac sodium 1.5% in 45.5% dimethyl sulfoxide solution (Pennsaid®, 2009). Neither formulation has been evaluated in patients with chronic low back pain.

Topical diclofenac diethylamine 1.16% gel and an indomethacin plaster were evaluated in 64 patients with mild to moderate, nonsurgical chronic low back pain (Waikakul et al., 1996). Both formulations provided statistically significant improvements in pain and function; however, topical NSAIDs have not been evaluated in clinical trials since this 1996 study.

2.5 Serotonin-norepinephrine reuptake inhibitors

Duloxetine has shown modest efficacy in two 12-week trials (Skljarevski et al., 2010a; Skljarevski et al., 2009) and in a 41-week open-label study (Skljarevski et al., 2010b). Active treatment was superior to placebo in both 12-week trials when a 30% improvement in pain was defined as a positive response (Skljarevski et al., 2010a; Skljarevski et al., 2009) but only in 1 trial when a 50% improvement was defined as a positive response (Skljarevski et al., 2010a). Given modest efficacy, duloxetine may be a helpful adjunctive therapy (discussed below).

2.6 Weak opioids

The weak opioids codeine, hydrocodone, and propoxyphene have not been studied extensively in patients with chronic low back pain. A single 1976 study of propoxyphene showed efficacy in patients with chronic low back pain (Baratta, 1976) and a 1998 study of an extended release formulation of codeine combined with acetaminophen demonstrated efficacy similar to tramadol (Muller et al., 1998). Hydrocodone has not been studied in patient with chronic low back pain. Nonetheless, a meta-analysis showed that weak opioids do not have a clear efficacy advantage compared with oral NSAIDs or tricyclic

antidepressants (Furlan et al., 2006). Several safety issues limit use of weak opioids. These agents are commonly combined with acetaminophen, imposing a dosage ceiling on their use (Victor et al., 2009). Codeine has been associated with a high rate of constipation. Moreover, though a weak opioid, propoxyphene is associated with more potent respiratory and cardiovascular depression than are strong opioids (Barkin et al., 2006; Ulens et al., 1999).

2.7 Combination weak opioid-norepinephrine reuptake inhibitors

A Cochrane review of 3 trials found that tramadol is more effective than placebo for treating pain and functional impairment (Deshpande et al., 2007). It should be observed that 2 of the 3 trials analyzed in the Cochrane review evaluated products combining tramadol with acetaminophen (Peloso et al., 2004; Ruoff et al., 2003). Although pure opioids theoretically have no analgesic dosage ceiling, the presence of acetaminophen imposes a dosage ceiling on the product because acetaminophen is hepatotoxic above a daily dose of 4 g (Watkins et al., 2006). Tramadol is not a pure opioid agonist but rather also has serotonergic effects that limit the recommended daily dose to 300 mg (Ultram ER®, 2009). Serotonergic effects of tramadol increase the risk of serotonin syndrome in patients receiving other serotonergic drugs, and must not be combined with SNRIs, SSRIs, and tricyclic antidepressants (Ultram ER®, 2009).

Two 6-week trials found that tramadol monotherapy was less effective than the selective cyclooxygenase-2 inhibitor celecoxib (O'Donnell et al., 2009). Likewise, tramadol was found to be no more effective than extended-release codeine, even though tramadol has the additional noradrenergic mechanism of action. The most common adverse events reported in the 3 trials of tramadol with or without acetaminophen were typical opioid effects, including nausea (8.7%–13%), headache (4.7%–6.6%), somnolence (9%–12.4%), dizziness (7.5%–10.8%), dry mouth (6%–8.1%), vomiting (6%), and constipation (10.2%–11.2%) (Peloso et al., 2004; Ruoff et al., 2003; Schnitzer et al., 2000).

Tramadol relies on the cytochrome P450 enzyme 2D6 for metabolism to its active metabolite, *O*-desmethyltramadol, giving it potential for pharmacokinetic interaction with drugs metabolized via this pathway. Five to 15% of the white population is classified as having either rapid or slow cytochrome P450 enzyme 2D6 metabolizers, meaning that some patients will have insufficient or increased sensitivity to both analgesic and adverse effects of the drug (Smith, 2009). Collectively, tramadol appears to offer no efficacy advantage compared with weak opioids despite its secondary norepinephrine reuptake inhibitor activity.

A second weak opioid-SNRI combination, tapentadol, differs from tramadol in several important respects. Tapentadol is metabolized via glucuronidation and therefore lacks the potential for pharmacokinetic interaction and variability response observed with tramadol (Kneip et al., 2008). Its noradrenergic effects are more potent than its serotonergic effects (Tzschentke et al., 2007), theoretically reducing the risk of serotonergic adverse events, although in the United States tapentadol has an FDA "black box" warning against its combined use with SSRIs or SNRIs. Analgesic effects of SNRIs are attributed primarily to the noradrenergic effects (Max et al., 1992); hence, reduced activity with respect to serotonergic function decreases adverse events without compromising analgesic efficacy.

In a prospective, randomized, double-blind, trial, 981 patients with chronic low back pain received tapentadol 100 to 250 mg/d, oxycodone controlled release, or placebo for a 3-week

titration period followed by a 12-week maintenance period. Tapentadol and oxycodone produced similar, statistically significant improvements in pain compared with placebo. Tapentadol was associated with a lower occurrence compared with oxycodone of total adverse events, constipation, nausea, and vomiting. A pooled analysis of this study and two 12-week studies of patients with osteoarthritis (n=2010) demonstrated that tapentadol was as effective as oxycodone controlled release in improving mean pain intensity, but more people treated with tapentadol experienced 30% and 50% reductions in pain (Lange et al., 2010). Only tapentadol was associated with significant improvements in quality of life, which may reflect superior tolerability with tapentadol. Tapentadol exhibited a superior gastrointestinal tolerability compared with oxycodone (Lange et al., 2010). A subsequent subanalyses of these trials found that the lower incidence of constipation with tapentadol (13%–18%) compared with oxycodone (27%–36%) should be associated with a lower rate of work absenteeism and productivity loss in tapentadol-treated patients, based on previous research correlating constipation with productivity (Cepeda et al., 2011).

A limitation of studies comparing tapentadol with oxycodone controlled release was the dosage ranges used. Patients assigned to oxycodone received a dose of 20 to 50 mg twice daily (Lange et al., 2010), which is well below the effective dose for many patients. All patients, including opioid-experienced patients, were started on oxycodone 10 mg. The maximum dose of 50 mg is much less than the maximum doses reported in oxycodone trials (Rauck et al., 2006a). Nonetheless, if patients were underdosed with respect to analgesia, they also would be expected to have more adverse events at higher, more effective doses. Thus, at optimal oxycodone doses with respect to analgesia, differences in tolerability favoring tapentadol might be even more pronounced.

Given statistically significant efficacy compared with placebo, a trial of a weak opioid-SNRI combination drug before prescribing a strong opioid may be a valuable option in many patients.

2.8 Strong opioids: Efficacy

Despite increasing use in patients with chronic noncancer pain in recent years, opioids have not been studied extensively in patients with chronic low back pain. A 2007 Cochrane review of opioids for chronic low back pain (Deshpande et al., 2007) included only 1 trial of a strong opioid (Jamison et al., 1998). This 1998 trial found that oxycodone immediate release and oxycodone combined with morphine extended release were both significantly superior to naproxen in patients with moderate to severe chronic low back pain (Jamison et al., 1998). Similarly a 2006 meta-analysis of opioids in chronic noncancer pain included the same single study of oxycodone in chronic low back pain and reached the same conclusion (Furlan et al., 2006). A 2011 meta-analysis included 4 additional studies, one of tramadol, 2 of oxymorphone extended release, and 1 of oxycodone with ultra-low-dose naltrexone (Kuijpers et al., 2011).

Oxymorphone extended release was evaluated in two 12-week randomized controlled trials in opioid-naive and opioid-experienced patients with moderate to severe chronic low back pain (Hale et al., 2007; Katz et al., 2007). Results from these studies demonstrated that use of a flexible, individualized titration schedule will allow the majority (60% in the 2 studies combined) of patients to be titrated to an effective, generally well-tolerated opioid dose

(Peniston & Gould, 2009). The trial in opioid-naïve patients demonstrated that the lowest available doses of oxymorphone extended release can be administered safety in patients who have never received an opioid. In contrast, some long-acting opioids are not appropriate as a starting medication for opioid-naïve patients; for example, the fentanyl transdermal patch and hydromorphone OROS (discussed following) (Duragesic®, 2009; EXALGO complete prescribing information, 2010). The trial of oxymorphone extended release in opioid-experienced patients demonstrated that patients who grow tolerant to one opioid formulation can be successfully transitioned to another opioid with ostensibly the same mechanism of action and experience adequate pain relief with acceptable tolerability.

This finding is important given the clinical observation that patients requiring long-term opioid therapy typically require successive trials of different opioids to find one that works, and that even after finding the right opioid, will frequently grow tolerant to the initial opioid and need to be rotated to another opioid to maintain analgesia or avoid adverse events that emerge with dose escalation (Grilo et al., 2002; Mercadante & Bruera, 2006; Quang-Cantagrel et al., 2000). It is important to have multiple effective opioids from which to choose an initial agent and have options for switching as tolerance develops (Slatkin, 2009). It remains to be determined whether after switching from an initial opioid to another, responsiveness to the original opioid will return over time to allow a switch back if tolerance to the second opioid emerges. In both opioid-naïve and –experienced patients, oxymorphone extended release analgesia and functional improvement remained significantly superior to placebo for the entire 12-week treatment period without dose escalation (Hale et al., 2007; Katz et al., 2007). Of patients successfully titrated and randomized to oxymorphone extended release, 69% completed 12 weeks of treatment (Peniston & Gould, 2009).

Oxycodone has been formulated with ultra-low-dose naltrexone in order to minimize adverse events (eg, respiratory depression, constipation, physical dependence) (Amass et al., 2000; Chindalore et al., 2005; Webster et al., 2006). In a double-blind trial, 719 patients with moderate to severe chronic low back pain received placebo, oxycodone immediate release 4 times daily, oxycodone with naltrexone 4 times daily, or oxycodone plus naltrexone twice daily for 12 weeks (Webster et al., 2006). All patients initiated treatment with a total daily oxycodone dose of 10 mg and were titrated over a period of 1 to 6 weeks to a dose that provided effective analgesia with acceptable tolerability or to a maximum daily dose of 80 mg. All oxycodone regimens provided significantly superior analgesia compared with placebo. The mean daily oxycodone dose was 12% lower with the oxycodone plus naltrexone regimens than with oxycodone. Compared with oxycodone administered 4 times daily, oxycodone plus naltrexone twice daily was associated with 44% less constipation, 33% less somnolence, and 51% less pruritus. Upon abrupt opioid discontinuation, the severity of withdrawal symptoms assessed using the Short Opiate Withdrawal Scale was 55.8% less with oxycodone plus naltrexone twice daily compared with oxycodone 4 times daily (Webster et al., 2006).

In a randomized, open-label trial, 392 patients with chronic low back pain were randomized to an effective, generally well-tolerated dose of once-daily morphine extended release or twice-daily oxycodone controlled release (Rauck et al., 2006a). Patients then entered an 8-week evaluation phase comparing the 2 treatments. As in the previous trials, use of a flexible titration schedule allowed 67.9% of patients (morphine extended release, 65.0%;

oxycodone controlled release, 70.9%) to be titrated successful. Once-daily morphine extended-release capsules provided significantly better analgesia with a lower morphine-equivalent daily dose compared with oxycodone twice daily (Rauck et al., 2006a). Sleep quality was significantly better with once-daily morphine, and rescue ibuprofen use was significantly less compared with twice-daily oxycodone. During a 4-month extension phase, patients receiving once-daily morphine continued to experience lower pain intensity and greater improvements in sleep quality (Rauck et al., 2006b).

A second once-daily opioid formulation, hydromorphone OROS, was also associated with statistically significant improvements in pain, quality of life measures, and sleep quality during a 6-week open-label trial (Wallace et al., 2007) and 6-month open-label follow-up (Wallace & Thipphawong, 2010). A clinical trial of hydromorphone OROS demonstrated that administration with ethanol does not result in premature release of hydromorphone from the capsule, a phenomenon referred to as "dose-dumping" (Sathyan et al., 2008). This is important because a previous formulation of hydromorphone extended release exhibited dose-dumping, resulting in its withdrawal from the US market (FDA asks Purdue Pharma to withdraw Palladone, 2005).

The efficacy and tolerability of fentanyl transdermal patch were demonstrated in open-label trials lasting 1 month (Simpson et al., 1997), 3 months (Lee et al., 2011), and 13 months (Allan et al., 2005), respectively. In the 13-month study (Allan et al., 2005), 673 patients with moderate to severe chronic low back pain ingested morphine sustained release once every 12 hours or applied a single fentanyl patch every 72 hours. Both treatments provided similar, significant analgesia throughout the study. Each opioid formulation was associated with typical opioid-associated adverse events such as constipation, nausea, vomiting, dizziness, diarrhea, and somnolence. Constipation was significantly less frequent with the fentanyl patch (52%) than with morphine sustained release (65%). The 3-month trial enrolled 1576 patients with severe, treatment-refractory chronic low back pain. Fentanyl provided significant improvements in measures of pain, function, and sleep quality. It should be noted, however, that <1% of patients enrolled in this trial had received a strong opioid as their prior medication; hence, the results support the use of transdermal fentanyl in patients with severe refractory pain but do not distinguish fentanyl from other opioids. Of note, the use of fentanyl transdermal patch for opioid-naïve patients in this study is contrary to the products' approved use.(Duragesic®, 2009) In contrast, studies of oxymorphone (Hale et al., 2007), oxycodone controlled release, and morphine extended release (Rauck et al., 2006a), and hydromorphone OROS (Wallace et al., 2007) have demonstrated efficacy in patients with chronic low back pain that was moderate to severe despite previous opioid therapy. Fentanyl may offer advantages over oral opioids for patients with compliance issues, including those with problems chewing or swallowing. Fentanyl clearance appears to be affected very little by renal failure (Dean, 2004) or hepatic cirrhosis (Haberer et al., 1982) impairment, making it an option that may be used with caution in these populations. However, fentanyl patch should not be administered to opioid-naïve patients because there is a significant risk of respiratory depression even with the lowest available fentanyl patch dose, 25 µg/hour (Duragesic®, 2009).

In a randomized, double-blind crossover study, 79 patients with chronic low back pain applied a 7-day buprenorphine transdermal patch or placebo patch for 4 weeks of treatment before crossing over to the alternate therapy for an additional 4 weeks (Gordon et al., 2010).

Patients began treatment with the 5 µg/h patch and were titrated with each successive application to the maximum tolerated dose (5, 10, or 20 µg/h). Fifty-four of 73 (74%) patients completed 4 weeks of treatment with buprenorphine patch. Mean reduction in pain (100-mm Visual Analog Scale) was 39.5% in the buprenorphine group and 29.8% in the placebo group, which was statistically significant. Improvements in Pain Disability Index scores were significant compared with baseline but not compared with placebo.

2.8.1 Summary of efficacy data

Flexible titration allows for successful titration in the majority of opioid-treated patients. The availability of formulations administered twice daily, daily, every 3 days, or once weekly allows for individualized treatment of patients to optimize treatment compliance. Studies of long-acting oxymorphone, oxycodone, morphine, hydromorphone, fentanyl, and buprenorphine confirm the analgesic efficacy in patients with chronic low back pain. Patients who do not respond or who grow tolerant to an opioid therapy can be transitioned to a second opioid with the same mechanism of action. The impact of opioids on functional status is variable.

2.8.2 Summary of safety data

The most common adverse events during opioid therapy include constipation (41%), nausea (32%), somnolence/sedation (29%), vomiting (15%), dizziness (20%), itching (15%), dry mouth (13%), and headache (8%) (Kalso et al., 2004). Approximately one quarter of patients discontinue clinical trials owing to adverse events (Kalso et al., 2004). Flexible titration reduces adverse events and allows the majority of patients to be titrated to an effective dose (Peniston & Gould, 2009; Rauck et al., 2006a). In 2 trials of oxymorphone extended release, nearly two thirds (348 of 575; 60.5%) of patients were successfully titrated to a well-tolerated oxymorphone extended release dose. Opioid-naïve patients were started at a low dose (10 mg/d) and opioid-experienced patients were transitioned from their previous opioid using published conversion ratios. Titration was gradual (5–10 mg every 3–7 days) and at investigators discretion. Discontinuations due to adverse events during titration (18.4%) were lower than typically observed in opioid trials (Peniston & Gould, 2009).

Similarly, in a trial comparing morphine extended release with oxycodone controlled release, use of a flexible titration schedule allowed 67.9% of patients (morphine extended release, 65.0%; oxycodone controlled release, 70.9%) to be titrated successfully (Rauck et al., 2006a). Discontinuations due to adverse events during the titration period were reported in 18.7% of patients treated with morphine extended release and 14.3% treated with oxycodone controlled release.

All opioids have a potential for clinically significant pharmacodynamic drug interactions, particularly when combined with drugs that cause respiratory depression (eg, barbiturates) or central nervous system depression (eg, alcohol, benzodiazepines), but opioids differ in their potential for pharmacokinetic drug interactions. The majority of opioids are metabolized by the cytochrome P450 system and have potential for pharmacokinetic interaction with many drugs (Smith, 2009). Exceptions to this are morphine (Coffman et al., 1997), oxymorphone (Adams et al., 2005; OPANA® ER, 2010), and hydromorphone (Hydromorphone-HP Injection 10 mg 2008), each of which primarily undergo phase 2

metabolism by glucuronidation. Selection of an opioid that is not metabolized via cytochrome P450 enzymes is important when there is a known cytochrome P450 pharmacokinetic interaction with a concurrent medication but may also be desirable in patients likely to be prescribed multiple medications, such as the elderly, patients with psychiatric illness, and patients with multiple medical problems (Smith & Bruckenthal, 2010).

The labels for all strong opioids recommend against concurrent use with alcohol because of the potential for clinically meaningful additive pharmacodynamic effects (Dilaudid® Oral Liquid and Dilaudid® Tablets, 2008; Duragesic®, 2009; Kadian®, 2007; OPANA® ER, 2010; OxyContin®, 2010). Additive effects when opioids are administered with alcohol are to be distinguished from the phenomenon of dose-dumping described previously with reference to hydromorphone extended release. Clinical trials have demonstrated the integrity of hydromorphone OROS (Sathyan et al., 2008) and morphine extended release (Barkin et al., 2009; Johnson et al., 2008) when administered with 240 mL of 4% to 40% ethanol. Coadministration of oxymorphone extended release with 240 mL of 4% and 20% ethanol, corresponding to modest and moderate alcohol consumption, did not cause premature release of oxymorphone from the extended release tablet (Fiske et al., 2011). Oxymorphone extended release administered with a 240 mL solution of 40% ethanol resulted in potentially clinically meaningful increases in oxymorphone maximum concentration (Fiske et al., 2011). It should be noted, however, that the 40% ethanol solution corresponds to heavy alcohol intake, which is to be avoided in any opioid-treated patient.

2.8.3 Minimize abuse potential

Before initiating opioid therapy, physicians should take a thorough patient history that includes a history of prior or current substance abuse or psychiatric disease, as well as accurate documentation of current prescribed medications. Patients should undergo a physical examination sufficient to confirm the diagnosis of chronic low back pain and determine pain intensity and the extent of disability. This will help establish that a request for an analgesic is legitimate rather than drug-seeking behavior (Cone & Caplan, 2009). Patients should also be screened for abuse risk using validated screening instruments such as the Opioid Risk Tool (Webster & Webster, 2005), Current Opioid Misuse Measure (Butler et al., 2007), and the revised Screener and Opioid Assessment for Patients with Pain (Butler et al., 2008).

Opioid therapy should be conducted using a plan that includes controlled substance agreements, frequent random urine drug testing, and confirmatory urine drug testing (Cone & Caplan, 2009; Manchikanti et al., 2008). Screening should be conducted in all patients, regardless of perceived risk of abuse (Gourlay et al., 2005). In patients believed to be at increased risk, selection of an opioid that does not produce metabolites that are identical to other opioids may simplify urine drug screening (Cone & Caplan, 2009). Positive test results for patients prescribed buprenorphine, fentanyl, oxymorphone, tapentadol, and tramadol will not be confused by the presence of multiple opioids.

Drug companies are currently attempting to develop formulations that incorporate obstacles to abuse. Most of these technologies are designed to resist common methods by which abusers tamper with an oral opioid formulation to facilitate intranasal or intravenous abuse

(Katz, 2008). Tamper-resistant opioids include formulations with physical barriers to crushing, chewing, and dissolution; formulations with sequestered antagonists that neutralize opioid effects if the formulation is chewed or crushed; and formulations with sequestered noxious components that are released if the opioid is chewed or crushed.

At present, 2 tamper-resistant formulations have received FDA approval. OXECTA® is a short-acting formulation of oxycodone with sequestered ingredients that are released if the opioid is chewed or crushed (OXECTA®, 2011). In addition to oxycodone, the formulation contains several ingredients that may cause irritation if swallowed or inhaled, including colloidal silicon dioxide (Amorim et al., 2010), crospovidone (Lowe et al., 2006), microcrystalline cellulose (Teshima et al., 2002), and sodium lauryl sulfate (Engel et al., 2008).

Oxycodone controlled release has also been reformulated in a polymer matrix that resists crushing or chewing (US Food and Drug Administration, 2010) and becomes a viscous gel if the product is immersed in fluid (Schneider et al., 2010). The value of tamper-resistant formulations of oxycodone and other opioids is likely to be limited unless all opioids are reformulated with this purpose in mind. Otherwise, the availability of one opioid in a tamper-resistant formulation may simply divert abusers to another opioid that has not been reformulated. Since the approval of reformulated oxycodone, oxycodone has seen a decline in abuse, with a corresponding increase in oxymorphone abuse (Goodnough, 2011; Nassau County executive: abuse of painkiller Opana is growing, 2011). Oxymorphone extended release is not currently available in a tamper resistant formulation, although such a formulation is in development.

2.9 Adjunctive therapies

Tricyclic antidepressants are recommended in both US and European guidelines for the management of chronic low back pain. Two systematic reviews concluded that tricyclic antidepressants have modest beneficial effects on pain but limited effects on functional status (Salerno et al., 2002; Staiger et al., 2003).

Duloxetine can be administered safely with NSAIDs, acetaminophen, and opioids that do not undergo cytochrome P450 metabolism, such as oxymorphone, hydromorphone, fentanyl, or morphine (Smith, 2009). Because it is a substrate and moderate inhibitor of the cytochrome P450 enzyme 2D6, pharmacokinetic interactions with oxycodone, tramadol, and codeine are possible (Cymbalta® Delayed-Release Capsules, 2010). Given its modest efficacy (discussed previously), addition of duloxetine to ongoing opioid or NSAID therapy may be a useful alternative to switching to another medication or increasing the dose of an opioid or NSAID. Duloxetine may be of particular value in chronic pain patients with comorbid depression. In an open-label pilot study (Karp et al., 2010), duloxetine administered to patients with comorbid chronic low back pain and major depression improved both pain and depression.

Guidelines in the United States state that gabapentin has modest efficacy in patients with chronic low back pain (Chou et al., 2007), whereas the European guidelines state that there is no convincing evidence (Airaksinen et al., 2006). Other anticonvulsants are not recommended. Benzodiazepines have been recommended for use as muscle relaxants for short-term therapy in both US and European guidelines (Airaksinen et al., 2006; Chou et al.,

2007). These anxiolytics have a high risk of addiction and abuse, and their combined use with opioids is of particular concern (Rich & Webster, 2011).

2.10 Invasive therapies

In US guidelines, epidural steroid injection is recommended for patients with persistent chronic low back pain and signs of radiculopathy or spinal stenosis (Chou et al., 2007). European guidelines state that epidural injections have insufficient evidence to support a recommendation (Airaksinen et al., 2006). Intrathecal opioids (morphine or methadone) have been administered for severe chronic low back pain, almost always following failed back surgery (Noble et al., 2010). Though effective, intrathecal delivery of opioids has been associated with granuloma formation (Allen et al., 2006). Neither intrathecal nor epidural opioid infusion is recommended in US or European treatment guidelines.

United States guidelines state that transcutaneous nerve stimulation has not been proven effective for chronic low back pain (Chou et al., 2007). European guidelines state that clinicians may consider percutaneous electrical nerve stimulation or neuroflexotherapy (Airaksinen et al., 2006). European guidelines also recommend against local facet nerve blocks, trigger point injections, and spinal cord stimulation (Airaksinen et al., 2006). Surgery is not recommended unless other treatment options have been unsuccessful for 1 year (US) (Chou et al., 2007) or 2 years (Europe) (Airaksinen et al., 2006).
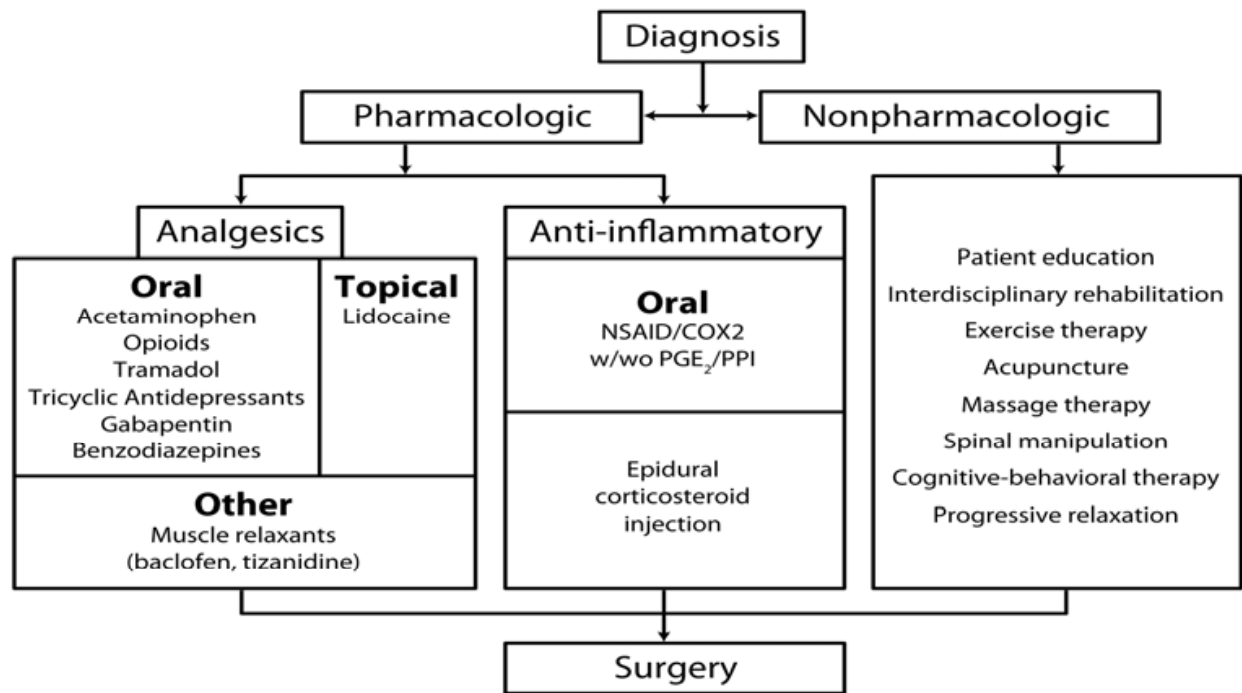
3. Treatment algorithm

Treatment recommendations based on the clinical data provided previously are summarized in **Figure 1**. Patients with mild to moderate chronic low back pain should begin pharmacotherapy with acetaminophen or an NSAID. Acetaminophen has limited efficacy, poses risks of liver failure with cumulative/escalating use, is not recommended in patients with hepatic impairment, and should be given cautiously to patients with depression or at risk of substance abuse because of its documented use by patients wishing to inflict self-harm. Patients with dementia may have difficulties reporting pain, so clinicians should be sure that patients are not in need of more potent analgesia.

Oral NSAIDs are more effective than acetaminophen but still have only modest efficacy, making their use best reserved for mild to moderate pain that does not respond to acetaminophen. NSAIDs should be administered for the shortest period of time at the lowest effective dose, and are not generally recommended in older patients and those with current or a history of gastrointestinal bleeding or significant cardiovascular or renal comorbidities. Caution is recommended when administering NSAIDs in patients taking SSRIs, corticosteroids, warfarin, cardioprotective aspirin (ibuprofen only), diuretics and angiotensin-converting enzyme inhibitors. An oral NSAID with a gastroprotective proton pump inhibitor should not be administered to patients receiving clopidogrel.

Topical lidocaine patch is recommended for the treatment of chronic low back pain in Europe but not the United States. Lidocaine patch has shown efficacy in patients with chronic low back pain. Capsaicin plasters have shown only very modest efficacy and cause localized burning that limits tolerability. Capsaicin patches are not recommended, and their

localized numbing effect is better achieved using a lidocaine patch. Topical NSAIDs have few data supporting their use for chronic low back pain and require further investigation of their potential value for this indication.

Symptomatic Therapy of Chronic Low Back Pain

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Fig. 1. Treatment algorithm for patients with chronic low back pain. COX2= cyclooxygenase -2, NSAID=nonsteroidal anti-inflammatory drug, PGE_2= prostaglandin E_2, PPI=proton pump inhibitor.

There are limited data supporting the use of tramadol in patients with chronic low back pain. Tramadol may be administered in combination products that include acetaminophen. This imposes a dosage ceiling on the product that may limit use of tramadol. There are more robust data for tapentadol; however, it is unclear whether this is because of a difference in efficacy or to it having been studied more rigorously. Both tramadol and tapentadol are associated with typical opioid adverse events, but gastrointestinal adverse events are less frequent than with strong opioids. Though less potent than strong opioids, tapentadol may be a safer option for patients who may benefit from an opioid but want to reduce risks. As noradrenergic agents may be administered as adjunctive therapy for chronic low back pain, tapentadol affords an opportunity to utilize 2 analgesic mechanisms in a single pill.

Opioids have a growing body of evidence supporting their use in patients with chronic low back pain. Much of these data have been published after the most recent US and European guidelines were developed. Trials of long-acting formulations of oxycodone, morphine, oxymorphone, hydromorphone, and buprenorphine have shown good efficacy with acceptable tolerability in patients with chronic low back pain. Starting with a low dose in

opioid-naïve patients and titrating slowly based on individual response increases the likelihood that treatment will be tolerated. Opioid-experienced patients can be transitioned to a new opioid at a dose slightly lower than that considered equipotent based on established conversion ratios. Titration should proceed slowly based on individual response. Opportunities for twice-daily, once-daily, or once-weekly dosing allow clinicians to tailor treatment in order to maximum compliance. In patients receiving multiple medications, it may be advisable to prescribe an opioid that is not metabolized by the cytochrome P450 enzyme system. Opioid therapy needs to be predicated on a full history, screening for abuse potential, and agreement to regular monitoring for treatment compliance and signs of abuse. Drugs that do not produce other opioids as metabolites will simplify urine drug screening.

Epidural corticosteroid injections should be reserved for patients with persistent pain that does not respond adequately to rehabilitation and pharmacotherapy. Surgery should be reserved for patients with prolonged, disabling, nonresponsive pain. Discussions of these more invasive therapies are reserved for elsewhere in this book.

4. Conclusion

Though ideally chronic low back pain would respond to self-management techniques, pharmacotherapy remains an essential component of treatment without which patients cannot maintain their levels of activity. There are clinical data that suggest uncontrolled pain can interfere with physical therapy, whereas improvements in pain are accompanied by improvements in function and response to therapy (Gross et al., 2008; Schein et al., 2008; Soin et al., 2008; Teske et al., 2008). Sufficient analgesia may be necessary to allow patients to effectively participate in a physical therapy program. The perceived choice facing clinicians is between medications with limited efficacy, but relatively benign adverse events profiles, and more potent analgesics with more substantial risks of adverse events or drug abuse.

Acetaminophen and NSAIDs have modest efficacy, but acetaminophen has significant risks of hepatic adverse events and NSAIDs with gastrointestinal, cardiovascular, renal and other systemic adverse events. Duloxetine has moderate efficacy comparable to acetaminophen or NSAIDs and is useful as an adjunctive medication. Tramadol and tapentadol offer advantages of opioid agonism paired with norepinephrine reuptake inhibition, but should not be combined with SNRIs or SSRIs. Opioids offer the greatest efficacy of available pharmacologic therapies, and, although opioids have significant risks of abuse, overdose, and distressing gastrointestinal adverse effects (nausea, constipation), they have a safety advantage over NSAIDs with respect to cardiovascular adverse events and gastrointestinal bleeding. The American Heart Association has stated that opioids may be preferred over NSAIDs in patients with significant cardiovascular risk (Antman et al., 2007).

5. Acknowledgments

6. References

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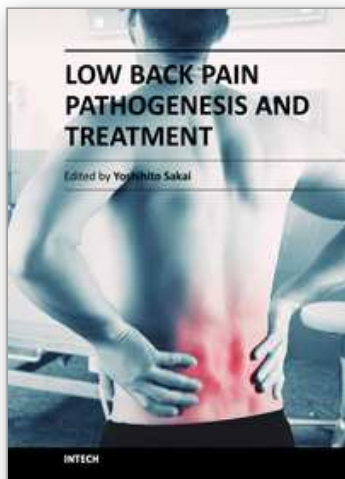
Low Back Pain Pathogenesis and Treatment

Edited by Dr. Yoshihito Sakai

Low back pain is a common disorder which affects the lumbar spine, and is associated with substantial morbidity for about 80% of the general population at some stages during their lives. Although low back pain usually is a self-limiting disorder that improves spontaneously over time, the etiology of low back pain is generally unknown and the diagnostic label, "non-specific low back pain", is frequently given. This book contains reviews and original articles with emphasis on pathogenesis and treatment of low back pain except for the rehabilitative aspect. Consisting of three sections, the first section of the book has a focus on pathogenesis of low back pain, while the second and third sections are on the treatment including conservative and surgical procedure, respectively.

How to reference

In order to correctly reference this scholarly work, feel free to copy and paste the following:

John H. Peniston (2012). Pharmacotherapy for Chronic Low Back Pain, Low Back Pain Pathogenesis and Treatment, Dr. Yoshihito Sakai (Ed.), ISBN: 978-953-51-0338-7, InTech, Available from: http://www.intechopen.com/books/low-back-pain-pathogenesis-and-treatment/pharmacotherapy-for-chronic-low-back-pain

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