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Pharmacologic Management of Low Back Pain

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Abstract

Chronic back pain is a complex process and similar to how each patient has a very individualized disease process the treatment regimen should be similarly individualized. There are several different medication classes, each with a unique mechanism of action that can assist the practitioner in targeting a specific aspect of a patient's pain. The goal of this chapter will be to provide an adequate overview of the different medication classes while providing enough drug-specific information to guide the practitioner in selecting and developing an adequate multimodal analgesic regimen. When designing an analgesic regimen, an emphasis should be placed using a modified stepwise approach similar to the World Health Organization's analgesic ladder. There should be a focus on a multimodal analgesia utilizing nonopioid medications for chronic pain. Patient-specific factors should always be considered when choosing class, strength, dosage form and possible adjuvant medications. Just like patients, no analgesic regimen should be exactly the same.

Keywords: analgesics, paracetamol, nonsteroidal anti-inflammatories, neuropathic pain, opioids

1. Introduction

Chronic back pain is a complex process and similar to how each patient has a very individualized disease process the treatment regimen should be similarly individualized. There are several different medication classes, each with a unique mechanism of action that can assist the practitioner in targeting a specific aspect of a patient's pain. Additionally, patient-specific factors must be considered when developing a regimen to ensure adherence and improve outcomes. The goal of this chapter will be to provide an adequate overview of the steps a practitioner needs to take during the regimen development process and share enough drug-specific information to guide the practitioner in selecting the most efficacious and best suited agents for the individual patient.

Prior to initiating any pharmacologic treatment regimen for a patient, current consensus recommendations include discussing realistic expectations with the patient [1]. This should include patient's expectations of pain relief as well as functional goals that the patient should work toward. Additionally, the clinician should encourage self-care and education with evidence-based materials. It is important to emphasize to the patient that acute low back pain has very favorable improvement in the first month of recovery. Generally speaking, staying active and exercising should be highly encouraged for all patients. Bed rest should only be recommended if it improves severe pain symptoms and its duration should only be temporary. Patients should also be encouraged to resume activity as quickly as possible.

2. Multimodal and targeted treatment approaches

There are several important concepts that a clinician must understand before they can adequately start the treatment of low back pain. The first is that there is more data on the use of medication for acute low back pain than chronic low back pain [1]. This does not mean that specific pharmacologic agents are not effective in the setting of chronic low back pain, but simply that there is less evidence due to constraints in studying the long-term side effects [1]. When initiating the therapy, the clinician should focus on medications with the most known efficacy for the specific cause of pain and that have the least risk for serious side effects [1]. Specifically, the drug class and sometimes the even the individual drug chosen will be dictated by side effects (short and long term) and targeted mechanism of pain.

Treatment should include a targeted approach to the individual's cause of low back pain. The majority of low back pain is caused by a mechanical etiology [2]. These causes include degenerative disk or joint disease, vertebral fracture, and deformities and occur in up to 80–90% of patients. Neurogenic (e.g., herniated disks, spinal stenosis) inflammatory (e.g., rheumatoid arthritis, ankylosing spondylitis) and other less common causes (e.g., neoplasm, referred pain) make up the remainder of etiologies. The pharmacologic agents first selected should be completely dependent on the underlying etiology. However, as the pain progresses to a chronic state, a broader approach typically must be taken due to decreased efficacy of the targeted treatment.

The majority of this chapter will focus on the treatment of low back pain with an underlying mechanical etiology since it is by far the most common. However, if the cause of low back pain is inflammatory in nature, targeted therapy should also focus on treatment with anti-inflammatory agents. This may mean early use of nonsteroidal anti-inflammatories (NSAIDs) and treatment with corticosteroids or disease-modifying antirheumatic drugs (DMARDs) in patients with rheumatoid arthritis or ankylosing spondylitis [3]. Additionally, these disease states have a higher incidence of neuropathic pain and thus may require adjuvant medications that target this specific pain type. Some patients with mechanical low back pain also have increased pain due to spasticity and may benefit from treatment with antispasmodics. These agents will be discussed in much greater detail later, but to put it simply treatment should be tailored to the individual.

While the treatment of acute low back pain is normally fairly straight forward, its progression into chronic pain tends to complicate treatment. This is primarily due to the fact that chronic pain can often be associated with not only physical pain, but also deleterious cognitive and behavioral effects [4]. Because of this, a patient's rehabilitation program should emphasize a biopsychosocial model or one that involves a combination of physical, psychological and educational components [4, 5]. This also means that treatment (including medications) should be used to treat any psychological processes that may be worsening the perception of pain such as depression or anxiety.

Lastly, it is important to understand that medication alone will likely not completely alleviate a patient's pain, and it is even less likely to do so if the pain is chronic. Thus, treatment as a whole should be tailored to the individual and a holistic approach should be taken [4]. In addition to pharmacologic treatments, nonpharmacologic treatments including topical heat for acute pain or cognitive behavioral therapy, exercise therapy, spinal manipulation and interdisciplinary rehabilitation for subacute or chronic pain should be considered [6, 7]. However, for the purpose of this chapter, we will be focusing primarily on pharmacologic treatments and how they should be combined, implemented and optimized.

3. World Health Organization's stepwise approach to pain

In 1986, the World Health Organization (WHO) published an analgesic treatment model that described in detail the appropriate way to escalate therapy in chronic pain associated with cancer [8]. This stepwise model focused on the incremental escalation of treatment from non-opioid analgesics to low-strength opioids and eventually to medium- or high-strength opioids. Since its publication this model has been adapted into the treatment of all types of pain including acute, chronic and noncancer pain [9]. Many attribute this to the increased opioid utilization for the management of all types of pain [10]. Additionally, many argue that opioid medications are being over utilized and the stepwise approach, while simple, is not the most ideal method in treating chronic pain. Even if the stepwise model is not perfect in its original form, several key components should be considered when implementing or modifying an analgesic treatment regimen [9].

Whether the patient has acute or chronic pain, a couple of components of the WHO's stepwise approach are critical to follow no matter the circumstance [9]. These key aspects include that the prescriber should utilize oral medications whenever possible, prescribe analgesics at fixed intervals dictated by their duration of action, the specific analgesic chosen should be dependent on pain intensity and its effect should be evaluated by a validated pain intensity scale [8]. When looking at the complete analgesic regimen, it should be uniquely tailored to the individual and once a regimen is established, a written personal program should be given to the patient, so they can be held accountable to taking medications at their appropriate times and others (family, friends and medical professionals) know how they take their medications in case of emergency. While these components should be cemented in the care of any patient with low back pain, the ideal stepwise escalation, de-escalation or type of adjuvant medication depends

upon the type of pain being treated and may not follow the originally proposed WHO's stepwise approach [9].

Several recommendations have been suggested for the alteration of the WHO's stepwise approach to pain [9]. The first is that when dealing with acute pain, it is sometimes necessary to start at a higher step than the first step of the ladder. This means that opposed to starting with a nonopioid agent alone, it may be necessary to start therapy with a weak, moderate or even strong opioid in addition to a nonopioid agent. However, because most acute pain resolves or markedly improves in a short period of time, there should be an emphasis on early alteration of the analgesic regimen. Rarely are opioids needed for longer than 7 days to treat acute pain [6]. The one major stipulation to treating acute pain in this way (skipping steps on the WHO's ladder) is that the provider is encouraged to rapidly step down the ladder or de-escalate therapy as pain diminishes or side effects are too severe. This requires a practitioner to have very close follow-up and may not be appropriate in all settings. This recommendation is not originally recommended by the WHO, but it is feasible when considering the acute pain process and the need to wean patients from regimens containing strong opioids [9].

As the patient transitions from an acute pain process to a chronic pain state (1–3 months), it is import to reassess the analgesic regimen. If de-escalation has not been performed, it should be done at this point to ensure that the patient is only prescribed the minimal amount of medications required to control their pain. When escalating in a stepwise manner, the cause and type of pain should be considered. The pain regimen should focus on nonopioid analgesics with nonsteroidal anti-inflammatories (NSAIDs) if the pain is caused or exacerbated by an inflammatory process. Adjuvant medications targeting neuropathic pain should be initiated and optimized at this time if there is a component of neuropathic pain [9]. Only when nonopioids and adjuvant medications have been fully optimized, an opioid should be scheduled at a fixed interval. Nonpharmacologic and nonopioid medications are preferred for chronic pain [6]. If the pain requires opioids, a weak opioid should be trialed first before escalating to a moderate or strong opioid [8, 9]. To appropriately escalate therapy, it is necessary to understand the specific attributes of each analgesic medication (nonopioids, opioids and adjuvants) so that the patient receives the maximum benefit while minimizing the potential for harm and side effects.

4. Paracetamol/acetaminophen

Paracetamol, also commonly referred to as acetaminophen, was first synthesized in 1878 by Morse, a researcher at Johns Hopkins Hospital [11]. It was not until 15 years later that paracetamol's antipyretic effects were first noted and a medical implication was suggested [11, 12]. The current consensus is that paracetamol is the first-line agent for both acute pain and chronic pain [1, 6, 11]. This is not because paracetamol is a more potent analgesic, but because it has a much better side effect profile than that of other nonopioid analgesics [1, 11].

Even though it has been well over a hundred years since its synthesis, not much is known about the mechanism of action of paracetamol and several have been proposed to explain

paracetamol's antipyretic and analgesic effects [11–13]. One in particular is that it indirectly inhibits the cyclooxygenase (COX) enzymes. The COX isoenzymes are responsible for converting arachidonic acid to prostaglandins, thromboxanes and prostacyclins. Prostaglandins are thought to be a primary mediator of pain, fever and inflammation both centrally and peripherally. Paracetamol is thought to only inhibit a certain isoenzyme of COX (COX-3) in the brain which is why many believe that it has minimal anti-inflammatory effects in peripheral tissues [11, 14]. While there are high concentrations of COX-1 and COX-2 in peripheral tissue, the proposed COX-3 enzyme is thought to have higher concentrations in the brain. It is through the inhibition of COX-3 that paracetamol may have its primary mechanism of action causing analgesic and antipyretic effects while exerting minimal anti-inflammatory effects [11, 12]. While this is a popular hypothesis, it does not explain the small amount of peripheral anti-inflammatory activity some researchers have found.

Another proposed hypothesis postulates that paracetamol inhibits COX isoenzymes in a unique manner and explains the mild anti-inflammatory effects it may have. Unlike NSAIDs, this hypothesis suggests paracetamol does not bind to the active site of COX to cause inhibition [11]. It instead reduces COX from its active form (Fe^{4+}) to its inactive form (Fe^{3+}) and in turn prevents the conversion of arachidonic acid to prostaglandins. Paracetamol's reducing effects are blocked by locally acting peroxides. This explains why paracetamol may be inactivated in the periphery where there are high levels of peroxides in the setting of cell damage, but not centrally where levels are significantly lower.

Side effects of paracetamol are relatively benign with the most worrisome being hepatotoxicity caused by toxic levels of its metabolite N-acetyl-p-benzoquinoneimine (NAPQI) [11, 14]. Close to 40% of all acute liver failure cases in the United States and United Kingdom can be attributable to paracetamol intoxication. Approximately 90% of paracetamol is metabolized in the liver through glucuronidation or sulfation. The remainder of the drug's metabolism through the liver is through the cytochrome P450 (CYP450) system. The specific subfamily that has been implicated in the majority of this process is CYP2E1. As the glucuronidation and sulfation pathways are saturated, the metabolism through the CYP450 system proportionately increases and more NAPQI is produced. NAPQI then exerts its toxic effects by binding covalently to macromolecules of hepatocytes. Total daily doses of paracetamol alone or in combination with other analgesics should not be greater than 4 g a day with most regimens being 325–650 mg given every 4–6 h [1, 11, 15]. However, recent increases in the use of paracetamol-containing combination products have brought concern to overdose risk. Due to this, some clinicians recommend a maximum daily dose of 2.4–3.2 g a day, especially in the elderly [16–18]. Of note, paracetamol is commonly combined with opioid analgesics and is found to have additive analgesic effects when done so. The risk for overdose is increased in this setting due to patients taking paracetamol alone in addition to the combination product. In 2011, the Food and Drug Administration (FDA) of the United States limited the amount of paracetamol to 325 mg in combination products due to this increased risk.

Other patient populations at risk for toxicity include those that are malnourished, those taking CYP450 inducers (isoniazid, anticonvulsants) and those with heavy alcohol consumption

[11, 14]. Chronic alcoholism is especially worrisome for patients taking high doses of paracetamol on a daily basis. Chronic alcohol intake causes hepatotoxicity through a completely independent pathway as well as increasing CYP450 activity and depleting glutathione stores. Both of these increase the production of NAPQI. Therefore, in alcoholics, total daily doses should be limited to 2 g [18].

Other less common, but notable side effects of paracetamol therapy include hypersensitivity reactions and elevations in international normalized ratio (INR) [11, 18, 19]. When patients were given 4 g of paracetamol a day for 14 days, there was a mild increase in INR as well as a mild decrease in vitamin K-dependent clotting factors. This supports closer monitoring when patients are being co-administered warfarin and paracetamol for long periods of time. Intravenous doses of 1 g have been shown to cause very minor decreases in platelet aggregation, but overall paracetamol should be considered safe to use in the setting of an elevated bleeding risk. It is because of the lack of side effects and relative tolerability of paracetamol that it is recommended as the first-line agent in treating acute and chronic pains.

5. Nonsteroidal anti-inflammatories

Similar to paracetamol, NSAIDs exert their analgesic, antipyretic and anti-inflammatory effects through the inhibition of COX isoenzymes [18, 20]. NSAIDs specifically target COX-1 and COX-2, and enzyme affinity varies among agents. It is this isoenzyme selectivity that determines the efficacy and safety profile of these agents. As a group, NSAIDs typically are used as second-line agents in the treatment of acute and chronic low back pains after paracetamol [1, 7]. NSAIDs are more potent analgesics when compared to paracetamol for the treatment acute pain, but they are also associated with gastrointestinal, renal and cardiovascular complications with chronic use [14, 21]. At high doses, NSAIDs can even have comparable analgesic effects to low-dose opioids without the respiratory depressant effects. When evaluating the clinical efficacy among NSAIDs, no study has shown that one agent is better than another [20]. Therefore, when selecting an agent, careful consideration of each agent's safety and pharmacokinetic profile should be considered.

There are several different classes of NSAIDs, and most classes have multiple agents as well. For the purposes of this chapter, we will be focusing on those agents commonly used to treat acute and chronic pains. In order to treat low back pain effectively, an NSAIDs must be available orally and have good bioavailability, a fast onset of action, convenient dosing interval and minimal drug-drug interactions (**Table 1**). Of note, several NSAIDs (diclofenac, ibuprofen and ketoprofen) have topical formulations that likely provide similar analgesic effects as their oral counter parts, but are associated with less systemic side effects [22]. Additionally, other dosage forms may be available to treat acute pain in patients unable to take oral medications. For example, there are intravenous formulations of ketorolac and ibuprofen that can be used in the hospitalized setting to treat acute pain. Similarly, rectal formulations are also available for several NSAIDs, but their long-term use for analgesia is inconvenient and comparative efficacy is unknown.

Drug name	Dosage forms	Typical dose (mg)	Dosing interval (h)	COX selectivity	Comments
Ketorolac	Oral; intravenous	10	4–6	COX-1	Potent analgesic
Ketoprofen	Oral (immediate release, extended release); Gel	Immediate release: 25–50; Extended release: 100	Immediate release: 6–8 Extended release: 24	COX-1	High incidence of GI side effects; maximum dose of 100 mg in patients with renal dysfunction
Indomethacin	Oral (immediate release, controlled release); Intravenous; Suppository	Immediate release: 25; Controlled release: 75	Immediate release: 8–12; Controlled release:	COX-1	High occurrence of headache as a side effect
Nabumetone	Oral	500–1000	12–24	COX-1	Long half-life (24 h) requires fixed interval dosing for best efficacy; well tolerated with less GI side effects; Variable dose reductions based on degree of renal dysfunction
Sulindac	Oral	150–200	12	Unselective	Undergoes enterohepatic recirculation
Naproxen	Oral (immediate release, extended release); Cream	Immediate release: 250–500; Extended release: 750	Immediate release: 12; Extended release: 24	Unselective	Long half-life (14 h) analgesic effect increases as it reaches steady-state (3 days)
Piroxicam	Oral	20	24	Unselective	Very long half-life (45–50 h) need to take on fixed interval for best efficacy
Ibuprofen	Oral; Cream; Intravenous; Suppository	200–600	6–8	Unselective	Very well tolerated at lower doses
Diflunisal	Oral	500–1000	8–12	Unselective	Weak antipyretic effects; excreted into breast milk
Meloxicam	Oral	7.5–15	24	COX-2	COX-2 selective at lower doses; long half-life (20 h) requires fixed interval dosing for best efficacy

Drug name	Dosage forms	Typical dose (mg)	Dosing interval (h)	COX selectivity	Comments
Diclofenac	Oral (immediate release, extended release); Suppository; Gel	Immediate release: 25–50; Extended release: 50–75	Immediate release: 6–8; Extended release: 24	COX-2	Edema is a common side effect (33% of patients)
Celecoxib	Oral	100–200	12	COX-2	Dose reduction is necessary in CYP2C9 poor metabolizers (*3/*3 allele) although not commonly known; May carry higher cardiovascular risk than other nonselective NSAIDs
Etodolac	Oral (immediate release, extended release)	Immediate release: 200–400; Extended release: 400–1000	Immediate release: 6–8; Extended release: 24	COX-2	Similar COX-2 selectivity as celecoxib

Table 1. Properties of common NSAIDs (ordered in increasing COX-2 selectivity).

The most common adverse reactions with chronic NSAID use are those associated with the upper GI tract [13, 19, 20]. These adverse reactions are dose dependent in nature, and patients are placed at increasing risk as doses are escalated for increased analgesia activity. For example, when ibuprofen is used at doses of 800–1200 mg a day, risk for GI bleed was not significantly different than placebo [13]. Additionally, as doses are escalated, the odds of a GI bleed nearly double when doses of ≤ 600 mg/day were compared to doses of >1200 mg/day [19]. Adverse reactions are uncommon with chronic NSAID use, with up to 20% of patients reporting dyspepsia during treatment [18, 20]. Other common adverse reactions include anorexia, nausea, abdominal pain and diarrhea.

GI adverse reactions are mediated through two possible mechanisms [18, 20]. Through inhibition of COX-1, NSAIDs decrease cytoprotective prostaglandin production in the gastric epithelial cells. This causes an increase in acid secretion, a decrease in mucosal blood flow and a decrease in the production of the protective mucous layer. The second proposed mechanism is through local irritation to mucosal cells. NSAIDs are weak acids, and in the acidic environment of the stomach, they stay unionized and readily diffuse into mucosal epithelial cells. Once inside cells, these acids trap hydrogen ions and cause cell damage. Risk factors for NSAID-induced GI injury include age > 65 years, tobacco use, alcohol consumption, concurrent use of steroids, anticoagulation, prior history of GI ulceration and increasing dose or duration of NSAIDs. Of note, formulations whose goal is to decrease direct contact with gastric mucosa (e.g., enteric coating) have not shown to reduce the incidence of major GI adverse reactions. However, it is recommended to utilize acid suppression therapy (histamine blockers

or proton pump inhibitors) in patients on chronic high doses of NSAIDs to aid in the prevention of gastric and duodenal ulcers [18, 19].

Due to these common side effects, a subset of NSAIDs was developed to selectively inhibit only the COX-2 isoenzyme. There are much lower concentrations of COX-2 in the upper GI tract, and by sparing inhibition to COX-1, the detrimental effects seen with nonselective NSAIDs on the GI mucosa are greatly diminished [19, 20]. Fortunately, this selective inhibition of COX-2 does not seem to decrease the analgesic effects of COX-2 selective NSAIDs when compared to nonselective NSAIDs [23]. However, because there are higher concentrations of COX-2 in cardiovascular (CV) tissue, COX-2 selective NSAIDs have been associated with increased CV risk. This has led to the majority of COX-2 selective agents to being pulled from the market [13]. With this consideration in mind, COX-2 selective NSAIDs may be advantages in patients with history of GI ulcers, dyspepsia, gastroesophageal reflux disease or other similar disorders and are otherwise good candidates for treatment with NSAIDs [20]. Similar to nonselective NSAIDs, use in the setting of acute pain is reasonable, but careful consideration must be made when used chronically as long-term risk likely outweighs benefit.

Another adverse effect of NSAIDs that goes hand in hand with the increased risk for GI adverse reactions is the risk of platelet inhibition. Through inhibition of the COX-1 isoenzyme, NSAIDs attenuate the production of thromboxane A₂ [19]. By decreasing the production of thromboxane A₂, NSAIDs reversibly inhibit platelet aggregation and clot formation and if combined with other drugs that carry a bleeding risk the effect is additive. One case-control study that looked at NSAID use combined with selective serotonin reuptake inhibitors found that the incidence of upper GI bleed or ulcer was three when the agents were used alone [24].

Other limiting factors shown with chronic therapy include an increased cardiovascular thrombotic risk, blood pressure and renal toxicity. While each of these adverse events occurs separately, they are intertwined through pathophysiology. CV risk is likely caused by decreased production of COX-2-dependent prostaglandins in the kidney. These prostaglandins normally blunt the effect that prothrombotic and atherogenic inputs have on the coronary vasculature [25]. Without this protection, the risk for CV-related events elevates. Blood pressure and renal toxicity are affected in a somewhat similar matter. In patients who have increased activation of the renin-angiotensin and elevated blood pressure, NSAIDs disrupt the tenuous balance that renal prostaglandins play a key role in maintaining homeostasis. When COX-2 is inhibited and these prostaglandins are reduced, antidiuretic hormone is blunted and chloride ions are reabsorbed to a greater degree. This causes sodium and water retention and an elevation in blood pressure [18]. A similar process is commonly described to explain the NSAID-induced renal injury. The same prostaglandins that regulate chloride reabsorption also maintain renal blood flow. Homeostasis normally occurs through reducing the effects of adrenergic or renin-angiotensin inputs. When removed, arterial constriction occurs, blood supply decreases and renal toxicity occurs [26].

Even with a large number of potential side effects, NSAIDs are a great option to treat low back pain, especially if it is only for a short duration. Caution should be advised when considering treating for longer durations and when a patient has co-morbid disease states or is at risk for adverse reactions. If it is used chronically, make sure the lowest efficacious dose is being

used. Additionally, if a clinician commonly prescribes NSAIDs, they should be diligent in following new evidence on efficacy and safety of individual agents to assist them in selecting the most ideal one. When considering a patient's analgesic regimen, NSAIDs are a viable first- or second-line treatment choice if the risks for drug-related complications are low [1, 6]. In relation to the WHO's stepwise ladder, adding a NSAID is especially useful if a patient has an acute increase in pain (acute injury, worsening breakthrough pain, etc.) and even more so if the acute pain process has an inflammatory component. Ideally, when the acute pain event is resolved or mitigated, the clinician can shift back down the pain ladder and remove the NSAID from the regimen.

6. Adjuvant medications

Medications that fall into the adjuvant medication category have a unique place in therapy. These medications typically fall into two categories and can be added at any point in therapy (any step of the WHO's analgesic ladder). They should be used to tailor treatment and are a mainstay in the targeted treatment of the individual. The two categories are drugs that target neuropathic pain and drugs that target somatic pain through an indirect mechanism [8, 10]. When initiating an adjuvant medication, it should have a clear target and purpose to aid in decreasing pain. Adjuvants should not be used simply to lower opioid requirements, especially in patients, on lower doses, with minimal side effects as most adjuvants are not benign and many have severe side effects themselves [27].

Neuropathic pain is a type of pain that originates through a dysfunction in the peripheral or central nervous system [28, 29]. It is estimated to effect up to 7–8% of the general population in Europe and is often so severe that it is disabling to patients. It can be caused by several different disease processes including chronic radiculopathy and has a high incidence in low back pain caused by inflammatory causes.

Gabapentin and pregabalin exert their mechanism of action through binding to voltage-gated calcium channels and result in a decrease in release of the neurotransmitters glutamate and substance P [27, 28]. These agents are commonly considered first-line agents due to their high efficacy and a relatively benign side effect profile. Efficacy seems to increase as dose increases, but so do side effects. Most commonly, patients experience dizziness, sedation, peripheral edema and dry mouth [30]. Both agents can aid in sleep disturbances, and pregabalin has a mild anxiolytic effect as well. These agents have also been used in acute pain and are now recommended in the postoperative setting with more clinicians claiming these agents should be used as true analgesics and not as adjuncts [31].

Antidepressants can alter pain through several different mechanisms. These include modulation of monoamine activation, interacting with opioid pathways, inhibiting descending pain pathways and blocking ion channels that are important in pain transmission [27]. Tricyclic antidepressants (TCAs) have the most robust evidence to support their use in neuropathic pain. While the exact mechanism is unknown, it is likely mediated through blocking the reuptake of norepinephrine. These agents are antagonistic at N-methyl-D-aspartate (NMDA)

receptors and may have a roll at reducing hyperalgesia caused by central windup. Agents in this class include the secondary amines nortriptyline and desipramine and tertiary amines amitriptyline and imipramine. When compared to each other, no agent has been found to be superior to another. Despite this, nortriptyline and desipramine are typically considered the preferred agents due to better side effect profile. TCAs are associated with increased risk for sedation, orthostatic hypotension, dry mouth, constipation, urinary retention and cognitive impairment especially in the elderly [15, 23, 28].

TCAs are not the only antidepressants that have been looked at for the treatment of neuropathic pain. SSRIs and serotonin norepinephrine reuptake inhibitors (SNRIs) have also been evaluated. Even though the SSRIs citalopram and paroxetine have shown efficacy in treating neuropathic pain, they are typically not as preferred compared to TCAs and SNRIs because they are less efficacious [28]. Previously, TCAs had been preferred due to more evidence and lower costs. However, costs of both venlafaxine and duloxetine have decreased recently and use has increased. Some guidelines even support their use as first-line agents [29]. Of the two, duloxetine seems to be preferred because it is associated with less hypertension and is well tolerated in the elderly [16, 28, 29]. Patients should be counseled on the fact that treating pain with antidepressants can take up to 2.5 weeks to reach their full effect and this can decrease compliance.

Other common adjuvant medications commonly added to analgesic regimens include muscle relaxants, corticosteroids, local anesthetics and topical agents [27, 32]. Muscle relaxants as a group have varying mechanisms of action, some of which are not fully understood. These agents may be considered for acute pain relief, but have very limited data to support continued use. They should only be used in patients who have increased somatic pain due to spasticity. The primary side effect of this drug class is central nervous system adverse effects (sedation, fatigue, dizziness, etc.), but because these drugs are not related in mechanism, they each have their own safety profiles. Due to the lack of data and risk for severe side effects (e.g., hepatotoxicity of dantrolene) use of skeletal muscle relaxants for back pain not associated with severe spasticity is discouraged.

Topical lidocaine may be of an advantage for patients who complain of localized neuropathic pain [28]. Lidocaine decreases the frequency of Na⁺ channel opening, thereby decreasing pain transmission. When it is used topically, systemic absorption is decreased, which makes systemic adverse reactions very rare. Evidence for use in low back pain is lacking, but its use should be considered if a patient complains of localized neuropathic pain.

Patients who suffer from chronic low back pain are sometimes prescribed corticosteroids. Many different doses of prednisone and dexamethasone have been studied, but there is no general consensus on an effective dose or duration [27]. Many guidelines recommend the use of corticosteroids as no major study has shown long-term efficacy. If they are used, a single injection or short duration should highly be emphasized due to severe side effects of chronic use including immunosuppression, metabolic disorders and GI bleeding.

Addition of an adjuvant medication should directly target a cause of pain (neuropathy, muscle spasm, etc.), and efficacy should be evaluated after initiation and periodically throughout. If a medication is found to not be efficacious, it should be removed or replaced. For additional

information, clinicians can refer to neuropathic pain guidelines that provide evidence-based recommendations for specific disease state-induced neuropathic pain [29]. If acute or chronic pain is completely neuropathic in nature, the WHO's stepwise ladder is not appropriate to follow and a medication regimen targeting neuropathy should be initiated.

7. Risk of opioids

After the addition of nonopioids and possible adjuvants, the WHO's analgesic ladder calls for low to strong opioids. However, if a patient is in severe acute pain, it is reasonable to start therapy with all three types of analgesics and then rapidly de-escalate to a lower step on the analgesic ladder [9]. When treating chronic pain, opioids should never be utilized as first-line agents outside of cancer or palliative care. Opioids have only been shown in the literature to have a short-term improvement in pain and carry a high risk for serious side effects and possibly even death [6]. Before initiating therapy, clinicians and patients should have a discussion regarding expected goals and potential risks. Goals should include how efficacy will be measured for both pain relief and functionality and what measures will indicate continued treatment. Patients should also be informed that opioids only show a short-term benefit in relieving pain and long-term efficacy is lacking. Expectations should be that opioids will likely never provide complete relief.

The addition of opioids to a chronic pain regimen should be considered carefully. Patients do not need to fail nonopioids or adjuvants prior to initiating opioids, benefits must simply outweigh the risks of starting opioid therapy [1, 8]. Another way to consider this is that opioids should be considered in patients with severe disabling pain that is likely not to be relieved from nonopioids and adjuvants alone. The worst risks are with overdose and potentially fatal respiratory depression. Overdose risk is dose dependent, and clinicians should be careful when doses are escalated. This is particularly important as there is technically no ceiling dose for opioids. Several other factors increase the risk for opioid-related overdose including methadone use, co-prescription with benzodiazepines, history of sleep-disordered breathing, reduced renal or hepatic function, increased age, pregnancy, history of substance abuse and psychiatric illness. Additionally, the risk of opioid-related overdose is elevated when starting patients on opioid therapy with long-acting or extended release formulations. For this reason, these dosage forms should only be utilized in opioid-tolerant patients. Risk mitigation strategies such as checking prescription refill history, urine drug screening and use of medications specifically for opioid use disorders (methadone, buprenorphine) increase retention in opioid treatment programs.

Prior to starting opioid therapy, the prescriber must fully understand the concepts of opioid abuse (opioid misuse disorders), tolerance and physical withdrawal [6]. Opioid abuse or opioid misuse disorders are described by patterned misuse of opioids that include unsuccessful attempts to curb use and results in social problems at home, work or school. Tolerance is simply a diminished response to a fixed dose of medication with repeated use. Physical dependence is when a medication causes the body to change in a way that when the medication is removed the body produces withdrawal symptoms. Both

physical dependence and tolerance can occur in the absence of opioid abuse. When treating a patient, it is necessary to keep these concepts separate and not to assume that because a patient is requiring higher doses of medication or is experiencing withdrawal symptoms that they are abusing opioids. Only after considering all of these things, a prescriber should initiate opioid therapy.

Opioid medications typically exert their analgesic effects through agonism at μ -, δ - and κ -opioid receptors [33, 34]. Opioid receptors are G-coupled protein receptors and are most commonly Gi/Go. Once these G-coupled protein receptors are activated, they decrease adenylyl cyclase activity, decrease calcium conductance and inhibit excitatory neurotransmission. This slows the transmission of pain that impulses both centrally and peripherally. Opioids activate centrally located receptors that play a key role in descending pain pathways and peripherally in the spinal cord. This spinal cord transmission regulates the relay of nociceptive pain inputs from the periphery to the brain. While all three opioid receptors mediate analgesia, activation of individual receptors will produce different effects [33]. μ -opioid receptors lower respiratory depression, sedation, euphoria, nausea, constipation and urinary retention. δ -opioid agonists have similar effects to those of μ -opioid agonists. These effects include respiratory depression, constipation and euphoria. While μ - and δ -opioid agonists have very similar effects, κ -opioid agonists have several unique effects. These agents can cause dysphoric, sedative, diuretic and sometimes aversive effects. An understanding of what receptor an individual opioid will activate will give the provider information in the common side effects that the medication will exhibit.

When acute or chronic low back pain necessitates the need to escalate to a weak opioid, the practitioner has several options to choose from. Drugs that are considered weak opioids are codeine, hydrocodone and oxycodone when used in combination with nonopioids (sometimes also tramadol), and all other full agonists (morphine, hydromorphone, oxycodone alone, oxymorphone and fentanyl) are considered moderate or strong opioids [15]. Weak opioids should be initiated with caution if the patient already is taking paracetamol at a fixed interval as it increases the risk of overdose. When starting opioid therapy with the intent to continue its long term, this initial phase should be considered a trial and should only be continued or escalated if pain relief occurs [6]. If a patient fails an initial trial of opioids, other agents should be considered for refractory pain. Once on opioid regimen is started, the practitioner should periodically assess the need to continue opioid therapy. If tolerance occurs or pain relief is reduced, the clinician should weight escalating therapy to a moderate or strong opioid versus the increase in risk. It is reasonable to abandon opioid therapy if, after an escalation in therapy, the patient does not experience an increase in analgesic effect.

8. Opioids

It is believed that opium was cultivated in Mesopotamia as early as 3400 BC [35]. Natural occurring opiates are the alkaloid compounds found in the poppy plant and include morphine and codeine while the term opioid refers to any compound that binds to opioid receptors. Narcotic

originally was used to describe a medication that causes sleep, but the common misuse of drugs like quaaludes and barbiturates along with opioids caused this to become an umbrella term for drugs that are commonly abused. It is even used in a legal sense to describe the drugs of abuse. Even though opioids are grouped together, they have a wide range effects and each medication has unique properties (**Table 2**). There are four major opioid classes, and understanding each of the groups allows for easier prescribing as efficacy and side effects are similar within classes.

Drug name	pertinent dosage forms	Equianalgesic oral dose (mg)	Starting oral dose (mg)	Dosing interval (h)	Comments
Morphine	Immediate release extended release (Ms contin and kadian)	30	30–60	Immediate release: 4–6 Extended-release: 8–24	Several different extended-release formulations each with their own dosing interval recommendations Strong opioid
Codeine	Immediate release (combination with paracetamol)	200	30–60	4–6	Only available in combination with paracetamol Weak opioid
Hydromorphone	Immediate release Extended release	7.5	4–8	Immediate release: 4–6 Extended release: 12–24	Several different extended release formulations each with their own dosing interval recommendations Strong opioid
Hydrocodone	Immediate release (combination with paracetamol)	30	5–7.5	4–6	Only available in combination with paracetamol Weak opioid
Oxymorphone	Immediate release Extended release	10	5–10	Immediate release: 4–6 Extended release: 12	Strong opioid
Oxycodone	Immediate release (alone and combination with paracetamol) Extended release	20	15–30	Immediate release: 4–6 Extended release: 12	Can use lower starting doses if using combination product with paracetamol Weak opioid (combination product) Strong opioid (when used alone at higher doses)
Fentanyl	Transdermal; Submucosal	–	0.025	Transdermal: 24 Submucosal:	Use only in patients suffering from severe chronic pain

Drug name	pertinent dosage forms	Equianalgesic oral dose (mg)	Starting oral dose (mg)	Dosing interval (h)	Comments
Levorphanol	Immediate release	4	2–4	6–8	Half-life of 12–16 h; Good long-acting agent for those that cannot tolerate morphine or methadone
Methadone	Immediate release	Variable	2.5 (analgesic) 10–20 (withdrawal)	For analgesic effects: every 8 h To prevent withdrawal: every 24 h	Morphine (mg)/methadone (mg) conversion changes as total daily doses of morphine increase 0–29 mg: 2/1 30–99 mg: 4/1 100–299 mg: 8/1 300–499 mg: 12/1 500–999 mg: 15/1 >1000 mg: 20/1

Table 2. Properties of common opioids.

The phenanthrenes are one of the larger classes of opioids and contain the prototypical opioid morphine. This class contains the most commonly used opioids including morphine, codeine, hydrocodone, hydromorphone, oxycodone, oxymorphone, levorphanol, buprenorphine, nalbuphine and butorphanol [35]. A majority of these agents are metabolized in the liver by the CYP450 isoenzyme CYP2D6. Some even require metabolism to exert analgesic effects. For example, codeine itself has no analgesic effect in its original state, and it is only through metabolism by CYP2D6 to morphine that it can produce an analgesic effect [36]. A similar process happens to both hydrocodone and oxycodone to be converted to hydromorphone and oxymorphone. Similar to codeine, hydrocodone has been proposed to be a prodrug and its analgesic effect is dependent on activation by CYP2D6. Oxycodone, on the other hand, is a μ -opioid agonist and does not require activation by CYP2D6. A serious issue arises with the fact that CYP2D6 has a very dramatic range of activity from one person to the next. It has been reported in literature that through a mutation, some patients have no activity of CYP2D6 (codeine produces no analgesic effect) whatsoever while others may be classified as ultrarapid metabolizers. This may explain the wide range of reported efficacy in patients who are prescribed codeine- and hydrocodone-containing products.

Another common attribute of drugs in the phenanthrene class is that they are typically glucuronidated and eliminated via the kidneys. This is especially important for morphine whose glucuronidated metabolite, morphine-6-glucuronide, is responsible for its analgesic effects [37]. In young and healthy individuals, this is not of importance, but in elderly or those with markedly reduced renal function, morphine's analgesic effects are prolonged. Morphine prescribed at fixed intervals in this patient population should be closely monitored as the respiratory side effects may accumulate as the medication is cleared more and more slowly. Additionally, drugs in this class with a 6-hydroxyl group (morphine and codeine) are associated with a higher incidence of nausea than those in the class that do not [35].

Phenylperidines include the agents' fentanyl, alfentanil, sufentanil and meperidine. Of these, fentanyl has the highest affinity for the μ -opioid receptor and is 80–100 times that of morphine [35, 37]. While incredibly potent fentanyl has a very short half-life leading to a short duration of action. Fentanyl's only advantage is that is highly lipophilic leading to its ability to be utilized nontraditional dosage forms. One of these dosage forms is the transdermal patch. Fentanyl transdermal patches should only be used in the most extreme cases of chronic low back pain. This dosage form possesses many nuances, and a complete understanding of them should be obtained before prescribing. When a fentanyl transdermal system is placed on a patient, it takes 6–12 h before taking effect [37]. Additionally, it will take 3–6 days to reach steady state and when removed a reservoir of drug will remain in effect up to 24 h. This makes initiating and weaning incredibly difficult and therefore should not be commonly done. Fentanyl also has a submucosal dosage form that may be beneficial in patients who suffer from acute breakthrough pain. The clinical applicability of this makes sense because of fentanyl's high potency and short duration of action. It is important to stress that this should not be prescribed on a regular basis and should only be utilized as a rescue medication in very rare cases. The majority of patients with chronic low back pain should not be prescribed fentanyl, but in rare circumstances, it may have clinical utility.

The other opioids in the phenylperidine class should not be used in the treatment of low back pain. Meperidine is a relatively weak opioid agonist with poor oral absorption that fell out of favor due to its neurotoxic and anticholinergic side effects [23, 37]. Its metabolite normeperidine accumulates in patients with renal insufficiency and lowers seizure threshold. Additionally, it has significant drug-drug interactions with monoamine oxidase inhibitors that lead to severe respiratory depression. The other agents that are sufentanil and alfentanil in this drug class have little to no role in the treatment of low back pain due to their short duration and lack of specialized dosage forms.

The remaining classes of opioids consist of the benzomorphans and the diphenylheptanes. The only agent in the benzomorphan class is pentazocine, which is a mixed opioid agonist-antagonist. The diphenylheptanes include propoxyphene and methadone. While methadone has established itself in a highly specific role, propoxyphene has fallen out of favor dramatically [16]. Propoxyphene is thought to be no more efficacious than paracetamol, and it has a plethora of side effects. It has been associated with dizziness, weakness, paradoxical excitement, falls, visual disturbances and insomnia [35]. Propoxyphene itself is thought to act directly on the central nervous system and increase the risk for seizure activity which ultimately leads to the product being pulled off the market in the United States.

Several opioids have mixed agonist-antagonist activity and have only a limited role in the treatment of pain. These drugs provide small analgesic effects in patients with little or no prior opioid exposure and may exacerbate withdrawal symptoms in patients who have a physical dependence on opioid medications [35, 37]. Drugs in this group are pentazocine, butorphanol and nalbuphine. These agents have a ceiling effect on both analgesia and respiratory depression and have limited abuse potential. As doses escalate so do the antagonistic effects against other opioids. This places the patient at risk for withdrawal. Also, the risk for psychotomimetic side effects (delirium, delusions and hallucinations) increases in conjunction with the

dose [37]. Pentazocine has the highest incidence of these side effects. The role of these agents in pain is limited by their antagonistic effects and lack of convenient dosage forms. Only pentazocine is available in an oral dosage form and has fallen out of favor to treat acute or chronic pain. The partial agonist buprenorphine acts similarly to the agonist-antagonists with the one caveat that it is not associated with psychotomimetic side effects. Similar to the agonist-antagonists, it can produce withdrawal symptoms when administered to patients taking high doses of other opioid medications. It is also combined with naloxone to reduce the risk of abuse. Buprenorphine is available as a sublingual dosage form in the United States and a transdermal extended release system in Europe. The sublingual form is commonly used in the United States in addiction treatment programs.

Methadone is another opioid with a unique mechanism of action other than being a μ -opioid receptor agonist. This mechanism may be particularly advantageous for patients who have "opioid-resistant" pain states or have a neuropathic component to their pain [37]. Similar to some of the agents to treat neuropathy, the R-isomer of methadone is antagonistic at the NMDA receptor and may be beneficial in treating the effects of hyperalgesia and allodynia seen in chronic pain states [37]. Methadone should be used with caution as mentioned before its use increases the risk for overdose and a misunderstanding of its pharmacokinetics and pharmacodynamics perpetuates this effect. The terminal half-life of the drug is typically thought to be 15–60 h, but has been cited as up to 120 h [38]. Because of this, it may take a week or longer to reach steady state, and therefore, the drug should be titrated no more often than weekly. Additionally, the analgesic effect of methadone is roughly 4–8 h and should be dosed on an every 8-h interval. Due to this discrepancy, the drug has a high risk for accumulation and may put the patient at risk for sedation, confusion, respiratory depression, cardiac abnormalities and death. The general consensus is that a dose of 2.5 mg every 8 h is a safe starting dose for opioid-naïve patients [38]. Careful monitoring should be performed on any patient starting on methadone. Another caveat to dosing methadone is that it has a nonlinear equianalgesic conversion. This means that patients on higher doses of opioids are more sensitive to the effects of methadone and when converting the ratio of morphine equivalents to methadone dose decreases. However, with caution, the practitioner can utilize this effect to their advantage in treating the most complicated of patients.

Lastly, there are two agents that are sometimes considered opioid analgesics, but have both opioid and nonopioid mechanisms. These two agents are tramadol and tapentadol. While both have activity at the μ -opioid receptor, this activity alone does not equate to the full analgesic effects seen with these agents [35, 39]. The remainder of their analgesic effects can be attributed to the inhibition of serotonin and norepinephrine reuptake. Similar to TCAs, this may be useful in treating neuropathic pain and caution should be used when combining therapy with other antidepressants or medications that increase the levels of serotonin as it increases the risk for serotonin syndrome [29]. Tramadol can be used for mild-to-moderate pain, but it should not be used as monotherapy when opioids are indicated based on the severity of pain. Tramadol's analgesic effect is at most equal to codeine and is probably less than that of hydrocodone [13, 16]. The maximum dose of tramadol is 100 mg every 6 h. Higher doses than 400 mg a day should not be used as it increases the risk for lethargy, nausea, tachycardia, agitation and hypertension. Additionally, tramadol has a neuroexcitatory effect so as

doses increase so does the risk for seizures [13]. For these reasons, tramadol should be used either as an adjuvant medication or prior to stepping up to moderate or strong opioid-containing regimens and is often seen as adjunct medications.

9. Conclusion

By blending together all of the concepts in this chapter, a practitioner can provide the best treatment for their patients suffering from low back pain. Through an understanding of a modified WHO's stepwise approach and a thorough understanding of all of the drug class available to them, they should be able to escalate and de-escalate therapy in a safe and effective manner. The practitioner will need to set expectations, incorporate a multimodal treatment approach, analyze potential contraindications for specific drug therapy and provide the most ideal medication regimen. This regimen should be based on ease and appropriateness for the individual patient and should be executed with a complete understanding of every drug class mentioned in this chapter (paracetamol, NSAIDs, adjuvant and opioid medications). If this is done, the practitioner will truly be an expert in the pharmacologic management of low back pain.

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