# Pharmacology

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## Overview

### Learning Objectives

- Identify medications commonly used to treat pain due to spinal conditions
- Compare the efficacy of different medications and their use in spine-related pain
- Recognize the advantages and disadvantages of medications used to treat spine-related pain
- Understand the dosing strategies for medications used for pain due to spinal conditions

## Acetaminophen

### Mechanism of Action

The exact mechanism of action of acetaminophen is unknown. It is believed to be a weak inhibitor of prostaglandin synthesis through cyclooxygenase (COX) inhibition. Other mechanisms of action are believed to be due to activation of central descending serotonergic pathways. Acetaminophen targets nociceptive pain. Other mechanisms of action are thought to include enhancement of the cannabinoid signaling pathways [52].

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**Table 8.1** Acetaminophen dosing

| Medication | Route | Dosing | Maximum daily dose |
|---|---|---|---|
| Acetaminophen | PO<br>IV | 325–1000 mg tid<br>650–1000 mg q4–6h | 3000 mg<br>4000 mg |

*PO* oral, *IV* intravascular

### Evidence in Spine

Minimal evidence exists to support the use of acetaminophen alone for the use of pain, but it is commonly recommended in guidelines as first line therapy either alone or in conjunction with other medications. Despite the lack of high-quality evidence, the opioid sparing or synergistic effects of acetaminophen in conjunction with other medications may justify its use [89].

### Adverse Effects

Acetaminophen is relatively well tolerated but can lead to gastrointestinal disturbance, such as nausea, vomiting, abdominal pain, diarrhea, constipation. At high doses or when combined with alcohol, acetaminophen can be hepatotoxic, leading to acute hepatotoxicity, liver failure, and death.

### Dosing

See Table 8.1 for common dosing of Acetaminophen.

## COX-Inhibitors

### Mechanism of Action

Two types of COX inhibitor medications are currently available to treat pain: nonsteroidal anti-inflammatory medications (NSAIDs) and selective COX-2 inhibitors. Inhibition of COX-1 causes a decrease in thromboxane, prostacyclin, and prostaglandins, leading to antipyretic, analgesic, antiplatelet, and anti-inflammatory effects. Inhibition of COX-2 causes a decrease in inflammatory prostaglandins, proteases, and reactive oxygen species that lead to inflammation, fever, and pain. The major differences between the available COX-inhibitors are their selectivity to COX-1 or COX-2 and each drug's particular pharmacokinetics and dosing strategies. NSAIDs target nociceptive pain.

### Evidence in Spine

NSAIDs are commonly recommended as first line treatment for low back pain with or without radiculopathy as they may be effective for short term relief of chronic

low back pain without radiculopathy [85]. There is conflicting evidence of whether one NSAID produces superior improvement in pain in comparison to others or if changing to another NSAID after a failed trial of one NSAID will prove to be efficacious [45, 85]. Hauk [45] suggests that if a trial with one NSAID is ineffective after a 2–4-week period, a different NSAID can be tried and may be more effective. In patients with chronic inflammatory spine conditions, such as ankyloses spondylitis, with axial low back pain, evidence suggests that NSAIDs may slow progression of disease [106].

Studies for the use of NSAIDs for the treatment of chronic pain or radiculopathy do not support their use. The outcome with the use of NSAIDs versus other commonly used pharmacotherapies, including opioids and muscle relaxants, in the treatment of chronic pain was no different. For the treatment of radicular symptoms, there is a lack of evidence for therapeutic benefit with NSAIDs compared to placebo [85].

Using NSAIDs as part of a multimodal pharmacological treatment strategy may be more efficacious than as monotherapy. Combination therapy with aceclofenac plus tizanidine (vs. aceclofenac alone) or diclofenac plus B vitamins (vs diclofenac alone) was effective in reducing pain intensity in patients with (sub)acute low back pain with or without leg pain but none provided a clinically important difference in pain intensity reduction [64].

Other benefits of NSAID treatment may include improvement in symptoms of other comorbid conditions, including depression. Depression is a common comorbidity in patients with chronic pain. In patients treated with naproxen or aspirin compared to acetaminophen, depression and suicidal ideation were less, but more depression was reported in patients treated with celecoxib compared to acetaminophen. In women but not men, ibuprofen was associated with fewer reports of depression [57].

## Adverse Effects

The risks of adverse events may limit the use of NSAIDS. The gastrointestinal (GI) and cardiovascular (CV) systems are two of the most common systems affected by adverse events with the use of NSAIDs. Ho et al. [46] propose an algorithm for choosing an anti-inflammatory medication in patients with a clinical indication for anti-inflammatory therapy but with GI and/or CV risks. In patients with high or low GI risk and high CV risk, they recommend celecoxib 200 mg/day with concomitant use of a proton pump inhibitor (PPI). In patients who are low GI and CV risk, NSAID of choice or celecoxib in combination with a PPI is recommended [46]. Another issue that may arise is that there is some evidence that NSAID use may cause delayed bone healing in patients who have recently undergone a posterolateral lumbar fusion. When administered for >2 days or at high doses, ketorolac may be associated with pseudarthrosis after posterolateral lumbar fusion. Ketorolac's use in smokers is also associated with pseudarthrosis [59].

**Table 8.2** Commonly used NSAID and COX-2 inhibitor dosing

| Medication | Route | Dosing | Maximum daily dose |
|---|---|---|---|
| Aspirin | PO | 350–1000 mg q4–6h | 6000 mg |
| Diclofenac | PO | 100–200 mg bid | 400 mg |
| | TD: Gel | 2 grams qid | 32 g |
| | TD: Patch | 1 patch (180 mg) bid | 360 mg |
| Etodolac | PO | 200–400 mg q6–8h | 1000 mg |
| Ibuprofen | PO | 200–800 mg tid | 2400 mg |
| Indomethacin | PO | 25–50 mg 2–3 times per day | 200 mg |
| Ketorolac | PO | 10 mg qid | 40 mg |
| | IV/IM | 15–30 mg q6h | 120 mg |
| Nabumetone | PO | 500–1000 mg once or twice daily | 2000 mg |
| Naproxen | PO | 250 q6–8h or 500 mg twice daily | 1000 mg |
| Piroxicam | PO | 20 mg once daily or 10 mg bid | 20 mg |
| Meloxicam | PO | 7.5–15 mg daily | 15 mg |
| Celebrex | PO | 100–200 mg bid | 400 mg |

*PO* oral, *TD* transdermal, *IV* intravenous, *IM* intramuscular

The most common adverse effects of NSAIDs include cardiovascular events, including heart attack; gastrointestinal toxicity, including stomach irritation and ulceration; hematological toxicity, including increased risk of bleeding; nephrotoxicity, more common with NSAIDs than COX-2 inhibitors; and hepatotoxicity.

Topical formulations can greatly reduce renal toxicity and GI effects, but patients who use topical patches or gels may experience skin irritation at the site of application [26].

### Dosing

See Table 8.2 for common dosing of commonly used NSAIDs and COX-2 inhibitors.

## Antidepressants

### Mechanism of Action

Multiple classes of antidepressants, including tricyclic antidepressants (TCAs), serotonin-norepinephrine reuptake inhibitors (SNRIs), and selective serotonin reuptake inhibitors (SSRIs), are used for the treatment of spine-related pain. Tricyclic antidepressants increase the levels of norepinephrine and serotonin in the synaptic cleft and act as an antagonist at histamine and acetylcholine receptors. SNRIs increase the levels of both norepinephrine and serotonin in the synaptic cleft. SSRIs increase the amount of serotonin in the synaptic cleft. Antidepressants have an effect on neuropathic pain. The exact mechanisms for the efficacy of antidepressants for the treatment of neuropathic pain is yet to be elucidated, and it is presumed that the mechanism may be different than the mechanisms for treatment of depression and mood stabilization. The mechanisms underlying antidepressants' ability to

treat neuropathic pain is to increase norepinephrine in the spinal cord as well as act on the locus ceruleus to directly inhibit pain and activate the impaired descending norepinephrine inhibitory system. Dopamine and serotonin are also increased in the central nervous system with antidepressant use and may enhance the inhibitory effects of norepinephrine [73].

## Evidence in Spine

Neuropathic pain is most responsive to analgesic effects of antidepressants. TCAs are the most effective and are used as first line agents. SNRIs are considered second line, and the effectiveness of SSRIs is limited for the treatment of persistent pain [29]. At low doses, tricyclic antidepressants may be helpful in treating both leg and back pain related to lumbar spinal stenosis [75]. Venlafaxine has been shown to be an effective treatment for both acute and chronic neuropathic pain [2]. However, milnacipran lacks evidence to support its use in the treatment of neuropathic pain [28].

Although antidepressants may be effective in treating neuropathic pain, multiple systematic reviews have concluded that there is no clear evidence for the efficacy of antidepressants over placebo for the treatment of low back pain [103]. Duloxetine has been shown to be useful in treating low back pain [5]. However, concomitant use of an NSAID or acetaminophen with duloxetine did not significantly change the efficacy of duloxetine alone for the treatment of chronic low back pain [93]. Of the SSRIs, Fluoxetine is the most studied for the treatment of chronic pain. Fluoxetine, fluvoxamine, and escitalopram seem to be the SSRIs that have the most supporting evidence for use in chronic pain treatment [78]. While TCAs may be effective in treating radicular pain, they do not seem to have much effect on chronic low back pain. Low-dose amitriptyline showed a nonsignificant improvement in pain intensity at 6 months [103]. After a single dose of imipramine, there was no analgesic effect in patients with chronic low-back pain. However, the anti-nociceptive effects may depend on CYP2D6 metabolizer status and may need to be take into account [92].

The advantages to using antidepressants in spine related pain may be due to their other effects instead of their direct analgesic effect. The efficacy of TCAs may be more related to mood and sleep modulation instead of a direct analgesic process [92]. Low-dose amitriptyline has been shown to lead to a reduction in disability at 3 months without improvement in pain intensity [103]. Depression is common among patients with spinal cord injury and other types of spine-related pain. Antidepressants may help modulate mood and can help with pain as well as quality of life after spine surgery [13].

In patients with spinal cord injury related pain the results of treatment with amitriptyline are mixed with a significant response in patients with comorbid depression receiving doses up to 150 mg daily [107].

The use of antidepressants may also help to decrease long-term costs and utilization of higher risk medications. The use of duloxetine in patients with chronic low

back pain versus other non-surgical treatment, including other pharmacological therapies, such as narcotics and NSAIDs, and non-invasive therapy, such as chiropractic therapy, physical therapy, and exercises therapy, was associated with reduced rates of non-surgical therapies and similar back surgery rates without increased costs [49]. Patients with chronic low back pain who initiated duloxetine treatment rather than muscle relaxants, gabapentin, pregabalin, venlafaxine, and tricyclic antidepressants had better compliance and lower likelihood of opioid use [5]. In addition, older patients with chronic low back pain and depression who are co-prescribed an opioid with venlafaxine are less likely to have an analgesic response to low-dose venlafaxine than patients who are not on opioid medications. Opioid morphine equivalent dosing was negatively correlated with pain response with venlafaxine [94].

Overall, the guidelines for antidepressant use are variable. TCAs and SNRIs are more effective for neuropathic pain and SNRIs and SSRIs may be more effective for low back pain treatment. In addition, these medications may work through modulation of comorbidities that commonly accompany pain. More studies should be performed to elucidate the best dosing strategy and efficacy for different etiologies of pain.

### Adverse Effects

Due to the anticholinergic effects of TCAs, potential adverse effects include cardiotoxicity, weight gain, blurred vision, dry mouth, constipation, sedation, and postural hypotension (dizziness). TCAs also pose a risk of anticholinergic toxicity. TCAs have a small therapeutic dose range and there is a risk of lethal overdose if not used properly. The most common side effects experienced with SNRIs and SSRIs include nausea, dry mouth, headache, dizziness, sedation, constipation, changes in sexual function. When combined with other medications that increase serotonin levels, TCAs, SNRIs, and SSRIs can all lead to serotonin syndrome.

### Dosing

See Table 8.3 for common dosing strategies of antidepressants.

## Anticonvulsants

### Mechanism of Action

The precise mechanism of action of gabapentin and pregabalin is still unknown. Studies have shown that gabapentin and pregabalin bind to voltage-gated calcium channels, but the exact therapeutic mechanism is yet to be elucidated. Topiramate blocks voltage-gated sodium and calcium channels and inhibits the glutamate

**Table 8.3** Antidepressant dosing

| Medication | Route | Dosing | Maximum daily dose |
|---|---|---|---|
| TCAs | | | |
| Nortriptyline | PO | 25 mg 3–4 times daily | 100 mg, if >100 mg is given, plasma levels should be monitored |
| Amitriptyline | PO | 25–150 mg 1–4 times per day | 150 mg |
| Imipramine | PO | 75–150 mg once a day | 200 mg |
| Desipramine | PO | 100–200 mg qhs or bid | 300 mg |
| SNRIs | | | |
| Duloxetine | PO | 30–60 mg daily | 60 mg |
| Venlafaxine | PO | 75–225 mg daily | 225 mg |
| SSRIs | | | |
| Fluoxetine | PO | 20–60 mg daily | 80 mg |
| Sertraline | PO | 25–200 mg daily | 200 mg |
| Paroxetine | PO | 12.5–60 mg daily | 60 mg |
| Citalopram | PO | 20–40 mg daily | 40 mg |
| Escitalopram | PO | 10–20 mg daily | 20 mg |

*PO* Oral

pathway while enhancing the GABA-pathways. It also inhibits carbonic anhydrase. The exact mechanism of action responsible for treatment of pain remains to be determined. Anticonvulsants target neuropathic pain.

## Evidence in Spine

Multiple meta-analyses have found that gabapentin and pregabalin are not effective for the treatment of low back pain either with or without radiculopathy [32, 34]. Specifically, in a randomized double blind cross over study, extended release gabapentin failed to demonstrate any significant decrease in pain score compared to placebo [41], and in a double-blind, placebo-controlled trial, pregabalin showed no increased efficacy than placebo in reducing leg-pain intensity in patients with both acute and chronic moderate to severe sciatica [65]. A randomized controlled trial in the Department of Veterans Affairs Healthcare System failed to demonstrate superiority of gabapentin compared to placebo for the treatment of low back pain [6]. Pregabalin has been shown to be no more effective than placebo in treating lower extremity radiculopathy as well [3]. Of the evidence available, there exists very low-quality evidence for the treatment of radicular leg pain, nerve injury pain, and spinal cord injury related pain with gabapentin [109].

Some evidence shows that gabapentin may be helpful in patients with lumbar radiculopathy pain. In patients with chronic lumbar radiculopathy, gabapentin may provide improvement in pain and quality of life [112]. A multicenter randomized double-blind study comparing the efficacy of gabapentin and epidural steroid injections for lumbosacral radicular pain in joint service military treatment facilities

found a modest improvement in both groups at 1 and 3 months that resulted in modest improvements in pain and function [24].

Topiramate provides a small effect for short term pain treatment [34]. In a double-blind, randomized, 2-period crossover trial of topiramate and diphenhydramine (placebo), topiramate titrated to maximal tolerated dose reduced average back and overall pain, worst leg and back scores, and global pain relief scores [51]. In a case report, topiramate helped a morbidly obese (BMI 61.4 kg/m$^2$) female with chronic low back pain achieve clinically meaningful and significant weight loss and improvement in her chronic low back pain and functionality [44]. Topiramate is more effective than placebo in the short-term treatment of chronic nonspecific low back pain [70].

In a Cochrane Review, there was little evidence to support the efficacy of oxcarbazepine in neuropathic radicular pain. Some very low-quality evidence suggests that it may provide some efficacy in treatment of pain but adverse effects, serious adverse effects, and adverse effects leading to discontinuation of the medication are more common with oxcarbazepine than placebo and limits its utility [113].

Pregabalin may be more effective when used in combination with other medications and in treating other common comorbidities associated with pain that can help improve patient quality of life. The combination of NSAIDs and pregabalin was no more effective in reducing pain than NSAIDs alone in patients with acute lumbar disc herniations. However, the combination of NSAID plus pregabalin showed to be more effective to treat sleep disturbance than NSAIDs alone. Patient global impressions of change were also significantly improved with a combination of NSAID and pregabalin instead of NSAID alone [72]. In an observational study of patients with chronic refractory cervical pain and radiculopathy, a significant improvement in self-reported sleep interference and pain was observed in patients treated with pregabalin as opposed to treatment with conventional analgesic care (acetaminophen, NSAIDs, opioids, antidepressants, other antiepileptic drugs) [96]. Pregabalin may produce beneficial effects for patients with central and mixed neuropathic pain at doses of 300–600 mg daily [27]. Pregabalin may be an effective treatment for neuropathic pain but adverse effects on balance at initial doses and with dose increases may limit its use [16].

In patients with spinal cord injury-related central pain, there is conflicting evidence for the efficacy of gabapentin (≥1800 mg daily) and pregabalin. Lamotrigine was effective for incomplete spinal cord injury-related pain at and below the level of injury. The data for carbamazepine for central pain is mixed [107].

## Adverse Effects

Gabapentinoids are associated with adverse events. There is high level evidence supporting the risk of harms with these medications [34]. Gabapentin and pregabalin have significant adverse effects and lack significant evidence for pain improvement in patients with chronic low back pain [91]. Pregabalin is associated with

higher rates of adverse events than placebo [65]. Gabapentin's use is limited due to the adverse events, including somnolence, dizziness, peripheral edema, and gait disturbance [109].

Gabapentin and pregabalin most commonly can cause unsteadiness, constipation, diarrhea, word-finding difficulties, sedation, nausea, vomiting, and dry mouth. In some rare instances, gabapentin and pregabalin may cause psychiatric disturbances, including suicidal ideation, depression, anxiety, or violent or aggressive behavior.

The most common side effects experienced with topiramate include nausea, anorexia, weight loss, fatigue, and paresthesias.

Common adverse effects of carbamazepine include dizziness, drowsiness, dry mouth, tongue swelling, balance and coordination problems, nausea, and vomiting. Serious adverse effects include severe skin reaction (rash, Stevens-Johnson syndrome, and toxic epidermal necrolysis) as well as neutropenia. If carbamazepine is prescribed, white blood cell count should be monitored regularly during treatment.

Lamotrigine adverse effects include dizziness, headache, ataxia, nausea, blurred vision, somnolence, psychiatric disturbance (depression, anxiety, emotional lability, difficulty concentrating, nervousness), and rash.

## Dosing

See Table 8.4 for common dosing strategies for commonly used anticonvulsants.

The anticonvulsant medications are typically administered using titration schedule. These medications should be used with caution in patients who are taking other sedating medications, and patients should not take these medications with other sedating medications. In the elderly, side effects can be amplified, and anticonvulsants should be prescribed with caution.

**Table 8.4** Anticonvulsant dosing

| Medication | Route | Dosing | Maximum daily dose |
|---|---|---|---|
| Gabapentin | PO (IR) | 100–1200 mg tid, titrated | 3600 mg |
| Pregabalin | PO | 25–300 mg bid, titrated | 600 mg |
| Topiramate | PO (IR)<br>PO (ER) | 25–50 mg once to twice per day<br>25–100 mg daily | 100 mg<br>100 mg |
| Lamotrigine | PO | Depends on other anticonvulsants patient is concurrently taking | |
| Carbamazepine | PO (IR)<br>PO (ER) | 100–600 mg bid<br>400–800 mg daily (initial dose 200 mg daily) | 1200 mg<br>1200 mg |

*PO* oral, *IR* immediate release, *ER* extended release

## Muscle Relaxers

### Mechanism of Action

The mechanisms of action for the multiple classes of muscle relaxers are unknown. Each muscle relaxer may work through different mechanisms and may be more or less efficacious for patients on an individual basis.

Baclofen is a gamma-aminobutyric acid (GABA) agonist. The precise mechanism of action is unknown. It inhibits both monosynaptic and polysynaptic reflexes at the spinal level and may cause the hyperpolarization of afferent terminals. Other binding sites occur at the supraspinal level and contribute to its clinical effect.

Cyclobenzaprine acts primarily in the brainstem by activating locus ceruleus neurons, increasing the release of norepinephrine in the ventral horn of the spinal cord, leading to increased inhibitory action of norepinephrine on gamma and alpha motor neurons to reduce tonic somatic motor activity.

Methocarbamol act as a general central nervous system depressant and seems to have no direct action on the contractile mechanism of striated muscle, the motor end plate, or the nerves.

Metaxalone does not directly act on skeletal muscle and potentially acts through central nervous system (CNS) depression.

Tizanidine is a central alpha-2-adrenergic receptor agonist and reduces spasms through increased presynaptic inhibition of motor neurons.

Carisoprodol acts via CNS depression.

Benzodiazepines bind to a receptor on GABA-A complexes and increase the frequency of chloride channel opening, leading to an increased inhibitory effect of GABA on neuronal excitability.

### Evidence in Spine

Overall, muscle relaxers have mixed effects in treating spine related pain. In a meta-analysis, cyclobenzaprine was more effective than placebo in treating back pain, but the effect is modest, and the risk of adverse effects is significant so it should be used at the lowest effective dose and avoided in elderly [15]. In patients with nonspecific back pain, cyclobenzaprine is effective, and no difference was noted between 5 mg dosing or 10 mg dosing [14]. Once daily cyclobenzaprine ER has also been shown to be effective in treating neck and back pain due to muscle spasm [62].

The use of combination therapy with muscle relaxants and analgesic medications is conflicting. Some studies have shown that combination therapy of cyclobenzaprine with ibuprofen or naproxen has shown no benefit for neck pain or acute nontraumatic low back pain without radiculopathy [14, 20, 37]. In patients with acute, nontraumatic low back pain without radiculopathy, a combination of methocarbamol or orphenadrine with naproxen compared with naproxen plus placebo showed no benefit [36]. In addition to a lack of pain improvement, combination therapy with

baclofen, metaxalone, or tizanidine with ibuprofen failed to lead to an improvement in function as well in patients with acute low back pain [39]. In a randomized, double-blind, comparative efficacy clinical trial, the combination of diazepam and naproxen vs naproxen with placebo, did not improve functional outcomes or pain in patients with acute, nontraumatic, nonradicular low back pain [38]. However, Toth and Urtis [100] found that combination of muscle relaxers, including cyclobenzaprine, metaxalone, and carisoprodol, can be used with analgesic medications to achieve improved pain control. In addition, a double-blind, double-dummy, randomized, multicentric, comparative study showed that patients using combination tizanidine-aceclofenac had significant increases in spinal flexion and improved pain intensity for the treatment of acute low back pain [77]. Also, patients treated with tizanidine and tramadol resulted in improvement in pain at rest and with effort [87].

In patients with spasticity, multiple muscle relaxers have been found to be effective. In a systematic review found fair evidence for treatment with baclofen and tizanidine, and in patients with neck or back pain due to musculoskeletal conditions, there is fair evidence that cyclobenzaprine, carisoprodol, orphenadrine, and tizanidine are effective [22]. Tizanidine is a useful medication in patients suffering from spasticity due to spinal cord injury as well as in patients with chronic myofascial neck and back pain [61].

Another route of administration for the muscle relaxer baclofen is via an intrathecal pump. A retrospective questionnaire of patients who had undergone intrathecal baclofen pump insertion who suffered from chronic mechanical low back pain or failed back pain demonstrated that spinal drug administration systems seem to be of benefit in alleviating pain in these conditions [82].

## Adverse Effects

Skeletal muscle relaxants have been shown to be beneficial in nonspecific chronic low back pain, but adverse effects may limit their use [104].

The most common side effects reported with all muscle relaxants are sedation, dizziness, vertigo, headache, memory problems, gastrointestinal disturbance, dry mouth. Sudden cessation of baclofen may lead to life-treating withdrawal. Carisoprodol should be prescribed judiciously as it has addictive properties and may lead to substance abuse.

## Dosing

See Table 8.5 for common dosing strategies for commonly prescribed muscle relaxants.

Special care should be taken when prescribing muscle relaxants with other sedating medications. In the elderly, side effects can be amplified, and muscle relaxants should be prescribed with caution.

**Table 8.5** Muscle relaxant dosing

| Medication | Route | Dosing | Maximum daily dose |
|---|---|---|---|
| Baclofen | PO | 5–20 mg tid prn | 80 mg |
| | IT | 22–1400 mcg daily infusion | – |
| Cyclobenzaprine | PO | 5–10 mg tid prn | 30 mg |
| Methocarbamol | PO | 500–1500 mg 3–4 times per day prn | 4500 mg |
| | IV | 1000 mg tid prn | 3000 mg |
| Metaxalone | PO | 800 mg 3–4 times per day prn | 2400 mg |
| Tizanidine | PO | 2–16 mg tid prn | 36 mg |
| Carisoprodol | PO | 250–350 mg qid prn | 1400 mg |
| Diazepam | PO | 2–10 mg 3–4 times daily prn | – |
| | IV/IM | 5–10 mg q3–4h prn | – |

*PO* oral, *IT* intrathecal, *IV* intravenous, *IM* intramuscular, *prn* as needed, *tid* three times daily, *qid* four times daily

## Corticosteroids

### Mechanism of Action

Exogenous corticosteroids mimic the endogenous glucocorticoids produced within the hypothalamic-pituitary-adrenal axis. They bind to receptors in the cytoplasm and migrate into the nucleus where the receptor-steroid complex binds to the DNA and alters genetic synthesis of proteins. Multiple cellular functions are modified, including the production of enzymes that regulate metabolic processes as well as those that regulate the synthesis of inflammatory cytokines.

### Evidence in Spine

The evidence for use of corticosteroids in spine related pain is lacking. In a randomized, controlled trial, oral corticosteroids were more effective in pain relief than gabapentin or pregabalin in patients with lumbar radiating pain [53]. However, for patients with acute low back pain, prednisone and oral systemic corticosteroids provided no improvement in pain [35, 42]. Corticosteroids may be effective in treating radicular pain but likely are not effective for low back pain with or without radiculopathy.

### Adverse Effects

Short term use is usually well tolerated but can cause hypertension, hyperglycemia, flushing and warmth, and psychological effects, including anxiety, psychosis. Chronic use of corticosteroids can lead to a myriad of complications, including, osteoporosis, decreased immunity, suppression of the HPA axis with the possibility of acute adrenal insufficiency if the exogenous source is abruptly discontinued, postoperative delayed wound healing or infection, weight gain.

**Table 8.6** Corticosteroid dosing

| Medication | Route | Dosing | Maximum daily dose |
|---|---|---|---|
| Prednisone | PO | 6-day taper: 30 mg, 25 mg, 20 mg, 15 mg, 10 mg, 5 mg in divided doses | – |
| Methylprednisolone (off label) | PO | 6-day taper: 24 mg, 20 mg, 16 mg, 12 mg, 8 mg, 4 mg in divided doses | – |

*PO* oral, *IM* intramuscular

### Dosing

See Table 8.6 for common dosing strategies for commonly prescribed corticosteroids.

## Local Anesthetics

### Mechanism of Action

Local anesthetics decrease neuronal excitation by antagonizing sodium channels. Local anesthetics affect neuropathic pain.

### Evidence in Spine

Lidocaine infusions have been used in the treatment of chronic pain [68]. A review of patients with intractable neuropathic pain treated with lidocaine infusions demonstrated significant decrease in pain [111]. However, lidocaine infusion has not been shown to be an effective treatment for acute lumbar radicular pain [97] and was no more effective in treating neuropathic pain of failed back surgery syndrome than placebo [76].

Mexiletine is an oral form of a local anesthetic and is not commonly used due to its high rate of adverse effects. In a meta-analysis, mexiletine was found to be an effective treatment for neuropathic pain [101]. Typically, response to a lidocaine infusion is used to identify patients who may have a positive response to mexiletine treatment [17]. More studies need to be performed examining the efficacy of mexiletine and the risks of adverse effects prior to recommending its routine use in treating spine-related pain.

Topical lidocaine formulations may be effective for neuropathic pain. In patients with localized neuropathic pain who previously were unable to tolerate or failed to improve with other medications, including antiepileptics, antidepressants, and opioids, lidocaine medicated plasters were effective in relieving pain [63]. In patients with cervical radiculopathy, lidocaine 5% medicated plaster improved pain symptoms and allowed patients to started rehabilitative treatment with physical therapy sooner [67]. Lidocaine 5% medicated plaster may be a valuable additional approach for the management of neuropathic low back pain [9, 10]. Topical lidocaine formulations are typically well tolerated with a low rate of discontinuation due to adverse effects.

**Table 8.7** Local Anesthetic dosing

| Medication | Route | Dosing | Maximum daily dose |
|---|---|---|---|
| Mexiletine | PO | 150–900 mg daily | 900 mg |
| Lidocaine | IV: Infusion<br>TD: Patch<br>TD: Gel, cream, lotion, ointment | 5.5 mg/kg infused over 2 hours<br>4–5%, apply patch(es) for up to 12 hours within a 12-hour period. Patches may be cut<br>3–5%, apply a thin film to affected area 2–4 times a day | 5 mg/kg maximum of 3 patches at a time<br>20 g |

*PO* oral, *IV* intravenous, *TD* transdermal

### Adverse Effects

Lidocaine infusions are overall well tolerated with side effects resolving quickly with interruption or discontinuation of the infusion [66].

The most common adverse effects with IV formulations include dizziness, nausea, lightheadedness, ringing in the ears, hypotension, cardiac arrhythmias, and local anesthetic systemic toxicity, which can lead to cardiac arrest, and seizure. Side effects with mexiletine include GI upset, headache, blurred vision, dizziness, sedation, paresthesias, weakness, elevated liver function tests. Mexiletine has a high rate of nausea and dizziness, which can limit its clinical use. However, in a recent study, mexiletine seemed to be well tolerated in its use to treat neuropathic pain [86]. Topical lidocaine can produce localized reactions after application.

### Dosing

See Table 8.7 for common dosing strategies for commonly used local anesthetics.

## Opioids

### Mechanism of Action

Opioids exert their effects through binding to mu, delta, and kappa G-protein-coupled receptors, which are widely distributed within the CNS and peripheral nervous system. The range of effect produced by opioids depends on the type and location of the receptor that is stimulated. Agonists of the mu receptors cause analgesia but also leads to sedation, respiratory depression, bradycardia, nausea, vomiting, and a reduction in gastric motility. Activation of the delta receptors causes spinal and supraspinal analgesia and reduced gastric motility. Activation of the kappa receptor produces spinal analgesia, diuresis, and dysphoria. Activation of all of these receptors leads to a net effect of cellular hyperpolarization and reduced neurotransmitter release [79].

Tramadol is an atypical opioid and in addition to its opioidergic effects, also has noradrenergic and serotonergic actions. It also has modulatory effects on several

mediators in pain signaling, such as voltage-gated sodium channels, V1 channels, glutamate receptors, alpha2 adrenoreceptors, adenosine receptors, and mechanisms involving substance P, calcitonin gene-related peptide, prostaglandin E2, and proinflammatory cytokines. Because of its broad spectrum of targets, tramadol can be used to relieve a broad range of pain, including low back, osteoarthritic, and neuropathic pain. In addition, tramadol has anxiolytic and antidepressant effects that improve pain outcomes [8].

Buprenorphine is a unique opioid that is a partial agonist at the mu receptor and a weak kappa receptor antagonist and delta receptor agonist.

The available pharmacologic formulations of opioids are divided into three categories: natural (morphine, codeine, thebaine), semi-synthetic (hydromorphone, hydrocodone, oxycodone), and synthetic (tramadol, methadone, fentanyl, tapentadol).

## Evidence in Spine

The evidence for use of opioids in the treatment of spine-related pain is conflicting. In most cases, the evidence suggests that the utility of opioids is limited in the treatment of spine-related pain due to its significant amount of adverse effects and addictive properties and if used, should not be used as a first line treatment option. In a randomized clinical trial in patients with chronic back, hip, or knee osteoarthritis pain, immediate-release opioids (morphine, oxycodone, or hydrocodone/acetaminophen) was not superior to nonopioid (acetaminophen or NSAID) in achieving pain relief at 12 months [55]. A systematic review and meta-analysis of placebo-controlled randomized controlled trials showed moderate quality evidence that opioids reduce pain in the short term. However, clinically relevant pain relief was not observed within a dose range of 40–240 mg morphine equivalents per day. Evidence for long-term efficacy is lacking, and the efficacy of opioid use for acute low back pain is unknown [1]. In a Cochrane Review, there is some evidence for the use of short-term opioids to treat chronic low back pain. However, the trials that compare opioids to NSAIDs or antidepressants did not show any differences did not show any significant differences regarding pain and function. There are no randomized controlled trials using opioids versus placebo to support the efficacy and safety of long-term opioid therapy to treat chronic low back pain [18]. In a Cochrane review, there is insufficient evidence to support or refute that morphine is efficacious for the treatment of neuropathic pain [25].

Combination of opioids with other analgesics has not been shown to be beneficial for spine-related pain treatment. The addition of oxycodone/acetaminophen to naproxen did not improve functional outcomes or pain in patients with acute nontraumatic low back pain without radiculopathy [37]. In a Cochrane Review, there is insufficient evidence to support or refute the use of paracetamol in combination with codeine or dihydrocodeine for neuropathic pain [110].

Tramadol is an opioid with some unique properties and may be more efficacious in treating spine-related pain. When used as part of combination treatment, the combination of tramadol and dexketoprofen resulted in effective treatment for nonspecific acute low back pain, higher compliance, fewer side effects, and less rescue-drug use [81], and the combination of tramadol with NSAID may decrease

the incidence of adverse events and may help prevent the transition of acute low back pain to chronic low back pain [48]. In patients with chronic low back pain, tramadol extended release (ER) was found to be more effective in treating pain than placebo [105]. In a randomized, double-blind, placebo-controlled, parallel-group study, tramadol ER was more effective than placebo in providing pain relief, functional improvements, and improved quality of life in patients with chronic low back pain [56]. Tramadol may also improve other comorbidities that often accompany pain. In a retrospective case-control study of patients with chronic low back pain, tramadol and acetaminophen versus celecoxib alone was more effective in conferring a motivational effect while also being effective in reducing chronic low back pain [99]. The combination of tramadol-acetaminophen was more effective than NSAIDs at in treating pain and also conferred an antidepressant effect that NSAIDs did not [98]. However, in a systematic review, there was no reliable indication for the use of tramadol to treat neuropathic pain [31].

A few studies have demonstrated that long acting opioids may be effective in spine-related pain. Once daily hydrocodone has been shown to be efficacious in treating uncontrolled moderate to severe chronic low back pain and was generally well tolerated [108]. In another study, oxycodone controlled-release was more effective than placebo in providing pain relief and improvements in quality of life and quality of sleep. However, oxycodone had significantly more side effects than placebo [60]. In addition, tapentadol prolonged release was more effective in treating neuropathic pain symptoms and at improving global health status than oxycodone/naloxone prolonged release and had improved gastrointestinal tolerability [9, 10].

A couple of opioids are available in transdermal and buccal formulations that bypass first pass metabolism. Buprenorphine buccal film has been effective in treating moderate to severe pain in patients with chronic low back pain [83], and transdermal fentanyl was noninferior to gabapentin for the treatment of lumbar radicular pain in terms of pain reduction with no difference in patient functional status, depressive symptoms, and the occurrence of adverse events [47].

Opioids may provide a synergistic effect when used in combination with other medications. In patients with chronic low back pain with or without leg pain, tramadol plus paracetamol versus placebo and buprenorphine plus pregabalin versus buprenorphine alone provided significant reduction in pain intensity [64].

Opioids can also be administered via intrathecal pump and may have some neuromodulatory effects. This will be further discussed in the neuromodulation chapter.

## Adverse Effects

The medium- and long-term use of opioids for chronic non-cancer pain is associated with a number of adverse events, including serious events [33]. The most common side effects of opioids include sedation, dizziness, nausea, vomiting, constipation, physical dependency, tolerance, addiction, and respiratory depression. Overdose can cause severe and life-threatening respiratory depression.

**Table 8.8** Opioid dosing

| Medication | Route | Dosing | Maximum daily dose |
|---|---|---|---|
| Codeine | PO | 15–60 mg q4–6h prn | 360 mg |
| Tramadol | PO (IR)<br>PO (ER) | 50–100 mg q4–6h prn<br>100 mg daily | 400 mg<br>300 mg |
| Morphine | PO (IR)<br>PO (ER) | 15–30 mg q4–12h prn<br>Once or twice daily dosing depending on formulation | –<br>– |
| Hydrocodone | PO (IR)<br>PO (ER) | 2.5–10 mg q4–12h prn<br>Once daily dosing | –<br>– |
| Oxycodone | PO (IR)<br>PO (ER) | 2.5–30 mg q4–12h prn<br>Twice daily dosing | –<br>– |
| Hydromorphone | PO (IR)<br>PO (ER) | 2–4 mg q4–12h prn<br>Once daily dosing | –<br>– |
| Methadone | PO | 10 mg 2–3 times daily | – |
| Fentanyl | TD: Patch | 12.5–100 mcg/h q72h | – |
| Tapentadol | PO (IR)<br>PO (ER) | 50–100 mg q4–6h prn<br>50–250 mg bid | –<br>– |
| Buprenorphine | Buccal<br>TD: Patch | 75–900 mg bid<br>5–20 mcg/h q7d | 1000 mg<br>20 mcg/h |

*PO* oral, *IR* immediate release, *ER* extended release, *TD* transdermal, *bid* twice daily, *prn* as needed

Aside from common side effects, in patients with chronic pain, night-time sleep disturbance is common and may be exacerbated by opioid treatment. In comparison to patients receiving non-opioid medications for chronic back pain, patients taking opioid medications (>100 mg morphine equivalent per day) for chronic back pain demonstrated distinctly abnormal brain activity during sleep [84].

### Dosing

See Table 8.8 for commonly prescribed opioid dosing strategies.

## Capsaicin

### Mechanism of Action

Topical capsaicin is an agonist for TRPV1 receptors, which are activated by high temperatures, pH <6.0, or a combination of the two. TRPV1 receptor activation leads to depolarization of C and A delta fibers, leading to a sensation of warmth, burning, stinging, or itching. Capsaicin generates a persistent effect and increases calcium permeability at multiple levels. Sustained high levels of intracellular calcium activates proteases and an induce the depolymerization of microtubules. High levels of intracellular calcium and chloride lead to osmotic swelling. An additional effect of capsaicin is to disrupt mitochondria respiration. The combination of these actions leads to impaired local nociceptor function and desensitization [4].

### Evidence in Spine

Capsaicin comes in a topical formulation that can be helpful in the treatment of neuropathic pain. Topical capsaicin capsaicin 8% patch may be a valuable additional approach for the management of neuropathic low back pain [9, 10]. Application of a high-dose capsaicin 8% patch within innervated territories helped to alleviate painful radiculopathy [11]. However, capsaicin's use is limited due to its high incidence of discontinuation due to intolerable adverse effects.

### Adverse Effects

Capsaicin typically does not systemic effects but can cause localized erythema, induration, burning, itching, and pain. Rare side effects include cardiac dysrhythmias and hypertension.

## N-Methyl-D-Aspartate (NMDA) Receptor Antagonists

### Mechanism of Action

Ketamine is the most commonly known and used NMDA receptor antagonist and alters the actions of glutamate.

### Evidence in Spine

Ketamine is most commonly used as an intravenous (IV) infusion in the treatment of pain. For patients with acute pain, ketamine may help to attenuate pain unrelieved by other modalities. In patients with acute pain who became tolerant to opioids and not achieving adequate pain control, ketamine could be used as an adjuvant for severe intractable pain [19]. In patients with acute pain, including low back pain, who presented to the emergency room, low dose-ketamine produced a significant analgesic effect within 5 minutes of administration and provided a moderate reduction in pain for 2 hours. However, this reduction in pain was not superior to morphine when analyzed using the numeric rating scale [69].

Ketamine infusions may be helpful in the treatment of chronic pain and may be aid in decreasing opioid medications. In a review analyzing previous trials of ketamine as a single dose, continuous infusion, patient-controlled analgesia, epidural ketamine with opioids, and studies in children, IV PCA with ketamine versus morphine alone did not improve analgesia. IV infusion or single bolus dose of ketamine resulted in a decrease in opioid requirements in a majority of studies, and a majority of trial with epidural ketamine showed beneficial effects. Low dose

ketamine may be a useful adjuvant in pain treatment [95]. In a retrospective analysis evaluating the efficacy of outpatient IV ketamine infusions for chronic intractable pain, patients obtained a significant decrease in visual analog scale (VAS) score and half of the patients had relief lasting up to 3 weeks with minimal side effects [80]. In patient with chronic whiplash associated pain, 7 out of 20 patients had no improvement with any of the interventions (placebo, placebo/remifentanil, ketamine/placebo, ketamine/remifentanil) but in the patients who did respond, the combination of ketamine and remifentanil showed an analgesic effect on habitual pain and ketamine seemed to enhance the effect of remifentanil on electrical pain thresholds [58].

Topical ketamine has been used to treat neuropathic pain, including lumbar radiculopathy, and patients reported a significant decrease in numerical analogue scale after initial application as well as alterations in temperature sensation, feelings of relaxation, and decreased tension in the area of relaxation. Ketamine gel may be a potential option for patients with chronic neuropathic pain [40].

### Adverse Effects

At low doses, ketamine is relatively well tolerated. Adverse effects include depressed mental state, feelings of detachment, slurred speech, hallucinations, dizziness, and nystagmus. Other more serious effects include, chest pain, hypertension, changes in heart rate, amnesia, coma, delirium, hyperthermia, seizures, nausea and vomiting, changes in respiratory rate, salivation, laryngeal spasm, anxiety, and muscle rigidity.

## Tumor Necrosis Factor (TNF) Inhibitors (Anti-TNF)

### Mechanism of Action

Anti-TNF medications suppress the immune system by blocking the action of TNF, which is a substance that leads to inflammation and auto-immune diseases.

### Evidence in Spine

Etanercept is an anti-TNF medication that has been used in patients with axial spondyloarthritis. In this patient population, it seems to slow the progression of sacroiliac joint changes compared to patients not receiving biologics [30] and has been shown to reduce spine and sacroiliac joint inflammation via MRI imaging [43]. In patients with rheumatologic etiologies of spine-pain, anti-TNF medications may be helpful in preventing progression of the disease and evaluation for disease modifying agents may be warranted.

### Adverse Effects

The most common side effects of etanercept include GI disturbance (nausea, vomiting, abdominal pain, diarrhea, gastroesophageal reflux), headache, weight changes, weakness, and pain or discomfort at the injection site. Other serious side effects can include seizures, swelling, rash or skin changes, increased risk of infection, GI bleed, joint pain or swelling.

## Prostaglandin E1 (PGE1) Derivatives

### Mechanism of Action

PGE1 derivatives are agonists of the E1 receptor, a G-protein receptor. PGE1 is a vasodilator and causes angiogenesis. It is thought that the improvement in circulation exerts an analgesic effect [50].

### Use in Spine

Limaprost has been used to treat pain due to lumbar spinal stenosis in Japan. Limaprost has also been shown to be effective in treating neuropathic pain [50]. In patients with cervical spondylotic radiculopathy, limaprost was superior to pregabalin in treating arm numbness [74]. Although it is not approved to treat pain in the United States currently, PGE1 derivatives may be an option for patients who fail to improve with other treatments.

### Adverse Effects

The most common adverse effects include headache, flushing and GI disturbance (diarrhea, nausea, vomiting, and abdominal pain).

## Other

There is a paucity of literature evaluating the efficacy of topical agents for the use of radicular pain. Topical compound formulations may provide localized delivery of medications without the adverse effects that may limit the use of systemic formulations in patients. Safaeian et al. [88] describe the use of topical formulation compound cream composed of diclofenac, ibuprofen, baclofen, cyclobenzaprine, bupivacaine, gabapentin, and pentoxifylline (T7) as an effective treatment for radicular pain.

## Conclusion

Many pharmacologic therapies have some evidence for effectiveness in treating chronic and acute low back pain [21]. However, the effects of pain reduction and improvement in function is typically small to moderate and is typically only short lasting [54]. Pharmacological treatment is often based on tradition and personal experience as the literature is lacking in studies that can be used to formulate evidence-based guidelines [71]. Multiple guidelines have been published regarding medication management for the treatment of pain [7, 12, 23, 85, 102]. However, significant differences between guidelines in terms of attitude towards pharmacotherapy, analgesics of first choice, and recommendations for or against the prescription of specific pharmacological treatments exist [90]. One overarching recommendation is that opioids should only be considered a last resort option in cases that all other pharmacological options have failed and after a discussion of risks and benefits has occurred. Of the medications available, type of pain (nociceptive versus neuropathic), diagnosis and origin of pain, safety profile, and patient-specific issues (ex. past medical history and past experiences with similar medications) are important factors that should influence medication choice should pharmacologic intervention be warranted.

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