

## Non-Analgesics for Pain Management

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Due to the adverse impact of prolonged long term opiate therapy including overdose, abuse, and dependence, there is increased interest in alternative therapies to manage chronic non-cancer pain.<sup>1</sup> Antidepressants and antiepileptics are two classes of medications that have been studied in neuropathic and other chronic pain conditions. The interpretation of pain trials is difficult to a number of potential biases in study design. Most of the trials are of short duration with a small number of subjects. In addition to evaluating the risk of potential biases, it is difficult to compare studies because randomized controlled trials (RCTs) differ substantially in research design.<sup>2</sup> The outcomes have also varied; newer RCTs have used measures such as daily numeric ratings of pain intensity and measures of health-related quality of life that were not collected in many older RCTs.<sup>3</sup> In general, most trials of effective treatments have found that less than 50% of patients achieve satisfactory pain relief.<sup>3</sup> The focus of this review will be on the comparative safety and effectiveness of non-analgesics such as antidepressants, antiepileptics and topical lidocaine used to manage various pain conditions outlined in **Table 1**.

**Table 1. FDA approved pain indications for selected medications<sup>4-8</sup>**

Condition	Duloxetine	Milnacipran	Gabapentin	Pregabalin	Carbamazepine	Topical Lidocaine
Diabetic Neuropathy	X			X		
Postherpetic Neuropathy			X	X		X
Fibromyalgia		X		X		
Chronic Musculoskeletal Pain						
Trigeminal Neuralgia					X	
Neuropathic pain associated with spinal cord injury				X		

### Tricyclic Antidepressants in Neuropathic Pain

Tricyclic antidepressants, which include amitriptyline, imipramine, nortriptyline and desipramine, have been shown to be effective in the off-label treatment of a variety of painful neuropathic conditions including diabetic peripheral neuropathy (DPN), post-herpetic neuropathy (PHN), polyneuropathy, and post-stroke pain.<sup>9</sup> Guidelines for neuropathic pain prefer nortriptyline and desipramine, over amitriptyline because they provide comparable pain relief while causing fewer anticholinergic side effects.<sup>3</sup>

The most recent Cochrane review evaluating the safety and efficacy of amitriptyline in neuropathic pain was published in 2015.<sup>10</sup> In a pooled analysis from the DPN, PHN and mixed neuropathic pain trials (n=382, 4 trials), amitriptyline was shown to be more beneficial than placebo in managing neuropathic pain (Relative Risk (RR) 2.0; 95% CI 1.5 to 2.8).<sup>10</sup> Due to the small sample size in many of these studies, they are at high risk for bias which compromises the quality of the evidence. More participants who received amitriptyline experienced at least one adverse event compared to placebo (55% vs. 36%, respectively; RR 1.5; 95% CI 1.3 to 1.8).<sup>10</sup> The number needed to harm (NNH) for one additional harmful outcome was 5 (95% CI 3.6 to 9.1).<sup>10</sup> Serious adverse events were rare.

A 2014 Cochrane review examined the efficacy of desipramine in 5 studies that treated 177 participants with DPN or PHN.<sup>11</sup> Desipramine doses ranged from 100 mg to 150 mg once daily following titration. Low quality evidence in individual studies indicated some improvement in pain relief with desipramine compared with placebo. There was insufficient data for active treatment comparisons.<sup>11</sup> Participants taking desipramine experienced more adverse events, and a higher rate of withdrawal due to adverse events, than did participants taking placebo.<sup>11</sup>

In summary, very low quality evidence demonstrates the marginal benefit of TCAs in managing neuropathic pain. Most of these studies are older and contain methodological deficiencies which makes it difficult to apply their results to patient care.

In addition, the adverse effects of TCAs, particularly in elderly patients, are well documented and limit their use. The possibility of over sedation leading to increased risk of falling and possible bone fracture is particularly problematic in older patients.

### Serotonin and Norepinephrine Reuptake Inhibitors in Neuropathic Pain

Another class of antidepressants, the serotonin and norepinephrine reuptake inhibitors (SNRIs), has also shown efficacy in treating peripheral neuropathic pain and other chronic pain conditions.<sup>3</sup> Specific SNRI's studied in pain management include duloxetine, milnacipran, and venlafaxine. Only duloxetine and milnacipran have FDA approved indications for treating specific pain conditions as summarized in **Table 1**. Milnacipran does not have FDA approval for management of depression and is only indicated for treatment of fibromyalgia. Although venlafaxine has been studied in pain management, it is primarily used to treat depression. Duloxetine has emerged as the SNRI with the most evidence to support its use in managing a variety of pain conditions including neuropathy, fibromyalgia, and chronic musculoskeletal pain.

A 2014 Cochrane review assessed the benefits and harms of duloxetine in treating painful neuropathy and chronic pain.<sup>9</sup> Duloxetine 60 mg once daily was shown to be effective compared to placebo in treatment of painful DPN, with a RR for ≥ 50% pain reduction at 12 weeks of 1.73 (95% CI 1.44 to 2.08).<sup>12</sup> The estimated NNT was 5 (95% CI 4 to 7).<sup>9</sup> When compared to placebo in 48 patients with central neuropathic pain, duloxetine showed no effect in improving pain over 12 weeks as measured on a 1-10 Visual Analog Scale (VAS) (Mean Difference (MD) -1.0; 95% CI -2.05 to 0.05).<sup>9</sup> Adverse events were common in both treatment and placebo arms but more common in the treatment arm, with a dose-dependent effect.<sup>9</sup> Serious adverse events were rare. However, 12.6% of trial participants stopped duloxetine due to adverse effects.<sup>12</sup> Moderate quality evidence supports the efficacy of duloxetine in treating DPN when compared to placebo. Adverse effects such as nausea, drowsiness, dry mouth and constipation increase when patients are titrated up to 120 mg per day of duloxetine.

### Antiepileptics in Neuropathic Pain

The first antiepileptic used in clinical trials to treat a neuropathic pain disorder was carbamazepine. Carbamazepine and its derivative oxcarbazepine are used for the treatment of trigeminal neuralgia, but have not been shown to be as effective in treating other neuropathic pain disorders.<sup>3</sup> Gabapentin and pregabalin have both been shown to be effective when compared with placebo in treating painful DPN, PHN, polyneuropathy, neuropathic cancer pain, central post-stroke pain, and spinal cord injury pain.<sup>3</sup> Other antiepileptic drugs such as topiramate, valproic acid, levetiracetam, zonisamide, tiagabine and lamotrigine have been studied for various neuropathic pain disorders; however, evidence of their effectiveness is lacking.<sup>3</sup> A 2007 systematic review of lamotrigine for acute and chronic pain concluded it does not have a place in the treatment of pain, given other more effective therapies.<sup>13</sup>

A 2013 Cochrane review assessed the evidence for antiepileptics in treatment of neuropathic pain.<sup>11</sup> Ninety-one studies including 17,955 subjects were included in the review. Antiepileptics studied for management of neuropathic pain included carbamazepine, gabapentin, lacosamide, lamotrigine, oxcarbazepine, pregabalin, topiramate, and valproic acid. Most of the studies were conducted over short durations (i.e., 6 weeks) in small sample sizes.

Trials for gabapentin versus placebo in DPN utilized a wide range of doses from 600 to 3600 mg per day to reduce pain intensity by 50% from baseline (RR 1.8; 95% CI 1.4-2.2) with a NNT of 5 (95% CI 4.3-9.0).<sup>14</sup> In contrast, relief of PHN with gabapentin required higher daily doses (1800-3600 mg) for at least a 50% reduction in pain intensity compared to placebo (RR 1.7; 95% CI 1.3-2.2) with a NNT of 8 (95% CI 6-14) in 3 studies comprised of 892 subjects.<sup>11</sup> Pregabalin 300

mg and 600 mg once daily gave similar results relative to placebo in reducing PHN pain intensity by 50% from baseline (RR 2.7; 95% CI 1.9-4.0 and RR 2.8; 95% CI 2.0-3.9, respectively).<sup>11</sup> For relief of central neuropathic pain, the only data available was with pregabalin 600 mg once daily. In 2 studies with a total of 176 patients, pregabalin compared to placebo showed a 50% pain reduction with a RR of 3.6 (95% CI 1.5-8.4) and NNT of 6 (95% CI 4-14).<sup>11</sup> Moderate quality evidence indicated little or no effect for lamotrigine, oxcarbazepine and topiramate in treatment of neuropathic pain.<sup>11</sup> There was insufficient evidence of efficacy for valproic acid, lacosamide, levetiracetam, and phenytoin in treatment of neuropathic pain.<sup>11</sup> Withdrawals due to adverse events were much higher with antiepileptics than placebo except for carbamazepine, where studies were of short duration, and for the low dose of pregabalin 150 mg once daily.<sup>11</sup> Numbers needed to harm (NNH) decreased as doses increased for pregabalin and lacosamide. About 80% of participants experienced an adverse event with an antiepileptic, compared to about 70% of participants receiving placebo.<sup>11</sup>

Moderate quality evidence supports the utilization of gabapentin and pregabalin in managing peripheral neuropathic pain. Pregabalin has the additional FDA indication to manage central neuropathic pain due to spinal cord injury. Carbamazepine is FDA approved for treating trigeminal neuralgia. Of note, patient withdrawals due to adverse effects with the antiepileptics were higher compared to placebo. Significant adverse effects include central nervous system depression, dry mouth, blurred vision, and peripheral edema.

#### Lidocaine Patch in Neuropathic Pain

The lidocaine patch is approved for relief of pain associated with PHN.<sup>7</sup> The FDA approval was based on one unpublished trial in a single dose study in 35 PHN patients whose pain intensity was monitored over 12 hours.<sup>6</sup> After reviewing the initial study, the FDA requested more data. Therefore, an additional open label, multiple dose, 2-week treatment trial was conducted in 32 subjects who had responded in the previous study. Statistically significant differences favoring the lidocaine patch over observation (no treatment) were noted in terms of time to exit from the trial (14 versus 3.8 days;  $p < 0.001$ ).<sup>7</sup> A 2014 Cochrane review found insufficient evidence to support the use of topical lidocaine formulations for peripheral neuropathic pain.<sup>15</sup>

#### Pharmacologic Treatments for Lower Back Pain

A 2016 Agency for Healthcare Research and Quality (AHRQ) report of noninvasive treatments for lower back pain (LBP) evaluated systematic reviews of pharmacologic treatments for nonradicular or radicular LBP.<sup>16</sup> Most of the trials enrolled patients with pain symptoms of at least moderate intensity (> 5 on a 0-10 numeric rating scale for pain).<sup>15</sup> Pain intensity was the most commonly reported outcome. Pharmacological treatments included nonsteroidal anti-inflammatory drugs, acetaminophen, opiates, muscle relaxants, antiepileptics, and antidepressants.<sup>15</sup> For LBP, one systematic review found no differences in pain between TCAs and placebo (4 trials; Standardized Mean Difference (SMD) = -0.10; 95% CI -0.51 to 0.31;  $I^2 = 32\%$ ).<sup>15</sup> Three placebo-controlled trials of moderate quality evaluated duloxetine in management of chronic LBP and found duloxetine was associated with lower pain intensity (differences: 0.58 to 0.74 on a 0-10 scale) and better function (differences 0.58 to 0.74 on the Brief Pain Inventory-Interference on a 0-10 scale) than placebo.<sup>15</sup> No studies compared TCAs with duloxetine. Moderate quality evidence showed TCAs were associated with high risk of adverse events compared with placebo, although there was no difference in the risk of serious adverse effects.<sup>15</sup> There was insufficient evidence to evaluate the effect of antiepileptics on controlling acute nonradicular LBP.<sup>15</sup>

#### Guidelines

The International Association for the Study of Pain (IASP) 2015 guidelines support the use of pregabalin, gabapentin, and duloxetine as first line agents for treatment of neuropathic pain based on their panel's assessment of high quality evidence.<sup>16</sup> Moderate to low quality evidence supports the use of TCAs as first line agents in managing neuropathic pain. Lidocaine patches are no longer recommended as first line agents due to the weak quality of evidence supporting their efficacy.<sup>16</sup> The National Institute for Health and Care Excellence (NICE) 2014 guidelines support IASP recommendations.<sup>17</sup>

#### Conclusions

Most of the studies evaluating treatment of pain are small, of short duration, and may overestimate treatment effect, so they are graded as low to moderate quality. Moderate quality evidence supports the safety and efficacy of duloxetine and pregabalin as alternatives to morphine in managing several non-cancer pain conditions including DPN, PHN and central neuropathic pain. Duloxetine has also shown to be marginally effective in managing lower back pain. Although the TCAs may be considered as morphine alternatives to managing pain, their adverse effects often limit patient satisfaction.

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