

Pharmacotherapy of Neuropathic Pain—The Evidence

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Neuropathic pain (NP) is defined as pain initiated or caused by a primary lesion or dysfunction of the nervous system.¹ The underlying pathophysiology is complex and often multifactorial. Central and/or peripheral mechanisms play a role, as do many etiologies such as toxins, infections, trauma, connective tissue disorders, cancer, nutritional and metabolic deficiencies, nerve compression syndrome and diseases of the peripheral nerves. The hallmarks of NP are paresthesias and dysesthesias. The two major types of NP include: 1) evoked pain (e.g. hyperalgesia and allodynia) and 2) spontaneous pain (e.g. shooting, lancinating, and burning).

Despite advances in research, mechanism-based and evidence-based treatments of NP are lacking. Currently there are no specific treatment guidelines available. As a result, treatment of NP is challenging and requires a multidisciplinary and multimodal approach, including nonpharmacologic therapy (e.g. education, rehabilitation, psychosocial therapy), interventional therapy, and pharmacotherapy. Prior to instituting drug therapy, the following should be conducted: 1) patient education on pain mechanisms and mechanism-based treatment, 2) establishing reasonable treatment goals (i.e. complete relief may not occur and drugs may take several weeks before benefit is evident), 3) addressing physical deconditioning, insomnia, and psychosocial comorbidities, and 4) a comprehensive review of previous treatment regimens including dosing, dose escalation, and tolerability.

When instituting drug therapy, clinicians should administer adequate trials (usually 6-8 weeks) of first-line agents. Doses should be escalated until intolerable adverse effects occur or until they are considered efficacious. Eleven-point pain visual analog tools and pain diaries are recommended for routine evaluation and monitoring of mutually-accepted treatment outcomes. Although not always possible, the best approach is to avoid simultaneous dose adjustments of different drugs and/or initiation of drugs to best evaluate response to individual agents. The simultaneous initiation and/or adjustment of medications make it nearly impossible to accurately assess efficacy and tolerability. This review will focus on the evidence and treatment approach of non-analgesic pharmacotherapy. Other valuable treatment options, including the lidocaine patch, will not be addressed in this article.

Non-analgesic pharmacotherapy is divided into two drug classes: antidepressants and anticonvulsants. Current FDA-approved medications include carbamazepine (trigeminal neuralgia), gabapentin (postherpetic neuralgia), duloxetine (diabetic peripheral neuropathy), and pregabalin, which is not yet available (diabetic peripheral neuropathy and postherpetic neuralgia). The following section, including Table 1, describes the evidence and appropriate use of antidepressants and anticonvulsants in the treatment of NP.

Evaluating the Evidence

Antidepressants

Based on the results of several randomized placebo-controlled trials, tricyclic antidepressants (TCAs) offer treatment options for both diabetic peripheral neuropathy (DPN) and postherpetic neuralgia (PHN).^{1,2,3} A quantitative systematic review published in 2000 reviewed all of the well-designed published trials of TCAs for DPN and PHN. This pooled analysis identified the number needed to treat (NNT= the number of patients who need to be treated in order to prevent one additional bad outcome) for at least 50% pain relief as 3.5 (2.5-5.6).⁴ TCAs have a number of side effects including dry mouth, constipation, urinary retention, and sedation. More serious adverse effects including postural hypotension, heart block, arrhythmias, and hip fractures can also occur. Avoid use in patients with untreated cardiac conduction disturbances. To

minimize medication intolerance, it is best to start TCAs at lower doses and titrate to the effective dosage range (typically 50-150mg/day). Tertiary amines, including nortriptyline, are associated with fewer anticholinergic side effects and are better tolerated.

Of the newer antidepressants, only the selective serotonin and norepinephrine reuptake inhibitor (SNRI) duloxetine has been FDA approved for the treatment of NP. Evidence supporting the efficacy of duloxetine comes from one published and one unpublished randomized, placebo-controlled trial (Studies XII and XIII, respectively).^{5,6} These studies were both fixed dose, routine care (patients were allowed up to 4g of acetaminophen daily) trials over 12-weeks. Duloxetine was superior to placebo in reducing 24-hour average pain scores on an 11-point Likert scale, but the reduction was moderate (average 2.7-2.9 points).^{5,6,7} The NNT for a 50% improvement in pain was 4 in Study XII. There was no statistically significant difference in the calculated relative benefit in Study XIII.⁵ In both studies, duloxetine failed to demonstrate benefit over placebo for the secondary outcome measure of dynamic allodynia.⁶ In addition, further titration may not be necessary as both studies found that there was no statistically significant difference between duloxetine 60mg QD and 60mg BID.⁶ Common adverse events included nausea, dry mouth, constipation, dizziness, fatigue, somnolence and sexual dysfunction. Duloxetine also increases the risk of elevation of serum transaminase levels and it is recommended that it not be administered to patients with any level of hepatic insufficiency. Future head to head trials comparing duloxetine to TCAs may help define its specific role in the treatment of NP. Until these studies are available, current data does not suggest any advantage in effectiveness to using duloxetine over TCAs, however because it does not appear to affect cardiac conduction, duloxetine may be preferred in elderly patients and those with cardiac disease. Finally, although often trialed, selective serotonin reuptake inhibitors (SSRIs) have not been proven effective for NP and should not be used first-line.^{3,4}

Anticonvulsants

Many of the anticonvulsant medications have been used for the treatment of NP. The Drug Effectiveness Review Project (DERP) produced a final report in December 2004 that reviewed the use of antiepileptic drugs in NP. They found no clear evidence of superior effectiveness of one antiepileptic drug over another.⁸ In addition, a systematic review comparing the relative efficacy of anticonvulsants (gabapentin, carbamazepine and phenytoin) and antidepressants (TCAs and SSRIs) concluded that TCAs and anticonvulsants were generally equivalent with NNT for at least 50% pain relief of 3.4 and 2 for DPN and 2.1 and 3.2 for PHN respectively.⁴ Traditionally, carbamazepine has been used for the treatment of trigeminal neuralgia and DPN. Its side effect profile and risk for serious harm often makes this drug less preferable to second-generation anticonvulsants such as gabapentin.⁹ The use of gabapentin in the treatment of NP is well supported in the clinical literature.¹⁰ In a head-to-head trial comparing gabapentin to amitriptyline, both drugs were found to be equally effective and equally tolerated in the treatment of DPN.¹¹ Due to its good safety data and freedom from drug interactions, gabapentin may be preferred to TCAs in certain patient populations, especially the elderly.¹²

The newest anticonvulsant, pregabalin is structurally and mechanistically similar to gabapentin. In randomized placebo-controlled trials, pregabalin at doses of 300 and 600mg/day (divided TID) was effective for the treatment of painful diabetic neuropathy^{13,14,15} and postherpetic neuralgia^{16,17,18} with a NNT of 3.45 and 3.33 respectively. The most frequent adverse effects were somnolence, dizziness, and peripheral

edema. Until head-to-head comparisons have been made, there appear to be no advantages to using pregabalin over gabapentin.

A limited number of studies reviewing the use of lamotrigine in DPN have been published.¹⁹ The only double-blind, placebo-controlled, randomized trial (n=59) demonstrated a modest, but significant, reduction in pain intensity scores compared to placebo at doses ranging from 200 to 400mg/day.²⁰ Lamotrigine failed to demonstrate superiority over placebo on two secondary outcome pain scales. Due to its adverse effect profile (e.g. potential for life-threatening rash) and relative lack of effectiveness data, lamotrigine is not recommended first-line for the treatment of neuropathic pain.

Conclusion

Neuropathic pain is a relatively common and debilitating diagnosis that is associated with a variety of etiologies. Tricyclic antidepressants and certain anticonvulsants can be used as first-line analgesics. The efficacy and side effect burden between the two drug classes is equivalent. The newer medications, including the antidepressant duloxetine and anticonvulsant pregabalin, do not appear to offer significant advantages over the traditionally used agents.

Reviewed by Gregory Johnson M.D., Willamette Falls Immediate Care, Sue Millar Pharm.D., Portland VA Medical Center; Francine Goodman Pharm.D., Southern California Evidence-based Practice Center; Brett Stacey, M.D., OHSU.

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Table 1. Recommended Agents for the Treatment of NP

DRUG	NNT FOR ≥50% REDUCTION IN PAIN SEVERITY	BEGINNING/TITRATION MAX DOSES	TREATMENT CONSIDERATIONS	COST*
Amitriptyline	Pooled TCAs & SSRIs: ⁴ DPN – 3.4 PHN – 2.1 Pooled TCAs for both indications combined: ⁴ 3.5 (2.5-5.6)	-10-25mg QHS -Increase by 10-25mg q 3-7 days as tolerated. -Max=200mg/day.	-Adequate trial is 6-8 weeks with at least 1-2 weeks at maximum tolerated dose. -Can be used to treat co-occurring depression. -Anticholinergic; use cautiously in elderly and patients with a history of cardiovascular disease.	\$3
Duloxetine	DPN – 4 ⁶	60mg QD	-Nausea, dry mouth, constipation, dizziness, fatigue, somnolence and sexual dysfunction. -Not recommended for patients with any level of hepatic insufficiency	\$115
Carbamazepine	Trigeminal neuralgia – NA	-200mg QD -Increase by 200mg weekly up to 400mg TID -Max=1200mg/day.	-Adequate trial will require up to 8 weeks of treatment. -CYP450 enzyme inducer; may cause drug interactions. -Dizziness, diplopia, nausea, aplastic anemia	\$20
Gabapentin	Pooled Anticonvulsants: ⁴ DPN – 2 PHN –3.2	-100-300mg QHS to TID -Increase by 100-300mg TID every 1-7 days. - Max=3600mg/day	-Adequate trial is 3-8 weeks plus 1-2 weeks at maximum tolerated dose. -If no effect is seen at a dose of 1800mg/day, discontinue the drug; if a partial effect occurs, titrate to 2,400 – 3,600mg/day -Drowsiness, dizziness, fatigue, nausea, sedation, weight gain	\$110
Pregabalin	DPN – 3.45 ¹² PHN – 3.33 ¹³	300 and 600mg/day (divided TID)	-Somnolence, dizziness, and peripheral edema	NA

NNT = Number Needed to Treat; the number of patients who need to be treated in order to prevent one additional bad outcome

*Cost = Average cost for 30-days to OHP; excludes rebate



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