REVIEW ARTICLE

Pharmacotherapy for Neuropathic Pain

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■ **Abstract:** Refractory neuropathic pain can be devastating to a patient's quality of life. Ideally, the primary goal of therapy would be to prevent the pain, yet even the most appropriate treatment strategy may be only able to reduce the pain to a more tolerable level. Pharmacotherapy is currently the mainstay of treatment in patients with neuropathic pain, although at present the drugs are used on a mainly "off-label" basis. A wide variety of agents are used, especially antidepressants (ie, tricyclic antidepressants, selective serotonin-reuptake inhibitors) and anticonvulsants, but also opioids and tramadol, topical agents (eg, lidocaine), systemic local anesthetics, and anti-inflammatories. Even so, effective pain relief is achieved in less than half of patients with chronic neuropathic pain. In refractory patients, combination therapy using two agents with synergistic mechanisms of action may offer greater pain relief without compromising the side-effect profile of each agent. ■

Key Words: medication guidelines, antidepressants, analgesics, neuropathic pain

INTRODUCTION

The management of refractory neuropathic pain represents a significant public health issue that can be costly to the healthcare system and devastating to a patient's quality of life. A survey conducted by the American Pain Society in 1998 found that most people with chronic pain had been experiencing pain for more than five years, that approximately one-third rated their pain as "the worst pain one can possibly imagine," and that many had to visit more than one doctor in an effort to gain relief from their pain.[1] Although the primary goal of therapy is to alleviate pain, clinicians recognize that even the most appropriate treatment strategy may only be able, at best, to reduce pain to a more tolerable level. At present, pharmacotherapy of neuropathic pain is largely limited to mainly "off-label" use of drugs approved for other conditions, especially tricyclic antidepressants (TCAs) (eg, amitriptyline) and anticonvulsants (eg, gabapentin). However, other pharmacotherapies have demonstrated efficacy in appropriate patient populations, such as opioids (eg, methadone, oxycodone), tramadol, and certain topical medications (eg, lidocaine, capsaicin). Some therapies have been used with mixed results, including mexiletine, baclofen, ketamine, and nonsteroidal anti-inflammatory drugs (NSAIDs). Despite the variety of these agents, clinically significant pain relief is achieved in less than half of patients with neuropathic pain.[2]

MECHANISM OF ACTION

Neuropathic pain is a term that describes a common feature of a heterogeneous group of conditions that cannot be explained by any single etiology or particular anatomical lesion. To date, no drug class or agent has been proved to be universally effective for patients with neuropathic pain from a given etiology, and treatment based on the underlying disease state may be less than optimal. For example, two patients with the same neuropathic pain syndrome may have different symptoma-

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tology and thus respond differently to the same treatment. However, despite the different etiology and the multiple lesions giving rise to neuropathic pain, many of these conditions share common clinical phenomena. This has led to the proposal that neuropathic pain may be explained by the same or similar mechanisms. Theoretically, the ability to identify the mechanism(s) underlying a patient's pain would enable the clinician to target pharmacologic treatment based on the mechanism of action of existing or novel drugs.[3,4]

Yet despite recent advances,[5–7] there is still limited understanding of the mechanisms of neuropathic pain, and the operational criteria for translating clinical symptoms and signs into distinct pathophysiological mechanisms remain problematic.[8–10] Similarly, there remains a paucity of evidence to explain the mechanisms of adjuvant analgesics in the treatment of neuropathic pain. Nevertheless, studies have attempted to clarify the mode of action of the most common drugs currently used in this indication.[6,11–13]

REVIEW OF THE EVIDENCE IN NEUROPATHIC PAIN

Although many pharmacological studies have been carried out in neuropathic pain, the majority have focused on just three indications: postherpetic neuralgia (PHN), painful diabetic peripheral neuropathy (DPN), and trigeminal neuralgia (TGN).[14] Supported by positive empiricism, drugs demonstrated to be efficacious in these indications are prescribed by physicians for other painful peripheral and central neuropathic conditions (such as complex regional pain syndrome [CRPS], low back pain, spinal cord injury, poststroke pain) where there is an absence or scarcity of scientific evidence for efficacy and no indication in the pharmacopoeia.[10,15] Currently, the most widely utilized treatment options for neuropathic pain are antidepressants, anticonvulsants, opioids, and topical treatments (eg, 5% lidocaine patch) (Table 1),[7] but FDA-approved treatments include the 5% lidocaine patch, gabapentin, and pregabalin for PHN, pregabalin and duloxetine for DPN, and carbamazepine for TGN. Although all of these agents may show some efficacy in clinical practice, well-conducted randomized controlled trials (RCTs) in different neuropathic pain conditions are urgently required. Future research also should focus on developing strategies for identifying optimal pharmacological targets, specifically for the treatment of neuropathic pain.[4]

Antidepressants

TCAs are often listed as first-line drugs for neuropathic pain. Typically, this class of agents is separated into two categories based on their chemical structure: tertiary and secondary amines. TCAs appear to affect pain transmission via multiple mechanisms including reuptake inhibition of both serotonin and norepinephrine at spinal cord receptor sites, including projections to the brain stem and dorsal horn nuclei. It has been postulated that the tertiary agents maintain a more balanced chemical profile, providing inhibition of both serotonin and norepinephrine. In contrast, the second-

Table 1. Guidelines for drug treatment of neuropathic pain[7]

Medication	Beginning Dosage	Titration	Maximum Dosage	Duration of Adequate Trial
Gabapentin	100–300 mg every night	Increase by 100–300 mg/day every 1–7 days as tolerated. Give in 3 divided doses daily.	3600 mg/day (1200 mg 3 × daily); reduce if low creatinine clearance	3–8 weeks for titration plus 1–2 weeks at maximum tolerated dosage
5% Lidocaine patch	Maximum of 3 patches daily for a maximum of 12 hours*	None needed	Maximum of 3 patches daily for a maximum of 12 hours	2 weeks
Opioid analgesics	Variable	After 1–2 weeks, convert total daily dosage to long-acting opioid analgesic and continue short-acting medication as needed	No maximum with careful titration; consider evaluation by pain specialist at dosages exceeding 120–180 mg/day	4–6 weeks
Tramadol hydrochloride	50 mg once or twice daily	Increase by 50–100 mg/day in divided doses every 3–7 days as tolerated	400 mg/day (100 mg 4 × daily); in patients older than 75 years, 300 mg/day in divided doses	4 weeks
Tricyclic antidepressants (eg, nortriptyline hydrochloride or desipramine hydrochloride)	10–25 mg every night	Increase by 10–25 mg/day every 3–7 days as tolerated	75–150 mg/day: if blood level of active drug and its metabolite is <100 ng/mL, continue titration with caution	6–8 weeks with at least 1–2 weeks at maximum tolerated dosage

*Studies have shown it to be safe for 18 hours, but current FDA labeling is for 12 hours.

ary amines appear to provide more reuptake inhibition of norepinephrine. The analgesic properties of TCAs appear to be independent of their antidepressant properties.[16,17] Other possible mechanisms of action include: alpha-adrenergic blockade; anticholinergic effects; antihistaminic effects; reuptake inhibition of dopamine; effects on gamma-aminobutyric acid (GABA)-B and adenosine; potassium, calcium and, most importantly, sodium channel blockade; N-methyl-D-aspartic acid (NMDA)-receptor antagonism.

Table 2. Side effects of tricyclic antidepressants[18]

Side effects	1. Anticholinergic effects Dry mouth, constipation, blurred vision, urinary retention, dizziness, tachycardia, memory impairment, delirium) 2. Sedation 3. Alpha-1-adrenergic effects Orthostatic hypotension/syncope 4. Cardiac conduction delays/heart block Arrhythmias, Q-T prolongation 5. Other side effects Weight gain, excessive perspiration, sexual dysfunction
Severity	Tertiary > secondary agents

The secondary amines (eg, desipramine and nortriptyline) appear to be as effective as the tertiary agents (eg, imipramine and amitriptyline) as analgesics in neuropathic pain and produce markedly fewer side effects (Table 2).[18] This favorable side-effect profile makes secondary amine TCAs more clinically appropriate for many patients.

In 2005, Stacey carried out a review of the literature regarding the management of peripheral neuropathic pain and summarized the results of RCTs with the major classes of available drugs (Table 3).[11] Evidence was graded using Best-evidence Synthesis (level 1–4 evidence, level 1 being the strongest).[19] The review determined that current evidence supports the use of antidepressants in the treatment of neuropathic pain (and confirmed the findings of previous reviews[7,14,15]). Results from several well-designed trials have demon-

Table 3. Pharmacological agents with demonstrated efficacy in neuropathic pain[11]

Drug Category	Type of Neuropathic Pain	Evidence Level	Daily Dosage	NNT
Antidepressants				
Amitriptyline	PHN	2	10–140 mg	4.1 (2.1–82.1)
				1.6 (1.2–2.4)
	DPN	2	105 mg (average)	2.1 (1.5–3.5)
Nortriptyline	PHN	2	10–160 mg	N/A
Desipramine	DPN	2	111 mg (average)	2.2 (1.4–5.1)
				6.0 (2.1–8)
Citalopram	DPN	2	40 mg	3.0 (1.6–35.9)
Paroxetine	DPN	2	40 mg	5.0 (2.3–8)
Bupropion[35,36]	Various	—	150–300 mg	N/A
Duloxetine[23]	DPN	—	60 mg	N/A
Venlafaxine	DPN	—	150–225 mg	4.5[40]
	Various types[37–39]			5.2[38]
Anticonvulsants				
Gabapentin	PHN	2	1800–3600 mg	3.2 (2.4–5.0)
		2	1800–3600 mg	5.0 (3.2–11.4)
	DPN	2	900–3600 mg	3.7 (2.4–8.3)
		2	900–1800 mg	N/A
Carbamazepine	Trigeminal neuralgia	2	400–800 mg	2.8 (2.3–3.7)
		2	100–4000 mg	1.4 (1.14–1.88)
	DPN	2	200–600 mg	3.3 (2.0–9.4)
Pregabalin	PHN	2	300–600 mg	3.4
Lidocaine patch, 5%	PHN	2	≤3 patches/12 hour	N/A
	Various types		≤4 patches/12 hour	4.4 (2.5–17.5)
Opioids				
CR oxycodone	PHN	2	≤60 mg	2.5 (1.6–5.1)
	DPN	2	≤120 mg	N/A
		2	40 mg (average)	2.6
CR morphine	Phantom limb pain	2	≤300 mg	N/A
	PHN	2	≤22 mg	N/A
Methadone	Various types	2	10–20 mg	N/A
Tramadol	DPN	2	≤400 mg	3.4
	Various types	2	≤400 mg	4.3

NNT, number needed to treat; CR, controlled release; DPN, diabetic peripheral neuropathy; PHN, postherpetic neuralgia.

strated that TCAs are an effective treatment for PHN and DPN (level 1 evidence). TCAs also seem to have some efficacy in CRPS (level 4 evidence), although they have never been properly studied in this indication.[20] TCAs have been recommended as first-line agents for all neuropathic pain, except TGN.[21]

Selective serotonin reuptake inhibitors (SSRIs—eg, citalopram and paroxetine) and serotonin-norepinephrine reuptake inhibitors (SNRIs—eg, duloxetine and venlafaxine) are two newer classes of antidepressants that act by selectively inhibiting the presynaptic reuptake of serotonin and norepinephrine as their names imply. These agents lack the postsynaptic receptor-blocking effects and the quinidine-like membrane stabilization seen with the TCAs.

Although SSRIs are better tolerated than TCAs, with fewer associated side effects and toxicities, they are believed to be less efficacious in the treatment of neuropathic pain and are not regarded as first-line agents.[11] In an analysis of patients with DPN, Max et al. (1992) found TCAs to be superior to fluoxetine and placebo.[16] Further, the SSRI produced results equal to placebo. In another report, the use of paroxetine in patients with diabetic neuropathy produced significantly more pain relief than placebo, but significantly less than imipramine.[22] In previous reports, SSRIs are stated as effective in the treatment of DPN (especially paroxetine and citalopram, 40 mg/day) (level 2 evidence),[11] but disappointing in PHN (level 2 evidence)[11] and CRPS (level 4 evidence).[20]

The SNRI duloxetine has recently received FDA approval for use in DPN. A 12-week, multicenter, double-blind study in 457 patients experiencing PDN caused by type 1 or type 2 diabetes mellitus has recently been published.[23] Subjects were randomly assigned to treatment with duloxetine 20 mg QD, 60 mg QD, 60 mg BID, or placebo. Duloxetine 60 mg QD and BID produced statistically significant improvements compared with placebo on the 24-hour average pain scores at 1 week following randomization and throughout the 12-week study. Duloxetine also was superior to placebo on nearly all the secondary measures, including health-related outcome measures. Patients on all three duloxetine regimens achieved a 50% reduction on the 24-hour average pain scores.

Anticonvulsants

As with epilepsy, the hallmark characteristic of neuropathic pain is thought to be neuronal hyperexcitability. Some of the known mechanisms of action of anticonvulsants include blockade of the membrane sodium currents, effects on calcium conductance, activation of the gamma-aminobutyric acid (GABA) inhibitory system by direct or indirect means, and reduction of the activity of the excitatory neurotransmitter glutamate. The net result is the depression of synaptic transmission and the elevation of the threshold for repetitive firing of nociceptive neurons, as well as a reduction in discharges of the dorsal root ganglion cells.

To date, only five agents have been evaluated in randomized double-blind clinical trials. These are carbamazepine, gabapentin, lamotrigine, phenytoin, and pregabalin. Of these, carbamazepine and phenytoin require intensive monitoring of serum levels and maintain a fairly extensive adverse effect profile. Lamotrigine use is limited by a risk of Stevens–Johnson syndrome and other serious dermatological adverse events. Gabapentin produces markedly fewer adverse effects than many other anticonvulsants, and does not require blood tests.

Gabapentin has recently been shown to be an effective treatment option for both DPN and PHN in two large multicenter, randomized, double-blind, placebo-controlled, parallel group trials.[24,25] Gabapentin was also compared to amitriptyline in a small-scale prospective, randomized, double-blind, double-dummy, crossover study in DPN.[26] Although both drugs provided analgesia, no significant difference was shown between gabapentin and amitriptyline with respect to pain scores or global pain assessment. The authors concluded that gabapentin is an effective alternative to amitriptyline for treatment of DPN pain, but could not be recommended over amitriptyline due to cost.

The most common side effects of gabapentin are drowsiness, somnolence, and generalized fatigue. These side effects are usually transient, lasting an average of 2 to 3 weeks. Treatment should be initiated at 300 mg at bedtime, with a test dose of 100 mg at bedtime for elderly patients. The dose is then increased by 300 mg every 3 to 5 days, until the patient has adequate pain relief. The median effective daily dose ranges between 900 and 1800 mg, although some patients respond to daily doses as low as 100 mg and others require 3600 mg. Gorson and colleagues reported that doses less than 900 mg per day (300 mg TID) are either ineffective or only minimally effective for the treatment of painful diabetic neuropathy.[27] The average age of the patients evaluated in this report was 62 years. Because of its short half-life, gabapentin should be administered on a TID schedule. The drug is excreted unchanged by

the kidneys, with clearance directly proportional to creatinine clearance. Therefore, dosage reduction may be needed in patients with renal impairment. As a result of the lack of drug–drug interactions, gabapentin may be an attractive agent for patients receiving multiple medications.

Stacey (2005) identified several randomized, double-blind clinical trials (level 2 evidence) demonstrating that gabapentin had significantly greater efficacy than placebo in PHN (at 1800 to 3600 mg/day) and DPN (900 to 3600 mg).[11] In DPN, gabapentin showed comparable efficacy to amitriptyline. Controlled clinical trials suggest that carbamazepine (100 to 4000 g/day) is effective in TGN and DPN, but not PHN or central pain (all level 2 evidence).[11] Compared to the first-generation anticonvulsants, gabapentin has a more favorable safety and tolerability profile. Pregabalin (300 or 600 mg/day) also appears to be effective in some types of neuropathic pain, with level 2 evidence indicating that 50% of patients with PHN achieved a decrease in pain of 50% or more.[11] Sodium valproate has demonstrated efficacy in painful DPN (level 2 evidence), but the evidence for other anticonvulsants (levetiracetam, oxcarbazepine, topiramate, zonisamide) in the treatment of neuropathic pain was not as good.[11] These results were in accordance with those from earlier studies.[7,14,15,28] Anticonvulsants are thought to hold significant promise in the treatment of CRPS.[20] Carbamazepine has a traditional and perhaps clinically important place in this indication, and gabapentin holds significant promise (level 4 evidence).

Opioids and Tramadol

Opioid agonists work by mimicking the activity of enkephalins and endorphins in the central descending pathways of the pain-processing loop. By binding to mu-opioid receptors in the central nervous system, opioid agonists dampen neuronal excitability and elicit pain relief. Despite concerns regarding the efficacy of opioids in neuropathic pain, several double-blind RCTs (level 2 evidence) have demonstrated that oxycodone, morphine, and methadone can be modestly effective in PHN, DPN, phantom limb pain, and other types of neuropathic pain.[7,11,14,15] A recent review demonstrated that opioids had significant efficacy over placebo for neuropathic pain in intermediate-term studies.[2] Although reported adverse events with opioids were common, they were not life-threatening. When compared to treatment with TCAs, opioids were as effective but resulted in a greater number of dropouts.[11] Nevertheless, patients who finished the study preferred treatment with opioids over TCA.

Tramadol is a centrally acting agent with a weak affinity for mu-opioid receptors and weak reuptake inhibition of the neurotransmitters norepinephrine and serotonin. It has shown utility in a variety of pain syndromes, most notably neuropathic pain.[12,29–31] Treatment should generally be initiated at a dose of 50 mg daily and increased by 50 mg increments every 3 to 5 days. Adverse events increase with more rapid dose titration. Effective daily doses range between 100 and 400 mg, administered in divided doses four times daily. The most common adverse effects of tramadol are dizziness, vertigo, nausea, constipation, headache, and somnolence. In addition, patients with a history or potential for seizure activity should avoid use of this agent.

Topical Agents

Topical agents work locally, directly at the site of application, with minimal systemic effects. Lidocaine, like other local anesthetics, seems to act through inhibition of voltage-gated sodium channels. Capsaicin is thought to elevate the pain threshold in which it is applied through depletion of the nociceptive neurotransmitter, substance P, from the terminals of unmyelinated C fibers. It also causes degeneration of substance P-positive epidermal nerve fibers. Ketamine works through antagonism of the NMDA receptors and clonidine is thought to act at the presynaptic alpha-2 adrenergic receptors, subsequently inhibiting release of norepinephrine.

The evidence supporting the 5% lidocaine patch for the treatment of neuropathic pain is strong.[7,11,14,15] The lidocaine patch is effective in PHN (level 2 evidence), with minimal risk of drug interactions or systemic adverse effects.[11] However, the current approved dose of 12-hour on/12-hour off was found to be insufficient for some patients. The lidocaine patch also has shown efficacy in DPN (level 2 evidence), with the number needed to treat in some studies comparing favorably to those of other treatments for neuropathic pain.[11] Complete or some pain relief has been noted in patients with myofascial pain (two-thirds of whom had lower back pain) and in those with lower back pain.[11] Both types of pain may result, in part, from neuropathic mechanisms. The lidocaine patch also may be useful in the treatment of CRPS.[20]

Capsaicin cream (0.075%) was evaluated in several clinical studies for DPN and PHN (both level 2 evi-

dence).[11] Although results were inconsistent, clinical experience suggests it may occasionally be effective in individual circumstances. Capsaicin also has partial efficacy in CRPS (level 3 evidence).[20] Level 3 evidence was noted for the efficacy of ketamine gel in the treatment of neuropathic pain.[11]

Systemic Local Anesthetics

Abnormal electrical activity in injured nerves and neuromas is partly generated by abnormal accumulation of sodium channels. Therefore, a sodium channel-blocking agent may help to relieve neuropathic pain. Such medications include intravenous lidocaine (which also depresses C-fiber polysynaptic evoked activity and thus suppresses dorsal horn neurons to the C-fiber input), oral mexiletine (which has a similar mode of action to lidocaine), and oral tocainamide. The GABAergic system in the spinal cord also plays a pivotal role in modulating pain control and as a result, baclofen (a GABA-B-receptor agonist) has been shown to be effective for neuropathic pain.

Mexilitene, an orally available lidocaine congener antiarrhythmic, has been evaluated in several double-blind clinical trials for treatment of painful diabetic neuropathy.[32–34] Only one of these trials demonstrated significant pain relief with mexilitene, and even then only limited nighttime pain relief with high doses (675 mg per day). Mexilitene is not a benign drug, and as such has a less than favorable adverse effect profile. Common adverse effects include chest pain, dizziness, gastrointestinal disturbances, palpitations, and tremor. As with other antiarrhythmics, mexilitene may worsen existing arrhythmia. The daily effective dose ranges between 450 and 675 mg, usually administered on a thrice daily schedule. As a function of its questionable efficacy and its toxicity, mexilitene should be considered an option only when other measures have failed.

Anti-Inflammatories

NSAIDs are widely used to treat inflammation, pain, and fever, and their analgesic effect results from their ability to block prostaglandin synthesis by inhibiting the precursor enzyme, cyclooxygenase (COX). However, the literature is inconsistent as to whether they are effective in neuropathic pain.[13] NSAIDs also are commonly used to relieve pain and treat inflammatory symptoms in CRPS type I, but again, long-term evidence and safety data is lacking.[11] Only oral corticosteroids were found to provide long-term beneficial results in CRPS (level 1 evidence).[20]

RATIONAL POLYPHARMACY

Although a primary goal of pain management is to relieve pain using a single agent, the reality is that monotherapy rarely provides adequate relief from chronic neuropathic pain. In these complex and refractory situations, combination therapy using two or more agents with synergistic mechanisms of action (eg, gabapentin + lamotrigine) is frequently necessary. In clinical practice, some patients begin to respond to a particular monotherapy, but often are restricted by dose-related side effects. In such cases, combination therapy with two or more agents with different modes of action at suboptimal doses may provide the additive effects or even synergistic effects necessary for optimal pain relief without compromising the side-effect profile of each agent. However, it is essential that a careful patient history is taken before initiating a polypharmacy regimen.

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