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Pharmacologic Management Part 1: Better-Studied Neuropathic Pain Diseases

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ABSTRACT

Neuropathic pain impacts millions of people in the United States and around the world. Patients experience one of many symptoms, such as pain, paresthesia, dysesthesia, hyperalgesia, and allodynia, for many years because of unavailable or inadequate treatment. One of the major challenges in treating patients with neuropathic pain syndromes is a lack of consensus concerning the appropriate first-line treatment options for conditions associated with neuropathic pain, including postherpetic neuralgia, diabetic peripheral neuropathy, and trigeminal neuralgia.

This review summarizes the published results of randomized trials involving treatment for neuropathic pain conditions. Anticonvulsants, such as gabapentin, carbamazepine, and lamotrigine, and tricyclic antidepressants, including amitriptyline and desipramine, have demonstrated efficacy in relieving pain associated with postherpetic neuralgia, diabetic peripheral neuropathy, and trigeminal neuralgia, in several studies. However, the lack of head-to-head comparison studies of these agents limits the conclusions that can be reached. Clinicians who must make decisions regarding the care of individual patients may find some guidance from the number of randomized trials with a positive outcome for each agent. Using quality-of-life study outcomes, treatment strategies must encompass the impact of therapeutic agents on the comorbid conditions of sleep disturbance and mood and anxiety disorders associated with neuropathic pain.

Looking to the future, emerging therapies, such as pregabalin and newer *N*-methyl-D-aspartate–receptor blockers, may provide physicians and patients with new treatment options for more effective relief of pain.

Key Words. Neuropathic Pain; Diabetic Peripheral Neuropathy (DPN); Postherpetic Neuralgia (PHN); Trigeminal Neuralgia (TGN); Anticonvulsants; Tricyclic Antidepressants.

Introduction

It is estimated that over 4 million people in the United States suffer from neuropathic pain [1], which is defined as "pain initiated or caused by a primary lesion or dysfunction in the nervous system" by the International Association for the Study of Pain [2]. A more specific definition calls for pain that is the result of injury to the nervous system, peripheral, central, or both, and manifests with positive and negative sensory phenomena [3]. Lesions that originate in the peripheral or central nervous system may manifest as different neuropathic pain syndromes, depending on the anatomic location and type of impairment. Noncancer neuropathic pain syndromes are listed in Table 1.

Patients with neuropathic pain experience a combination of positive and negative sensory, motor, and autonomic signs and symptoms. Positive sensory symptoms include pain, paresthesia (abnormal sensation, either evoked or spontaneous), dysesthesia (evoked or spontaneous unpleasant, abnormal sensation), hyperalgesia (increased response to a normally painful stimulus), and allodynia (painful response to a nonnoxious stimulus). Negative sensory symptoms involve a loss of sensitivity to stimulation in general and painful stimuli in particular (hypoes-

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Table 1 Noncancer neuropathic pain syndromes

Peripheral	Complex regional pain syndrome (type I and II)
	Posttraumatic nerve injury
	Radiculopathy
	HIV sensory neuropathy
	Diabetic peripheral neuropathy
	Phantom limb pain
	Postherpetic neuralgia
	Trigeminal neuralgia
Central	Central poststroke pain
	Multiple sclerosis pain
	Spinal cord injury pain

Adapted with permission from Dworkin [90].

thesia and hypoalgesia, respectively) [4]. Often, these symptoms of neuropathic pain are chronic and endure for many years with either no treatment or inadequate treatment [5]. A survey conducted by the American Pain Society in 1998 found that most people with chronic pain had been experiencing pain for over 5 years, that approximately one third of chronic pain sufferers rated their pain as "the worst pain one can possibly imagine," and that many chronic pain sufferers had to visit more than one doctor in an effort to gain relief from their pain [6].

Despite the large number of people who are affected by neuropathic pain and the degree of suffering they endure, there does not appear to be consensus regarding the best way to treat the more commonly encountered neuropathic pain conditions [7]. No one therapeutic drug class or agent has been proven to be effective for all patients with neuropathic pain from a given etiology. Identification of an effective pharmacologic regimen for a specific patient is further complicated by the fact that a particular pain symptom may be produced by different mechanisms and that one underlying mechanism may manifest as several different symptoms [8,9]. Theoretically, the ability to identify the mechanism(s) underlying a patient's pain would enable the clinician to target pharmacologic treatment based on a drug's mechanism of action [10]. Currently, patients with neuropathic pain are often treated with agents such as nonsteroidal anti-inflammatory drugs, which do not have proven efficacy in relieving neuropathic pain, or are treated with inappropriately low doses of agents that have demonstrated efficacy.

In addition, as Nicholson and Verma discuss elsewhere in this issue, an understanding of the impact of comorbid conditions on pain and the effect of pain treatment on comorbidities is a key component in the successful management of patients with neuropathic pain [11].

In this first part of our review of the pharmacologic management of neuropathic pain, we discuss three of the better-studied neuropathic pain conditions—postherpetic neuralgia (PHN), diabetic peripheral neuropathy (DPN), and trigeminal neuralgia (TGN)—by examining published reports of clinical trials to draw conclusions from the available data.

Methods

This review is not intended to be a complete, systematic analysis of all available data concerning the treatment of these three neuropathic pain conditions. Rather, it provides a summary of published data from well-designed, randomized trials. We discuss several selected studies within the context of each specific neuropathic pain syndrome, highlighting those that have a quantitatively measured effect on the treatment of specific neuropathic pain symptoms or quality-of-life parameters. We have excluded open-label studies, case studies, unpublished data, and study results reported only in abstracts or poster presentations.

Postherpetic Neuralgia

Disease Overview

The varicella zoster virus that causes chicken pox can remain latent in sensory ganglia for many years following the original infection [12]. Each year in the United States, reactivation of this virus manifests as herpes zoster (i.e., shingles) in an estimated 800,000 people [13]. During the acute phase of herpes zoster, a painful rash usually forms along a single dermatome related to the affected dorsal root or cranial nerve ganglion [12]. The rash and severe pain associated with herpes zoster usually lasts less than 4 weeks [14]. However, a common sequela of herpes zoster is PHN, a condition in which pain along the involved nerve territory persists for a prolonged period after the acute rash resolves. Evidence suggests that the pathogenesis of PHN involves both peripheral and central mechanisms that change over time, such as irritable peripheral nociceptors and central sensitization [9,15].

People 50 years of age and older are most likely to develop PHN following herpes zoster, and this painful condition can severely impact all aspects of life, including mood, sleep, physical activity, appetite, social activity, and the performance of necessary functions of daily living [13]. Therefore, the identification of an appropriate treatment to optimize outcome is essential.

Treatment Options

Published data from randomized trials assessing the effect of various pharmacotherapeutic agents on pain in patients with PHN are summarized in Table 2 and discussed briefly below. The most commonly studied therapeutic classes in PHN are anticonvulsants and antidepressants; however, many other systemic and topical agents, including vincristine and magnesium sulfate, have also been investigated.

Anticonvulsants

The efficacy of anticonvulsants in relieving the pain associated with PHN has been demonstrated in several randomized, placebo-controlled trials. For example, Rice et al. [16] and Rowbotham et al. [17] demonstrated that gabapentin, at doses of 1,800 mg/day, 2,400 mg/day, and 3,600 mg/day, was significantly better than placebo at reducing pain in patients with PHN ($P < 0.01$ for 1,800-mg and 2,400-mg doses [16]; $P < 0.001$ for 3,600-mg dose) [17]. In both of those studies, improvements in quality-of-life parameters were significantly greater in gabapentin-treated patients compared with patients who received placebo, including vitality ($P < 0.05$), mental health ($P < 0.05$) [16], sleep interference ($P < 0.001$) [17], mood, depression, anger, fatigue ($P < 0.001$ for each), and confusion ($P = 0.01$) [17].

The mechanisms by which gabapentin alleviates neuropathic pain have not been fully elucidated. Gabapentin binds to the $\alpha_2\delta$ subunit of neurotransmitter-gated calcium ion channels [18]; however, ongoing research suggests other mechanisms may be involved [19].

Tricyclic Antidepressants

Tricyclic antidepressants (TCAs) are prescribed frequently for the treatment of PHN. In 1982, Watson et al. demonstrated the efficacy of amitriptyline, versus placebo, in significantly ($P \leq 0.0001$) reducing pain in patients with PHN, specifically paroxysmal, lancinating pain [20]. Subsequent studies found that amitriptyline was more effective in relieving PHN-related pain than lorazepam [21], fluphenazine [22], and maprotiline [23]. However, nortriptyline was as effective as amitriptyline in ameliorating neuropathic pain in patients with PHN [24], and other TCAs, such as desipramine, also have demonstrated efficacy [25]. Indeed, Raja et al. found no significant difference between pain relief with nortriptyline or desipramine and that seen with opioids in patients with PHN [26].

Inhibiting the reuptake of norepinephrine and serotonin is how TCAs exert their effect. In general, the most common adverse events observed during treatment with these agents include sedation, anticholinergic effects (i.e., dry mouth, constipation), and hypotension. However, amitriptyline, clomipramine, and imipramine, which inhibit both norepinephrine and serotonin reuptake, have worse side-effect profiles than agents such as desipramine and nortriptyline that act on serotonin only [27].

Opioids

Controversy exists concerning the use of opioids to treat neuropathic pain. Although some pain specialists believe that opioids are either ineffective or effective only at doses that cause intolerable side effects, others feel that it is possible to achieve pain relief while maintaining an acceptable side-effect profile [28]. Significant decreases in pain scores have been noted in patients with PHN during treatment with opioids [26,29]. Oxycodone in extended-release form was significantly more effective than placebo at relieving allodynia ($P = 0.0004$) and paroxysmal pain ($P = 0.0001$) in patients with PHN [29]. However, oxycodone had no effect on mood and depression, and adverse events included constipation, nausea, and sedation. Extended-release morphine was associated with less cognitive side effects than nortriptyline, and it was preferred by patients over nortriptyline [26].

Tramadol, a centrally acting analgesic, although chemically different from the opioids, has been shown to be effective in relieving the pain associated with PHN. Tramadol was also shown to be more effective than placebo in decreasing visual analog scale (VAS) pain scores ($P < 0.05$), and patients in the tramadol group in that study required less rescue medication ($P < 0.05$) than those given placebo [30].

Topical Agents

The 5% lidocaine patch, a local anesthetic, has been shown to reduce the pain and allodynia associated with PHN in several randomized studies [31–33], possibly by reducing ectopic activity in the involved sensory nerves, and by providing a physical barrier to mechanical stimulation from contact with clothing, etc. [31,32]. In one study, involving 96 patients with PHN, the lidocaine patch was significantly more effective in relieving neuropathic pain than a vehicle patch ($P = 0.043$), and significant benefits were experienced by patients with nonallodynic pain ($P = 0.022$) and patients with "sharp," "hot," "dull," and "deep" pain ($P = 0.013$) [33]. In a similar study, the only side effect reported was a mild redness at the

Table 2 Pharmacotherapy of PHN

Study	Patients	Treatment	Outcomes	Adverse events/withdrawals
Randomized, double-blind, placebo-controlled trials				
Boureau et al., 2003 [30]	Pts with PHN (N = 125)	Tramadol ≤400 mg/d (N = 63) (≤300 mg/d if 75 y or older) or placebo (N = 62) ×6 wks	Mean pain intensity was significantly lower in the tramadol group than in the placebo group ($P < 0.05$) and required less rescue medication ($P < 0.05$)	No difference in rates of AEs, tramadol (29.7%) vs placebo (31.8%) or total AEs, tramadol (31) vs placebo (28)
Dowd et al., 1999 [91]	Pts with PHN (N = 20)	Vincristine 0.01% (N = 11) or placebo (saline, N = 9) administered by iontophoresis over 1 h daily ×20 days	Pain scores were significantly lower in both groups on Day 20 vs baseline. Pain relief was moderate or greater in 40% of vincristine-treated patients and 55% of placebo-treated pts	No neurological deficits or changes in blood profiles were detected in either group
Dworkin et al., 2003 [37]	Pts with PHN (N = 173)	Pregabalin, 600 mg/d (N = 59) if creatinine clearance >60 mL/min or 300 mg/d (N = 30) if creatinine clearance 30–60 mL/min, or placebo (N = 84) ×8 wks	Pregabalin vs placebo demonstrated significantly greater decreases in pain (end point mean pain scores 3.60 vs 5.29, $P = 0.0001$) and sleep interference ($P = 0.0001$)	Withdrawals due to AEs: pregabalin 32% vs placebo 5%; AEs, pregabalin vs placebo: dizziness, 28% vs 12%; somnolence, 25% vs 7%; peripheral edema, 19% vs 2%; amblyopia, 11% vs 1%; dry mouth, 11% vs 2%; abnormal gait, 8% vs 1%; headache, 8% vs 8%; ataxia, 7% vs 0%; confusion, 7% vs 0%; diarrhea, 7% vs 5%; speech disorder, 6% vs 0%
Galer et al., 2002 [33]	Pts with PHN (N = 96)	5% lidocaine patch vs vehicle patch ×3 wks	Lidocaine patch improved pain qualities as measured by NPS to a greater extent than vehicle patch ($P = 0.043$)	NA
Graff-Radford et al., 2000 [22]	Pts with PHN (N = 49)	Pts randomly assigned to 1 of 4 groups: G1, amitriptyline; G2, amitriptyline and fluphenazine; G3, fluphenazine; G4, active placebo, ×8 wks	Statistically significant decrease in pain (measured by VAS) compared with baseline occurred in G1 and G2 ($P < 0.001$ and $P = 0.04$, respectively)	G2 (amitriptyline and fluphenazine) had the highest incidence of sleepiness and G1 (amitriptyline) had the highest incidence of dry mouth
Rice et al., 2001 [16]	Pts with PHN (N = 334)	Gabapentin, 1,800 mg/d (N = 115), gabapentin, 2,400 mg/d (N = 108), or placebo (N = 111) ×7 wks (with dose titration during first 2 wks)	Differences in pain scores vs baseline were –34.5% (1,800-mg dose), –34.4% (2,400-mg dose), and –15.7% (placebo). Both gabapentin doses were significantly better than placebo ($P < 0.01$ for each dose)	AEs: dizziness and somnolence, particularly during titration phase
Rowbotham et al., 1998 [17]	Pts with PHN (N = 229)	Gabapentin maximum dose: 3,600 mg/d (range: 1,200–3,600 mg/d, N = 113) or placebo (N = 116) ×8 wks; dose titration during first 4 wks	Reduction in pain scores significantly greater with gabapentin vs placebo (from 6.3 to 4.2 points vs 6.5 to 6.0 points, respectively, $P < 0.001$)	Withdrawals: 13.3% with gabapentin; 9.5% with placebo; AEs: somnolence, dizziness, ataxia, peripheral edema, and infections were more frequent with gabapentin than placebo
Serpell et al., 2002 [39]	Pts with various symptoms (N = 307), PHN (43/307)	Gabapentin, 900 mg/d (titrated over 3 days), with escalation to 1,800 mg/d or 2,400 mg/d, for a total of 8 wks (N = 153), or placebo (N = 152)	Gabapentin demonstrated greater improvement in pain score than placebo (21% vs 14%, $P = 0.048$)	Withdrawals: gabapentin, 32 pts; placebo, 41 pts; AEs, gabapentin vs placebo: dizziness, 24% vs 8%; somnolence, 14% vs 5%; infection, 9% vs 13%; headache, 9% vs 14%; nausea, 9% vs 9%; flu syndrome, 7% vs 5%; abdominal pain, 7% vs 4%; accidental injury, 6% vs 5%; diarrhea, 5% vs 4%
Watson et al., 1993 [35]	Pts with PHN (N = 143)	Capsaicin 0.075% cream vs placebo (vehicle) cream	Capsaicin resulted in greater decrease in pain than placebo (measured by VAS) at 2 wks (19% vs 0.4%, $P < 0.05$) and 6 wks ($P = 0.032$). Long-term follow up (≤2 years, N = 77) showed clinical benefit in	AEs: burning and stinging at application site in 60% of pts using capsaicin and 33% using placebo

Table 2 Continued

Study	Patients	Treatment	Outcomes	Adverse events/withdrawals
Randomized, double-blind, placebo-controlled, crossover trials				
Baranowski et al., 1999 [92]	Pts with PHN (N = 24)	Pts received each of the following IV infusions over 2 h ≥1 wk apart: placebo (normal saline), lidocaine 1 mg/kg, and lidocaine 5 mg/kg	Ongoing pain (measured by VAS) was significantly reduced after all infusions ($P < 0.05$); dynamic pressure-evoked pain was significantly reduced by both lidocaine infusions ($P < 0.05$, for each dosage level); area of allodynia declined with lidocaine 1 and 5 mg/kg ($P < 0.05$ and $P < 0.001$, respectively)	No pts at the lower dose reached toxic plasma levels; however, several pts at the higher dose did reach toxic levels. Thus, the lower doses may be considered safe
Brill et al., 2002 [93]	Pts with PHN (N = 7)	Magnesium sulphate, 30 mg/kg, IV, or saline	Mean pain score decreased from 6.7 to 1.9 at 30 minutes posttreatment with magnesium sulphate. Pain scores were significantly lower with magnesium sulphate than with placebo at 20 and 30 minutes ($P = 0.016$)	No side effects were reported during treatment with magnesium sulphate
De Benedittis and Lorenzetti, 1996 [94]	Pts with PHN (N = 22) AHN (N = 15)	Pts had 1 of 4 suspension/diethyl ether solutions applied to affected areas in a randomized order on 4 different days. Median doses of active suspensions: aspirin 1,000 mg; indomethacin 75 mg; diclofenac 100 mg; lactose was used for placebo	Only aspirin was significantly superior to placebo for reduction in pain (based on VAS score) from baseline ($P < 0.05$) and duration of pain ($P < 0.01$). Good-to-excellent results were reported in >81% of PHN pts with topical aspirin suspension	Mild cutaneous rash in 1 pt each with indomethacin and diclofenac
Galer et al., 1999 [31]	Pts with PHN (N = 33)	Topical 5% lidocaine patch vs placebo (vehicle) patch for 2–14 days, depending on increase in pain; then patients crossed over to alternative treatment	Primary end point was "time to exit," i.e., pts were allowed to discontinue treatment if pain relief diminished. Median time to exit was significantly better with lidocaine than placebo (14 d vs 3.8 d, $P < 0.001$). Lidocaine patch was preferred by 78.1% of pts vs 9.4% for placebo ($P < 0.001$)	Withdrawals: 1 pt suffered a stroke prior to receiving study medication; 1 pt withdrew during placebo period because of increased pain and insomnia; 1 pt stopped placebo because of red, irritated skin; AEs were mild or moderate; application site reaction redness/rash reported in 9 pts with lidocaine patch and 11 pts with placebo patch
Kishore-Kumar et al., 1990 [25]	Pts with PHN (N = 26)	Desipramine (mean dose: 167 mg/d) or placebo ×6 wks; then pts crossed over to alternative treatment	Pain relief with desipramine was significantly greater from weeks 3 to 6 than with placebo ($P < 0.001$)	Withdrawals: 8 pts because of AEs or intercurrent medical illnesses; AEs: desipramine: syncope, 1 pt; left bundle branch block, 1 pt; jitteriness and atypical chest pain, 1 pt; fever, 1 pt; and vertigo, 1 pt; placebo: vertigo and nausea, 1 pt; skin rash, 1 pt; unsteadiness + mental fogginess, 1 pt
Max et al., 1988 [21]	Pts with PHN (N = 58)	Amitriptyline (12.5–150 mg/d), lorazepam (0.5–6 mg/d), or placebo (lactose) ×2 wks; followed by 1-wk washout; then crossed to alternative treatment	Moderate or greater pain relief was reported by 47% of pts with amitriptyline, 16% of pts with placebo, and 15% of pts with lorazepam	AEs: dry mouth, sedation, dizziness; occurred with both active treatments
Nelson et al., 1997 [95]	Pts with DPN (N = 14) and with PHN (N = 18)	Oral dextromethorphan (mean dose in PHN: 439 mg/d) or placebo ×6 wks followed by 1-wk washout; then crossed over to alternative treatment	Dextromethorphan did not reduce pain in pts with PHN to a greater extent than placebo ($P = 0.72$)	Withdrawals: 5 PHN pts due to sedation, ataxia and confusion, and (unrelated) 6th cranial nerve palsy

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