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# Treatment of Painful Polyneuropathies

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The treatment of painful polpyneuropathies has begun to improve over the past several years. This is based on an evolving understanding of the pathogenesis related to the development of diabetic neuropathy and other diseases that may lead to peripheral nerve injury. Consensus on evaluation strategies for patients presenting with pain has furthered our ability to define neuropathic pain and accompanying signs and symptoms that may respond to particular therapeutic approaches. Recent therapeutic advances in medical management have demonstrated improved outcomes in pain relief. This, along with lower side effect–related issues, has led to improved compliance and patient satisfaction. The assessment and treatment of comorbid conditions, which include sleep, anxiety, and depression, have further advanced the management of painful polyneuropathies in patients. New antiepileptics, antidepressants, and topical therapies have contributed to improved patient outcomes.

## Introduction

As our understanding of the pathophysiology related to the development of peripheral neuropathies continues to expand, so will effective strategies for their treatment. Changing population demographics and prevalences of diseases may lead to the increased development of painful peripheral neuropathies (PPN), which will continue to challenge the practicing clinician [1].

Diabetes mellitus (mainly type II) has become one of the most common medical conditions, affecting approximately 100 million people worldwide. When blood glucose levels are not well controlled, end-stage organ damage is an all to common consequence related to diabetes. Various organ systems including the peripheral nervous system may sustain damage as a result of elevated glucose levels. Estimates of diabetic polyneuropathy range from 40% to 90% of patients; of this group, 30% to 50% of the individuals affected will experience painful symptoms. Unfortunately, even with tight glucose control, individuals with type II diabetes may progress on to develop painful diabetic neuropathy [2].

Other less common, but equally debilitating forms of PPN may include inflammatory and chemotherapy-induced neuropathies [3] (

1). A significant percentage of individuals who present with idiopathic polyneuropathy may develop an identifiable cause such as diabetes mellitus.

Current research efforts continue to focus on the prevention, pathogenesis, and treatment of painful polyneuropathies. The recognition that PPNs most often are chronic in nature presents specific challenges for problems beyond the management of pain. Common comorbid conditions that may complicate treatment include sleep deprivation, anxiety, depression, and alteration in social function. Hence, successful treatment of PPN requires an understanding of the etiologic cause for the pain and an understanding of the physical and emotional consequences related to chronic pain [4].

## Pathogenesis

The manifestation of clinical findings related to neuropathic pain are a result of a "primary lesion or dysfunction in the nervous system" as defined by the International Association for the Study of Pain [5]. Pathogenesis surrounding the cause of the primary lesion or dysfunction may vary significantly from one person to the next. However, the resultant lesions most often will lead to changes in processing of sensory stimuli at the level of the peripheral and central nervous system.

Injury to the "small fiber peripheral nervous system" leading to disruption of normal sensory processing may involve a mix of pain-transmitting fibers (A-δ, C-fibers) and A-β mechanoreceptor non–pain-transmitting fibers. The consequences of peripheral sensory nerve activation often lead to central nervous system changes that are characterized by central sensitization [6].

The initiating factors for the development of the most common form of neuropathy, diabetic sensorimotor neuropathy, are thought to be the result of elevated blood glucose levels. The neurovascular system does not require insulin to uptake or maintain intracellular glucose levels; consequently, when glucose levels are elevated, secondary pathologic processes including oxidative stress and protein glycation lead to neurovascular injury. Progression of peripheral nerve injury also occurs when metabolic factors such as activation of the polyol pathway leads to accumulation of

**Table 1. Pathogenesis of painful polyneuropathy**

| |
|---|
| Diabetes |
| Idiopathic |
| Infectious |
| Immune inflammatory |
| Inflammatory polyradiculopathy |
| Toxic |
| Nutritional deficiencies |
| Monoclonal gammopathy |
| Familial/inherited neuropathies |
| Alcoholic |
| Chemotherapy |
| HIV |
| Metabolic |
| Vasculitic |

sorbitol within the peripheral nerve membranes and microvascular system. This combined with myoinositol reduction is thought to lead to structural nerve damage. Various other factors that may play a role include endoneural hypoxia secondary to arterio-venous shunting [7].

Infection or inflammation may be the underlying pathology in at least 50% of all clinical cases of peripheral neuropathic pain [8]. Recent work points toward evidence that supports involvement of the immune system in the development of neuropathies and related neuropathic pain. The importance of several factors, which include proinflammatory cytokines, tumor necrosis factor, and interleukins, have been demonstrated in animal models. These inflammatory immune responses may lead to damage of the myelin sheath and the nerve blood supply [3].

The manifestation of the pathologic processes as outlined previously may result in a combination of positive and negative symptoms and signs, which can be confusing for the patient and clinician.

## Evaluation

Guidelines recently were agreed on for the diagnosis and assessment of patients suspected of having neuropathic pain [9••] (Table 2). In addition to examination, patients should be evaluated for spontaneous pain (stimulus-independent) such as dysesthesias and stimulus-dependent pain (*ie*, allodynia). It is important to recognize that although routine, the standard electrodiagnostic studies such as the electromyography/nerve velocity conduction studies do not test for the small nociceptive and non-nociceptive afferent sensory fibers that are involved in neuropathic pain states.

However, electromyography/nerve velocity conduction testing still may be of value to rule out axonal or demyelinating neuropathies with treatable underlying etiologies, except in the clear cases of diabetic polyneuropathy or small fiber idiopathic neuropathy. Specific testing such as the sudomotor-axon reflex examination has a demonstrated 80% sensitivity for identification of small fiber injury [9••]. Unfortunately, even this test is unable to correlate small fiber injury with pain. More precise detection of cold and heat pain thresholds may be achieved with quantitative sensory testing. Krämer *et al.* [10] recently demonstrated with quantitative sensory testing a correlation between visual analog pain ratings and impairment of small fiber function in patients with painful diabetic neuropathy.

Peripheral neuropathic pain has multiple dimensions, which significantly impact the daily function of the affected individual. Recent work has demonstrated that poorly controlled pain leads to reductions in quality of life and reduced work productivity [4]. The implications of chronic pain as a major health and economic problem have led to the suggestion that we should consider it as a disease entity with its own pathology, symptoms, and signs.

## Treatment

The treatment of most painful polyneuropathies must be considered as symptom management. With the exception of a few specific conditions, the treatment of the underlying condition will have little impact on the pain and distress that patients experience from painful polyneuropathies. The Diabetes Control and Complications Trial has demonstrated that aggressive glucose control can slow the progression of end-organ injury including peripheral neuropathy in type-I diabetics. However, little is known regarding whether tight glucose control will impact the development of polyneuropathies in type II diabetes patients [7].

Recent trials with the aldose reductase inhibitor AS-3201 have been encouraging. Patients demonstrated a dose-dependent improvement in nerve conduction velocity that, for the first time, may lead to a diabetic neuropathy disease-modifying therapy [11].

The concept of mechanism-based therapy has been proposed as an approach that characterizes symptoms, signs, and related pathogenesis [12]. Unfortunately, despite intensive investigation and modeling of the pathogenesis related to peripheral neuropathy, our approach to treatment remains marginally effective [13,14]. Multiple reviews have demonstrated that at best, with the current pharmacologic management, only 50% of patients will obtain 50% or more relief of pain with a single agent [15]. Recent work indicates that a patient with chronic pain will perceive a clinically significant improvement in their pain with a 30% reduction in pain intensity [16]. Whether this translates into improvements in functionally related outcomes remains to be demonstrated.

Most of the trials completed before 1998 were designed to evaluate pain improvement only. As recently pointed out in a study of painful diabetic neuropathy patients, the consequences of pain encompass many quality-of-life related domains that are important to consider when evaluating treatment outcomes [4,17].

**Table 2. Diagnosis and assessment of patients suspected of having neuropathic pain**

| Fibers | Sensation | Tools/examination | Symptom/sign |
|---|---|---|---|
| A-δ | Cold, pinprick | Cold tuning fork, sharp object | Deep pain, numbness |
| C-fiber | Heat | Warm object | Spontaneous pain, allodynia |
| A-β | Touch, vibration | Coarse gauze, tuning fork | Numbness, allodynia |

Several therapeutic options are available for the treatment of PPN; however, none have been developed specifically for PPN treatment and only one has approval by the US Food and Drug Administration (FDA) and is exclusively for the treatment of PDN. Antidepressant and anticonvulsants medications are the most widely studied and are used for treating painful polyneuropathies. Comparisons among trials are difficult, as studies of the various drugs used different types of neuropathy and diverse tools for assessing clinical outcome.

A review by Collins *et al.* [18] evaluated 11 trials of antidepressants (eight using tricyclic antidepressants [TCAs] and three using selective serotonin reuptake inhibitors [SSRIs]) used to treat chronic pain resulting from PDN or painful herpetic neuropathy, with 445 patient episodes (active-treatment periods: 283 with TCAs and 162 with SSRIs). For TCAs, the numbers needed to treat (NNT) for at least 50% pain relief was 3.5 (95% confidence interval [CI], 2.5–5.6). The number needed to harm was 2.7 (95% CI, 2.1–3.9) for minor adverse events compared with placebo and 17 (95% CI, 11–43) for major adverse events. More importantly, the relative benefit of SSRIs was not found to be significantly different from that of placebo for the treatment of PDN.

Amitriptyline is a TCA that has been studied the most extensively. However, its usefulness often is limited by common anticholinergic side effects, from constipation and impaired cognition (pseudodementia) to potentially serious and life-threatening cardiac conduction abnormalities [19•]. Nortriptyline and desipramine offer a better side-effect profile, but still may cause anticholinergic side effects at higher doses and may affect cardiac conduction. Prescribing information for TCAs recommends extreme caution for patients with cardiovascular disease because of the risk for conduction defects, arrhythmias, stroke, and acute myocardial infarction [20,21].

Serotonin-norepinephrine reuptake inhibitors (SNRIs), a recent addition to the antidepressant drug class, are used to treat major depressive disorders and anxiety disorders and have efficacy based on their dual serotonin-norepinephrine mechanism of action. Venlafaxine, a serotonin and weak norepinephrine reuptake inhibitor, has proven to be efficacious when compared with placebo in a randomized, double-blind, three-way crossover study of 40 patients with painful polyneuropathy [22]. The treatment groups for venlafaxine 112.5 mg twice daily and for imipramine 75 mg twice daily demonstrated similar improvements when compared with placebo. A recent trial of 244 adult patients with PDN who were randomized to receive 75 mg daily (81 patients), 150 to 225 mg daily (82 patients), or placebo (81 patients) demonstrated that sustained-release venlafaxine is efficacious and safe at clinical doses between 150 and 225 mg daily [23].

Duloxetine, a recently approved SNRI, is the first drug to receive FDA approval for the treatment of PDN [24]. Studies indicate that doses of 60 mg daily and 60 mg twice daily were safe and produced greater improvement in 24-hour average pain severity scores (11-point Likert scale) compared with placebo in the treatment of PDN. The longer-term efficacy of duloxetine for the treatment of PDN was established when the randomized, 12-week, double-blind, placebo-controlled study groups continued into a 52-week open-extension study. Treatment with duloxetine 60 mg daily significantly improved the primary endpoint mean pain scores from baseline, along with many secondary measures, when compared with placebo. Duloxetine 60 mg twice daily versus placebo also proved to be equally efficacious and demonstrated positive effects on the Short-form McGill Pain Questionnaire total score sensory portion [25].

The introduction of seven new antiepileptic drugs throughout the past decade have added safer alternatives to the use of TCAs [26]. Various mechanisms of action, which include stabilization of neuronal membranes, increased inhibitory neurotransmission and decreased release of neurotransmitter [27].

Gabapentin has been approved by the FDA for the treatment of postherpetic neuralgia (PHN) and has demonstrated efficacy in three clinical trials in patients with PDN. A recent article by Bennett and Simpson [28] reviewed the pharmacology and clinical effectiveness of gabapentin in the treatment of neuropathic pain. Equal efficacy of gabapentin (average, 1565 mg daily) when compared with amitriptyline (average, 59 mg daily) was demonstrated in a prospective study [29].

Pregabalin, an amino acid derivative of γ-amino butyric acid, has demonstrated superior efficacy in several randomized, double-blinded, placebo-controlled trials for the treatment of neuropathic pain. An 8-week study of patients with PDN demonstrated relief ($P < 0.0001$) beginning at week 1 of the trial and lasting throughout the remainder of the study [30]. The study enrolled 146 patients who had a history of 1 to 5 years of PDN and randomized them to placebo ($n = 70$) or pregabalin ($n = 76$; 300 mg/d) groups. The primary efficacy measure was the endpoint mean pain score (11-point numerical pain

rating scale) and several secondary endpoints such as sleep were significantly improved. A second similarly designed pregabalin trial, which evaluated a total of 338 patients, demonstrated improved outcomes in patient global impression of change at 600 mg daily versus 300 mg daily.

More than 2700 patients have participated in 10 placebo-controlled pregabalin clinical trials for the treatment of neuropathic pain (PDN/PHN) [30]. FDA approval is pending for the treatment of PHN and PDN.

In a randomized trial of 146 patients, oxcarbazepine, a second-generation antiepileptic drug (AED), was proven to be efficacious and safe for the treatment of PDN. The mean maintenance dose of 1445 mg daily ($n$ = 69) significantly decreased pain from PDN measured by a visual analog scale (VAS; -24.3) compared with placebo (-14.7; $P$ = 9.01) [31]. When compared with carbamazepine, the safety profile is superior and adverse effects of oxcarbazepine, which include hyponatremia, are relatively few clinically [32].

In a double-blind, placebo-controlled, parallel group trial of 59 patients with PDN, lamotrigine was found to decrease pain intensity from 6.4 to 4.2 at the end of treatment. However, even at the effective dose of 200 to 400 mg daily, no improvement was found in secondary outcome measures [33]. A review by Verma *et al.* [34], which focused on the treatment of neuropathic pain in patients with HIV, suggested that a slow titration of lamotrigine over 6 to 8 weeks to 200 mg twice daily may benefit patients with painful distal sensory polyneuropathy who are receiving antiretrovirals.

Tiagabine was evaluated in 17 patients with painful sensory neuropathies in an open-label pilot trial; however, only seven of the patients completed the 4-week study, with eight dropouts attributed to adverse events [35]. Improvement of pain symptoms was seen with low doses of 4 to 8 mg of tiagabine. With higher doses, pain was not improved further; however, side effects increased.

In a small, randomized, placebo-controlled trial of topiramate, a total of 27 patients were evaluated for improvement in symptoms and positive objective measurements of peripheral neuropathy, which were positive. However, in a 12-week, multicenter, randomized, double-blind trial of 323 patients with PDN, topiramate-treated patients did not have significantly greater reduction in pain (VAS from 68.0 to 46.2 mm) compared with patients treated with placebo (VAS from 69.1 to 54.0 mm; $P$ = 0.038) [36].

In a randomized, placebo-controlled, crossover trial, valproic acid was found to be no more effective than placebo (daily dose of 1500 mg) for the treatment of painful polyneuropathy [37].

Opiate compounds have demonstrated efficacy for the treatment of numerous chronic pain conditions [38]. Tramadol has norepinephrine and serotonin reuptake inhibition capability and when metabolized, it also has weak μ-receptor agonist activity. Clinical data from controlled trials demonstrate that an average daily dose of 210 mg is required for the effective treatment of PPN, including PDN [39]. In a placebo-controlled, 4-week study (34 evaluable patients), controlled-release oxycodone was found to be effective in controlling pain due to diabetic neuropathy [40]. Study patients were allowed to continue taking stable doses of antidepressants, AEDs, analgesics, and nonsteroidal anti-inflammatory drugs. The mean daily dose of controlled-release oxycodone required to achieve improvement in steady pain, brief pain, and skin pain ($P$ = 0.0001) was 40.0 ± 18.5 mg.

In two separate trials, topical therapy for the treatment of focal peripheral neuropathies and polyneuropathies were studied for efficacy and impact on quality of life. The efficacy of the lidocaine 5% patch was demonstrated in 40 patients with peripheral neuropathic pain syndromes [40]. A randomized, placebo-controlled, two-way, crossover design revealed that ongoing pain and allodynia were significantly improved over 7 days. NNT to decrease ongoing pain by 50% were quite favorable at 4.4. In an open-label study of 56 patients with PDN that used up to four patches for a maximum of 18 hours daily, safety and efficacy were established [42]. Sleep, pain, and quality-of-life measures were improved significantly in this study. In a subgroup of patients treated for an additional period of 5 weeks, a decreased use of concomitant analgesic therapy was observed.

Several compounds are being investigated, although not all of the agents have been studied in controlled clinical trials. α-Lipoic acid is thought to decrease oxidative stress and possibly improve microcirculation and has shown efficacy in pain control in phase-4 European studies when administered by infusion to patients with PDN [43]. The oral formulation of α-lipoic acid is undergoing clinical trials. Amantadine, a noncompetitive *N*-methyl-D-aspartate receptor inhibitor, was effective in reducing pain when administered intravenously to 17 patients with PDN in a 4-week, randomized, double-blind, placebo-controlled, crossover study [44].

## Conclusions

Painful peripheral neuropathy results from distinct neuropathophysiologic changes and is a discrete clinical syndrome that presents particular challenges in diagnosis and treatment. Past treatment options primarily have included TCAs and older AEDs; unfortunately, significant side effects have limited their usefulness. The introduction of second-generation AEDs, SNRIs, and topical therapies with unique mechanisms of action have significantly increased the availability of effective and safe treatment options [25,30,32,42,45].

Future options for the management of PPN hold significant promise as a better understanding of pathogenesis guides the investigation and development of specific therapies [3,46,47]. Along with the introduction of several new agents for the treatment of PPN, the evaluation of disease

processes will continue to provide insight into better management strategies [9••,19•,48,49].

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