

# Painful Diabetic Neuropathy: A Management-Centered Review

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## Background

Neuropathy is a common complication of diabetes, affecting up to 50% of patients.<sup>1-5</sup> A consensus statement produced by an international meeting on the diagnosis and management of diabetic neuropathy defined it as “the presence of symptoms and/or signs of peripheral nerve dysfunction in people with diabetes after the exclusion of other causes.”<sup>6</sup> There are many types of neuropathy with a variety of clinical presentations. This article focuses on one phenotype of neuropathy: painful diabetic neuropathy (PDN). A review of the epidemiology, risk factors, prevention, diagnosis, and management of PDN is presented. This review will focus on a discussion of the myriad agents used in the treatment of PDN. The efficacy, dose, and duration for an appropriate therapeutic trial, contraindications, adverse effects, and monitoring parameters of each agent used in the treatment of PDN will be discussed.

## THE CLINICAL PROBLEM

### Case Study 1

A 52-year-old white man presents with lower-extremity pain. The pain is bilateral and is described as sharp and needle-like. The pain increases when he stands. He also experiences pain with any touch, including fabric, on his skin. The pain has been present for ~ 6 months and is not relieved with acetaminophen. He was diagnosed with diabetes 6 years ago. At the time of diagnosis, his hemoglobin A<sub>1c</sub> (A1C) was 12.3%. He was started on insulin and metformin therapy, and since then his glycemic control has been excellent, with his latest A1C

result 6.2%. Other medical history includes coronary artery disease, stage II diabetic nephropathy, morbid obesity, dyslipidemia, and atrial fibrillation.

### Case Study 2

A 78-year-old white woman complains of lower extremity pain that keeps her awake at night. She describes the pain as a deep aching in both feet. The pain started ~ 6 weeks ago. Until that time, she had been treated with amitriptyline for depression. The amitriptyline was discontinued after a series of falls, and she was started on a selective serotonin reuptake inhibitor (SSRI) for depression. She was diagnosed with diabetes ~ 18 years ago at the time of a coronary artery bypass grafting. Her diabetes has been well controlled on a minimal dose of glyburide since then. Her A1C has never been > 8% and has been ~ 7% for the past 4 years. Other past medical problems include vascular dementia,

coronary artery disease, hypertension, and dyslipidemia.

At the end of the review, we will return to these patients and discuss appropriate evaluation and management of their complaints.

## CLINICAL MANIFESTATIONS

The pain associated with PDN is often described as “tingling pain,” “numbness,” or “increased due to touch.”<sup>7</sup> However, it may also be described as burning, electrical, or stabbing with parasthesia, hyperesthesia, and deep aching. The pain is typically greater at night.<sup>8</sup> PDN typically develops in the feet and lower legs; however, it may also involve the hands.<sup>9</sup> Neuropathy is chronic and progressive. The pain in PDN is usually excruciating but rarely may spontaneously revert.<sup>10</sup> PDN greatly affects all areas of a patient’s life, including mood, sleep, self-worth, independence, ability to work, and interpersonal relationships.<sup>11,12</sup>

Although patients with PDN typically voice their symptoms, many patients may not report their symptoms until the pain is severe.<sup>13</sup> Screening for neuropathy should be considered annually. Physical exam may reveal a decrease in pressure or vibratory sensation or altered superficial pain and temperature sensation. A simple vibratory sensation exam consists of a tuning fork placed on the bony prominence at the dorsum of the great toe. Patients should be asked to state when they first feel the vibration and when it ceases. This should be repeated twice on each foot. Pressure sensation is gauged with a 10-g monofilament. The monofilament is placed at a

## IN BRIEF

Painful diabetic neuropathy is a common complication of diabetes and can affect many aspects of life and severely limit patients’ daily functions. This article reviews the diagnosis, prevention, and management of painful diabetic neuropathy. This condition can be difficult to treat, which frustrates both providers and patients. Commonly used agents, including the recently approved duloxetine and pregabalin, are reviewed, and their effective dose ranges, titration schemes, contraindications, and recommended monitoring are discussed.

right angle on the plantar surface of the foot, and pressure is applied until the monofilament bends. Patients are asked if they detect the sensation. Superficial pain sensation is tested with a pinprick. Monofilament examination, vibration testing with a tuning fork, and superficial pain sensation testing have similar efficacy in detecting neuropathy.<sup>14</sup> A single test is sufficient. One study performed by the U.S. Department of Veterans Affairs found that examination with a 10-g monofilament was the single most practical predictor of neuropathy.<sup>15</sup> Patients' mobility, gait, and balance should also be assessed.

The physical exam should also evaluate for signs of decreased arterial flow, altered reflexes, deformities, ulcers, or slow-healing wounds. Signs of decreased arterial flow may include absence of foot pulses, decrease in skin temperature, thin skin, lack of skin hair, and bluish skin color. Deformities associated with diabetic neuropathy include claw toes and Charcot's arthropathy. Claw toes are subluxations of the proximal interphalangeal-metatarsal joints. Charcot's arthropathy is a late finding in which there is collapse of the mid-foot arch, leading to bony prominences in various areas. These deformities are caused by small muscle wasting and decreased sensation that leads to altered weight distribution when standing. Sweating is often diminished in peripheral neuropathy, and the skin may appear cracked and dry.

### CLASSIFICATION

Although there are several classifications of diabetic neuropathies, only two will be reviewed here. The two most common types of diabetic neuropathies associated with pain are acute sensory neuropathy and chronic sensorimotor neuropathy. Acute sensory neuropathy is the acute or subacute onset of severe discomfort without associated signs. It is usually associated with hyperglycemia or intensification of glycemic control and may gradually lessen as euglycemia is obtained. Chronic sensorimotor neuropathy is the primary focus of this

review. It is a long-term complication of diabetes associated with symptomatic pain and clinical signs of neuropathy.<sup>16</sup>

### DIAGNOSIS

The diagnosis of PDN is a diagnosis of exclusion; all other etiologies of painful sensory neuropathy should be ruled out. In the Rochester Diabetic Neuropathy Study,<sup>1</sup> ~ 10% of diabetic patients with peripheral neuropathy were diagnosed with a neuropathy not related to diabetes. In the *Textbook of Diabetic Neuropathy*,<sup>17</sup> Dyck recommends a minimum of two abnormalities (from symptoms, signs, nerve conduction abnormalities, or quantitative sensory tests).

Patients with diabetes are at an increased risk to develop other types of neuropathy, including chronic inflammatory demyelinating polyneuropathy, B<sub>12</sub> deficiency, hypothyroidism, and uremia. Patients with peripheral neuropathy should also be evaluated for these types of neuropathies. This evaluation should be dictated by the clinical scenario but would frequently include serum B<sub>12</sub>, thyroid function tests, blood urea nitrogen, and serum creatinine. Tests for HIV and serum protein electrophoresis should be completed if HIV or monoclonal gammopathy are suspected. The presentation of typical pain description, decreased sensation, and absent reflexes is highly suggestive of PDN.<sup>8</sup>

### EPIDEMIOLOGY

Approximately 50% of patients who have had diabetes for > 25 years will develop neuropathy.<sup>3</sup> Approximately 50% will have pain as a symptom of neuropathy.<sup>8</sup> Neuropathy is usually a late finding in type 1 diabetes; however, it can be an early finding in type 2 diabetes. In fact, one study conducted in Finland found a neuropathy prevalence of 8.3% in newly diagnosed type 2 diabetes.<sup>18</sup>

Hyperglycemia is highly correlated with the development and progression of all neuropathies, including PDN.<sup>19,20</sup> The Diabetes Control and Complications Trial (DCCT) showed that tight glycemic

control will reduce the incidence of neuropathy by 60%.<sup>21</sup> However, even in patients with long-term excellent glycemic control (A1C < 8%), the lifetime incidence of PDN remains 20%.<sup>22</sup>

Other risk factors thought to be associated with diabetic neuropathy are hyperlipidemia, hypertension, cigarette smoking, consumption of alcohol, and weight. Although there have been no trials that show a reduction in neuropathy when addressing these modifiable risk factors, these factors are generally addressed in patients with diabetes to prevent other long-term complications, such as coronary artery disease, peripheral vascular disease, and stroke.

### MANAGEMENT

Neuropathic pain is difficult to treat, and patients rarely experience complete pain relief.<sup>23</sup> It is a frustrating problem for both providers and patients. The pain is often chronic and can be debilitating. There are no treatments that will relieve the pain completely; prevention remains the best strategy.

#### Prevention

Strict glycemic control is perhaps the single greatest prevention measure for neuropathy.<sup>21</sup> Also, controlling hyperlipidemia and hypertension, taking daily aspirin, ceasing smoking, and consuming alcohol only in moderation may also be important in the prevention of PDN.

#### Treatment

The first step in the management of PDN is glycemic control and correction of any other metabolic derangements. In the DCCT, strict glycemic control not only decreased the incidence of neuropathy but also slowed its progression by 57%.<sup>21</sup>

In addition to controlling hyperglycemia, patients often require management of their pain symptoms. However, many patients are unable to achieve complete pain relief. A thorough understanding of therapeutic options and of the likely benefits and potential adverse effects of each option should be considered

before starting a medication. This will help patients and providers set realistic goals for pain reduction.

Several agents, predominantly antidepressants and antiepileptics, have been used with varying degrees of success in the treatment of PDN. There are several limitations in the treatment of PDN and in determining the most appropriate medication to use in each patient. Often, patients expect 100% pain relief after the first dose. Unfortunately, there is no agent that will provide that type of relief. In most studies that have evaluated the effectiveness of treatments for PDN, treatment was deemed successful if patients obtained a 50% reduction in pain. It often takes several weeks for the agents to become effective. To complicate the use of these medications, careful titration is needed to reduce adverse events and increase tolerability. It is easy to understand the aggravation patients often feel with therapies if they expect instant, complete pain relief.

### Medications for Treatment of PDN

The major classes of drugs used to treat PDN are antidepressants (primarily tricyclic antidepressants [TCAs] and antiepileptics). The first medication studied in a randomized, controlled trial for the treatment of PDN was carbamazepine in 1969.<sup>24</sup> Amitriptyline was first studied in an open-label study in 1977.<sup>25</sup> Since that time, many drugs have been found to have possible efficacy in the treatment of PDN. However, the first drug to be approved for the indication of PDN was duloxetine in 2004. Since then, a second agent, pregabalin, has also received U.S. Food and Drug Administration (FDA) approval for the indication of PDN.

Many of the agents used to treat PDN have not been compared to each other. Also, the end points in many of the studies have varied, making it difficult to compare agents between studies. Although a randomized, controlled trial of all agents would be desirable to determine the most efficacious agents, such a study would be impractical. To increase

the comparability, this article uses as a measure of efficacy the number needed to treat (NNT) to obtain one patient with 50% pain reduction. The NNT is the inverse of the absolute risk reduction. Unfortunately, some studies (especially older ones) do not contain enough information to calculate NNT. In those cases, NNT has been calculated only from studies that contain the necessary information. There are many limitations to this type of comparison. These studies were performed in different populations, at different times, and with different methods. However, because of the limitations in the available data, this is likely the most appropriate method of comparing these agents. Table 1 lists the NNT for each agent, as well as the effective dose ranges and sample titration schemes. Table 2 lists adverse side effects, contraindications, and recommended monitoring for the most commonly used agents for PDN.

### TCAs

TCAs were introduced in the late 1950s. This class is the most studied of all agents in the treatment of PDN. Amitriptyline was the first TCA to be studied in 1977.<sup>25</sup> Amitriptyline and imipramine are balanced serotonin and noradrenaline reuptake inhibitors. They also block  $\alpha$ -adrenergic, H1-histamine, muscarinic cholinergic, and N-methyl-D-aspartate receptors.<sup>26</sup> Nortriptyline and desipramine are the metabolites of amitriptyline and imipramine, respectively, and are primarily noradrenaline reuptake inhibitors. They also block  $\alpha$ -adrenergic, H1-histamine, muscarinic cholinergic, and NMDA receptors.<sup>26</sup> TCAs act centrally to reduce the perception of pain.

TCAs generally have the lowest NNT of the medications used to treat PDN. In summarizing the trials performed for treatment of PDN with TCAs, ~30% of patients obtain 50% pain relief.<sup>27–29</sup> The balanced serotonin and noradrenaline reuptake inhibitors amitriptyline and imipramine have an NNT of 2.1 (95% confidence interval

[CI] 1.8–2.6) to obtain one patient with a 50% pain reduction.<sup>30</sup> Amitriptyline has been evaluated in five placebo-controlled trials.<sup>31–35</sup> Imipramine has been studied in six placebo-controlled trials.<sup>36–41</sup> The primarily noradrenaline reuptake inhibitor desipramine has an NNT of 2.5 (1.9–3.6) to obtain one patient with a 50% pain reduction.<sup>30</sup> The efficacy of desipramine in the treatment of PDN has been evaluated in three placebo-controlled trials.<sup>32,42,43</sup> No NNT can be calculated for nortriptyline because there have been no trials of monotherapy in the treatment of PDN, but it is considered to be similar to desipramine. Doxepin, which is similar in function to amitriptyline and imipramine, has not been evaluated in the treatment of PDN but likely has similar efficacy.

TCAs are often contraindicated. Also, there is a high incidence of adverse effects, and TCAs are often not tolerated by patients. TCAs should be used with caution in patients who have a history of cardiovascular disease or are >65 years of age. Amitriptyline and nortriptyline are relatively contraindicated in patients with a history of ischemic cardiovascular disease, whereas doxepin is thought to be the least cardiotoxic of the TCAs.<sup>44</sup> TCAs have been associated with orthostatic hypotension and should be used cautiously in patients with a history of orthostasis or frequent falls. Some side effects, such as dizziness and sedation, can be lessened by careful titration. Sedation also lessens after 3–4 weeks of use. TCAs have been associated with significant weight gain in the treatment of depression. Amitriptyline typically causes a rapid weight gain, whereas the other TCAs are usually associated with a slower weight gain.<sup>45</sup>

### Other antidepressants

Venlafaxine has also been studied in the treatment of PDN in three separate trials.<sup>41,46,47</sup> Venlafaxine and its active metabolite are potent inhibitors of neuronal serotonin and norepinephrine reuptake and weak inhibitors of dopamine reuptake. Venlafaxine is also thought to

**Table 1. Usual Effective Dosages and Titration Schemes for the Treatment of PDN**

Medication	Usual effective dosage range	Titration scheme	NNT (95% CI) to achieve 50% pain reduction	Time to effect
<b>Tricyclic antidepressants</b>				
Amitriptyline	100–150 mg/day (150 mg at bedtime or 75 mg twice daily)	Day 1: 12.5 mg/day Days 2–7: 25 mg/day Week 2: 50 mg/day Week 3: 75 mg/day Week 4: 100 mg/day Weeks 5–8: 150 mg/day	2.1 (1.8–2.6) <sup>30</sup>	6–8 weeks
Nortriptyline	100–150 mg/day (50 mg three times daily)	Day 1: 12.5 mg/day Days 2–7: 25 mg/day Week 2: 50 mg/day Week 3: 75 mg/day Week 4: 100 mg/day Weeks 5–8: 150 mg/day	Cannot calculate NNT; similar to desipramine	6 weeks
Imipramine	150 mg/day (75 mg twice daily)	Week 1: 25 mg twice daily Week 2: 50 mg twice daily Week 3: 75 mg twice daily	2.1 (1.8–2.6) <sup>30</sup>	4 weeks
Desipramine	200–250 mg/day (250 mg daily or 125 mg twice daily)	Week 1: 50 mg/day Week 2: 100 mg/day Week 3: 200 mg/day Week 4: 250 mg/day	2.5 (1.9–3.6) <sup>30</sup>	6 weeks
<b>Other antidepressants</b>				
Venlafaxine	150–225 mg/day (75 mg three times daily or extended release formulation daily)	Week 1: 37.5 mg/day Week 2: 75 mg/day Week 3: 150 mg/day Week 4: 225 mg/day	5.5 (3.4–14) <sup>30</sup>	4–6 weeks
Duloxetine	60–120 mg/day (60 every day or twice a day)	Week 1: 10 mg/day Week 2: 20 mg/day Week 3: 60 mg/day Week 4: 120 mg/day	4 (3–9) <sup>82</sup>	4 weeks
<b>Antiepileptics</b>				
Carbamazepine	600 mg/day (200 mg three times daily)	Weeks 1–2: 100 mg three times daily Week 3: 200 mg three times daily	2.3 (1.6–3.9) <sup>30</sup>	4 weeks
Lamotrigine	200–400 mg/day (200 mg twice daily)	Week 1: 25 mg/day Week 2: 50 mg/day Week 3: 100 mg/day Week 4: 200 mg/day Week 5: 400 mg/day	4.0 (2.1–42) <sup>30</sup>	6–8 weeks
Valproate	1,000–1,200 mg/day (500 mg twice daily or 400 mg three times daily)	Week 1: 600 mg/day Week 2: 1,200 mg/day	2.5 (1.8–4.1) <sup>30</sup>	4 weeks
Topiramate	300–400 mg/day (200 mg twice daily)	Week 1: 25 mg/day Week 2: 50 mg/day Week 3: 75 mg/day Week 4: 100 mg/day Week 5: 150 mg/day Week 6: 200 mg/day Week 7: 300 mg/day Week 8: 400 mg/day	7.4 (4.3–28) <sup>30</sup>	12 weeks
Gabapentin	2,400–3,600 mg/day (1,200 mg three times daily or 900 mg four times daily)	Week 1: 300 mg at bedtime Week 2: 300 mg twice daily Week 3: 300 mg three times daily Week 4: 600 mg three times daily Week 5: 900 mg three times daily	3.9 (3.2–5.1) for doses ≥ 2,400 mg/day <sup>30</sup>	4 weeks

*cont'd on page 10*

**Table 1. Usual Effective Dosages and Titration Schemes for the Treatment of PDN (cont'd from page 9)**

Medication	Usual effective dosage range	Titration scheme	NNT (95% CI) to achieve 50% pain reduction	Time to effect
<b>Antiepileptics, cont'd</b>				
Pregabalin	300–600 mg/day (300 mg twice daily or 200 mg three times daily)	Week 1: 150 mg/day Week 2: 300 mg/day Week 3: 600 mg/day (Dosed twice or three times daily)	4.2 (3.4–5.4) <sup>30</sup>	4–6 weeks
<b>Others</b>				
Capsaicin cream	0.075% four times daily	No titration needed	6.7 (4.6–12)	8 weeks
Tramadol	200–400 mg/day (100 mg four times daily)	Week 1: 50 mg/day Week 2: 100 mg/day Week 3: 150 mg/day Week 4: 200 mg/day Week 5: 300 mg/day Week 6: 400 mg/day	3.5 (2.4–6.4) <sup>30</sup>	6 weeks
Mexilitine	450–675 mg/day (225 mg three times daily)	Week 1: 225 mg/day Week 2: 450 mg/day Week 3: 675 mg/day	2.2 (1.3–8.7) <sup>30</sup>	1–4 days

work centrally by decreasing the perception of pain. The calculated NNT from two of these trials is 5.5 (95% CI 3.4–14).<sup>30</sup> Adverse events are less frequent with venlafaxine than with the TCAs and include somnolence, nausea, and sweating. When taking venlafaxine, patients' mean heart rate may increase by 4–9 bpm. Also, blood pressure must be carefully monitored because venlafaxine may lead to an increase in blood pressure, especially in patients with a history of hypertension.

Duloxetine was the first agent approved by the FDA for the treatment of PDN. However, there have been no trials comparing the efficacy of duloxetine to other agents used in the treatment of PDN. Duloxetine inhibits both serotonin and norepinephrine transporters.<sup>48</sup> The precise mechanism of the central pain inhibition of duloxetine is not known. Two blinded, placebo-controlled, randomized trials of 12 weeks' duration have been performed by the manufacturer to evaluate the efficacy of duloxetine in the treatment of PDN. However, only one has been published,<sup>49</sup> and it showed statistically significant benefit at dosages of 60 and 120 mg/day. Duloxetine must be avoided in patients with any degree of hepatic insufficiency or substantial alcohol use. Patients on duloxetine therapy

should have their blood pressure, heart rate, and liver enzymes monitored.

SSRIs have also been studied in the treatment of PDN. The studies have not shown great efficacy. One study found paroxetine was not as effective as imipramine.<sup>39</sup> Another found that fluoxetine was equivalent to placebo in the treatment of PDN.<sup>32</sup> A study of citalopram found that it relieved symptoms of PDN but was not much more effective than placebo.<sup>50</sup>

**Antiepileptics**

Carbamazepine was the first agent studied in the treatment of PDN.<sup>24</sup> Since then, there have been three additional trials investigating the efficacy of carbamazepine in the treatment of PDN.<sup>51–53</sup> Carbamazepine works peripherally by blocking the sodium channels on the Aδ nerve fibers. Although carbamazepine has good efficacy in the treatment of PDN, it also is associated with serious adverse events, including aplastic anemia. Patients must be carefully monitored if placed on carbamazepine.

Lamotrigine also acts peripherally as a sodium channel blocker. The efficacy of lamotrigine has been evaluated in two studies—one parallel placebo-controlled<sup>54</sup> and one open label.<sup>55</sup> Lamotrigine is less efficacious than carba-

mazepine and is associated with aplastic anemia and toxic epidermal necrolysis.

Valproate has been studied in three placebo-controlled trials. Valproate was found to be efficacious in two studies<sup>56,57</sup> but equivalent to placebo in the other.<sup>58</sup> Valproate is another peripherally acting agent. The use of valproate is associated with thrombocytopenia, aplastic anemia, toxic epidermal necrolysis, and pancreatitis. Patients taking valproate must be monitored with serial liver function tests and complete blood count with platelets.

Topiramate is one of the few agents used in the treatment of PDN that is associated with weight loss.<sup>59</sup> Unfortunately, topiramate has not been shown to be highly efficacious in the treatment of PDN, with a calculated NNT of 7.4, which is equivalent to placebo.<sup>30</sup> It acts peripherally as a sodium channel blocker and at the GABA receptor. There have been two parallel, placebo-controlled studies of topiramate in the treatment of PDN. One showed efficacy after 8 weeks,<sup>60</sup> whereas the other, a much larger study, showed no difference between topiramate and placebo.<sup>61</sup> Topiramate has many adverse effects, such as cognitive slowing, dizziness, and a small risk of kidney stones and closed-angle glaucoma, and it often is not tolerated by patients. In the larger of the studies, 24%

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**Table 2. Adverse Events, Contraindications, and Monitoring Recommendations for Commonly Used Agents in the Treatment of PDN**

Medication	Adverse events	Contraindications for use	Recommended monitoring
<b>Tricyclic antidepressants</b>			
Amitriptyline	Dry mouth, sedation, dizziness, confusion, orthostatic hypotension, constipation, urinary retention, blurred vision, weight gain, arrhythmias	Cardiovascular disease; with or within 14 days use of MAO inhibitors; concurrent use of cisapride	Blood pressure and heart rate before and during initiation; weight; EKG before and during initiation; mental status
Nortriptyline	Dry mouth, sedation, dizziness, confusion, orthostatic hypotension, constipation, urinary retention, blurred vision, weight gain, arrhythmias	Cardiovascular disease; with or within 14 days use of MAO inhibitors; pregnancy	Blood pressure and heart rate before and during initiation; weight
Imipramine	Dry mouth, sedation, dizziness, confusion, orthostatic hypotension, constipation, urinary retention, blurred vision, weight gain, arrhythmias	Acute recovery phase of myocardial infarction; with or within 14 days use of MAO inhibitors; pregnancy	Blood pressure and heart rate before and during initiation; weight; EKG in older adults; mental status
Desipramine	Dry mouth, sedation, dizziness, confusion, orthostatic hypotension, constipation, urinary retention, blurred vision, weight gain, arrhythmias	Acute recovery phase of myocardial infarction; with or within 14 days use of MAO inhibitors	Blood pressure and heart rate before and during initiation; weight; EKG before and during initiation; mental status
<b>Other antidepressants</b>			
Venlafaxine	Headache, nausea, sedation, constipation, diarrhea, dizziness, dry mouth, sexual dysfunction, hypertension, seizures Rare: SIADH (syndrome of inappropriate antidiuretic hormone secretion), hyponatremia	With or within 14 days use of MAO inhibitors	Blood pressure; cholesterol; heart rate
Duloxetine	Nausea, somnolence, dizziness, dry mouth, constipation, sweating, weakness, headache, diarrhea	Hepatic insufficiency of any degree; substantial alcohol use; creatinine clearance < 30 ml/min; with or within 14 days use of MAO inhibitors; uncontrolled narrow angle glaucoma; caution in patients with delayed gastric emptying	Blood pressure; mental status; liver enzymes
<b>Antiepileptics</b>			
Carbamazepine	Agitation, dry mouth, sedation, ataxia, nausea, vomiting, blurred vision, confusion, fatigue, nystagmus Rare: aplastic anemia	Hypersensitivity to TCAs; bone marrow depression; with or within 14 days of MAO inhibitor use; pregnancy	Complete blood count with platelet count, reticulocytes, serum iron, lipid panel, liver function tests, urinalysis, BUN, serum carbamazepine levels, thyroid function tests, serum sodium; ophthalmic exams (pupillary reflexes); observe patient for excessive sedation, especially when instituting or increasing therapeutical pacemaker
Lamotrigine	Dizziness, ataxia, sedation, headache, blurred vision, diplopia, nausea, confusion, nystagmus, rhinitis Rare: aplastic anemia, toxic epidermal necrolysis	Use with caution with valproic acid	Serum levels of concurrent antiepileptics; hypersensitivity reactions, especially rash
Valproate	Dizziness, somnolence, alopecia, insomnia, nausea, diarrhea, vomiting, thrombocytopenia, tremor, weakness Rare: aplastic anemia, pancreatitis, toxic epidermal necrolysis	Hepatic dysfunction, urea cycle disorders, pregnancy; concurrent use with topiramate	Liver enzymes; complete blood count with platelet count
BUN, blood urea nitrogen; MAO, monoamine oxidase.			<i>cont'd on page 12</i>

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**Table 2. Adverse Events, Contraindications, and Monitoring Recommendations for Commonly Used Agents in the Treatment of PDN (cont'd from page 11)**

Medication	Adverse events	Contraindications for use	Recommended monitoring
<b>Antiepileptics cont'd</b>			
Topiramate	Dizziness, ataxia, psychomotor slowing, memory problems, speech difficulties, serum bicarbonate decreased, nausea, migraine, weight loss, anorexia Significant: metabolic acidosis (hyperchloremic, non-anion gap), nephrolithiasis, hyperthermia, central nervous system effects, secondary angle closure glaucoma. Must be tapered to avoid withdrawal.	Use with caution in hepatic and renal impairment; concurrent use with valproic acid	Hydration status; electrolytes prior and periodically during treatment; acute acidosis, complications of chronic acidosis (nephrolithiasis, osteomalacia); ammonia for unexplained lethargy; symptoms of acute glaucoma
Gabapentin	Somnolence, dizziness, ataxia, nausea, dry mouth, constipation, nystagmus, leucopenia, weight gain	Cautiously in patients with severe renal dysfunction	Serum levels of concomitant antiepileptic therapy
Pregabalin	Peripheral edema, dizziness, somnolence, ataxia, tremor, blurred vision, diplopia, weight gain. Rare: rhabdomyolysis, acute renal failure, prolong PR interval, thrombocytopenia. Must be tapered to avoid withdrawal.	Cautiously in patients with congestive heart failure, hypertension; concurrent use of thiazolidinedione	Degree of sedation; symptoms of myopathy or ocular disturbance; weight gain/edema; creatine phosphokinase; skin integrity (in diabetic patients)
<b>Others</b>			
Capsaicin cream	Localized burning and itching, cough, sneezing	Open wounds	Skin breakdown
Tramadol	Nausea, sedation, constipation, headache, dry mouth, urinary retention, confusion, tremor, seizures	Substantial alcohol use	Respiratory rate, blood pressure, heart rate; signs of tolerance or abuse
Mexilitine	Dyspepsia, dizziness, tremor, ataxia, insomnia, diarrhea, constipation, headache, nervousness, hepatotoxicity, arrhythmia Rare: agranulocytosis, toxic epidermal necrolysis	History of cardiogenic shock; second- or third-degree atrioventricular block (unless with functional pacemaker)	EKG prior to and during therapy; complete blood count with platelets; liver enzymes

of patients discontinued topiramate because of side effects.<sup>61</sup> Topiramate requires careful titration during initiation and withdrawal.

Gabapentin is commonly used in the treatment of neuropathic pain. Like the other antiepileptics, it acts peripherally to decrease pain perception. The efficacy of gabapentin has been evaluated in four studies. Two of the studies showed statistically significant efficacy of gabapentin over placebo.<sup>62,63</sup> One other study did not show a statistically significant difference between gabapentin and placebo; however, the dose of gabapentin used was low (900 mg).<sup>64</sup> The fourth study directly compared gabapentin to amitriptyline in a cross-over study. In that study, 15 of 30 patients had greater pain relief with

amitriptyline, whereas 7 of 30 had greater pain relief with gabapentin.<sup>35</sup> The NNT for gabapentin is 3.9.<sup>30</sup> Gabapentin is typically thought to have few side effects and interactions. The most common adverse events are sedation and dizziness. Significant weight gain has been described with long-term use of gabapentin in the treatment of seizure disorder, typically starting 2–3 months after initiation.<sup>65</sup> Unlike the other antiepileptics, gabapentin is not hepatically metabolized, significantly decreasing its interaction with other medications.

Pregabalin is the second agent approved by the FDA for the indication of PDN. It acts peripherally at the GABA receptor to block the perception of pain.

Pregabalin has been evaluated in three parallel, placebo-controlled studies in the treatment of PDN.<sup>66–68</sup> The NNT is 4.2.<sup>30</sup> Pregabalin is relatively well tolerated and causes less sedation than gabapentin. However, it is associated with other rare but serious adverse events, including rhabdomyolysis, acute renal failure, central nervous system effects, hyperthermia, and secondary acute-angle glaucoma. Patients on pregabalin therapy must be monitored closely for myopathy and ocular complaints. Pregabalin is also significantly associated with peripheral edema and weight gain. This effect is intensified when given concurrently with thiazolidinediones. Pregabalin should be avoided in patients with hypertension and congestive heart failure.

### Other agents

Capsaicin is an alkaloid derived from chilies. It acts peripherally by depleting the neurotransmitter substance P from sensory nerves. It is applied topically and is not absorbed significantly into the systemic circulation. The only adverse effects are local stinging and burning and sneezing or coughing during application. It must be applied while wearing gloves, and patients must be careful not to touch their face until after carefully washing their hands. Capsaicin cream 0.075% has been evaluated in five studies.<sup>33,69–73</sup> Although efficacious in the clinical trial setting, its complexity may limit the clinical applicability in nontrial settings. It is logistically difficult for patients to apply, must be applied 4 times a day to the entire painful area, and often is very painful during the 1st week of application. However, if patients have contraindications or intolerance to oral agents, capsaicin is a reasonable alternative. The pain with application decreases after the 1st week of use.

Tramadol acts through both monoaminergic (like the TCAs) and opioid mechanisms and acts centrally to block pain perception. Tramadol has lower abuse potential than other opioids. It has been evaluated in the treatment of PDN in two placebo-controlled studies.<sup>74,75</sup> The NNT is 3.5.<sup>30</sup> Tramadol should be titrated so that the effects on the respiratory system may be monitored. Tramadol has side effects common to opioids, such as constipation, urinary retention, and central nervous system effects. It should be avoided in patients with substantial alcohol use or a history of opioid abuse.

Mexilitine is an oral analog of lidocaine. It is a class IB antiarrhythmic agent and acts peripherally as an ion channel blocker to prevent the perception of pain. It has been evaluated in five placebo-controlled trials and was found to be efficacious in all but one.<sup>76–80</sup> Interestingly, no study found any increase in proarrhythmic effects, although arrhythmia would certainly be a concern with the use of this medica-

tion. Of all the agents used in the treatment of PDN, mexilitine has the fastest onset of pain relief, which is usually within 1–4 days. Mexilitine has been associated with agranulocytosis, hepatotoxicity, and toxic epidermal necrosis. It is absolutely contraindicated in patients with second- and third-degree atrioventricular block unless an artificial pacemaker is utilized. Patients on mexilitine therapy should be monitored with complete blood count with platelet measurement, electrocardiogram, and liver enzyme tests.

Nonsteroidal anti-inflammatory drugs (NSAIDs) have also been used in the treatment of PDN. However, great caution must be exercised when using NSAIDs in this population because this may worsen underlying renal dysfunction.

### DISCUSSION

PDN is a common and difficult complication of diabetes. It is often debilitating and affects every aspect of a patient's life. The pain associated with PDN is difficult to treat and may not completely resolve with any of the agents discussed in this article. Different agents may be appropriate for different patients, and patients may try multiple agents before finding one that works for them. Combination therapies, especially those that combine centrally acting agents with peripherally acting agents, may provide increased pain relief but remain largely unstudied.

The rate of relapse of pain symptoms in PDN is unknown; however, in clinical practice, many patients treated for pain symptoms relapse or have a recurrence of pain symptoms after initial control. This may be because of change of pathology, but it may also be related to patient adherence to the regimen and to patients' expectations of the medication.<sup>81</sup> It is important that patients and their providers discuss the likely efficacy and duration of treatment before any therapy is initiated. Patients and providers should have realistic goals for the treatment of PDN.

### Return to the Cases

The 52-year-old white man in Case Study 1 at the beginning of this article demonstrated decreased sensation in both feet during a monofilament exam, as well as decreased Achilles reflexes. Because of his history of diabetes, symptomology, and exam, it is reasonable to assume a diagnosis of PDN if his laboratory evaluation is within normal limits. His B<sub>12</sub>, thyroid function tests, blood urea nitrogen, and creatinine were within normal limits. HIV antibody testing was negative. Because of his recent coronary artery disease, TCAs were contraindicated, and he was started on gabapentin. He was titrated to 3,600 mg over 8 weeks; he had ~50% pain reduction on that dose. He continued to use acetaminophen for additional pain relief. After initial adequate response, he had progression of his nighttime symptoms. Tramadol, 100 mg every night, was added to his regimen with resultant good control of nighttime symptoms. He checks his feet daily for signs of ulceration.

The 78-year-old woman described in Case Study 2 also had decreased sensation in both feet during a monofilament exam and decreased Achilles reflexes. On laboratory evaluation, her B<sub>12</sub> was noted to be low; other tests were within normal limits. She was treated with B<sub>12</sub> replacement, but her symptoms continued. Electromyography revealed neuropathic changes. Because of her multiple medical problems and extensive medication list, capsaicin cream was the first agent prescribed. However, because of her vascular dementia, she was unable to adhere to the regimen. Gabapentin was next tried with a slow titration. She complained of excessive fatigue on gabapentin and continued pain; the effective dosage was unable to be achieved because of adverse effects. She was initiated on pregabalin with excellent control of symptoms. There is a concern for weight gain and congestive heart failure with her history of hypertension and coronary artery disease. Therefore, she monitors her weight

weekly and checks daily for signs of foot ulceration and peripheral edema.

**Conclusions**

PDN is a very difficult disease to treat and requires excellent communication between patient and provider for diagnosis, decisions about which medication to start, expectations of a medication's effectiveness, monitoring for adverse events, and adherence to the medication plan to prevent relapse of symptoms. Patients should be educated on the likely effectiveness, titration plan, and time to effectiveness for each agent so that they may have realistic expectations before initiation of therapy.

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