Pain Associated with Diabetic Peripheral Neuropathy
A Review of Available Treatments
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Educational Objectives
After reviewing this article, readers should be able to:
- Describe the pathophysiology of diabetic peripheral neuropathy.
- Evaluate pharmacotherapy for diabetic peripheral neuropathy.
- Compare current medications used to treat diabetic peripheral neuropathy.
- Formulate recommendations for the treatment of diabetic peripheral neuropathy.

Introduction
Diabetic peripheral neuropathy (DPN) affects 20% to 30% of patients with diabetes and is a significant cause of morbidity and mortality. Although the true prevalence of DPN is difficult to determine, it may be responsible for up to 75% of nontraumatic amputations. These alarming statistics emphasize the need for practitioners to adopt the following primary recommendations from the American Diabetes Association’s Standards of Medical Care 2007:

- Patients should be screened for DPN at their baseline examination and annually.
- After a diagnosis of DPN has been made, specialized foot care should be instituted to decrease the risk of amputation
- If decreased sensation occurs in the feet, the feet should be inspected every three to six months.

Hyperglycemia is an important risk factor for the development of peripheral neuropathy. Other risk factors include the duration of diabetes, the patient’s age, cigarette smoking, alcohol consumption, hypertension, hypercholesterolemia, and taller height (the longer the nerve fibers, the greater the susceptibility to damage from external trauma or vascular complications). Most practitioners are aware of the severe pain that accompanies DPN, but only 10% to 30% of patients experience painful symptoms. Instead, the disorder begins as a change in or loss of sensation that can be detected only by clinical tests. Symptoms associated with sensory loss are more common; these include an inability to feel, identify, or manipulate small objects; a loss of ability to judge temperature or painful stimuli; and muscle atrophy, which may lead to physical deformities.

The pathophysiology of DPN is multifactorial (Figure 1). Increased oxidative stress, increased sorbitol, decreased nitric oxide, and increased homocysteine have been identified as the primary factors involved.

Elevated blood glucose levels can lead to glycosylated proteins that are easily harmed by free radicals. These proteins may then combine with fats to produce advanced glycosylated end-products that have been linked to abnormalities in vascular tissue, lipid metabolism, and platelets.

Increased sorbitol results from passive diffusion of glucose into nerve cells. After the glucose is inside the cell, it is converted to sorbitol (and other polyols). Sorbitol does not diffuse out of the cell very easily and thus accumulates within the neuron. Studies of diabetic rats suggest that nitric oxide deficiency

\[ \text{Oxidative stress} \rightarrow \text{Advanced glycosylated End-products (AGEs)} \]

\[ \text{Sorbitol} \rightarrow \text{(Na\(^+\)/K\(^+\))–ATPase activity} \rightarrow \text{Free carnitine and myo-inositol} \]

\[ \text{Nitric oxide} \rightarrow \text{Homocysteine} \rightarrow \text{Impaired endothelial function} \]

Figure 1  Pathophysiology of diabetic peripheral neuropathy. (Reproduced with permission from Head KA. Altern Med Rev 2006;11(4):294–329. Courtesy of Thorne Research, Inc.)
may lead to diminished blood flow, another major dysfunction in DPN.

Finally, increased homocysteine levels, a well-known cause of endothelial dysfunction, are present in many patients with diabetes mellitus.4

In this article, we provide a comprehensive review of the drug therapies commonly used to treat the pain associated with DPN. We also present a stepwise approach to selecting an appropriate agent.

Pharmacological Agents

Antidepressants

Tricyclic Antidepressants

The tricyclic antidepressants (TCAs) are commonly prescribed to treat depression as well as various chronic pain states. These agents appear to relieve pain by blocking the neuronal reuptake of norepinephrine (NE) and serotonin (5-HT), thereby causing more of these neurotransmitters to be available in the synapse.1

The analgesic effects of TCAs seem to be independent of their antidepressant effects.5,6 The adverse effects associated with this class are anticholinergic in nature and include constipation, dizziness, blurred vision, urinary retention, cardiacoarrhythmias, and dry mouth.6 Affinities for the muscarinic (cholinergic) receptor vary within this class; amitriptyline has the highest affinity, followed by protriptyline (Vivactil, Merck), clomipramine (Anafranil, Mallinckrodt), doxepin (Sinequan, Pfizer), imipramine (Tofranil, Mallinckrodt), nortriptyline (Pamelor, Mallinckrodt), and desipramine (Norpramin, Aventis). The tertiary amine TCAs (amitriptyline, imipramine, clomipramine, and doxepin) also have the greatest affinity for histamine and alpha1-adrenergic receptors and are associated with more sedation and orthostatic hypotension.5

Although the Food and Drug Administration (FDA) has not approved TCAs for the treatment of DPN,8 the efficacy of these products has been highlighted in many trials (Table 1).9–13 Amitriptyline is the most studied TCA for DPN and has been compared with placebo, imipramine, and desipramine.

Amitriptyline, when compared with placebo, reduced pain to a significant degree. Pain relief was evident as early as the second week of therapy, with greater pain relief noted at higher doses (at a mean dose of 90 mg). A decrease in pain was not associated with improvement in mood. A systematic review of the TCAs, including fewer than 200 patients, found no difference in efficacy between the agents.6

Desipramine is associated with fewer adverse events than amitriptyline and is thus the preferred TCA in elderly patients if a TCA is desired.

Duloxetine

Duloxetine HCl (Cymbalta, Eli Lilly) is a potent dual reuptake inhibitor of both 5-HT (serotonin) and norepinephrine (NE), and it has a weak affinity for dopamine, muscarinic, histamine, and other receptors. Subsequently, adverse effects, when compared with those resulting from TCAs, are typically more tolerable and include asthenia, constipation, dizziness, dry mouth, hyperhidrosis, nausea, and somnolence.14

Duloxetine has been an effective therapy for depression in several randomized clinical trials.15–17 In these studies, duloxetine also improved painful symptoms associated with depression. More than 50% of the reduction in painful symptoms was attributed to duloxetine rather than to a secondary effect of improving depression.18

Duloxetine is the first FDA-approved medication indicated for the treatment of DPN. The recommended dose is 60 mg once daily without regard to meals. Higher doses have been shown to be safe and effective, although doses above 60 mg provide little benefit and confer increased adverse effects.19,20

Data from clinical trials involving duloxetine in patients with DPN are summarized in Table 2. In the first published trial, patients’ pain scores began improving as early as the first week of therapy. Patients also reported improvements in body pain and mental health. Duloxetine did not significantly change

Table 1 Clinical Trials of Tricyclic Antidepressants

<table>
<thead>
<tr>
<th>Reference</th>
<th>No.</th>
<th>Design</th>
<th>Treatment</th>
<th>Study Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Max5</td>
<td>29</td>
<td>R, DB, PC, CO</td>
<td>AMI 25 mg/day (titrated to 150 mg/day) or PBO</td>
<td>Significantly greater pain relief with higher doses of AMI; Ach side effects noted</td>
</tr>
<tr>
<td>Sindrup9</td>
<td>9</td>
<td>R, DB, PC, CO</td>
<td>IMI 125–200 mg/day or PBO</td>
<td>89% patients reported improvement in pain with IMI; more Ach side effects seen with IMI</td>
</tr>
<tr>
<td>Kvniesdal10</td>
<td>12</td>
<td>R, DB, PC, CO</td>
<td>IMI 50–100 mg/day or PBO</td>
<td>No difference in symptom score but notable improvement in global assessment</td>
</tr>
<tr>
<td>Turkington11</td>
<td>59</td>
<td>R</td>
<td>IMI 100 mg/ day, AMI 100 mg/day, or DIAZ 5 mg t.i.d.</td>
<td>Complete pain relief with IMI and AMI; no statistics reported, weak study</td>
</tr>
<tr>
<td>Max12</td>
<td>20</td>
<td>R, CO, DB</td>
<td>DES 12.5 mg (up to a mean of 201 mg/day)</td>
<td>DES significantly decreased pain intensity; no association with dose or pain relief</td>
</tr>
<tr>
<td>Max13</td>
<td>29</td>
<td>R, CO, DB, PC</td>
<td>AMI 12.5 mg (up to 150 mg/day) or DES 12.5 mg (up to 150 mg/day)</td>
<td>AMI and DES are superior to PBO in pain relief; more relief noted in AMI group</td>
</tr>
</tbody>
</table>

Ach = anticholinergic; AMI = amitriptyline; CO = crossover; DB = double-blind; DES = desipramine; DIAZ = diazepam; IMI = imipramine; PBO = placebo; PC = placebo-controlled; R = randomized; t.i.d. = three times daily.
concentrations of hemoglobin A1c, low-density lipoprotein, high-density lipoprotein, or triglycerides.

Subsequent trials have helped to establish the efficacy and safety of duloxetine for the treatment of DPN. Patients can expect improvement after one week of treatment, but they may experience somnolence and constipation; these effects appear better tolerated at a dose of 60 mg/day. Patients with depression were typically excluded in the duloxetine trials, suggesting that analgesia was independent of antidepressant effects. The advantages of duloxetine include once-daily dosing and its efficacy for comorbid depression.6

Venlafaxine

Similar to duloxetine, venlafaxine (Effexor, Wyeth) is an antidepressant that inhibits the reuptake of the neurotransmitters 5-HT and NE. Common adverse effects associated with this agent include dizziness, somnolence, dry mouth, nausea, and sweating.21

Venlafaxine has been compared with placebo and imipramine in patients with DPN, with doses of 150 to 225 mg showing the greatest efficacy (Table 3).22,23 When it was compared with placebo, patients receiving extended-release (ER) venlafaxine reported significantly reduced pain intensity and greater pain relief. Common adverse events in these trials included nausea and somnolence; anorexia, dyspepsia, insomnia, sweating, and impotence were reported to a lesser extent.

The trial that compared venlafaxine and imipramine showed no significant difference between the agents in terms of efficacy or tolerability. Patients reported more fatigue and nausea with venlafaxine and more dry mouth and sweating with imipramine.

Anticonvulsant Agents

Gabapentin

Gabapentin (Neurontin, Pfizer) is an anticonvulsant agent with a structure similar to that of gamma-aminobutyric acid (GABA), but it does not interact with the GABA receptors. In fact, the true mechanism of action of gabapentin is unknown. Commonly associated adverse effects include somnolence, dizziness, ataxia, and fatigue. The recommended dosage range for gabapentin in the treatment of DPN is 1,800 to 3,600 mg/day.21

Gabapentin has been used to treat a variety of painful conditions. In the treatment of DPN, gabapentin has been compared with placebo as well as with amitriptyline (Table 4).24–27 When compared with placebo, gabapentin 900 to 3,600 mg/day was required to produce significant changes in pain scores. In comparative trials, gabapentin was at least equivalent to amitriptyline in treating pain associated with DPN. However, the cost of gabapentin, coupled with limited data on its efficacy, may preclude its use as a first-line agent.

Pregabalin

Pregabalin (Lyrica, Pfizer) is an anticonvulsant structurally similar to its predecessor drug, gabapentin. Although it is a structural analogue of GABA, it does not interact with GABA-A or GABA-B receptors, and it does not affect the uptake of GABA. Pregabalin is believed to exert its action by altering the presynaptic release of NE and glutamate. The most common adverse effects associated with pregabalin therapy include dizziness, somnolence, peripheral edema, headache, blurred vision, and constipation. The recommended dosage range for the treatment of diabetic neuropathy is 150 to

| Table 2  Clinical Trials of Duloxetine |
|-----------------------------|-----------------------------|-----------------------------|
| Reference                  | No.                        | Design                     | Treatment                                                                 | Study Conclusions                                                                 |
| Goldstein17                | 457                        | R, DB, PC                  | DUL 20 mg/day, DUL 60 mg/day, DUL 120 mg/day, or PBO                       | Improvement in pain with 60 and 120 mg; more constipation and somnolence in the 60-mg group |
| Raskin19                   | 348                        | R, DB, PC, P               | DUL 60 mg/day, DUL 60 mg b.i.d., or PBO                                    | Both DUL doses significantly improved pain beginning at week 1; more patient dropouts in the twice-daily group because of adverse events |
| Raskin20                   | 237                        | R, OL                      | DUL 60 mg twice daily or routine care*                                     | DUL was safe and well tolerated compared with routine care                             |

* Routine care consisted primarily of gabapentin, amitriptyline, or venlafaxine.

b.i.d. = twice daily; DB = double-blind; DUL = duloxetine; OL = open-label; P = parallel; PBO = placebo; PC = placebo-controlled; R = randomized.

| Table 3  Clinical Trials of Venlafaxine |
|-----------------------------|-----------------------------|-----------------------------|
| Reference                  | No.                        | Design                     | Treatment                                                                 | Study Conclusions                                                                 |
| Row-botham22               | 244                        | R, DB, PC                  | VEN 75 mg /day, VEN 150–225 mg/day, or PBO                                | Significantly greater pain control with 150–225 mg; common adverse effects include nausea and somnolence |
| Sindrup23                  | 40                         | R, DB, PC, CO              | VEN 225 mg/day, IMI 150 mg/day, or PBO                                    | Both VEN and IMI provided significant pain relief; no difference in efficacy or tolerability |

CO = crossover; DB = double-blind; IMI = imipramine; PBO = placebo; PC = placebo-controlled; R = randomized; VEN = venlafaxine.
600 mg/day divided into two to three doses.28 

As one of the few medications approved by the FDA for the treatment of DPN, pregabalin has been studied in several clinical trials (Table 5).29–32 The doses of pregabalin studied ranged from 75 mg up to 600 mg/day. In all of the studies, doses of 300 mg to 600 mg/day were required to produce significant improvements in mean pain scores. Common adverse events noted in clinical trials included dizziness, somnolence, headache, peripheral edema, and weight gain. In each trial reviewed, the investigators concluded that pregabalin was safe and effective for patients with DPN.

Oxcarbazepine

Oxcarbazepine (Trileptal, Novartis) acts by blocking voltage-sensitive sodium channels and by altering potassium conductance and modulating calcium channel activity. It is best known as an anticonvulsant, but it has also been used to treat bipolar disorder as well as painful conditions such as DPN. Common adverse effects include dizziness, somnolence, headache, ataxia, fatigue, vertigo, vomiting, nausea, abdominal pain, abnormal gait, tremor, diplopia, nystagmus, and abnormal vision.21

Oxcarbazepine has been studied in doses ranging from 1,200 to 1,800 mg/day with conflicting results (Table 6).33–35 Although one study showed that oxcarbazepine at doses of 300 to 1,800 mg/day produced significant improvements in Visual Analogue Scale (VAS) pain scores, two other trials examining doses from 600 to 1,800 mg/day showed no benefit. Because a trend toward significance was found in at least one trial, the investigators concluded that additional studies should be conducted to fully elucidate the role of oxcarbazepine in treating DPN.

Lamotrigine

The anticonvulsant agent lamotrigine (Lamictal, GlaxoSmithKline) is often used to treat seizure disorders and bipolar disorder. It inhibits the release of glutamate and stabilizes neuronal membranes by inhibiting voltage-sensitive sodium channels. The most common side effects associated with lamotrigine therapy include headache, dizziness, ataxia, somnolence, nausea, diplopia, blurred vision, and rhinitis.21

Lamotrigine has been studied in patients with DPN with mixed results. It has been compared with placebo as well as with amitriptyline (Table 7).36–38 In one study, lamotrigine 200,
300, and 400 mg/day produced significant improvements in pain scores. However, in two identical trials that were being conducted simultaneously, only lamotrigine 400 mg/day was effective; furthermore, these results were only seen in one of the two trials. Yet in another small trial comparing lamotrigine and amitriptyline, lamotrigine was as effective as amitriptyline. Because clinical trial results with lamotrigine are so inconsistent, further trials are needed to determine its place in therapy.

### Topical Agents

#### Lidocaine

Topical 5% lidocaine patches (Lidoderm, Endo) have been approved by the FDA for the treatment of postherpetic neuralgia. The patch lacks systemic adverse events and has minimal drug interactions. The approved dosing for postherpetic neuralgia is three patches for a maximum of 12 hours in a 24-hour period. Titrination is not necessary; two weeks is considered an adequate trial.

The lidocaine patch is not indicated for DPN, but small trials support its role as adjunctive therapy. In these studies, treatment consisted of up to four patches daily (18 hours on and six hours off) applied to the area of maximal DPN pain. Overall, significant improvements were seen in pain diary ratings.

Tapering of concomitant analgesics was noted in one trial, with an eventual discontinuation of supplemental pain medications in three patients. The evidence indicates that the lidocaine 5% patch is an effective add-on therapy for ongoing pain.

#### Capsaicin

Capsaicin (Zostrix, Health Care Products), is extracted from hot chili peppers and produces a dose-dependent stimulation of unmyelinated C-fiber afferent neurons. This causes the release of substance P, thereby depleting stores from sensory nerve endings and reducing the transmission of painful stimuli. This analgesic is applied topically three to four times daily. It is not associated with severe systemic side effects, but transient burning may occur, and this may be intolerable for some patients. Clinical studies have shown that capsaicin is a consistently effective analgesic for neuropathic pain.

The Capsaicin Study Group published the largest study to date (Table 8). Patients with DPN, radiculopathy, or both were randomly assigned to receive capsaicin or an inactive cream four times daily. They were allowed to use aspirin, acetaminophen, or ibuprofen to help alleviate the transient burning. Results of this trial were favorable. Capsaicin was more effective than placebo in providing pain relief, decreasing pain intensity, and improving global assessment.

Functional measures, such as walking, working, and sleeping, also improved. Although the study protocol stated that

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### Table 6 Clinical Trials of Oxcarbazepine

<table>
<thead>
<tr>
<th>Reference</th>
<th>No.</th>
<th>Design</th>
<th>Treatment</th>
<th>Study Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dogra33</td>
<td>146</td>
<td>R, DB, PC</td>
<td>OX 300 mg daily (up to 1,800 mg daily) or PBO</td>
<td>OX 300–1,800 mg/day produced significant decreases in VAS scores for pain severity</td>
</tr>
<tr>
<td>Beydoun34</td>
<td>347</td>
<td>R, DB, PC, PG, DR</td>
<td>OX 600 mg/day, OX 1,200 mg/day, OX 1,800 mg/day or PBO</td>
<td>Despite a trend toward significance in the 1,200-mg and 1,800-mg groups, no statistically significant improvements in VAS scores in any OX group compared with PBO</td>
</tr>
<tr>
<td>Grosskopf35</td>
<td>141</td>
<td>R, DB, PC</td>
<td>OX 1,200 mg/day or PBO</td>
<td>No significant improvement in VAS scores in OX group compared with PBO</td>
</tr>
</tbody>
</table>

DB = double-blind; DR = dose-ranging; OX = oxcarbazepine; PBO = placebo; PC = placebo-controlled; PG = parallel-group; R = randomized; VAS = Visual Analogue Scale.

### Table 7 Lamotrigine Clinical Trials

<table>
<thead>
<tr>
<th>Reference</th>
<th>No.</th>
<th>Design</th>
<th>Treatment</th>
<th>Study Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eisenberg36</td>
<td>59</td>
<td>R, DB, PC, PG</td>
<td>LMT 25 mg/day (up to 400 mg/day) or PBO</td>
<td>LMT 200, 300, and 400 mg/day significantly reduced mean pain scores compared with PBO</td>
</tr>
<tr>
<td>Vinik37</td>
<td>360</td>
<td>R, DB, PC (two identical studies conducted simultaneously)</td>
<td>LMT 200 mg/day, LMT 300 mg/day, LMT 400 mg/day or PBO</td>
<td>Only LMT 400 mg/day produced significant reductions in pain scores (not duplicated in second study) compared with PBO</td>
</tr>
<tr>
<td>Jose38</td>
<td>53</td>
<td>R, DB, CO,AC</td>
<td>AMI 50 mg h.s. or LMT 100 mg b.i.d.</td>
<td>No significant differences found between groups in patient’s global assessment of safety and efficacy</td>
</tr>
</tbody>
</table>

AC = active-control; AMI = amitriptyline; b.i.d. = twice daily; CO = crossover; DB = double-blind; h.s. = at bedtime; LMT = lamotrigine; PBO = placebo; PC = placebo-controlled; PG = parallel-group; R = randomized.
patients were not supposed to adjust medications, patients in both groups decreased or discontinued oral analgesics. Temporary burning was the most frequently reported side effect. The authors concluded that capsaicin, a nonprescription product, was effective in decreasing pain, improving daily activities, and enhancing quality of life in patients with DPN.

**Opioids**

**Oxycodone**

Oxycodone (e.g., Percocet, Endo) is a narcotic analgesic that binds to opiate receptors in the central nervous system (CNS), producing alterations in the perception of and response to pain. The most commonly associated side effects include fatigue, drowsiness, dizziness, somnolence, pruritus, nausea, vomiting, constipation, and weakness.21

Much evidence exists to support the use of oxycodone for treating moderate-to-severe pain; however, clinical trial data supporting the use of oxycodone for pain associated with DPN are limited (Table 9).46,47

Two studies compared the effect of placebo and oxycodone 10 mg (up to 60 to 80 mg) every 12 hours. In both trials, oxycodone was more effective than placebo in reducing pain scores in patients with DPN. An average dose of 37 mg/day was reported in one study as the dose required for significant pain relief. In addition to pain relief, one study looked at the effect of oxycodone on health-related quality of life. Mean daily pain, steady pain, brief pain, skin pain, and total pain and disability were significantly lower in the oxycodone group.

**Tramadol**

Tramadol (Ultram, Ortho-McNeil) is a “non-narcotic” analgesic that binds to mu-receptors in the CNS, causing a change in the perception of and response to pain. Tramadol also inhibits the reuptake of NE and 5-HT, thereby further

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**Table 8 Clinical Trials of Topical Agents**

<table>
<thead>
<tr>
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<th>No.</th>
<th>Design</th>
<th>Treatment</th>
<th>Study Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meier</td>
<td>58</td>
<td>R, DB, PC, CO</td>
<td>LID 5% q 12 hr or PBO</td>
<td>Significant improvement in pain in LID arm on day 4; no difference in adverse events</td>
</tr>
<tr>
<td>Barbano</td>
<td>56</td>
<td>OL</td>
<td>LID 5% q 18 hr</td>
<td>LID 5% allowed improved pain; tapering of concomitant analgesics noted</td>
</tr>
<tr>
<td>Argoft</td>
<td>77</td>
<td>OL</td>
<td>LID 5% q 24 hr</td>
<td>Significant improvement in pain from PHN, DN, or LBP; no serious adverse events</td>
</tr>
<tr>
<td>Donofrio</td>
<td>277</td>
<td>R, DB, PC</td>
<td>CAP 0.075% q.i.d. or PBO</td>
<td>CAP was significantly more effective in pain relief, well tolerated; burning was noted more in CAP group</td>
</tr>
<tr>
<td>Donofrio</td>
<td>277</td>
<td>R, DB, PC</td>
<td>CAP 0.075% q.i.d. or PBO</td>
<td>Improved quality of life, including improvement in recreational activities</td>
</tr>
</tbody>
</table>

CAP = capsaicin; CO = crossover; DB = double-blind; DN = diabetic neuropathy; LBP = lower back pain; LID = lidocaine; OL = open-label; PBO = placebo; PC = placebo-controlled; PHN = postherpetic neuralgia; q.i.d. = four times daily; q 12 hr = every 12 hours; q 18 hr = every 18 hours; q 24 hr = every 24 hours; R = randomized.

**Table 9 Clinical Trials of Oxycodone and Tramadol**

<table>
<thead>
<tr>
<th>Reference</th>
<th>No.</th>
<th>Design</th>
<th>Treatment</th>
<th>Study Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gimbel</td>
<td>159</td>
<td>R, DB, PC, PG</td>
<td>OXY 10 mg (up to 60 mg) q 12 hr or PBO</td>
<td>OXY at average dose of 37 mg/day provided significantly better pain relief than PBO</td>
</tr>
<tr>
<td>Watson</td>
<td>45</td>
<td>R, DB, CO</td>
<td>OXY 10 mg (up to 80 mg) q 12 hr or PBO</td>
<td>Mean daily pain, total pain, and disability scores significantly lower in the OXY-treated group</td>
</tr>
<tr>
<td>Harati</td>
<td>120</td>
<td>After six-week DB, PC portion patients could enroll in a six-month open-extension period</td>
<td>TRAM (up to a maximum dose of 400 mg/day)</td>
<td>Original PBO group had higher pain scores on day 1 of open period, but by day 30, pain relief scores were similar in all patients despite initial therapy during six-week DB, PC portion of trial</td>
</tr>
<tr>
<td>Freeman</td>
<td>313</td>
<td>R, DB, PC, PG</td>
<td>TRAM 37.5 mg/APAP 325 mg (up to eight tablets daily) or PBO</td>
<td>TRAM/APAP produced significant reduction in mean daily pain scores from baseline to study’s end compared with PBO</td>
</tr>
</tbody>
</table>

APAP = acetaminophen; CO = crossover; DB = double-blind; OXY = oxycodone; PBO = placebo; PC = placebo-controlled; PG = parallel-group; q 12 hr = every 12 hours; R = randomized; TRAM = tramadol.
altering the pain pathway. The most common adverse effects associated with tramadol include dizziness, headache, somnolence, vertigo, constipation, and nausea. The tramadol dose for moderate-to-severe chronic pain is 50 to 100 mg every four to six hours, not to exceed 400 mg/day. Few studies of tramadol in DPN are available; however, it has been studied alone and in combination with acetaminophen (see Table 9). In the study examining the use of tramadol alone, patients who completed a six-week double-blind, placebo-controlled portion of the study were eligible to enroll in an open-extension period for up to six months. On the first day of the open-extension period, the group previously treated with placebo had significantly higher pain scores than those previously treated with tramadol; however, by the 30th day, mean pain relief scores were similar between the two groups. These results continued throughout the rest of the study period. On the basis of these findings, the authors concluded that tramadol provided effective relief of DPN pain over a six-month period.

When tramadol plus acetaminophen was compared with placebo, patients reported a significant reduction in average daily pain scores with the combination. The authors of this study concluded that tramadol plus acetaminophen was effective in producing significant pain relief in patients with DPN and was generally well tolerated.

**Agents with Limited Use**

**Metanx**

Metanx (Pamlab), a B-complex vitamin, does not carry the FDA indication for DPN, but it has been used anecdotally. This nutritional supplement is a prescription product. It is the metabolically active form of folic acid (methylfolate), vitamin B6 (pyridoxal), and vitamin B12 (methylcobalamin) and thus does not require enzymatic activation.

Elevated total homocysteine concentrations exhibit toxic effects on vascular endothelial cells and are an independent risk factor for atherosclerotic disease. Deficiencies in folic acid, vitamin B6, and vitamin B12 are associated with elevated homocysteine levels. However, it is not well established that hyperhomocysteinemia is related to DPN. Subsequently, it is not confirmed that the use of a vitamin B supplement to decrease homocysteine levels is an effective therapy for DPN. Studies that support these claims are not well designed. At this time, evidence for the use of Metanx in DPN does not support routine use.

**Topiramate**

Topiramate (Topamax, Ortho-McNeil) is an anticonvulsant with numerous possible mechanisms of action. It is believed to block voltage-dependent sodium channels, increase GABA activity, antagonize glutamate receptors, and inhibit carbonic anhydrase activity. Commonly associated adverse effects are dizziness, somnolence, fatigue, anorexia, paresthesia, and nystagmus. In addition to its use as an anticonvulsant agent, topiramate has been used for painful conditions such as migraine prophylaxis, cluster headaches, and neuropathic pain.

Studies of DPN have produced conflicting results. A 12-week trial of 323 patients comparing topiramate (up to 40 mg/day) with placebo revealed that topiramate significantly reduced VAS scores and body weight in patients with DPN. Another trial of 205 patients also demonstrated positive results supporting the use of topiramate in DPN. However, pooled results from three other trials involving a total of 1,269 patients showed no significant difference between topiramate and placebo in treating painful DPN. Because of the availability of numerous agents with better efficacy profiles, topiramate should not be considered a first-line therapy for DPN.

**Treatment Selection**

Recommendations for choosing a treatment are based on the Diabetic Peripheral Neuropathic Pain consensus Treatment Guidelines Advisory Board and are based on clinical trials and expert opinion (Table 10). First-line agents that have been evaluated in at least two randomized controlled trials for DPN include duloxetine, oxycodone CR, pregabalin, and the TCAs. Oxcarbazepine, gabapentin, lamotrigine, and venlafaxine are considered second-line agents and have been evaluated in at least one randomized controlled trial involving DPN patients.

Topical agents, including capsaicin and lidocaine, may be used as adjuncts at any time during treatment. Agents that have limited use include topiramate, tramadol, and others, because trials specific to DPN are lacking.

### Table 10 Recommendations for First-Tier and Second-Tier Agents for Diabetic Peripheral Neuropathic Pain (DPN)

<table>
<thead>
<tr>
<th>First-Tier Agent</th>
<th>Second-Tier Agent</th>
<th>Topical Agent</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Why: ≥2 RCTs in DPN</td>
<td>Why: 1 RCT in DPN; ≥1 in other PN</td>
<td>Why: mechanism of action</td>
<td>Why: ≥1 RCT in other PN or other evidence</td>
</tr>
<tr>
<td>• Duloxetine</td>
<td>• Carbamazepine</td>
<td>• Capsaicin</td>
<td>• Bupropion</td>
</tr>
<tr>
<td>• Oxycodone CR</td>
<td>• Gabapentin</td>
<td>• Lidocaine</td>
<td>• Citalopram</td>
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<tr>
<td>• Pregabalin</td>
<td>• Lamotrigine</td>
<td></td>
<td>• Methadone</td>
</tr>
<tr>
<td>• TCAs</td>
<td>• Tramadol</td>
<td></td>
<td>• Paroxetine</td>
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<tr>
<td></td>
<td>• Venlafaxine ER</td>
<td></td>
<td>• Phenytoin</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>• Topiramate</td>
</tr>
</tbody>
</table>

Choosing a First-Line Agent

Because of their proven clinical efficacy in DPN, a first-line agent should be used to initiate treatment. When choosing among agents, prescribers should consider cost; comorbid conditions, including depression (Table 11); and the patient’s overall clinical picture. Because of the concern for potential drug interactions and contraindications, a review of the patient’s current medication profile is warranted.

If a TCA is chosen, agents with the most consistently proven efficacy should be considered. From studies reviewed, it is reasonable to try imipramine, desipramine, and amitriptyline. Desipramine is preferred in the elderly, because it is associated with fewer anticholinergic effects.

If an opioid is chosen as a first-line therapy, health care providers should exercise caution in patients with an active abuse disorder, a history of substance abuse, or those whose risk of opioid abuse is unclear. Health care providers and patients should agree upon a structured treatment plan, and methods of assessing adherence to the regimen should be developed; for example, pill counts, urine toxicology screenings, and unscheduled office visits should be considered.

Considerations for Older Adults

The prevalence of pain in patients older than 60 years of age is twice as high as in younger patients. Treatment may be complicated by the presence of dementia, renal and liver impairment, and increased sensitivity to adverse effects. Although these barriers exist, careful treatment selection allows elderly patients to be optimally managed.

TCAs cause a number of side effects to which older adults may already be prone. These include heart block, orthostatic hypotension, dry mouth, urinary retention, and constipation.

<table>
<thead>
<tr>
<th>Table 11 Factors to Consider in Choosing First-Tier Agents</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Medical comorbidities</strong></td>
</tr>
<tr>
<td>Glaucoma</td>
</tr>
<tr>
<td>Orthostatic phenomena</td>
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<tr>
<td>Cardiac or electrocardiographic abnormality</td>
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<tr>
<td>Hypertension</td>
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<tr>
<td>Renal insufficiency</td>
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<tr>
<td>Hepatic insufficiency</td>
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<tr>
<td>Falls or balance issues</td>
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<tr>
<td><strong>Psychiatric comorbidities</strong></td>
</tr>
<tr>
<td>Depression§</td>
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<tr>
<td>Anxiety</td>
</tr>
<tr>
<td>Suicidal ideation</td>
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<tr>
<td><strong>Somatic problems</strong></td>
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<tr>
<td>Sleep</td>
</tr>
<tr>
<td>Erectile dysfunction</td>
</tr>
<tr>
<td><strong>Other factors</strong></td>
</tr>
<tr>
<td>Cost</td>
</tr>
<tr>
<td>Drug interactions</td>
</tr>
<tr>
<td>Weight gain</td>
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<tr>
<td>Edema</td>
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</tbody>
</table>

* Duloxetine is contraindicated only for patients with uncontrolled narrow-angle glaucoma and may be appropriate for other glaucoma patients.† Dosage adjustment of oxycodone CR and pregabalin is recommended for patients with a creatinine clearance below 60 mL/minute.‡ Duloxetine is not recommended for patients with a creatinine clearance below 30 mL/minute.§ Before treatment with an antidepressant is initiated, patients with depressive symptoms should be adequately screened to determine whether they are at risk for bipolar disorder.// The prescribing information should be consulted for individual agents concerning specific drug–drug interactions and contraindications. CR = controlled-release; TCAs = tricyclic antidepressants.

Sedation associated with these agents may be useful therapeutically; however, it is advisable to titrate the dose slowly. If the anticholinergic effects are pronounced, desipramine should be avoided. Such side effects may occur at the expense of additional side effects.

**Treatment Monitoring**

Many drugs used to treat DPN are gradually titrated; therefore, frequent monitoring is desired. Pain control should be assessed at each visit. Attention should be paid to improvements (or the lack thereof) and to physical and social functioning. If the agent does not provide adequate relief, changing to another first-line medication is reasonable. If the next agent is not effective or if maximizing the dose is not an option, combination treatment may be warranted.

**Combination Treatment**

Ideally, a single agent should be adequate in providing pain relief. Because of the multiple mechanisms causing DPN, partial effects to monotherapy are to be expected. In fact, only about 70% of patients with neuropathic pain actually respond to a single agent. Therefore, the use of agents with different mechanisms of action may provide substantial relief. Despite a lack of controlled data with combination first-line therapies, several recommendations may be made, as presented in Table 12. Patients should be warned that pain relief may occur at the expense of additional side effects.

**Conclusion**

Diabetic peripheral neuropathy is a devastating complication of diabetes mellitus that causes significant morbidity and mortality. The pain associated with DPN is described as excruciating by some and may be lessened or relieved by a variety of agents. Much evidence exists to support the use of duloxetine, oxycodone, pregabalin, and TCAs as first-line therapies. However, patients who find these therapies inadequate for pain relief may require an additional agent. Therefore, practitioners should become familiar with the many therapies available to treat patients with DPN, including their mechanism of action, adverse effects, recommended doses, and the available clinical evidence.

**References**

52. Dornuis DA, Fernandez N, Arranz ML, et al. Total homocysteine levels: Relation with chronic complications of diabetes, body composition, and other cardiovascular risk factors in a population of


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**Conflict of Interest (COI) Statement**

Drs. St. Onge and Miller have no relationships to disclose. The content of this article has been reviewed under Jefferson’s Continuing Medical Education COI policy.
Continuing Education Questions for Physicians and Pharmacists

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ACPE Program #079-000-08-015-H04-P
Expiration Date: March 31, 2009

TOPIC: Pain Associated with Diabetic Peripheral Neuropathy: A Review of Available Treatments

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Continuing Education Questions for Physicians and Pharmacists

**TOPIC:** Pain Associated with Diabetic Peripheral Neuropathy: A Review of Available Treatments

ACPE Program #079-000-08-015-HO4-P

**Multiple Choice**

Select the one correct answer.

1. Sensory loss associated with DPN:
   a. occurs in 10% to 30% of patients.
   b. is easily detected by clinical tests.
   c. may include an inability to judge temperature.
   d. does not result in physical deformities.

2. Primary factors that contribute to the pathophysiology of DPN are:
   a. increased oxidative stress, decreased sorbitol, and decreased nitric oxide.
   b. increased homocysteine, increased sorbitol, and increased oxidative stress.
   c. increased nitric oxide, decreased homocysteine, and increased sorbitol.
   d. decreased sorbitol, increased nitric oxide, and decreased homocysteine.

3. An antidepressant that is FDA-approved for the treatment of DPN includes:
   a. fluoxetine.
   b. duloxetine.
   c. venlafaxine.
   d. amitriptyline.

4. The analgesic effect of antidepressants on DPN:
   a. depends upon their antidepressant effects.
   b. occurs because of improvements in hemoglobin A1c levels.
   c. results in immediate improvements in pain.
   d. may be a result of blocked reuptake of norepinephrine and serotonin.

5. Commonly prescribed anticonvulsant agents used to treat DPN include:
   a. lamotrigine and phenytoin.
   b. pregabalin and gabapentin.
   c. topiramate and felbamate.
   d. oxcarbazepine and valproic acid.

6. The lidocaine patch has been approved by the FDA for the treatment of pain associated with DPN.
   a. true
   b. false

7. According to the article, what is the mechanism of action for capsaicin that reduces DPN pain?
   a. The release of substance P, via stimulation by capsaicin of unmyelinated C fiber afferent neurons, causes the reduction in the transmission of painful stimuli.
   b. The release of substance P causes stimulation of unmyelinated C fiber afferent neurons that results in a reduction of pain stimuli.
   c. Substance P inhibits the transmission of pain stimuli by blocking pain receptors on afferent neurons.
   d. The euphoric effect from substance P release helps to alleviate pain stimuli that are still present.

8. Which of the following is a non-narcotic analgesic used to treat pain in DPN, that binds to mu-receptors in the central nervous system?
   a. oxycodone
   b. tramadol
   c. topiramate
   d. Metanx

9. According to the literature, which of the following is not a first-tier or a second-tier pharmacological agent used in the treatment of pain associated with DPN?
   a. duloxetine
   b. paroxetine
   c. tramadol
   d. oxycodone ER

10. What percentage of patients respond to monotherapy in the treatment of pain associated with DPN?
    a. 10%
    b. 90%
    c. 50%
    d. 70%
Date of publication: March 2008
Title: Pain Associated with Diabetic Peripheral Neuropathy: A Review of Available Treatments
Authors: Erin L. St. Onge, PharmD, and Shannon A. Miller, PharmD
Submission deadline: March 31, 2009
ACPE Program #079-000-08-015-HO4-P

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Signature (required) Date _______________

Answer Sheet
Please fill in the box next to the letter corresponding to the correct answer
1. a □ b □ c □ d □ 6. a □ b □ c □ d □
2. a □ b □ c □ d □ 7. a □ b □ c □ d □
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5. a □ b □ c □ d □ 10. a □ b □ c □ d □

Evaluation
Rate the extent to which:

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<th>Very High</th>
<th>High</th>
<th>Moderate</th>
<th>Low</th>
<th>Very Low</th>
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1. Objectives of this activity were met
2. You were satisfied with the overall quality of this activity
3. Content was relevant to your practice needs
4. Participation in this activity changed your knowledge/attitudes
5. You will make a change in your practice as a result of participation in this activity
6. This activity presented scientifically rigorous, unbiased, and balanced information
7. Individual presentations were free of commercial bias
8. Adequate time was available for Q&A
9. Which ONE of the following best describes the impact of this activity on your performance:
   □ This program will not change my behavior because my current practice is consistent with what was taught.
   □ This activity will not change my behavior because I do not agree with the information presented.
   □ I need more information before I can change my practice behavior.
   □ I will immediately implement the information into my practice.
10. Will you take any of the following actions as a result of participating in this educational activity (check all that apply)
    □ Discuss new information with other professionals □ Consult the literature
    □ Discuss with industry representative(s) □ Participate in another educational activity
    □ Other _________________________ □ None

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