SUPPLEMENT ARTICLE

Consensus Guidelines: Treatment Planning and Options

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Despite the number of patients affected by diabetic peripheral neuropathic pain (DPNP), little consensus exists about the pathophysiology, best diagnostic tools, and primary treatment choices. Theories about the causes of DPNP are inextricably linked with the causes of diabetic neuropathies, yet most patients with such neuropathies do not experience pain. The factors that differentiate patients with pain from those without remain unknown and are the subject of much research. When choosing treatment for patients with DPNP, physicians are confronted with a myriad of choices, none of which has been shown to be effective for all patients. This article reviews the evidence for these treatments and attempts to guide physicians in choosing those treatments based on evidence from well-designed clinical trials to support their use. Two agents, duloxetine and pregabalin, are formally approved by the Food and Drug Administration for the treatment of DPNP. In addition, several other agents, including the tricyclic class of antidepressants, have been effective in clinical trials. Ultimately, treatment choice must also include consideration of adverse effects, individual patient factors such as comorbidities, and often cost.

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APS = average pain score; CI = confidence interval; CR = controlled release; DPN = diabetic peripheral neuropathy; DPNP = diabetic peripheral neuropathic pain; ER = extended release; FDA = Food and Drug Administration; NNT = number needed to treat; PHN = postherpetic neuralgia; SF-36 = Medical Outcomes Study 36-Item Short-Form Health Survey; SNRI = serotonin-norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor; TCA = tricyclic antidepressant; VAS = visual analog scale

Treatment planning for patients with diabetic peripheral neuropathic pain (DPNP) must be based on clinical evidence of efficacy for the drugs chosen, individual patient factors such as comorbid medical or psychological illness, and an assessment of the probable benefits of treatment vs its associated adverse effects. Patients who think that they are a part of this decision-making process are better invested in their treatment and less likely to develop negative behaviors.

Patients with DPNP and their physicians face a challenging course but one that can be navigated with informed treatment planning and realistic expectations. Although a goal of 100% pain relief is ideal, in reality many patients achieve no more than 30% to 50% pain reduction. This is where measurements of function play a role because for many patients, that amount of relief may translate to an ability to return to work or social activities and thus vastly improve their quality of life and mood. As with other chronic pain states, it is important for the physician and patient to set and assess goals together, and physicians must keep in mind that patients' goals for treatment and perception of relief may differ from their own.

TREATMENT PLANNING

Developing a treatment plan for DPNP is a dynamic process, too often overlooked or not fully discussed in busy primary care practices, that includes discussion and negotiation between the patient and physician regarding the

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goals for therapy. A key part of this negotiation is explaining to the patient that, despite the best efforts of all involved, 100% relief of pain may not be achieved. The patient must be helped to understand that failure to achieve 100% pain relief is *not* necessarily a reflection of lack of commitment on the part of the physician or a reflection on the patient's efforts to get well (Table 1).

During this process, it may help to review some of the mechanisms of neuropathic pain and provide frank information on what is currently known and unknown. Patients who feel confident that their physicians are providing complete information and giving them full attention may be more satisfied with their treatment, even if some degree of pain remains.

For the primary care physician, an important part of managing DPNP is to reinforce for the patient the crucial roles played by glycemic control, foot care, and analgesic medications. The physician also must have a high index of suspicion for psychiatric comorbidity, such as depression, in patients with chronic DPNP and be prepared to refer these patients if their care requires.

If the treatment plan includes drugs used in a way not indicated by the Food and Drug Administration (FDA), patient consent should be obtained. For medicolegal and other reasons, the use of FDA-approved drugs may be preferred over off-label medications. Similarly, if opioids are part of the treatment plan, an opioid agreement may be negotiated with the patient. In either case, patients must be made aware of the issues surrounding their treatment, including adverse events and potential for abuse or development of tolerance.

When planning treatment, the physician has to acknowledge current gaps in management, including inadequate treatment and treatment with agents not effective for neuropathic pain, and strive to avoid these common pitfalls. Underuse of available resources should be avoided; there are many avenues for patients and physicians to obtain information about DPNP. Physicians must make a conscientious attempt to overcome their own resistance to treating neuropathic pain; in the face of moderate efficacy for even the best treatments, it may seem like a futile effort. In the context of a busy practice, neuropathic pain presents a challenge, but it is one that can be overcome in partnership with patients.

TABLE 1. **What Are the Goals of Treating Diabetic Peripheral Neuropathic Pain?**

Primary	Zero pain, but be realistic. However, do not let "realistic" lead to a less aggressive pursuit of maximum relief
Secondary	Restoration or improvement in functional measures and quality of life. These secondary goals are important but are not a substitute for pain relief. Pain and function are modified differently; treatment should be modifying pain and hopefully improved function will follow. If improved function does not follow, take measures to help patients optimize function in the presence of residual pain

PHARMACOLOGICAL THERAPIES

To start a discussion of the possible pharmacological approaches to managing painful diabetic peripheral neuropathy (DPN), it may help to look at how patients with neuropathic pain are currently treated. Are they getting the correct therapy? Recent data suggest they are not and that almost one quarter are receiving no treatment for pain.[1] In that study of 55,686 patients with painful peripheral neuropathies, including almost 6000 with DPNP, the largest percentage of patients received a short-acting opioid for treatment (53.2%), and opioids of any type were the most commonly used class (53.9%). The next largest percentage (39.7%) was being treated with nonsteroidal anti-inflammatory drugs (including cyclooxygenase 2 inhibitors), which have no effect on neuropathic pain. Two other classes of agents with little or no evidence of efficacy in neuropathic pain, benzodiazepines and selective serotonin reuptake inhibitors (SSRIs), also were widely used, with 21.1% and 14.3% of patients, respectively, receiving them for treatment.

In the study by Berger et al,[1] the 2 classes of agents with the best evidence of efficacy in neuropathic pain, anticonvulsants and tricyclic antidepressants (TCAs), were used by the smallest percentage of patients (11.1% and 11.3%, respectively). More patients were receiving *no* treatment for their pain (24.4%) than were being treated with the most effective medications. That study was conducted before the recent approval of duloxetine, a serotonin-norepinephrine reuptake inhibitor (SNRI), and pregabalin, an anticonvulsant, for treatment of DPNP.

These findings suggest a failure on the part of the medical community to recognize and adequately treat neuropathic pain. It is imperative that physicians recognize and treat patients' DPN-related pain, even though patients may have difficulty describing their symptoms and assessing improvement or response to treatment is difficult.

CLASSES OF DRUGS USED TO TREAT DPNP

As is true for other chronic pain types, many types of drugs have been investigated for the treatment of DPNP in the hope of finding one or more that can relieve patients' pain. Many types of agents have been reported effective in case studies of individual patients, but few have demonstrated good efficacy in larger randomized clinical trials with placebo comparators. None to date reliably relieves 100% of

TABLE 2. **Pharmacological Treatment of Diabetic Peripheral Neuropathic Pain by Drug Class***

Class	Individual agents
SNRI (highly specific inhibition of serotonin and norepinephrine reuptake)	Duloxetine (Cymbalta), venlafaxine (Effexor)
$\alpha_2\delta$ ligands (modulate voltage-gated calcium channels)	Pregabalin (Lyrica), gabapentin (Neurontin)
TCAs (inhibit reuptake of serotonin and norepinephrine)	Tertiary: amitriptyline (generic); secondary: desipramine (generic)
Opioids (block μ-opioid receptors)	Tramadol† (Ultram), oxycodone CR (OxyContin), morphine (generic), methadone (Dolophine, Methadose), levorphanol (Levo-Dromoran), hydromorphone (Dilaudid)
Topical agents	Capsaicin (Zostrix, Zostrix HP), lidocaine (Lidoderm)
Agents to AVOID (never use)	Meperidine (due to normeperidine central nervous system toxicity); propoxyphene (due to norpropoxyphene central nervous system toxicity); NSAIDs (due to increased risk of bleeding, gastrointestinal upset, cardiovascular or cerebrovascular events); acetaminophen (due to hepatic toxicity with large doses and over time); amitriptyline (for patients >60 years); vitamin B_6 (>250 mg/d due to its potential for neurotoxicity); pentazocine (due to central nervous system toxicity and reversal of its analgesic effect [it is a mixed agonist-antagonist])

*Individual agents are listed alphabetically. NSAIDs = nonsteroidal anti-inflammatory drugs; SNRI = serotonin-norepinephrine reuptake inhibitors; TCAs = tricyclic antidepressants.
†Tramadol also weakly inhibits serotonin and norepinephrine reuptake.

pain for 100% of patients. Undoubtedly, this reflects the different mechanisms involved in the development and propagation of neuropathic pain.

Classes of drugs and individual agents with the best evidence of effectiveness in treating DPNP and/or other neuropathic pain states include antidepressants, anticonvulsants, and opioids (Table 2). Two agents, duloxetine[2] and pregabalin,[3] have received specific FDA approval for treatment of DPNP.

The following sections review the evidence of efficacy of these agents in DPNP and neuropathic pain and the nature and probability of adverse events with each agent or class of agents. The best studied in DPNP are duloxetine, oxycodone controlled-release (CR), pregabalin, and the TCAs, principally amitriptyline. In each class of drugs, those with specific FDA approval for treatment of DPNP are reviewed first.

Evidence-based medicine can provide a way to compare treatments across differing clinical trials by calculating, for example, the number needed to treat (NNT) to improve 1 patient who would otherwise not have improved without treatment. A meta-analysis of 16 studies (N=491 patients) comparing antidepressants (TCAs, SSRIs) with placebo for treatment of DPNP arrived at an NNT to achieve at least 50% pain relief of 3.4 (95% confidence interval [CI], 2.6-4.7) for the class.[4] Data from 3 studies (N=321 patients) comparing anticonvulsants with placebo for treatment of DPNP led to an NNT of 2.7 (95% CI, 2.2-3.8) for that class.[4] Interpretation of these data is limited by the inclusion of relatively ineffective SSRIs (NNT=6.7 in another review)[5] and the fact that this analysis was published before data for duloxetine, pregabalin, and venlafaxine were available. Clearly, both these classes of drugs are effective for treating DPNP, and newer agents may have better efficacy and tolerability than those analyzed.

ANTIDEPRESSANTS

Serotonin-Norepinephrine Reuptake Inhibitors.

Duloxetine. Duloxetine has been studied in 2 randomized, double-blind, placebo-controlled trials for relief of pain in patients with DPNP and is approved by the FDA for treatment of DPNP at total dosages of 60 mg/d and 120 mg/d, with the recommended dosage being 60 mg/d.[2] In the first published trial, 457 patients with type 1 or type 2 diabetes mellitus and pain were randomly assigned to receive either placebo or treatment with 20, 60, or 120 mg of duloxetine once daily.[6] The primary efficacy end point of this study was change in the weekly mean score of the 24-hour average pain score (APS), an 11-point Likert scale (0 indicating no pain to 10 indicating worst possible pain). Secondary end points included assessments of safety, worst pain severity, and mood. The trial lasted for 12 weeks of treatment. Beginning at week 1 and continuing throughout the study, patients receiving 60 or 120 mg of duloxetine showed significantly greater reductions in weekly mean APS. In addition, significantly more patients in the 60-mg and 120-mg treatment groups achieved 50% or greater reduction in pain. The group of patients who received 20 mg per day of duloxetine did not differ from the placebo group on the weekly mean APS, but significantly ($P<.05$) more of that group had a 50% or greater improvement. Duloxetine, 60 and 120 mg, also significantly ($P<.05$) improved night pain scores, Brief Pain Inventory severity and interference scores, Clinical Global Impression severity

scores and Patient Global Impression scores, McGill Pain Questionnaire total score, and Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36) measures of bodily pain and mental health. Patients in the 120-mg treatment arm saw a statistically significant ($P \leq .01$) improvement in SF-36 mental and general health perception domains as well. All doses of duloxetine were well tolerated, with no significant changes in concentrations of hemoglobin A_{1c}, low-density lipoprotein, high-density lipoprotein, or triglycerides. Adverse events that were reported more often in the duloxetine groups than in the placebo group were somnolence and constipation with 60 mg daily and nausea, somnolence, dizziness, constipation, dry mouth, sweating, increased appetite, anorexia, and weakness with 120 mg daily. Adverse events in the group treated with 60 mg/d were mild or moderate. Overall, 10.7% of patients treated with duloxetine withdrew from the study because of adverse events, including 19.5% of patients in the group treated with 120 mg/d of duloxetine.

In another trial, patients with DPNP were randomly assigned to placebo (n=116) or treatment with duloxetine, 60 mg daily (n=116) or 60 mg twice daily (n=116).[7] The primary efficacy end point of this study again was change in weekly mean score of the 24-hour APS. Beginning at week 1 and continuing throughout the 12-week study, patients treated with duloxetine had statistically significant ($P \leq .01$) improvements in the primary end point and secondary end points of worst pain severity and night pain scores. Patients treated with duloxetine also had improvement in scores on the severity and interference scales of the Brief Pain Inventory, McGill Pain Questionnaire, and other secondary measures. Patients treated with either dose of duloxetine reported statistically significantly ($P \leq .05$) more nausea, somnolence, hyperhidrosis, and anorexia than placebo-treated patients, and the 60-mg twice daily group also had more vomiting and constipation. Overall, 2.6%, 4.3%, and 12.1% of patients in the placebo, 60-mg/d duloxetine, and 60-mg twice daily duloxetine groups, respectively, discontinued participation in the study because of adverse events, with the difference statistically significant ($P=.01$) between the 60-mg twice daily duloxetine and placebo groups. No clinically significant increases or changes in laboratory values were seen in any of the groups.

Duloxetine appears to be safe for older patients (≥65 years)[8] and patients with comorbid hypertension, gastroesophageal reflux disease, erectile dysfunction, and hyperlipidemia or hypercholesterolemia. Duloxetine is contraindicated for patients with uncontrolled narrow-angle glaucoma and for patients being treated with monoamine oxidase inhibitors.[2] Taken together, these trials established the efficacy and safety of duloxetine, 60 mg daily, for treatment of DPNP. All patients in these trials underwent a complete psychiatric evaluation to exclude depression. Patients identified as having depression were excluded from the trial, ensuring that analgesic effects were independent of underlying depressive disorders.[6,7] Significant improvements in 24-hour APS can be expected after 1 week of treatment, and approximately half of patients will experience a 50% or greater improvement in their pain. In addition, duloxetine exerted positive effects on measures of quality of life, such as the interference score of the Brief Pain Inventory. With the 60-mg/d dosage, mild to moderate adverse events of somnolence and constipation may occur in approximately 20% and 14%, respectively, of patients.[6] Advantages of duloxetine include once-daily dosing and antidepressant efficacy for patients with comorbid depression. Disadvantages include adverse effects, which appear to be manageable at the approved dosage of 60 mg/d. Another disadvantage is that concomitant use with monoamine oxidase inhibitors is contraindicated.

Venlafaxine. Another SNRI, venlafaxine, has been studied for treatment of DPNP in one randomized trial in patients with DPNP[9] and another trial that compared venlafaxine with imipramine for treatment of painful neuropathies.[10] In a randomized, placebo-controlled trial, venlafaxine extended-release (ER) at 2 dosages (75 mg/d or 150-225 mg/d) was compared with placebo for treatment of painful DPN.[9] Patients with a 3-month or longer history of painful DPN (at least moderate in intensity) and without comorbid depression were randomly assigned to treatment with 75 mg/d (n=80) or 150 to 225 mg/d (n=82) of venlafaxine ER or placebo (n=80). The primary efficacy end points for this study were changes from baseline on the 100-mm visual analog scale (VAS) subscales of pain intensity and pain relief. After a 3-week, double-blind titration phase, patients received full-dose medication or placebo for a 3-week treatment trial. A 2-week tapering-off period and 4- to 10-day poststudy period followed. The final visit was conducted at that time. Results for the primary end point of pain intensity on the VAS showed that the higher dose of venlafaxine ER significantly reduced pain intensity compared with placebo and also compared with venlafaxine ER, 75 mg/d, at week 6. Results with the lower dose were not different from those with placebo. Less than 10% of patients in the active treatment arms discontinued study participation because of adverse events. The most common adverse events in the venlafaxine groups were nausea (>10%) and somnolence (>10%). In the group treated with 150 to 225 mg/d, dyspepsia, insomnia, and sweating also occurred in more than 10% of patients. In the 75-mg/d and 150- to 225-mg/d treatment groups, impotence was reported by 6% and 5% of men, respectively.

Another trial evaluated treatment of painful neuropathies with 225 mg/d of venlafaxine or 150 mg/d of imip-

ramine.[10] This was a double-blind, placebo-controlled, 3-way crossover study in which 40 patients were randomly assigned to one of the treatment groups or placebo for 4 weeks and then switched to a second group for 4 weeks and finally the third group for 4 weeks. Each 4-week period was separated by a washout period of at least 7 days. Thirty-two patients completed the trial, 15 of whom had DPNP. Patients rated their daily pain by use of an 11-point scale for 4 pain qualities: constant pain, paroxysmal pain, touch-evoked pain, and pain on pressure. The sum of these daily pain measures was used to determine treatment efficacy. Treatment with either venlafaxine (P=.004) or imipramine (P<.001) significantly reduced pain compared with placebo; no significant difference was seen between the venlafaxine and imipramine groups. In terms of tolerability, no significant differences in adverse events were seen among venlafaxine, imipramine, or placebo. Patients tended to report more dry mouth and sweating when being treated with imipramine and more tiredness when treated with venlafaxine.

Venlafaxine and venlafaxine ER appear to be effective for relief of DPNP with minimal adverse events; the ER formulation has the benefit of once-daily dosing. Until further studies conducted specifically in populations with DPNP are published, the data from these 2 trials support the use of venlafaxine for patients who do not respond to or cannot tolerate first-tier agents.

Tricyclic Antidepressants

The TCAs are widely used to treat chronic pain states, including low back pain and other types of neuropathic pain. Their analgesic effect is independent of their antidepressant effect[11] and, like the SNRIs, is thought to be related to inhibition of serotonin and norepinephrine reuptake, leading to more of these neurotransmitters available in the synapse.[12] Despite their widespread use, none of the TCAs has been approved by the FDA for treatment of DPNP or any type of pain, and a systematic review published in 1996 found the total number of patients in clinical trials of the various agents for treatment of DPNP to be less than 200, with no single study having more than 50 patients.[13] That review found no difference in efficacy among the various kinds of TCAs, with an NNT of 3 (95% CI, 2.4-4.0) for improvement of pain of 50% or more. Few studies of TCAs for treatment of DPNP have been published in the interim, but in a 2005 Cochrane Collaborative analysis of 5 diabetic neuropathic pain trials of antidepressants the NNT for amitriptyline's effectiveness was 1.3 (95% CI, 1.2-1.5; relative risk, 12.4; 95% CI, 5.2-29.2).[14] Tricyclic antidepressants have a considerable adverse event burden and are less well tolerated than SNRIs or SSRIs.

Amitriptyline is the best studied TCA in DPNP; other agents in this class include imipramine, clomipramine, desipramine, and nortriptyline. Amitriptyline was compared with placebo for treatment of DPNP in patients with or without depressed mood.[11] Although this was a small crossover study with 29 patients, it helped to establish the efficacy of amitriptyline and the independence of its analgesic properties from mood. Patients were randomly assigned to treatment with amitriptyline for 6 weeks followed by placebo (n=16) or placebo for 6 weeks followed by amitriptyline (n=13). The dosage of amitriptyline was between 25 and 150 mg/d; patients who could tolerate the higher doses reported greater relief of pain. Beginning at week 3 (P<.05) and continuing through week 6 (P<.01), patients treated with amitriptyline had significantly less pain than patients receiving placebo.

Desipramine was compared with placebo and in a head-to-head comparison with amitriptyline.[15] In a small (N=20) crossover study, desipramine at a mean dosage of 201 mg/d provided moderate relief of DPNP for 11 patients compared with 2 patients who reported improvement with placebo. Significant (P<.05) improvement was noted at approximately week 5 of treatment. In that study, pain relief appeared to be greater for patients with depression but was also reported by patients without depression. Desipramine was compared with amitriptyline for treatment of DPNP in another small crossover trial (N=38).[16] Mean dosages of each drug were 105 mg/d for amitriptyline and 111 mg/d for desipramine. Moderate or greater relief of pain was reported by 28 (74%) of 38 patients during treatment with amitriptyline and 23 (61%) of 38 patients during treatment with desipramine. The difference between the 2 treatments was not significant, and desipramine was better tolerated. Another TCA, nortriptyline, combined with fluphenazine was found to be equivalent to the anticonvulsant carbamazepine for treatment of DPNP in a crossover study with 16 patients.[17]

The adverse effects of TCAs are fairly predictable and mostly anticholinergic in nature and include dry mouth, constipation, dizziness, blurred vision, cardiac arrhythmias, and urinary retention. Amitriptyline has the highest affinity for the muscarinic (cholinergic) receptors, followed by clomipramine, doxepin, imipramine, nortriptyline, and desipramine.[12] The tertiary amine TCAs (amitriptyline, imipramine, and clomipramine) are associated with more severe effects, including extreme sedation and orthostatic hypotension, limiting their usefulness in many patients. Amitriptyline is contraindicated for older patients and patients with any cardiovascular disease because it has been shown to prolong QT intervals. A retrospective cohort study that included 1.28 million person-years of follow-up for subjects 15 to 84 years old identified an excess number

of sudden cardiac deaths associated with TCAs, particularly at higher doses (which may result if more medication than is prescribed is taken but not necessarily at the lower doses used for the management of pain).[18] The rate ratio for patients taking the equivalent of 300 mg/d of amitriptyline was 2.53 compared with 0.97 for patients taking less than 100 mg/d.

The analgesic efficacy of TCAs for patients with DPNP must be weighed against the adverse events associated with these agents. Little difference in efficacy was seen among the agents in a systematic review, and agents with the lowest risk of adverse events (eg, desipramine) should be considered before more agents that produce adverse effects are used (eg, amitriptyline). Tricyclic antidepressants have the advantages of low cost and demonstrated efficacy in relieving DPNP. Their disadvantages are adverse events that can affect patient compliance and, at higher doses, an increased risk of sudden cardiac death.

ANTICONVULSANTS

The $\alpha_2\delta$ Ligands. *Pregabalin.* Pregabalin has been studied in 3 randomized, double-blind, placebo-controlled trials for treatment of DPNP. It was first approved for use in Europe and then received FDA approval for the treatment of DPNP, postherpetic neuralgia (PHN), and partial seizures in December 2004 but was not available in the United States because of Drug Enforcement Agency concerns about its potential for abuse. It finally came to the US market in September 2005.

Pregabalin has been studied at dosages of 75, 150, 300, and 600 mg/d.[19-21] Both the 75-mg/d and 150-mg/d dosages were found not to differ significantly from placebo, but the 300-mg/d and 600-mg/d dosages showed good efficacy on pain and function measures. Results for those doses are reviewed herein.

In one 6-week study, 246 patients with DPNP were randomly assigned to placebo or treatment with 150 mg/d or 600 mg/d of pregabalin.[20] The primary efficacy end point in that study was the mean change in pain score at the end of treatment. Pregabalin, 600 mg/d, significantly decreased the mean pain score to 4.3 compared with 5.6 for placebo ($P<.001$) and increased the proportion of patients who had a 50% or greater decrease from baseline pain (39% vs 15% for placebo; $P=.002$). Treatment for 6 weeks with pregabalin also reduced sleep interference, pain intensity, sensory and affective pain scores, and bodily pain and decreased by 50% or more the number of patients who described their pain as "gnawing, sickening, fearful" or "punishing-cruel." The most common adverse effect associated with 600 mg/d of pregabalin was dizziness.

Another study assessed the efficacy of pregabalin, 75, 300, or 600 mg/d, for treatment of DPNP in 338 patients. Pregabalin or placebo was administered on a 3 times daily schedule (eg, 100 or 200 mg 3 times daily).[19] The 600-mg dose was titrated throughout 6 days, and the lower doses were initiated on day 1. The primary efficacy measure was change in mean pain score from baseline, using an 11-point Likert scale (0 indicating no pain to 10 indicating worst possible pain). Beginning at week 1 and continuing throughout the 5-week trial, treatment with 300 or 600 mg/d resulted in statistically significantly ($P<.001$) lower mean pain scores than placebo. These doses of pregabalin also statistically significantly ($P<.001$) improved sleep beginning at 1 week and throughout the study. Statistically significant ($P<.001$) improvements in Short-Form McGill Pain Questionnaire scores, VAS scores, and present pain intensity were observed for both the 300- and 600-mg/d dosages. Although similar percentages of patients in the 300- and 600-mg/d groups reported a 50% or greater improvement in pain (46% and 48%, respectively), a larger percentage of patients treated with 600 mg reported a 70% or greater improvement (27% vs 16%), suggesting some advantage for the higher dose.

The 300- and 600-mg/d dosages were generally well tolerated. One patient in the 300-mg group and 3 in the placebo group experienced weight gain of 7% or more of baseline weight.[19] The most common treatment-related adverse events in the 300- and 600-mg/d groups were dizziness (27.2% and 39%, respectively), somnolence (23.5% and 26.8%, respectively), and peripheral edema (7.4% and 13.4%, respectively). Overall, adverse events were more common among patients treated with 600 mg/d of pregabalin, particularly central nervous system events, such as confusion (8.5% compared with 2.1% in the placebo group). Less than 10% of patients in any group reported constipation or dry mouth.

A smaller study compared treatment with 300 mg/d of pregabalin (100 mg 3 times daily) with placebo.[21] Patients with DPNP were randomly assigned to receive pregabalin (n=76) or placebo (n=70) for 8 weeks. The primary efficacy end point was change in the mean pain score (11-point Likert scale) from baseline. At baseline, the mean pain score was 6.1 in the placebo group and 6.5 in the pregabalin group. Beginning at week 1 and continuing throughout the study, patients in the pregabalin group ($P<.01$) separated from the placebo group on the primary end point. At study end, mean pain score for the patients treated with pregabalin was 3.99 compared with 5.46 for patients in the placebo group ($P<.001$). Patients treated with pregabalin also saw significant improvements in mean sleep interference score ($P<.001$); Short-Form McGill Pain Questionnaire total ($P=.003$), VAS ($P<.001$), and present pain intensity ($P<.04$) scores; and SF-36 bodily pain score ($P<.03$). These improvements were observed beginning at week 1

and lasted throughout the study. The 300-mg dose of pregabalin was well tolerated in this study. The most commonly reported adverse events, dizziness (35.4%), somnolence (19.7%), infection (14.5%), and peripheral edema (10.5%), all occurred more often in the pregabalin group than in the placebo group. Only dizziness (11.4%) and headache (10%) occurred in 10% or more of patients in the placebo group. The infections in the study were mostly classified as colds or upper respiratory tract infections and not considered related to treatment with pregabalin. Eight patients (11%) in the pregabalin group and 2 (3%) in the placebo group discontinued study participation because of adverse events. In the pregabalin group, 2 patients each discontinued participation because of somnolence and dizziness. Median time to onset of peripheral edema in the pregabalin group was 31 days, and median duration was 18 days. Edema did not coincide with worsening cardiovascular or renal function. No changes in diabetes-related parameters were seen.

Taken together, these studies establish the efficacy and safety of 300 and 600 mg/d of pregabalin for treatment of DPNP.[19-21] Increased efficacy associated with the 600-mg/d dosage may be offset by an increase in adverse events, and these factors must be weighed for each patient (the product insert for pregabalin establishes the 300-mg dose for DPNP and the 600-mg dose for PHN[3]). Although common and bothersome, adverse events such as somnolence and dizziness led to few withdrawals from these studies. Approximately 50% of patients can expect to achieve a 50% or greater improvement in average daily pain with 300 mg/d of pregabalin, and almost 30% can achieve a 70% or greater improvement with 600 mg/d. Patients should notice improvements after 1 week of therapy. An advantage of pregabalin is that it has no known drug-drug interactions; disadvantages are the requirement of 3 daily doses and the need to titrate up to higher doses.

Gabapentin. Gabapentin was studied for the treatment of DPNP in one randomized trial.[22] It showed efficacy in PHN[23] and in another study[24] of patients with various painful neuropathies, although in the latter study results for the primary end point of reduction in pain were barely statistically significant ($P<.05$). Gabapentin is approved by the FDA for the treatment of partial seizures and PHN but not specifically for DPNP.[25]

Patients with a 1- to 5-year history of painful DPN were randomly assigned to treatment with gabapentin (n=84) or placebo (n=81).[22] Gabapentin was initiated at a dosage of 300 mg 3 times daily and increased during a period of 4 weeks in increments of 300 mg (from 900 to a maximum of 3600 mg/d). The primary efficacy end point in this study was daily pain severity measured on an 11-point Likert scale (0 indicating no pain to 10 indicating worst possible pain). Secondary end points included sleep interference scores, Short-Form McGill Pain Questionnaire scores, and patient Global Impression of Change and Clinical Global Impression of Change scores. At study end, patients who were treated with gabapentin showed significant improvement on all end points compared with those who received placebo. Beginning at week 2 and continuing throughout the trial, patients treated with gabapentin showed statistically significant ($P<.01$) improvement in pain scores compared with those who received placebo. Mean baseline pain scores were 6.4 in the gabapentin group and 6.5 in the placebo group. At study end, mean pain scores were 3.9 in the gabapentin group and 5.1 in the placebo group. Patients who were treated with gabapentin also had statistically significantly ($P=.001$) better overall impressions of their treatment, with 47 of 79 reporting that they were much or moderately improved and 30 of 70 saying they were minimally improved or had no change, compared with only 25 of 76 who received placebo saying they were much or moderately improved and 13 of 76 saying they were worse than at the beginning of the study. Gabapentin was well tolerated in the study, with 70 (83%) of 84 patients completing treatment. Dizziness and somnolence were reported by significantly more patients receiving gabapentin than placebo.

Gabapentin was compared with amitriptyline for treatment of DPNP in a crossover study with 25 patients.[26] A mean dosage of 1565 mg/d was equivalent to a mean dosage of 59 mg/d of amitriptyline in terms of changes on mean daily score and the percentage of patients who achieved moderate or greater pain relief. Common adverse events for both treatments were sedation, dry mouth, dizziness, postural hypotension, weight gain, ataxia, and lethargy. With the exception of weight gain with amitriptyline, the incidence of these adverse effects did not differ significantly between the groups. In that study, gabapentin was well tolerated and effective but offered no advantage over amitriptyline.

In patients with PHN, treatment with up to 3600 mg/d of gabapentin statistically significantly ($P<.001$) improved pain severity and measures of sleep interference.[23] However, in another randomized trial that enrolled 307 patients with painful neuropathies (including 7 with DPNP), treatment with gabapentin up to 3600 mg/d for 8 weeks improved pain scores on an 11-point scale by 1.5 points (21%) compared with 1 point (14%) for placebo, a barely statistically significant difference ($P<.05$).[24] In the latter study, gabapentin was effective ($P<.05$) on secondary measures of Clinical Global Impression of Change and Patient Global Impression-Change scores and the SF-36 domains of bodily pain, social functioning, and role-emotional. In both studies, gabapentin was fairly well

tolerated, with dizziness and somnolence occurring more often with gabapentin than with placebo.[23,24] Among patients with PHN, 13.3% of gabapentin and 9.5% of placebo subjects withdrew because of adverse events.[23] In the group of patients with painful neuropathies of varying origins, however, 15.7% of gabapentin and 16.4% of placebo subjects withdrew because of adverse events.[24] Another study found that the combination of gabapentin and morphine was more effective than either treatment alone for treatment of neuropathic pain and allowed lower doses of each to be used.[27]

These studies suggest that gabapentin is probably an effective treatment for patients with DPNP. Further studies specifically enrolling patients with DPNP would help to confirm the results of the previously published study. Until such time, gabapentin is an appropriate second-tier choice for patients who do not respond to or cannot tolerate first-tier agents. Gabapentin has the disadvantage of requiring titrated dosing and multiple daily doses for patients who require dosages higher than 300 mg/d.

Other Anticonvulsants. Although anticonvulsant agents are used for pain, no evidence of a class effect exists; the $\alpha_2\delta$ ligands are the anticonvulsants with the best evidence of efficacy. Other anticonvulsants, with different mechanisms of action, have not been as well studied. However, several anticonvulsants have some evidence in treating DPNP and are reviewed herein.

Carbamazepine. Carbamazepine was one of the first anticonvulsants studied for treatment of painful DPN. It has been examined in several small clinical trials. Two small placebo-controlled studies found that carbamazepine effectively reduced pain. In a crossover study, 28 of 30 patients reported pain relief when treated with carbamazepine, 600 mg/d; adverse events were mild but led to study discontinuation for 2 patients.[28] In another study with 40 patients, those treated with carbamazepine, 200 mg 3 times daily, had statistically significantly ($P<.05$) less pain on days 10 and 14 than those who received placebo.[29]

The efficacy and tolerability of the combination of nortriptyline-fluphenazine were compared with carbamazepine for treatment of patients with severe, predominantly sensitive DPNP in a randomized, double-blind crossover trial with 16 patients.[17] Patients received either nortriptyline-fluphenazine or carbamazepine treatment for 4 weeks; after a 2-week washout period, they were crossed over to receive the other drug. A VAS was used to evaluate the percentage of changes in pain and paresthesia. Both therapies produced significant improvement of pain and paresthesia. No statistically significant differences were observed between the therapies for either pain or paresthesia. Adverse effects were mild and more frequent when patients were being treated with nortriptyline-fluphenazine.

Lamotrigine. Lamotrigine is an anticonvulsant that also has antidepressant properties in patients with bipolar disorder. It has 2 antinociceptive features: stabilization of neural membranes through voltage-gated sodium channels and inhibition of presynaptic release of glutamate. Lamotrigine must be titrated slowly to avoid a small but real risk of serious treatment-related rash (Stevens-Johnson syndrome and/or toxic epidermal necrolysis).[30]

Lamotrigine has been studied in a randomized placebo-controlled trial that enrolled 59 patients with painful DPN.[30] Although a significant decrease in pain on the Numerical Pain Scale was noted in the patients taking lamotrigine, no significant differences were seen on secondary end points of change in the Beck Depression Inventory, McGill Pain Questionnaire, or Pain Disability Index. Lamotrigine appeared to be effective at a dosage of 200 to 400 mg/d. The most common adverse events in both groups were nausea, epigastric pain, headache, drowsiness, and dizziness. None occurred in more than 4 patients in either group. Two patients in each group withdrew due to adverse events. Two patients developed rash while being treated with lamotrigine, one at a 50-mg/d dosage and the other at a 300-mg/d dosage. In both patients, the rash resolved without incident when lamotrigine therapy was discontinued.

Similar doses of lamotrigine have been shown in 2 randomized, placebo-controlled trials to effectively relieve neuropathic pain associated with human immunodeficiency virus–associated neuropathy.[31,32] Lamotrigine appears to effectively reduce neuropathic pain symptoms among patients with DPNP and human immunodeficiency virus–associated neuropathy. It has an antidepressant effect that may make it an appropriate second-tier choice for patients with DPNP and comorbid depression who cannot tolerate or do not respond to duloxetine, TCAs, or venlafaxine. Lamotrigine has the disadvantage of requiring a strict titration regimen to reduce the risk of serious cutaneous reactions, which means several weeks may pass before patients reach an effective analgesic dose. Although rare when lamotrigine is properly titrated, the risk of Stevens-Johnson syndrome and toxic epidermal necrolysis must be considered and weighed against potential benefit when prescribing this drug.

Opioids

Oxycodone CR. Long-acting oxycodone CR has been studied in 2 randomized controlled trials for relief of pain in patients with DPNP.[33,34] In both trials, treatment with oxycodone CR decreased pain measured by VAS or APSs. A parallel-group, placebo-controlled trial randomly assigned patients to treatment with oxycodone CR (begin-

ning at 10 mg every 12 hours to a maximum dose of 60 mg every 12 hours) (n=82) or placebo (n=77) for a 6-week study.[33] At an average dosage of 37 mg/d, treatment with oxycodone CR significantly reduced average pain intensity ($P<.001$), worst pain ($P=.001$), and present pain ($P=.002$) compared with placebo. Average pain intensity scores recorded in daily diaries from days 28 to 42 were reduced by 2.0 from baseline with the use of oxycodone CR compared with 1.0 from baseline with placebo ($P<.001$). Adverse events led to 7 withdrawals in the oxycodone CR group and 4 in the placebo group. Constipation (42%), somnolence (40%), nausea (36%), dizziness (32%), pruritus (24%), vomiting (21%), and dry mouth (16%) all were reported by statistically significantly ($P\leq.005$) more patients taking oxycodone CR than by patients taking placebo.

Another study enrolled 45 patients with DPNP and randomly assigned them to treatment with 10 to 40 mg every 12 hours of oxycodone CR or an active placebo (0.25 mg/d of benztropine) for 4 weeks followed by crossover to the opposite treatment without an intervening washout period.[34] Patients treated with oxycodone CR had significantly lower scores on the 100-mm VAS for mean daily pain intensity (21.8 vs 48.6 for placebo; $P<.001$). Statistically significant ($P<.05$) improvements also were seen in measures on the Pain and Disability Indicator. Seven patients in the oxycodone CR group (n=22) and 1 in the placebo group (n=11) withdrew because of adverse events. Constipation and dry mouth occurred statistically significantly ($P=.02$) more often when patients were treated with oxycodone CR than with placebo.

These studies show that oxycodone CR is effective in reducing measures of DPNP at the expense of high rates of adverse events, such as constipation, sedation, dizziness, and dry mouth. Most of these adverse events were considered mild to moderate in severity, and few of the patients treated with oxycodone CR discontinued the study because of adverse events in the larger trial. When considering whether to prescribe oxycodone CR for DPNP, it is important to evaluate your patient for warning signs of possible abuse and to discuss with your patient the pros and cons of using opioid analgesics. If oxycodone CR is decided as the best treatment for a patient, an opioid agreement signed by the patient and physician may prove useful.

Tramadol. Tramadol is a centrally acting analgesic with unique properties as a weak inhibitor of norepinephrine and serotonin reuptake and low-affinity binding to μ-opioid receptors. In a randomized, double-blind, placebo-controlled 6-week trial, tramadol (average dosage, 210 mg/d) significantly improved pain and physical and social functioning for patients with DPNP.[35] However, tramadol treatment did not improve sleep disturbance. Patients were randomly assigned to treatment with tramadol (n=65) or placebo (n=66). Tramadol was titrated from 50 to 200 mg/d throughout 10 days; afterward, patients could increase their dosage up to 400 mg/d. The starting dose was administered as 12.5 mg 4 times daily, and 4 times daily dosing was used throughout the study. At days 14, 28, and 42, those treated with tramadol reported more relief compared with placebo, but the difference was only statistically significant ($P<.001$) at the final visit. The most common adverse events associated with tramadol treatment were nausea (23.1%), constipation (21.5%), headache (16.9%), and somnolence (12.3%). Approximately 14% of patients in the tramadol group discontinued the study because of adverse events.

Another study evaluated tramadol for treatment of pain and allodynia in 34 patients with polyneuropathies, including 15 with DPNP.[36] Patients were treated with tramadol at dosages of 200 to 400 mg/d or placebo in a crossover fashion. Treatment with tramadol statistically significantly ($P\leq.001$) reduced ratings for pain, paraesthesia, and touch-evoked pain, as well as allodynia ($P<.01$). The NNT for tramadol in this mixed group of painful neuropathies was 4.3 (95% CI, 2.4-20.0). Adverse events, including tiredness, dizziness, dry mouth, sweating, constipation, nausea, and urinary retention, occurred more frequently when patients were treated with tramadol (all except nausea and urinary retention, $P<.02$ vs placebo).

Results from one study in patients with DPNP suggest tramadol may be an effective way to relieve pain for these patients.[35] Until further confirmed, tramadol is a valuable second-tier treatment. Its disadvantages include a high incidence of adverse events including seizures, need for 4 times daily dosing, and concerns about dependence or abuse similar to those with other opioid drugs.

Topical Agents

Capsaicin. Capsaicin, the active principle of hot chili pepper, selectively stimulates unmyelinated C fiber afferent neurons and causes the release of substance P, as well as producing complete or nearly complete denervation of the epidermis.[37] Prolonged application of capsaicin reversibly depletes stores of substance P, and possibly other neurotransmitters, from sensory nerve endings. This reduces or abolishes the transmission of painful stimuli from the peripheral nerve fibers to the higher centers.

In clinical studies of patients with DPNP, adjunctive therapy with topical capsaicin achieved better relief than its inactive vehicle comparator.[38-40] Topical capsaicin is not associated with any severe systemic adverse effects. However, stinging and burning, particularly during the first week of therapy, are reported by many patients.

The Capsaicin Study Group evaluated the use of capsaicin for treatment of DPNP in a randomized trial.[38,39] Pa-

tients (N=277) with DPNP and/or radiculopathy were randomly assigned to treatment with 0.075% capsaicin or vehicle creams, 4 times daily, in an 8-week double-blind, vehicle-controlled study. Participants were unresponsive or intolerant to conventional therapy and were experiencing pain that interfered with functional activities and/or sleep. Pain intensity and relief were recorded at 2-week intervals using the Physician's Global Evaluation and the VAS. Analysis at the final visit for 252 patients significantly favored capsaicin compared with vehicle for pain improvement on the Physician's Global Evaluation (69.5% vs 53.4%, respectively; $P \leq .01$), decrease in pain intensity (38.1% vs 27.4%, respectively), and improvement in pain relief (58.4% vs 45.3%, respectively). Significant differences in favor of capsaicin vs vehicle also were observed for functional measures, including improvement in walking (26.1% vs 14.6%, respectively; $P<.03$), improvement in working (18.3% vs 9.2%, respectively; $P<.02$), improvement in sleeping (29.5% vs 20.3%, respectively; $P<.04$), and improvement in participating in recreational activities (22.8% vs 12.1%, respectively; $P<.04$). With the exception of transient burning, sneezing, and coughing, capsaicin was well tolerated.[39] These results suggest that topical capsaicin cream is safe and effective in treating DPNP, with the caveat that patients who are already experiencing pain may have to endure treatment-related burning effects for the first few weeks of treatment.

Lidocaine. The 5% lidocaine patch is commonly used in primary care to treat painful conditions. Evidence from small randomized or open-label trials supports the efficacy of topical lidocaine for relief of DPNP, with minimal adverse events.[41-43]

Topical 5% lidocaine patches appear to benefit patients with neuropathic pain. In a randomized, placebo-controlled crossover study, the 5% lidocaine patch was studied in 58 patients with focal peripheral neuropathic pain syndromes, including 32 with postherpetic neuropathy and 1 with DPNP.[41] Patients were randomly assigned to treatment with the 5% lidocaine patch or placebo for 7 days, then switched to the opposite treatment after a 1-week washout period. A maximum of 4 patches every 24 hours was allowed, and patients were to wear them 12 hours per day. Patients used an average of 2 patches per day; statistically significant ($P \leq .05$) improvements in ongoing pain and intensity of allodynia were noted at several periods for patients who received active treatment compared with placebo. Pain intensity was lower at 2 and 4 hours and on treatment days 4, 5, and 7; allodynia was less intense at 2, 4, and 6 hours and on treatment day 4. There was no difference in adverse events between the lidocaine and placebo groups, and the most commonly reported events were rash and pruritus.

In an open-label study of patients with neuropathic pain, 5% lidocaine patches significantly ($P<.001$) improved 4 composite measures of the Neuropathic Pain Scale in patients with DPNP (n=41) with only mild to moderate adverse events reported.[42] Systemic effects of lidocaine treatment were reported in 5% of patients and included a single case each of headache, elevated aspartate aminotransferase levels, elevated blood pressure, burning sensation, muscle spasms, and tingling sensation.

In another open-label study, 56 patients with DPNP of at least 3 months' duration were instructed to use 4 or fewer 5% lidocaine patches for up to 18 hours per day.[43] As measured by patient pain diaries, use of the lidocaine patch improved pain during the 3-week study. Significant improvements in quality-of-life measures also were seen. Among patients who continued the therapy for 5 more weeks, some tapering of other analgesics was possible.

Intravenous lidocaine and oral mexiletine also have been investigated for neuropathic pain. The requirement for intravenous administration and potential adverse effects make the use of intravenous lidocaine problematic. Mexiletine has been studied in 4 controlled trials with no evidence of efficacy superior to placebo.[12] In addition, use of mexiletine, a type 1b antiarrhythmic drug, requires regular electrocardiographic monitoring and is contraindicated for patients with any type of cardiac disease.

OTHER AGENTS WITH LIMITED EVIDENCE IN DPN OR PAINFUL NEUROPATHY

Several other agents have demonstrated efficacy in other forms of painful neuropathy or in less well-controlled or open-label trials of patients with DPNP. Table 3 summarizes information on these agents. Of these, the anticonvulsant topiramate has the largest positive trial in DPNP,[44] but this evidence must be weighed against 3 smaller negative trials that were published in the same year.[52]

Many patients use and perceive benefit from complementary approaches, but no good evidence exists of their efficacy in DPNP. Some of these approaches may have value as adjunctive therapy for individual patients, and patients' interest in or use of such therapies should be discussed during office visits. When discussing these approaches with patients, it is imperative to review with them the costs, risks, and evidence. Some therapies have little or no risk but also no evidence of efficacy. Others, such as spinal cord stimulation, have high costs and risks and no evidence. There is no reason to encourage patients to explore treatments in this latter group and many reasons to discourage them.

TABLE 3. **Summary of Treatments With Limited Evidence[44-51]***

Treatment	Pain type	Dose	Response
Bupropion (2001), RDBPC crossover	Neuropathic pain (N=41)	150-300 mg/d	70% improved or much improved
Citalopram (1992), RDBPC crossover	DPN (N=15)	40 mg/d	Improved symptoms ($P \leq .02$) on observer- and patient-rated scales
Methadone (2003), RDB crossover	Neuropathic pain (N=18)	10 or 20 mg/d	20 mg reduced pain on VAS ($P \leq .02$)
NMDA antagonists (2002), active PC crossover	DPN (n=23), dextromethorphan, memantine	400 mg of dextromethorphan, 55 mg/d of memantine	33% reduction from baseline with dextromethorphan; no benefit with memantine
Dextromethorphan (1997), RDBPC crossover	DPN (N=14)	381 mg/d	24% > pain reduction than placebo
Paroxetine (1990), RDBPC crossover	DPN (N=19)	40 mg/d	Imipramine > paroxetine > placebo; paroxetine better tolerated than imipramine
Phenytoin (1999), RDBPC crossover	Neuropathic pain (N=20)	15 mg/kg intravenously	Reduced overall and individual pain measures ($P \leq .05$)
Topiramate (2004), RDBPC	DPN (N=323)	400 mg/d or maximum tolerated dose	50% achieved ≥30% improvement

*DPN = diabetic peripheral neuropathy; NMDA = *N*-methyl-D-aspartate; PC = placebo-controlled; RDB = randomized double-blind; RDBPC= randomized, double-blind, placebo-controlled; VAS = visual analog scale.

Acupuncture probably falls somewhere between these 2 groups; it has minimal but not insignificant risks but also some evidence of analgesic efficacy in chronic pain and DPNP. It was evaluated in 46 patients with DPNP, 29 of whom were receiving drug treatment.[53] Patients received 6 sessions of traditional Chinese acupuncture throughout 10 weeks. Thirty-four (77%) reported significant improvement in symptoms ($P<.01$), including 7 (21%) who reported complete resolution of symptoms. Patients who completed the study (n=44) were then followed up for 18 to 52 weeks. During the follow-up period, 66% of patients reported they could stop or reduce pain medications. Only 8 required additional acupuncture. No adverse events related to the acupuncture were reported, and there were no changes in peripheral neurologic examination scores or hemoglobin A_{1c} levels. Acupuncture may relieve pain and/or reduce the need for pain medications in selected patients with DPNP.

Currently, no good evidence exists that other modalities, such as transcutaneous electrical nerve stimulation or magnetic insoles, are effective in relieving DPN-associated pain. However, some limited evidence has shown that spinal cord stimulation and frequency-modulated electromagnetic neural stimulation may be helpful.[54,55]

TABLE 4. **Recommendations for First- and Second-Tier Agents for DPNP[6,7,9-12,15-17,19-21,23-30,33-35,38-40,42,44,46,47,50,51]***

Agent type	Reason for recommendation	Agent names
First tier	≥2 RCTs in DPN	Duloxetine, oxycodone CR, pregabalin, TCAs
Second tier	1 RCT in DPN; ≥1 in other painful neuropathies	Carbamazepine, gabapentin, lamotrigine, tramadol, venlafaxine ER
Topical	Mechanism of action	Capsaicin, lidocaine
Other	≥1 RCTs in other painful neuropathies or other evidence	Bupropion, citalopram, methadone, paroxetine, phenytoin, topiramate

*CR = controlled release; DPN = diabetic peripheral neuropathy; DPNP = diabetic peripheral neuropathic pain; ER = extended release; RCT = randomized controlled trial; TCAs = tricyclic antidepressants.

RECOMMENDATIONS FOR IMPLEMENTING THERAPIES

Table 4 presents the Diabetic Peripheral Neuropathic Pain Consensus Treatment Guidelines Advisory Board's recommendations for first- and second-tier agents to treat DPNP based on the level of evidence available from clinical trials and the committee's clinical experience. These recommendations were developed by consensus after a 2-day meeting in which the committee reviewed clinical trial evidence, the strengths and weaknesses of various clinical trials, their own experience with the agents in real-world patient treatment situations, and a recognition of accepted primary care practice.

Table 5 presents a list of patient- or treatment-related factors to use when choosing among the first-tier agents. Mechanism of action should *not* be a criterion for choosing a first-tier agent. The recommendations in Table 5 are based on patient comorbidities, drug adverse event profiles and contraindications, and clinical scenarios. These recommendations are general, and physicians should consult each agent's prescribing information before deciding on a first-line treatment.

RECOMMENDATIONS FOR MONITORING THERAPY

Once therapy is initiated, patients must be asked at each visit whether their pain is improved and if so to what degree. They should also be asked whether the pain has become worse and whether the nature of the pain has in any

way changed. Patients should be asked specific questions about physical and social function and whether it is has improved, worsened, or remained unchanged. They must be asked about adverse events and should be allowed to describe any in their own words. Finally, they should be asked whether they are satisfied with the treatment effect. If they are not, they should be offered the option to add therapy, along with an explanation that they may receive more relief at the expense of more potential adverse events.

We recommend the use of a VAS or other simple scales for patients to monitor their treatment response, with the caveat that these scales are subjective and on any given visit may be influenced by experiences of the day (eg, outdoor temperature or stress levels).

First-tier agents should be titrated to maximum tolerated doses. A reduction in pain of at least 50% from baseline should be expected if the agent is effective for that patient. For all first-tier agents, some improvement in pain levels should be expected within 3 weeks of initiating therapy. If no improvement is seen, modification of therapy may be warranted.

RECOMMENDATIONS FOR MODIFYING THERAPY

If patients do not respond adequately to first-line treatment or complain of adverse events, it may be necessary to modify their treatment. The recommended next steps are as follows:

- Change to another first-line agent—use mechanism of action to guide switch (eg, choose an agent with a different mechanism)
- Change to second-line agent—use mechanism of action to guide switch
- Add a different first or second agent (Table 6)—use principles of rational polypharmacy (eg, complementary mechanisms of action, avoid additive adverse events; consider possible synergies)

CONCLUSION

Many theories exist for the pathogenesis of DPN, but none fully explain why some patients develop chronic pain related to their neuropathy. Clearly, poor glycemic control contributes over time to the development of several devastating long-term complications of diabetes mellitus, including DPN, a necessary prerequisite for DPNP. Some evidence suggests pain severity and flux in glucose levels are related, but there is no evidence at this time that strict control of glucose levels prevents or resolves DPNP. Still, it is good practice and must be encouraged. Several pharmacological options for symptomatic treatment of DPNP have good evidence of efficacy, and 2 agents currently have FDA approval for that purpose. First-tier agents, based on positive results from 2 or more randomized clinical trials, include duloxetine, pregabalin, oxycodone CR, and the TCAs. Choices for individual patients must take into account patient factors such as comorbidities, other medication, and goals of treatment; adverse event profiles of the agents; and perhaps factors such as cost or local availability. Additional agents that can be considered based on evidence of efficacy from a single trial in patients with DPN and evidence from studies of other painful neuropathies are gabapentin, venlafaxine, tramadol, and perhaps

TABLE 5. **Factors to Consider in Choosing First-Tier Agents***

Factor	Recommended	Avoid
Medical comorbidities		
Glaucoma	Any other first-tier agent†	TCAs
Orthostatic phenomena	Any other first-tier agent	TCAs
Cardiac or electrocardiographic abnormality	Any other first-tier agent	TCAs
Hypertension	Any other first-tier agent	TCAs
Renal insufficiency	Any first-tier agent‡§	
Hepatic insufficiency	Any other first-tier agent	Duloxetine
Falls or balance issues	Any other first-tier agent	Pregabalin, TCAs
Psychiatric comorbidities		
Depression¶	Duloxetine, TCAs	Oxycodone CR, pregabalin
Anxiety	Any other first-tier agent	Oycodone CR
Suicidal ideation	Duloxetine, pregabalin	TCAs, oxycodone CR
Somatic issues		
Sleep	Any first-tier agent	
Erectile dysfunction	Second-tier agent venlafaxine	All first-tier agents
Other factors		
Cost	TCAs, generic oxycodone CR	Duloxetine, pregabalin
Drug interactions	Oxycodone CR, pregabalin	Duloxetine, TCAs//
Weight gain	Duloxetine, oxycodone CR	TCAs, pregabalin
Edema	Any other first-tier agent	Pregabalin

*The first-tier agents are duloxetine, oxycodone controlled release (CR), pregabalin, and tricyclic antidepressants (TCAs).
†Duloxetine is contraindicated only for patients with uncontrolled narrow-angle glaucoma and may be appropriate for other patients with glaucoma.
‡Dosage adjustment of oxycodone CR and pregabalin is recommended for patients with a creatinine clearance less than 60 mL/min.
§Duloxetine is not recommended for patients with a creatinine clearance less than 30 mL/min.
¶Before initiating treatment with an antidepressant, patients with depressive symptoms should be adequately screened to determine if they are at risk of bipolar disorder.
//Consult prescribing information for individual agents concerning specific drug-drug interactions and contraindications.

TABLE 6. **Rational Polypharmacy for Diabetic Peripheral Neuropathic Pain***

First-tier agent	Add-on therapy	Avoid
SNRIs	$\alpha_2\delta$ ligands, opioids, topical agents	Other SNRIs, TCAs, tramadol
$\alpha_2\delta$ ligands	SNRIs, TCAs, opioids, tramadol, topicals	Other $\alpha_2\delta$ ligands
TCAs	$\alpha_2\delta$ ligands, opioids, topicals	SNRIs, tramadol
Opioids	SNRIs, $\alpha_2\delta$ ligands, TCAs, topicals	Other opioids
Tramadol	$\alpha_2\delta$ ligands, opioids, topicals	SNRIs, TCAs
Topical agents	SNRIs, $\alpha_2\delta$ ligands, TCAs, opioids, tramadol, topicals	None

*Rationale for polypharmacy includes the ability to decrease toxicity, address treatment failures, take advantage of complementary mechanisms of action, and decrease drug-drug interactions. SNRI = serotonin-norepinephrine reuptake inhibitor; TCAs = tricyclic antidepressants.

carbamazepine and lamotrigine. Topical therapies may be appropriate early in treatment and for specific individuals. Despite these many options, the reality is that few patients will achieve 100% relief of DPNP, and some may require therapy with multiple agents. Polypharmacy decisions should be based on mechanism of action and adverse events profiles. Finally, patients with DPNP share some features with patients with chronic pain and may benefit from a referral to a multidisciplinary pain center that incorporates elements of psychosocial therapy (eg, cognitive behavioral therapy), biofeedback, physical therapy, and other modalities.

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