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SUPPLEMENT

CONSENSUS GUIDELINES: ASSESSMENT, DIAGNOSIS, AND TREATMENT OF DIABETIC PERIPHERAL NEUROPATHIC PAIN

Accreditation and Credit Designation

This activity has been planned and implemented in accordance with the Essential Areas and Policies of the Accreditation Council for Continuing Medical Education through the joint sponsorship of The Johns Hopkins University School of Medicine and the American Society of Pain Educators. The Johns Hopkins University School of Medicine is accredited by the ACCME to provide continuing medical education for physicians.

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Learning Objectives

Following this program, the participant should be able to: (please list objectives)

- Recognize the symptoms of diabetic peripheral neuropathic pain
- Understand mechanisms of action of available treatment options
- Describe patients at risk for diabetic neuropathic pain

Target Audience

Primary care physicians, internal medicine physicians, geriatric physicians, and psychiatrists treating chronic pain.

Method of Participation

The estimated time to complete this activity is 2 hours. In order to obtain credit, you must read the monograph and complete the post-test and evaluation on-line by April 30, 2008.

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Off-Label Mention

As it is only in the last two years that there have been two products specifically indicated to treat diabetic peripheral neuropathic pain (DPNP), this supplement contains mention of off-label uses for several medications that have been used to treat DPNP.

Disclaimer Statement

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SUPPLEMENT

CONSENSUS GUIDELINES: ASSESSMENT, DIAGNOSIS, AND TREATMENT OF DIABETIC PERIPHERAL NEUROPATHIC PAIN

A continuing medical education activity jointly sponsored by The Johns Hopkins University School of Medicine and the American Society of Pain Educators

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Foreword

Diabetes mellitus is a difficult disease with a potentially very painful prognosis. The relentless inevitability of diabetes leads to serious neurologic dysfunction over the years. Although most patients with diabetic peripheral neuropathy rarely experience excruciating pain, enough do that we must have strategies and treatment options for addressing their pain.

From June 10 to 12, 2005, 11 pain specialists (Charles E. Argoff, MD; Misha-Miroslav Backonja, MD; Miles J. Belgrade, MD; Gary J. Bennett, PhD; Michael R. Clark, MD; B. Eliot Cole, MD, MPA; Robert H. Dworkin, PhD; David A. Fishbain, MD, FAPA; Gordon A. Irving, MBBS, FFA (SA), MMed, MSc; Bill McCarberg, MD; and Michael J. McLean, MD, PhD) convened in New Orleans, La, as the Diabetic Peripheral Neuropathic Pain (DPNP) Consensus Treatment Guidelines Advisory Board to create the first DPNP recommendations. The intended audience for these guidelines included primary care practitioners, other pain practitioners, and anyone interested in helping a population with seemingly few options. The intent of this work group was to review the existing neuropathic literature, focus on specific therapies for DPNP, and establish a schema for better patient care.

It was understood by the group that only 2 medications were formally approved for DPNP, but there were many off-label trials establishing the efficacy of many anticonvulsant, antidepressant, and analgesic agents. Using the strength of blind, randomized, placebo-controlled trials, the group weighed the available evidence and ranked treatments into first-tier, second-tier, and "honorable mention" categories. Attempts were made to examine nonpharmacological therapies, but evidence was sorely lacking for these.

In the end, 4 medications were thought to be first-tier therapies for DPNP: duloxetine, oxycodone (controlled release), pregabalin, and the tricyclic antidepressants as a class. Second-tier agents included the anticonvulsants carbamazepine, gabapentin, and lamotrigine; the mixed "antidepressant-opioid" tramadol; and the antidepressant venlafaxine (extended release). The topical agents capsaicin and lidocaine; antidepressants bupropion, citalopram, and paroxetine; anticonvulsants phenytoin and topiramate; and opioid methadone were honorable mentions. In all groupings, anticonvulsants, antidepressants, and opioids were present, demonstrating that the underlying pathophysiology of DPNP must be connected to the presumed mechanisms of action for these various agents.

The members of the DPNP Consensus Treatment Guidelines Advisory Board believe that the introductory article addressing the clinical and quality-of-life issues associated with DPNP and the case studies article will help the practitioner better understand the link between diabetes and pain and be better prepared to care for those so afflicted. As Americans age and live longer with diabetes mellitus, there is a need for DPNP guidelines and for other pain-related conditions. Collectively, the members of the DPNP Consensus Treatment Guidelines Advisory Board thank the editors of *Mayo Clinic Proceedings* for providing a forum for this discussion, express their gratitude to the Johns Hopkins University School of Medicine for providing the Continuing Medical Education credit, and thank Eli Lilly and Company for providing an educational grant.

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Diabetic Peripheral Neuropathic Pain: Clinical and Quality-of-Life Issues

CHARLES E. ARGOFF, MD; B. ELIOT COLE, MD, MPA; DAVID A. FISHBAIN, MD, FAPA (DISTINGUISHED); AND GORDON A. IRVING, MBBS, FFA (SA), MMED, MSC

Diabetic peripheral neuropathy (DPN) is estimated to be present in 50% of people living with diabetes mellitus (DM). Comorbidities of DM, such as macrovascular and microvascular changes, also interact with DPN and affect its course. In patients with DM, DPN is the leading cause of foot ulcers, which in turn are a major cause of amputation in the United States. Although most patients with DPN do not have pain, approximately 11% of patients with DPN have chronic, painful symptoms that diminish quality of life, disrupt sleep, and can lead to depression. Despite the number of patients affected by DPN pain, little consensus exists about the pathophysiology, best diagnostic tools, and primary treatment choices. This article reviews the current knowledge about and presents recommendations for diagnostic assessment of DPN pain based on a review of the literature.

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BPI = Brief Pain Inventory; BPI-DPN = Brief Pain Inventory for Diabetic Peripheral Neuropathy; DM = diabetes mellitus; DPN = diabetic peripheral neuropathy; DPNP = diabetic peripheral neuropathic pain; IGT = impaired glucose tolerance

Diabetic peripheral neuropathic pain (DPNP) affects approximately 11% of patients with diabetic peripheral neuropathy (DPN). Its pathogenesis remains unknown, and none of the various treatments used can be considered a cure. It shares certain similarities in clinical signs and response to treatment with other forms of neuropathic pain but is also distinct in its apparent association with glucose-related metabolic changes. Most patients with DPN do not experience pain, and in fact many have a lack of sensation. The reason why some patients with DPN develop DPNP is unknown. Furthermore, not all patients with DPNP have a neuropathic condition; the underlying source of pain in some patients may be something other than diabetes mellitus (DM), which is important to remember when making a diagnosis.

According to the National Diabetes Information Clearinghouse (National Institutes of Health, Bethesda, Md), 20.8 million people in the United States (7% of the US population) were estimated to have DM in 2005, including 6.2 million whose conditions were undiagnosed.[1] The number of people with DM more than doubled between 1980 and 2004, from 5.8 million to 14.7 million.[2] Diabetes mellitus was responsible for more than 73,249 deaths in 2002, making it the sixth leading cause of death in the United States.[3] The prevalence of type 2 DM is expected to continue to increase as the US population ages and as a larger proportion of the population remains overweight. Although type 2 DM has traditionally been a disease of those older than 40 years and exact numbers are not known for people younger than 20 years, clinic-based reports and regional studies suggest that it is becoming more common among children and adolescents.[1] In 2005, an estimated 176,500 young people (<20 years old) had DM in the United States.[1]

Because DPN is closely associated with DM, its prevalence and effect on patients' quality of life and health care costs also can be expected to increase. The average annual cost of pain medication per patient with DPNP is approximately $1000, and patients who take 2 or more medications, as most do, have average annual medication costs of almost $1600.[4] Overall, patients with painful neuropathies have annual health care costs almost 3 times higher than the costs for matched control populations.[5]

Using Ovid, we searched full-text online journals published from 1995 to 2005 and used the terms *diabetic peripheral neuropathy*, *diabetic peripheral neuropathic pain*, and *neuropathic pain* to examine the prevalence of DPN and DPNP, the diagnostic assessment and differential diagnosis of DPN, and the comorbidities associated with DPNP, including quality-of-life effects and safety issues such as foot care. This article defines key terms associated with the diagnosis and treatment of DPNP (Table 1).

PREVALENCE OF DPN AND DPNP

To understand the prevalence of DPN, it helps to understand the various forms it takes. Diabetes-associated neurop-

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TABLE 1. **Definitions Related to Diabetes Mellitus and Pain[6-12]***

Condition	Definition
Disease related	
Diabetes mellitus	Serum glucose ≥200 mg/dL 2 h after 75-g oral glucose load or FPG ≥126 mg/dL (7.0 mmol/L)
Impaired glucose tolerance	Serum glucose ≥140 mg/dL but <200 mg/dL 2 h after 75-g oral glucose load
Impaired fasting glucose	FPG ≥100 mg/dL but <126 mg/dL (5.6-6.9 mmol/L)
Diabetic pain	Pain associated with neuropathy caused by DM; DPNP
Positive symptoms	Arise spontaneously or as a response to stimuli; often painful
Distal symmetrical painful neuropathy	Neuropathic pain syndrome in distal, symmetrical body areas, generally the feet but sometimes also the hands; DPN
Negative (absence) symptoms	Decreased response to stimuli, eg, loss of sensation in the foot
Pain related	
Allodynia	Pain from normally innocuous stimuli; reduced threshold for eliciting pain
Analgesia	Absence of pain in response to normally painful stimuli
Anesthesia dolorosa	Pain in areas that are otherwise insensate
Dysesthesia	Unpleasant abnormal sensations
Hyperalgesia	Exaggerated, prolonged response to noxious stimuli
Neuropathic pain	Pain resulting from lesion or dysfunction of the nervous system
Numbness (absence of sensation or anesthesia)	Loss of sensation in a body area, eg, the insensate foot
Paresthesia	Nonpainful abnormal or impaired skin sensation, eg, tingling
Paroxysms of pain	Brief, recurrent shock-like pain sensations; may occur in isolation or in a series

*DM = diabetes mellitus; DPN = diabetic peripheral neuropathy; DPNP = diabetic peripheral neuropathic pain; FPG = fasting plasma glucose.

athy is in the broad categories of generalized symmetrical polyneuropathies and focal or multifocal neuropathies.[13] The symmetrical neuropathies include acute sensory neuropathy, DPN (also known as chronic sensorimotor distal symmetrical polyneuropathy), and autonomic neuropathy.[13]

The most common type of neuropathy in DM is DPN, with up to 50% of patients experiencing some degree of painful symptoms[13] and 10% to 20% having symptoms severe enough to warrant treatment.[14,15] A classic population-based study found some degree of neuropathy in 66% of patients with DM.[9] Among those with type 1 and type 2 DM, 54% and 45%, respectively, had DPN and 15% and 13%, respectively, were symptomatic.[16] The most commonly found condition was DPN, which occurred in more than 80% of the patients with neuropathy. A study that assessed symptoms of neuropathy in 350 patients with DM, using the Michigan Neuropathy Screening Instrument, found that nearly a third of those with type 1 and more than half of those with type 2 DM had at least 1 neuropathic symptom.[17] Patients with type 2 DM were significantly more likely to have paresthesia and/or burning pain ($P<.05$).[17] Another study of US adults older than 40 years found that 28.5% of those with DM had evidence of DPN on the basis of neurologic examination, but only 10.9% of all patients with DM (38% of those with DPN) were symptomatic.[18] In both these studies, positive (painful) and negative (loss of sensation) symptoms were included.

Although DPN may be present in up to 10% of patients with type 2 DM at diagnosis,[14] the prevalence of neuropathic symptoms increases with duration of disease,[19] with the highest rates of neuropathy found among patients who have had DM for at least 25 years.[20] However, peripheral neuropathy in patients with DM is not always related to their diabetes. The Rochester Diabetic Neuropathy Study[16] found that 10% of patients with DM had neurologic deficits unrelated to the disease.

Estimates of the prevalence of DPNP vary and are difficult to ascertain because of differing definitions used in studies. One review estimated that DPNP affects 20% to 24% of all patients with DM,[21] whereas the Rochester Diabetic Neuropathy Study found that 20% of patients with DM have some degree of symptoms, but only 6% of patients with type 1 DM and 1% of patients with type 2 DM have severe symptoms.[16] A recent review suggests that between 10% and 20% of patients with DM will have DPNP with symptoms severe enough to require treatment.[14] Older studies found that the prevalence of DPNP ranged from 11% in insulin-treated diabetic patients older than 60 years[22] to 21% among patients with type 2 DM for more than 10 years.[19] Estimates of the number of people in the United States with DPNP range from 600,000 to 3.6 million (R. H. Dworkin, PhD, oral communication, June 2005).

Further complicating our understanding of the prevalence of DPNP is the presence of painful neuropathy in patients without confirmed DM. Some experts estimate that for every patient with DPNP, there may be 1 patient with impaired glucose tolerance (IGT) and painful neuropathy. The American Diabetes Association estimates that 16 million people in the United States have IGT,[23] and the National Diabetes Information Clearinghouse estimates that 41 million Americans are prediabetic.[1] Generally, IGT is believed to precede and increase patients' risk of DM, and several studies have found an association between IGT and peripheral neuropathy.[24-26] In those studies, approximately 35% of patients with painful neuropathy but without DM had IGT.[24,25] Most patients with IGT-associated neuropathy were obese and had metabolic evidence of insulin resistance.[26] In patients with painful neuropathy and IGT, there was a direct dose-response relationship between

the degree of glucose dysmetabolism and the severity of the neuropathy.[27]

For some patients, painful peripheral neuropathy may be the presenting symptom that leads to recognition of IGT.[27] Results of oral glucose tolerance tests from a group of 73 patients who presented with peripheral neuropathy of unknown cause indicated that 41 patients (56%) had abnormal results, including 26 with IGT and 15 with DM.[28] Patients with IGT tended to have small-fiber neuropathy and those with DM had more large-fiber involvement. The patients with IGT usually had less severe neuropathy based on electrophysiologic measures.[28]

In patients with IGT-associated painful neuropathy, an oral glucose tolerance test result is abnormal, but hemoglobin A_{1c}, which reflects glycemia during the past 2 to 3 months, and fasting blood glucose concentrations often are within normal limits.[24] Impaired fasting glucose is diagnosed when the fasting plasma glucose level is greater than 100 mg/dL (5.6 mmol/L) but less than 126 mg/dL (7 mmol/L). Impaired glucose tolerance is diagnosed when the plasma glucose level drawn 2 hours after the 75-g fasting glucose load is between 140 mg/dL (7.8 mmol/L) and 200 mg/dL (11.1 mmol/L).[27] These findings suggest that patients who present with peripheral sensory neuropathies of unknown etiology should be evaluated for IGT by using the 2-hour oral glucose tolerance test and the IGT treated, if found.[27]

NATURAL HISTORY

The natural history of DPN and DPNP is largely unknown, because information on their progression is limited. A decrease in pain during a period of 3.6 years was observed in one small study, although quantitative measures of sensory function worsened, which is consistent with the theory that pain can decrease as DPN progresses.[29] This was true whether or not patients also had peripheral artery disease. However, in another small study, no overall change in pain severity was seen over a mean follow-up of almost 5 years.[30] Recently, the 1-year natural history of DPN from the placebo cohort of a clinical study was reported.[31] Patients had mild to moderate DPN at study entry. After 1 year, sensory and motor nerve conduction declined in all tested nerves, but only sural sensory nerve conduction velocity was significantly (P=.0008) lower.[31] Results on a subjective pain and quality-of-life assessment measure also worsened from baseline, but the change (–0.17 points), although statistically significant (P=.0087), was not considered clinically significant.[31] These changes did not correlate in any way with baseline hemoglobin A_{1c} levels.

Risk factors for DPNP have not been well defined, although duration of diabetic disease has been identified in several studies.[19,32] An association between hyperglycemia and DPN is well established.[33-36] In patients with type 1 or type 2 DM, intensive glucose control (maintenance of hemoglobin A_{1c} ≤7 g/dL), particularly when instituted early in the disease, reduces the prevalence of DPN, compared with that for patients whose glucose is not as tightly controlled.[33,36] Among patients with type 1 DM, intensive glucose control also delays or prevents the development of clinically manifest DPN.[34] Whether glycemic control plays a major factor in risk of DPNP is uncertain, with one study finding an association[32] and another finding no connection among patients with type 2 DM.[19]

TABLE 2. **Typical Descriptors for Neuropathic Pain**

Painful	Not painful
Burning pain	Asleep
Knife-like	"Dead"
Electrical sensations	Numbness
Squeezing	Tingling
Constricting	Prickling
Hurting	
Freezing	
Throbbing	
Allodynia	

From *Clin Diabetes*.[14] Reprinted with permission from *The American Diabetes Association.* Copyright 2005.

DIAGNOSTIC ASSESSMENT AND DIFFERENTIAL DIAGNOSIS

Neuropathic pain is defined as spontaneous pain and hypersensitivity to pain in association with damage to or a lesion of the nervous system.[6] Unlike pain in response to a harmful stimulus, neuropathic pain is maladaptive and represents pain as a disease rather than a warning system.[6] Neuropathic pain may be stimulus-evoked (eg, allodynia) or stimulus-independent (spontaneous) pain that is present in the absence of stimuli and may be continuous or intermittent.[7] Spontaneous pain often is paroxysmal and described by patients as shooting, stabbing, or electric in nature.[7]

Neuropathic pain, including DPNP, does not generally respond to the treatments effectively used for inflammatory or nociceptive pain (eg, nonsteroidal anti-inflammatory drugs), underscoring the importance of its correct diagnosis. Neuropathic pain can be diagnosed clinically on the basis of distinct features and simple questionnaires that help differentiate it from other pain types. Oddly, patients may use words usually not associated with pain, such as numbness, to describe neuropathic pain symptoms (Table 2). Neuropathic symptoms are often difficult for patients to describe, and physicians should not try to interpret patients' descriptors.

TABLE 3. **Assessment of Neuropathic Pain**[33,37-39]

Differentiate stimulus-evoked from spontaneous pain
Assess intensity, quality, and duration of pain
Assess distribution of pain (is the pain symmetrical? peripheral? radicular?)
Use validated pain rating scales
Leeds Assessment of Neuropathic Symptoms and Signs
Differentiates between neuropathic and nonneuropathic pain
7-item questionnaire
Maximum score is 24; score of ≥12 suggests neuropathic pain
Sensitivity is 83% and specificity is 87%
Neuropathic Pain Scale
Has 2 global pain domains (pain intensity and unpleasantness), 6 pain qualities (sharp, hot, dull, cold, sensitive, and itchy pain), and 2 pain locations (deep and surface pain)
Able to distinguish patients from different diagnostic groups
Shows different levels of responsivity to pain treatment
10-item questionnaire
Neuropathic Pain Questionnaire
Items able to differentiate neuropathic pain patients from nonneuropathic pain patients
Assesses pain qualities distinct to neuropathic pain 12-item questionnaire
Often used to assess the effect of treatment
Sensitivity is 67% and specificity 74%
Brief Pain Inventory for Diabetic Peripheral Neuropathy
Assesses the severity of pain, its impact on daily functioning, and other aspects of pain (location, relief from medication)
11 items (4-item pain severity scale and 7-item pain interference scale)
Pain severity scale uses worst pain, least pain, average pain, and pain now; worst pain is most predictive of mild, moderate, and severe pain
Sensitivity using worst pain is 58% and specificity is 79%
Assess physical, emotional, and social function and psychological comorbidity (depression, anxiety, substance abuse)

From *Arch Neurol*,[40] with permission.

In assessing neuropathic pain, the use of instruments specifically designed for neuropathic pain can provide important insight into patients' pain experience and is recommended (Table 3).[41] The Leeds Assessment of Neuropathic Symptoms and Signs and the Neuropathic Pain Questionnaire are designed to differentiate neuropathic from nonneuropathic pain types.[42,43] The Neuropathic Pain Scale is designed to assess pain qualities that are distinct to neuropathic pain.[37] The first 2 instruments may be helpful in determining a neuropathic etiology for the pain, whereas the latter can help to define the pain characteristics of the individual patient and to monitor the effect of pain treatments.

In addition to these screening questionnaires, several other simple questionnaires may be valuable to use in the clinic. These include the 15-item Michigan Neuropathy Screening Instrument, the Brief Pain Inventory (BPI), and basic visual analog or verbal descriptor scales.[44] The Michigan Neuropathy Screening Instrument was developed at the University of Michigan and is designed for use in outpatient primary care settings to screen for the presence of DPN. The BPI, which was developed to assess cancer pain, includes a body map where patients can indicate the location of their pain and questions that assess pain severity and the effect of pain on quality of life and interference with daily activities.[44]

A version of the BPI modified specifically for use in assessing DPNP (BPI-DPN) was recently validated.[45] The BPI-DPN uses 4 questions to assess pain severity (worst pain, least pain, average pain, and pain now) and 7 items to assess interference with daily life (general activity, mood, walking ability, normal work, relations with others, sleep, and enjoyment of life). Each question uses an 11-point scale (0 indicating no pain or effect to 10 indicating worst pain imaginable or completely interferes) and asks patients specifically about pain related to their diabetes during the past 24 hours.[46] Item scores from 0 to 3 suggest mild pain or interference, whereas scores from 4 to 6 suggest moderate effect and those 7 or higher suggest severe pain or interference.[46]

Clinical Presentation of DPNP

Paradoxically, some patients with DPN may present with severe pain but only minimal neurologic deficits, whereas others present with foot ulcers but have no pain or neurologic symptoms. The diagnosis of DPNP relies heavily on a thorough physical examination and patient history along with clinical judgment rather than on any particular neurologic test or finding.

In contrast to acute sensory neuropathies, DPNP is insidious in onset and usually characterized by burning-type pain, paresthesia, and numbness of mild to moderate severity.[14] Commonly, DPN first affects the feet and lower limbs, with the hands affected later.[13] Symptoms occur symmetrically in a "stocking and glove" pattern.[15] Patients may lose vibration and proprioceptive sensation, temperature sensitivity, and eventually pain sensation.[47] Loss of proprioception can lead to impaired gait and falls.

The classic presentation of DPNP is pain or tingling in the feet that can be described not only as "burning" or "shooting" (Table 2) but also as severe aching pain.[47] Less commonly, patients may describe the pain as itching, tearing, or like a toothache. The pain may be accompanied by allodynia and hyperalgesia and an absence of symptoms, such as numbness or feeling "dead."[47] Symptoms tend to be worse at night.[47] Pronounced motor signs or asymmetrical distribution of symptoms should suggest a nondiabetic origin of the neuropathy.[15]

A less common form of DPN is acute sensory neuropathy. It is characterized by a rapid onset of symptoms of severe burning pain and aching, which are worse at night and often accompanied by weight loss.[14] Symptoms often appear after periods of poor metabolic control or sudden changes in glycemic control.[13] Electrophysiologic tests may have normal results or show only minor abnormalities.

The natural history of acute sensory neuropathies in DM is complete resolution within 12 months of onset.[14] Blood glucose concentrations are strongly associated with pain in this condition, and a return to euglycemia often results in resolution of painful symptoms.[14]

Diagnosis

Although challenging, DPN can be diagnosed, classified, and managed on the basis of the patient's history and results of a thorough physical examination.[48] In most cases, further neurologic testing is unnecessary (Table 4). Although such tests can confirm the presence of a neuropathy, they cannot identify the underlying cause. In addition, DPNP does not correlate with nerve conduction velocity,[8] and the diagnosis of DPNP does not require evidence of a large-fiber abnormality. If motor signs are noted on the clinical examination (weakness during muscle testing), referral to a neurologist for electrodiagnostic testing is certainly warranted.

Although the initial recognition of neuropathy may be clinically confirmed by the relative loss of sharp vs light touch discrimination over the distal lower extremities during the physical examination, the use of the 10-g Semmes-Weinstein monofilament permits more careful assessment for pressure perception. The nylon filament is gently pressed against the skin until it just buckles, generating the equivalent of 10 *g* of force. The sensitivity for predicting feet at risk of ulceration ranges from 86% to 100% in cross-sectional studies using the Semmes-Weinstein monofilament.[15] Pressure perception assessments are usually taken at the hallux and metatarsal heads I, III, and V, although there is uncertainty regarding the necessity for multiple measurements. No consensus exists on whether 1, 2, or more abnormal measurements constitute a diagnosis of neuropathy.[15]

The absence of symptoms should not be equated with the absence of neuropathy; up to 50% of patients with DPN may be asymptomatic but are still at risk of foot ulcers.[13] Therefore, monitoring for neuropathy should be a regular part of the clinical care of patients with DM.[47] Such monitoring should include assessment with a 128-Hz tuning fork to check for vibration sensation, a broken tongue depressor to check for sharp sensation, test tubes that contain warm or cold water to evaluate temperature sensation, the 10-*g* monofilament to check pressure sensation, and cotton wool to check light touch sensation and the presence of abnormal pain responses from nonpainful stimuli.[47] Table 5 summarizes the key elements in the diagnosis of DPNP.

Differential Diagnosis

When assessing patients with DM, a simple yet key question to ask is, "Do your feet burn, hurt, or tingle?" A positive answer is highly suggestive of DPNP. Although DPNP is the most likely diagnosis in these patients, other potential causes of DPNP exist that must be excluded before the DPNP diagnosis can be made.[13] Conditions that should be considered and ruled out as sources of neuropathy or pain include malignant disease, toxic causes (eg, alcohol), and infections, particularly human immunodeficiency virus.[14] The patient's history may suggest other diagnoses as well, such as postherpetic neuralgia. Other pain syndromes that may mimic DPNP include tarsal tunnel syndrome, osteoarthritis, idiopathic distal small fiber neuropathy, and erythromelalgia (Table 6). The clinical presentation of these syndromes differs from that of DPNP in ways that help in the diagnosis. However, no single test can definitely diagnose DPNP, and clinical judgment must play a role.

The warning signs typically used to assess patients with other forms of chronic pain may be useful in evaluating patients with DPNP to exclude other sources of their pain.

TABLE 4. **Neurologic Testing for Assessment of DPN[8,15]***

Test	Description
Quantitative sensory testing	Computer-based, noninvasive, psychophysical, semiobjective measure
	Measures thermal (cold/warm) and vibration sensations and cold- or heat-evoked pain thresholds
	Not specific to peripheral nerve function
	Requires specialized equipment
Nerve conduction velocity	Useful to exclude other causes of neuropathy
	Depressed nerve conduction velocity usually indicates demyelination
	Nerve conduction velocity diminishes gradually in DPN
	Changes in nerve conduction velocity are related to glycemic control
	Changes in nerve conduction velocity do not correlate with onset or severity of DPNP or other clinical symptoms
	Insensitive to pathologic changes associated with DPNP

*DPN = diabetic peripheral neuropathy; DPNP = diabetic peripheral neuropathic pain.

TABLE 5. **Key Elements in Diagnosis of DPNP***

Establish diagnosis of DM or IGT
2-hour OGTT >200 mg/dL for diabetes and 140-199 mg/dL for IGT
Establish presence of neuropathy
Use validated questionnaires (NPQ, BPI-DPN, MNSI)
Use simple, handheld screening devices (10-g monofilament, 128-Hz tuning fork)
Assess pain characteristics
Distal, symmetrical
Numbness, tingling vs burning, aching, throbbing pain
Spontaneous pain (continuous or intermittent) vs stimulus-evoked pain
Rule out nondiabetic causes for neuropathy and/or pain
Metastatic disease
Infection
Toxic substances

*BPI-DPN = Brief Pain Inventory for Diabetic Peripheral Neuropathy; DM = diabetes mellitus; DPN = diabetic peripheral neuropathy; DPNP = diabetic peripheral neuropathic pain; IGT = impaired glucose tolerance; MNSI = Michigan Neuropathy Screening Instrument; NPQ = Neuropathic Pain Questionnaire; OGTT = oral glucose tolerance test.

TABLE 6. **Differential Diagnosis: Common Pain Syndromes Similar to Diabetic Peripheral Neuropathy Pain**[49-51]

Condition	Key characteristics and differentiating features
Claudication	Doppler ultrasonography confirms clinical diagnosis of arterial occlusion
	Patients with diabetes may present with normal extremities and absent foot pulses
	Peripheral arterial occlusion with underlying atherosclerosis
	Usually intermittent, worsened by walking; remits with rest; other signs or symptoms suggest arterial insufficiency
Morton neuroma	Benign neuroma formation on third plantar digital nerve
	Generally unilateral
	More frequent in women
	Pain elicited when pressure is applied with the thumb between the first and fourth metatarsal heads
Osteoarthritis	Can be secondary to diabetes mellitus, but pain is usually gradual in onset and in 1 or 2 joints
	Differential diagnosis based on radiograph
	Morning stiffness, diminished joint motion, and flexion contractures are characteristic
	Pain worsens with exercise and improves with rest
	Radiculopathy can result
Radiculopathy	Can be caused by diabetes; also can result from arthritis or metastatic disease
	Neurologic examination and imaging can localize lesion site
	Pain can occur in thorax, extremities, shoulder, or arm, depending on site of lesion
Charcot neuroarthropathy	May result from osteopenia caused by increased blood flow after repeated minor trauma in individuals with diabetic peripheral neuropathy
	Warm-to-hot foot with increased blood flow
	Decreased warm sensory perception, vibration detection
Plantar fasciitis	Pain in the plantar region of the foot
	Tenderness along the plantar fascia when ankle is dorsiflexed
	Shooting or burning pain in the heel with each step
	Worsening pain with prolonged activity
	Often associated with calcaneal spur on radiography
Tarsal tunnel syndrome	Caused by entrapment of the posterior tibial nerve
	Pain and numbness radiate from beneath the medial malleolus to the sole
	Clinical examination includes percussion, palpation for possible soft tissue matter, nerve conduction studies, magnetic resonance imaging
Vitamin B_{12} deficiency	Neurologic symptoms include paresthesias, peripheral neuropathy
	More common as patients age; use of gastric acid–blocking agents may contribute
	Comorbid hematologic (megaloblastic anemia, pancytopenia) and psychiatric symptoms (eg, irritability, personality change, memory impairment or dementia) may be present
	Diagnose with measurement of serum methylmalonic acid and homocysteine levels
Idiopathic distal small fiber neuropathy	Syndrome of burning, painful paresthesias, and dysesthesias in the feet, lancinating pains, moderate to severe distal small fiber sensory loss, absent ankle reflexes, and minimal or no distal foot weakness in elderly patients
	Associated with mild loss of vibration sense but no pronounced proprioceptive loss or sensory ataxia
	Progression is slow, with pain is troublesome, but patients do not typically become disabled
	Symptoms are reported to be refractory to most symptomatic therapies, but some patients improve with γ-globulin infusions
Erythromelalgia	Burning pain and bright red color change of toes, forefoot, and hands in association with ambient temperature changes
	Patients avoid wearing stockings and shoes
	Pain is relieved by walking on cold surfaces or soaking feet in cold water, with rest and elevation of legs
	There are no motor, sensory, or reflex changes seen

Adapted from *Med Clin North Am*,[8] with permission from Elsevier.

These signs include pronounced trauma, unexplained weight loss, substance abuse, bladder or bowel incontinence, history of malignancy, use of systemic corticosteroids, human immunodeficiency virus infection, temperature of 38°C or higher, presence of persistent pain, and compensation issues.[52] Signs for when to refer to specialist care include retinopathy, diabetic carpal tunnel syndrome, diabetic mononeuropathy, bony food abnormalities, presence of motor signs, and asymmetrical distribution.

COMORBIDITIES

Both DPN and DPNP are closely associated with a number of comorbid conditions, including diabetic retinopathy, de-

pression and sleep disturbances, progressive muscle weakness, and foot ulceration. The Rochester Diabetic Neuropathy Study found a highly significant association between patients with DPN and retinopathy ($P<.001$) and nephropathy ($P=.003$).[16] Other neuropathies were not associated with comorbid retinopathy or nephropathy.[16]

Comorbidities associated with DPNP include those commonly associated with chronic pain, such as sleep disruption, depression, and interference with activities of daily living,[53] as well as those associated with DM. Patients who present with DPNP should be evaluated for comorbid depression, and if present, necessary action should be undertaken to control its potential disruptive effect on their lives in association with chronic pain.[54]

QUALITY-OF-LIFE ISSUES

Like all chronic pain, DPNP takes a toll on patients' quality of life. One small study found that quality of life was significantly ($P<.01$) more impaired among patients with DPNP than among diabetic patients without neuropathy.[53] Patients with DPNP had more impairment on measures of emotional reactions, energy, pain, physical mobility, and sleep.[53] Another study of 105 patients with DPNP reported high levels of interference with sleep and enjoyment of life and moderate interference with mobility, employment, and recreational and social activities.[55]

These findings emphasize the need to develop a good relationship between the physician and patient. Paramount to this is helping the patient understand that pain is not a punishment for failing to comply with medications or diet regimens. It is important to emphasize the positive rather than allow the patient to focus on pain-related limitations. It can be helpful to explain pain mechanisms to the patient, including the concepts of pain as a warning vs pain as a disease. A useful metaphor may be that pain usually functions as an alarm, warning of injury or toxic effects, but that in some cases, including DPNP, the alarm has broken and continues to go off when no injury is imminent. Approaches to chronic pain from other disciplines, such as low back pain, may be useful. Physicians should look for signs of "catastrophizing," a detrimental cognitive factor that increases risk of disability.[56] Catastrophic thinking about pain includes factors such as rumination, magnification, excessive focus on negative aspects of pain, and helplessness.[56] Patients with neuropathic pain, including DPNP, who scored higher on the Pain Catastrophizing Scale also rated their pain as more intense and considered themselves more disabled by their pain.[57] In particular, a feeling of helplessness was strongly associated with the experience of neuropathic pain.[57]

SAFETY ISSUES DUE TO DISEASE

Loss of sensations of light touch, pain, and temperature typically occur early in DPN.[58] Patients with DPN are at very high risk of foot ulcers, usually as a result of loss of sensation in the foot. Foot ulcers may result from ill-fitting shoes or an unfelt foreign body in the shoe, as well as from excessive pressure in walking or plantar callus.[14] In a study of lower extremity disease among people older than 40 years, 7.7% of patients with DM reported having ulcers or sores that took longer than 4 weeks to heal.[18] More than half of all lower limb amputations in the United States (86,000 per year) occur in people with DM,[20] and more than 80% of amputations occur after a foot ulcer or injury.[15] These cases are largely preventable with good care.

Patients should be instructed to wash their feet twice daily to require them to carefully examine their feet and inform their physicians immediately if they notice any areas of redness, blistering, or skin breakdown, as well as if they have any changes in sensation while caring for their feet, such as numbness in a certain area or uncomfortable sensations. It may be helpful to explain to patients that their feet are "sentinels" for them in monitoring their DM and that these early warnings signs, if properly attended to, can help avoid serious future complications.

Loss of proprioception may occur later in DPN and results in patients being uncertain of where their feet are, leading to falls or injuries from stubbed toes.[58] Such patients may benefit from simple safety measures, such as nightlights in the bedroom or bathroom.

Loss of sensation in the foot mandates special attention to the feet; patients should check their feet twice a day (even if painful), and a thorough foot examination should be part of any primary care physician visit (Table 7). These examinations offer a good opportunity to work with patients and to encourage them to become stakeholders in their own care.

Patients should be referred to podiatric care if foot abnormalities (eg, bony deformities, ingrown nails, corns) are present. For patients with unstable gaits or walking deficits, physical therapy or other rehabilitation services can be considered. These approaches also should benefit patients with muscle or leg weakness.[58] At least half of all foot ulcers are preventable with patient education and proper care. Although patients may resist examining their feet or trimming nails because of pain or discomfort, the importance of these simple preventive measures cannot be overemphasized.

TABLE 7. **Foot Care for Patients With Diabetic Peripheral Neuropathy**

Clean feet daily using warm water and mild soap; avoid soaking feet; dry with soft towel; carefully dry between toes
Inspect feet and toes twice daily for cuts, blisters, redness, swelling, calluses; use a mirror (try placing on floor) to inspect bottoms of feet if movement is limited
Moisturize feet with lotion, but avoid area between toes
After cleaning, file corns and calluses gently with pumice stone
Cut toenails regularly to the shape of your toes and file edges
Always wear shoes or slippers to protect feet from injuries; wear thick, seamless socks
Wear well-fitted shoes that allow toe movement; break in new shoes gradually
Before wearing shoes, check inside for tears, sharp edges, or objects that might cause injury
Inform your physician if you notice any changes in the appearance of or any unusual sensations in your feet
Other information available at http://ndep.nih.gov/materials/pubs/feet/feet.htm

Modified from National Diabetes Information Clearinghouse. Available at: http://diabetes.niddk.nih.gov/dm/pubs/neuropathies.

CONCLUSION

In treating DPNP, it is crucial to encourage patients to become partners with the health care professionals in managing their disease. This begins with educating patients about pain mechanisms, which can help allay fears of undiagnosed malignancies or other disease.[9] A frank discussion of the benefits and limitations of the treatments used to control pain must include the understanding that patients may not achieve complete relief; however, the health care professional should assure the patient that together they will work to achieve the best possible result. The following are key points to remember: (1) nondiabetic neuropathies can be present in patients with DM, (2) up to 50% of patients with DPN may be asymptomatic, (3) asymptomatic patients are still at risk of insensate foot injury, (4) patients with DPNP are at risk of medical and psychological comorbidities, (5) a number of treatment options exist for symptomatic DPN, and (6) patients benefit from education and a feeling of partnership in their care.

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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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SUPPLEMENT ARTICLE

Diabetic Peripheral Neuropathic Pain: Case Studies

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Three case reports in this article illustrate the diagnostic methods used and the treatment course encountered for many patients with diabetic peripheral neuropathic pain (DPNP). Each case addresses an aspect of DPNP: pain that appears to be refractory to initial therapy, DPNP occurring with other medical conditions, and nondiabetic neuropathy occurring in patients with diabetes mellitus. Together, these cases bring clarity to the confusing clinical experience for patients who have decreased sensation in combination with burning pain, and they apply the consensus guidelines for DPNP. Recently approved medications by the Food and Drug Administration for the treatment of DPNP offer hope for many patients whose pain was thought to be refractory to treatment.

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DM = diabetes mellitus; DPN = diabetic peripheral neuropathy; DPNP = diabetic peripheral neuropathic pain; FDA = Food and Drug Administration; PD = Parkinson disease; TCA = tricyclic antidepressant

In patients with diabetes mellitus (DM), diabetic peripheral neuropathic pain (DPNP) involves simultaneously decreased sensation usually in the distal extremities manifested by loss of sharp vs light touch discrimination, numbness, and tingling in combination with burning pain. Patients may be frustrated and depressed when they initially present for treatment because DPNP may interfere with their sleep and compromise the quality of their lives. Patients may become more frustrated during the initial efforts made to remedy their pain if these therapies prove to be ineffective, result in intolerable adverse effects, and do not provide some improvement or resolution of the pain. Proper patient education and preparation can resolve some of the treatment uncertainties and help patients understand the meaning and cause of their symptoms and the signs present, leading to realistic expectations for therapy.

The prevalence of diabetic peripheral neuropathy (DPN) increases with age, duration of DM, and suboptimal glycemic control. However, DPN occurs even when blood sugar levels are well controlled. The clinical diagnosis is not generally difficult to make but should be based on the presence of at least 2 symptoms being present or laboratory test abnormalities, and it is important to consider other medical and psychiatric comorbidities.

The Food and Drug Administration (FDA) has approved 2 medications specifically for the treatment of DPNP, duloxetine and pregabalin. Although many older anticonvulsant and antidepressant medications have been used off label (not with FDA approval) for the treatment of those with DPNP, duloxetine's effect on mood may benefit depressed patients. With DPNP, physicians and patients must understand that treatment is dynamic and that by working together the best outcome is realized. This article presents 3 cases to illustrate the diagnosis and treatment course of DPNP. These cases address DPNP that appears to be refractory to initial therapy, DPNP occurring with comorbidities, and nondiabetic neuropathy occurring in patients with DM.

REPORT OF CASES

CASE 1: A PATIENT WITH DPNP REFRACTORY TO INITIAL THERAPIES

Presentation and Patient History. A 68-year-old widowed woman living alone with osteoarthritis and type 2 DM controlled with diet and oral medication presented with numbness and pain in the distal aspect of the calves and feet, which she said was much worse at night when she tried to sleep. She scored her pain on an 11-point numeric analog scale (0 indicating no pain, 10 indicating worst pain imagined) as a 7/10 during the day (ranging from 5 to 8/10) and 9/10 at night (ranging from 7 to 10/10). The patient said the pain felt as though her feet were "burning on hot concrete in the summertime, with someone jabbing pins and needles into me." At times she recalled feeling electrical shocks and tingling. She had previously been active in her retirement community, serving on many committees, being politically active, and playing golf many times weekly, but she could no longer do the things she enjoyed

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because of the unrelenting pain. She maintained satisfactory glycemic control (hemoglobin $A_{1c,}$ 6.7%).

The patient used acetaminophen to control her osteoarthritis pain. She tried to control the DPNP by increasing the acetaminophen dose to 1000 mg 4 times daily, but when that dose did not relieve the pain in her feet and she learned that this amount of acetaminophen might eventually cause liver or kidney toxic effects she resumed her previous dose of 500 mg 4 times daily (2 g/d). The patient was not able to tolerate over-the-counter ibuprofen because of pronounced stomach discomfort. She tried a friend's capsaicin cream but immediately stopped using the cream when it made her pain worse.

The patient described feeling anxious and irritable, as well as having difficulty sleeping. She was no longer engaging in pleasurable activities. She was unhappy about being in pain but did not think that she was depressed. The patient rated her mood as 3/10 (0 indicating no depression, 10 indicating as depressed as she could imagine). She denied any prior history of mental illness or substance abuse but expressed concern about the use of "narcotics" to control her pain because of media reports about people abusing these medications and the risk she might have of becoming addicted to them.

On physical examination, the patient's vital signs were normal, and no pronounced abnormalities involving the major organs were noted. Abnormalities of the peripheral nervous system, skin, and vascular supply for her distal lower extremities were observed. The skin of her feet was shinny and thin, with a bluish coloration, and her feet were cool to the physician's touch. Pulses in her feet were bilaterally diminished but symmetrical. Lower extremity strength testing was 5/5. Deep tendon reflexes were diminished at the ankles (1/4) relative to the knees (2/4) bilaterally. Sharp, thermal, and vibration sensations were absent from her midcalves distally, and placement of the cool tuning fork directly against her feet caused an increase in her pain level.

Diagnosis. The prevalence of DPN increases with age, duration of DM, and/or suboptimal glycemic control.[1] Patients with good glycemic control can still develop neuropathic symptoms. Although DM is the most likely explanation for DPNP, further examination is often necessary to rule out other neuropathic causes. In the Rochester Diabetic Neuropathy Study, neuropathic symptoms were unrelated to the presence of DM in 10% of patients.[2] Diabetic peripheral neuropathic pain should not be diagnosed on the basis of a single symptom, sign, or test alone; a minimum of 2 abnormal findings is recommended.[1] The diagnosis of DPNP was made based on the physical examination of the patient, which revealed no other pronounced abnormalities, coupled with her description of bilateral burning pain and dysesthesia in her feet, abnormal skin appearance, and diminished pulses.

Treatment. Desipramine, a tricyclic antidepressant (TCA), was prescribed off label at a starting dose of 10 mg to be taken at bedtime. At a 2-week follow-up visit, the patient reported that the drug reduced her pain intensity to 7/10 at night but had no effect on her pain level during the day. The desipramine dose was increased to 20 mg at bedtime to improve her pain, but she called her physician 3 days later to report that her pain intensity was still not improved and that the higher dose of medication was causing her to have considerable dry mouth, dry eyes, urinary hesitancy, constipation, and dizziness when she stood up. Her physician decreased her desipramine dose to 10 mg nightly and added gabapentin.

Treatment with gabapentin, a medication binding to the $\alpha_2\delta$-subunit of calcium channels in the spinal cord and decreasing their excitability, was started at 100 mg at bedtime. The patient reported that gabapentin with the desipramine greatly improved her sleep and also helped reduce nighttime pain. However, her daytime pain intensity was unchanged, and a subsequent gradual increase in the gabapentin dose up to 600 mg/d caused her to have unacceptable daytime fatigue and difficulty with memory. She was discouraged by these events yet knew that her physician was working hard to control her pain. "I'm just getting old, and I guess there is not much more you can do for me," she told her physician as he considered the next therapeutic option for her.

Treatment with duloxetine at 30 mg/d was started, and the gabapentin dose was decreased to 300 mg/d. Treatment with desipramine was discontinued. The patient was told to take duloxetine in the morning and that nausea could occur early in treatment but would not persist as she became accustomed to the medication. She developed mild upset stomach but was able to successfully increase the dose to the target dosage of 60 mg/d after 1 week, with her daytime pain level decreasing from 7/10 to 4/10. This level of pain was still considered moderate, but it was acceptable to her and she tried playing golf again. However, the patient found that by the end of a round of golf the pain in her feet became unbearable again.

To continue to improve her clinical condition and better control her pain, the patient's physician switched from gabapentin to pregabalin while maintaining the duloxetine dose at 60 mg/d. In general, patients taking gabapentin usually need to taper their dose to discontinue it, but at the 300-mg/d dose, use of the drug was stopped without tapering and the pregabalin treatment was started at 25 mg twice daily and then was progressively increased every 3 days up to 150 mg twice daily without difficulties. Once stabilized with duloxetine and pregabalin, her pain intensity during

the day was 3/10 with an intensity during the night of 4/10. Because she still had incidental pain with golfing, a 5-mg dose of single-entity oxycodone taken before golfing was added to her other medications. With this final addition, she was able to play 9 holes of golf.

Discussion. This case illustrates several important points. The patient gave a fairly common description of her pain-related symptoms and expressed some tendency to possibly give up in frustration when her pain was not immediately improved by the first or second medication. She seemingly expected little help and was willing to ascribe her pain to her age, not the underlying DM disease process.

The patient's absence of sharp, thermal, and vibratory sensation distally and her increased sensitivity to the touch of the cool tuning fork were consistent with neuropathic pain.[1] Providing her with appropriate education regarding her neuropathic pain would help her better cope with the painful aspects of DM. Explaining the nature of neuropathic pain, including a simple explanation of the abnormal firing of sensory nerves, would help her better understand the reason for her pain. Offering her reassurance that continuing efforts would be made to relieve her pain and giving her an opportunity to talk about her concerns would be valuable.

Tricyclic antidepressants have demonstrated analgesic efficacy in many randomized trials for many pain states, including peripheral neuropathy.[3-6] Amitriptyline has the most demonstrated efficacy from randomized trials but produces many unpleasant anticholinergic adverse effects. According to the American Geriatric Analgesic Guide, amitriptyline is a particularly hazardous drug for patients older than 60 years. At high doses it may be associated with an increased risk of cardiovascular events.[7]

The TCA desipramine appeared to be a good initial medication for this patient because of its known effectiveness for neuropathic pain comparable to amitriptyline, its better tolerability by older patients, and its availability in inexpensive generic formulations.[5] However, desipramine was not the best medication for this patient as the primary treatment of her DPNP because of its side effects profile, and discontinuation was necessary. Gabapentin has an FDA-approved indication for neuropathic pain, but only to treat postherpetic neuralgia, yet has been widely used off label for many other pain states.[8] Gabapentin has demonstrated efficacy in improving DPNP.[9] However, its use by the patient in this case study resulted in fatigue and cognitive impairment with overt memory disruption. In all likelihood, the dose may have been titrated up too quickly or there may have been renal insufficiency that altered the elimination of the medication.

Gabapentin, 100 mg at bedtime, is the proper dose for fragile patients, but 300 mg can be initiated for healthier people. "Add-on therapy" or "rational polypharmacy" is common for patients with difficult-to-control pain. However, the combination of 10 mg of desipramine plus 100 mg of gabapentin would likely not be sufficient medication for most patients with DPNP.

Although many primary care physicians stop treating DPNP with only the combination of low-dose TCAs and a subtherapeutic dose of gabapentin, believing that everything has been done, this was far from helpful for this patient. Multiple treatment options are still available, including referrals to patient support groups, the use of cognitive behavioral therapy, and many other pharmacological options.

Patients such as this one may benefit from the off-label use of topical 5% lidocaine transdermal patches. If pain is particularly bothersome at night, patches placed on the feet (a maximum of 3 patches used at one time and only worn for up to 12 hours) might prove helpful. Lidocaine patches stay on the feet well when patients are lying down. Preliminary randomized trial data support the use of 5% lidocaine patches for many neuropathies, including DPNP.[10,11]

Most of the pain treatments used for neuropathic pain have not been approved by the FDA, including all the TCAs and most of the anticonvulsants. Approval of the FDA ensures that at least 2 randomized placebo-controlled trials and long-term safety studies have been completed (a complete review of available treatments for DPNP is presented in this supplement). Two medications are currently approved by the FDA for use in DPNP, duloxetine and pregabalin.[12,13]

Patients with DPNP may respond well to duloxetine. In clinical trials, duloxetine has been shown to effectively relieve DPNP beginning after the first week and then lasting throughout the trial.[14,15] For patients such as this one, it is likely that they might have had some relief from their feelings of helplessness as their pain intensity lessened.

Although this patient believed she was not depressed, when she volunteered that it was time for her physician to give up on her, it might have been a sign of depression. Because duloxetine is also approved by the FDA as an antidepressant medication, the use of duloxetine for her DPNP would additionally treat depression. Close initial observation would be warranted to detect the potential unmasking of mania or bipolar disease, and all patients taking antidepressant therapy must be observed for suicidal ideation. However, without a prior history of depression or bipolar disorder, a first episode of mania would be highly unlikely for someone in this patient's age group.

Pregabalin is also approved by the FDA for the treatment of DPNP. It has demonstrated efficacy in relieving pain associated with DPNP[16,17] and in postherpetic neuralgia[13] and is chemically related to gabapentin. Patients in whom gabapentin therapy has failed have been shown to respond to pregabalin, and it is appropriate to offer a trial of pregabalin even if other anticonvulsant medications have not been effective.

The value of opioids for the management of DPNP should not be overlooked. Both controlled-release oxycodone[18,19] and tramadol[20] have been studied and found effective for treatment of DPNP. Although many patients are resistant to taking "narcotics" because of adverse media reports and concerns about potential psychological dependence, most patients who receive such medications find them helpful. Patients expressing fear of physical dependence, tolerance, or psychological dependence (addiction) need to be informed about the meaning of these different terms and their likelihood of occurrence if opioids are prescribed. Patient education, obtaining informed consent, and agreeing to a management plan will help patients understand the issues of abuse, tolerance, physical dependence, and addiction.

In summary, this patient ultimately had good around-the-clock control of her DPNP, using pregabalin and duloxetine together. However, she still had incidental pain when she attempted to increase her activity by playing golf, for which a short-acting, immediate-release opioid medication was prescribed.

Case 2: Managing DPNP in the Presence of Comorbidities

Presentation and Patient History. A 78-year-old former machinist, with a history of long-standing type 2 DM for more than 20 years, Parkinson disease (PD) for the past 12 years, and recurrent episodes of depression throughout his adult life presented for treatment. The hospitalist at the nursing home where the patient lived was asked to evaluate him because of frequent falls presumably due to PD. He complained to the physician that he often fell because he could not "feel the ground" when he stood on his feet and also said that there was a steady aching, scratching, burning, or tingling sensation in both feet, with intermittent electrical sensations. The patient said he had mentioned his inability to feel the ground with his feet to the nursing home staff, but because there were no obvious injuries after the falls, the staff had not given him any analgesic medications despite his requests for them. He was afraid that he was losing his "grip" because there appeared to be no outward reason for the intense pain he was feeling. His current medications included rosiglitazone maleate to treat his DM, a carbidopa, levodopa, and entacapone combination for his PD, and sertraline for his depression.

On a body map drawing, the patient illustrated the presence of steady pain in both feet. On a numeric analog scale, using 0 for no pain and 10 for worst pain imaginable, he marked his daily pain as 7/10 and the pain he experienced at night when he tried to sleep as 8/10.

Physical examination revealed that the patient was alert but only oriented to person and place and not to time specifically. His fund of knowledge was intact for weights, measures, and geographic facts. He could recall distant information but not current events. The patient recalled only 1 of 3 words initially and then 2 of 3 words with prompting. He was concrete in his pattern of associations. His mood was dysphoric with his affect congruent. He was afebrile with normal blood pressure, heart rate, and respirations. No major abnormalities involving his heart, liver, or kidneys were apparent, although changes consistent with chronic obstructive pulmonary disease were noted. Cranial nerve testing showed limited facial expression, some hearing loss, cogwheeling eye movements, and some swallowing difficulties. Muscle strength testing revealed mild weakness diffusely that was consistent with his mostly inactive status without marked loss of any muscle groups. His tone was increased throughout with cogwheeling rigidity noted in his neck, elbows, wrists, and thumbs. A resting tremor and lack of spontaneous facial movement were noted. Deep tendon reflexes were 2+/4 at the biceps, triceps, brachioradialis, quadriceps, and hamstrings but were absent at the ankles. Sensations for sharp, light touch, vibration, and proprioception were all impaired in his lower extremities below his knees. When asked to stand up, the patient had apparent unsteadiness rising to his feet and tested Romberg positive. He walked by shuffling his feet with small steps and executed turns with great difficulty, nearly falling over each time he turned. A 10-*g* monofilament test revealed a loss of pressure sensation in both feet. No ulcers were noted, but his feet had long toenails, were dusky in color, were cool to touch, and had minimal dorsalis pedis pulses present. His random glucose level of 142 mg/dL was consistent with historical fasting glucose levels that were maintained in the 120- to 140-mg/dL range, and his hemoglobin A_{1c} level was 6.4% with dietary modification and rosiglitazone maleate. No other abnormal laboratory values were found to explain his falling episodes, but his blood urea nitrogen and creatinine levels were both modestly elevated, with normal alanine transaminase and aspartate transaminase levels.

Diagnosis. Moderate distal symmetrical polyneuropathy was diagnosed, which, combined with his history of PD, explained his tendency to fall. Pronounced motor signs or asymmetrical distribution of symptoms more likely suggested a nondiabetic origin for the neuropathy.[21] However, in DPN symmetrical and asymmetrical nerve dysfunction may be seen, often due to lumbosacral plexopathies, mononeuritis, and truncal neuropathies. In this patient's case, the neuropathy was most likely due to his DM because his pain was symmetrical, and his motor signs were better explained by PD.

Distal symmetrical polyneuropathy is a common diagnosis in patients with type 1 and type 2 DM, affecting up to 50% of those with type 2 DM; it is symptomatic in 10% to

TABLE 1. **Key Elements in Diagnosis of Diabetic Peripheral Neuropathic Pain***

Establish diagnosis of diabetes mellitus or impaired fasting glucose
Fasting plasma glucose ≥126 mg/dL or serum glucose ≥200 mg/dL 2 h after 75-g oral glucose load for diabetes
Serum glucose ≥140 mg/dL but <200 mg/dL 2 h after 75-g oral glucose load for impaired glucose tolerance
Establish presence of neuropathy
Use validated questionnaires (NPQ, BPI-DPN, MNSI)
Use simple handheld screening devices (10-*g* monofilament, 128-Hz tuning fork)
Assess pain characteristics
Distal, symmetrical
Numbness, tingling vs burning, aching, throbbing pain
Spontaneous pain (continuous or intermittent) vs stimulus-evoked pain
Rule out nondiabetic causes for neuropathy and/or pain
Neoplastic disease
Infection and/or inflammation
Endocrine and metabolic disorders
Toxic substances
Trauma

*Hyperglycemia in diabetes should be treated pharmacologically in addition to diet and physical activity to achieve glucose levels as close to normal as possible while avoiding hypoglycemia. BPI-DPN = Brief Pain Inventory for Diabetic Peripheral Neuropathy; MNSI = Michigan Neuropathy Screening Instrument; NPQ = Neuropathic Pain Questionnaire.

20% of patients.[1] The classic presentation of DPNP involves pain or tingling in the feet that is described as "burning" or "shooting" but also as severe aching pain. Less commonly, patients may describe the pain as itching, tearing, or like a toothache. The pain may be accompanied by allodynia and hyperalgesia and also may be accompanied by the absence of symptoms, such as numbness or feeling that the affected area is "dead." Symptoms tend to be worse at night.[22]

Diabetic peripheral neuropathic pain is a diagnosis of exclusion (Table 1). Physicians should exclude other possible and potentially correctable causes of neuropathy, particularly in older patients or those with comorbidities. In this case, the patient was assessed for abnormal laboratory findings and given a complete physical examination to rule out metastatic disease, infection, or exposure to toxic substances.

Loss of proprioception may occur late in the course of DPN, and patients are uncertain of where their feet are relative to their bodies, leading to falls and resultant injuries ranging from bruises to fractures. These patients may benefit from simple safety measures, such as using nightlights in the bedroom or bathroom and being instructed to call for assistance before getting out of bed. Patients with DPN are at high risk of foot injuries, leading to serious infections, ulcerations, and even amputations. Loss of sensation in the foot mandates special attention to the feet, and patients should be instructed to check their feet twice a day, even if painful to do so, and a thorough foot examination by a physician should be part of every visit. These examinations offer a good opportunity to work with patients and to encourage them to become invested in their own care.

Treatment. Because of the patient's preexisting depression, the decision was made to treat his DPNP with an antidepressant medication; however, the belief was that he would respond better to an agent other than his current medication, the selective serotonin reuptake inhibitor sertraline, because selective serotonin reuptake inhibitors are generally believed not to provide any relief for DPNP. Duloxetine, 30 mg/d, was given for the first 2 weeks; then the dose was increased to 60 mg/d. The sertraline dosage was slowly decreased and discontinued throughout 4 weeks as duloxetine was titrated up from 30 to 60 mg/d to maintain continuous antidepressant coverage during the crossover process in light of his long history of depression. After 1 month of duloxetine treatment, the patient said his usual daily pain was 5/10 and the pain he experienced at night when he tried to sleep was 6/10. This was not considered enough relief of his pain, and he was then given gabapentin (due to formulary considerations he was required to try gabapentin off label for pain and have it fail before he could receive a second brand name medication), started at 100 mg at bedtime. Gabapentin was increased every 3 days up to 200 mg 3 times daily for more than 2 weeks with no change in his mental status. The patient then reported his usual daily pain as 3/10 and the pain he experienced at night when he tried to sleep as 4/10. This level of discomfort was generally acceptable to him, and his physician did not add anything else.

Discussion. This case illustrates the importance of considering all the medical and psychiatric comorbidities when therapy is selected for the management of DPNP. Symmetrical foot pain in the setting of DM certainly suggests DPNP. The presence of allodynia (sensitivity of the feet to nonnoxious stimuli such as the weight of the bed sheets) strengthens the presumptive diagnosis of DPNP. The choice of drug therapy must take into consideration the patient's risk of falling due to the postural instability from PD, compounded by the loss of proprioception due to neuropathy. Anticonvulsant medications may be problematic to use with older, frail patients with renal insufficiency because ataxia is a potential adverse effect, complicating the treatment of any patient who is already known to have unsteadiness. A meta-analysis found that selective serotonin reuptake inhibitors have minimal analgesic efficacy in neuropathic pain and less than TCAs in particular.[23] Amitriptyline and desipramine are superior to placebo in clinical trials, but fluoxetine is not effective in patients with DPNP.[5] However, TCAs are relatively contraindicated in older adults because of cardiovascular adverse events and their association with a high incidence of anticholinergic adverse effects.

A TCA was not recommended for this patient because of the potential for creating cardiac arrhythmias, orthostatic hypotension, and urinary retention. Duloxetine was recom-

mended as first-line therapy because of its beneficial effect on mood for those with depression and because it is associated with a low risk of exacerbating postural instability. Its efficacy in reducing pain associated with DPN was demonstrated in 2 large clinical trials.[14,15] Another choice that could have been considered was the 5% transdermal lidocaine patch.[11] Lidocaine patches have been recommended off label as a local measure to further manage DPNP and allodynia with minimal risk of systemic toxicity.

Case 3: Nondiabetic Neuropathy in a Patient With DM

Presentation and Patient History. A 74-year-old retired man with type 2 DM of 30 years' duration presented with symmetrical lower extremity pain that interfered with his sleep, ability to participate in volunteer work, and ability to drive. He noted a 15-lb weight loss during the past year but claimed to have been dieting to help manage his underlying DM. His pain intensity was 7/10 at the worst, 2/10 at the least, and usually 5/10. The pain was described as "my feet and legs tingle with shooting jabs at times." On a body map illustration, he indicated that his pain reached up his calves; he said the pain was equally bad during the day and night, marking an 8/10 on the 11-point numeric analog scale. Physical examination revealed a slightly elevated blood pressure of 150/95 mm Hg. The patient had no bruits in his great vessels, heart murmurs, organomegaly, or other overt manifestation of generalized illness. Neurologic examination established that his mental status was intact, his tone was normal, and his strength was 5/5 throughout, with deep tendon reflexes of 2+ and symmetrical for his biceps, triceps, quadriceps, and hamstrings but 1+ for the brachioradialis and absent at the ankles. Sharp, thermal, and vibratory sensations were diminished distally in all extremities but more so in the lower extremities. Monofilament testing revealed loss of pressure sensation in both feet. His hemoglobin A_{1c} level was 7.5%, resulting in an immediate change from his oral medication to insulin therapy, with his hemoglobin A_{1c} decreasing to 6.1%.

Diagnosis. On the basis of the history of long-standing DM, symmetrical distribution of pain in the lower extremities, and lack of other important symptoms and signs of an underlying medical condition, a presumptive diagnosis of DPNP was made. The patient was cautioned to examine his feet twice daily despite the pain and to report any evidence of infection or ulceration immediately.

Treatment. The patient was treated empirically with gabapentin off label (to save him money), with a starting dose of 300 mg/d taken as one nightly dose, which was increased to 300 mg twice daily on day 2 and to 300 mg 3 times daily on day 3. He was told to take the gabapentin before bedtime each night. He reported to his physician 1 week later that his pain level was decreased to what he described as a "moderate" level (6/10 on average using the visual analog scale). His physician attempted to increase the gabapentin dose to 1200 mg/d, but this resulted in the patient reporting dizziness and interference with his daily activities due to "sleepiness." Because of the dizziness, the patient did not drive his car.

The gabapentin dose was reduced to 900 mg/d, and low-dose (10 mg every 12 hours) extended-release oxycodone was prescribed. After 1 week, the patient called to report that he could not tolerate the adverse effects of the oxycodone. He particularly complained about nausea and said that the oxycodone made him feel much more intoxicated than the gabapentin had. He was instructed to only take the controlled-release oxycodone at 7 PM nightly, and he was then able to tolerate the oxycodone in this asymmetrical dosing pattern with relief of the nausea and daytime sedation.

The patient returned the following month for a 6-week checkup since starting gabapentin therapy. He was still reporting moderate pain intensity with gabapentin and the oxycodone but was pleased with the improvement in his sleep. However, he also reported a general feeling of malaise and wondered whether this was due to his medication or being "tired of having his pain." Extended-release venlafaxine, 75 mg/d, a selective serotonin and norepinephrine reuptake inhibitor antidepressant, was added to the gabapentin initially and then increased to 150 mg/d after 2 weeks. It was hoped that the venlafaxine might "energize" him and give additional pain relief.

At the next 4-week follow-up appointment, the patient said that the addition of venlafaxine had not improved his feeling of malaise and he now felt weak at times. He said that the addition of venlafaxine had little effect on his overall pain intensity, which he now scored as a 5/10 usually. He had lost a noticeable amount of weight since his first visit for pain, and when queried about this, he said that the weight loss, 20 lb throughout 3 months, had not been due to any pronounced change in his diet or level of activity. On physical examination the patient was noted to have 4/5 muscle strength in his ankle and foot musculature bilaterally, with 5/5 strength testing elsewhere. Some muscle wasting was present distally. Because of these new physical findings, an additional work-up was ordered to identify non–diabetes-related causes for his pain, weakness, and weight loss.

Discussion. It is not unusual for patients with DPNP to have incomplete pain relief even with appropriate multidrug regimens. The additional features in this case of weakness, weight loss, and malaise warrant a reassessment of the underlying condition. A work-up for other causes of peripheral neuropathy beyond DM potentially includes complete blood cell count, thyroid function tests, vitamin B_{12} and folate levels, serum protein electrophoresis, liver

enzyme concentrations, hepatitis titers, and human immunodeficiency virus testing.

The patient was found to have a monoclonal gammopathy as a result of the testing and was referred for hematologic and neurologic consultations to further evaluate and manage his condition. Monoclonal gammopathy of undetermined significance signifies nonneoplastic excessive levels of immunoglobulin without malignant plasma cells.

As seen in this case, proper assessment, patient evaluation, and ongoing monitoring over time should allow for the detection of signs that indicate metastatic disease, infection, autoimmune disorder, or exposure to toxic substances (eg, neurotoxic drugs or chemicals). Phenomena of concern specific for patients with DM that warrant referral for specialty services include the presence of retinopathy, diabetic carpal tunnel syndrome, diabetic mononeuropathy, bony foot abnormalities, motor signs, and asymmetrical distribution of pain.

The treatments chosen for the patient had been studied in the setting of DPNP, but none had been approved by the FDA specifically for the treatment of DPNP. Gabapentin was studied in clinical trials at doses of up to 3600 mg/d, but the recommended dose for neuropathic pain (postherpetic neuralgia) was 1800 mg/d, because no further benefit was found with the higher doses.[8] Common adverse effects of gabapentin seen in clinical trials of patients with DPNP include dizziness, somnolence, and peripheral edema,[8] all of which are concern for older patients.

Extended-release oxycodone was effective in relieving DPNP in 2 clinical trials[18,19] but was associated with high rates of adverse effects, including constipation (42%), somnolence (40%), nausea (36%), dizziness (32%), pruritus (24%), vomiting (21%), and dry mouth (16%). All were reported by significantly ($P \leq .001$) more patients taking extended-release oxycodone than by patients taking placebo.[18]

In a randomized, placebo-controlled trial, extended-release venlafaxine at 2 doses (75 mg/d or 150-225 mg/d) was compared with placebo for treatment of DPNP.[24] The higher dose of venlafaxine significantly reduced pain intensity compared with placebo and also compared with venlafaxine at 75 mg/d, at week 6. Results with the lower dose were not different from those with placebo. The most common adverse events (>10%) with the higher doses of venlafaxine were nausea, somnolence, dyspepsia, insomnia, and sweating.

CONCLUSION

Not all cases of DPNP are straightforward and easily managed. Most people with DPNP can achieve lower levels of pain and better enjoyment of life with the fewest adverse effects through the methods described in these case reports. Use of more than one medication, rational polypharmacy, is common in the management of DPNP. Ongoing monitoring of therapy and a close working relationship between physicians and patients are necessary to maximize treatment efficacy and achieve the best outcome.

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