CLINICAL PRACTICE

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Diabetic Sensory and Motor Neuropathy

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This Journal *feature begins with a case vignette highlighting a common clinical problem. Evidence supporting various strategies is then presented, followed by a review of formal guidelines, when they exist. The article ends with the author's clinical recommendations.*

A 65-year-old woman with a 5-year history of type 2 diabetes (a recent hemoglobin A_{1c} level was 9.5%) reports the recent onset of burning, tingling, and stabbing pain in her feet that is worse at night and interferes with sleep and activities of daily living. Her medications include 500 mg of metformin and 2 mg of glimepiride, each taken twice daily. On physical examination, the patient is alert and oriented to person, place, and time. Her blood pressure is 140/90 mm Hg. She has reduced sensation to pinpricks in the knees, reduced ability to detect vibration from a 128-Hz tuning fork, and a loss of proprioception and of sensation to a 1-g monofilament (but not to a 10-g monofilament) in her toes. Strength in the lower legs is 5 out of 5 (normal) proximally and 4 out of 5 distally, and there is slightly weak dorsiflexion of both big toes, with no indication of entrapment. Her ankle reflexes are absent. She has no foot ulcers, and her pulses are easily palpable. How should her case be further evaluated and managed?

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THE CLINICAL PROBLEM

Neuropathy in diabetes is a heterogeneous condition that manifests in different forms. It may occur in proximal or distal nerve fibers, may take the form of mononeuritis or entrapments involving small or large fibers, and may affect the somatic or autonomic nervous system.[1] Distal symmetric polyneuropathy, the most common form of diabetic neuropathy, is a chronic, nerve-length–dependent, sensorimotor polyneuropathy[2,3] that affects at least one third of persons with type 1 or type 2 diabetes and up to one quarter of persons with impaired glucose tolerance.[1,4] Biopsy specimens of the skin have shown progressive reduction in the intraepidermal nerve fibers from the time of diagnosis of diabetes; this reduction is seen even in persons with prediabetes.[5,6]

Persons with distal symmetric polyneuropathy often have length-dependent symptoms, which usually affect the feet first and progress proximally. The symptoms are predominantly sensory and can be classified as "positive" (tingling, burning, stabbing pain, and other abnormal sensations) or "negative" (sensory loss, weakness, and numbness) (Table 1). Motor symptoms are less common and occur later in the disease process. Decreased sensation in the feet and legs confers a predisposition to painless foot ulcers and subsequent amputations if the ulcers are not promptly recognized and treated, particularly in patients with concomitant

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KEY CLINICAL POINTS

DIABETIC SENSORY AND MOTOR NEUROPATHY

- Symptoms of distal symmetric motor and sensory polyneuropathy may be "positive" (manifested as sensations of tingling, burning, or stabbing pain) or "negative" (manifested as sensory loss, weakness, or numbness). These symptoms occur in one third of patients with type 1 or 2 diabetes.
- Decreased sensation confers a predisposition to painless foot ulcers and to amputations. Proprioceptive impairment leads to imbalance and unsteadiness in gait and to an increased likelihood of falls and serious traumatic injury.
- Laboratory testing should be used to rule out other causes of neuropathy, including vitamin B_{12} deficiency, which may occur with metformin use.
- Lifestyle interventions (diet and exercise) may restore nerve fibers, and exercises that improve strength and balance may reduce the risk of falls.
- Medications most commonly used in pain management include anticonvulsants (particularly gabapentin and pregabalin), tricyclic antidepressants, and serotonin–norepinephrine reuptake inhibitors.
- Treatment choices should take into account coexisting conditions, such as insomnia, depression, and anxiety.

peripheral artery disease. The lifetime risk of a foot lesion, including an ulcer or gangrene, in persons with distal symmetric polyneuropathy is 15 to 25%.[1] In addition, sensory loss, combined with loss of proprioception, leads to imbalance and unsteadiness in gait, increasing the likelihood of a fall that may result in lacerations, fractures, or traumatic brain injury.[7]

Alternatively, some persons with distal symmetric polyneuropathy may be asymptomatic, and signs of disease may be detected only by means of a detailed neurologic examination.[4] In a recent survey of 25,000 patients with diabetes in which the Norfolk quality-of-life questionnaire for diabetic neuropathy was administered, 13,854 patients were aware of the presence of neuropathy, whereas 6600 patients reported symptoms of neuropathy but were neither aware that the symptoms were related to neuropathy nor had been informed of this relationship by their health care provider.[8]

Painful diabetic peripheral neuropathy occurs in 10 to 26% of patients with diabetes[1] and can have a profound negative effect on quality of life, sleep, and mood.[8,9] Neuropathic pain that is the result of small-fiber dysfunction usually causes burning sensations, is superficial, is often worse at night, and is associated with allodynia — the perception of a nonpainful stimulus as painful (e.g., contact with socks or bedclothes) — and paresthesias. The pain has been likened to the sensation of bees stinging through socks or of standing on hot coals. In contrast, pain caused by large-fiber dysfunction is deep-seated; patients describe it as the pain they would feel if a dog were gnawing at the bones of the feet or as the sensation they would have if their feet were encased in concrete.[3] Pain occurs more often in patients with poor long-term control of blood glucose levels, and greater variability in the range of blood glucose levels may contribute to the frequency and severity of painful symptoms.[10] Age, obesity, smoking, hypertension, dyslipidemia, and peripheral artery disease are also associated with an increased risk of pain.[11,12]

STRATEGIES AND EVIDENCE

DIAGNOSIS AND EVALUATION

Early diagnosis of distal symmetric polyneuropathy is imperative to prevent irreversible damage. Diagnosis is primarily clinical and involves a thorough history and physical examination with a focus on vascular and neurologic tests, along with a detailed assessment of the feet.[13] All sensory perceptions can be affected, particularly the sensation of vibration and touch and the perception of position, all of which can be affected by damage to large, A-type α- and β-fibers. Pain and abnormal perceptions of hot and cold temperatures may also be present, which result from damage to small, thinly myelinated A-type δ-fibers and small, unmyelinated C-type fibers (Table 1). Reduced sensation of vibration, detect-

Table 1. Approaches to the Diagnosis of Neuropathies of Large and Small Nerve Fibers.

Approach	Large Myelinated A-Type α- and β-Fibers	Small Myelinated and Unmyelinated A-Type δ-Fibers and Small Unmyelinated A-Type δ-Fibers and C-Type Fibers
Assess symptoms	Numbness, tingling, deep-seated gnawing or aching pain, weakness, ataxia with poor balance, falling	Burning pain with sensation of stabbing and electric shocks, allodynia, hyperalgesia, hyperesthesia
Conduct physical examination	Impaired reflexes, loss of proprioception and perception of vibration, wasting of small muscles of hands and feet, weakness in feet	Impaired sensation of warm and cold temperatures and of pinprick; normal strength, reflexes, and nerve conduction; impaired autonomic function, with dry skin, poor blood flow, cold feet, and impaired sweating
Recognize clinical implications	Impaired sense of pressure and balance; susceptibility to falls, traumatic fractures, and Charcot's arthropathy	Impaired nociception, susceptibility to foot ulcers, increased risk of amputation
Conduct diagnostic tests	Nerve conduction: abnormal test results (e.g., median, sural, and peroneal nerves) Quantitative sensory testing to detect loss of perception of vibration	Nerve conduction: normal results despite presence of symptoms Skin biopsy to detect loss of intraepidermal nerve fibers Corneal confocal microscopy Quantitative sensory tests to detect sensitivity to hot and cold and impairment of pain perception Sudorimetry (performed with neuropad or sudoscan) to obtain objective measures of sweating
Consider differential diagnosis	Consider chronic inflammatory demyelinating polyneuropathy, monoclonal gammopathies, Guillain–Barré syndrome, and myopathies, B_{12} or folate deficiency, hypothyroidism, paraneoplastic syndromes, and effects of chemotherapy	Consider metabolic causes such as uremia, hypothyroidism, B_{12} or folate deficiency, acute intermittent porphyria, toxic alcohol, heavy metals, industrial hydrocarbons, inflammation or infection, connective-tissue diseases, vasculitis, celiac disease, sarcoidosis, Lyme disease, human immunodeficiency virus, hepatitis B or C virus, hereditary diseases, monoclonal gammopathies, paraneoplastic syndromes, and amyloidosis

ed with the use of a 128-Hz tuning fork, is an early indicator of neuropathy. A 1-g Semmes–Weinstein monofilament can be used to detect changes in sensitivity, and the detection of abnormal sensation with a 10-g monofilament indicates an increased risk of ulcers. Examination of the feet should include checking for peripheral pulses to assess for peripheral artery disease and conducting a visual inspection for ulcers. Deep-tendon reflexes may be absent or reduced, especially in the lower legs. Mild muscle wasting may be seen, but severe weakness is rare and suggests a nondiabetic cause.[2] In more severe cases, the hands may be involved. Patients with asymmetric symptoms or signs, greater impairment of motor function than sensory function, entrapment, or rapid progression should be carefully assessed for other conditions. A history of drug or chemical exposures and a family history of inherited neuropathies should be obtained.[2]

Objective testing for neuropathy (including quantitative sensory testing, measurement of nerve-conduction velocities, and tests of autonomic function) is required to make a definitive diagnosis of neuropathy, although it is not essential for clinical care. Laboratory studies should include tests for thyrotropin level (thyroid dysfunction is a common coexisting condition), a complete blood count, serum levels of folate and vitamin B_{12} (metformin has been associated with vitamin B_{12} deficiency), and serum immunoelectrophoresis, the results of which are often abnormal in patients with chronic inflammatory demyelinating polyneuropathy, which is a common condition in persons with diabetes (Table 1).

CLINICAL MANAGEMENT

Management of painful distal symmetric polyneuropathy involves nonpharmacologic and pharmacologic approaches to minimize disease progression and relieve symptoms. Lifestyle interventions may prevent or possibly reverse neuropathy. Among patients with neuropathy associated with impaired glucose tolerance, a diet and exercise regimen was shown to be associated with increased intraepidermal nerve-fiber density and reduced pain.[14] A randomized trial involving persons with diabetes mellitus who did not have indications of neuropathy showed a reduced risk of the development of neuropathy among those assigned to exercise on a treadmill.[15] However, these trials did not include participants with established diabetic neuropathy. Strength and balance training to increase the strength of knee extension and foot dorsiflexion and improve gait stability may reduce the risk of falls among patients with large-fiber neuropathy.[16]

Although overzealous control of blood pressure and blood glucose levels should be avoided, rational glycemic control is recommended to manage symptoms and prevent further damage, including falls and foot ulcers. In randomized trials conducted among patients with type 1 diabetes, tight glucose control reduced the risk of the development of neuropathy by 78% as compared with conventional glucose control[17]; however, the effects of glycemic control on neuropathy among patients with type 2 diabetes have been less clear. In the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial, tight glycemic control resulted in modest reductions in neuropathic symptoms but no significant reduction in the risk of the development of neuropathy after 5 years.[18] In the Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) trial, patients randomly assigned to receive insulin-sensitizing agents as compared with insulin-providing agents had improved glycemic control and had a significantly (albeit modestly) lower incidence of neuropathy at 4 years.[19] In another trial based on a multifactorial strategy that involved control of blood pressure and lipid levels, the use of antioxidants, and lifestyle modification (intensive therapy) as compared with conventional therapy, the incidence of autonomic neuropathy but not somatic neuropathy was significantly lower among those receiving intensive therapy, although the assessment of somatic neuropathy was limited to vibration testing.[20] An overly rapid lowering of blood glucose levels (a reduction of >1% per month in hemoglobin A_{1C} level) may induce a neuritis with severe pain, although the neuritis generally resolves within 6 months.[21]

PHARMACOTHERAPY

Table 2 lists agents that are commonly used for pain relief in patients with distal symmetric polyneuropathy and that have been shown to be effective in randomized clinical trials. The table also lists reported benefits (the number needed to treat to in order to reduce pain by 50% in one patient) and adverse effects. Many treatments require careful dose adjustment (e.g., every 2 to 4 weeks) based on efficacy and side effects. First-line monotherapy frequently does not provide satisfactory relief at maximally tolerated doses.[1,23,24] Options then include switching to a different agent within the same class, switching to a new class, or adding a second agent. The classes of medications commonly used for treatment are reviewed below.

Topical Capsaicin

In early studies, capsaicin 0.075% cream was not effective in relieving pain and caused a burning sensation at the site of application. More recent studies in which an 8.0% patch was applied for 30 to 60 minutes (after the administration of a local anesthetic at the site) have shown that patients had pain relief that began within a few days and persisted for 3 to 6 months after a single application. Patients reported improvement in quality of life. Although researchers worried that this agent might damage C-type fibers originating in the skin, no sensory deficit at the site of application has been reported.[25,26]

Anticonvulsants

Gabapentin and pregabalin are $\alpha_2\delta_2$ voltage-gated calcium modulators that are frequently used to treat painful diabetic neuropathy. These agents relieve pain by means of direct mechanisms and by improving sleep.[27,28] In contrast to gabapentin, pregabalin has linear and dose-proportional absorption in the therapeutic dose range (150 to 600 mg per day); it also has a more rapid onset

of action than gabapentin and a more limited dose range that requires less adjustment. Gabapentin requires gradual adjustment to the dose that is usually clinically effective (1800 to 3600 mg per day).[27-29] Topiramate has also been shown to reduce the intensity of pain and to improve sleep; studies indicate that it stimulates the growth of intraepidermal nerve fibers.[30,31] Unlike pregabalin and gabapentin, which can cause weight gain, topiramate causes weight loss, which has been accompanied by improvements in lipid levels and blood pressure and increases in the density of intraepidermal nerve fibers of 0.5 to 2.0 fibers per millimeter per year, as compared with a decline of 0.5 to 1.0 fibers per millimeter per year in untreated patients.[31]

Tricyclic Antidepressants

Tricyclic antidepressants may offer substantial relief from neuropathic pain through mechanisms that are unrelated to their antidepressant effects.[32] However, their use is often limited by adverse cholinergic effects such as blurred vision, dry mouth, constipation, and urinary retention, particularly in elderly patients. The secondary amines, nortriptyline and desipramine, tend to have less bothersome anticholinergic effects than amitriptyline or imipramine and are generally preferred. Tricyclic antidepressants should be used with caution in patients with known or suspected cardiac disease; electrocardiography should be performed before these drugs are initiated to rule out the presence of QT-interval prolongation and rhythm disturbances (Table 2).

Serotonin–Norepinephrine Reuptake Inhibitors

The serotonin–norepinephrine reuptake inhibitors (SNRIs) venlafaxine[33] and duloxetine have proved to be effective in relieving neuropathic pain[34]; duloxetine has also been shown to improve quality of life.[35] These agents inhibit reuptake of both serotonin and norepinephrine without the muscarinic, histamine-related, and adrenergic side effects that accompany the use of the tricyclic antidepressants.

Opioid Analgesics

Opioids may be effective in the treatment of neuropathic pain caused by distal symmetric polyneuropathy. However, given the attendant risks of abuse, addiction, and diversion, opioids should generally be used only in selected cases and only after other medications have failed to be effective. Tramadol, an atypical opiate analgesic, also inhibits the reuptake of norepinephrine and serotonin and provides effective pain relief.[36] This drug also has a lower potential for abuse than other opioids. Extended-release tapentadol has similar actions and has been approved for the treatment of diabetic neuropathic pain by the Food and Drug Administration.[37,38] In one study, the combined use of gabapentin and sustained-release morphine achieved better analgesia at lower doses of each drug than the use of either drug alone but was accompanied by an increase in adverse effects, including constipation, sedation, and dry mouth.[29]

COEXISTING CONDITIONS AND CHOICE OF THERAPY

Coexisting conditions, including sleep loss, depression, and anxiety, should be considered in choosing therapy.[1,3,13,27,28] In contrast to duloxetine, which increases fragmentation of sleep, pregabalin and gabapentin have been shown to improve the quality of sleep, both directly and through relief of pain; the response to treatment with pregabalin correlates with the degree of sleep loss before treatment.[27,28] An SNRI or a tricyclic antidepressant may be preferred in patients with depression.[3,39] Pregabalin, gabapentin, or an SNRI may be appropriate choices for patients with anxiety, although gabapentin and pregabalin may cause weight gain. Caution is warranted regarding the use of tricyclic antidepressants and high doses of pregabalin or gabapentin in elderly patients, since these patients may be more susceptible to the adverse effects of these therapies than younger patients.[1,7,23]

AREAS OF UNCERTAINTY

Most trials of drugs that are used to control pain follow the patients for only a month and do not provide information on enduring effects; in addition, they typically compare a single agent with placebo. Long-term, head-to-head trials that compare the effects of various agents are needed, as are trials that compare the effects of monotherapies with those of combination therapies. More data are needed to inform the choice of initial therapy on the basis of the characteris-

Table 2. Pharmacologic Agents Often Used for Pain Relief in Patients with Distal Symmetric Polyneuropathy.*

Drug Class and Agent	Dose		NNT for Improvement of 50% in One Person†	Common Adverse Events‡	Serious Adverse Events§
	Initial	Effective			
Anticonvulsants					
Pregabalin (Lyrica)¶	25–75 mg, 1 to 3 times/day	300–600 mg/day	7.7 (6.5–9.4)	Somnolence, dizziness, peripheral edema, headache, ataxia, fatigue, xerostomia, weight gain	Angioedema, hepatotoxicity, rhabdomyolysis, seizures after abrupt discontinuation, suicidal thoughts and behavior, thrombocytopenia
Gabapentin (Neurontin)	100–300 mg, 1–3 times/day	900–3600 mg/day	6.3 (5.0–8.3)	Somnolence, dizziness, ataxia, fatigue, weight gain	Seizures after rapid discontinuation, Stevens–Johnson syndrome, suicidal thoughts and behavior
Topiramate (Topamax)	25 mg/day	25–100 mg/day	No estimate¶	Metabolic acidosis, paresthesia, somnolence, dizziness, anorexia, cognitive dysfunction, tremor, changes in taste	Glaucoma, hypokalemia, nephrolithiasis, osteomalacia, Stevens–Johnson syndrome, suicidality, toxic epidermal necrolysis
Antidepressants					
SNRIs					
Duloxetine (Cymbalta)‖	20–30 mg/day	60–120 mg/day	6.4 (5.2–8.4)	Nausea, somnolence, dizziness, constipation, dyspepsia, diarrhea, xerostomia, anorexia, headache, diaphoresis, insomnia, fatigue, decreased libido, shift to mania in patients with bipolar disorder	Bone fractures, cardiac arrhythmias, delirium, gastrointestinal hemorrhage, glaucoma, hepatotoxicity, hypertensive crisis, myocardial infarction, neuroleptic malignant syndrome, Stevens–Johnson syndrome, seizures, serotonin syndrome, severe hyponatremia, suicidal thoughts and behavior
Venlafaxine (Effexor)	37.5 mg/day	75–225 mg/day	4.5**	Nausea, somnolence, dizziness, constipation, dyspepsia, diarrhea, xerostomia, anorexia, headache, diaphoresis, insomnia, fatigue, decreased libido	Bone fractures, cardiac arrhythmias, delirium, gastrointestinal hemorrhage, glaucoma, hepatotoxicity, hypertensive crisis, myocardial infarction, neuroleptic malignant syndrome, Stevens–Johnson syndrome, seizures, serotonin syndrome, severe hyponatremia, suicidal thoughts and behavior
Tricyclic agents					
Amitriptyline (Elavil)	10–25 mg/day	25–150 mg/day	3.6 (2.1–4.4)	Xerostomia, somnolence, fatigue, headache, dizziness, insomnia, orthostasis with conduction block, hypotension, anorexia, nausea, urinary retention, constipation, blurred vision, accommodation disturbance, mydriasis, weight gain	Bone fractures, bone marrow suppression, fragility, hepatotoxicity, neuroleptic malignant syndrome, serotonin syndrome, severe hyponatremia, shift to mania in patients with bipolar disorder, suicidal thoughts and behavior
Nortriptyline (Pamelor)	25–50 mg at bedtime	Increase from 25–50 mg/day every 2–3 days to maximum of 150 mg/day	No estimate¶	Fewer anticholinergic effects than with amitriptyline	

Opioids					
Tapentadol (Nucynta)‖††	Immediate release, 50–100 mg, 4–6 times/day; extended release, 50 mg, 2 times/day	Immediate release, day 1, 700 mg, after day 1, 60 mg/day; extended release, 50 mg, 2 times/day	10.2 (5.3–18.5)	Somnolence, nausea, vomiting, constipation, dizziness, respiratory depression, serotonin syndrome, seizures	Hypertension, neonatal opioid-withdrawal syndrome
Tramadol (Ultram)‖	50 mg, 1–2 times/day	100–200 mg/day	4.7 (3.6–6.7)	Somnolence, nausea, vomiting, constipation, light headedness, dizziness, headache	Cardiac arrhythmias, confusion, hypersensitivity reactions, hypertension, seizures, Stevens–Johnson syndrome
Capsaicin 8.0% patch (Qutenza)	Apply for 30 min	Apply for 60 min	10.0 (7.4–19)	Burning at site of application	Damage to C-type fibers, with loss of sensation

* The data reported are based on the findings of 12 studies of amitriptyline, 3 studies of nortriptyline, 9 studies of duloxetine, 4 studies of venlafaxine, 25 studies of pregabalin, 14 studies of gabapentin, 6 studies of gabapentin ER (extended release), 3 studies of topiramate, 7 studies of tramadol, 12 studies of tapentadol, and 7 studies of the capsaicin 8% patch and were adapted from Vinik[13] and Finnerup et al.[22]

† The Food and Drug Administration (FDA) also considers an improvement of 30% to be significant. NNT denotes number needed to treat. Numbers in parentheses represent the range.

‡ Common adverse events are generally listed according to frequency.

§ Serious adverse events are listed alphabetically.

¶ Studies of topiramate and nortriptyline were too small to provide an NNT.

‖ This drug has been approved for this indication by the FDA.

** No range is provided because the numbers were based on one study.

†† This drug is generally not used for first-line therapy.

tics of the individual patient and to guide subsequent therapy when efficacy is lost or is insufficient.

Data are also needed to inform the benefits and risks of agents other than those being used now. A randomized trial that evaluated a combination of methylcobalamin, methylfolate, and pyridoxal phosphate in patients with diabetic peripheral neuropathy showed no significant benefit with respect to the primary outcome of threshold for vibration perception,[40] but several types of pain were alleviated and quality of life was improved.[40] It is possible that the methylcobalamin component was helpful for persons taking metformin who had vitamin B_{12} deficiency; the role of the other components in this regard and the overall effectiveness of this treatment regimen are uncertain. Whereas neuropathy associated with vitamin B_{12} deficiency has typically been considered to occur at levels below 250 pg per milliliter, one study indicated that the threshold for the development of impaired nerve conduction is approximately 450 pg per milliliter[41]; this finding suggests that there is a need for more study of the role of vitamin B_{12} supplementation in persons with diabetic peripheral neuropathy.

Data suggest that oxidative and nitrosative stress are central to the pathogenesis of neuropathy, and antioxidants have been proposed for treatment. A randomized trial involving patients with diabetes who had moderate distal symmetric polyneuropathy showed that alpha lipoic acid had no significant benefit with regard to the primary outcome (a composite score calculated on the basis of neuropathic impairment and results of neurophysiological testing) at 4 years, although improvements were noted in the scores assessing neuropathic impairment.[42,43]

GUIDELINES

Several guidelines from professional societies offer recommendations for the management of pain resulting from distal symmetric polyneuropathy.[44-46] The guidelines generally recommend the use of anticonvulsant agents, SNRIs and other antidepressants, and topical agents, although the order of preference differs among the societies; anticonvulsant agents, SNRIs, and other antidepressants are largely considered to

be first-line agents. The recommendations in this article are generally consistent with these guidelines.

SUMMARY AND RECOMMENDATIONS

The woman described in the vignette has characteristic features of large-fiber and small-fiber neuropathy that are consistent with diabetic sensorimotor neuropathy. Laboratory tests should include measurement of glucose, hemoglobin A_{1C}, lipid, and thyrotropin levels, a complete blood count, serum protein electrophoresis, and an assessment of vitamin B_{12} and folate levels; vitamin B_{12} deficiency is associated with metformin use and is manifested as impaired perception of vibration and loss of ankle reflexes. Quantitative tests of sensory and autonomic function should also be performed to obtain a definitive diagnosis and serve as baselines from which the progression or resolution of the neuropathy can be followed.

In patients with distal predominantly sensory neuropathy, as is seen in this patient, lifestyle changes (diet and exercise) and adjustment of medications should be recommended routinely to improve glycemic control, lipid levels, and blood pressure. An overly rapid lowering of the hemoglobin A_{1C} level (by more than 1% per month) and the development of hypotension should be avoided. For this patient, physical therapy should be recommended for strength training (and focused on the weakness of dorsiflexion of the big toe), and training to improve balance and reaction times would be advisable to reduce the risks of falls and fractures.

Agents that have proved to be effective in randomized trials involving patients with distal predominantly sensory neuropathy and that are most commonly used for treatment include pregabalin or gabapentin, tricyclic antidepressants, and SNRIs. Since this patient has a sleep disturbance, pregabalin or gabapentin may be appropriate first choices, but monitoring will be required for weight gain, fluid retention, and diminished glycemic control. It would be best to start with lower doses (e.g., 75 mg of pregabalin twice daily) and to adjust the dose upward if there is no reduction in pain within the first 2 weeks. If there is no response after 1 month of treatment, a switch to an agent from another drug class would be advisable. If the vitamin B_{12} level is below 450 pg per milliliter, supplementation with oral methylcobalamin (2000 μg per day) could be initiated, although there are as yet no data that show that supplementation reduces neuropathy in the absence of frank deficiency. Alpha lipoic acid can be given to relieve pain (starting at a twice-daily oral dose of 300 mg), although formal studies of its use in this regard have not been conducted.

Dr. Vinik reports receiving fees for serving on advisory boards from Merck, NeuroMetrix, Ipsen, and Astellas, consulting fees from Merck, IONIS Pharmaceuticals, Pfizer, Daiichi Sankyo, NeuroMetrix, Santarus, Nestle Health Science–Pamlab, Medikinetics, Ipsen, Janssen, Bayer, Astellas, Alnylam, Cline Davis Mann, and System Analytic, lecture fees from Merck and Nestle Health Science–Pamlab, grant support from Pfizer, Daiichi Sankyo, Tercica, ViroMed, Intarcia, Impeto Medical, VeroScience, and Novo Nordisk, and royalties for the use of the Norfolk QOLDN tool, a quality-of-life instrument owned by his medical school, which he codeveloped for use in clinical trials involving patients with diabetic neuropathy. He also reports being the inventor of a dietary supplement that includes a mixture of alpha lipoic acid, methylcobalamin, benfotiamine, dihomo-γ-linoleic acid, cholecalciferol, and ascorbic acid, the rights to which were assigned to his medical school. Dr. Vinik reports that he, his laboratory, and his department have not received and will not receive any income that might derive from this product. No other potential conflict of interest relevant to this article was reported.

Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

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