A 52-Year-Old Woman With Disabling Peripheral Neuropathy
Review of Diabetic Polyneuropathy

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Ms Q is a 52-year-old woman who has had progressive polyneuropathy in the setting of diabetes for the past 8 years. Ms Q's major disability is that of increasingly severe neuropathic pain and cramps that have been poorly responsive to a variety of therapies, including gabapentin and topiramate. The diagnosis of and differential diagnosis for diabetic polyneuropathy are reviewed herein. In general, treatment options for diabetic polyneuropathy remain primarily symptomatic. Improving the metabolic profile through weight loss, exercise, and if necessary, medications may help slow neuropathy progression. Many medications are effective in reducing pain, and newly developed ones, such as pregabalin and duloxetine, while specifically marketed for diabetic neuropathy, are likely to be no better and are considerably more expensive than older ones. α-Lipoic acid appears to be effective as well.

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Dr Ship: Ms Q is a 52-year-old registered nurse with lower extremity neuropathy diagnosed 6 years ago. She lives in the greater Boston area and has managed care health insurance.

Ms Q's symptoms began about 8 years ago with pain at the base of her left foot. She was seen by a podiatrist, initially diagnosed with plantar fasciitis, and underwent serial cortisone injections. The injections minimized symptoms initially, but her pain persisted. Her pain spread to her right foot, and, given the lack of improvement, she was referred for nerve conduction studies and electromyography (EMG). The studies showed mild reduction in the sural sensory response amplitudes bilaterally with normal conduction velocities; these findings were consistent with a mild distal axonal sensorimotor polyneuropathy.

Ms Q was diagnosed with diabetes about a year before her EMG findings. Her hemoglobin A_{1C} was 7.6% at the time of diagnosis.

Ms Q says that her neuropathic symptoms, which include numbness, tingling, pain, and burning bilaterally, have worsened over the years. Her symptoms seem to worsen when her diabetes is less well controlled. She has had difficulty keeping her diabetes under tight control, however, and her hemoglobin A_{1C} is currently 8.8%.

She has tried a range of medications with only moderate relief. Amitriptyline caused intolerable mouth dryness. Topiramate and gabapentin were ineffective. To treat her pain, she currently uses lidocaine patches, takes 60 mg of duloxetine daily, and uses alternative treatments including arnica cream. Her other medications include atenolol, 100 mg once a day; atorvastatin, 80 mg once a day; fluticasone, 50 µg spray, 1 to 2 sprays daily; glyburide, 10 mg twice daily; hydrochlorothiazide, 25 mg once a day; lisinopril, 40 mg 4 times a day; metformin, 1000 mg twice daily; oxycodone/acetaminophen (5 mg/325 mg), 1 to 2 tablets every 4 hours as needed for pain; trazodone, 100 mg before bed; and ranitidine, 150 mg twice daily.

Ms Q's other medical problems include obesity, hypercholesterolemia, depression, hypertension, and back pain which persists after a left L5 to S1 hemilaminectomy, medial facetectomy, and microdiskectomy for disk disease in 2000.

Her vitamin B_{12} and thyrotropin levels were normal. On examination, her blood pressure was 146/74 mm Hg; pulse, 68/min; weight, 237 lb (106.6 kg); and height, 5 ft, 4 in

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(162.5 cm). Distal strength in the legs and feet was normal. Reflexes were 2+ at the knees and trace at both ankles; no Babinski signs were present. There was a graded reduction in sensation to pinprick and cold in both feet, normalizing at the midshins bilaterally. Vibration was reduced to 2 to 3 seconds in the great toes but was normal proximally. Joint position sense was intact in both feet. Gait was narrow-based, and a Romberg sign was absent.

MS Q: HER VIEW

I noticed pain in my left foot—it was always the left foot first—and that's when I had just started nursing, back in '88. I spoke to a friend who was a podiatrist and he started wrapping it and giving me cortisone shots. As time went by, it started developing in my right foot as well. Years later, he sent me for an EMG, and they came back with the finding that I had diabetic neuropathy.

Initially I was put on small dose of amitriptyline at bed time and that caused terrible dryness of my mouth. I would wake up and not even be able to open my mouth. So that stopped. Then I started on Neurontin [gabapentin], and I think dry mouth was still a problem.

My diabetic doctor started me on [lidocaine] patches, and prior to that, he started me on [duloxetine], 60 mg at bedtime. The [duloxetine] really helped initially, a whole lot. It was like a wonder drug for me.

Other things that help are sometimes a massage or arnica rubbed into it to create a little bit of heat. Also ice massages help quite a bit, but I'm hesitant to use that because of vascular complications from the diabetes. Acupuncture helped, but the price of the acupuncture is a deterrent.

I notice a correlation between the control of the diabetes and the pain, the neuropathy symptoms. If I lapse into a sugar binge, I will feel heat and pain in my feet.

My symptoms have gotten much worse since it was first diagnosed. There are cramps that have recently kicked in. My pain has become bilateral, and the numbness seems to be crawling up my legs as well as the swelling in my ankles and my legs.

My understanding of the treatment of neuropathy is that ultimately, there is very little to do for it. Treat the symptoms is what I've been doing. It is not something that is going to go away. It may, with better control of the diabetes, become less uncomfortable. I was planning to have a gastric bypass to help reduce my intake, but that's a little too scary for me. So now I'm reconsidering having a band done.

I'd like to know if it ever gets better, instead of progressively worse. There are new medications on the market that are supposed to help it—I don't know why I'm not on them, or if those medications could be helpful for me, or if there is anything else that I could do.

AT THE CROSSROADS: QUESTIONS FOR DR RUTKOVE

What is the epidemiology of diabetic neuropathy? Who should be tested and how? What are the treatment options and their outcomes and adverse effects? What do you recommend for Ms Q?

DR RUTKOVE: This 52-year-old woman with a history of lumbosacral disk disease presents with diabetic polyneuropathy. Her symptoms were initially attributed to plantar fasciitis, likely because the foot pain was initially unilateral. The spreading of the pain to the other side alerted a physician to the possibility of neuropathy, and she was sent for electrophysiologic testing that revealed a mild axonal polyneuropathy. Because she had been diagnosed with diabetes a year earlier, a diagnosis of diabetic polyneuropathy was made. She has had progression of symptoms since then and is currently treated with lidocaine patches and 60 mg of duloxetine. She also takes 100 mg of trazodone at bedtime and 5 mg/325 mg oxycodone/acetaminophen as needed. In addition to neuropathic pain, she notes painful cramping in both feet. Her physicians are trying to improve her pain control while forestalling the progression of the neuropathy.

Nomenclature of Diabetic Neuropathy

Diabetic neuropathies can be grouped into 2 major categories: focal and diffuse. The focal neuropathies include a variety of conditions that have an increased incidence in diabetes compared with the general population, including focal appendicular mononeuropathies, such as median neuropathy at the wrist, and ulnar neuropathy at the elbow, cranial mononeuropathies (such as Bells palsy) or lumbosacral radiculoplexoneuropathy (diabetic amyotrophy).[1,2] Of the diffuse diabetic neuropathies, diabetic polyneuropathy—the disorder producing generalized, distally predominant, relatively symmetric dysfunction with sensory function affected more than motor function—is the most common and is the focus of this review. Diabetes has also been associated with a form of generalized polyneuropathy known as chronic inflammatory demyelinating polyradiculoneuropathy; however, recent evidence suggests that the incidence of this disorder in patients with diabetes is no more common than that of the general population.[3]

The American Diabetic Association defines *diabetes* as a fasting glucose level of 126 mg/dL or greater (to convert to millimoles per liter, multiply by 0.0555) or a glucose level of 200 mg/dL or greater with an oral glucose tolerance test.[4] *Impaired glucose tolerance* is defined as a plasma glucose level of 140 to 199 mg/dL 2 hours after an oral glucose tolerance test, whereas *impaired fasting glucose* is defined as a fasting plasma glucose level of 100 to 125 mg/dL. *Metabolic syndrome* refers to the state of insulin resistance in the setting of increased waist circumference, elevated blood pressure, and fasting glucose level greater than 100 mg/dL. Because polyneuropathy appears to be associated with these prediabetic states,[5] for the purposes of this review, I will refer to the condition as forms of diabetic polyneuropathy without regard to category or type of diabetes, except where noted. Ms Q has been previously diagnosed with diabetes, which is poorly controlled with a hemoglobin A_{1c} of 8.8%.

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Epidemiology

Diabetes is the most common cause of polyneuropathy in Western countries; however, the proportion of patients with polyneuropathy is unknown. In patients with diabetes, the prevalence of polyneuropathy ranges from 28% to 55%. In one set of studies, 4400 patients with diabetes were followed up for more than 25 years and clinically defined polyneuropathy affected 50% of individuals by the 25th year of study.[6-8] The Europe and Diabetes Study (EURODIAB) found a prevalence of polyneuropathy of about 28% in 3250 randomly selected patients with insulin-dependent diabetes from across Europe.[9] Among individuals with diabetes in Olmstead County, Minnesota, 55% of those insulin dependent vs 54% of those noninsulin dependent had polyneuropathy, but of those only 15% of the insulin-dependent group and 13% of the noninsulin-dependent group were symptomatic.[10] Finally, patients with type 2 diabetes but no polyneuropathy developed polyneuropathy at the rate of 6.1 per 100 person-years.[11]

Table 1. Disorders That Mimic Polyneuropathy

Disorder	Features That Help Discriminate From Diabetic Polyneuropathy
Cervical myelopathy	Increased reflexes, bladder involvement, arms and trunk affected
Lumbar stenosis	Asymmetric sensory examination and reflexes, back pain, symptoms worse with exercise
Tarsal tunnel syndrome	Typically unilateral, Tinel sign over tibial nerve at ankle, sensory loss mainly affecting the sole of the foot
Digital neuropathies, including Morton neuroma	Localized pain in the sole of the foot, sensory loss limited to just 1 or 2 toes, Tinel sign over the ball of the foot
Orthopedic foot problems	Varied; for plantar fasciitis, pain is usually present just anterior to the heel
Raynaud syndrome	Temperature-induced symptoms with color change, hands also affected, normal examination
Anxiety	Fleeting paresthesias; pain uncommon

Clinical Symptoms and Examination

Diabetic polyneuropathy can present in a variety of ways. As noted in the Olmstead County study, it is often asymptomatic, and evidence for the disorder is only found on examination. However, in many patients, symptoms will goad individuals to seek medical help. Generally, small fiber neuropathy develops before large fiber,[12] so many patients will present with complaints of burning, uncomfortable feet. However, for unknown reasons, a large proportion of individuals with diabetic polyneuropathy do not develop pain and only present with large fiber symptoms of numbness, weakness, or gait disturbance.

The most readily identifiable feature of diabetic polyneuropathy is the reduction of pinprick sensation distally with normalization proximally. To identify this, the physician should "march" the pin up from the toes looking for a point at which the pinprick sensation becomes fully sharp. Occasionally during this procedure, patients will complain of hypersensitivity distally. Temperature sensation should be similarly evaluated, most conveniently by sliding the cool round end of a 128-Hz tuning fork up the leg. Sensation to light touch should be tested in a similar manner. Joint position sense should be assessed by making small excursions of the interphalangeal joint of the great toe and determining the patient's ability to accurately identify the direction of movement. Finally, the physician should apply the tip of a 128-Hz tuning fork to the great toe after striking it firmly nearby, while counting out seconds. Feeling the vibration for at least 12 seconds is generally considered normal. Although the reliability of other types of sensory testing have not been reported, timed vibration testing has an interrater correlation coefficient as high as 0.93 at the great toe.[13] Ms Q has reduced sensation to pin prick, cold, and vibration, but other findings were absent.

After completing the sensory examination, the strength of toe extensors and flexors and foot dorsiflexion should be assessed, followed by examination of the deep tendon reflexes. In patients with diabetic polyneuropathy, these are usually normal in the arms and knees and reduced or absent in the ankles. Absence of the Achilles reflex and reduced vibration perception and position sense at the great toe has been found to have a 92.8% positive predictive value for the presence of polyneuropathy.[14] Gait often becomes impaired in the presence of diabetic polyneuropathy, with slower walking speeds, longer stance phases, and reduced flexion of the ankle.[15]

Differential Diagnosis

When evaluating the constellation of symptoms and signs with which patients with presumed diabetic polyneuropathy present, other neurological diagnoses should be considered. First, polyradiculopathy (lumbosacral stenosis) should be considered. For example, one study showed that 14% of 162 patients referred to an EMG laboratory for a diagnosis of possible polyneuropathy were found to have radiculopathy or polyradiculopathy as the likely cause of their symptoms.[16] Asymmetries in sensation and reflex testing indicated a radicular etiology over polyneuropathy. Spinal cord disorders, especially cervical spondylotic myelopathy, also can present with predominantly distal complaints and should be excluded .[17] Another diagnosis sometimes considered is tarsal tunnel syndrome; however, this syndrome is very rare.[18] Other nonneurological diagnoses should also be considered, including plantar fasciitis, which was Ms Q's initial diagnosis. Planter fasciitis usually produces localized pain just anterior to the heel (Table 1).[19]

The physician should consider other clues in the patient's history to assist with diagnosis. For example, does the patient have other past or ongoing medical problems that may predispose him/her to developing polyneuropathy, such as rheumatologic disease,[20] kidney dysfunction,[21] or monoclonal gammopathy?[22] Is there a family history of neuropa-

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thy? Has the patient taken medications with neuropathic adverse effects (such as isoniazid,[23] chemotherapeutic agents,[24] or high doses of vitamin B_6 [pyridoxine hydrochloride][25])? Some have suggested that statin medications may be associated with polyneuropathy, but the risk appears to be small.[26]

Laboratory Findings

Even for a patient with known diabetes, excluding other causes of polyneuropathy is important because they may be potentially treatable. Although no study has addressed the utility of specific screening laboratory studies, in practice, vitamin B_{12} levels, thyroid stimulating hormone, serum and urine protein electrophoresis, and rapid plasma reagin should be obtained. Some, however, have advocated additional tests, including vitamin B_1 and B_6 levels.[27]

In patients with known diabetes and typical clinical features of the disorder, nerve conduction studies and EMG are not mandatory. However, in my view, such testing is warranted if the presentation is atypical, such as a rapidly progressive course, marked asymmetry, weakness being greater than sensory loss, or if upper extremity symptoms are greater than lower. A typical pattern of electrophysiological abnormalities is usually found in diabetic polyneuropathy as follows.[28] Early in its course, mild reduction in distal sensory response amplitudes (eg, those of the sural nerves) will be observed, with more advanced disease producing further reductions in these responses until they are absent. Motor response amplitudes, in contrast, are generally preserved early in the disease course but will decrease with more advanced disease. Mild to moderate degrees of conduction velocity slowing and F-wave prolongation are usually also present. Concomitant median neuropathy at the wrists is often identified in patients even without any upper extremity symptoms. Needle EMG may reveal mildly enlarged motor unit potentials in distal muscles. Importantly, in patients with early diabetic polyneuropathy affecting only small, unmyelinated nerve fibers, electrophysiological testing will have entirely normal results.[12]

Autonomic testing should be considered if the patient has physically limiting symptoms such as orthostasis or gastrointestinal tract difficulties (eg, early satiety, constipation).[29] Such testing can take various forms including tilt-table testing, heart-rate variability with deep breathing, or quantitative sudomotor axon reflex testing. Such tests are good at detecting autonomic neuropathy (eg, for heart variability, a sensitivity of 96% and specificity of 70%[30]).

Skin biopsy for intraepidermal nerve fiber assessment should be considered in patients with symptoms and signs suggestive of isolated small-fiber polyneuropathy.[31] A standard skin punch biopsy is obtained and stained with an antibody to the intraepidermal nerve fibers, and these fibers are then counted. Studies have shown a sensitivity of this test to polyneuropathy between 40% and 95% with a specificity of 95% to 97%.[29] Although nonspecific in the sense that it does not provide a diagnosis of diabetic polyneuropathy per se, skin biopsy can be helpful in confirming that pathology exists before embarking on a treatment program that might require multiple medications, especially in patients with prediabetic states. Sural nerve biopsy is rarely warranted.[32]

Thus, the diagnosis of diabetic polyneuropathy should be based on the clinical history and examination, the diagnosis of diabetes or a prediabetic state, the exclusion of other common causes, and electrophysiological and other testing as needed.

Mechanisms

A common theme among many of the proposed mechanisms leading to diabetic polyneuropathy is that of microvascular injury from reactive oxygen species formation.[33,34] Elevated glucose also leads to the development of sorbitol through activity of aldose reductase; this has several adverse effects on neuronal functioning, including the development of reactive oxygen species. Protein kinase C activation, immune complex deposition, the development of advanced glycation end products, and impairment of normal cellular processing, including axonal transport, may play important roles in the development of diabetic polyneuropathy.[35] One important aspect of diabetic polyneuropathy is that pathology is also present in the dorsal horn of the spinal cord, suggesting that remodeling occurs centrally either in response to distal pathology or separately from it.[36]

Treatment Options

Treatment can be separated into 2 basic categories: protective and symptomatic. With the possible exception of α-lipoic acid treatment, protective therapy, or therapy that addresses the underlying cause of diabetic polyneuropathy, is limited to tight control of serum glucose, which can slow diabetic polyneuropathy development and progression, with a 60% reduction in the development of signs and symptoms at 5 years.[37] Thus, improved glucose control should be recommended to all individuals with the diagnosis. However, ongoing research that aims at slowing its progression by decreasing sorbitol production through aldose reductase blockade,[38] inhibiting reactive oxygen species formation,[34] and reducing the activity of protein kinase C may yield additional therapies.[39]

Unlike protective therapy, many symptomatic treatments are available. First, tight glycemic control can also improve symptoms over short time intervals, albeit only shown in uncontrolled trials.[40,41] Ms Q has noted a difference in her symptoms depending on her adherence to her diabetic diet. In most patients, tight glycemic control alone will be insufficient. However, before initiating drug therapy, patients should be informed that 100% pain relief is not usually possible regardless of the therapy approach chosen.[42] Remarkably, almost one-quarter of individuals with neuropathic pain do not receive any medical therapy at all, despite the many effective therapies that are available.[43]

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Efficacy of drug treatment can be difficult to compare because trial designs differ. One approach to circumvent this problem is by comparing numbers needed to treat (NNT)[44] across trials. For neuropathic pain, the NNT is usually represents the number of patients that need to be treated so that 1 patient experiences at least 50% pain relief.[45] Thus, the higher the NNT value, the less efficacious is the medication. Such comparisons (**TABLE 2**) demonstrate that the NNT values for most drugs are quite similar, suggesting that they are similarly effective, even those not specifically labeled for use for diabetic polyneuropathy. However, it is also important to realize that the quality of the studies is not the same and the patient populations differ (eg, in diabetic polyneuropathy severity), and thus such an analysis can be overly simplistic. Still, such an analysis provides a basic handle for evaluating a large number of potential therapies.

Specifically Approved Medications. The manufacturers of duloxetine and pregabalin have sought and obtained US Food and Drug Administration (FDA) approval for diabetic polyneuropathy, but their approval should not be interpreted as evidence that that they are superior to other available treatments. Table 2 shows that they may be no more effective than many other medications but are considerably more expensive. Two trials that involved 791 patients showed that duloxetine had improved pain more frequently than did placebo (31% more frequently for 60 mg/d and 51% for 120 mg).[60,61] A pooled analysis of 7 trials showed that pregabalin was more effective than placebo.[52] However, given their higher cost and lack of proven long-term benefit over standard therapies, they generally should not be considered first-line therapy.

Medications Supported by at Least 2 Randomized Trials. The only other medications that have withstood the rigor of multiple clinical trials are the tricyclic antidepressants and controlled-release oxycodone. Among tricyclic antidepressants, 1 study compared amitriptyline, desipramine, and the serotonin reuptake inhibitor fluoxetine.[62] Amitriptyline and desipramine had similar efficacy with the latter having fewer adverse effects; fluoxetine was ineffective. A recent review found that the tricyclic antidepressants were more effective for short-term pain relief than any of the newer anticonvulsants, including pregabalin.[63] Two studies also demonstrated that controlled-release oxycodone was more effective than placebo.[48,64]

Table 2. Comparison of Selected Medications Based on Number Needed to Treat

Drug or Drug Class, Dose	Mechanism or Drug Class	No. Needed to Treat (95% CI)[a]	Cost per Month, US $[b]	Dose	Common Adverse Effects
Anticonvulsants, meta-analysis[46]		2.7 (2.2-3.8)			
Antidepressants, meta-analysis[46]	SSRIs and tricyclic antidepressants[c]	3.4 (2.6-4.7)			
Phenytoin[47]	Sodium channel blockade	2.1 (1.5-3.6)	43.12	100 mg 3 per d	Gingival hyperplasia
Carbamazepine[48]	Sodium channel blockade	2.3 (NA)	13.99	200 mg 3 per d	Hepatic toxicity, dizziness, somnolence
Amitriptyline[49]	Norepinephrine and serotonin reuptake inhibition	2.5 (NA)	3.73	25 mg 4 per d	Dry mouth, lightheadedness
Oxycodone[48]	Opioid receptor	2.6 (NA)	214.68	20 mg 2 per d, extended release	Nausea, constipation
α-Lipoic acid, 1800 mg or 600 mg/d[50]	Antioxidant	2.7 (1.8-5.8)	8.31	600 mg 1 per d	Muscle cramps, headache
Paroxetine[47]	SSRI	2.9 (NA)	28.97	20 mg 2 per d	Sweating, anxiety
Tramadol[47]	Opioid agonist	3.4 (2.3-6.4)	95.14	50 mg 6 tabs per d	Nausea, constipation, headache, and sleepiness[51]
Gabapentin[47]	Uncertain; voltage-gated calciumion channel modulation	3.7 (2.4-8.3)	92.99	600 mg 3 per d	Dizziness, somnolence, and peripheral edema
Pregabalin 600, mg/d[52]	Blocks release of excitatory neurotransmitters; calcium channel modulation[53,54]	4.0 (3.3-5.3)	149.52	300 mg 2 per d	Dizziness, somnolence, peripheral edema, and a mild weight gain
Lidoderm patches[55]	Sodium channel blockade	4.4 (2.5-17)	770.82	5%, 4 per d	Erythema, skin irritation
Venlafaxine[56]	Inhibition of serotonin, norepinephrine reuptake	4.5 (NA)	112.00	150 mg 4 per d, extended release	Nausea, somnolence
Duloxetine, 60 2/d[57]	Serotonin and norepinephrine reuptake inhibition	4.9 (3.6-7.6)	261.84	60 mg 2 per d	Nausea, elevated plasma glucose[58]
Duloxetine, 60 4/d[57,58]	See above	5.2 (3.8-8.3)	130.92	60 mg 4 per d	See above
Pregabalin, 300 mg/d[52]	See above	6.0 (4.2-10.4)	154.62	150 mg 2 per d	See above
Citalopram[47]	SSRI	7.7 (NA)	27.99	20 mg 2 per d	Nausea, dizziness, headache
Capsaicin[59]	Local depletion of substance P	8.1 (4.6-34)	17.99		Local burning and stinging

Abbreviations: CI, confidence interval; NA, not available; SSRI, selective serotonin reuptake inhibitor.
[a] Number of patientes who would need to be treated to provide 1 patient with at least 50% pain relief. The number needed to treat may not be strictly comparable across studies because quality of studies and patient populations vary (eg, in diabetic polyneuropathy severity).
[b] Prices are based on drugstore.com as of August 2009.
[c] Fluoxetine has been found to be ineffective for diabetic polyneuropathy.[62]

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Medications Supported by at Least 1 Randomized Trial. Table 2 shows that carbamazepine, gabapentin, lamotrigine, tramadol, and extended-release venlafaxine have relatively similar efficacies for treating polyneuropathy. Two trials demonstrated that gabapentin was effective in daily doses as high as 3600 mg.[65,66] Other anticonvulsants, including carbamazepine and lamotrigine, have been shown to have some efficacy greater than placebo in treating diabetic polyneuropathic pain.[45,67] Topiramate has been found to be only equivocally helpful, with one study showing efficacy[68] but another not.[69] Despite this, topiramate has the benefit of causing mild anorexia, leading to an average reduction in body weight of 2.6 kg over 12 weeks.[68]

Tramadol and venlafaxine have also been supported by at least 1 large clinical trial for treating polyneuropathic pain. For tramadol, an average dose of 210 mg/d was found to be effective in relieving pain.[51] Similarly, extended-release venlafaxine at doses of about 150 mg to 225 mg daily was associated with better pain relief than placebo.[56]

Several placebo-controlled studies demonstrated that α-lipoic acid, an antioxidant nutritional supplement, reduced pain. The largest trial found that 600 mg/d taken orally effectively reduced pain within 2 weeks of initiating treatment.[49] This study also found that symptoms of numbness and paresthesia improved, a result supported by a second smaller study that showed a significant improvement in the Neuropathy Disability Score.[70] Thus, its apparent ability to reduce both pain and neurological deficits with few adverse effects makes it unique.

Of topical medications, only capsaicin has been found to significantly improve function and reduce pain,[71] but given its somewhat weaker efficacy, it should be considered primarily an ancillary therapy.[59] The same is true for lidocaine patches, which have been shown to reduce pain and improve quality of life but only in an open-label study[72] and a small blinded study that included other conditions.[73]

Other Medications and Treatments. Although trazodone,[74] acetyl-L-carnitine,[75] isosorbide,[76] nonsteroidal anti-inflammatory drugs,[77] transcutaneous electrical nerve stimulation,[78] and acupuncture[79] have been studied for treating polyneuropathy, data are limited. A variety of other potential therapies including herbal medications, anodyne light therapy, and nutritional supplements have all been suggested but have either been found to be unhelpful[80] or not studied adequately. Dextromethorphan alone or in combination with quinidine appeared to have some benefits in an open-label study.[81,82] Although some advocate surgical release of multiple lower extremity nerves, this treatment approach is unproven and a blinded study has been suggested.[83] Finally, Ms Q has used arnica cream, an herbal homeopathic cream that includes the *Arnica montana* plant. Its efficacy in polyneuropathy has not been studied.

TREATING ASSOCIATED CONDITIONS

Ms Q also complains of foot cramps. Cramps are likely generated in the distal axon. That she is experiencing cramps is to be expected because nerve hyperexcitability has been reported in a variety of peripheral nerve disorders.[84,85] Quinine sulfate is an effective treatment,[86] but given its poor adverse effect profile, the FDA has warned against its use. Fortunately, other medications may also be beneficial, with carbamazepine chief among them.[87]

Polyneuropathy in general predisposes to the development of restless leg syndrome,[88] which is also associated with diabetic polyneuropathy. One study confirmed that about one-third of those with diabetic polyneuropathy are affected to some extent.[89] Restless leg syndrome generally responds best to dopamine agonists such as ropinirole or pramipaxole[90] rather than to the medications used to treat neuropathic pain.

Given the prominent role of microvascular ischemia in the development of diabetic polyneuropathy, the aggressive management of other risk factors including blood pressure, serum cholesterol, and triglycerides and maintaining tight control of serum glucose should be pursued. In one study, the hazard ratio for developing autonomic neuropathy was 0.37 (95% CI, 0.18-0.79) with tight control compared with conventional treatment; however, there was no effect on the progression of distal polyneuropathy.[91]

Putting It All Together

Given the many potential treatment approaches for treating diabetic polyneuropathic pain, identifying a single best approach is not straightforward. Various reviews have outlined a general approach to implementing therapy.[42,92] After excluding nondiabetic etiologies and stabilizing glycemic control, primary treatment usually should be initiated with either an antidepressant (eg, desipramine) or an anticonvulsant (eg, gabapentin or carbamazepine). α-Lipoic acid should be added, given its safety and potential for improving neuropathic symptoms. For patients still experiencing insufficient relief, switching to a newer medication such as duloxetine or pregabalin can be considered, recognizing that they may be no better than the older, less expensive medications. An opioid medication can also be added, although the potential for developing serotonin syndrome should be appreciated if the patient is being treated with an antidepressant.[93] If the patient is experiencing substantial cramps or restless leg syndrome, condition-specific treatment should be considered.

RECOMMENDATIONS FOR MS Q

Although Ms Q has had some pain relief with duloxetine and lidocaine patches, she remains in considerable discomfort. However, much of this discomfort is in the form of cramping rather than just neuropathic pain. Thus, carbamazepine could be added to her regimen; this drug has the potential of even obviating the need for duloxetine given its separate efficacy for treating neuropathic pain. If her nocturnal pain is better controlled, it may then be possible to discontinue the trazodone. Supplementing her regimen with 600 mg/d of α-lipoic acid may help further reduce her pain and offers the promise of improved function. Although her statin therapy could be contributing to her polyneuropathy, the potential ben-

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efit of discontinuing it needs to be weighed against the benefits of its continuation. Clearly, all efforts to improve her metabolic profile may also help in her long-term prognosis, including weight loss, lowered cholesterol levels, and good control of both serum glucose and blood pressure.

QUESTIONS AND COMMENT

Question: If this patient is really able to control her sugar, can there be repair and recovery of her nerves?

Dr Rutkove: The peripheral nervous system is capable of repair to some extent, but patients with diabetic polyneuropathy rarely completely recover, even with normalization of the metabolic profile through diet, exercise, and medications. This may be due to remodeling of pathways in the central nervous system, resulting in a persistent pain syndrome.[94]

Question: How do patients who have good control of their diabetes and progressive peripheral neuropathy differ from those who don't, both in terms of treatment options and underlying mechanism of the disease?

Dr Rutkove: Although good glycemic control will, in general, help slow the progression of polyneuropathy, the severity of polyneuropathy can vary remarkably.[95] One person with good control may have debilitating pain, whereas another with poor control may have only mild painless sensory loss in the feet. Nevertheless, treatment options are the same for both types of patients.

Question: How can you definitively know that diabetes is the source of neuropathy?

Dr Rutkove: It is always possible that another factor may be at play inducing the polyneuropathy; thus, reviewing the patient's relevant history and ordering screening tests for common causes of polyneuropathy is important. One study suggested that by ordering an exhaustive panel of tests in a group of patients with idiopathic polyneuropathy, an explanation could be reached in a very high percentage.[27] For patients with rapidly progressive polyneuropathy, seeking alternative explanations is always warranted. Still, there is a point of diminishing return when both physician and patient are forced to concede the absence of another treatable process.

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