

CLINICAL PRACTICE

Painful Sensory 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 authors' clinical recommendations.

A 67-year-old woman who had been in excellent health noticed the onset of burning pain in the left great toe two years before evaluation. The pain subsequently extended to involve both feet, from the toes to the heels, and was associated with numbness, tingling, and burning. The discomfort has become severe, is present throughout the day, and disrupts sleep. A physical examination reveals normal muscle strength, muscle-stretch reflexes, proprioception, and vibratory sensation; only pinprick sensation in the toes and feet is diminished. How should this patient be evaluated and treated?

THE CLINICAL PROBLEM

There are many causes of painful sensory neuropathy (Table 1). In one subtype referred to as "small-fiber painful sensory neuropathy," only the A- δ (small myelinated) and nociceptive C (unmyelinated) nerve fibers are affected. Studies indicate that this condition represents the most common type of painful sensory neuropathy in patients older than 50 years of age. It is vastly underrecognized, and in most cases, no cause can be found.¹⁻³ In another group of neuropathies associated with pain, the discomfort is caused in part by damage to small nerve fibers, but large nerve fibers (A- β and A- α nerve fibers) that are responsible for proprioception, vibratory sensation, muscle-stretch reflexes, and muscle strength are also affected. The distinction between the two subtypes of painful sensory neuropathies is not trivial, since the underlying cause is more likely to be identifiable when both large and small fibers are affected.¹ Irrespective of the subtype of neuropathy, the pain generated by damage to small nerve fibers is debilitating and responds poorly to treatment. Finding and treating the cause is the best long-term strategy but is not routinely possible, and even when it is possible, treatment may not begin to relieve pain for many months or longer.

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STRATEGIES AND EVIDENCE

INITIAL EVALUATION

Since neuropathy is not the only cause of pain in the feet, one must first determine whether the peripheral nerve is the source of discomfort. Typical symptoms of neuropathic pain related to small fibers include burning (the sensation that the feet are on fire), sharp pain (described as knife-like, jabbing, or pins and needles), shooting pain, and aching in the toes and feet (reflecting damage to the longest axons). Pain emanating from the peripheral nerves is indicated by the description of the feet as tingling, numb, or feeling tight, wooden, or dead. Peripheral-nerve pain is often exacerbated at night, but some patients describe pressure-induced pain with standing or walking. The history will help distinguish among problems associated with plantar fasciitis, arthritis, bursitis, tendonitis, and polymyalgia rheumatica.⁴ Lumbosacral radiculopathies (with or without spinal stenosis) are not dependent on nerve length and may be accompanied

Table 1. Primary Types of Painful Sensory Neuropathy.*

Type of Neuropathy	Predisposing Factors	Features on Examination	Laboratory Findings
Idiopathic small-fiber painful sensory neuropathy	Age >50 yr	Normal muscle-stretch reflexes Normal muscle strength Normal sensation of position and vibration Reduced pinprick sensation in lower extremities	Normal EMG and NCS Reduced sudomotor function Abnormal skin biopsy Normal blood tests
Diabetic peripheral neuropathy	Family history Obesity	Reduced muscle-stretch reflexes Reduced distal sensation May have orthostatic hypotension (rarely, may have findings similar to those in idiopathic small-fiber painful sensory neuropathy)	Abnormal EMG and NCS (rarely, normal EMG and NCS) 2-Hr glucose-tolerance test ≥ 200 mg/dl Fasting blood glucose concentration ≥ 126 mg/dl
Inherited neuropathies	Family history	Pes cavus or hammer toe Usually reduced muscle-stretch reflexes Reduced distal sensation	Abnormal EMG and NCS Normal blood tests
Peripheral neuropathy with connective-tissue disease	History of rheumatoid arthritis, systemic lupus erythematosus, mixed connective-tissue disease, Sjögren's syndrome, or symptoms of sicca syndrome	Reduced muscle-stretch reflexes Reduced distal sensation	Abnormal EMG and NCS Positive for antinuclear antibodies, extractable nuclear antigens, or rheumatoid factor
Peripheral-nerve vasculitis	Known systemic vasculitis (nonsystemic vasculitis may occur without systemic features)	Multifocal examination findings (may mimic polyneuropathy)	Abnormal EMG and NCS Blood-test abnormalities may include antineutrophilic cytoplasmic antibodies, antinuclear antibodies, rheumatoid factor, hepatitis C, cryoglobulins
MGUS neuropathy	Age >50 yr	Variable findings Reduced or normal reflexes Reduced distal sensation	Abnormal EMG and NCS (may be normal in rare cases) Monoclonal gammopathy
Paraneoplastic sensory neuropathy	Tobacco smoking, family history, asbestos exposure, occupational exposure to dyes, paints, printing rubber, textiles, or leather	Reduced muscle-stretch reflexes Reduced distal sensation	Abnormal EMG and NCS Anti-Hu antibodies
Familial amyloid polyneuropathy	Family history	Reduced muscle-stretch reflexes Sensory loss preferentially small-fiber Postural hypotension	Abnormal EMG and NCS NCS may show carpal tunnel syndrome
Acquired amyloid polyneuropathy	Known plasma-cell dyscrasia or monoclonal gammopathy	Reduced muscle-stretch reflexes Sensory loss preferentially small-fiber Postural hypotension	Abnormal EMG and NCS NCS may show carpal tunnel syndrome Monoclonal gammopathy

Table 1. (Continued.)			
Type of Neuropathy	Predisposing Factors	Features on Examination	Laboratory Findings
Neuropathy with renal failure	Known renal disease	Reduced muscle-stretch reflexes Variable sensory examination	Abnormal EMG and NCS Abnormal renal function
Hereditary sensory autonomic neuropathy	Family history, foot ulcers, painless injuries	Reduced muscle-stretch reflexes Variable sensory examination Pes cavus and hammer toe Foot ulcers	Abnormal EMG and NCS
Sarcoid polyneuropathy	Pulmonary sarcoidosis	Multiple mononeuropathy or features of polyneuropathy	Abnormal EMG and NCS Elevated angiotensin-converting enzyme Abnormal chest radiography
Arsenic neuropathy	Industrial exposure to pesticides, wood preservatives, copper smelting	Reduced muscle-stretch reflexes Loss of all types of sensation Usually some distal weakness Mees' lines	Abnormal EMG and NCS Elevated arsenic levels (in plasma, urine, nails, hair)
Fabry's disease	Onset before 20 yr of age Renal failure, stroke	Normal muscle-stretch reflexes Normal muscle strength Normal sensation of position and vibration Normal or reduced pinprick sensation in feet	Normal EMG and NCS Reduced levels of α -galactosidase A in serum, leukocytes, or tears
Celiac disease	Gastrointestinal symptoms	Variable features may be normal except for loss of distal pinprick sensation or loss of all types of sensation Reduced muscle-stretch reflexes	EMG and NCS may be normal or abnormal Positive serologic test for celiac disease (IgA anti-tissue transglutaminase and IgA endomysial antibodies)
HIV-related neuropathy	Homosexual activity, drug abuse, blood transfusions, treatment with antinucleosides	Variable features may be normal except for loss of distal pinprick sensation or loss of all types of sensation Reduced muscle-stretch reflexes	EMG and NCS usually abnormal HIV antibody

* EMG denotes electromyography, NCS nerve-conduction studies, MGUS monoclonal gammopathy of undetermined significance, and HIV human immunodeficiency virus.

by paraspinal muscle spasm and aggravated by activities (such as lifting). Pain in the toes, related to entrapment of the posterior tibial nerve at the tarsal tunnel (the space beneath the flexor retinaculum and behind the medial malleolus), may mimic painful sensory neuropathy.⁵ Nerve entrapment at the carpal tunnel accompanying painful sensory neuropathy may point to diabetes mellitus or amyloidosis.

In disorders with exclusive or predominant involvement of small nerve fibers, there is a dramatic mismatch between symptoms and observable neurologic deficits. In the typical small-fiber sensory neuropathy affecting patients older than 50 years of age,¹ there is an abnormal loss of pinprick sensation in the feet, which may extend centripetally to the level of the knees but rarely above the knees. The sensation of touch may also be diminished, whereas other types of sensation are preserved. In painful sensory neuropathies affecting both large and small fibers, there is reduced proprioception, loss of muscle-stretch reflexes, and muscle weakness, reflecting the loss of large fibers. Loss of vibratory sensation that is restricted to the toes can be a normal finding in the elderly but is abnormal if it extends to the ankles.

Two findings on physical examination may help distinguish the pain of tarsal tunnel syndrome from small-fiber neuropathy: Tinel's sign (tingling in the limb served by the nerve after percussion) over the tarsal tunnel and tenderness to palpation over the flexor retinaculum.⁵ A loss of sensation that is restricted to the medial aspect of the foot, sparing the heel, also points to tarsal tunnel syndrome.

The initial evaluation must include electromyography and nerve-conduction studies, unless the diagnosis is known (for example, in a patient with diabetes and known microvascular disease). Electrodiagnostic studies are useful in patients with painful sensory neuropathy for identifying a mononeuropathy (such as focal entrapment at the tarsal tunnel); differentiating multiple mononeuropathy (which is characteristic of peripheral-nerve vasculitis) from polyneuropathy (which is symmetric); and distinguishing axonal neuropathies (e.g., diabetic neuropathy) from demyelinating neuropathies.⁶ Normal studies are consistent with pure small-fiber neuropathy.

Laboratory evaluation should be guided by the results of electrodiagnostic testing (Fig. 1). If electrodiagnostic studies are normal, nonneuropathic causes of pain (including local inflammation, such as arthritis or plantar fasciitis, or central nervous

system causes, such as myelopathy) must be considered; further testing is warranted to establish the diagnosis of small-fiber neuropathy. The sudomotor-axon reflex test, which quantitates sweating, is a practical, highly specific, and sensitive method (sensitivity, approximately 80 percent) for documenting damage to small nerve fibers.⁷ Skin biopsies that demonstrate loss of intraepidermal nerve fibers represent an alternative method with slightly greater sensitivity for documenting small-fiber neuropathy: approximately 10 percent of patients with a normal sweat test will have abnormal skin biopsies.^{1,2} However, skin biopsies are not widely available, and the morphometric analysis is laborious. Quantitative sensory testing assesses small-fiber damage by measuring pain and temperature thresholds in the skin.³ Sensitivity and specificity are lower than those of skin biopsies or sudomotor testing,^{1,3} and performance depends on patients' cooperation and attention.⁸

TREATMENT OF PAINFUL NEUROPATHIES

Management of the neuropathy is guided by two principles: treatment of the underlying condition (which will not be discussed here) and strategies designed to relieve peripheral-nerve pain irrespective of cause.

PATHOPHYSIOLOGY OF PAINFUL NEUROPATHY

Pain is a protective response to tissue injury, but persistent pain is maladaptive. Pain can occur without provocation (be stimulus-independent, as with burning and paresthesias accompanying small-fiber neuropathies) or can be stimulus-evoked (for example, hyperalgesia in response to noxious stimuli or allodynia induced by non-noxious stimuli).

The cause of the nerve damage does not dictate the type of pain, and nonspecific therapies that are effective for one cause should also be applicable to others. Figure 2 summarizes the pathophysiology of pain from peripheral neuropathy and suggests potential pharmacologic strategies for treatment.

SUMMARY OF CLINICAL TRIALS

Judging the efficacy of treatments for painful neuropathies is challenging. Reports can be misleading, because results for a given drug can be statistically significant despite the fact that good or excellent pain relief has been achieved in relatively few patients. In addition, patients expect substantial pain relief with relatively few side effects. Failure to meet these expectations leads to disappointment.

We summarize here the results of randomized,

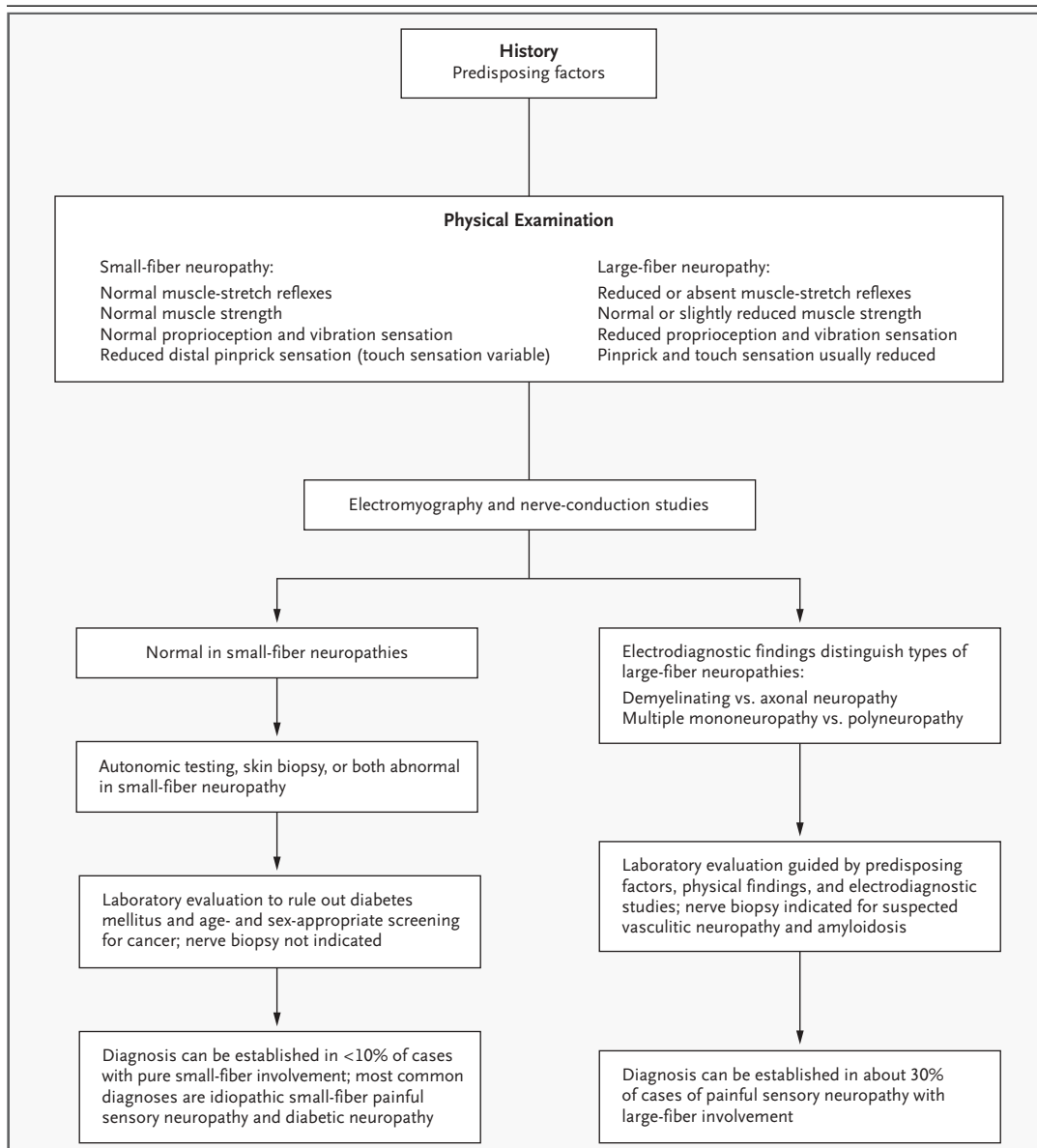


Figure 1. Algorithm for the Evaluation of Painful Sensory Neuropathy.

The physical findings are used to distinguish between small-fiber and large-fiber neuropathy. If electrodiagnostic studies and autonomic testing or skin biopsy suggest pure small-fiber neuropathy, the plasma glucose level should be assessed while the patient is fasting; if it or a random measurement of glucose is not diagnostic of diabetes mellitus, a two-hour glucose-tolerance test should be performed. Paraneoplastic neuropathies rarely affect exclusively small fibers, but a test for anti-Hu antibodies should be obtained if there is a history of smoking, and age-related screening for cancer should be performed. Screening for Fabry's disease (α -galactosidase A in serum, leukocytes, or tears) is indicated in patients with an onset of symptoms before 20 years of age. Large-fiber neuropathy includes loss of large and small fibers. The laboratory evaluation for large-fiber neuropathy depends on the results of the electrodiagnostic studies. In patients with multiple mononeuropathies, screening for vasculitis and connective-tissue disease is appropriate (evaluation of the erythrocyte sedimentation rate and evaluation for antineutrophil cytoplasmic antibodies [with a cytoplasmic or perinuclear pattern of staining], hepatitis C, cryoglobulins, antinuclear antibodies, rheumatoid factor, and extractable nuclear antigens). Associated ataxia suggests Sjögren's syndrome or cancer, and testing for antinuclear antibodies and antibodies against SS-A, SS-B, and Hu should be performed. Older patients should have serum electrophoresis with immunofixation to rule out monoclonal gammopathy. If the workup is unrevealing and the fasting and randomly measured glucose levels are normal, a two-hour glucose-tolerance test is warranted. Screening of urine or serum for heavy metals is appropriate only if there has been industrial exposure or if there are findings on physical examination that suggest arsenic poisoning (Mees' lines).

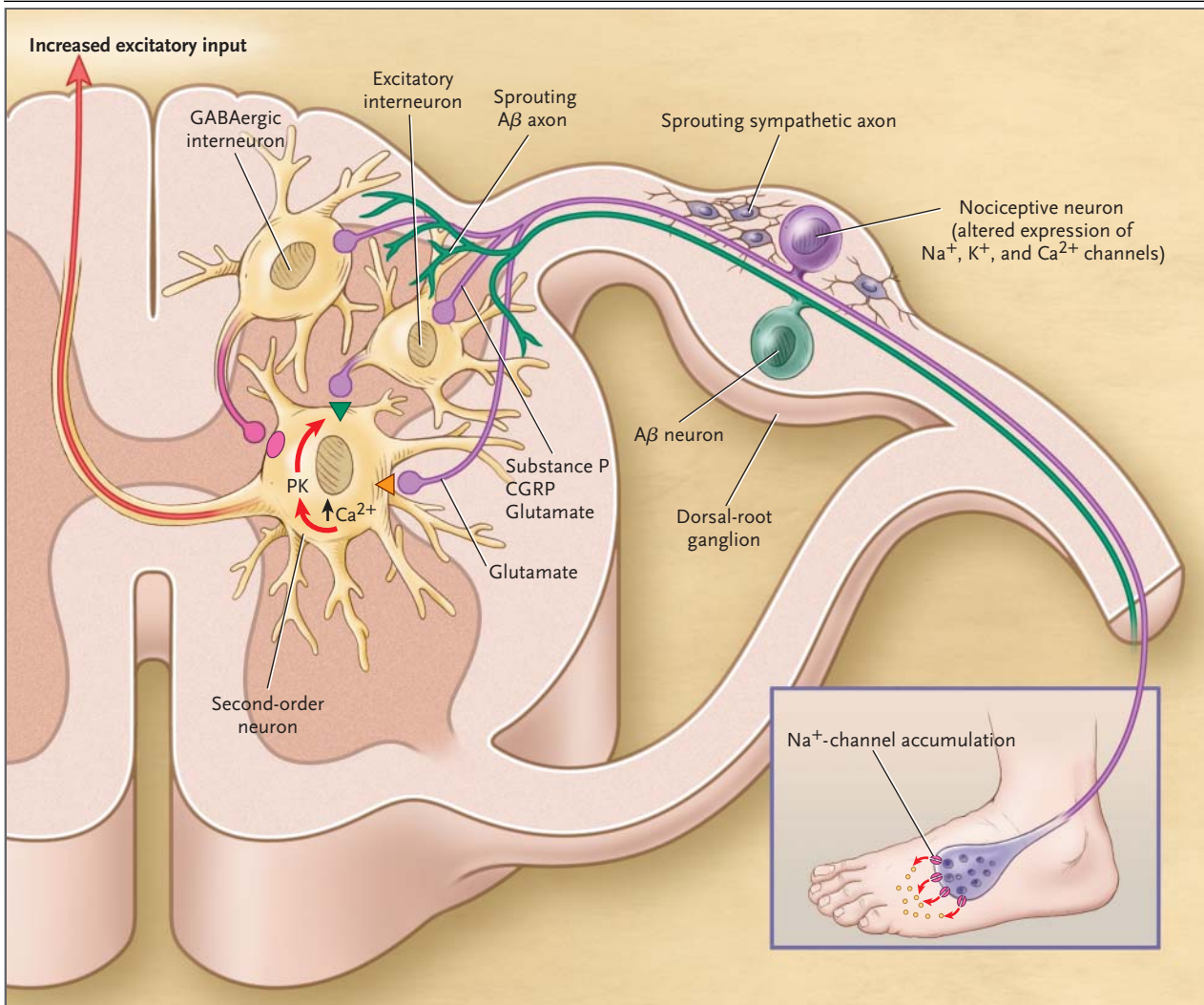


Figure 2. Pathways Leading to Pain in Peripheral Neuropathy and Potential Sites of Pharmacologic Interventions.

After peripheral-nerve injury, a cascade of events up-regulates expression of membrane channels in the nociceptive neurons of the dorsal-root ganglion. Potential inhibitors of the sodium channel include tricyclic antidepressants, carbamazepine, oxcarbazepine, phenytoin, topiramate, lamotrigine, mexiletine, and lidocaine; a potential inhibitor of the potassium channel is gabapentin; and potential inhibitors of the calcium channel are gabapentin and lamotrigine. Sprouting sympathetic axons form interwoven baskets around cell bodies, causing exaggerated pain, which may be inhibited by tricyclic antidepressants, bupropion, or venlafaxine. At the site of peripheral-nerve damage (inset), sodium channels (which may be inhibited by the agents listed above) spread along the axon, resulting in ectopic neural discharges. Projections from nociceptive neurons in the dorsal-root ganglion to spinal interneurons enhance excitation by release of substance P, calcitonin gene-related protein (CGRP), and glutamate. The second-order neuron in the spinal cord, which is normally activated by glutamate through the α -amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) receptors (orange triangle), is induced to fire spontaneously (central sensitization) through activation of the *N*-methyl-D-aspartate (NMDA) receptor (green triangle). Excitation of the second-order neuron leads to an increase in intracellular calcium and activation of protein kinases (PK) that phosphorylate intracellular proteins such as NMDA receptors. Potential inhibitors include gabapentin, lamotrigine, oxcarbazepine, topiramate, dextromethorphan, tramadol, opiates, selective serotonin-reuptake inhibitors, and venlafaxine. Dynorphin, an opioid neuropeptide whose levels are elevated in chronic pain syndromes, can also contribute to ectopic excitation of the second-order neuron through activation of NMDA receptors. There is loss of inhibition of second-order neurons by reduction of input from γ -aminobutyric acid (GABA) through down-regulation of GABA_A receptors (pink oval). Sprouts of central terminals of nonnociceptive neurons in the dorsal-root ganglion ($A\beta$ neurons) express nociceptive substances (potentially inhibited by levodopa) in the dorsal horn, contributing to hyperalgesia and tactile allodynia.

controlled trials of agents for painful sensory neuropathy. Although the “number needed to treat” (an estimate of the total number of patients who would need to be treated in order to achieve 50 percent pain relief in one patient) has merits, because it provides information on both the rate and the magnitude of response,⁹ it also has limitations, especially when it is used to compare studies performed in different populations of patients or for different durations. Thus, we provide the size of the treated cohort and the percentage of cohort members who have a response to treatment.

ANTIDEPRESSANT DRUGS

Tricyclic Antidepressants

No agents have been as thoroughly studied for relief of neuropathic pain as the tricyclic antidepressants.¹⁰ These drugs block reuptake of serotonin and noradrenaline and presumably relieve pain by inhibition of the sodium channel. Both spontaneous pain and hyperalgesia respond to tricyclic agents. Approximately 300 subjects with diabetic neuropathy have participated in controlled trials of various tricyclic agents. The accumulative efficacy suggests that about one third of patients achieve a 50 percent reduction in neuropathic pain.¹¹⁻¹³ Responses are often insufficient in clinical practice, and benefits are sometimes outweighed by side effects, especially among the elderly (Table 2).

Selective Serotonin-Reuptake Inhibitors

Selective serotonin-reuptake inhibitors differ from tricyclic antidepressants in that they selectively block serotonin reuptake. Clinical trials of these agents (which have involved fewer than 100 patients overall) suggest that their efficacy is lower than that of tricyclic agents.¹⁴⁻¹⁶ Paroxetine reduces the pain of diabetic neuropathy better than placebo but was not as effective as the tricyclic antidepressant imipramine in a head-to-head comparison.¹⁴ Citalopram diminishes neuropathic pain with an efficacy equal to that of paroxetine,¹⁵ whereas fluoxetine showed no benefit in diabetic neuropathy.¹⁶

Other Antidepressants

Venlafaxine has fewer side effects than typical tricyclic antidepressants because of reduced binding to muscarinic, histamine, and α_1 -adrenergic receptors; one small randomized study suggested that the drug had benefit in patients with painful sensory neuropathy related to cancer.¹⁷ Bupropion, a second-generation, specific inhibitor of neuronal nor-

epinephrine reuptake, diminished neuropathic pain by about 30 percent in a cohort of 41 subjects with neuropathy from multiple causes who were treated for six weeks.¹⁸

ANTICONVULSANTS

Carbamazepine

Carbamazepine stabilizes membranes by inhibiting sodium channels. Although it is effective for trigeminal neuralgia, data with regard to painful peripheral neuropathy are limited. One placebo-controlled trial involving 30 subjects¹⁹ suggested a benefit in diabetic neuropathy equivalent to that of tricyclic antidepressants. In practice, intolerance to the side effects of carbamazepine limits its use, especially in the elderly. Oxcarbazepine, a keto-acid analogue of carbamazepine, is better tolerated. Data on the drug's efficacy for painful sensory neuropathy are not available, but its efficacy for trigeminal neuralgia is similar to that of carbamazepine.²⁰

Phenytoin

Phenytoin, which also blocks sodium channels, is rarely used as first-line therapy for neuropathic pain, since it has inconsistent effectiveness in patients with painful diabetic neuropathy.^{21,22} However, possible benefit was suggested by a recent small study reporting a reduction in pain due to neuropathy from various causes after a single intravenous infusion of phenytoin.²³

Gabapentin

Gabapentin was designed as a γ -aminobutyric-acid agonist, but its precise mechanism of action remains uncertain. Two clinical trials demonstrated pain relief in patients with diabetic neuropathy,^{24,25} whereas a third trial did not.²⁶ When compared head-to-head with amitriptyline, gabapentin had equal efficacy.²⁵ Reduction in neuropathic pain required doses higher than 1600 mg per day — an important consideration, since many patients are given doses that are too small. The side-effect profile of gabapentin is more favorable than those of many other agents, but nearly 25 percent of patients report dizziness, and 30 percent report sedation.

Lamotrigine

Lamotrigine (at a dose of 400 to 600 mg per day) resulted in moderate pain relief with minimal side effects in a single small trial involving patients with diabetic or human immunodeficiency virus (HIV)-associated neuropathy.²⁷

Table 2. Drug Treatment of Painful Sensory Neuropathy.*

Drug	Starting Dose and Increase	Usual Range of Doses	Drug Interactions	Side Effects
Antidepressants				
Tricyclic antidepressants†				
Amitriptyline	10 mg/day; increase by 10 mg/wk	75–150 mg/day	Monoamine oxidase inhibitors contraindicated with all tricyclic agents	Common to all tricyclic agents: dry mouth, drowsiness, dizziness, constipation, urinary retention, blurred vision, confusion, disorientation, increased appetite, tachycardia
Nortriptyline	10 mg/day; increase by 10 mg/wk	75–150 mg/day		
Desipramine	25 mg at bedtime; increase by 25 mg every 5–7 days	75–200 mg/day		
SSRIs				
Paroxetine	10 mg/day; increase by 10 mg/wk	20–60 mg/day	Monoamine oxidase inhibitors contraindicated; antagonizes codeines and hydrocodones; potentiates effects of bupropion, phenytoin, tricyclic agents; increases risk of serotonin syndrome with other SSRIs, tramadol, venlafaxine	Sweating, nausea, anorexia, diarrhea, dizziness, dry mouth, nervousness, delayed ejaculation, impotence, decreased libido, constipation, tremor, headache, somnolence, insomnia, tremor, blurred vision, flushing, hyponatremia, serotonin syndrome, extrapyramidal symptoms
Citalopram	10 mg/day; increase by 10 mg/wk	20–60 mg/day	Same as paroxetine	Same as paroxetine
Other antidepressants				
Venlafaxine	37.5 mg/day; increase by 37.5 mg/wk	150–375 mg/day	Monoamine oxidase inhibitors contraindicated; potentiates risk of serotonin syndrome with SSRIs; potentiates central nervous system depression with tramadol and tricyclic agents	Headache, nausea, somnolence, weight loss, anorexia, constipation, diarrhea, dizziness, dry mouth, insomnia, weakness, sweating, delayed ejaculation, hypertension, seizures
Bupropion	100 mg/day; increase by 100 mg/wk	200–400 mg/day	Monoamine oxidase inhibitors contraindicated; antagonized by phenytoin; potentiates effects of SSRIs and tricyclic agents	Agitation, dry mouth, insomnia, tachycardia, headache, dizziness, sweating, nausea, vomiting, constipation, anorexia, tremor, sedation, weight loss, blurred vision, confusion, seizures (risk increased by a factor of 10 with doses >450 mg/day), cardiac arrhythmia, rhabdomyolysis
Anticonvulsants				
Carbamazepine	200 mg/day; increase by 200 mg/wk	1000–1600 mg/day	Monoamine oxidase inhibitors contraindicated; antagonized by phenytoin; antagonizes lamotrigine, methadone, phenytoin, and tramadol; potentiates risk of central nervous system depression with tricyclic agents	Dizziness, drowsiness, ataxia, nausea, vomiting, blurred vision, confusion, weakness, fatigue, nystagmus, aplastic anemia

Table 2. (Continued.)

Drug	Starting Dose and Increase	Usual Range of Doses	Drug Interactions	Side Effects
Oxcarbazepine†	300 mg/day; increase by 300 mg/wk	1200–2400 mg/day	Antagonized by carbamazepine, phenytoin, lamotrigine; potentiates effects of phenytoin and risk of central nervous system depression with tricyclic agents	Dizziness, somnolence, fatigue, nausea, vomiting, ataxia, abdominal pain, tremor, dyspepsia, nystagmus, hyponatremia, confusion, leukopenia, thrombocytopenia
Phenytoin	100 mg/day; increase by 100 mg/wk	300–500 mg/day	Antagonized by bupropion, carbamazepine, fentanyl, lamotrigine, tramadol; antagonizes tricyclic agents; effects potentiated by oxcarbazepine, paroxetine, and SSRIs	Nausea, vomiting, nystagmus, ataxia, dizziness, confusion, blurred vision, somnolence, constipation, headache, insomnia, gum hypertrophy, osteomalacia, lymphadenopathy, hepatotoxicity, systemic lupus erythematosus, blood dyscrasias, hypertrichosis
Gabapentin§	900 mg/day; increase by 300 mg/wk	1800–3600 mg/day	Antacids may decrease absorption (separate by 2 hr); potentiates effects of other central nervous system depressants	Somnolence, dizziness, ataxia, fatigue, nystagmus, diplopia, blurred vision, tremor, dyspepsia, dry mouth, nausea, vomiting, constipation, leukopenia
Lamotrigine	50 mg/day; increase by 100 mg biweekly	200–600 mg/day	Antagonized by carbamazepine, oxcarbazepine, phenytoin	Dizziness, ataxia, somnolence, headache, diplopia, blurred vision, nausea, vomiting, fatigue, confusion, impaired memory, nystagmus, aplastic anemia
Clonazepam¶	0.5 mg/day; increase by 0.5 mg every 3–5 days	5–20 mg/day	Potentiates central nervous system depression with carbamazepine, oxcarbazepine, phenytoin, tramadol, tricyclic agents, venlafaxine	Drowsiness, ataxia, confusion, dry mouth, memory loss, blood dyscrasias
Topiramate	25 mg/day; increase by 25 mg/wk	400–800 mg/day	Antagonized by phenytoin, carbamazepine; potentiates effects of phenytoin	Somnolence, dizziness, ataxia, memory loss, psychomotor slowing, language disturbance, confusion, nystagmus, fatigue, paresthesias, tremor, abdominal pain, anxiety

Table 2. (Continued.)

Drug	Starting Dose and Increase	Usual Range of Doses	Drug Interactions	Side Effects
Antiarrhythmic drugs				
Mexiletine	150 mg/day; increase by 150 mg/wk	600–1200 mg/day	May cause cardiac arrhythmia with transdermal lidocaine	Dyspepsia, dizziness, tremor, ataxia, insomnia, diarrhea, nervousness, headache, tinnitus, hepatotoxicity, arrhythmia
Nonnarcotic analgesics				
Tramadol	150 mg/day; increase by 50 mg/wk	200–400 mg/day	Increased risk of serotonin syndrome with monoamine oxidase inhibitors, SSRIs, tricyclic agents, venlafazine; antagonized by carbamazepine, phenytoin; effects potentiated by paroxetine, tricyclic agents	Nausea, constipation, somnolence, headache, dry mouth, seizures, confusion, tremor, anorexia, urinary retention
Narcotic analgesics				
Oxycodone	20 mg every 12 hr; increase by 10 mg/wk	40–160 mg/day	Increased risk of central nervous system depression with tramadol, tricyclic agents, clonazepam	Somnolence, dizziness, constipation, nausea, vomiting, headache, dry mouth, sweating, respiratory depression, hypotension
Morphine (oral)**	15–30 mg every 8 hr	90–360 mg/day	Increased risk of central nervous system depression with tramadol, tricyclic agents, clonazepam	Sedation, dizziness, constipation, urinary retention, respiratory depression, hypotension
Topical anesthetics				
5% Lidocaine patch	Apply patch to painful area	3 patches for 12 hr	Potentiates cardiac toxicity from mexiletine	Localized erythema, burning, edema

* SSRI denotes selective serotonin-reuptake inhibitor.
 † Tricyclic antidepressants are effective but poorly tolerated in elderly patients. It is difficult to reach the doses that are required for adequate pain relief.
 ‡ Oxcarbazepine is better tolerated than carbamazepine and is often helpful to add to a multidrug regimen.
 § Gabapentin is a good choice for initial treatment, but adequate treatment usually requires 1800 mg per day or more.
 ¶ Clonazepam is useful in multidrug regimens because of its antianxiety properties.
 || Tramadol is well tolerated and is useful in multidrug regimens.
 **Oral morphine may be necessary for refractory painful sensory neuropathy.

ANTIARRHYTHMIC DRUGS*Mexiletine*

Intravenous lidocaine produced moderate reductions in pain in patients with diabetic neuropathy, but this method of administration is impractical.²⁸ There have been inconsistent results with the use of mexiletine, the oral analogue of lidocaine. Two studies in patients with diabetic neuropathy showed a beneficial effect^{29,30}; another demonstrated efficacy with regard to secondary outcomes but not with regard to global pain relief³¹; and a fourth trial in patients with diabetic neuropathy,³² as well as a trial in patients with HIV-associated neuropathy,^{33,34} failed to demonstrate benefit.

N-METHYL-D-ASPARTATE GLUTAMATE ANTAGONISTS

Very few controlled studies, involving only a small number of patients with diabetic neuropathy, have addressed the efficacy of N-methyl-D-aspartate glutamate antagonists (e.g., dextromethorphan) in painful sensory neuropathy.^{35,36} The studies suggest a beneficial effect in selected patients who can tolerate the sedation, but there are numerous side effects, including impairment of memory, ataxia, and motor incoordination.

NARCOTIC AND NONNARCOTIC ANALGESICS

Clinicians whose patients have refractory painful sensory neuropathy may feel pressure to use opioid analgesics, although there is concern about the potential for addiction. Oxycodone has been shown to reduce pain in postherpetic neuralgia,³⁷ but data are sparse regarding the effects of opioid analgesics on painful sensory neuropathy. An article in this issue of the *Journal*³⁸ demonstrates that the opioid agonist levorphanol reduced neuropathic pain (including pain in 32 patients with sensory neuropathy) by 36 percent, at an average daily dose of 8.9 mg. However, side effects were frequent — including itching, mood changes, weakness, and confusion. These side effects were less common when lower doses were used, but lower doses were less effective. Efficacy was lower for painful sensory neuropathy than for postherpetic neuralgia, spinal cord injury, or multiple sclerosis, underscoring the refractory nature of pain from damage to peripheral nerves.

Tramadol is a drug that shares properties with opioid analgesics but demonstrates low-affinity binding to μ -opioid receptors. It is well tolerated and

less likely than other opioid agonists to cause dependence and lead to abuse. Data from trials involving approximately 100 patients with painful sensory neuropathy related to diabetes or other causes^{39,40} suggest that the efficacy of tramadol is similar to that of tricyclic antidepressants or levorphanol. Nausea and constipation occur in about 20 percent of patients, and headache and somnolence occur in about 15 percent, but generally the drug is well tolerated.

LEVODOPA

Dopamine agonists can modify pain, presumably through the inhibition of input to segments of the spinal cord. A single study demonstrated a reduction of pain in a small cohort of subjects with diabetic neuropathy.⁴¹

TOPICAL AGENTS*Capsaicin*

Capsaicin depletes substance P from sensory nerves in the skin, but outcomes in patients with neuropathy have been inconsistent. At least three studies involving more than 250 subjects in total have shown moderate efficacy in diabetic neuropathy.⁴²⁻⁴⁴ In contrast, no pain relief was achieved in patients with chronic painful distal neuropathy or HIV-associated neuropathy.^{45,46} In practice, the effects of capsaicin are inconsistent, and a disincentive to use it is that pain is exacerbated when it is first administered.

Topical Lidocaine

Topically applied lidocaine exerts effects by reducing ectopic neural discharges in superficial nerves. Patches containing 5 percent lidocaine have been approved by the Food and Drug Administration for postherpetic neuralgia. In peripheral neuropathies, the pain extends over wider areas, which limits the usefulness of such patches, but some patients may benefit from patches trimmed to match a specific area where there is excessive pain.

ALTERNATIVE THERAPIES

In the only controlled study of acupuncture for peripheral-nerve pain related to HIV, the placement of needles in traditional sites resulted in no greater relief of pain than the use of sham sites.⁴⁷ Although transcutaneous stimulation of nerves showed short-term benefit among subjects with diabetic neuropathy,^{48,49} it has not been effective in practice.

AREAS OF UNCERTAINTY

At best, current therapies for painful sensory neuropathy result in a 30 to 50 percent reduction in pain, and such a reduction rarely meets patients' expectations. Randomized trials are warranted for established anticonvulsant agents (such as valproic acid and clonazepam) as well as the newer anticonvulsant agents⁴⁹ (such as oxcarbazepine, tiagabine,⁵⁰ topiramate, pregabalin, and vigabatrin). The antidepressants venlafaxine and bupropion also merit additional study.

It remains uncertain whether adequate pain relief can be achieved with a multidrug strategy, particularly with the use of pharmacologic agents targeted at more than one site in the pain pathway.

GUIDELINES

There are no guidelines available from professional organizations for the treatment of painful sensory neuropathy.

SUMMARY AND CONCLUSIONS

Treatment of painful sensory neuropathy presents enormous challenges and is currently inadequate. The evaluation of patients with this condition does not necessarily require a neurologist, but it does require clinicians experienced with electromyography and autonomic nervous system testing (Fig. 1). Education of the patient is critical in order to define realistic goals and expectations. Patients must understand that complete relief of pain is unlikely to be achieved with our current armamentarium of agents (Table 2). A diary of side effects and perceived benefits should be maintained by patients and shared with the physician so that drug regi-

mens can be adjusted as necessary. Because monotherapy generally results in a 30 to 50 percent reduction in pain at best, a multidrug regimen may be helpful. Although data are lacking to support the use of combination therapy, a logical strategy is to use combinations of drugs that target different sites in the pain pathway (Fig. 2).

There is no one set approach to the treatment of patients with painful sensory neuropathy such as the patient described in the vignette. We consider gabapentin to be a reasonable first choice on the basis of clinical trials showing efficacy and its relatively favorable side-effect profile. A starting dose of 900 mg per day is well tolerated, but in all probability, higher doses will be necessary. The dose should be slowly increased to at least 1600 mg per day and can be as high as 3600 mg per day, if necessary. If pain relief is inadequate at the maximal dose, then another drug should be added and its dose slowly increased. Tramadol has shown efficacy in clinical trials and is also well tolerated; we would therefore add this agent in patients who have inadequate pain relief with gabapentin alone and would substitute tramadol for gabapentin in patients who are intolerant of gabapentin. If pain persists, any of several drugs can be considered as additions to the treatment regimen (Table 2). Tricyclic antidepressants have been the best studied, but they are not well tolerated. In practice, we have found oxcarbazepine to be better tolerated than tricyclic agents (Table 2). If a three-drug regimen is ineffective, it is reasonable to substitute a narcotic analgesic. Oxycodone or levorphanol can be used, but we prefer sustained-release oral morphine. Methadone treatment may also be appropriate for some patients. However, even opioid agonists are unlikely to provide complete pain relief in patients with painful sensory neuropathy.

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