ABSTRACT: Small-fiber neuropathy is a common disorder. It is often “idiopathic” and typically presents with painful feet in patients over the age of 60. Autoimmune mechanisms are often suspected, but rarely identified. Known causes of small-fiber neuropathy include diabetes mellitus, amyloidosis, toxins, and inherited sensory and autonomic neuropathies. Occasionally, small-fiber neuropathy is diffuse or multifocal. Depending on the type of small-fiber neuropathy, autonomic dysfunction can be significant or subclinical. Diagnosis is made on the basis of the clinical features, normal nerve conduction studies, and abnormal specialized tests of small-fiber function. These specialized studies include assessment of epidermal nerve fiber density as well as sudomotor, quantitative sensory, and cardiovagal testing. The sensitivities of these tests range from 59–88%. Each has certain advantages and disadvantages, and the tests may be complementary. Unless an underlying disease is identified, treatment is usually directed toward alleviation of neuropathic pain.


SMALL-FIBER NEUROPATHY

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Small-fiber neuropathy is a commonly encountered disorder.66,73 It is particularly troublesome to patients when it is painful. It is frustrating to clinicians because of difficulties both in proving the diagnosis and in treatment. Fortunately, over the past 15 years, new electrophysiologic and histologic methods have led to improvement in diagnosis, and these methods are becoming more widely available. It is likely that advances in treatment will follow, as it is now easier to design small-fiber neuropathy treatment trials that quantitate small-fiber dysfunction. This review will summarize the major features of small-fiber neuropathy and emphasize the newer diagnostic methods. Because some sensory or sensorimotor polyneuropathies begin with small-fiber involvement and evolve to substantially affect large fibers, this review will also discuss sensory neuropathies with this evolutionary pattern.

Abbreviations: EBV, Epstein-Barr virus; EMG, electromyographic; HSAN, hereditary sensory autonomic neuropathy; JND, just noticeable difference; PRMMA, proximal myotonic myopathy; QART, quantitative sudomotor axon reflex test; QST, quantitative sensory testing

Key words: amyloidosis; autonomic neuropathy; diabetic neuropathy; peripheral nervous system diseases; peripheral neuropathy; sensory neuropathy; small-fiber neuropathy

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DEFINITION

Small-fiber neuropathy is a subtype of sensory neuropathy. It has a small number of known causes and requires special diagnostic investigation; thus, it is useful to separate this entity from other forms of neuropathy. Small-fiber neuropathy can be defined physiologically or anatomically as a sensory neuropathy that exclusively or predominately affects small fibers and their functions. Small somatic or autonomic fibers, or both, may be involved. Because many patients with predominantly small-fiber neuropathy have mild, often subclinical large-fiber involvement, a practical working definition allows the presence of mild large-fiber dysfunction. There is no agreement in the literature regarding the amount of large-fiber dysfunction that can coexist and still allow the diagnosis of small-fiber neuropathy.

Stewart et al. defined small-fiber neuropathy as a peripheral neuropathy manifest by paresthesias (abnormal sensations) with findings of small-fiber dysfunction on neurologic examination.97 The paresthesias are typically painful. Included are patients with loss of vibratory sensation at the toes, absent ankle reflexes, or both. However, more significant indicators of large-fiber dysfunction are exclusionary, including decreased proprioception at the toes, vibratory loss at or above the ankles, any distal wasting or weakness, generalized areflexia, or abnormal
findings on routine nerve conduction studies or needle electromyography. This definition is useful for clinicians and for inclusion and exclusion criteria for small-fiber neuropathy for research purposes. There is one caveat, however. As discussed later, some patients with paresthesias and electrophysiologic or histologic features of small-fiber neuropathy have an essentially normal neurologic examination. Thus, the first part of the definition can be restated as "small-fiber neuropathy is a sensory neuropathy manifest by paresthesias that are typically painful, along with abnormal findings of small-fiber function on at least one of the following: neurologic examination, specialized electrodiagnostic testing, or pathologic studies."

ANATOMY

There is a relative abundance of small fibers in peripheral nerves. In most somatic nerves, unmyelinated axon myelinated axons fourfold. Of the myelinated axons, 32 to 45% are small (<7 μm diameter). Most unmyelinated axon diameters measure 1.0 to 1.6 μm. There is a significant variation in unmyelinated fiber densities, ranging between 19,000 and 65,000/mm² of endoneurium. The physiologic functions performed by small somatic fibers include warm perception which is mediated by type C unmyelinated fibers. These fibers also play a minor role in cold thermoreception. Their conduction velocity is less than 2 m/s in the monkey. In addition, polymodal nociceptors on type C pain fibers respond to pressure and some chemical stimuli in addition to heat pain. Type Aδ are small myelinated fibers that are the main afferents for cold perception, and they also play a role in cutaneous nociception. They conduct at about 20 m/s.

Autonomic fibers have multiple functions. Preganglionic sympathetic and parasympathetic cholinergic efferent fibers are myelinated with diameters ranging from 1.5 to 4.7 μm. Postganglionic fibers are unmyelinated. Nonsudomotor, postganglionic sympathetic fibers are adrenergic. Afferents originate from many sources, including arterial baroreceptors, cardiac mechanoreceptors, the viscera and urogenital system, and pulmonary stretch receptors. Sudomotor fibers innervating sweat glands are cholinergic, postganglionic, sympathetic, and unmyelinated. They travel with other peripheral nerves. Their preganglionic fibers originate in the spinal cord interstitial cell column, exit in the white rami, and synapse in the paravertebral sympathetic ganglia.

CLINICAL FEATURES OF SMALL-FIBER NEUROPATHY

Patients typically present with positive sensory symptoms, including tingling, burning, pricking, shooting pain, or aching. The pain is often worse at night and may interfere with sleep. Allodynia and cramps may also occur. Although common, pain is not synonymous with small-fiber dysfunction. Pain also occurs with large-fiber disorders, perhaps related to the rate of axonal degeneration. Furthermore, pain may not be a feature of small-fiber neuropathy. Patients may also have negative symptoms, including numbness, "tightness," and "coldness." Symptoms are usually distal and "length-dependent," but they are sometimes patchy or diffuse. Subclinical small-fiber neuropathy sometimes presents with late-onset restless legs syndrome.

Regarding autonomic symptoms, patients occasionally have increased or decreased sweating. Facial flushing, skin discoloration, dry eyes and mouth, and changes in skin temperature can occur in less than half. Erectile dysfunction occurs in up to 40% of males. Symptoms of orthostatic hypotension or gastrointestinal dysmotility are uncommon except in disorders such as amyloidosis and diabetes.

The clinical findings often include a reduction in thermal and pain sensitivity in association with normal strength, proprioception, and tendon reflexes. Vibration is usually normal, although patients are "allowed"—by definition—to have some vibratory loss at the great toes, consistent with mild large-fiber involvement. In many patients, abnormal clinical findings are minimal or nonexistent.

TESTING FOR SMALL-FIBER NEUROPATHY

Nerve Conduction Studies. As routine nerve conduction studies assess large-fiber function, they are generally normal. Of course, elderly patients who lack sural sensory responses can still be diagnosed with small-fiber neuropathy. Oh et al. also found evidence of axon loss in plantar nerves via near-nerve needle recordings in 65 of 100 patients with sensory neuropathy. These patients had normal sural sensory responses. This finding underscores the observation of some large-fiber loss in many patients with predominantly small-fiber neuropathy. However, a confounding feature of the study was the presence of proprioceptive dysfunction in 45 of 100 patients, signifying more large-fiber loss than is typically expected.

Patients with both the clinical features of small-
fiber neuropathy and normal nerve conduction studies should be considered to have small-fiber neuropathy until proven otherwise. The possible methods of establishing the diagnosis of small-fiber dysfunction follow.

**Sympathetic Skin Response.** The sympathetic skin response is an older, widely available, inexpensive method of assessing small-fiber sudomotor function. It is a reflex change in the sweat-related skin electrical potential elicited by various unexpected, "adrenergic" stimuli such as an electric shock to a somatic nerve. A major advantage is that it is measured on routine electromyographic (EMG) equipment.\(^8\) This reflex arc includes central autonomic connections.

Although the sensitivity of the sympathetic skin response in small-fiber neuropathy is uncertain, it is probably low. Evans et al.\(^26\) concluded that the sympathetic skin response might be useful even in the absence of overt autonomic symptoms, but only 10% of 54 patients with suspected small-fiber neuropathy had an abnormal sympathetic skin response. Other tests of small-fiber function were not performed in order to determine the true incidence of neuropathy in these patients. Further study is required to determine the true sensitivity of the sympathetic skin response in small-fiber neuropathy. Conversely, the sympathetic skin response may correlate with the quantitative sudomotor axon reflex test (QSART) in advanced diabetic neuropathy,\(^58\) but QSART is probably better than the sympathetic skin response in detecting small-fiber neuropathy.

The specificity of the sympathetic skin response for small-fiber dysfunction is probably also low, and the responses are not easily quantitated. The responses habituate and amplitudes decline. A study of 337 diabetics, with and without peripheral neuropathy, and 38 control subjects found that an absent sympathetic skin response was associated with neuropathy and the duration of diabetes, but it did not correlate with symptoms of small-fiber sensory or autonomic dysfunction. Furthermore, the sympathetic skin response correlated more strongly with vibration perception.\(^12\) In another study of 53 patients with peripheral neuropathies and 30 normal subjects, the sympathetic skin response did not correlate with autonomic symptoms. The amplitudes varied from test to test in the same subject.\(^57\)

Last, there may be a limited role for the sympathetic skin response in differentiating certain causes of mixed small- and large-fiber sensory neuropathy. In a study of patients with hereditary sensory and autonomic neuropathy (HSAN) or familial amyloid polyneuropathy, the foot sympathetic skin response was preserved in HSAN patients, whereas the median sensory responses were significantly impaired;\(^88\) by contrast, the foot sympathetic skin response was often absent, and median sensory responses were frequently abnormal in patients with familial amyloid polyneuropathy. The sympathetic skin response may also be useful in differentiating HSAN types III and IV. In HSAN-III, the sympathetic skin response may be preserved, whereas it is absent in HSAN-IV.\(^35\)

**Quantitative Sensory Testing.** Quantitative sensory testing (QST) has been reviewed previously in this journal.\(^105\) It has become an important tool in assessing the function of small as well as large sensory fiber functions. It is commonly used for serial measurements in neuropathy treatment trials and for diagnosis of small-fiber neuropathy. Small caliber fibers are assessed by measuring temperature thresholds, and large fibers by vibratory thresholds. Cooling may be a more accurate measure than warming due to a low density of warm receptors in some normals.\(^33\) The threshold at which warming causes pain may also be assessed.

A number of commercially produced devices are available. These devices have been used extensively, clinically and in research, and their sensitivities and specificities have been validated. Methodologies vary, but some commonly used measures are discussed here. In temperature testing, the skin base temperature is typically used, and the temperature is then increased or decreased at a rate of 4°C per second to the desired stimulus intensities. The maximum temperatures are 9°C for cooling and 45°C for warming.\(^35\) Stimulus steps are expressed in physical units or as the just noticeable difference (JND) at which a difference between stimulus intensities is typically perceived.\(^45,100\) Various algorithms can be used.\(^33\) The 4-2-1 stepping algorithm,\(^103\) for example, is illustrated in Figure 1. Sensory thresholds equal or greater than the 95th percentile for age are abnormal. In the "forced choice" algorithm, stimuli are presented in a series of individual trials in one of two time periods, and the computer selects the one in which the stimulus occurs. The patient notes whether a stimulus is perceived, and the threshold is determined. In heat-pain testing, the heat-pain probe warms the skin to 34°C and advances at 4°C intervals until a subjective 5 of 10 pain intensity is detected or a maximum temperature of 48°C is reached.

The utility of QST in diagnosing small-fiber neuropathy was noted by Jamal et al. who assessed heat, cold, and vibration thresholds in 25 patients with
suspected small-fiber neuropathy. The patients had normal nerve conduction studies. Thirteen were diabetics. Compared to normals, all had abnormal thermal thresholds whereas vibration thresholds were normal. More recent studies have not revealed such high sensitivity and specificity for QST in diagnosing small-fiber neuropathy. The studies usually assessed cooling thresholds. Table 1 compares QST to other modalities, and these comparisons will be discussed later. Sensitivities range from 60–83%.36,60,73,101 Further study is required to determine whether heat-pain testing is diagnostically more sensitive than cooling.

It should also be noted that studies often also reveal subclinical vibratory abnormalities in many patients with small-fiber neuropathy, and that central nervous system sensory dysfunction can also cause an abnormal QST. Lower sensitivities may be due to technical and patient factors. The testing is subjective. Patients must concentrate and be cooperative. There is also a relatively broad range of normality, so some patients with small-fiber dysfunction may be undetected. Technical variables include the equipment types. For example, Khalili et al. found that QST of heat-pain sensation was useful in detecting very early and reversible sensory deficits in a capsaicin model of small-fiber neuropathy when a smaller thermode (stimulating probe) was used.45

Regardless of the systems used for QST, it is paramount that testing is validated and standardized. Quality reference values must be available, and patients must be tested in the appropriate environment. Although the test is subjective, these safeguards help keep the sensitivity and reliability relatively high.22

Table 1. Comparisons of the diagnostic sensitivities of different diagnostic methods and epidermal nerve fiber assessment in small-fiber neuropathy.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Abnormal pin or cold sensation on clinical examination (%)</th>
<th>Abnormal QSART (%)</th>
<th>Abnormal QST (cool or heat pain) (%)</th>
<th>Reduced epidermal nerve fiber density (%)</th>
<th>Abnormal cardiovagal testing (%)</th>
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</table>

QSART, quantitative sudomotor axon reflex test; QST, quantitative sensory test.

*Cold or vibration.

QSART. The quantitative sudomotor axon reflex test (QSART) evaluates postganglionic sympathetic sudomotor function. Axons in the skin are activated locally through acetylcholine iontophoresis.55 Antidromic transmission to an axon branch point elicits action potentials that travel orthodromically to release acetylcholine from nerve terminals producing
sweat. The sweat is measured at the skin surface with a sudorometer. The sweat cells are generally placed over four locations (the lateral foot, distal leg, proximal leg, and forearm). Sweat output varies by sex and age. QSART requires specialized equipment that has been available at a small number of centers. However, a commercially-distributed system is now being produced. The equipment is moderately expensive, but it costs less than a sophisticated EMG machine.

QSART is a sensitive indicator of small-fiber neuropathy even in patients lacking symptoms of sudomotor dysfunction. Length-dependent reductions in sweat volume can often be identified. Occasionally excessive or persistent sweating occurs, usually in the forearm. The sensitivity of QSART in small-fiber neuropathy is 60–80% (Table 1). Interestingly, a sudorometer that measures sweat volumes on the thumb has been devised. It allows earlier detection of upper extremity distal-onset neuropathies. It would be useful to have such a device for the great toe.

QSART is objective, reproducible, only modestly time-consuming, and specific to peripheral nervous system dysfunction. It could be used serially to monitor disease progression or treatment responses, although such use has not been reported. Tested patients must refrain from taking medications that affect sweating, including tricyclic antidepressants. QSART is also useful for diagnosis of complex regional pain syndrome.

Other Tests of Sudomotor Function. Other methods of assessing sudomotor function include the thermoregulatory sweat test and the Silastic skin imprint method. Thermoregulatory sweat testing is only available in a few centers. It involves dusting a patient with an indicator powder that turns purple when moist. The patient is placed in a hot enclosure; the core temperature is increased; and the pattern of body surface covered by sweat is assessed semi-quantitatively. The sensitivity of the thermoregulatory sweat test in small-fiber neuropathy is high. It is especially useful for detecting very distal loss of sweating. In a study of 39 patients with suspected small-fiber neuropathy, 31 had an abnormal thermoregulatory sweat test as did 72% of the patients reported by Stewart et al. Thermoregulatory sweat testing, in contrast to QSART, also assesses the central sudomotor pathway. The disadvantages of thermoregulatory sweat testing are that it is messy, semi-quantitative, and requires a special room. It is also somewhat time-consuming and may not be economically feasible for many institutions. The Silastic skin imprint method is performed by applying Silastic material to stimulated skin. Sweat droplets indent the Silastic material and are counted within a certain surface area. Pilocarpine or acetylcholine is used as the direct sweat stimulus. There is no axon reflex. The sensitivity of the Silastic method is uncertain because it has not been compared to other modalities used for diagnosis of small-fiber neuropathy. It is probably lower than QSART.

Other Autonomic Tests. Cardiovagal and adrenergic autonomic testing have been thoroughly reviewed previously in this journal. In brief, the sympathetic nervous system is assessed by the Valsalva maneuver (especially late phase II and phase IV responses) and by the blood pressure response to standing or tilt. The parasympathetic, cardiovagal axis can be assessed by measuring the heart rate variation during deep breathing and during the Valsalva maneuver.

McLeod reviewed autonomic dysfunction in peripheral nerve disease. Orthostatic hypotension seems to occur primarily when small myelinated and unmyelinated baroreflex fibers in the splanchnic vascular bed are damaged as in advanced diabetic neuropathy, primary amyloidosis, and some hereditary neuropathies. However, tests of cardiac and vascular autonomic regulation may still reveal abnormalities that are often subclinical in many patients with other forms of small-fiber neuropathy (Table 1). In a study of 47 patients with painful, primarily small-fiber neuropathy, 27 (57%) had abnormal cardiovagal testing. The Valsalva ratio was slightly more sensitive than heart rate variability to deep breathing. Minor heart rate abnormalities were also present in another 11 of 40 (28%) patients with distal small-fiber neuropathy. None had postural hypotension. Six had abnormalities with Valsalva maneuver only. Among 15 patients with small-fiber neuropathy in a third study, 75% had asymptomatic cardiovagal dysfunction (heart rate response to deep breathing). For those who do not have an autonomic laboratory, heart rate variability can be assessed on some EMG equipment, and patients can be assessed manually (via sphygmomanometer) for orthostatic hypotension. However, it is likely that the subtle abnormalities associated with most small-fiber neuropathies will not be detected by these methods.

Other physiologic tests that have been utilized for small-fiber neuropathy but require further study include current perception threshold testing and laser-evoked potentials.
Pathology. Epidermal Nerve Fibers. In the early 1980s, an antibody against protein gene product 9.5, which is present in all axons, was developed, allowing for better analysis of unmyelinated epidermal nerve endings. Subsequent immunohistochemical use of this antibody produced elegant quantitative studies of epidermal innervation in skin punch biopsy or blister specimens. Dermal innervation was also assessed, but it does not appear to be as clinically useful.

Epidermal nerve fiber analysis has been used extensively by several groups. Kennedy et al. recently reviewed the methodology. In brief, the skin biopsy specimens are placed in a formaldehyde-based solution and fixed in cryoprotectant with sucrose. Thick sections (50–100 μm) are cut perpendicular to the skin surface, and then immunohistochemistry (immunofluorescence or immunohistochemistry) with a protein gene product 9.5 antibody is performed. The 20x objective on a confocal microscope may be used for microscopy, and the density of epidermal nerve fibers passing through a 50-μm section of basement membrane is determined. Imaging software can be used for quantitation.

The Johns Hopkins group does not use confocal microscopy or imaging software. They count the epidermal twigs that breach the basal lamina in a 1-mm section using conventional microscopy. They compared their technique to stereology and found no significant difference. The normal density of intraepidermal nerve fibers is 21.1 ± 10.4/mm (mean ± SD) in the thigh and 13.8 ± 6.7/mm in the distal leg (fifth percentile, 3.8/mm). There was no significant effect of age on intraepidermal nerve fiber density. Quantitation of epidermal nerve fibers had a positive predictive value of 75% and a negative predictive value of 90%, with a diagnostic efficiency of 88% for patients with sensory neuropathies.

In neuropathies affecting epidermal innervation, the most frequently reported abnormality is a reduction in nerve fiber numbers (Fig. 2). Nerve swellings and a change in branching may occur. Excessive proximal branching suggests reinnervation. As most neuropathies are length-dependent, the fiber loss is usually worse distally. Epidermal nerve fiber loss correlates with loss of small fibers in sural nerve biopsy specimens. There is also some correlation with large-fiber loss. In some neuropathy patients, epidermal nerve fiber assessment is more sensitive than sural nerve histopathology. In one study, 11% of 26 patients with features of small-fiber neuropathy had loss of epidermal nerve fibers without loss of small myelinated or unmyelinated fibers in sural nerve specimens. The sensitivities of epidermal nerve fiber assessment from several patients with

FIGURE 2. Skin biopsies from a normal patient (A) and from a patient with a small-fiber neuropathy (B) viewed by confocal microscopy. The epidermal nerve fibers appear red and are reacted with an antibody against protein gene product 9.5. The basal lamina appears green due to its immunoreactivity against a collagen IV antibody. The epidermal nerve fiber density and branching pattern are normal in (A), whereas only a single nerve (arrow) extends beyond the basal lamina in the neuropathy patient’s specimen (B). (Reproduced from reference 73 with permission from Lippincott Williams & Wilkins, Inc.)
Small-fiber neuropathy are shown in Table 1; the range is 74–87%. In addition, Hermann evaluated 28 patients and found that 22 (79%) had reduced epidermal nerve fiber densities. Other modalities for small-fiber neuropathy assessment were not utilized.

Although this diagnostic method is very useful, a limitation is that it is available only in several academic centers. It takes some effort for an institution to set up the infrastructure to perform the studies just as it does to perform other specialized diagnostic procedures. Skin biopsy itself is simple; multiple sites can be examined easily and studied serially. However, the histologic technique is moderately complicated, and a subset of normals should be studied to compare with published normals. In addition, it is not useful in detecting features of amyloidosis or inflammation as can be seen in peripheral nerve specimens. Nevertheless, it is an excellent method for diagnosis of small-fiber neuropathy. It is to be hoped that clinicians will eventually be able to send skin biopsy specimens to a reference laboratory or academic center for analysis if their institution does not provide this service.

Peripheral Nerve. Sensory nerve biopsies are not commonly utilized in evaluating patients with small-fiber neuropathy unless amyloidosis or an inflammatory process is strongly suspected. Demyelinating processes do not exclusively affect small fibers. Therefore, distal axonal loss or perhaps rarely neuronal degeneration causes small-fiber neuropathy. Uncovering nonspecific pathologic changes of axonal degeneration in sensory nerves often requires specialized studies including morphometry on semi-thin plastic sections and quantitative ultrastructural studies. Morphometry might reveal a loss of small myelinated fibers, but regenerative axon sprouting might cause an increase. Signs of acute axonal degeneration (including myelin ovoids) of small myelinated fibers may be seen in plastic-embedded sections or by ultrastructural study.

Ochoa has extensively studied the pathologic changes of unmyelinated fibers in sensory nerves. The following features are consistent with unmyelinated fiber pathology: (1) mild proliferation of Schwann cell projections next to unmyelinated axons; (2) dropout in the total number of unmyelinated axons, linked with increased numbers of Schwann cell bands devoid of axons (Fig. 3); (3) early regeneration as suggested by the presence of many flat Schwann cell bands devoid of axons and associated with a normal number of unmyelinated axons; and (4) advanced regeneration as evidenced by an increased total number of unmyelinated axons and increased Schwann cell projections.

There is also some interest in evaluating immunohistochemical markers for neurotransmitters in small fibers. Antibodies against calcitonin-gene-related peptide and substance P may be used as markers in afferent somatic fibers, and antibodies against neuropeptide Y, vasoactive-intestinal polypeptide, or tyrosine-hydroxylase have been assessed in autonomic fibers. One study utilizing sural nerve biopsies suggested that the density of tyrosine-hydroxylase correlated with tests of C-fiber function, thus identifying a potential histologic marker.

**FIGURE 3.** An electron photomicrograph of a sural nerve specimen from a patient with a hereditary sensory autonomic neuropathy reveals flat stacks of Schwann cell processes, consistent with loss of unmyelinated axons. Projections of nonmyelinating Schwann cell cytoplasm, including one forming a collagen pocket (just below inset) are present. Normal, unmyelinated fibers are shown for comparison (inset). (Bars, 0.5 μm.)
COMPARISON OF DIAGNOSTIC MODALITIES IN SMALL-FIBER NEUROPATHY

Most centers do not have all of the available tools for diagnosing small-fiber neuropathies; thus, most studies have not utilized or compared all possible investigative modalities. However, there are several studies that compare some of the newer physiologic and histologic methods. They are listed in Table 1. The largest prospective study included 117 consecutive patients referred for evaluation of burning feet in association with normal strength. Skin biopsies and nerve conduction studies were performed on all; 44 (38%) had normal nerve conduction studies, consistent with small-fiber neuropathy. Among these, 32 underwent QSART and QST. QSART and QST were less sensitive in detecting small-fiber loss (Table 1) than skin biopsy.73 The same group extensively evaluated autonomic function, QST, and epidermal nerve fibers in 126 patients with burning feet,69 47 of whom had normal nerve conduction studies, consistent with small-fiber neuropathy. In this cohort, there was excellent correlation between QSART and cooling thresholds and loss of intraepidermal nerve fibers. QSART and skin biopsy had similar sensitivities (Table 1). QST was abnormal in more patients, but about one-third of the abnormalities were in vibratory function. Mild to moderate cardiovascular autonomic dysfunction was present in more than half. In a retrospective study of 15 patients with small-fiber neuropathy, Tobin et al. found that QSART was more sensitive than QST and cardiovascular testing. However, many patients did have mild cardiovascular dysfunction. Epidermal nerve fibers were not assessed.101 In a preliminary report, QSART and skin biopsy were compared in 10 normal subjects and 15 patients with peripheral neuropathy. The two techniques correlated well in normals and in patients with small-fiber neuropathy. QSART was abnormal in all four patients with idiopathic small-fiber neuropathy, and epidermal nerve fiber density was reduced in three of these. Both tests were abnormal in four patients with diabetic neuropathy and in three with autonomic neuropathy.96

Finally, Pan et al. compared skin biopsies to QST in 35 normal subjects and 35 patients with peripheral neuropathy. Most neuropathy patients had large- as well as small-fiber involvement, so these results are not directly comparable to those addressed above. Epidermal nerve densities were reduced in 80% of the neuropathy patients; 54% had abnormal warm sensation thresholds and 71% had abnormal cold sensation thresholds.72 Of interest, the authors concluded that degeneration of epidermal nerve fibers might precede elevation in thermal thresholds.

CHOICE OF METHOD

Individuals and institutions interested in obtaining equipment for proving the diagnosis of small-fiber neuropathy have to make a somewhat difficult decision. Most institutions are not able to utilize all of the methods described above. Without access to any of the specialized physiologic tools or to histologic assessment of epidermal nerve fibers, testing is limited to the sympathetic skin response for sudomotor function and bedside assessment of heart rate and orthostatic blood pressure changes for assessment of cardiovascular autonomic function. It is likely that the sensitivity of such testing is low, but these tests should nevertheless be undertaken if no other methodologies are available. Regarding the other methodologies, a comparison of their advantages and disadvantages is listed in Table 2. Many of these tests

| Table 2. Advantages and disadvantages of specialized tests for small-fiber dysfunction. |
|----------------------------------------|--------------------------------------|---------------------------------|
| Method                                | Advantages                           | Disadvantages                   |
| Quantitative sudomotor axon reflex test (QSART) | Sensitive for small-fiber neuropathy. Objective, reproducible, allows sampling of multiple sites. Quantitative. Can be used for serial testing. | Requires special equipment. Moderately time-consuming. |
| Cardiovascular and autonomic testing   | Objective. Quantitative. May identify subclinical, as well as symptomatic, autonomic dysfunction. | Only moderate sensitivity for mostly subclinical autonomic dysfunction. Requires special equipment. Moderately time-consuming. |
| Epidermal nerve fiber analysis         | Quantitative. Sensitive. Can sample multiple sites. Can be used for serial testing. | Limited availability. Histologic technique can be complicated, depending on method. |
| Quantitative sensory test (QST)        | Evaluates different sensory receptors and small and large fibers. Can detect pain threshold. Reproducible. Can be used for serial testing. | Subjective component. Requires special equipment. |

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are actually complementary, and the yield for diagnosis of small-fiber neuropathy probably increases as tests are combined.

The economic advantages or disadvantages of these methods have not been fully described or compared. The cost of equipment for QSART and QST is approximately similar to that of a moderately sophisticated EMG machine. Reimbursement for these studies, however, may be lower than for nerve conduction studies and electromyography. Cardiovascular and adrenergic autonomic testing requires specialized equipment as well as a tilt table. The cost of the monitoring equipment is similar to that of commercially available QSART.

The likelihood of identifying cardiovascular dysfunction in small-fiber neuropathy is less than for identifying sudomotor dysfunction. Therefore, QSART is more desirable than cardiovascular autonomic testing. QSART can also be used for testing patients with complex regional pain syndrome, whereas autonomic cardiovascular testing may be used for evaluating other disorders, including central disorders of autonomic function.

Quantitative sensory testing is another consideration, as this apparatus may also be used for large-fiber assessment. The sensitivity of QST is slightly lower than that of QSART or epidermal nerve fiber assessment. Epidermal nerve fiber assessment may be the most sensitive test for small-fiber neuropathy, although QSART may be equivalent. The skin biopsies are easy to perform and can be obtained in the office. However, the infrastructure for the histologic processing and evaluation must be developed. The economics of assessment of epidermal nerve fibers have not been reported.

**CAUSES OF SMALL-FIBER NEUROPATHY**

Unfortunately, a cause for small-fiber neuropathy, especially in patients over the age of 60, is rarely found. When a cause is found, it is usually *diabetes mellitus* (Table 3). In general, diabetic polyneuropathy is primarily a sensory disturbance. A subset of patients have symptomatic, primarily small somatic fiber involvement with or without autonomic dysfunction. Sosenko et al. also found that asymptomatic diabetics were more likely to have abnormalities in warming and cooling sensitivity on QST compared to nondiabetic subjects. Presumably, such symptomatic and asymptomatic patients may later develop large-fiber involvement if the hyperglycemia is not tightly controlled.

There is recent evidence that even impaired glucose tolerance (2-h glucose of 140–199 mg/dl after a 75-g oral glucose load) or abnormal fasting glucose may be associated with small-fiber neuropathy. Of 121 retrospectively-studied patients thought to have idiopathic polyneuropathy, 89 were screened with glucose tolerance testing and 15 (25%) had impaired glucose handling. Many had symptoms of predominantly small-fiber neuropathy; four had normal nerve conduction studies; and two had epidermal nerve fiber loss on skin biopsy. In another report, an additional six patients with sensory neuropathy and impaired glucose tolerance had abnormal epidermal innervation. It therefore appears that patients with small-fiber neuropathy may have a higher incidence of impaired glucose handling compared to a historical case control population. However, a direct-comparison, prospective, cohort study has not been completed. At this point, impaired glucose tolerance is thought to be associated with small-fiber neuropathy, but a causal relationship has not

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Evaluation</th>
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<td>Diabetes or impaired glucose handling</td>
<td>2-h oral glucose tolerance test</td>
</tr>
<tr>
<td>Systemic amyloidosis</td>
<td>Serum and urine protein electrophoresis, consider biopsy of nerve, muscle, abdominal fat, or rectum</td>
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<tr>
<td>Alcohol</td>
<td>History</td>
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<tr>
<td>Sjögren’s syndrome</td>
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</tr>
<tr>
<td>Pharmacologic toxins, e.g., metronidazole</td>
<td>History</td>
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<tr>
<td>Environmental toxins</td>
<td>History, specialized toxicologic studies</td>
</tr>
<tr>
<td>Acquired immunodeficiency syndrome</td>
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</tr>
<tr>
<td>Hyperlipidemia</td>
<td>Fasting lipid panel</td>
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<tr>
<td>Familial “burning feet” neuropathy</td>
<td>History, exclude amyloidosis</td>
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<tr>
<td>Tangier disease</td>
<td>Alpha (high-density) lipoproteins</td>
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<tr>
<td>Familial amyloidosis</td>
<td>Transferrin gene test, biopsy of affected tissues</td>
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<tr>
<td>Fabry’s disease</td>
<td>Alpha-galactosidase assay</td>
</tr>
<tr>
<td>Hereditary sensory neuropathies</td>
<td>History, examination, possible DNA study when available</td>
</tr>
<tr>
<td>Monoclonal gammopathy</td>
<td>Serum and urine protein electrophoresis, quantitative immunoglobulins</td>
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Small-Fiber Neuropathy
been proven. Nevertheless, it seems prudent to obtain a 2-h oral glucose tolerance test in all patients with such a neuropathy of unknown etiology.

Idiopathic small-fiber neuropathy is the largest category. For example, 93% of 44 patients studied by Periquest et al. had small-fiber neuropathy of unknown etiology. Of course, this is a wastebasket group indicating failure to find a cause despite an adequate evaluation. Most of these patients are over the age of 60 years and have predominantly foot symptoms. Their paresthesias are usually painful and may be accompanied by "negative" symptoms. Examination findings are usually minimal. Symptoms often spread proximally, but usually small-fiber dysfunction remains the predominant or only feature. Weakness or substantial large sensory fiber dysfunction usually does not occur.

A smaller number of patients of various ages develop more acute diffuse involvement including the thorax and face. In addition, a multifocal variant of small-fiber neuropathy also occurs. It has been hypothesized that the diffuse involvement is due to a sensory neuronopathy. The multifocal or diffuse variants may slowly recover after a plateau, but symptom fluctuations may persist.

In some patients with idiopathic small-fiber neuropathy, an inflammatory autoimmune basis has been hypothesized, and circumstantial evidence is available. Sural nerve biopsy specimens from 12 patients with clinical features of small-fiber neuropathy, including burning feet, revealed multifocal axon loss in 5 and epineurial perivascular lymphocytes in all. This inflammation was deemed "significant" in seven. Vasculitis was not observed. A confounder was that a few had large-fiber sensory and even motor involvement. In addition, Gorson and Ropper described 20 elderly patients with idiopathic small-fiber neuropathy, 3 of whom seemed to respond to intravenous gammaglobulin. However, the study was uncontrolled and unblinded.

In another report, two patients with small-fiber neuropathy had vasculitis. One had probable systemic lupus erythematosus and improved with prednisone and cyclophosphamide. The other lacked systemic manifestations of vasculitis and did not improve with prednisone and a brief course of cyclophosphamide. Four other patients with a multifocal pattern of small-fiber neuropathy had antecedent infectious illnesses. Four other patients with an acute, diffuse small-fiber neuropathy after an infectious illness. Seneviratne and Gunasekera reported six patients with acute onset of small-fiber neuropathy and cerebrospinal fluid albumino cytologic dissociation. Four had an antecedent illness. In 39 patients studied by Giuliani et al., 15 had evidence suggestive of an autoimmune disposition. Findings included antinuclear antibodies, history of autoimmune or autoimmunne thyroid disease, vasculitis, and mitochondrial antibodies. Suarez et al. also postulated an immunemediated mechanism in idiopathic autonomic neuropathies that followed a viral illness. In one, a nerve biopsy specimen showed perivascular inflammation. Bennett et al. reported a patient who developed acute onset of an autonomic neuropathy with parasympathetic dysfunction in conjunction with a painful small-fiber neuropathy. The cerebrospinal fluid contained both Epstein-Barr virus (EBV) DNA and antibody, suggesting that EBV or the response to EBV had caused the neuropathy. The pain improved with intravenous immunoglobulin. Finally, 3 of 40 patients with small-fiber neuropathy studied by Stewart et al. had onset after a viral illness. Thus, there is evidence that suggests, but does not prove, that infections or autoimmune processes may cause small-fiber neuropathy. Unfortunately, there are no good laboratory markers of the autoimmune process.

To date, serum antineur antibodies have not been particularly useful in diagnosis. Dabby et al. did identify a subgroup patients with antisulfatide antibodies. Unfortunately, antisulfatide antibodies were also present in patients with mixed large- and small-fiber neuropathies, and even in demyelinating neuropathies. Periquest et al. did not find any antisulfatide antibodies in their patients with small-fiber neuropathy. As the pathogenic and potential treatment implications of finding antisulfatide antibodies are still uncertain and because they are not specific, antisulfatide antibody assessment has not been recommended in the routine clinical evaluation of patients with small-fiber neuropathy.

Another cause of small-fiber neuropathy is Sjögren's syndrome, which primarily affects middle-aged women. The pathogenesis is probably autoimmune. Sensory neuronopathy and trigeminal neuropathy may occur. Distal sensorimotor axonal polyneuropathies are also relatively common. In fact, approximately two-thirds of patients with neuropathy from Sjögren's syndrome first note sensory symptoms in the feet. Primarily small-fiber dysfunction may sometimes account for the sensory symptoms, and autonomic fibers may also be affected. The presentation may be asymmetric. Mellgren et al. reported that 16 of 24 patients had normal sural responses, supporting the notion that small-fiber neuropathy is an important cause of paresthesias in patients with Sjögren's syndrome. Some authors believe that a...
distal small-fiber neuropathy may be the most common form of neuropathy in this disorder.61

Recognition that the neuropathy is due to Sjögren’s syndrome may be difficult when neuropathy is the presenting manifestation. Sometimes neuropathy even precedes sicca symptoms.27,65 The diagnosis can be made when antinuclear, SS-A, and SS-B antibodies are present. When these antibodies are negative, the diagnosis is made by Schirmer tear testing, rose-bengal corneal staining, and lip (minor salivary gland) biopsy92 that shows at least two foci of 50 or more mononuclear cells/4 mm². In a series of 54 patients with sicca syndrome and peripheral neuropathy, neuropathy was the presenting problem in 87%. Five patients exhibited a distal small-fiber pattern. A positive minor salivary gland biopsy was obtained in 73% of patients. Nonspecific inflammation was present in the majority of nerve biopsy specimens that were obtained. Serologic markers for Sjögren’s syndrome were only present in 10.4%.92 Anti-nuclear antibody (ANA) was positive in 23 of 54 patients. Only 11 had a titer ≥1:160.92

Erythromelalgia is a syndrome that has been considered a form of small-fiber neuropathy, and one study suggested sympathetic fiber involvement.89 Erythromelalgia refers to episodic burning limb pain that occurs especially during standing or walking, or is due to heat. It is relieved by cold and sometimes the horizontal position. The painful limb becomes red and hot, and throbs with engorged veins. Erythromelalgia can be inherited as a childhood-onset autosomal dominant disorder. Secondary erythromelalgia can occur in association with essential thrombocythemia, connective tissue diseases, diabetes mellitus, and perhaps certain drugs. The disorder might be caused by sensitization of cutaneous polymodal C-fibers that become abnormally activated by heat at a lower temperature than normal. An activated axon reflex could also occur, thereby leading to dilatation of superficial blood vessels. In patients with essential thrombocythemia, aspirin relieves the pain, but aspirin is not beneficial in other forms of erythromelalgia. Cold and ice do reduce the pain, but such treatment can also exacerbate the problem and cause frostbite.51

Painful alcoholic polyneuropathy affects small myelinated and unmyelinated fibers more that large myelinated fibers, especially in the early stages. A histopathologic study of 18 patients with alcoholic polyneuropathy and a normal thiamine status disclosed a marked reduction in small myelinated fibers in those with a shorter history. Some large-fiber sensory and motor dysfunction was evident by nerve conduction studies. Eight had mild autonomic symp-

toms, but autonomic testing was not performed.46 Earlier studies showed more chronic loss and active degeneration of large sensory axons, but some of those alcoholics had poor diets, and parameters of thiamine function were not assessed.103

Most other environmental and pharmacologic peripheral nerve toxins substantially affect large fibers. An exception is metronidazole. Although its toxicity can involve large fibers,11 some patients have predominantly small-fiber involvement. Four, who developed paresthesias during metronidazole treatment, had clinical features of small-fiber dysfunction and normal nerve conduction studies. Three had either an abnormal QSART or elevated cooling thresholds. One sural nerve specimen exhibited loss of small myelinated fibers.106 A preliminary report also identified electrophysiologic evidence of small-without-large fiber sensory involvement in four patients who were exposed to a mixture of solvents.2

Monoclonal gammopathy is sometimes associated with small-fiber neuropathy, but a causal relationship has not been proven. A study of 18 patients with monoclonal gammopathies disclosed that small-fiber dysfunction, as noted by QST, was always present in the setting of either subclinical or only mild large-fiber axonal involvement.6 Stewart et al.97 found that 1 of 40 patients with a small-fiber neuropathy had a monoclonal gammopathy, and the experience of Periquet et al. was similar.75

Human immunodeficiency virus (HIV)-1 causes various types of neuropathies.89 A distal sensory neuropathy is common. Typically, large fibers are affected, but small-fiber dysfunction often predominates.16

It is somewhat controversial as to whether small-fiber neuropathy may be a remote effect of cancer. Among 29 cancer patients who underwent QST, 43% had elevated thermal thresholds. Subclinical small-fiber involvement was presumed. Apparently patients were not symptomatic.54 However, most patients with symptomatic sensory neuropathy from malignancy have significant large-fiber involvement.13 It remains to be seen whether there is a paraneoplastic form of small-fiber neuropathy or whether paraneoplastic sensory neuronopathy may present as small-fiber neuropathy and then evolve to affect large fibers. To date, there is no serologic marker of small-fiber neuropathy in cancer patients. Anti-Hu (antineuronal nuclear type 1) antibodies have been seen in patients with large-fiber involvement.

Hyperlipidemia, especially with a marked increase in serum triglycerides, may be associated with small-fiber neuropathy. Six patients with triglyceride levels
>800 mg/dl had no other cause for small-fiber neuropathy. One improved after normalization of the serum triglycerides. A cause-and-effect relationship has not been proven. Latov has observed an association between celiac sprue and small-fiber neuropathy (Latov N, personal communication 2002). Further investigation is required to confirm this association.

**Hereditary** processes also cause small-fiber neuropathy. Among 40 patients with small-fiber neuropathy studied by Stewart et al., 10% had a family history consistent with small-fiber neuropathy, as did 26% of patients reported by Novak et al. and 5% of those of Periquet et al. There are at least five forms of hereditary neuropathies primarily affecting small fibers.

**Hereditary Sensory Autonomic Neuropathy I (HSAN-I)** is a rare, autosomal dominant condition, with the typical onset of symptoms in early adulthood. Patients have primarily distal lower extremity loss of pain and temperature sensations, potentially leading to digital ulcerations and even bone destruction. Motor involvement sometimes occurs. Patients may be unaware that other family members have the disorder. High arches and hammertoes may alert the clinician to the diagnosis. The disorder primarily affects C fibers, but larger Aδ and even Aα fibers can be affected. It has been linked to chromosome 9q22, and it is now associated with a mutation in the gene coding for a subunit of serine palmitoyltransferase.

**HSAN-II** is a more severe autosomal recessive form with early onset including ulcerations. HSAN-III (Riley-Day syndrome) is autosomal recessive, occurs in Ashkenazi Jews, and is associated with postural hypotension, reduced tears, impaired pain and sensation, and preserved sweating. HSAN-IV is also autosomal recessive and is associated with anhidrosis, congenital insensitivity to pain, and mutations in the gene for the high affinity nerve growth factor receptor, TrkA. HSAN-V is phenotypically similar to HSAN-IV, but there is less anhidrosis and a selective loss of small myelinated fibers, whereas HSAN-IV affects mostly unmyelinated fibers. At least some patients with the HSAN-V phenotype also have a defect in the TrkA gene.

A dominantly inherited "burning feet syndrome" has been reported. The genetics are unknown. Only mild pathologic abnormalities were detected in sural nerve biopsy specimens. Another family with a dominantly inherited form of burning feet syndrome was reported by Stögbauer et al., who excluded linkage to the known HSAN-I locus on chromosome 9q92. In this kindred, neurologic examinations were essentially normal and only minimal changes were found on nerve conduction studies. In one patient's sural nerve biopsy specimen, there was a moderate reduction of small myelinated fibers and a marked reduction of unmyelinated fibers.

In addition, Serrano-Munuera et al. identified a group of patients with painful sensory neuropathy and skeletal foot deformities. Most had a family history of foot deformities; some members also had painful feet. Among 87 patients, 18 had normal sural nerve responses consistent with small-fiber neuropathy. Other patients had electrophysiologic evidence of a length-dependent sensorimotor axonopathy. There was a varying degree of unmyelinated fiber loss, degeneration, and regeneration in 27 sural nerve biopsy specimens. Occasional enlarged (dystrophic) axons and "ghost axons" encircled by Schwann cell processes in close proximity to unmyelinated axons were present. Last, Periquet et al. also noted that one patient with proximal myotonic myopathy (PROMM) had small-fiber neuropathy. The frequency of this association, which may have been fortuitous, is unknown.

**Amyloidosis** is an uncommon disorder that can present with a primary small-fiber neuropathy. However, eventually all sensory modalities are affected, and motor involvement occurs. At some point, prominent autonomic dysfunction also develops. The primary form is due to light chain deposition, and it can be associated with multiple myeloma. Up to 86% of these patients have monoclonal proteins detected in serum, urine, or both; 25% of patients have carpal tunnel syndrome, and other organ involvement also occurs.

The familial form is autosomal dominant, but onset is late and as many as 65% of patients lack a family history. Most patients present with sensory symptoms and essentially all develop sensory, motor, and autonomic involvement; 25% have carpal tunnel syndrome. In the familial form, diagnosis is made by identifying the presence of amyloid in various tissues, including rectum, peripheral nerve, or abdominal fat pad. Mutations, especially in the transthyretin gene, should then be sought. Liver transplantation is useful in treating the familial form. Some patients with amyloidosis and peripheral neuropathy may have an initially negative sural nerve biopsy. Patients who present with small-fiber neuropathy and develop large-fiber involvement and autonomic dysfunction should be carefully and serially evaluated for amyloidosis.

**Fabry's disease** is a rare X-linked condition that can be manifest as severe burning pain as well as visceral pain. Changes in temperature due to fever or exer-
cise can trigger the attacks. There is a preferential loss of small myelinated and unmyelinated fibers. Patients may have renal failure as well as stroke and heart attacks. This disorder is caused by a deficiency of alpha-galactosidase and is also characterized by the presence of angiookeratoma corporis, a rash that occurs in the "bathing trunk" area and is composed of scaly red to red-blue macules or papules.

Tangier disease is a very rare autosomal recessive disorder caused by a deficiency of HDL-cholesterol and a mutation in the ATP-binding cassette transporter 2 gene. Patients have orange or yellow tonsils, splenomegaly, and peripheral neuropathy. The neuropathy may be painful and simulate syringomyelia. The neuropathy onset varies from the first to seventh decade. Other forms of neuropathy are characterized by multiple mononeuropathies or motor involvement.

**SYMPTOMATIC TREATMENTS**

Unless an identifiable cause, such as diabetes mellitus, is found, the management of small-fiber neuropathy usually centers upon treatment of neuropathic pain. Patients should be counseled that the goal of treatment is to reduce pain, and that pain is often not totally relieved. Most of the drugs that are efficacious reduce pain intensity by only 20–40%. Useful drug classes include anticonvulsants, tricyclic antidepressants, opiates, lidocaine and lidocaine derivatives, and antihistaminergic drugs. Drugs can be tried as monotherapy or in combination. Treatment should be initiated at a low dose and titrated to the maximum tolerable dose until benefit is achieved or intolerable side effects occur. Drugs may be chosen based upon their side-effect profile, the patient's associated medical conditions, and potential for drug interactions.

Treatment of neuropathic pain has been the subject of a number of recent reviews. Table 4 summarizes the features of drugs that are often used to treat neuropathic pain of various origins and have been shown to be efficacious in placebo-controlled trials. Most of these drugs have not been studied specifically in small-fiber neuropathy. In addition, topical lidocaine, dextromethorphan, and bupropion have been studied to a lesser degree.

Nonpharmacologic methods for pain management are also very important. Cool soaks help some patients, but care must be taken to avoid frostbite or skin injury. Some patients find relief with heat, massage, or limb elevation or lowering. Skin moisturizers may be useful. Shoes must not be tight. Exercise may be beneficial as well.

Other modalities that have been used to treat neuropathic pain include physical and psychologic therapy. Spinal cord stimulators and intrathecal morphine may be helpful in a select group of patients, but the long-term benefit is unknown.

There has been therapeutic interest in nerve growth factor, a trophic factor in small somatic sensory and sympathetic neurons. Intradermal injections lower heat-pain thresholds and induce pressure allodynia in humans. However, nerve growth factor has not yet been shown effective in human neuropathies such as diabetic neuropathy. It did lead to a reduction in pain in HIV sensory neuropathy, but improvement in objective measures of neuropathy

<table>
<thead>
<tr>
<th>Drug class</th>
<th>Drug example</th>
<th>Daily dose range</th>
<th>Side-effects and limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anticonvulsant</td>
<td>Gabapentin</td>
<td>300-3,600 mg</td>
<td>Somnolence, dizziness, confusion, edema; adjust with renal failure</td>
</tr>
<tr>
<td></td>
<td>Lamotrigine</td>
<td>25-400 mg</td>
<td>Rash, including Stevens-Johnson syndrome; dizziness, constipation, nausea</td>
</tr>
<tr>
<td></td>
<td>Topiramate</td>
<td>50-400 mg</td>
<td>Sedation, poor concentration, weight loss, nephrolithiasis, myopia, glaucoma</td>
</tr>
<tr>
<td>Antidepressant</td>
<td>Amitriptyline</td>
<td>10-100 mg</td>
<td>Anticholinergic side-effects, cardiac arrhythmia, weight gain</td>
</tr>
<tr>
<td></td>
<td>Nortriptyline</td>
<td>10-100 mg</td>
<td>As indicated for amitriptyline, but milder</td>
</tr>
<tr>
<td></td>
<td>Venlafaxine XR</td>
<td>150-225 mg</td>
<td>Nausea, anorexia, hypertension, mydriasis, sweating, dizziness, sexual dysfunction</td>
</tr>
<tr>
<td>Antiarrhythmic</td>
<td>Mexiletine XR</td>
<td>To 750 mg</td>
<td>Liver dysfunction, nausea, heartburn, arrhythmia, dizziness, tremor</td>
</tr>
<tr>
<td>Opioids</td>
<td>Tramadol</td>
<td>200-400 mg</td>
<td>Nausea, constipation, dizziness, seizures</td>
</tr>
<tr>
<td></td>
<td>Controlled-release oxycodone</td>
<td>20-60 mg</td>
<td>Constipation, nausea, sedation; potential for abuse; burning, initially; complicated application limiting compliance</td>
</tr>
<tr>
<td>Topical</td>
<td>Capsaicin (0.075%)</td>
<td>Apply locally lid or qid</td>
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was not evident. Nerve growth factor has not been used to treat small-fiber neuropathy specifically, and further study is indicated.

CONCLUSIONS AND FUTURE DIRECTIONS

Small-fiber neuropathy is a common, important clinical problem. A number of investigative tools are now available for confirming the diagnosis. Based on the advantages and disadvantages as well as economic issues regarding these techniques, one or a combination of these modalities can be utilized. In all patients with small-fiber neuropathy, evaluation for diabetes mellitus or impaired glucose tolerance should be undertaken. Other causes may be identified by history (Table 3). Especially in patients with a positive family history of sensory neuropathy, paraproteinemia, or multiorgan involvement, amyloidosis should be sought. Amyloidosis should also be considered in patients with coexisting carpal tunnel syndrome or evolution of the neuropathy to affect large-fiber sensory modalities and motor fibers and when there is prominent autonomic involvement.

In the future, it will be important to determine whether a marker for an autoimmune cause of "idiopathic" small-fiber neuropathy can be established. Treatment trials with immune-modulating agents should be considered. It would also be useful to determine how many middle-aged women with primary small-fiber neuropathy actually have Sjögren's syndrome. Better treatments for neuropathic pain and small-fiber degeneration are also highly desired.

REFERENCES