MAYO CLINIC

Peripheral Neuropathy: A Practical Approach to Diagnosis and Symptom Management

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CME Activity

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Learning Objectives: On completion of this article, you should be able to (1) understand how to clinically define forms of neuropathy to identify those that may benefit from specialty consultation and those that can be evaluated and treated without further consultation; (2) understand the role of laboratory and electrodiagnostic testing in the evaluation of length-dependent sensorimotor peripheral neuropathies; and (3) understand a practical algorithmic approach to neuropathic pain associated with peripheral neuropathy and appropriate dosing guidelines.

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Abstract

Peripheral neuropathy is one of the most prevalent neurologic conditions encountered by physicians of all specialties. Physicians are faced with 3 distinct challenges in caring for patients with peripheral neuropathy: (1) how to efficiently and effectively screen (in less than 2 minutes) an asymptomatic patient for peripheral neuropathy when they have a disorder in which peripheral neuropathy is highly prevalent (eg, diabetes mellitus), (2) how to clinically stratify patients presenting with symptoms of neuropathy to determine who would benefit from specialty consultation and what testing is appropriate for those who do not need consultation, and (3) how to treat the symptoms of painful peripheral neuropathy. In this concise review, we address these 3 common clinical scenarios. Easily defined clinical patterns of involvement are used to identify patients in need of neurologic consultation, the yield of laboratory and other diagnostic testing is reviewed for the evaluation of length-dependent, sensorimotor peripheral neuropathies (the most common form of neuropathy), and an algorithmic approach with dosing recommendations is provided for the treatment of neuropathic pain associated with peripheral neuropathy.

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In adults, chronic neurologic disease symptoms are one of the most common reasons for physician visits (even if headache is excluded),[1,2] and evaluation of sensory disturbance, including peripheral neuropathy, is one of the 5 most common reasons for neurologic consultation.[3] The prevalence of peripheral neuropathy in the general population is 2.4% and increases with age to an estimated 8% in those older than 55 years.[4,5] Peripheral neuropathy is more common in patients with diabetes mellitus, human immunodeficiency virus infection, and dysproteinemic disorders and in those receiving chemotherapy. In patients with

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diabetes, for example, length-dependent sensorimotor peripheral neuropathy is evident in 8% at the time of diagnosis[6,7] but increases in frequency with disease duration to 30% to 66%,[6-9] depending on whether the neuropathy is defined by clinical or electrophysiologic criteria.

The primary care physician is presented with 3 distinct clinical challenges in caring for patients with peripheral neuropathy: (1) how to efficiently and effectively screen (in less than 2 minutes) an asymptomatic patient for peripheral neuropathy when they have a disorder in which peripheral neuropathy is highly prevalent (eg, diabetes mellitus), (2) how to clinically stratify patients presenting with symptoms of neuropathy to determine who would benefit from specialty consultation and what testing is appropriate for those who do not need consultation, and (3) how to treat the symptoms of painful peripheral neuropathy.

SCREENING FOR PERIPHERAL NEUROPATHY

The recognition of peripheral neuropathy in patients with disorders in which it is highly prevalent may affect the management for that disease. Annual screening for peripheral neuropathy is recommended in diabetic patients.[10,11] Physicians must be able to screen these patients in an efficient manner during return office visits that are often focused on other components of the disease and its treatments. Most recommendations for office screening for neuropathy have utilized light touch perception to a 10-g Semmes-Weinstein monofilament, vibration testing with a 128-Hz tuning fork, superficial pain (pinprick) perception, or testing of ankle deep tendon reflexes.[12-16] Clinical history alone is an insufficient screen to recognize peripheral neuropathy.[15] Although most patients with objective evidence of diabetic length-dependent peripheral neuropathy are clinically asymptomatic, they remain at risk for injury to insensate feet.[17]

If single-modality screening is used, monofilament light touch or vibration testing appears to be more sensitive and specific than superficial pain (pinprick) or ankle reflex testing.[12,13,15] Because peripheral neuropathies may affect different types of nerve fibers to different degrees, single-modality testing may miss 25% to 50% of those with diabetic neuropathy.[15] In diabetic cohorts, combination testing of vibration plus 10-g monofilament testing provides the best balance of an efficient (less than 2-minute), sensitive (90%), and specific (85%-89%) screen for diabetic peripheral neuropathy and correlates with the development of diabetic foot ulcers.[15-17] Light touch with a cotton swab is often substituted for monofilament testing in clinical practice, although its effect on sensitivity and specificity is unknown.

There is an age-related decline in vibration sensation, with almost one-quarter of those older than age 65 years and one-third of those older than 75 years having absent vibration sensation on clinical examination.[18] As such, reduced or absent vibration sensation in isolation should not be overinterpreted in elderly patients and should instead prompt further history and consideration of other sensory modalities to determine its relevance.

Importantly, screening is meant to identify whether an asymptomatic patient, at risk for peripheral neuropathy secondary to a systemic disease, is likely or unlikely to have a peripheral neuropathy. Alone, it is insufficient to fully characterize the neuropathy or direct the necessity of further diagnostic tests or consultations. Patients with a positive screening result (ie, clinical signs of probable neuropathy) require further clinical history and examination and can be evaluated similarly to a patient who presents with clinical symptoms concerning for neuropathy.

EVALUATING PATIENTS PRESENTING WITH CLINICAL SIGNS OR SYMPTOMS SUGGESTING PERIPHERAL NEUROPATHY

Clinically Stratifying Patients With Peripheral Neuropathy

Sensory symptoms (eg, numbness, tingling), weakness, autonomic symptoms (eg, early satiety, impotence, orthostatic hypotension, sweat abnormalities), or neuropathic (burning, stabbing, electrical) pain may suggest the presence of a peripheral neuropathy. Once a neuropathy is suspected (from patient history or screening examination in at-risk patients), the clinical history and a detailed examination (including strength, sensation, reflexes, and gait) allow the neuropathy to be categorized by either clinical symptom distribution (length dependent, length independent, or multifocal)

or by which clinical modality is affected (motor, sensory, autonomic, or some combination).

The most common pattern of clinical involvement is that of a length-dependent peripheral neuropathy. This form of neuropathy is symmetric, and symptoms begin in the longest nerves at their terminals (ie, distal foot). Negative (lack of feeling) or positive (prickling, tingling, burning) sensory symptoms usually precede motor weakness. The symptoms ascend insidiously up the leg, with hand symptoms often becoming evident around the time leg symptoms approach the knee. Upper limb involvement may never occur. Development of symptoms in the hands and feet at the same time is atypical for a diabetic length-dependent neuropathy and may indicate coexisting carpal tunnel syndrome or an alternative cause of neuropathy (eg, a toxic etiology). Proprioception is spared relative to other sensory modalities in mild to moderate length-dependent neuropathies and only becomes affected as the neuropathy severity progresses. Patients with notable early proprioceptive deficits (gait ataxia, imbalance with eyes closed) require further evaluation for posterior column disease (eg, vitamin B_{12} deficiency) or for sensory cell body dysfunction (a sensory ganglionopathy as seen in Sjögren syndrome or a paraneoplastic disorder). In length-dependent neuropathies, as the sensory signs and symptoms progress, weakness and reflex abnormalities develop distally.

The majority of peripheral neuropathies are length dependent, sensory predominant, and clinically mild to moderate in severity without major functional limitations. These neuropathies can often be effectively evaluated and managed without specialty consultation.

Sensory and/or motor symptoms in a more diffuse, length-independent pattern (ie, involving both proximal and distal limbs) suggest a polyradiculoneuropathy. Although these neuropathies may still be sensory predominant, motor manifestations are usually more evident than in length-dependent neuropathies. Reflexes can be useful in these cases because they are globally reduced or absent. Rare patients present with multifocal clinical symptoms (eg, a wrist drop, followed by a foot drop). As multifocal processes progress, further neurologic deficits accrue, and the process may begin to look more diffuse. Careful history and examination are necessary to recognize these multifocal neuropathies.

Polyradiculoneuropathies and multifocal neuropathies have a distinct differential diagnosis from that for length-dependent neuropathies. Etiologies include sarcoidosis, amyloidosis, and neoplastic, paraneoplastic, vasculitic, infectious, and inflammatory immune-mediated causes (such as chronic inflammatory demyelinating polyradiculoneuropathy), all of which have distinct treatment algorithms. Patients with a polyradiculoneuropathy or a multifocal neuropathy therefore warrant specialty consultation.

Patients with pure motor or autonomic signs and symptoms are uncommon and would benefit from neurologic consultation. Those with isolated sensory symptoms that are mild and length dependent can be evaluated similarly to those with length-dependent sensorimotor peripheral neuropathies, whereas patients with severe or diffuse sensory neuropathies causing gait ataxia and proprioceptive dysfunction would benefit from specialty consultation.

Regardless of clinical pattern of involvement, patients with acute or subacute onset of symptoms or progressive or functionally limiting neuropathies should be considered for neurologic consultation (Table 1). Similarly, clinicians should refer any patient when there is clinical uncertainty.

TABLE 1. Neuropathies in Which Specialty Consultation Would Be Beneficial

• Acute, subacute in onset • Rapidly progressive • Severe, functionally limiting	Regardless of clinical pattern or affected modality
• Length independent (polyradiculoneuropathy)	
• Multifocal	
• Motor predominant	
• Associated with severe dysautonomia	

Evaluation of Length-Dependent Peripheral Neuropathies

The combination of history (including family history), examination, ancillary testing, and serologic evaluation yields the etiology of a length-dependent peripheral neuropathy in 74% to 82% of cases.[19] Importantly, although the etiology of 20% to 25% of these neuropathies remains uncertain, the natural history of these idiopathic neuropathies is that they progress slowly and are unlikely to cause severe physical disability.[19]

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Serologic Evaluation. The American Academy of Neurology has published a practice parameter for the evaluation of clinically mild to moderate, symmetric, sensory-predominant length-dependent peripheral neuropathies.[19] The highest-yield testing includes screens for diabetes mellitus, vitamin B_{12} with methylmalonic acid, and serum protein immunofixation electrophoresis (SPIEP).[19] A practical evaluation for chronic, length-dependent peripheral neuropathy is presented in Table 2. Clinical practice reviews have revealed poor adherence to screening recommendations.[20] In a review of 1031 cases of peripheral neuropathy, more than 400 patterns of diagnostic testing were identified.[20] In an analysis of patients without known diabetes mellitus to explain their neuropathy, low-cost, high-yield studies were underutilized (fasting glucose, <20%; hemoglobin A_{1c}, 17%; vitamin B_{12}, 41%; monoclonal protein, 19%).[20]

Diabetic Neuropathy. Diabetes mellitus is the most common cause of peripheral neuropathy in Western societies, with a prevalence of up to 30% to 66%[6-9] of diabetic patients, depending on whether the neuropathy is defined by clinical or electrophysiologic criteria. Despite the objective evidence of neuropathy, only 10% to 15% of patients with diabetic neuropathy are neurologically symptomatic (from motor, sensory, or autonomic dysfunction),[8] whereas 11% to 26% are limited by associated neuropathic pain.[21-23] Although many patients with objective evidence of diabetic neuropathy are asymptomatic, they remain at risk for injury to insensate feet.[17] All patients presenting with signs or symptoms of peripheral neuropathy should be screened for diabetes mellitus with fasting glucose and/or hemoglobin A_{1c} measurements.[19] The risk of diabetic neuropathy, and other late microvascular complications of diabetes mellitus, can be reduced with tight glycemic control.[17,24-26]

Diabetic neuropathy can take many forms. A chronic, length-dependent, sensorimotor peripheral neuropathy is the most common form. It is a late complication of poorly controlled diabetes. It usually occurs with other late microvascular complications of diabetes mellitus, namely retinopathy and nephropathy. This association is so strong that if there is no clinical evidence of retinopathy or nephropathy in a patient with suspected diabetic distal symmetric neuropathy, alternative nondiabetic etiologies should be considered.[8] In up to 10% of diabetic patients, neurologic deficits can be attributed to an alternative cause.[8] Inherited neuropathy is one of the common alternative causes. Although diabetes is the likely cause in diabetic patients presenting with a length-dependent peripheral neuropathy, a limited screening laboratory evaluation (eg, serum protein immunofixation electrophoresis, vitamin B_{12} with methylmalonic acid, thyroid studies) for other treatable metabolic disorders is reasonable before attributing the neuropathy to diabetes.

Diabetes can cause other patterns of neuropathy including mononeuropathies, thoracic radiculopathy, a length-independent polyradiculoneuropathy, and diabetic lumbosacral radiculoplexus neuropathy (also known as diabetic amyotrophy), so called because of its pathologic predilection toward the lumbosacral segments (although thoracic or cervical involvement is possible) at the root ("radiculo"), plexus, and peripheral nerve ("neuropathy") levels. Diabetic radiculoplexus neuropathy is a unique subacute neuropathy that affects 1% of patients with diabetes.[8] It begins with severe pain, often involving the proximal aspect of the thigh and mimicking a radiculopathy. Weakness follows and may remain localized or progress multifocally within the limb or to other limbs. Weight loss often precedes the onset of symptoms.[27]

Impaired Glucose Tolerance. There has been increasing interest in the role of impaired glucose tolerance (IGT) as a potential explanation for many of the cases of otherwise

TABLE 2. Recommended Evaluation of Chronic, Length-Dependent Peripheral Neuropathy

- Complete blood cell count
- Renal function
- Liver function tests
- Erythrocyte sedimentation rate (extractable nuclear antigen if dry eyes/mouth and sensory neuropathy are present)
- Fasting glucose[a] (11%) or hemoglobin A_{1c}[a] (26%)
- Thyroid stimulating hormone
- Monoclonal protein[a] (serum protein immunofixation electrophoresis) (10%)
- Vitamin B_{12} (2%) (with methylmalonic acid 9%)[a]
- Infectious (if risk factors or endemic region): Lyme disease, human immunodeficiency virus
- Family history of peripheral neuropathy, pes cavus, hammertoes[a]

[a]Indicates highest-yield serologic tests with percentage of cases identified.

idiopathic, chronic, sensory-predominant, length-dependent peripheral neuropathies. Impaired glucose tolerance has been noted to be more prevalent in those with idiopathic neuropathy than in controls.[28-30] It has been suggested that 25% to 50% of idiopathic neuropathies (especially painful small-fiber neuropathies) may be explained by IGT.[19] The glucose tolerance test is more sensitive in identifying IGT than fasting glucose or hemoglobin A_{1c} measurements, and many have advocated its use as a standard laboratory screen in unexplained length-dependent neuropathies.[19,30] These associations, however, have not proven cause and effect, and other studies have not found this association.[31]

A recent large, controlled trial has addressed this question.[32] Patients with new-onset diabetes mellitus or IGT and healthy controls had clinically blinded assessments (history, examination, nerve conduction studies, quantitative sensory testing) for evidence of large- or small-fiber peripheral neuropathy, as well as nephropathy and retinopathy. Although as expected, patients with new-onset type 2 diabetes had a higher prevalence of peripheral neuropathy, retinopathy, and nephropathy than healthy controls or patients with IGT, there was no difference in the prevalence of clinically or electrophysiologically defined peripheral neuropathy, retinopathy, or nephropathy between the IGT cohort and the healthy control cohort. This study strongly challenges the assertion that IGT causes peripheral neuropathy or is a frequent cause of idiopathic neuropathies. If a patient being evaluated for a peripheral neuropathy has evidence of IGT, an alternative etiology should be considered (by defining clinical pattern of involvement, laboratory and electrophysiologic testing, and family history). If this same patient subsequently has progression to diabetes, the patient is at risk for the diabetes worsening the neuropathy.

Vitamin B_{12} Deficiency. In the nervous system, vitamin B_{12} is integral in the initial development of and maintenance of myelin.[33] Vitamin B_{12} deficiency can cause classic subacute combined degeneration or an isolated peripheral neuropathy without central nervous system involvement.[34] In patients presenting with a length-dependent peripheral neuropathy, the serum B_{12} level should be measured. Among patients with low-normal serum B_{12} levels (200-500 pg/mL [to convert to pmol/L, multiply by 0.7378]), 5% to 10% will have elevated serum methylmalonic acid concentrations indicating cellular B_{12} deficiency.[19] Adding methylmalonic acid (with or without homocysteine) to a screen of serum B_{12} level improves the yield of identifying cellular B_{12} deficiency as a cause of neuropathy from 2% to 8%.[34,35]

Dysproteinemias. Up to 10% of peripheral neuropathies are associated with dysproteinemias (a 6-fold increase over the general population), with the majority being a monoclonal gammopathy of undetermined significance (MGUS).[36] Evaluation by SPIEP is more sensitive in identifying a monoclonal protein than serum protein electrophoresis (SPEP); SPEP misses 17% of all monoclonal proteins identified with immunofixation and 30% of all IgM monoclonal gammopathies.[37] The most common monoclonal protein associated with peripheral neuropathy is IgM. For the evaluation of patients presenting with peripheral neuropathy, SPIEP is recommended over SPEP.[19]

The finding of a monoclonal protein necessitates further evaluation, and possible hematologic evaluation, to exclude disorders such as amyloidosis, multiple myeloma, osteosclerotic myeloma (POEMS [polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, skin abnormalities] syndrome), lymphoma, Waldenström macroglobulinemia, or cryoglobulinemia.

Most MGUS neuropathies occur in the setting of IgM, IgG, or IgA paraproteinemias (IgM being the most common) and usually cause axonal, length-dependent sensorimotor neuropathies (although polyradiculoneuropathies can also occur). Most IgM paraproteinemias are associated with an MGUS; however, some are associated with a distinct demyelinating (distinguishing it from MGUS-associated axonal neuropathies) clinical syndrome with severe symmetric distal sensory-predominant deficits (distal acquired demyelinating symmetric neuropathy).[38,39] Two-thirds of patients with distal acquired demyelinating symmetric neuropathy have serum antimyelin-associated glycoprotein antibodies.[38] This syndrome is important because it may respond to immunomodulatory treatments.[40]

The peripheral neuropathy associated with POEMS syndrome is typically a uniform mixed demyelinating and axonal length-independent

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polyradiculoneuropathy in the setting of an IgG or IgA paraproteinemia with a λ light chain.[41] POEMS syndrome is associated with osteosclerotic myeloma and increased levels of serum vascular endothelial growth factor.

Electrophysiologic characterization of the neuropathy and neurologic consultation should be considered in patients with non-MGUS paraproteinemias, IgM paraproteinemias, and/or functionally limiting neuropathies.

Other Laboratory Tests. Although patients presenting with a thyroid disorder often have neuromuscular complaints, hypothyroidism is an uncommon cause of a length-dependent peripheral neuropathy. Because hypothyroidism is a prevalent treatable disorder, however, patients presenting with peripheral neuropathy are commonly tested for this disease.[35]

In geographic regions where Lyme disease is prevalent or in patient populations with risk factors for human immunodeficiency virus infection, routine screening may be appropriate as part of the evaluation of peripheral neuropathy.

Celiac disease was found to be responsible for 2.5% of peripheral neuropathy cases presenting to a tertiary referral center.[42] Usually, these patients have sensory-predominant neuropathies and associated gastrointestinal symptoms, although neurologic signs and symptoms may precede gastrointestinal symptoms and some recommend screening all patients.[42] Anti—tissue transglutaminase antibodies are the most sensitive serologic screen, but their specificity is limited in association with neurologic disease, and confirmation with small-bowel biopsy should be obtained before attributing neuropathy to celiac disease.[42,43]

Copper deficiency can mimic vitamin B_{12} deficiency clinically (with a myelopathy and sensory-predominant neuropathy) and should be considered when patients have a history of bariatric surgery or multiple nutritional deficiencies or if high zinc exposure (nutritional supplement or in some denture pastes) is suspected.[44,45]

Vitamin E deficiency may be considered in patients at risk for fat malabsorption.

Toxic Neuropathies. Many neuropathies are the result of toxic effects of prescribed medications. Contextual cues that a neuropathy may be related to medication toxicity include the use of a known neurotoxic medication (eg, chemotherapeutic agents), temporal onset of symptoms with initiation or dosage adjustment of an implicated medication, worsening symptoms with higher dosages, onset of symptoms in the hands and feet concomitantly, and symptom stabilization or resolution following discontinuation of the offending agent.[46] Of note, although most toxic neuropathies show at least stabilization soon after the toxic agent is discontinued, some medications (particularly platinum-based chemotherapeutic agents) may remain active for several weeks or months after discontinuation, and stabilization or improvement may not be evident immediately.[47]

Excessive, long-term alcohol use can cause peripheral neuropathy, usually in the context of other systemic complications including nutritional deficiencies, particularly thiamine deficiency. Long-term alcohol use may also have a direct neurotoxic effect.[46]

A comprehensive list of potentially neurotoxic medications or supplements is beyond the scope of this article but has been addressed by others.[46,48]

Hereditary Neuropathies. Inherited neuropathies are the most common inherited neuromuscular condition worldwide and likely represent the most commonly overlooked etiology of peripheral neuropathy.[49-51] In fact, they may be the most common cause of peripheral neuropathy (although this has not been firmly established). Charcot-Marie-Tooth disease, also referred to as hereditary motor and sensory neuropathy, is the most common form of hereditary neuropathy and can be categorized into axonal and demyelinating forms. In Western countries, these neuropathies are most commonly autosomal and X-linked dominant.[52]

Clinically, a hereditary neuropathy is suggested by an insidious onset of symptoms with a slow progressive course over years, distal-predominant motor greater than sensory complaints, lack of positive sensory symptoms (dysesthesias, burning), associated structural foot and ankle deformity (pes cavus, hammertoes, and inverted champagne bottle legs with very thin ankles), and a family history of neuropathy. It is common that family members are unaware of a family history even when one is

TABLE 3. Neuropathic Pain Treatment Tiers[a]

Agent	Dosing	Maximum dosage	Precautions	Common and notable adverse effects	Comorbid conditions treated	Comments
Tier 1						
Anticonvulsants						
Gabapentin[b]	300 mg at bedtime, increase every 4-7 d by 300-mg increments initially to 3 times daily, then to goal of 1800 mg/d as necessary to 3600 mg/d	3600 mg/ d (split TID)	Renal insufficiency (dosage adjust); risk of seizure if abruptly stopped	Sedation, dizziness, confusion, edema, tremor	Seizure disorder, sleep disturbance, chronic migraine, hot flashes	100-mg increments available for slower titration; no notable drug interactions
Pregabalin[b]	75 mg twice daily; after 4-7 d, increase by same dosage to goal of 300 mg/d as necessary to 600 mg/d	600 mg/d (split BID)	Renal insufficiency (dosage adjust); risk of seizure if abruptly stopped; psychiatric disease or addiction history (euphoria risk)	Sedation, dizziness, confusion, edema, tremor, euphoria (Schedule V controlled substance)	Seizure disorder, sleep disturbance, fibromyalgia, central pain related to spinal cord injury, anxiety	Can split 3 times daily but better compliance with 2 times daily dosing with similar efficacy; 25- and 50-mg dosing available for slower titration; no notable drug interactions
Antidepressants						
Amitriptyline, nortriptyline[b]	10-25 mg at bedtime, increase every 4-7 d to goal of 100 mg at bedtime	150 mg/d	Risk of serotonin syndrome; caution if cardiac disease or dysrhythmia history	Sedation, dry mouth, orthostatic hypotension, confusion, weight gain, urinary retention, constipation, blurred vision	Depression, fibromyalgia, chronic migraine, sleep disturbance, irritable bowel syndrome	Goal dosing for pain usually inadequate for mood effect; higher dosages (~100 mg/d) often necessary for neuropathic pain; secondary amine TCAs (nortriptyline, desipramine) have lower adverse effect profile than tertiary amine TCAs (amitriptyline)
Duloxetine[b]	20-30 mg once daily, then increase weekly by same dosage to goal of 60 mg/d	120 mg/d (split BID)	Risk of serotonin syndrome; increased bleeding risk (care with anticoagulants), withdrawal syndromes with abrupt discontinuation, caution with hepatic failure	Sedation, fatigue, nausea, hyperhidrosis, dizziness, modest hypertension	Depression, anxiety, fibromyalgia, chronic musculoskeletal pain, urinary incontinence	Dosing for neuropathic pain is adequate for treatment of depression/anxiety
Supplements						
α-Lipoic acid	600 mg once daily	600 mg/d	Caution if tendency toward hypoglycemia	Nausea, rash, hypothyroidism	None	Generally well tolerated
Acetyl-L-carnitine	1000 mg 3 times per day	3000 mg/d (split TID)	None	Nausea, bloating, agitation	None	Generally well-tolerated
Topicals						
Lidocaine (5%) patch	Apply patch for 12 h	3 patches per application	Avoid over broken skin	Localized skin irritation; no notable systemic toxicity	None	May cut patch to shape

Continued on next page

TABLE 3. Continued

Agent	Dosing	Maximum dosage	Precautions	Common and notable adverse effects	Comorbid conditions treated	Comments
Tier 1, continued						
Capsaicin (8%) patch	Should be placed by medical staff trained in its usage using nonlatex gloves; pretreat area with 4% topical lidocaine for 60 min, confirm anesthesia, apply patch(es) to affected area (may cut to shape) for 60 min, wipe clean with provided soap	4 patches per application	Avoid face or placing over broken skin	Localized skin irritation; no notable systemic toxicity	None	Postprocedural skin irritation common; prescription oral analgesics frequently required for 7-10 d after application; single application may provide pain relief for up to 3 mo
Tier 2						
Antidepressants						
Venlafaxine[b]	37.5 mg once (extended release) or twice (immediate release) daily; increase by 75 mg/d weekly to initial goal of 150 mg/d	225 mg/d	Risk of serotonin syndrome; withdrawal syndrome with abrupt discontinuation; caution with cardiac disease or poorly controlled hypertension	Sedation, nausea, dizziness, headache, insomnia, nervousness, abnormal ejaculation, modest hypertension (dosage >150 mg/d)	Depression, anxiety, panic attacks, social phobia, hot flashes	Similar mechanism of action to duloxetine; consider trial if duloxetine not covered by insurance; higher dosages (150-225 mg/d) required for neuropathic pain; increasing blockage of norepinephrine reuptake at higher dosages causes increased risk of hypertension
Analgesics						
Tramadol	50 mg twice daily; increase every 4-7 d to maximum of 100 mg per dose 4 times per day	400 mg/d	Caution if history of addiction, analgesic misuse or diversion, severe psychiatric comorbidities, seizure disorder, taking other serotonergic agents, hepatic or renal dysfunction	Nausea, constipation, sedation, dizziness, flushing, seizures (dosages >400 mg/d)	Is a nonspecific analgesic that will cover multiple pain types	Blocks reuptake of serotonin and norepinephrine (like antidepressants) in addition to being μ-opioid receptor agonist; risk of serotonin syndrome when used with other serotonergic agents
Tier 3						
Analgesics						
Tapentadol	50 mg every 4-6 h prn; increase every 4-7 d to maximum of 100 mg every 4 h prn	600 mg/d	Caution if history of addiction, analgesic misuse or diversion, severe psychiatric comorbidities, seizure disorder, taking other serotonergic agents, hepatic dysfunction	Nausea, sedation, constipation, dizziness, pruritus, headache, hypotension, respiratory depression, seizure	Is a nonspecific analgesic that will cover multiple pain types	FDA approved for painful diabetic peripheral neuropathy; blocks reuptake of serotonin and norepinephrine (like antidepressants) in addition to being μ-opioid receptor agonist; risk of serotonin syndrome when used with other serotonergic agents
Opioids	15 mg oral immediate release morphine (or another opioid of equianalgesic dose such as 10 mg oxycodone) 3-4 times per day, transition to long-acting agents if regular use of short-acting agents	No maximum dosage	Caution if history of addiction, analgesic misuse or diversion, severe psychiatric comorbidities	Nausea, sedation, constipation, dizziness, pruritus, headache, respiratory depression	Is a nonspecific analgesic that will cover multiple pain types	Neuropathic pain studies used long-acting agents that should not be used in opioid-naive patients; begin with short-acting agents

[a]BID = twice daily; FDA = US Food and Drug Administration; prn = as needed; TID = 3 times daily; TCA = tricyclic antidepressant.

[b]All antidepressants and anticonvulsants carry an FDA warning that they may paradoxically cause worsening mood or emerging suicidality in a very small percentage of patients. Patients should be aware of both physical and emotional adverse effects of medications.

present. All patients with an idiopathic neuropathy should be encouraged to discuss this further with their family. If a family member accompanies the patient, a screening examination may suggest the diagnosis.

Algorithms have been developed to direct sequential genetic testing in suspected cases of hereditary neuropathy based on the inheritance pattern and whether the neuropathy is axonal or demyelinating.[19,52] Indiscriminate, nondirected serologic screens for hereditary neuropathies are expensive, have low yield, and often do not alter management, especially if there are no clinical features or family history to suggest a hereditary neuropathy.

Other Diagnostic Tests

Nerve Conduction Studies and Electromyography. In patients presenting with neurologic signs or symptoms suggestive of a peripheral neuropathy, electromyography (EMG) and nerve conduction studies (NCSs) are useful to confirm the suspected diagnosis, exclude mimickers (S1 radiculopathies in a patient with foot symptoms or carpal tunnel syndrome in a patient with hand paresthesias), localize the process (length dependent, length independent, multifocal), confirm the modalities affected (sensory, motor), define whether the neuropathy is secondary to axonal loss, demyelination, or both, and define the severity of the neuropathy. In cases of mild, non–functionally limiting length-dependent neuropathies in which there is little clinical uncertainty, EMG may not be necessary. Electromyography/NCSs are central to the evaluation of cases with diagnostic uncertainty, length-independent or multifocal processes, functionally limiting neuropathies, or any neuropathy severe enough to require neurologic consultation. Because the electrophysiologic pattern and pathophysiology are so central to the evaluation of atypical neuropathies, specialists will likely prefer to perform their own EMGs in patients with length-independent, multifocal, or severe neuropathies. Electromyography can still be useful directly to the nonspecialist for confirming the suspected diagnosis and excluding common mimickers such as mononeuropathies or radiculopathies.

Electromyography/NCSs assess the function and integrity of large, myelinated A beta nerve fibers. They do not assess small nerve fibers (C fiber and small myelinated A delta). As such, normal findings on EMG do not exclude a small-fiber peripheral neuropathy (which clinically presents with prominent pain, sensory loss, and dysautonomia).

Test of Small Nerve Fiber Function. A number of tests can evaluate possible small-fiber peripheral neuropathies (autonomic reflex screen, testing of sweat function, quantitative sensory testing, and epidermal skin biopsy for nerve fiber density); however, some are not widely available. Like peripheral pain pathways, the autonomic nervous system is under the control of small thinly myelinated and unmyelinated fibers. As such, tests of sweat (sudomotor) function, heart rate variability to respiration and Valsalva maneuver, blood pressure, and heart rate response to tilt (orthostatic hypotension) can objectively identify small nerve fiber dysfunction. These autonomic tests are most useful in neuropathies with notable autonomic impairment. In the evaluation of small-fiber neuropathies without clinical dysautonomia, tests of sweat function are more useful. All of these autonomic and sweat tests can be substantially influenced by medications, adversely affecting specificity.

Skin biopsy is a validated technique for determining intraepidermal nerve fiber density (somatic unmyelinated C-fiber nerve terminals) and has increasing availability. It has a sensitivity of 90% in diagnosing a small-fiber neuropathy, with specificity of 95% to 97%.[19]

Quantitative sensory testing refers to controlled applications of large- and small-fiber sensations to the skin to determine the threshold for detection. In small-fiber neuropathies, the response to thermal (hot and cold) stimuli is most pertinent, and the heat-pain threshold has very good sensitivity for a small-fiber neuropathy. Patient cooperation is necessary for an accurate measurement, although testing paradigms can help identify inconsistencies suggesting malingering or inattentiveness.

Nerve Biopsy. A nerve biopsy may be useful to assess for possible inflammatory-mediated neuropathies (vasculitis, sarcoidosis, chronic inflammatory demyelinating polyradiculoneuropathy), some infectious neuropathies (leprosy), or infiltrative neuropathies (carcinoma, lymphoma, amyloidosis, polyglucosan bodies). These

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neuropathies are frequently severe, progressive, and not otherwise explained by serologic and other ancillary testing. Neurologic consultation should be obtained before nerve biopsy. The sural nerve is most commonly biopsied, although the nerve selected for biopsy should be clinically involved. Importantly, a sural nerve biopsy is not indicated just because a neuropathy is idiopathic and unexplained by serologic and ancillary testing.

SYMPTOMATIC MANAGEMENT OF PERIPHERAL NEUROPATHY

The primary goal in the evaluation of neuropathy is to identify the etiology and if possible treat the underlying cause. However, even when the neuropathy has a treatable etiology (such as diabetes mellitus, vitamin B_{12} deficiency, or toxic exposure), treatment serves primarily to prevent further progression of the neuropathic symptoms. Symptoms present at the start of treatment or when a toxic agent is removed may improve and occasionally resolve. However, more commonly patients are left with lingering symptoms from the pretreatment neurogenic injury. In these cases and in those in which the neuropathy is idiopathic or untreatable, management is symptomatic.

Because most patients with a length-dependent peripheral neuropathy have sensory-predominant symptoms, patients should be counseled on the importance of foot care and properly fitted footwear. Patients should monitor their feet for early signs of ulceration or injury that sensory loss may mask.

One of the most limiting symptoms from peripheral neuropathy is neuropathic pain. Among diabetic patients with neuropathy, 11% to 26% have neuropathic pain.[21-23] Common neuropathic pain descriptors (burning, pins and needles, electrical, or shooting pain), whether used alone or in standardized surveys meant to identify neuropathic pain, are limited in regard to sensitivity and specificity.[53] In one diabetic cohort of patients with lower limb pain, the pain was attributable to diabetic neuropathy in only one-third of cases.[21] Allodynia (pain from a nonpainful stimulus such as the light touch of clothing) or hyperalgesia (excessive painful response to a normally painful stimulus such as pinprick) are highly specific for neuropathic pain but are uncommon.

Patients with neuropathic pain can be challenging to treat and have annual health care expenditures three times higher than those without pain.[54] As with any chronic pain state, comorbid depression, anxiety, and sleep disturbances are common, occurring in up to one-half of those with painful neuropathy.[55]

Several consensus algorithms for the treatment of chronic neuropathic pain have been proposed and compared.[56-60] Only one has focused explicitly on painful diabetic peripheral neuropathy.[61] However, because most randomized controlled trials for neuropathic pain have been performed for painful diabetic neuropathy or postherpetic neuralgia, this guideline mirrors the other algorithms (Table 3). First-line agents include anticonvulsants that block the α_2-δ ligand of the presynaptic calcium channel (gabapentin or pregabalin) and thereby decrease nociceptive transmission, tricyclic antidepressants (secondary amines such as nortriptyline and desipramine have a lower adverse effect profile than tertiary amines such as amitriptyline), or selective serotonin-norepinephrine reuptake inhibitors (duloxetine). The choice of first-line agents is based on patient comorbidities. For example, patients with comorbid depression may benefit from duloxetine, which can be used to treat both the depression and the neuropathic pain with similar dosing, whereas the effective dosage of tricyclic antidepressants for neuropathic pain is usually insufficient for therapeutic treatment of depression or anxiety. Similarly, tricyclic antidepressants, duloxetine, or pregabalin may be a good first-line agent in patients with comorbid fibromyalgia, whereas patients with comorbid chronic migraine may benefit from gabapentin or a tricyclic antidepressant. Comorbidities may also relatively contraindicate a particular agent. For example, tricyclic antidepressants should be avoided or used with caution in patients with preexisting orthostatic hypotension, cardiac dysrhythmia, or urinary hesitancy. Patients with small areas of localized pain may be able to be treated with topical agents (Table 3).

Effective dosages for neuropathic pain have been defined (Table 3), but failed medication trials are commonly caused by inadequate dosing. If a patient has a partial response to a first-line agent, a second first-line agent with a distinct mechanism of action should be added to the first agent. Combination therapy utilizing neuropathic pain medications with different mechanisms of action

has been repeatedly found to be more efficacious than single-agent treatment.[62] If a first-line agent fails, taper the agent and try another first-line agent. Second- and third-line agents include opioid analgesics. These agents are efficacious for neuropathic pain but have a higher long-term risk profile and should only be used in carefully selected patients with predefined pain relief and functional goals. If these goals are not met, then analgesics can be considered a failed trial similar to other neuropathic pain agents.

CONCLUSION

Peripheral neuropathy is commonly encountered in the primary care setting. In patients with systemic disease such as diabetes mellitus, peripheral neuropathy can be efficiently identified or ruled out by screening with a combination of vibration and light touch testing. Most peripheral neuropathies are length dependent, sensory predominant, and clinically mild to moderate in severity without notable functional limitations. These neuropathies can usually be effectively worked up and managed without specialty consultation. The highest-yield screening is for diabetes mellitus, vitamin B_{12} with methylmalonic acid, SPIEP, and family history suggesting an inherited neuropathy. Neuropathies that are length independent (polyradiculoneuropathies), multifocal, severe, functionally limiting, or rapidly progressive warrant neurologic consultation. Neuropathic pain can be effectively treated with an algorithmic approach.

Abbreviations and Acronyms: **EMG** = electromyography; **IGT** = impaired glucose tolerance; **MGUS** = monoclonal gammopathy of undetermined significance; **NCS** = nerve conduction study; **POEMS** = polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, skin abnormalities; **SPEP** = serum protein electrophoresis; **SPIEP** = serum protein immunofixation electrophoresis

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