

JAMA | Review

# Peripheral Neuropathy

## A Review

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**IMPORTANCE** Peripheral neuropathy, defined as damage to peripheral nerves, affects approximately 1% of adults worldwide. More than 200 causes of peripheral neuropathy exist, with symptoms ranging in severity from mild toe numbness to debilitating symptoms that can require a wheelchair. Diabetes is the most common cause of neuropathy, affecting approximately 206 million people worldwide.

**OBSERVATIONS** Peripheral neuropathy is typically length-dependent, which means that symptoms appear in the longest nerve axons (toes) and progress proximally over time. Peripheral neuropathy is typically symmetric and affects sensory axons more than motor axons. Diabetic neuropathy, which is often associated with both sensory symptoms, such as pain, tingling, or numbness; mild weakness; and autonomic symptoms, such as orthostatic hypotension, accounts for more than 50% of peripheral neuropathy in Western populations. Other causes of neuropathy include hereditary causes, such as Charcot-Marie-Tooth disease, toxic neuropathy from medications (chemotherapies [eg, cisplatin, paclitaxel, vincristine], amiodarone, or HIV nucleotide reverse transcriptase inhibitors [eg, stavudine, zalcitabine]); alcohol; vitamin deficiencies such as vitamin B<sub>12</sub>; and monoclonal gammopathies. Up to 27% of adults with neuropathy have no identifiable etiology for their neuropathy after diagnostic testing. Recommended initial testing includes blood glucose (for diabetes), serum B<sub>12</sub> with metabolites (methylmalonic acid with or without homocysteine), and serum protein electrophoresis with immunofixation (for monoclonal gammopathies). First-line medications for neuropathic pain are the  $\alpha$ 2- $\delta$  calcium channel subunit ligands, such as gabapentin and pregabalin; serotonin norepinephrine reuptake inhibitors, such as duloxetine and venlafaxine; and tricyclic antidepressants, such as amitriptyline and nortriptyline. Pain often persists despite medical management. At least a 50% reduction in pain was observed in 38% of those with painful diabetic peripheral neuropathy receiving 1200 mg of gabapentin daily. Combination drug therapies for neuropathic pain may provide added benefit. The prognosis of peripheral neuropathy depends on its underlying cause, but complete reversal of nerve damage is uncommon even in cases for which there are available treatments.

**CONCLUSIONS AND RELEVANCE** Peripheral neuropathy affects approximately 1% of adults worldwide and may cause sensory, motor, and autonomic symptoms. Diabetes is the most common cause of peripheral neuropathy in Western countries. First-line therapies for neuropathic pain include gabapentin, pregabalin, duloxetine, and amitriptyline.

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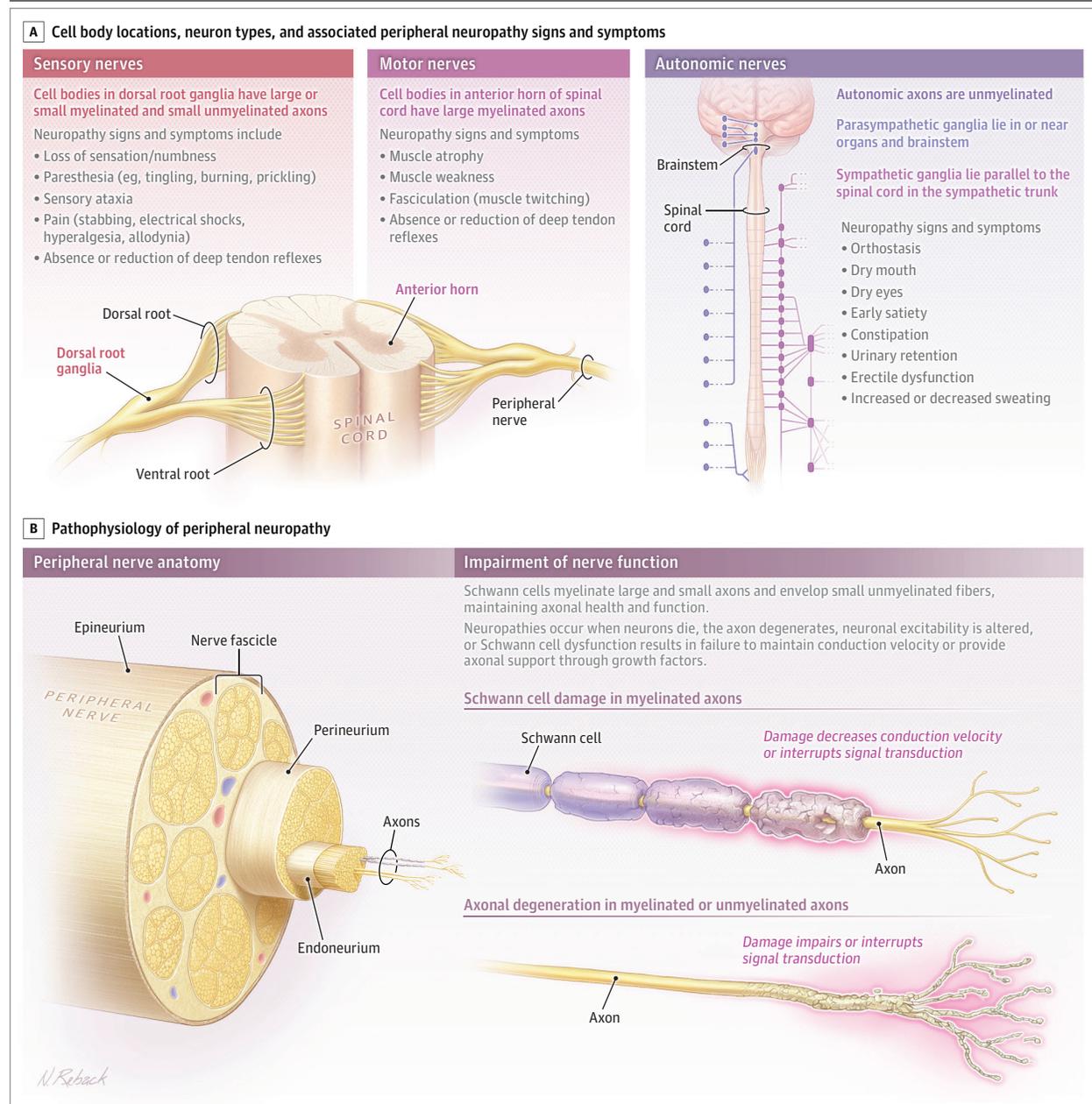
**P**eripheral neuropathy, defined as damage to the peripheral nerves, affects approximately 1% of adults worldwide.<sup>1</sup> Symptoms range in severity from mild numbness in the toes to, in rare instances, a severe neuropathy that may result in need for a wheelchair.

The prevalence of peripheral neuropathy increases with age and has been estimated to affect 6% to 10% of the population older than 60 years.<sup>1,2</sup> Diabetic neuropathy affects approximately 206 million people worldwide and was identified in 2021 as the fifth most common neurological cause of disability by the Global Burden of Disease.<sup>3</sup> In the US and Europe, diabetes, alcohol use, neurotoxic

chemotherapies (such as paclitaxel, vincristine, and cisplatin), and genetic factors are the most common causes of peripheral neuropathy. In lower-income countries, infectious etiologies including leprosy and HIV are more common causes of neuropathy.<sup>4</sup>

Length-dependent peripheral neuropathy (LDPN), also known as *distal symmetric polyneuropathy*, is the most common type of neuropathy seen by generalist clinicians and has features that are more sensory than motor. LDPN typically begins in the toes and may slowly progress proximally toward the knees and hands. This review summarizes current evidence regarding diagnosis and treatment of LDPN.

Figure 1. Anatomic Basis for Peripheral Neuropathy Symptoms



Neuronal cell bodies reside in the anterior horn of spinal cord (motor neurons), dorsal root ganglia (sensory neurons), or autonomic ganglia (autonomic neurons). Motor neuron axons are primarily large diameter and myelinated. Sensory neuron axons range from large myelinated, small myelinated, or small

unmyelinated. Autonomic neuron axons are small unmyelinated. Peripheral neuropathy may be due to primary damage to axon, which most often manifests as Wallerian degeneration, or primary damage to the myelin, which most often manifests as demyelination.

## Methods

We searched PubMed for English-language articles published between February 1, 2015, and August 31, 2025, for studies of humans using the search terms *length-dependent peripheral neuropathy*, *length-dependent polyneuropathy*, *distal symmetric neuropathy*, and *distal symmetric polyneuropathy*. Articles from PubMed-indexed journals were also identified through the use of the authors' own files. Of 787

articles identified, 100 were included, consisting of 13 randomized clinical trials, 16 meta-analyses, 9 clinical guidelines, 35 cross-sectional studies, 11 longitudinal cohort studies, and 16 reviews.

## Pathophysiology

Peripheral neuropathy results from damage to sensory, motor, and autonomic neurons (Figure 1). Chronic hyperglycemia damages

peripheral nerves through several interrelated biochemical, vascular, and inflammatory mechanisms. Schwann cells, which myelinate large axons or envelop small unmyelinated fibers, maintain axonal health through growth factors (eg, nerve growth factor, brain-derived neurotrophic factor, vascular endothelial growth factor) and by regulating axonal iron and lactate metabolism. Damage to Schwann cells slows conduction and may contribute to axonal degeneration.<sup>5</sup> Neuropathies develop when neurons die, axons degenerate, neuronal excitability is altered, or support from Schwann cells fails. If neuronal survival is preserved, axonal regeneration can occur at a rate of 1 to 3 mm per day after the cause of the injury is corrected. LDPN typically manifests primarily as sensory signs and symptoms, such as numbness and paresthesia, indicative of damage to the large fiber sensory axons involved in proprioception and vibration sensation and/or the small fiber sensory axons responsible for temperature and pain sensations. The sensory predominance of LDPN is not fully understood, but it may be partly due to the presence of fenestrated capillaries in the dorsal root ganglia, which reduce the blood-neuron barrier and increase susceptibility to systemic factors such as hyperglycemia or exposure to neurotoxic medications.<sup>6,7</sup> Axons innervating the toes can be up to 3 feet long and require high metabolic support for axonal transport, which explains why LDPN first affects the toes and later the lower legs and hands.<sup>8</sup>

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## Clinical Presentation of LDPN

### History

Typically, LDPN initially affects the sensory function of a peripheral nerve and progresses slowly over weeks to months in a symmetric fashion. Symptoms are typically sensory loss (numbness) and paresthesias (tingling, prickling) beginning in the toes and feet. Neuropathic pain (eg, burning, stabbing, electrical shocks, hyperalgesia, allodynia) may be present (Figure 2). As the neuropathy progresses, symptoms extend proximally up the lower legs. Patients with symptoms up to the knees often report symptoms in the fingertips because the length of the nerves to the fingertips is similar to the distance to of the nerves to the knees. When present, motor weakness begins in the toes with weakness of flexion and extension and is typically mild. Patients with LDPN may have autonomic symptoms, such as lack of sweating in the feet, and those with diabetes or amyloidosis may experience postural lightheadedness, dry eyes/dry mouth, postprandial nausea and vomiting, diarrhea, constipation, and erectile dysfunction.<sup>9,10</sup>

Clinicians should assess patients for common causes of LDPN including diabetes, alcohol use disorder, conditions associated with vitamin B<sub>12</sub> deficiency such as inflammatory bowel disease, celiac disease, bariatric surgery, and lack of intake of meat, poultry, and eggs. Medications that can impair peripheral nerve function include chemotherapies such as paclitaxel, vincristine, and cisplatin, pyridoxine (vitamin B<sub>6</sub>), amiodarone, and HIV-related treatments such as nucleotide reverse transcriptase inhibitors, eg, stavudine and zalcitabine (Table 1).<sup>11-14</sup> Clinicians should determine whether patients have foot deformities such as pes cavus (high arches) or hammer toes (curled toes) and whether they use walking aids. Patients should also be asked about family history, including questions about family history of neuropathy symptoms. Approximately one-third

to one-half of all idiopathic neuropathies are likely inherited, most commonly Charcot-Marie-Tooth disease.<sup>15</sup>

### Physical Examination

Clinicians should assess sensation beginning at the dorsum of the great toe and index finger and moving proximally up the leg and arm until a level of normal sensation is established. Large fiber (vibration, proprioception, and light touch) and small fiber (pinprick and temperature) function should be assessed. The presence of a Romberg sign (unsteadiness with feet together, arms outstretched, and eyes closed) indicates impaired proprioception. Motor examination may show intrinsic foot atrophy and toe flexion/extension weakness and may involve the ankles and hands. Ankle deep tendon reflexes are commonly reduced or absent in patients with LDPN. Although gait is normal in patients with mild sensory predominant LDPN, those with more severe neuropathy may have an unsteady, wide-based gait due to large fiber proprioceptive sensory loss (sensory ataxia). Patients with Charcot-Marie-Tooth disease typically present with distal foot and ankle weakness, absence of positive neuropathic sensory symptoms (tingling, burning, electrical), and presence of pes cavus and hammer toes.

### Atypical Neuropathy Features

Characteristics that are atypical for LDPN include severe motor weakness; prominent autonomic symptoms such as orthostatic intolerance, postprandial nausea, and vomiting and diarrhea; symptom onset and progression over days to weeks (instead of a slower onset); non-length-dependent patterns of sensory loss or weakness; asymmetry of the neuropathy; and presence of weight loss, fever, rash, and other organ system involvement.<sup>16</sup> These features may be associated with an immune, inflammatory, infectious, or neoplastic process and should lead to a prompt referral to a neurologist and potentially other specialists (rheumatology, infectious disease, oncology) to aid in the evaluation. Failure to recognize atypical presentations may lead to delayed treatment and poorer outcomes.

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## Diagnostic Testing

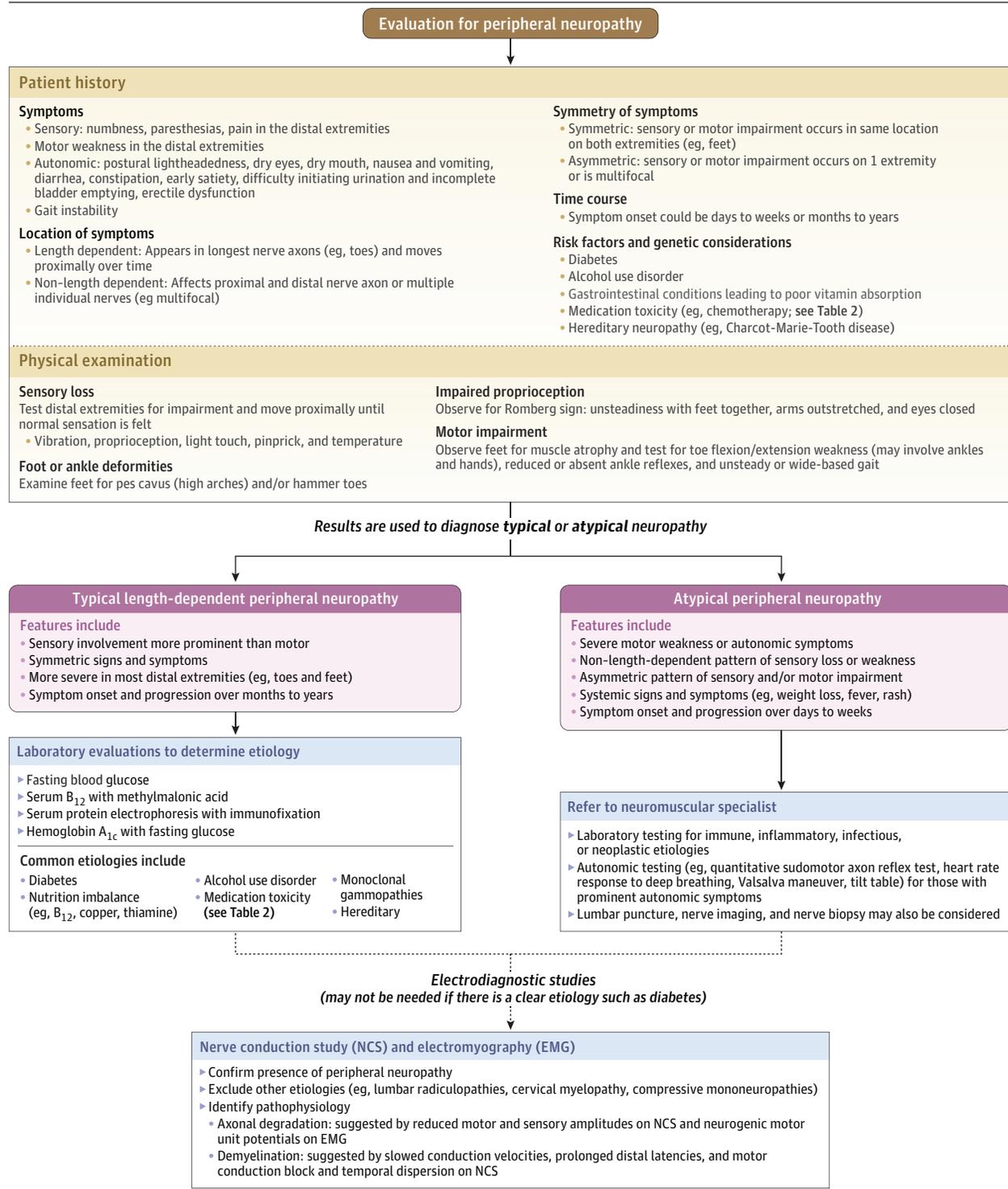
### Laboratory Studies

The diagnosis of LDPN is based on clinical signs and symptoms. Laboratory tests can identify specific etiologies associated with LDPN, such as diabetes, vitamin B<sub>12</sub> deficiency, or monoclonal gammopathies (Box).<sup>17,18</sup> Recommended testing includes blood glucose, serum B12 with metabolites (methylmalonic acid with or without homocysteine), and serum protein electrophoresis with immunofixation.<sup>17</sup> If an etiology is not identified and routine fasting blood glucose testing is normal, other tests for pre-diabetes or diabetes such as hemoglobin A<sub>1c</sub> (HbA<sub>1c</sub>) or a glucose tolerance test may be considered, especially if the peripheral neuropathy is accompanied by pain.

### Electrodiagnostic Studies

Electrodiagnostic studies, consisting of nerve conduction studies (NCS) to assess large-fiber nerves and electromyography (EMG), can help diagnose peripheral neuropathy.<sup>19</sup> Findings on NCS that suggest LDPN include (1) sensory nerves affected earlier and more severely than motor fibers; (2) lower limb NCS affected

Figure 2. Diagnostic Algorithm for Peripheral Neuropathy



earlier and more severely than the upper limbs; and (3) symmetric NCS abnormalities in nerves of similar length. NCS can help identify the underlying pathophysiology (ie, axonal or demyelinating). Axonal features include reduced motor and sensory amplitudes on NCS and neurogenic motor unit potentials on EMG. NCS findings that suggest demyelination include slowed conduction velocities, prolonged distal latencies, conduction block, and temporal disper-

sion. Most length-dependent neuropathies are axonal, including diabetes, vitamin B<sub>12</sub> deficiency, chemotherapy-induced peripheral neuropathy and the axonal subtype of Charcot-Marie-Tooth type 2. Etiologies of demyelinating LDPN include variants of chronic inflammatory demyelinating neuropathy (CIPD) (including antibodies to neurofascin and contactin), and Charcot-Marie-Tooth type 1 disease. Although electrodiagnostic testing is recommended

Table 1. Medication-Induced Neuropathies

Medication	Develop symptoms <sup>a</sup>	Onset time <sup>b</sup>	Characteristic features of neurotoxicity <sup>c,d</sup>
<b>Chemotherapeutics</b>			
Cisplatin, carboplatin	Dose-dependent; 30%-80% <sup>e</sup>	Subacute	When severe, there is sensory ataxia; neuropathy can progress for weeks after drug discontinuation
Oxaliplatin	Dose-dependent; 30%-80% <sup>e</sup>	Acute to subacute	Cold-induced dysesthesia acutely; when severe, there is sensory ataxia; neuropathy can progress for weeks after drug discontinuation
Paclitaxel	Dose-dependent; 30%-80% <sup>e</sup>	Subacute	Acute pain syndrome
Vincristine	Dose-dependent; 30%-80% <sup>e</sup>	Subacute	More likely to cause weakness
Bortezomib	Dose-dependent; 30%-80% <sup>e</sup>	Subacute	Rare mononeuritis multiplex or polyradiculoneuropathy
Ixabepilone	Dose-dependent; 30%-80% <sup>e</sup>	Subacute	
Ado-trastuzumab emtansine	Common; 30%	Subacute	
Brentuximab vedotin	Common; >50%	Subacute	
Suramin	Common at high doses	Subacute	Often demyelinating
Podophyllotoxins (etoposide, teniposide)	Rare; <5%	Subacute	
Eribulin mesylate	Common; 30%	Subacute	
Thalidomide	Common; 30%	Subacute	
Immune checkpoint inhibitors	Rare; <10%	Acute to subacute	Polyradiculoneuropathy, plexopathy, cranial neuropathy, and mononeuritis multiplex; may recover with immunotherapy
<b>Antibiotics</b>			
Metronidazole	Common at high doses, but rare if <42 g over 4 wk <sup>11</sup>	Subacute	
Triazole antifungals	Rare, but may be higher with chronic use	Chronic	
Isoniazid	Rare with vitamin B <sub>6</sub> supplementation	Subacute	
Ethambutol	Rare	Subacute	May also cause retrobulbar optic neuropathy
Linezolid	30% With chronic use		
Fluoroquinolones	Rare	Subacute	Controversial whether it causes peripheral neuropathy
Dapsone	Rare	Subacute to chronic	Motor-predominant axonal; may mimic mononeuritis multiplex or motor neuron disease; poor recovery
Nitrofurantoin	Very rare	Chronic	Can be severe, mimicking Guillain-Barré syndrome
Chloramphenicol	Rare	Chronic	
Zalcitabine (ddC), didanosine (ddl), stavudine (d4T)	Common; 30%	Subacute to chronic	
<b>Immunomodulators</b>			
Leflunomide	Rare; <10%	Subacute to chronic	
Tumor necrosis factor- $\alpha$ antagonists (infliximab, etanercept, adalimumab, certolizumab, golimumab)	Rare	Subacute	Most often polyradiculopathy mimicking Guillain-Barré syndrome or CIDP
Colchicine	Rare	Subacute to chronic	Typically neuromyopathy with proximal weakness <sup>12</sup>
Chloroquine	Rare	Subacute to chronic	Often with neuromyopathy with proximal weakness; may be demyelinating
<b>Miscellaneous</b>			
Nitrous oxide	Rare; <10% in frequent users	Chronic	Myeloneuropathy with subacute combined degeneration via vitamin B <sub>12</sub> deficiency mechanisms <sup>13</sup>
Pyridoxine	Common with prolonged doses >100 mg daily	Chronic	When severe there is sensory ataxia
Amiodarone	Common	Subacute to chronic	May be demyelinating
Disulfiram	Rare	Subacute	Weakness common
Procainamide	Rare	Subacute	Sensorimotor demyelinating; can mimic CIDP
Hydralazine	Rare	Subacute	Related to vitamin B <sub>6</sub> deficiency
Phenytoin	Rare	Chronic	

Abbreviation: CIDP, chronic inflammatory demyelinating neuropathy.

<sup>a</sup> Reliable frequency data are not available for most drugs.

<sup>b</sup> Acute indicates hours to days; subacute, days to weeks; and chronic, weeks to months.

<sup>c</sup> Presents as an axonal length-dependent sensory-predominant peripheral neuropathy unless otherwise described.

<sup>d</sup> Reversibility of toxic axonal sensory-predominant peripheral neuropathies is

inconsistently reported. Some patients experience complete recovery, typically over several months, while others continue to have permanent neuropathic symptoms. Generally, the severity of the neuropathy predicts the likelihood of recovery.

<sup>e</sup> Chemotherapy-induced peripheral neuropathy frequency and severity are dose dependent; frequency ranges based on dosage and sensitivity of neuropathy assessments.

**Box. Common Questions About Peripheral Neuropathy****What blood laboratory tests can help identify the etiology of a length-dependent peripheral neuropathy?**

Fasting glucose or hemoglobin A<sub>1c</sub>, vitamin B<sub>12</sub> and methylmalonic acid, and serum monoclonal protein studies (serum protein electrophoresis and immunofixation) are laboratory tests that can help identify the etiology of a length-dependent peripheral neuropathy.

**What chemotherapy treatments are most commonly associated with peripheral neuropathy and what is the typical time course of symptoms?**

Taxanes (paclitaxel), vinca alkaloids (vincristine), platinates (cisplatin, oxaliplatin), and proteasome inhibitors (bortezomib) are neurotoxic chemotherapeutics most commonly associated with chemotherapy-induced peripheral neuropathy (CIPN). CIPN typically appears during the course of chemotherapy treatment, may limit the chemotherapy dose that can be received, and typically improves (albeit often incompletely) after cessation of drug (except in the case of platinates, which may worsen for weeks after drug cessation).

**What are the first-line medications for neuropathic pain?**

First-line medications are the  $\alpha$ 2- $\delta$  calcium channel subunit ligands (gabapentin and pregabalin), serotonin norepinephrine reuptake inhibitors (duloxetine, venlafaxine), and tricyclic antidepressants (amitriptyline, nortriptyline). The selection of medication should consider the adverse effect profile and interactions with concomitant medications. Addition of a second first-line agent from a different class may further improve neuropathic pain symptoms.

for patients with peripheral neuropathies who have atypical features, electrodiagnostic testing to diagnose symmetric LDPN is controversial. The American Diabetes Association stated that routine EMG is not necessary in patients with diabetes who present with a symmetric neuropathy.<sup>20</sup> However, EMG may change the diagnosis or management in 24% to 43% of patients undergoing evaluation for peripheral neuropathy,<sup>21</sup> including patients with typical signs and symptoms of neuropathy. Electrodiagnostic testing can identify other conditions that may present similarly to peripheral neuropathy, including compressive neuropathies and lumbosacral radiculopathies, which require different evaluation and treatment.<sup>22</sup>

**Autonomic Testing**

Autonomic testing is typically reserved for patients with LDPN who have prominent autonomic symptoms such as postural lightheadedness, postprandial nausea and vomiting, and diarrhea and constipation. The quantitative sudomotor axon reflex test, which measures sweating, is performed at 4 sites (foot, distal leg, proximal leg, and forearm) and consists of iontophoresis, a noninvasive device that uses an electrical current to deliver acetylcholine into the skin, which activates the axon terminal. This causes release of acetylcholine, which stimulates muscarinic receptors on the eccrine sweat glands and the volume of sweat is collected and quantified. Quantitative sudomotor axon reflex tests are 73% to 80% sensitive for detection of distal small fiber neuropathy.<sup>23</sup> Cardiovascular testing evaluates the heart rate response to deep breathing. A reduction in this response, adjusted for age, is nearly as sensi-

tive as NCS for detecting polyneuropathy (no quantitative data available).<sup>24</sup> The presence of autonomic neuropathy is more common in diabetes, amyloidosis, toxic causes (ie, vincristine), and other less common etiologies such as Sjogren syndrome or paraneoplastic causes.

**Skin Biopsy for Epidermal Nerve Fiber Density**

Skin biopsy can help identify a distal small fiber neuropathy, which is a length-dependent neuropathy limited to pain and temperature dysfunction. Skin biopsy has limited utility in determining the cause of distal small fiber neuropathy. When performed, skin punch biopsies are obtained approximately 10 cm above the lateral malleolus and, in some instances, performed at a second site such as the distal thigh. Epidermal nerve fiber density values less than the 5th percentile compared with age- and sex-matched controls are considered abnormal.<sup>25</sup> Skin biopsy has a sensitivity of 80% and specificity of 90% for diagnosis of small fiber neuropathy, with history and examination as the criterion standard.<sup>26,27</sup> A substantial limitation with skin biopsy is the variability between normative values among different laboratories, which can result in the same biopsy being interpreted differently by various laboratories.<sup>25,28</sup>

**Diagnosis and Treatment of Common Forms of LDPN****Neuropathy Associated With Diabetes**

Diabetes accounts for up to 50% of all peripheral neuropathy cases worldwide.<sup>1</sup> Approximately 20% to 40% of patients with diabetes report symptoms of LDPN. When objective testing, such as quantitative sensory testing or NCS, is used, approximately 50% of people with diabetes have peripheral neuropathy.<sup>29-31</sup> The risk of developing diabetes LDPN is associated with longer duration of diabetes, older age, higher HbA<sub>1c</sub> values, presence of diabetic retinopathy, obesity, and hyperlipidemia.<sup>32,33</sup> In newly diagnosed diabetes, LDPN typically presents with painful sensory-predominant symptoms in the feet, and has been associated with concomitant metabolic syndrome such as obesity, hyperlipidemia, and hypertension.<sup>33,34</sup> Compressive mononeuropathies such as compression of the median nerve at the wrist (carpal tunnel syndrome) or compression of the ulnar nerve at the elbow are common in patients with diabetes.<sup>35,36</sup> Chronic hyperglycemia, often over decades, can cause LDPN with sensory, motor, and autonomic symptoms. Treatment consists of controlling glucose and treating conditions such as obesity, hyperlipidemia, and hypertension.<sup>37</sup> Glycemic control, defined as HbA<sub>1c</sub> less than 5.7%, is more effective at preventing peripheral neuropathy in people with type 1 diabetes, compared with people with type 2 diabetes. However, glycemic control has modest effects on improving peripheral neuropathy symptoms or preventing progression in those with established peripheral neuropathy from type 2 diabetes.<sup>37,38</sup>

Treatment-induced neuropathy of diabetes (or insulin neuritis) is a variant of diabetic LDPN that may occur after rapid correction of hyperglycemia ( $\geq 2\%$  drop in HbA<sub>1c</sub> over 3 months).<sup>39</sup> This condition is characterized by acute severe painful small fiber and autonomic neuropathy developing within 8 weeks of the rapid decrease in HbA<sub>1c</sub>. Although the incidence is unknown, in a 2015 retrospective review from a tertiary outpatient diabetic center, 10.9% (104

of 954) of patients with diabetes developed treatment-induced neuropathy of diabetes over a 5-year period.<sup>40</sup> In that study, an overall reduction in HbA<sub>1c</sub> of more than 4 percentage points over 3 months was associated with a risk of developing treatment-induced neuropathy in diabetes of more than 80%.<sup>40</sup> Inflammatory diabetic radiculoplexus neuropathy is a rare but severe type of neuropathy associated with type 2 diabetes mellitus that typically presents as sudden-onset unilateral painful neuropathy that localizes to the lumbar plexus affecting the proximal leg, causing severe weakness and muscle atrophy in the thigh and hip, and often associated with weight loss.<sup>41</sup> Based on a 2019 study of all residents of Olmsted County, Minnesota, the annual incidence of diabetic radiculoplexus neuropathy was estimated to be 2.79 per 100 000.<sup>42</sup>

### Neuropathy Due to Nutritional Imbalances

#### Vitamin B<sub>12</sub>

Vitamin B<sub>12</sub> deficiency is uncommon except among people who avoid all foods derived from animals and those with poor gastrointestinal absorption of vitamin B<sub>12</sub>, such as due to atrophic gastritis, gastric bypass, prolonged proton pump inhibitor use, pernicious anemia, inflammatory bowel disease such as Crohn disease, surgical resection of the ileum, and metformin use. Patients with B<sub>12</sub> deficiency often present with sensory loss, paresthesia, ataxia, preserved reflexes, and potential cognitive deficits reflecting concomitant central nervous system involvement.

Treatment typically involves subcutaneous or intramuscular injections of 1 mg of vitamin B<sub>12</sub> weekly for 1 month, followed by monthly 1-mg B<sub>12</sub> intramuscular injections. High-dose oral replacements (1-2 mg daily) can be similarly effective.<sup>43</sup>

#### Copper

While rare, copper deficiency can present similarly to B<sub>12</sub> deficiency and should be considered in patients with sensory ataxia that develops over weeks to months.<sup>44</sup> Copper deficiency is associated with small intestine malabsorption or zinc ingestion and is treated with oral or parenteral replacement (2-4 mg daily).<sup>45</sup>

#### Vitamin B<sub>6</sub> (Pyridoxine)

Vitamin B<sub>6</sub> toxicity is associated with sensory neuropathy, which affects the dorsal root ganglia and may cause sensory loss and ataxia that are irreversible. Vitamin B<sub>6</sub> toxicity is primarily due to excessive intake of vitamin B<sub>6</sub>, typically from supplements of more than 2 g per day.<sup>46</sup> However, neuropathy has been reported even with long-term (more than 6 months) use of 50 mg per day of vitamin B<sub>6</sub>. Vitamin B<sub>6</sub> deficiency, which primarily occurs with medications (isoniazid, hydralazine, levodopa, and vincristine), dialysis, autoimmune diseases such as rheumatoid arthritis, and malabsorption, can be prevented by administering vitamin B<sub>6</sub>. However, there is no clear evidence that vitamin B<sub>6</sub> supplementation prevents peripheral neuropathy in these settings.<sup>47</sup> The recommended dosage to replace vitamin B<sub>6</sub> is 50 mg per day, but should only be administered in cases of deficiency or prophylactically for the above-described instances.

#### Thiamine

Thiamine (vitamin B<sub>1</sub>) deficiency manifests as wet (heart failure) or dry (neuropathic) beriberi, although overlapping presentations

are common. No precise epidemiology data are available, but beriberi appears to be uncommon in high-income countries, except among individuals with severe alcohol use disorder or malnutrition and after bariatric surgery. Beriberi can appear as axonal LDPN, often involving cranial nerves II, III, IV, VI, VII, VIII, IX, and X, or as polyradiculoneuropathy similar to Guillain-Barré syndrome.<sup>48</sup> It may also present with Wernicke-Korsakoff syndrome, which involves confusion, ataxia, and eye movement abnormalities (such as gaze-evoked nystagmus, impaired abduction, conjugate gaze palsy, impaired vestibulo-ocular reflex); memory loss; and chronic confabulation. Patients with thiamine deficiency should receive thiamine before glucose administration to avoid exacerbating the deficiency (carbohydrate metabolism consumes thiamine as a co-factor), especially in Wernicke-Korsakoff syndrome. Acute thiamine replacement is typically given at a dosage of 100 to 200 mg intravenously 3 times daily for 3 days, followed by long-term oral supplementation of 100 mg daily. A daily oral dose of 100 mg of thiamine is recommended for high-risk individuals, such as those with malnutrition or alcohol use disorder.

### Neuropathy Due to Alcohol

Excessive alcohol use is commonly associated with LDPN, with a prevalence of approximately 46% in individuals with chronic alcohol use disorder.<sup>49</sup> However, because alcohol consumption is often underreported, it can be challenging to determine whether alcohol-related neuropathy is due to alcohol neurotoxicity or vitamin deficiencies, such as thiamine deficiency. One study reported that in the presence of adequate thiamine levels, long-term alcohol use, defined as regular intake of more than 100 g (>7 glasses of wine or cans of beer) of ethanol daily for at least 10 years, was associated with a painful small fiber neuropathy.<sup>50</sup> Avoidance of alcohol or reduced alcohol intake is advised for individuals with peripheral neuropathy due to its neurotoxicity.<sup>51</sup>

### Neuropathies Associated With Monoclonal Proteins

Approximately 10% of patients with peripheral neuropathy diagnosed by electrodiagnostic studies have a monoclonal gammopathy.<sup>52</sup> Neuropathy is more common with IgM than with IgA or IgG monoclonal proteins.<sup>53</sup> Testing requires assessment of serum protein electrophoresis, serum immunofixation, and free light chains quantification.<sup>54</sup> Monoclonal gammopathies occur in 3.2% of individuals older than 50 years and in 5% of those older than 70 years.<sup>55</sup> Because the prevalence of peripheral neuropathy and monoclonal gammopathy both increase with age, their coexistence may be coincidental. People diagnosed with monoclonal gammopathy should be referred to hematology for evaluation of plasma cell disorders (eg, multiple myeloma, Waldenstrom macroglobulinemia, amyloid light chain amyloidosis, POEMS [polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes] syndrome).<sup>9,56,57</sup>

LDPN can occur with IgM-associated disorders (neuropathy with antibodies to myelin-associated glycoprotein [antimyelin-associated glycoprotein] and Waldenstrom macroglobulinemia) and amyloid light chain amyloidosis. Antimyelin-associated glycoprotein neuropathy presents with progressive distal lower limb sensory loss and marked gait ataxia with demyelinating findings on EMG.<sup>58,59</sup> Patients with Waldenstrom macroglobulinemia

can have atypical features of neuropathy such as onset over days to weeks, non-length-dependent pattern, and asymmetry or may have symptoms similar to antimyelin-associated glycoprotein.<sup>60</sup> Amyloid light chain amyloidosis presents with a painful LDPN with autonomic symptoms such as orthostatic hypotension, diarrhea, erectile dysfunction, cardiac involvement (heart failure, orthopnea, lower extremity edema), weight loss, and fatigue.<sup>9,61</sup> Treatment of the underlying plasma cell disorder may stabilize or improve neuropathy.<sup>62,63</sup>

### Hereditary Neuropathies

Hereditary neuropathies range from mildly symptomatic to severe disability.<sup>64</sup> The most common hereditary neuropathy is Charcot-Marie-Tooth disease, which affects both motor and sensory nerves causing muscle weakness and atrophy in distal extremities and is often associated with foot deformities (pes cavus, hammer toes).<sup>65</sup> Typically, patients experience minimal pain or sensory symptoms. Charcot-Marie-Tooth disease has a prevalence of 10 to 30 per 100 000 and should be considered in patients with peripheral neuropathy who have a family history of neuropathy.<sup>66</sup> The most common form of Charcot-Marie-Tooth disease presents before the age of 10 years in 50% of patients, and before the age of 20 years in 70% of patients.<sup>67</sup> Charcot-Marie-Tooth disease has more than 100 known genetic causes, leading to different subtypes with varied severity and progression. Electrodiagnostic testing can distinguish between axonal or demyelinating subtypes.<sup>68</sup> The most frequent genetic subtypes of Charcot-Marie-Tooth disease are autosomal dominant and are caused by duplication of *PMP22* gene (CMT1A), deletion in *PMP22* (HNPP), or point variants in *GJB1* (CMTX1), *MPZ* (CMT1B), or *MFN2* (CMT2A).<sup>67,69-71</sup> Patients with Charcot-Marie-Tooth disease should first be tested for *PMP22* duplications/deletions. If not present, next-generation sequencing techniques should be performed to assess for pathogenic variants frequently associated with Charcot-Marie-Tooth disease.<sup>72</sup>

Other hereditary neuropathies affect only motor nerves (distal hereditary motor neuropathies), sensory and autonomic nerves (hereditary sensory and autonomic neuropathies), or may include both the central and peripheral nervous system (spinocerebellar ataxias and hereditary spastic paraplegias). Pathogenic repeat expansion of the *RFC1* gene is a common cause of sensory LDPN.<sup>73</sup> Hereditary transthyretin amyloidosis, caused by genetic variants in the transthyretin gene, can present with a length-dependent sensory neuropathy and is commonly associated with autonomic symptoms such as orthostatic hypotension and diarrhea. Most inherited neuropathies lack specific therapies. However, hereditary transthyretin amyloidosis can be treated with medications that stabilize the variant form of transthyretin, which prevents dissociation, misfolding, and assembly into amyloid (diflunisal, tafamidis), and medications that reduce transthyretin synthesis (patisiran, vutrisiran, eplontersen).<sup>74-79</sup> A randomized clinical trial of 130 participants reported that 29.7% of patients treated with diflunisal had neuropathic stabilization, compared with 9.4% of those who received placebo.<sup>78</sup> Phase 3 randomized clinical trials of the medications that reduce transthyretin synthesis have reported marked improvement in neuropathy impairment scores and Norfolk quality of life measures compared with placebo at 15 or 18 months.<sup>74,75,79</sup>

### Neuropathy Due to Medications

Multiple medications are associated with neuropathies<sup>80</sup> (Table 1). Chemotherapy-induced peripheral neuropathy (CIPN), which causes a sensory-predominant neuropathy, affects approximately 50% of patients receiving neurotoxic chemotherapy and may be a dose-limiting toxicity that negatively affects cancer treatment.<sup>81,82</sup> There are no preventive measures for CIPN. Taxanes (ie, paclitaxel), vinca alkaloid medications (ie, vincristine), platinates (ie, cisplatin and oxaliplatin), and proteasome inhibitors (ie, bortezomib) are the most common causes of dose-limiting CIPN and cause CIPN in a dose-dependent manner. Vinca alkaloid medications may also cause length-dependent weakness. Platinates are more commonly associated with sensory ataxia, and CIPN can worsen for weeks after discontinuation of platinates. Although CIPN can resolve after drug cessation in some individuals, studies have reported that CIPN symptoms may persist for years.<sup>81,83</sup>

### Autoimmune and Inflammatory Neuropathies

Although less common and not usually presenting as LDPN, neuropathies caused by autoimmune or inflammatory conditions such as CIDP, vasculitis, or sarcoidosis are important to identify because they can be treated with immunomodulatory or immunosuppressive medications such as prednisone or intravenous immunoglobulin.<sup>84-86</sup> Patients presenting with neuropathy progressing over days to weeks should be promptly evaluated by a neuromuscular neurologist to establish a specific diagnosis, which often has treatment options tailored to the underlying immune disorder that halt progression and may improve the peripheral neuropathy (Figure 2).

### Management of Peripheral Neuropathy Symptoms

#### Sensory Symptoms

Lack of sensation due to LDPN can lead to unrecognized injuries (burns, cuts) that may ulcerate and become infected. Patients with diabetes may also have concurrent microvascular disease that impedes wound healing. To mitigate complications from sensory loss, patients with LDPN should perform daily foot inspections, wear properly fitting shoes to prevent blistering, and check water temperature with their hands prior to immersing their feet in hot water. Podiatric consultations should be considered for patients at high risk of foot ulcers (eg, patients with diabetes).<sup>37</sup>

Neuropathic pain and paresthesia due to LDPN may be managed with conservative measures, topical treatments, oral medications, and invasive neuromodulation (Table 2).<sup>87-97</sup> For some patients, foot soaks in cool water and applying moisturizing cream to prevent skin drying are sufficient to manage neuropathic pain. Topical treatments such as capsaicin or lidocaine are variably effective to treat neuropathic pain. FDA-approved treatments for neuropathic pain include gabapentin, pregabalin, duloxetine, topical lidocaine, topical capsaicin, and extended-release tapentadol. First-line oral medications for neuropathic pain include  $\alpha$ 2- $\delta$  calcium channel subunit ligands (gabapentin and pregabalin), serotonin norepinephrine reuptake inhibitors (duloxetine, venlafaxine), and tricyclic antidepressants (amitriptyline, nortriptyline), although not all are FDA approved for neuropathic pain due to LDPN.<sup>98</sup> The selection of the first medication should consider comorbidities, adverse effects, and potential interactions with other medications. Combining therapy with a second medication of a different medication class

Table 2. Treatment of Neuropathic Pain

Drug class	Treatment	Total daily dose and regimen	Efficacy	Adverse effects
<b>Topical medications</b>				
Voltage-gated sodium channel antagonist	Lidocaine <sup>a</sup>	1-3 Patches to region of pain daily for up to 12 h	After 3 weeks of treatment, 70% of patients with diabetic PN demonstrated a reduction of at least 30% in the weekly mean daily pain diary ratings <sup>87</sup>	Mild skin reactions including erythema, rash, itching (rare)
TRPV1 agonist	Capsaicin 8% patches <sup>a</sup>	1-4 Patches to painful area for 30-60 min every 3 mo	In HIV-associated LDPN, 22.8% reduction in pain vs 10.7% in controls <sup>88</sup> ; in postherpetic neuralgia, 42% had 30% reduction in pain score vs 32% in controls <sup>89</sup>	Initial burning sensation and erythema of skin (common)
<b>Oral medications</b>				
α2-δ Calcium channel subunit ligand	Gabapentin <sup>a</sup>	1200-3600 mg, in 3 divided doses	In diabetic PN, higher numbers with at least 50% pain intensity reduction with gabapentin, <sup>4</sup> 1200 mg daily, than with placebo (38% vs 23%; RR, 1.7 [95% CI, 1.4-2.0]) and higher numbers with at least 30% pain intensity reduction with gabapentin, <sup>3</sup> 1200 mg, than with placebo (52% vs 37%; RR, 1.4 [95% CI, 1.3-1.6]) <sup>90</sup>	Dizziness, somnolence, peripheral edema
α2-δ Calcium channel subunit ligand	Pregabalin <sup>a</sup>	300-600 mg, in 2 divided doses	In diabetic PN, higher numbers with at least 30% pain intensity reduction with pregabalin, 300 mg, than with placebo (47% vs 42%; RR, 1.1 [95% CI, 1.01-1.20]) and with pregabalin, 600 mg, than with placebo (63% vs 52%; RR, 1.2 [95% CI, 1.04-1.40]; NNT, 9.6 [95% CI, 5.5-41]) <sup>91</sup>	Somnolence, dizziness
Selective serotonin and norepinephrine reuptake inhibitor	Duloxetine <sup>a</sup>	60-120 mg, once daily	In diabetic PN, at <12 weeks the RR of ≥50% improvement with any dose was 1.53 (95% CI, 1.21-1.92) compared with placebo <sup>92</sup> ; in painful PN, higher numbers with at least 50% pain intensity reduction with duloxetine, 60 mg daily, than with pregabalin, 300 mg daily (RR, 1.46 [95% CI, 1.19-1.80]) <sup>93</sup>	Headache, drowsiness, fatigue
Tricyclic antidepressant	Amitriptyline	10-75 mg, once daily	In study comparing monotherapy (amitriptyline, duloxetine, pregabalin) and combination therapy in diabetic PN, the 7-day mean (SD) Pain Numerical Rating Scale scores at week 16 decreased from a mean 6.6 (1.5) at baseline to 3.3 (1.8) at week 16, with no differences between the combination therapies <sup>94,95</sup>	Constipation, dizziness, dry mouth, somnolence (fewer adverse effects with nortriptyline)
<b>Neuromodulation</b>				
Peripheral nerve stimulation <sup>a</sup>			Insufficient evidence for efficacy in LDPN, but is FDA approved for neuropathic pain	
Spinal cord stimulation <sup>a</sup>			In diabetic PN, at 3 mo, 79% with spinal cord stimulator had ≥50% improvement in pain vs 5% receiving conventional medical management <sup>96</sup>	Headache, paresthesia, device infection

Abbreviations: LDPN, length-dependent peripheral neuropathy; NNT, number needed to treat; RR, risk ratio; TRPV1, transient receptor potential vanilloid 1.

<sup>a</sup> US Food and Drug Administration (FDA) approved for neuropathic pain.

may have additive benefit.<sup>94</sup> Given the limited efficacy of the aforementioned medications, other antiseizure and antidepressant medications such as valproic acid and venlafaxine are often prescribed off label. Opioids are not recommended for treatment of neuropathic pain.<sup>98</sup> Referral to a pain clinic that offers multidisciplinary approaches (behavioral therapy, medications, and neurostimulation) can be beneficial for people with persistent neuropathic pain. Spinal cord stimulation, which is an implanted device that provides epidural electrical stimulation to alter pain transmission, is FDA cleared for neuropathic pain.

## Motor Symptoms

People with lower extremity weakness from peripheral neuropathy may have impaired gait due to a combination of weakness and proprioceptive sensory loss, which leads to an increased risk of falling.<sup>2</sup> Physical therapy focused on gait safety may be helpful for patients with mild weakness. Occupational therapy is indicated for patients with upper limb weakness, particularly if fine hand movements (eg, buttoning, writing, self-care) are impaired.

Patients with LDPN and motor symptoms who develop foot deformities and contractures may benefit from treatment by orthopedic surgery. For patients with LDPN and severe motor impairment, use of foot orthoses, a walker, or wheelchair may be necessary.

tients with other age-related issues such as osteoarthritis, reduced vision/hearing, or central nervous system diseases such as stroke or Parkinson disease.

## Prognosis

The prognosis of peripheral neuropathy varies based on its cause. Even in treatable peripheral neuropathies, such as CIDP, vasculitis, and amyloidosis, damage to peripheral nerves cannot be completely reversed and symptoms almost always persist. Similarly, neuropathies from toxins or chemotherapeutics may improve with cessation of the causative agent, but symptoms often remain. While attaining normoglycemia may prevent LDPN in people with type 1 diabetes, glycemic control has modest effects on improving peripheral neuropathy symptoms in those with established peripheral neuropathy due to type 2 diabetes. Late-onset hereditary neuropathies including the axonal types of Charcot-Marie-Tooth typically do not cause severe disability, but can negatively affect gait in pa-

## Limitations

This review has several limitations. First, some relevant articles may have been missed. Second, the review is limited by the quality of the evidence available. Third, some topics, such as neuropathies with atypical features, were not covered in detail. Fourth, quality of included literature was not evaluated.

## Conclusions

Peripheral neuropathy affects approximately 1% of adults worldwide and may cause sensory, motor, and autonomic symptoms. Diabetes is the most common cause of peripheral neuropathy in Western countries. First-line therapies for neuropathic pain include gabapentin, pregabalin, duloxetine, and amitriptyline.

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**Submissions:** We encourage authors to submit papers for consideration as a Review. Please contact Kristin Walter, MD, at [kristin.walter@jamanetwork.org](mailto:kristin.walter@jamanetwork.org).

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