Review

Distal Symmetric Polyneuropathy
A Review

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IMPORTANCE Peripheral neuropathy is a highly prevalent and morbid condition affecting 2% to 7% of the population. Patients frequently experience pain and are at risk of falls, ulcerations, and amputations. We aimed to review recent diagnostic and therapeutic advances in distal symmetric polyneuropathy, the most common subtype of peripheral neuropathy.

OBSERVATIONS Current evidence supports limited routine laboratory testing in patients with distal symmetric polyneuropathy. Patients without a known cause should undergo a complete blood cell count, comprehensive metabolic panel, vitamin B_{12} measurement, serum protein electrophoresis with immunofixation, fasting glucose measurement, and glucose tolerance test. The presence of atypical features such as asymmetry, non–length dependence, motor predominance, acute or subacute onset, and prominent autonomic involvement should prompt a consultation with a neurologist or neuromuscular specialist. Electrodiagnostic tests and magnetic resonance imaging of the neuroaxis contribute substantial cost to the diagnostic evaluation, but evidence supporting their use is lacking. Strong evidence supports the use of tricyclic antidepressants, serotonin norepinephrine reuptake inhibitors, and voltage-gated calcium channel ligands in the treatment of neuropathic pain. More intensive glucose control substantially reduces the incidence of distal symmetric polyneuropathy in patients with type 1 diabetes but not in those with type 2 diabetes.

CONCLUSIONS AND RELEVANCE The opportunity exists to improve guideline-concordant testing in patients with distal symmetric polyneuropathy. Moreover, the role of electrodiagnostic tests needs to be further defined, and interventions to reduce magnetic resonance imaging use in this population are needed. Even though several efficacious medications exist for neuropathic pain treatment, pain is still underrecognized and undertreated. New disease-modifying medications are needed to prevent and treat peripheral neuropathy, particularly in type 2 diabetes.

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The overall prevalence of peripheral neuropathy is difficult to establish because of the heterogeneity of the different peripheral nervous system diseases in this category. Although studies in the United States are lacking, door-to-door screening studies performed in Sicily and Bombay estimated that the prevalence of peripheral neuropathy was 7% and 2.4%, respectively.[1,2] Regarding the most common peripheral neuropathy subtype, distal symmetric polyneuropathy (DSP), Italian general practitioners screened more than 4000 patients older than 55 years and found that the prevalence was 3.4% to 3.7%, increasing to 4.2% to 5.3% in those older than 75 years.[3] In this study, more than 40% of those with DSP had diabetes,[3] the most commonly identified cause of this condition.[4] Another study in a Dutch population revealed an incidence of polyneuropathy of 77 per 100 000 person-years in those aged 18 years or older, with diabetes the most frequent cause (32%).[5] In contrast to the few studies on peripheral neuropathy and DSP in general, many studies have investigated the incidence and prevalence of DSP in patients with type 1 and type 2 diabetes. Investigators found that the prevalence of DSP ranges from 10% to 34% in patients with type 1 diabetes and from 8% to 25% in patients with type 2 diabetes.[6-10] One study of type 2 diabetes revealed an increasing prevalence from 8% to 42% when patients were reevaluated after 10 years. Of note, the prevalence of DSP including those with asymptomatic disease is likely even higher, with 54% of patients with type 1 diabetes and 45% of patients with type 2 diabetes affected.[7] In patients with type 1 diabetes, the incidence of DSP is 2800 per 100 000 person-years compared with 6100 per 100 000 person-years in those with type 2 diabetes.[11,12] Beyond DSP, peripheral neuropathy also includes radiculopathies and mononeuropathies; their estimated incidences are listed in Table 1.

CMT disease *Charcot-Marie-Tooth disease*

DSP *distal symmetric polyneuropathy*

MRI *magnetic resonance imaging*

SNRI *serotonin norepinephrine reuptake inhibitor*

TCA *tricyclic antidepressant*

Table 1. Incidence of Polyneuropathies, Mononeuropathies, and Radiculopathies

	Population Studied	Incidence per 100 000 Person-Years
Distal symmetric polyneuropathy		
All causes	Netherlands[5]	77
Type 1 diabetes	United States[11]	2800
Type 2 diabetes	United States[12]	6100
Mononeuropathies		
Median neuropathy at the wrist (carpal tunnel syndrome)	United Kingdom[13,14]	103 (Men, 87.8; women, 192.8)
	United States[15]	99
Ulnar neuropathy	United Kingdom[14]	Men, 25.2; women, 18.9
	Siena, Italy[16]	24.7 (Men, 32.7; women, 17.2)
Lateral femoral cutaneous neuropathy (meralgia paresthetica)	United Kingdom[14]	Men, 10.7; women, 13.2
	Netherlands[17]	43
Radial neuropathy	United Kingdom[14]	Men, 2.97; Women, 1.42
Idiopathic facial neuropathy (Bell palsy)	United Kingdom[18]	20.2
	Rochester, Minnesota[19]	25 (Men, 22.8; women, 26.9)
	Rome, Italy[20]	53.3
Radiculopathies		
Lumbar	US military[21]	486 (1079 in patients aged >40 y)
Cervical	US military[22]	179 (616 in patients aged >40 y)
	Rochester, Minnesota[23]	83.2 (202.9 in patients aged 50-54 y; men, 107.3; women, 63.5)

Subtypes of Peripheral Neuropathy

Peripheral neuropathy encompasses all disorders that result in injury to nerves within the peripheral nervous system. Peripheral neuropathy is best categorized by the localization of the nerve injury. One of the most common types, DSP, is a diffuse, length-dependent process.[1] Patients present with numbness, tingling, pain, or a combination of these that typically starts in their toes and slowly spreads proximally (**Box**). The distribution of neurologic symptoms and signs is often referred to as a stocking-glove pattern. Generally, symptoms reach the level of the knees before spreading to the fingertips. Weakness is usually a late sign in DSP and often is first noticed with weakness of toe extension followed by ankle dorsiflexion. One exception is that patients with Charcot-Marie-Tooth (CMT) disease often present with weakness as an early sign. Ankle dorsiflexion is best tested by having a patient walk on his/her heels. Another frequent symptom is difficulties with balance, which can result in falls and fractures.[24] Patients with DSP are also at risk of ulcerations and amputations, especially patients with diabetes.[25] Neuropathic pain is present in approximately one-third of patients with DSP and is often underrecognized and undertreated.[26,27]

Another common localization of peripheral neuropathy is radiculopathy, with lumbar nerve roots affected more commonly than cervical nerve roots. Radiculopathy typically results in numbness, tingling, pain, or a combination that starts in the neck or back and radiates into an extremity in a dermatomal pattern. Weakness is in a myotomal pattern. For example, a L5 radiculopathy presents with neuropathic symptoms radiating down the posterior leg and wrapping around to the top of the foot. Weakness involves ankle dorsiflexion and eversion but, unlike with a peroneal neuropathy, affects ankle inversion as well.

Mononeuropathy is also a common nerve injury. Median neuropathy at the wrist (carpal tunnel syndrome) is by far the most common mononeuropathy, followed by ulnar neuropathy at the elbow, facial neuropathy, and lateral femoral cutaneous neuropathy of the thigh (meralgia paresthetica). Carpal tunnel syndrome classically presents with paresthesias and pain in the first 3 digits and the radial half of the fourth digit. Weakness of thumb abduction and opposition is a late finding.[28] The thenar eminence may also reveal atrophy. Ulnar neuropathy at the elbow typically presents with paresthesias, pain, or both in the ulnar half of the fourth digit and in the fifth digit. Similar to carpal tunnel syndrome, weakness is a later finding and manifests as difficulty with finger abduction and atrophy of the first dorsal interosseous muscle.[29] Facial neuropathy typically presents with the acute onset of weakness in one side of the face. The peripheral localization of this neuropathy is indicated by the involvement of upper and lower facial muscle weakness (central causes result in lower facial muscle weakness that is greater than upper facial muscle weakness). Accompanying symptoms include decreased tearing, hyperacusis, and decreased taste in the anterior two-thirds of the tongue. Patients with meralgia paresthetica experience neuropathic symptoms in the lateral thigh without weakness, as this is solely a sensory nerve.

A companion article in *JAMA Neurology* reviewed rare locations of peripheral neuropathy including diffuse, non–length-dependent neuropathies, multiple mononeuropathies, plexopathies, and radiculoplexus neuropathies.[30]

Causes of DSP

Distal symmetric polyneuropathy can be caused by a multitude of conditions (**Table 2**). The most common etiology of DSP is diabetes, accounting for 32% to 53% of cases.[31-33] Given the high prevalence of neuropathy in the population with diabetes, screening tests for neuropathy should be considered. Vibration perception with a 128-Hz tuning fork (likelihood ratio, 16-35) and pressure sensation with a 5.07 Semmes-Weinstein monofilament (likelihood ratio, 11-16) are the best bedside tests to discriminate those with and without a large-fiber neuropathy.[34] Some patients have involvement only of small nerve fibers. Diagnosis can be difficult in these patients because they usually have difficulties only with pinprick and temperature sensation on neurologic examination. Moreover, electrodiagnostic test results in these patients are normal, which can lead to diagnostic confusion. Prediabetes is also a frequent etiology of DSP.[8,35] Alcohol is the next most common cause, but patients often do not provide accurate estimates of intake without detailed questioning. Of note, alcohol usually causes neuropathy in those with decades of daily use. Other common causes of neuropathy include vitamin B_{12} deficiency, inherited conditions, chemotherapy, chronic kidney disease, and paraproteinemia.[31-33,36] Although these are the most frequent etiologies, the causes of DSP are numerous and include infectious, inflammatory, toxic, vascular, autoimmune, metabolic, nutritional, iatrogenic, neoplastic, and paraneoplastic causes. Even after extensive evaluation, the cause of DSP remains idiopathic in 24% to 27% of cases.[31-33,37]

Hereditary motor and sensory neuropathy (CMT disease) is an often overlooked cause of DSP.[37] Unlike most patients with DSP, pa-

Box. History and Physical Examination Findings and Recommended Diagnostic Tests for Common Subtypes of Peripheral Neuropathy

Distal Symmetric Polyneuropathy

Symptoms
- Numbness, tingling, pain, and weakness starting in the toes

Examination
- Sensory examination
  - Decreased pinprick and vibration sensation in a stocking-glove distribution
- Motor examination
  - Weakness of toe extension or trouble walking on heels
- Reflexes
  - Decreased reflexes starting at the ankles

Diagnostic testing
- See Figure

Mononeuropathy

Symptoms
- Numbness, tingling, pain, and weakness in the distribution of 1 nerve

Examination
- Sensory examination
  - Decreased pinprick and vibration sensation in the distribution of 1 nerve (ie, decreased pinprick in digits 1-3 and the lateral half of digit 4 in median neuropathy)
- Motor examination
  - Weakness in the distribution of 1 nerve (ie, finger abduction weakness in ulnar neuropathy)

Diagnostic testing
- Electromyography and nerve conduction studies when diagnostic uncertainty exists or surgery is contemplated

Radiculopathy

Symptoms
- Numbness, tingling, pain radiating from the neck or back into the extremities in a dermatomal pattern
- Weakness in a myotomal pattern

Examination
- Sensory examination
  - Results usually normal given the overlapping innervation of dermatomes
- Motor examination
  - Weakness in myotomal pattern (ie, dorsiflexion, ankle eversion and inversion weakness in L5 radiculopathy)
- Reflexes
  - Decreased reflexes in dermatomal pattern (ie, absent ankle jerk in S1 radiculopathy)

Diagnostic testing
- Electromyography and nerve conduction studies when diagnostic uncertainty exists (of note, test is not sensitive for the detection of a sensory predominant radiculopathy)
- Magnetic resonance imaging (cervical or lumbar) for patients with progressive neurologic dysfunction or when surgery is contemplated; lack of high-quality evidence to define precise clinical scenarios in which magnetic resonance imaging should be ordered

tients with CMT disease often present with distal weakness. Clues to this diagnosis include a family history of neuropathy (particularly outside the context of diabetes), hammer toes, high arches, symptoms that slowly progress over many years, and neurologic examination abnormalities that are more pronounced than the patient's symptoms. Recognition of CMT disease is important because the diagnostic workup is different and this diagnosis has implications for other family members. Family history is an important component of the diagnostic evaluation of DSP, and many patients will not volunteer information pertaining to neuropathy in other family members. Extensive questioning is required, including asking patients about neuropathic symptoms, hammer toes, high arches, and use of a walking assistance device in family members.

Potentially treatable causes of peripheral neuropathy are especially important for physicians to identify. Most of these neuropathies present with atypical features, such as asymmetry, non–length dependence, motor involvement, acute or subacute onset, and prominent autonomic involvement, or less common localizations of nerve injury, such as diffuse, non–length-dependent neuropathies, multiple mononeuropathies, plexopathies, and radiculoplexus neuropathies. Peripheral neuropathies in this group include Guillain-Barré syndrome, chronic inflammatory demyelinating polyneuropathy, and paraprotein-associated demyelinating neuropathy including POEMS (polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes) syndrome, multifocal motor neuropathy, vasculitic neuropathy, and diabetic amyotrophy. More detailed discussion of these peripheral neuropathies is included in a previously published review.[30]

Methods

References were identified from PubMed and Ovid searches from 2009 to 2015 with an emphasis on recently published meta-analyses, randomized clinical trials, and guidelines. Articles were also identified through the use of the authors' own files. For diagnosis, the following search terms were used: *diagnosis* or *evaluation* or *testing* AND *distal symmetric polyneuropathy*. For treatment of DSP-associated neuropathic pain, the following search terms were used: *treatment* AND *pain* AND *polyneuropathy* or *neuropathy*. For disease-modifying therapies for DSP, the following search terms were used: *therapy* AND *distal symmetric polyneuropathy*.

Diagnosis

One of the most important questions facing physicians when they see a patient with peripheral neuropathy is what tests to order. The evidence to support testing in DSP was systematically reviewed by the American Academy of Neurology (AAN) in 2009. The review found evidence to support fasting glucose, vitamin B_{12}, serum protein electrophoresis with immunofixation, and glucose tolerance tests in the routine evaluation of DSP without a clear cause.[38] No other laboratory tests, magnetic resonance imaging (MRI), or electrodiagnostic tests were discussed. Other studies have also supported limited routine diagnostic testing of patients with DSP.[31,39-41] According to a national physician survey, a consensus exists to order a comprehensive metabolic panel

Table 2. Common Causes of Distal Symmetric Polyneuropathy

Diseases	Comment
Metabolic	
Diabetes	Most common cause, accounting for 32%-53% of cases[a]
Prediabetes	Glucose tolerance test has highest sensitivity[a]
Chronic kidney disease	Neuropathy particularly severe when chronic kidney disease is caused by diabetes
Chronic liver disease	Neuropathy typically mild
Idiopathic	24%-27% of all cases[a]
Toxin (alcohol)	Second most common cause (requires in-depth questioning)[a]
Inherited	Detailed family history required; ask about hammer toes, high arches[a]
Charcot-Marie-Tooth disease type 1	Inherited demyelinating sensory motor neuropathy
Charcot-Marie-Tooth disease type 2	Inherited axonal sensory motor neuropathy
Familial amyloidosis	Transthyretin mutation most common
Nutritional	
Vitamin B_{12} deficiency	Methylmalonic acid level important when vitamin B_{12} level is 200-400 pg/mL[a]
Vitamin E deficiency	Can cause cerebellar ataxia
Vitamin B_6 deficiency	Can cause neuropathy when level is too high or too low
Thiamine deficiency	Can present with ataxia, ophthalmoparesis, and confusion
Copper deficiency	Often presents with a myeloneuropathy
Gastric bypass surgery	Often difficult to determine which factor responsible
Malabsorption syndromes	Often difficult to determine which factor responsible
Medication	
Chemotherapy (vincristine, cisplatin, taxol, bortezomib)	Known dose limiting side effect of many agents
Amiodarone	Can cause a demyelinating neuropathy
Phenytoin	Typically after many years of use
Nucleosides	Can be difficult to distinguish cause of neuropathy (human immunodeficiency virus vs medication)
Nitrofurantoin	Worse in the setting of renal failure
Metronidazole	Usually after high, prolonged intravenous doses
Hydralazine	Avoid by concomitant use of vitamin B_6
Isoniazid	Avoid by concomitant use of vitamin B_6
Colchicine	Can also cause myopathy
Autoimmune	
Rheumatoid arthritis	Can also cause mononeuritis multiplex
Lupus	Can also cause mononeuritis multiplex
Sjögren syndrome	Can also cause a sensory neuronopathy or mononeuritis multiplex
Sarcoidosis	Can present with several neurologic manifestations
Secondary amyloidosis	Diagnosis aided by fat pad biopsy or sural nerve biopsy
Infectious	
Human immunodeficiency virus	Medications used to treat can also cause neuropathy
Hepatitis B/C	Can also cause mononeuritis multiplex associated with polyarteritis nodosa and cryoglobulinemia
Neoplastic	
Monoclonal gammopathy of unclear clinical significance	Immunofixation increases sensitivity of paraprotein detection[a]
Multiple myeloma	Associated with IgG or IgA paraproteinemia
Primary amyloidosis	Diagnosis aided by fat pad biopsy or sural nerve biopsy

[a] These statements are the most important take-home points.

and a complete blood count.[42] In contrast, rheumatologic and thyroid testing have a low yield in the routine evaluation of DSP.[40] Despite the AAN guidelines, both general practitioners and neurologists order a large number of tests, with great variation in the type of tests ordered.[42,43] Even when a large number of tests are ordered, the AAN-recommended tests are often not performed. These simple, inexpensive blood tests frequently lead to a change in management of patients with DSP.[31] In contrast, electrodiagnostic tests and MRI of the brain and spine rarely change management of these patients despite being frequently performed and contributing to most of the cost associated with the evaluation of DSP.[44] Electrodiagnostic tests led to a change in management in only 2 of 458 DSP patients seen by community neurologists despite being ordered in 80% of the population.[31] Electrodiagnostic tests clearly have a role in the evaluation of some patients with DSP, but the precise subgroup of patients that benefits has not been well defined. The diagnostic workup presented in the **Figure** can be performed by the primary care physician. Patients with atypical features such as asymmetry, non–length dependence, motor involvement, acute or subacute onset, and prominent autonomic involvement may be the most likely to benefit from electrodiagnostic testing, but future stud-

ies are needed to precisely define the role of these tests. These atypical features should also prompt referral to a neurologist or neuromuscular specialist. Magnetic resonance imaging of the brain and spine would be expected to be ordered rarely in this population but are ordered in one-quarter of these patients.[43] Unlike electrodiagnostic tests, MRI has little role in the evaluation of DSP given that it primarily evaluates the central nervous system. Exceptions include uncommon cases of suspected central or radicular involvement.

The most important components of the evaluation of DSP are the medical history and neurologic examination (**Video**). In one study, community neurologists were able to diagnose the cause of DSP in 64% of cases prior to their diagnostic evaluation.[31] An etiology was discovered in an additional 10% of patients after diagnostic tests by the neurologist, with prediabetes, vitamin B_{12} deficiency, diabetes, and hypothyroidism the most common causes found. In this population, 27% of cases remained idiopathic despite evaluation, which is a proportion comparable with other studies.[31-33,37] How a general medicine population would compare is unclear.

The diagnostic evaluation of patients with suspected CMT disease is rapidly evolving. Historically, patients would have an electrodiagnostic test to determine if they had a demyelinating (usually CMT-1) or axonal (usually CMT-2) variant. Genetic testing for CMT-1 disease produced high yields with only a few genes tested.[45] In contrast, CMT-2 genetic testing required testing several genes without a high yield of diagnosis. However, next-generation sequencing panels and whole exomic and genomic sequencing approaches are quickly becoming cost-effective, with much higher yields.[46] These approaches also have the potential to identify novel genes and to allow reanalysis of variants as bioinformatics information becomes more robust. Unfortunately, insurance coverage of these tests remains problematic. Because the cost of genetic testing remains expensive and false-positive results are possible, only patients with a high degree of suspicion for inherited neuropathy should be tested.

Treatment

Treatment of DSP-Associated Neuropathic Pain

The prevalence of chronic painful DSP among patients with diabetes attending general practitioner clinics in the United Kingdom was 16.2%.[27] Almost 40% of these patients had never been treated for their neuropathic pain and 12% had never reported symptoms to their physician. Given the high prevalence of painful DSP among patients with diabetes, physicians must frequently inquire about neuropathic pain and know which medications have high levels of evidence to support their use.

Many studies have focused on the pharmacologic treatment of neuropathic pain in DSP secondary to diabetes. The primary medications with high-quality evidence are tricyclic antidepressants (TCAs) such as amitriptyline, nortriptyline, and imipramine; serotonin norepinephrine reuptake inhibitors (SNRIs) such as duloxetine and venlafaxine; and voltage-gated calcium channel ligands such as gabapentin and pregabalin, as reviewed in the 2011 AAN practice parameter and the 2010 European Federation of Neurological Societies (EFNS) updated guidelines (based on systematic reviews requiring multiple class I/II studies for level A/B evidence).[47,48] Class I randomized controlled trials must have allocation concealment, clearly defined primary outcomes and inclusion and exclusion criteria, and greater than 80% of patients completing the study. Class II randomized controlled trials lack 1 or more of the requirements previously listed. A summary of the class I and class II randomized placebo-controlled trials from the AAN and EFNS systematic reviews for each of these drugs including effective dosage, onset of efficacy, magnitude of efficacy, and common adverse effects is provided in **Table 3**.

A recent network meta-analysis also concluded that TCAs, SNRIs, and voltage-gated calcium channel ligands are better than placebo for short-term pain control in diabetes-associated DSP.[62] The comparative effectiveness of these medications was difficult to establish because few head-to-head trials have been performed, trial results are heterogeneous, and the risk of bias in these studies is high. Given that the comparative effectiveness is difficult to ascertain, physicians should prescribe medications within these 3 drug classes based on patient comorbidities, potential adverse effects, and cost.[63] Cost is one of the main differences among these medications, with TCAs, gabapentin, and venlafaxine ($4-$33 per month) being less expensive than duloxetine and pregabalin ($239-$257 per month).

Of note, the AAN and EFNS systematic reviews both state that oxcarbazepine, lamotrigine, lacosamide, clonidine, and mexiletine should not be used to treat diabetic neuropathic pain.[47,48] The AAN (positive) and EFNS (discrepant) have different conclusions regarding valproic acid and capsaicin. The reason for the discrepancy is that the EFNS review included more clinical trials than the AAN review, including trials with negative results. The adverse effect profiles of valproic acid and capsaicin limit their utility. Although evidence exists to support opioid medications for short-term neuropathic pain relief, a recent position statement by the AAN advised against their use for long-term management of chronic noncancer pain.[64] The statement is based on emerging evidence of increased morbidity and mortality in patients taking opioid medications.

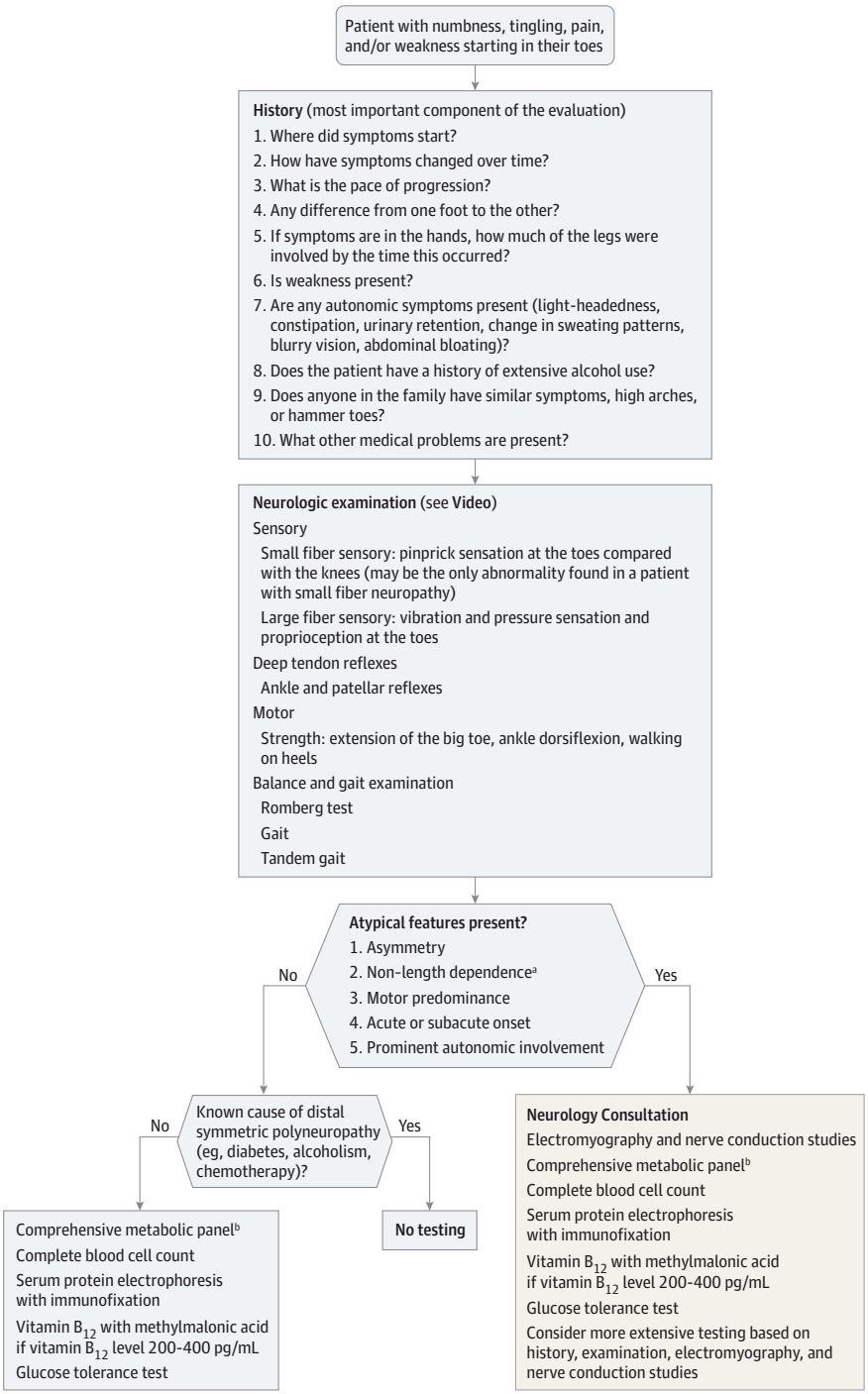
Less evidence exists to support neuropathic pain treatment in other neuropathy subtypes and secondary to causes other than diabetes; however, a 2015 systematic review summarized all neuropathic pain treatment trials (55% of included trials studied diabetic DSP or postherpetic neuralgia).[65] The review detailed numbers needed to treat for a 50% reduction in pain of 3.6 for TCAs, 6.4 for SNRIs, 7.2 for gabapentin, and 7.7 for pregabalin. Based on GRADE criteria,[66] the review found strong evidence for TCAs, SNRIs, and voltage-gated calcium channel ligands, the same classes of medications as detailed for diabetic DSP. The recommendation applied to all neuropathic pain conditions, not just DSP. Therefore, current evidence supports the use of TCAs, SNRIs, and voltage-gated calcium channel ligands for all neuropathic pain conditions.

One potential treatment algorithm for neuropathic pain is to start with a medication from 1 of these 3 classes based on patient comorbidities, potential adverse effects, and cost. If the medication fails because of lack of efficacy or adverse effects, try a medication from 1 of the other 2 classes. Continue trials of at least 2 medications from each of the 3 classes before trials of medications with lower levels of evidence to support their use, such as tramadol and lidocaine patches. Combination therapy with medications from the different classes may also be helpful. For example, if a medication provides partial relief at the highest tolerated dosage, the addition of a second medication from a different class is advised.

Disease-Modifying Therapy for DSP

As discussed in a 2012 Cochrane systematic review, many studies have investigated the effect of glycemic control on the development of

Figure. Proposed Diagnostic Algorithm for the Evaluation of Distal Symmetric Polyneuropathy by Primary Care Physicians



Patients with a known cause of neuropathy typically do not require further diagnostic testing. Patients without a known cause need limited diagnostic testing unless atypical neuropathy features are present. Atypical neuropathy features, including non–length-dependent distribution, acute/subacute onset, asymmetry, prominent autonomic involvement, and/or motor predominant signs, should prompt consultation with a neurologist or neuromuscular specialist. Of note, magnetic resonance images of the brain and/or spine are rarely indicated but frequently performed.

[a] Length-dependent neuropathy starts in the toes and spreads proximally to at least the knee before involvement of the hands.

[b] Comprehensive metabolic panel includes panel 7 (electrolytes [sodium, potassium, chloride, bicarbonate]; blood urea nitrogen; creatinine; and glucose), calcium, and hepatic function panel.

DSP.[67] In this review, a meta-analysis of 2 trials showed that enhanced glucose control reduced the annual absolute risk of developing DSP by 1.84% in patients with type 1 diabetes. This result was primarily driven by the Diabetes Control and Complications Trials in 1993, which contributed 96% of the patients in the meta-analysis.[68,69] Of note, patients in the enhanced glycemic control group were 3 times

Table 3. Class I and Class II Randomized Controlled Trials From the AAN and EFNS Guidelines on the Treatment of Painful Diabetic Distal Symmetric Polyneuropathy

Source	Treatment per Day	Evidence Class[a]	Study Duration, wk	No. Receiving Treatment/ Total Sample[b]	Mean Pain Reduction on 0-10 Rating Scale vs Placebo (95% CI)	Patients With >50% Pain Reduction		Common Adverse Effects
						Treatment Effect, %	Placebo Effect, %	
Lesser et al,[49] 2004	Pregabalin, 300 mg		5	81/337	−1.26 (−1.86 to −0.65)	46	18	Dizziness, somnolence, peripheral edema, confusion, blurry vision
Rosenstock et al,[50] 2004	Pregabalin, 300 mg	I	8	76/146	−1.47 (−2.19 to −0.75)	40	14.5	
Lesser et al,[49] 2004	Pregabalin, 600 mg	I	5	82/337	−1.45 (−2.06 to −0.85)	48	18	
Richter et al,[51] 2005	Pregabalin, 600 mg	I	6	72/223	−1.26 (−1.89 to −0.64)	39	15	
Freynhagen et al,[52] 2005	Pregabalin, 300-600 mg	II	12	82/209	Approximately −1.4 to 1.6 (P = .002)	48-52	24	
Backonja et al,[53] 1998	Gabapentin, 900-3600 mg	I	8	70/135	−1.2 (−1.9 to −0.6)	Not reported; 60% treated with gabapentin had at least moderate improvement (>30%) vs 33% treated with placebo		Dizziness, somnolence, confusion
Gorson et al,[54] 1999	Gabapentin, 900 mg	II	6	19/30	No difference	Not reported; 42.5% treated with gabapentin reported moderate or excellent pain relief vs 22.5% treated with placebo		
Simpson,[55] 2001	Gabapentin, 900-3600 mg	II	8	27/54	−1.9 (Not reported; P < .01)	Not reported; 55.5% treated with gabapentin reported much to moderate improvement vs 25.9% treated with placebo		
Vrethem et al,[56] 1997	Amitriptyline, 75 mg	I	4	33/99	−1.8 (Not reported; P < .001)	Not reported; 63% of patients treated with amitriptyline had at least 20% improvement vs 22% treated with placebo		Dry mouth, sedation, vertigo
Max et al,[57] 1987	Amitriptyline, 25-150 mg	II	6	29 (Crossover)	Not reported	Not reported; 65.5% treated with amitriptyline reported moderate to complete improvement vs 3.5% treated with placebo		
Raskin et al,[58] 2005	Duloxetine, 60 mg	I	12	116/348	−0.9 (−1.39 to −0.42)	50	30	Nausea, somnolence, hyperhidrosis, anorexia
Goldstein et al,[59] 2005	Duloxetine, 60 mg	II	12	86/344	−1.17 (−1.84 to −0.5)	49	26	
Wernicke et al,[60] 2006	Duloxetine, 60 mg	II	12	85/248	−1.32 (−1.95 to −0.69)	43	27	
Raskin et al,[58] 2005	Duloxetine, 120 mg	I	12	116/348	−0.87 (−1.36 to −0.39)	39	30	
Goldstein et al,[59] 2005	Duloxetine, 120 mg	II	12	80/344	−1.45 (−2.13 to −0.78)	52	26	
Wernicke et al,[60] 2006	Duloxetine, 120 mg	II	12	78/248	−1.44 (−2.08 to −0.81)	53	27	
Rowbotham et al,[61] 2004	Venlafaxine, 150-225 mg	I	6	82/242	−0.7 (Not reported; P < .001)	56	34	Nausea, dyspepsia, sweating, somnolence, insomnia, blood pressure and cardiac rhythm changes

Abbreviations: AAN, American Academy of Neurology; EFNS, European Federation of Neurological Societies.

[a] Class I randomized controlled trials must have allocation concealment, clearly defined primary outcomes, and inclusion and exclusion criteria with greater than 80% of patients completing the study. Class II randomized controlled trials lack 1 or more of the requirements listed for class I studies.

[b] Number of participants receiving the dosage in column 2 out of the total number of participants in the trial. Many trials had multiple intervention groups.

as likely to experience a serious hypoglycemic episode in the Diabetes Control and Complications Trials.

In contrast, it remains unclear if enhanced glycemic control reduces the annual risk of developing DSP in patients with type 2 diabetes. In a large study of 10 251 patients randomized to a target hemoglobin A_{1c} of less than 6% or between 7% and 7.9%, there was a nonsignificant trend toward an annual risk reduction of developing DSP by 0.7%.[70] Of note, there was increased mortality (relative risk, 1.26; 95% CI, 1.06-1.51) in patients in the enhanced glycemic control group. In a study of 1791 military veterans randomized to standard or intensive glycemic control, there was a nonsignificant trend toward an annual risk reduction of developing DSP by 0.29%.[71] When these 2 studies were combined in a meta-analysis with 2 smaller studies, neither of which had shown a significant difference in the development of DSP, the result was again a nonsignificant trend toward an annual risk reduction of developing DSP by 0.58%.[67] Like patients with type 1 diabetes, patients with type 2 diabetes in the enhanced glycemic group were 3 times as likely to experience a serious hypoglycemic episode compared with the control group. Since the 2012 systematic review, another group randomized 3057 patients with recently diagnosed type 2 diabetes based on screening to either intense goal-directed therapy of glucose, blood pressure, and cholesterol management or routine care.[72] Similar to previous studies, the prevalence of neuropathy was lower in the intense goal-directed group (4.9% vs 5.9%; odds ratio, 0.95; 95% CI, 0.68-1.34), but the result was not statistically significant. In contrast to type 1 diabetes, the effect of glycemic control in the prevention of DSP in type 2 diabetes is likely quite small, emphasizing the need for new disease-modifying therapies.

Prediabetes is another common cause of DSP, but whether treatment is effective in preventing or treating DSP is unclear. Diet and exercise has been shown to increase nerve fiber density and reduce pain in those with prediabetic neuropathy, but no control group was available for comparison.[73] Both diet/exercise and treatment with metformin can prevent prediabetes from progressing to diabetes, but the effect on prevention of neuropathy is unclear.[74] Future studies are needed to establish which interventions are effective in patients with prediabetic neuropathy.

There are no currently available treatments for CMT disease. Two recent double-blind, placebo-controlled trials revealed that ascorbic acid is not effective for the treatment of CMT-1A disease despite promising animal data.[75,76] In contrast, 2 recent double-blind, placebo-controlled trials in patients with familial amyloid polyneuropathy show promise. Diflusinal was shown to reduce neuropathy progression and preserve quality of life.[77] Tafamidis revealed similar results in the efficacy-evaluable subgroup, but not in the intention-to-treat population, which was the focus of the primary end points.[78]

Discussion

Advances have been made regarding which diagnostic tests should be used for patients with DSP; however, much work remains to be done. Although the clinical history and examination remain the most critical components of the evaluation of DSP, diagnostic testing also remains important when the cause remains unclear.[31] Unfortunately, physicians order a large number of tests, with high variation in practice patterns.[42,43] Despite the magnitude of tests ordered, the AAN-recommended tests are often omitted.[42,43,79] As a result, a great opportunity exists to enhance guideline-concordant testing for this common condition. Furthermore, the role of electrodiagnostic testing is not currently clear. The precise clinical scenarios in which this test aids the management of patients with DSP need to be ascertained, especially because this test is painful and drives a large proportion of the costs associated with the diagnostic evaluation. This information could be used to generate clinical decision support tools to help physicians encountering this common scenario. Interventions to limit MRI of the neuroaxis are also needed given the high utilization and costs of this test with little utility in this peripheral nervous system disorder.[31]

Strong evidence exists to support treatment of painful diabetic DSP with TCAs, SNRIs, and voltage-gated calcium channel ligands.[47,48,62,65] However, new head-to-head comparative effectiveness studies are needed to enable physicians to decide which medications to use first. Until those data exist, patient comorbidities, potential adverse effects, and cost should be the determining factors.[63] Cost makes TCAs, gabapentin, and venlafaxine particularly attractive choices. New medications with novel mechanisms of action are also needed. The number needed to treat is high for all current medications, highlighting the need for more potent medications with lower adverse effect profiles than currently available drugs.[65] Strong evidence also supports glucose control in the prevention of DSP in patients with type 1 diabetes.[67] Unfortunately, the effect of glucose control in type 2 diabetes is much lower, and novel treatments that target mechanisms unrelated to glucose levels are sorely needed. For patients with idiopathic DSP, no current disease-modifying treatment exists, as most therapies for DSP involve addressing the underlying cause with the goal of preventing further nerve injury. Therapies that promote nerve healing have the potential to dramatically affect patient quality of life.

Clinical Bottom Line

- Diabetes, prediabetes, alcohol use, vitamin B_{12} deficiency, inherited conditions, chemotherapy, chronic kidney disease, and paraproteinemia are the most common causes of DSP.
- Even after appropriate testing, the cause of DSP is unknown (idiopathic) in 24% to 27% of cases.
- The clinical history and examination are the most important components of evaluation of DSP, but routine testing with a comprehensive metabolic panel, complete blood cell count, vitamin B_{12} measurement, serum protein electrophoresis with immunofixation, and glucose tolerance test should be performed when the cause remains unclear. Further laboratory testing is needed only when atypical findings are present such as asymmetry, non–length dependence, motor involvement, acute or subacute onset, and prominent autonomic involvement.
- For patients presenting with DSP, the role of electrodiagnostic tests needs to be further defined and interventions to reduce MRI are needed.
- Tricyclic antidepressants, SNRIs, and voltage-gated calcium channel ligands all have strong evidence for reducing neuropathic pain, particularly in patients with diabetic DSP, but pain is underrecognized and undertreated in this population.
- Glucose control is effective in the prevention of type 1 diabetes–associated DSP but is at best minimally effective in the prevention of type 2 diabetes–associated DSP; therefore, new therapies are needed to prevent and treat this common condition.

ARTICLE INFORMATION

Author Contributions: Dr Callaghan had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of data analysis. All authors contributed equally to the preparation of content, writing, and revision of the manuscript.

Study concept and design: Callaghan, Feldman.
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Drafting of the manuscript: Callaghan, Price, Feldman.
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