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Diagnostic and Therapeutic Advances: Distal Symmetric Polyneuropathy

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Abstract

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

Observations and Advances—Current evidence supports limited routine laboratory testing in patients with distal symmetric polyneuropathy. Patients without a known cause should have a complete blood count, comprehensive metabolic panel, B12, serum protein electrophoresis with immunofixation, fasting glucose, and a glucose tolerance test. The presence of atypical features such as asymmetry, non-length-dependence, motor predominance, acute or subacute onset, and/or prominent autonomic involvement should prompt a consultation with a neurologist or neuromuscular specialist. Electrodiagnostic tests and magnetic resonance imaging of the neuroaxis are the main drivers of the cost of the diagnostic evaluation, but evidence supporting their use is lacking. Strong evidence supports the use of tricyclic antidepressants, serotonin and 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 does not in type 2 diabetes.

Conclusions and Relevance—The opportunity exists to improve guideline concordant testing in distal symmetric polyneuropathy patients. 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 under-recognized and undertreated. New disease modifying medications are needed to prevent and treat peripheral neuropathy, particularly in type 2 diabetes.

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Introduction

The overall prevalence of peripheral neuropathy is difficult to establish due to the heterogeneity of the different peripheral nervous system diseases in this category. While 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} In regards to the most common peripheral neuropathy subtype, distal symmetric polyneuropathy (DSP), Italian general practitioners screened more than 4000 patients over the age of 55 and found that the prevalence was 3.4–3.7%, increasing to 4.2–5.3% in those over the age of 75.³ In this study, more than 40% of all those with DSP had diabetes³, the most commonly identified cause of this condition⁴. 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 (T1DM) and type 2 diabetes (T2DM). Investigators found that the prevalence of DSP ranges from 10–34% in T1DM and 8–25% in T2DM patients.^{6–10} One study in T2DM revealed an increasing prevalence from 8% to 42% when patients were re-evaluated after 10 years. Of note, the prevalence of DSP including those with asymptomatic disease is likely even higher, with 54% of T1DM and 45% of T2DM patients affected.⁷ In patients with T1DM, the incidence of DSP is 2800 per 100,000 person-years compared with 6100 per 100,000 person-years in those with T2DM.^{11,12} Beyond DSP, peripheral neuropathy also includes radiculopathies and mononeuropathies and their estimated incidences are listed in Table 1.

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 localization is a diffuse, length-dependent process called distal symmetric polyneuropathy (DSP).¹ Patients present with numbness, tingling, and/or pain that typically started 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 to this rule is that patients with Charcot-Marie Tooth disease often present with weakness as an early sign. Ankle dorsiflexion is best tested by having a patient walk on his heels. Another frequent symptom is difficulties with balance, which can result in falls and fractures.¹³ Patients with DSP are also at risk for ulcerations and amputations, especially those with diabetes.¹⁴ Neuropathic pain is present in approximately one third of DSP patients, and is often under-recognized and under-treated.^{15,16}

Another common localization of peripheral neuropathy is radiculopathy, with lumbar nerve roots being affected more commonly than cervical nerve roots. Radiculopathy typically results in numbness, tingling, and/or pain that starts in the neck or back and radiates into an extremity in a dermatomal pattern. Weakness is in 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 site of nerve injury. Median neuropathy at the wrist (carpal tunnel syndrome; CTS) 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). CTS classically presents with paresthesias and pain in the first three digits and the radial half of the fourth digit. Weakness of thumb abduction and opposition is a late finding.¹⁷ The thenar eminence may also reveal atrophy. Ulnar neuropathy at the elbow typically presents with paresthesias and/or pain in the ulnar half of the fourth digit and in the fifth digit. Similar to CTS, weakness is a later finding and manifests as difficulty with finger abduction and atrophy of the first dorsal interosseous muscle.¹⁸ Facial neuropathy typically presents with the acute onset of weakness of one side of the face. The peripheral localization of this neuropathy is indicated by the involvement of upper and lower face weakness (central causes result in lower greater than upper face weakness). Accompanying symptoms include decreased tearing, hyperacusis, and decreased taste from 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.

Rare locations of peripheral neuropathy include diffuse, non-length-dependent neuropathies, multiple mononeuropathies, plexopathies, and radiculoplexus neuropathies, which are covered in an accompanying review in JAMA Neurology (*In press – citation to be provided when available*).

Causes of distal symmetric polyneuropathy

DSP can be caused by a multitude of conditions (Table 2). The most common etiology of DSP is diabetes, accounting for 32–53% of cases.^{19–21} Given the high prevalence of neuropathy in the diabetic population, 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.²² Of note, some patients only have involvement of small nerve fibers. These patients can be hard to diagnose because they usually only have difficulties with pinprick and temperature sensation on neurologic examination. Moreover, electrodiagnostic testing in these patients is normal, which can lead to diagnostic confusion. Pre-diabetes is also a frequent etiology of DSP.^{8,23} 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 B12 deficiency, inherited conditions, chemotherapy, chronic kidney disease, and paraproteinemia.^{19–21,24} While 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 an extensive evaluation, the cause of DSP remains idiopathic in 24–27% of cases.^{19–21,25}

Hereditary motor and sensory neuropathy, also known as Charcot Marie Tooth (CMT) disease, is an often overlooked cause of DSP.²⁵ Unlike most patients with DSP, CMT patients 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 is important because the diagnostic work up is different and this diagnosis has implications for other family members. The 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 assist device in family members.

Potentially treatable causes of peripheral neuropathy are especially important for the physician to identify. Most of these neuropathies present with atypical features, such as asymmetry, non-length-dependence, motor involvement, acute or subacute onset, and/or 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-Barre syndrome (GBS), chronic inflammatory demyelinating polyneuropathy (CIDP), paraprotein-associated demyelinating neuropathy including POEMS, multifocal motor neuropathy (MMN), vasculitic neuropathy, and diabetic amyotrophy. More detailed discussion of these peripheral neuropathies is included in the accompanying review in JAMA Neurology (*In press – citation to be provided when available*).

Methods

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

Major Diagnostic Advances

DSP (Figure 1)—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, B12, serum protein electrophoresis (SPEP) with immunofixation, and glucose tolerance tests in the routine evaluation of DSP.²⁶ 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.^{19,27–29} According to a national physician survey, a consensus exists to order a comprehensive metabolic panel and a complete blood count.³⁰ On the other hand, rheumatologic and thyroid testing have a low yield in the routine evaluation of DSP.²⁸ Despite the AAN guidelines, both general practitioners and neurologists order a large number of tests, with great variation in the type of tests ordered.^{30,31} Even with a high number of tests ordered, the AAN recommended tests are often not performed. These simple, inexpensive blood tests frequently lead to a change in management of DSP patients.¹⁹ In contrast, electrodiagnostic tests and MRI of the brain and/or spine rarely change management of these patients despite being frequently performed and contributing to most of the cost associated with the evaluation of DSP.³² 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.¹⁹ Electrodiagnostic tests clearly have a role in the evaluation of some DSP patients, but the precise subgroup of patients that benefits has not been well defined. The diagnostic work up presented in Figure 1 should be performed by the primary care physician. Patients with atypical features such as asymmetry, non-length-dependent, motor involvement, acute or subacute onset, and/or prominent autonomic involvement may be the most likely to benefit from electrodiagnostic testing, but future studies are needed to precisely define the role of these tests. These atypical features should also prompt referral to a neurologist or neuromuscular specialist. MRI of the brain and/or spine would be expected to be ordered rarely in this population, but are ordered in one quarter of these patients.³¹ Unlike electrodiagnostic tests, MRI has little role in the evaluation of DSP given that this test primarily evaluates the central nervous system. Exceptions include uncommon cases expected of having central or radicular involvement.

The most important component of the evaluation of DSP is the medical history and neurologic examination. In one study, community neurologists were able to diagnose the cause of DSP in 64% of cases prior to their diagnostic evaluation.¹⁹ An etiology was discovered in an additional 10% of patients after diagnostic tests by the neurologist, with pre-diabetes, B12 deficiency, diabetes, and hypothyroidism being the most common causes found. In this population, 27% remained idiopathic despite evaluation, which is a comparable proportion to other studies.^{19–21,25} How a general medicine population would compare is unclear.

The diagnostic work up for a patient suspected of having CMT is rapidly evolving. Historically, patients would have an electrodiagnostic test to determine if they had a demyelinating (usually CMT1) or axonal (usually CMT2) variant. Genetic testing for CMT1 produced high yields with only a few genes tested.³³ In contrast, CMT2 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.³⁴ These approaches also have the potential to identify novel genes, and to allow re-analysis of variants as our bioinformatics information becomes more robust. Unfortunately, insurance coverage of these tests remains problematic. Since 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.

Major Therapeutic Advances

Neuropathic pain treatment for DSP—The prevalence of chronic painful DSP amongst patients with diabetes attending general practitioner clinics in the United Kingdom was 16.2%.¹⁶ 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 diabetes patients, 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 and 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 and/or II studies for level A/B evidence).^{35,36} 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 one 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 side 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 diabetic DSP.³⁷ 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 three drug classes based on patient comorbidities, potential side effects, and cost.³⁸ Cost is one of the main differences between these medications, with TCAs, gabapentin, and venlafaxine (\$4–33/month) being much cheaper than duloxetine and pregabalin (\$239–257/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.^{35,36} 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. Of note, the side effect profiles of valproic acid and capsaicin limit their utility. While evidence exists to support opioid medications for short term neuropathic pain relief, a recent position paper by the AAN advises against their use for long term management of chronic non-cancer pain.³⁹ The statement is based on emerging evidence of increased morbidity and mortality in those taking opioid medications.

While less evidence exists to support neuropathic pain treatment in other neuropathy subtypes and secondary to causes other than diabetes, a 2015 systematic review summarized

all neuropathic pain treatment trials (55% of included trials studied diabetic DSP or post-herpetic neuralgia).⁴⁰ 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, 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 one of these three classes based on patient comorbidities, potential side effects, and cost. If the medication fails due to lack of efficacy or side effects, try a medication from one of the other two classes. Continue trials of at least two medications from each of the three 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 dose, 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 DSP.⁴¹ In this review, a meta-analysis of two trials showed that enhanced glucose control reduced the annual absolute risk of developing DSP by 1.84% in T1DM patients. This result was primarily driven by the Diabetes Control and Complications Trials (DCCT) trial in 1993, which contributed 96% of the patients in the meta-analysis.^{42,43} Of note, patients in the enhanced glycemic control group were three times as likely to experience a serious hypoglycemic episode in the DCCT.

In contrast, it remains unclear if enhanced glycemic control reduces the annual risk of developing DSP in T2DM patients. In a large study of 10,251 patients randomized to target hemoglobin A1C of <6% or between 7–7.9%, there was a non-significant trend toward an annual risk reduction of developing DSP by 0.7%.⁴⁴ Of note, there was increased mortality (relative risk 1.26, 95% confidence interval (CI) 1.06–1.51) in patients in the enhanced glycemic control group. In a study of 1,791 military veterans randomized to standard or intensive glycemic control, there was a non-significant trend toward an annual risk reduction of developing DSP by 0.29%.⁴⁵ When these two studies were combined in a meta-analysis with two smaller studies, neither of which had shown a significant difference in the development of DSP, the result was again a non-significant trend toward an annual risk reduction of developing DSP by 0.58%.⁴¹ Like the T1DM patients, T2DM patients in the enhanced glycemic group were three times as likely to experience a serious hypoglycemic episode compared to the control group. Since the 2012 systematic review, another group randomized 3,057 patients with recently diagnosed T2DM based on screening to either intense goal directed therapy of glucose, blood pressure, and cholesterol or routine care.⁴⁶ Similar to previous studies, the prevalence of neuropathy was lower in the intense goal directed group (4.9% versus 5.9%, OR=0.95, 95% CI 0.68–1.34), but the result was not statistically significant. In contrast to T1DM, the effect of glycemic control in the prevention

of DSP in T2DM is likely quite small, emphasizing the need for new disease modifying therapies.

Pre-diabetes 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 pre-diabetic neuropathy, but no control group was available for comparison.⁴⁷ Diet and exercise and metformin can both prevent pre-diabetes from progressing to diabetes, but the effect on the prevention of neuropathy is unclear.⁴⁸ Future studies are needed to establish which interventions are effective in those with pre-diabetic neuropathy.

There are no currently available treatments for CMT. Two recent double blind placebo controlled trials revealed that ascorbic acid is not effective for the treatment of CMT1A despite promising animal data.^{49,50} In contrast, two 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.⁵¹ Tafamidis revealed similar results in the efficacy evaluable subgroup, but not in the intention to treat population, which was the focus of the primary endpoints.⁵²

Discussion

Advances have been made regarding which diagnostic tests should be used for patients with DSP; however, much work remains to be done. While 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.¹⁹ Unfortunately, physicians order a large number of tests with high variation in practice patterns.^{30,31} Despite the magnitude of tests ordered, the AAN recommended tests are often omitted.^{30,31,53} 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 when this test aids the management of DSP patients need to be ascertained, especially since 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 when 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.¹⁹

Strong evidence exists to support treatment of painful diabetic DSP with TCAs, SNRIs, and voltage-gated calcium channel ligands.^{35–37,40} However, new head to head comparative effectiveness studies are needed to enable physicians to decide which medications to use first. Until that data exists, patient comorbidities, potential side effects, and cost should be the determining factors.³⁸ 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 side effect profiles than currently available drugs.⁴⁰ Strong evidence also supports glucose control in the prevention of DSP in patients with T1DM.⁴¹ Unfortunately, the effect of glucose control in T2DM is much less 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 impact patient quality of life.

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Clinical Bottom Line

- Diabetes, pre-diabetes, alcohol use, B12 deficiency, inherited conditions, chemotherapy, chronic kidney disease, and paraproteinemia are the most common causes of distal symmetric polyneuropathy.
- Even after appropriate testing, the cause of distal symmetric polyneuropathy is unknown (idiopathic) in 24–27%.
- The clinical history and examination are the most important components of the evaluation of DSP, but routine testing with a comprehensive metabolic panel, complete blood count, B12, SPEP with immunofixation, and glucose tolerance test should be performed when the cause remains unclear. Further laboratory testing is only needed when atypical findings are present such as asymmetry, non-length-dependence, motor involvement, acute or subacute onset, and/or 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.
- TCAs, SNRIs, and voltage-gated calcium channel ligands all have strong evidence that they reduce neuropathic pain, particularly in patients with diabetic DSP, but pain is under-recognized and undertreated in this population.
- Glucose control is effective in the prevention of T1DM DSP, but is at best minimally effective in the prevention of T2DM DSP; therefore, new treatments are needed to prevent and treat this common condition.

Box: History and physical examination findings and recommended diagnostic tests for the common subtypes of peripheral neuropathy

DSP

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

Examination:

1. Decreased pinprick and vibration sensation in a stocking-glove distribution
2. Decreased reflexes starting at the ankles
3. Weakness of toe extension or trouble walking on heels

Diagnostic testing- See Figure 1

Radiculopathy

Symptoms:

1. Numbness, tingling, pain radiating from the neck or back into the extremities in a dermatomal pattern
2. Weakness in a myotomal pattern

Examination:

1. Sensory examination is usually normal given the overlapping innervation of dermatomes
2. Decreased reflexes in dermatomal pattern (i.e. absent ankle jerk in S1 radiculopathy)
3. Weakness in myotomal pattern (i.e. dorsiflexion, ankle eversion and inversion weakness in L5 radiculopathy)

Diagnostic testing:

1. EMG/NCS when diagnostic uncertainty exists. Of note, test is not sensitive for the detection of a sensory predominant radiculopathy
2. MRI (cervical or lumbar) for patients with progressive neurologic dysfunction or when surgery is contemplated; lack of high quality evidence to define precise clinical scenarios when MRI should be ordered

Mononeuropathy

Symptoms- Numbness, tingling, pain, and/or weakness in the distribution of one nerve

Examination:

1. Decreased pinprick and vibration sensation in the distribution of one nerve (i.e. decreased pinprick in digits 1–3 and the lateral half of digit 4 in median neuropathy)

- 2.** Weakness in the distribution of one nerve (i.e. finger abduction weakness in ulnar neuropathy)

Diagnostic testing- EMG/NCS when diagnostic uncertainty exists or surgery is contemplated

EMG/NCS=electromyography and nerve conduction studies

Figure 1. 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, MRIs of the brain and/or spine are rarely indicated, but frequently performed.

EMG= electromyography, NCS= nerve conduction studies

*=length dependent neuropathy should start in the toes and spread proximally to at least the knee before involvement of the hands

**=to be ordered by neurologist

Comprehensive metabolic panel includes panel 7, calcium, and hepatic function panel

Table 1

The incidence of polyneuropathies, mononeuropathies, and radiculopathies

Polyneuropathy	Population Studied	Incidence per 100,000 person years
All causes	Netherlands ⁵	77.0
Type 1 diabetes	USA ¹¹	2,800
Type 2 diabetes	USA ¹²	6,100
Mononeuropathies	Population Studied	Incidence per 100,000 person years
Median Neuropathy at the Wrist (Carpal Tunnel Syndrome)	UK ^{54,55} USA ⁵⁶	103 (men 87.8, women 192.8) 99
Ulnar Neuropathy	UK ⁵⁵ Italy (Siena) ⁵⁷	men 25.2, women 18.9 24.7 (men 32.7, women 17.2)
Lateral Femoral Cutaneous Neuropathy (Meralgia Paresthetica)	UK ⁵⁵ Netherlands ⁵⁸	men 10.7, women 13.2 43
Radial Neuropathy	UK ⁵⁵	men 2.97, women 1.42
Idiopathic Facial Neuropathy (Bell's Palsy)	UK ⁵⁹ USA (Rochester, MN) ⁶⁰ Italy (Rome) ⁶¹	20.2 25 (men 22.8, women 26.9) 53.3
Radiculopathies	Population Studied	Incidence per 100,000 person years
Lumbar	USA Military ⁶²	486 (1,079 in patients over 40)
Cervical	USA Military ⁶³ USA (Rochester, MN) ⁶⁴	179 (616 in patients over 40) 83.2 (202.9 in patients 50–54; men 107.3, women 63.5)

USA=United States of America, UK=United Kingdom

Table 2

Common causes of distal symmetric polyneuropathy

Disease	Comment
Metabolic	
Diabetes	Most common cause, accounting for 32–53% of cases
Pre-diabetes	Glucose tolerance test has highest sensitivity
Chronic kidney disease (CKD)	Neuropathy particularly severe when CKD caused by diabetes
Chronic liver disease	Neuropathy typically mild
Idiopathic	24–27% of all cases
Toxin	
Alcohol	Second most common cause (requires in depth questioning)
Inherited	Detailed family history required, ask about hammer toes, high arches
CMT1	Inherited demyelinating sensory motor neuropathy
CMT2	Inherited axonal sensory motor neuropathy
Familial amyloidosis	Transthyretin mutation most common
Nutritional	Methylmalonic acid level important when B12 level 200–400 pg/mL
Vitamin B12 deficiency	Can cause cerebellar ataxia
Vitamin E deficiency	Can cause neuropathy when level too high or too low
Vitamin B6 deficiency	Can present with ataxia, ophthalmoparesis, and confusion
Thiamine deficiency	Often presents with a myeloneuropathy
Copper deficiency	Often difficult to determine which factor responsible
Gastric bypass surgery	Often difficult to determine which factor responsible
Malabsorption syndromes	
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 hard to distinguish cause of neuropathy (HIV vs. medication)
Nitrofurantoin	Worse in the setting of renal failure
Metronidazole	Usually after high, prolonged IV doses
Hydralazine	Avoid by concomitant use of B6
Isoniazid	Avoid by concomitant use of B6
Colchicine	Can also cause myopathy
Autoimmune	
Rheumatoid arthritis	Can also cause mononeuritis multiplex
Lupus	Can also cause mononeuritis multiplex
Sjogren's syndrome	Can also cause a sensory neuronopathy or mononeuritis multiplex

Disease	Comment
Sarcoidosis	Can present with several neurologic manifestations
Secondary amyloidosis	Diagnosis aided by fat pad biopsy or sural nerve biopsy
Infectious	
HIV	Medications used to treat can also cause neuropathy
Hepatitis B/C	Can also cause mononeuritis multiplex associated with polyarteritis nodosa and cryoglobulinemia
Neoplastic	
MGUS	Immunofixation increases sensitivity of paraprotein detection
Multiple myeloma	Associated with IgG or IgA paraproteinemia
Primary amyloidosis	Diagnosis aided by fat pad biopsy or sural nerve biopsy

Bold statements indicate most important take home points

CMT=Charcot Marie Tooth disease, HIV=human immunodeficiency virus, MGUS=monoclonal gammopathy of unclear clinical significance

Table 3
Class I and Class II studies from the AAN and EFNS guidelines on the treatment of painful diabetic DSP

Treatment	Class of Evidence	Duration of Study	Mean Pain reduction on a 0/10 rating scale compared to placebo (95% CI)	Patients with >50% pain reduction		Common Side Effects
				Treatment effect	Placebo effect	
Pregabalin 300 mg ⁶⁵	I ^a	5 weeks	-1.26 (-1.86, -0.65)	46%	18%	Dizziness
Pregabalin 300 mg ⁶⁶	I	8 weeks	-1.47 (-2.19, -0.75)	40%	14.5%	Somnolence
Pregabalin 600 mg ⁶⁵	I	5 weeks	-1.45 (-2.06, -0.85)	48%	18%	Peripheral edema
Pregabalin 600 mg ⁶⁷	I	6 weeks	-1.26 (-1.89, -0.64)	39%	15%	Confusion
Pregabalin 300-600 mg ⁶⁸	II ^b	12 weeks	≈ -1.4-1.6 (P=0.002)	48-52%	24%	Blurry Vision
Gabapentin 900-3600 mg ⁶⁹	I	8 weeks	-1.2 (-1.9, -0.6)	Not reported [*]		Dizziness
Gabapentin 900 mg ⁷⁰	II	6 weeks	No difference	Not reported ^{**}		Somnolence
Gabapentin 900-3600 mg ⁷¹	II	8 weeks	-1.9 (NR, P<0.01)	Not reported ^{***}		Confusion
Amitriptyline 75 mg ⁷²	I	4 weeks	-1.8 (Not reported, P<0.0001)	Not reported ^{****}		Dry mouth
Amitriptyline 25-150 mg ⁷³	II	6 weeks	Not reported	Not reported ^{*****}		Sedation
						Vertigo
Duloxetine 60 mg ⁷⁴	I	12 weeks	-0.9 (-1.39, -0.42)	50%	30%	Nausea
Duloxetine 60 mg ⁷⁵	II	12 weeks	-1.17 (-1.84, -0.5)	49%	26%	Somnolence
Duloxetine 60 mg ⁷⁶	II	12 weeks	-1.32 (-1.95, -0.69)	43%	27%	Hyperhidrosis
Duloxetine 120 mg ⁷⁴	I	12 weeks	-0.87 (-1.36, -0.39)	39%	30%	Anorexia
Duloxetine 120 mg ⁷⁵	II	12 weeks	-1.45 (-2.13, -0.78)	52%	26%	
Duloxetine 120 mg ⁷⁶	II	12 weeks	-1.44 (-2.08, -0.81)	53%	27%	
Venlafaxine 150-225 mg ⁷⁷	I	6 weeks	-0.7 (Not reported, p<0.001)	56%	34%	Nausea
						Dyspepsia
						Sweating
						Somnolence
						Insomnia

Treatment	Class of Evidence	Duration of Study	Mean Pain reduction on a 010 rating scale compared to placebo (95% CI)	Patients with >50% pain reduction		Common Side Effects
				Treatment effect	Placebo effect	
						Blood pressure and cardiac rhythm changes

* 60% of patients treated with gabapentin had at least moderate improvement (>30%) compared to 33% treated with placebo

** 42.5% of patients treated with gabapentin reported moderate or excellent pain relief compared to 22.5% treated with placebo

*** 55.5% of patients treated with gabapentin reported much to moderate improvement compared to 25.9% treated with placebo

**** 63% of patients treated with amitriptyline had at least 20% improvement compared to 22% treated with placebo

***** 65.5% of patients treated with amitriptyline reported moderate to complete improvement compared to 3.5% treated with placebo

²Class 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

⁷Class II randomized-controlled trials lack one or more of the requirements previously listed for Class I studies