Neuropathy, and Foot Care: Standards of Care in Diabetes—2026

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Diabetic Neuropathy: Definition and Scope

- Diabetic neuropathies represent a **heterogeneous group of disorders** that present with a wide range of clinical manifestations.
- Early recognition and appropriate management of neuropathy in individuals with diabetes are essential to prevent complications and improve outcomes.
- Diabetic neuropathy is considered a diagnosis of exclusion, meaning other potential causes of neuropathy must be ruled out.
- Nondiabetic neuropathies may coexist in individuals with diabetes and, in some cases, may be treatable.

• BOX 38.2 Classification for Diabetic Neuropathies

Diabetic Neuropathies

A. **Diffuse neuropathy**
   DSPN
   - Primarily small fiber neuropathy
   - Primarily large fiber neuropathy
   - Mixed small and large fiber neuropathy (most common)

   Autonomic
   Cardiovascular
   - Reduced HRV
   - Resting tachycardia
   - Orthostatic hypotension
   - Sudden death (malignant arrhythmia)

   Gastrointestinal
   - Diabetic gastroparesis (gastropathy)
   - Diabetic enteropathy (diarrhea)
   - Colonic hypomotility (constipation)

   Urogenital
   - Diabetic cystopathy (neurogenic bladder)
   - Erectile dysfunction
   - Female sexual dysfunction

   Sudomotor dysfunction
   - Distal hypohydrosis/anhidrosis
   - Gustatory sweating

   Hypoglycemia unawareness
   Abnormal pupillary function

B. **Mononeuropathy (mononeuritis multiplex) (atypical forms)**
   Isolated cranial or peripheral nerve (e.g., cranial nerve III, ulnar, median, femoral, peroneal)
   Mononeuritis multiplex (if confluent, may resemble polyneuropathy)

C. **Radiculopathy or polyradiculopathy (atypical forms)**
   Radiculoplexus neuropathy (a.k.a. lumbosacral polyradiculopathy, proximal motor amyotrophy)
   Thoracic radiculopathy

Nondiabetic Neuropathies Common in Diabetes

Pressure palsies
Chronic inflammatory demyelinating polyneuropathy
Radiculoplexus neuropathy
Acute painful small-fiber neuropathies (treatment induced)

DSPN, *distal symmetric polyneuropathy.*

From Pop-Busui R, Boulton AJM, Feldman EL, et al. Diabetic neuropathies: a position statement by the American Diabetes Association. Diabetes Care. *2017;40:136–154. Copyright and Material from this publication has been used with the permission of the American Diabetes Association.*

TABLE 38.10 Mononeuritis and Entrapment Syndromes

Feature	Mononeuritis	Entrapment
Onset	Sudden	Gradual
Nerves	Usually single but may be multiple	Single nerves exposed to trauma
Common nerves	C3, C6, C7, ulnar, median, peroneal	Median, ulnar, peroneal, medial and lateral plantar
Progression	Not progressive; resolves spontaneously	Progressive
Treatment	Symptomatic	Rest, splints, diuretics, steroid injections, surgery for paralysis

C3, *C6*, *C7*, cervical spinal nerves 3, 6, and 7.

Modified from Vinik AI, Mehrabyan A. Diabetic neuropathies. *Med Clin North Am.* 2004;88:947–999.

Clinical Importance of Diabetic Neuropathy

- Up to 50% of individuals with diabetic peripheral neuropathy (DPN) may be **asymptomatic**.

Autonomic Neuropathy and Clinical Consequences

- Recognition and treatment of diabetic autonomic neuropathy may improve symptoms, reduce complications, and enhance quality of life.
- Cardiovascular autonomic neuropathy (CAN) is a serious and potentially life-threatening complication of diabetes.
- CAN may worsen existing **cardiovascular disease** and contribute to **heart failure** and sudden cardiac death.

Screening Recommendations: General Principles

- All individuals with diabetes should be routinely assessed for diabetic neuropathy.
- Screening for **diabetic peripheral neuropathy** should begin at the time of diagnosis for type 2 diabetes.
- Screening for diabetic peripheral neuropathy should begin 5 years after diagnosis for type 1 diabetes.
- Neuropathy screening should be conducted at least annually thereafter.

Screening for Distal Symmetric Polyneuropathy

- Assessment should include a detailed medical history and a thorough neurological examination.
- Small-fiber nerve function should be evaluated using temperature sensation or pinprick testing.
- Large-fiber nerve function should be evaluated using vibration sensation with a **128-Hz tuning fork.**
- All individuals with diabetes should undergo annual 10-g monofilament testing to identify feet at increased risk for ulceration and amputation.

Screening for Diabetic Autonomic Neuropathy

- Individuals with type 2 diabetes should be assessed for autonomic neuropathy starting at diagnosis.
- Individuals with type 1 diabetes should be assessed for autonomic neuropathy beginning 5 years after diagnosis.
- Screening should be performed annually and in individuals with evidence of other microvascular complications.
- Symptoms to assess include orthostatic dizziness, syncope, early satiety, erectile dysfunction, abnormal sweating, and dry or cracked skin.

Signs of Autonomic Neuropathy

- **Orthostatic hypotension** may be present and should be evaluated during physical examination.
- Resting tachycardia may indicate cardiovascular autonomic involvement.
- Peripheral skin dryness or cracking may suggest impaired sudomotor function.

TABLE 38.17 Symptoms and Signs Associated With Diabetic Autonomic Neuropathy

Cardiac Autonomic Neuropathy	Gastrointestinal	Urogenital	Sudomotor
Resting tachycardia Abnormal blood pressure regulation Nondipping Reverse dipping	Gastroparesis (gastropathy) Nausea Bloating Loss of appetite Early satiety Postprandial vomiting Brittle diabetes	Bladder dysfunction Frequency Urgency Nocturia Hesitancy Weak stream Dribbling Urinary incontinence Urinary retention	Dry skin Anhidrosis Gustatory sweating
Orthostatic hypotension (all with standing) Lightheadedness Weakness Faintness Visual impairment Syncope	Esophageal dysfunction Heartburn Dysphagia for solids	Male sexual dysfunction Erectile dysfunction Decreased libido Abnormal ejaculation	
Orthostatic tachycardia or bradycardia and chronotropic incompetence (all with standing) Lightheadedness Weakness Faintness Dizziness Visual impairment Syncope	Diabetic diarrhea Profuse and watery diarrhea Fecal incontinence May alternate with constipation	Female sexual dysfunction Decreased sexual desire Increased pain during intercourse Decreased sexual arousal Inadequate lubrication	
Exercise intolerance	Constipation May alternate with explosive diarrhea		

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Diagnosis of Diabetic Peripheral Neuropathy

- ✓All individuals with type 2 diabetes and those with type 1 diabetes for at least 5 years should be assessed annually for DPN.
- ✓Diagnosis relies on medical history and simple clinical tests rather than advanced imaging.
- ✓Symptoms and signs of DPN vary depending on the class of sensory fibers involved.

• BOX 38.3 Diagnosis of Diabetic Peripheral Neuropathy (DPN)

Diagnostic methods in routine clinical use

Clinical history

Diabetes is the most common cause of peripheral neuropathy. Long diabetes duration, uncontrolled diabetes (high levels of hemoglobin A_{1c}), obesity, dyslipidemia, hypertension, and age are risk factors for DPN.

Clinical presentation

Positive symptoms (e.g., tingling, burning, and lancinating pain) and negative sensations, such as numbness, usually occur in a symmetric, distal-to-proximal formation, starting in the feet up to the calves and then progressing to the fingers.

Physical examination

Temperature or pinprick sensation tests assess small-fiber neuropathy. Vibration tests assess large-fiber neuropathy. Monofilament tests assess ulcer risk. Small-fiber neuropathy usually precedes large-fiber neuropathy. Isolated small- and large-fiber neuropathy can also occur.

Methods for clinical diagnosis of atypical presentations or in research settings

Nerve conduction studies

Electrodiagnostic measures of nerve conduction velocities in sensory (sural, peroneal, tibial) and motor (peroneal, tibial) nerves using surface or needle electrodes. Nerve conduction velocities and amplitudes drop with progressive large-fiber neuropathy. Abnormality (velocity or amplitude) in the sural nerve with at least one other nerve conduction abnormality signifies large-fiber neuropathy. Alternatively, a composite Z-score summation from multiple nerves is compared to normative values.

Intraepidermal nerve fiber density

Intraepidermal nerve fiber density is the gold standard for small-fiber neuropathy.[44] Immunohistochemical tests can be done on skin punch biopsy, generally on the distal leg. Stained small fibers are counted and compared to normative values. Intraepidermal nerve fiber density drops with progressive small-fiber neuropathy. Morphologic (e.g., fiber length, branching, axonal swellings) and molecular (e.g., substance P, calcitonin gene–related peptide, and growth-associated protein 43) changes can be assessed.

Diagnostic criteria

Hierarchical classification schemes rate the degree of certainty in the diagnosis, ranging from possible to probable to definite, using a combination of signs and symptoms (e.g., the Toronto Consensus Panel).

Diagnostic methods in research settings

Corneal confocal microscopy

Noninvasive imaging of corneal fibers, which are counted and compared to normative values. Corneal confocal microscopy can also assess fiber length and branching. Studies suggest that decline in nerve fiber density can correlate with DPN progression. Sensitivity is 60.0% to 91.0%, and specificity is 40.0% to 87.0%.

Hand-held electrodiagnostic device

A handheld point-of-care device is able to measure sural nerve conduction velocity and response amplitude in a few minutes. Sensitivity is 84.3% to 90.5%, and specificity ranges from 68.3% to 86.1%.

Sticker sweat detector

A sticker affixed to the plantar surface of the foot measures moisture (sweat) by turning from blue to pink. Sensitivity ranges from 65.1% to 100.0%, and specificity ranges from 32.0% to 78.5%.

Instrument sweat detector

Measures conductance of chloride ions from sweat released from hands and soles of the feet after electrical stimulation of sweat glands. Measures sudomotor function in a few minutes. Sensitivity is 87.5%, and specificity is 76.2%.

Diagnostic methods for painful DPN in research settings

Quantitative sensory testing

Standardized protocols can measure the response to well-defined sensory stimuli. Parameters include thermal and mechanical detection; pain, vibration, and pressure pain thresholds; dynamic mechanical allodynia; and wind-up ratio, which assesses function in all fiber types (Aβ large myelinated, Aδ thinly myelinated, and C unmyelinated).

Microneurography

A needle electrode measures spontaneous activity and stimulus-evoked activity of unmyelinated C fibers in peripheral nerves, usually peroneal. Irregular so-called saw-tooth baselines in abnormal nerves have been observed. This is a labor-intensive technique that requires cross-laboratory validation.

Hoffman-Reflex rate-dependent depression

Differentiates pain of spinal disinhibition origin from pain of peripheral origin by measuring the deep tendon reflex response neural pathways.

Functional brain imaging (fMRI)

fMRI uses different protocols, including the blood oxygen level–dependent (BOLD) response, arterial spin labeling, and connectivity analysis. This type of imaging relates these changes to both spontaneous and evoked pain states, illustrating the distributed cortical network involved in the discriminative and affective pain components, as well as the descending pain modulatory system.

From Elafros MA, Andersen H, Bennett DL, et al. Towards prevention of diabetic peripheral neuropathy: clinical presentation, pathogenesis, and new treatments. Lancet Neurol. 2022;21(10):922–936.

Clinical Manifestations: Small-Fiber Neuropathy

- Early involvement of small nerve fibers typically causes neuropathic pain.
- Patients may experience dysesthesia, which includes unpleasant sensations such as burning and tingling.
- These symptoms often occur before objective sensory loss is detected.

Clinical Manifestations: Large-Fiber Neuropathy

- Involvement of large nerve fibers may result in balance impairment and an increased risk of falls.
- Patients may experience numbness and loss of protective sensation (LOPS).
- LOPS significantly increases the risk of diabetic foot ulceration due to unrecognized minor trauma.

Clinical Tests for Diabetic Peripheral Neuropathy

- Several simple bedside clinical tests can be used to assess small-fiber and large-fiber nerve function.
- These tests are useful not only for screening but also for predicting future risk of complications.
- Advanced diagnostic tests are usually not required unless the clinical presentation is atypical or unclear.

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Assessment of Small-Fiber Nerve Function

- Small-fiber nerve function can be evaluated using pinprick sensation testing.
- **Temperature sensation testing** is another method used to assess small-fiber involvement.
- Early small-fiber dysfunction is often responsible for pain and dysesthesia in diabetic peripheral neuropathy.

Assessment of Large-Fiber Nerve Function

- Large-fiber nerve function can be evaluated by assessing vibration perception.
- A **128-Hz tuning fork** is commonly used to test vibration sensation.
- Additional assessments include lower-extremity reflexes and proprioception.
- Large-fiber involvement contributes to balance problems and increased fall risk.

Assessment of Protective Sensation

- Protective sensation is critical in preventing foot injuries and ulceration.
- The **10-g monofilament test** is the primary method for assessing loss of protective sensation.
- The **Ipswich touch test** is an alternative method used in some countries.
- Loss of protective sensation significantly increases the risk of diabetic foot ulcers.

When Advanced Testing Is Indicated

- **Electrophysiological testing** is rarely required in routine diagnosis.
- **MRI** of the spine or referral to a neurologist should be considered only in atypical cases.
- Atypical features include acute or subacute onset, asymmetry, non–length-dependent neuropathy, or predominant motor involvement.
- **Advanced testing** is also considered when the diagnosis of diabetic neuropathy is uncertain.

Excluding Other Causes of Neuropathy

- ✓In all individuals with diabetes and neuropathy, alternative causes should be evaluated.
- ✓Toxins such as **chronic alcohol** use can cause neuropathy.
- ✓Neurotoxic medications, including **chemotherapy agents**, should be considered.
- ✓**Vitamin B12 deficiency**, particularly in individuals treated long-term with **metformin**, should be assessed.

Additional Non-Diabetic Causes of Neuropathy

- Other nutritional deficiencies, such as **copper deficiency after metabolic surgery**, may contribute to neuropathy.
- **Endocrine disorders** including **hypothyroidism** can cause neuropathy.
- **Chronic kidney disease** is an important contributor to neuropathic symptoms.
- **Malignancies** such as **multiple myeloma and bronchogenic carcinoma** should be considered.
- Infections including **HIV** and **hepatitis C** may cause neuropathy.
- **Autoimmune** and **inflammatory** conditions such as **chronic inflammatory demyelinating** polyneuropathy and **vasculitis** should be excluded.

TABLE 38.13 Common Causes of Rare Subtypes of Peripheral Neuropathy

Localization	Condition
Diffuse, non–length-dependent neuropathy; demyelinating sensory motor	AIDP; CIDP; CIDP variants: POEMS syndrome, IgM anti-MAG neuropathy, Waldenstrom acroglobulinemia, and MGUS; diphtheria; and toxic exposures (hexane, arsenic, and amiodarone)
Demyelinating sensory	Sensory CIDP or AIDP; and DADS (IgM anti-MAG neuropathy)
Demyelinating motor	MMN
Axonal sensory motor	Toxic exposures; ASMAN; and AIP
Axonal sensory	Paraneoplastic (Hu, CRMP5, and amphiphysin); Sjögren syndrome; chemotherapy (platinum based, bortezomib); vitamin B_6 toxicity; idiopathic; HIV, HTLV; autoimmune hepatitis; celiac disease; HSAN; Friedrich ataxia; CANVAS; SANDO; and CANOMAD
Axonal motor	ALS; PMA; postpolio syndrome; HIV, HTLV, WNV, enterovirus D68; MMN without conduction block; radiation; monomelic amyotrophy; HMN; SMA (including Kennedy syndrome); and complicated HSP
Multiple mononeuropathies	Systemic vasculitic neuropathy: microscopic polyangiitis, Wegener granulomatosis, polyarteritis nodosa, Churg-Strauss syndrome, cryoglobulinemia, Sjögren syndrome, rheumatoid arthritis, and SLE; nonsystemic vasculitic neuropathy; neoplasm (malignant and benign); HNPP; sarcoidosis; amyloidosis; MMN; and MADSAM
Polyradiculopathy	Compressive: disc herniation/spondylosis, osteomyelitis, and neoplasm; noncompressive: infection (CMV, VZV, Lyme, and tuberculosis), inflammatory (sarcoidosis), neoplastic (leukemia and lymphoma), and radiation
Plexopathy	Compressive: neoplasm and hemorrhage; noncompressive: infection (VZV, HSV, CMV, and Lyme), inflammatory (sarcoidosis), neoplastic (leukemia, lymphoma), and radiation
Radiculoplexus neuropathy	Diabetic lumbar (diabetic amyotrophy); diabetic cervical; postsurgical inflammatory; nondiabetic lumbar or cervical; infection (VZV, HSV, CMV, and Lyme); inflammatory (sarcoidosis); neoplastic (leukemia and lymphoma); and radiation

AIDP, acute inflammatory demyelinating polyneuropathy; *AIP*, acute intermittent porphyria; *ALS*, amyotrophic lateral sclerosis; *ASMAN*, acute sensory motor axonal neuropathy; *CANOMAD*, chronic ataxic neuropathy, ophthalmoplegia, monoclonal IgM protein, cold agglutinins, disialosyl antibodies; *CANVAS*, cerebellar ataxia neuropathy vestibular areflexia syndrome; *CIDP*, chronic inflammatory demyelinating polyneuropathy; *CMV*, cytomegalovirus; *CRMP5*, collapsing response mediator protein 5; *DADS*, distal-acquired demyelinating syndrome; *HIV*, human immunodeficiency virus; *HMN*, hereditary motor neuropathy; *HNPP*, hereditary neuropathy with liability to pressure palsies; *HSAN*, hereditary sensory autonomic neuropathy; *HSP*, hereditary spastic paraplegia; *HSV*, herpes simplex virus; *HTLV*, human T-lymphotrophic virus; *IgM*, immunoglobulin M; *MADSAM*, multifocal acquired demyelinating sensory and motor neuropathy; *MGUS*, monoclonal gammopathy of unclear significance; *MMN*, multifocal motor neuropathy; *PMA*, progressive muscular atrophy; *POEMS*, polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes; *SANDO*, sensory ataxia neuropathy dysarthria ophthalmoplegia; *SLE*, systemic lupus erythematosus; *SMA*, spinal muscular atrophy; *VZV*, varicella zoster virus; *WNV*, West Nile virus.

Diabetic Autonomic Neuropathy: Overview

- Individuals with type 1 diabetes for at least 5 years and all individuals with type 2 diabetes should be assessed annually for autonomic neuropathy.
- Symptoms and signs should be carefully elicited during history taking and physical examination.
- Autonomic neuropathy affects multiple organ systems and has diverse clinical manifestations.

Clinical Manifestations of Diabetic Autonomic Neuropathy

- **Resting tachycardia** is a common cardiovascular manifestation.
- **Orthostatic hypotension** may occur due to impaired autonomic regulation.
- **Gastrointestinal manifestations** include **gastroparesis**, **constipation**, **diarrhea**, and **fecal incontinence**.
- **Genitourinary manifestations** include **erectile dysfunction**, **neurogenic bladder, and urinary retention.**
- **Sudomotor dysfunction** may present as increased or decreased **sweating**.

Screening for Autonomic Neuropathy Symptoms

- Screening includes asking about **dizziness**, **light-headedness**, or **weakness** upon standing.
- **Syncope** and **exercise intolerance** should be assessed.
- **Gastrointestinal symptoms** such as **constipation** and **diarrhea** should be evaluated.
- **Urinary symptoms** including **retention and incontinence** should be assessed.
- Changes in **sweating** patterns should be documented.

Diagnostic Testing for Autonomic Neuropathy

- Further testing is guided by the **organ system involved.**
- **Cardiovascular autonomic testing** may be performed when symptoms are present.
- **Sweat testing** may be used to evaluate **sudomotor dysfunction**.
- **Urodynamic studies** can assess **bladder dysfunction**.
- **Gastric emptying studies**, **endoscopy**, or **colonoscopy** may be indicated for gastrointestinal symptoms.

Cardiovascular Autonomic Neuropathy (CAN): Overview

- Cardiovascular autonomic neuropathy is associated with increased mortality independent of other cardiovascular risk factors.
- Early-stage CAN may be completely asymptomatic.
- Reduced heart rate variability with deep breathing is an early marker of CAN.

Advanced Cardiovascular Autonomic Neuropathy

- **Advanced CAN** may present with **resting tachycardia** greater than 100 beats per minute.
- **Orthostatic hypotension** is defined as a fall in systolic blood pressure greater than 20 mmHg or diastolic blood pressure greater than 10 mmHg upon standing.
- These changes occur without an appropriate compensatory increase in heart rate.
- Advanced CAN significantly increases the risk of cardiovascular events and mortality.

Gastrointestinal Neuropathies in Diabetes

- Gastrointestinal neuropathies are a diagnosis of exclusion.
- Medication-related adverse effects, such as those caused by metformin **or GLP-1–based therapies**, must be considered.
- Gastrointestinal neuropathy can affect any part of the gastrointestinal tract.

Clinical Features of Gastrointestinal Neuropathy

- **Esophageal dysmotility** may cause difficulty swallowing.
- **Gastroparesis** can cause **delayed gastric emptying** and **erratic glycemic control.**
- Other manifestations include **biliary dysfunction**, **constipation**, **diarrhea**, and **fecal incontinence**.
- **Gastroparesis** should be suspected in individuals with unexplained upper gastrointestinal symptoms.

Diagnosis of Diabetic Gastroparesis

- Diabetic gastroparesis should be suspected in individuals with **erratic glycemic control** or unexplained upper gastrointestinal symptoms.
- Reversible and iatrogenic causes, including medications such as **GLP-1 receptor agonists** and **opioids**, must be excluded.
- Organic causes such as **gastric outlet obstruction** or **peptic ulcer disease** should be ruled out using endoscopy or imaging.
- Specialized diagnostic testing should only be considered after exclusion of these conditions.

Diagnostic Tests for Gastroparesis

- The **diagnostic gold standard** for gastroparesis is gastric emptying scintigraphy.
- This test measures gastric emptying of digestible solid food at 15-minute intervals over 4 hours.
- **The 13C-octanoic acid breath test** is an approved alternative diagnostic method.
- These tests confirm delayed gastric emptying in the absence of mechanical obstruction.

Genitourinary Disturbances in Diabetic Autonomic Neuropathy

- Diabetic autonomic neuropathy can cause significant **genitourinary dysfunction**.
- In men, manifestations include **erectile dysfunction** and **retrograde ejaculation**.
- Symptoms in women include **decreased sexual desire**, **dyspareunia**, **reduced arousal,** and **inadequate lubrication.**

Bladder Dysfunction in Diabetes

- **Lower urinary tract symptoms** may include **urinary urgency**, **frequency**, **nocturia**, and **weak urinary stream**.
- **Urinary incontinence** and **urinary retention** may also occur.
- Bladder dysfunction should be evaluated in individuals with **recurrent urinary tract infections or pyelonephritis.**
- Evaluation is also indicated in individuals with incontinence or a palpable bladder.

Treatment

• BOX 38.4 Scales and Questionnaires for Clinical Management of Diabetic Peripheral Neuropathy (DPN)

Clinical scales

These scales measure a combination of signs and symptoms and are used to screen for and monitor DPN progression.

Diabetic Neuropathy Examination Score
Eight-item examination tool that consists of muscle strength; muscle jerk reflex at the triceps; pinprick in the index finger and great toe; and vibration, joint position, and touch in the great toe.

Michigan Neuropathy Screening Instrument Examination (MNSI-E)
A physical exam consisting of great toe vibration with a 128-Hz tuning fork, muscle jerk reflex at the ankle joint, monofilament testing, and foot exam (appearance, ulcerations).

Modified Toronto Clinical Neuropathy Score (mTCNS)
Includes six questions regarding impact of symptoms on daily living and examination of the loss of sensation to five modalities (touch, pinprick, temperature, vibration, and proprioception) in lower extremities. The mTCNS is a modification of the Toronto Clinical Neuropathy Score, which included ankle and knee jerk reflexes and did not include gradation of symptom impact or severity of sensory loss.

Neuropathy Impairment Score (NIS)
Examination-based measure that includes muscle strength in 24 muscle groups; jerk reflexes at the biceps, triceps, brachioradialis, quadriceps, and ankle; and sensation to touch, vibration, and joint position in the index finger and great toe. The NIS-LL is a condensed measure focused on the lower extremities. The NIS-LL+7 was developed specifically to measure impairment in DPN and includes nerve conduction studies of sural, tibial, and peroneal nerves, vibratory threshold at the great toe using quantitative sensory testing, and heart rate response to deep breathing.

Total Neuropathy Score
Multimodality measure that includes history of sensory, motor, and autonomic symptoms; strength at major muscle groups; muscle jerk reflex at the ankle joint; vibratory threshold at the great toes bilaterally and right index finger using quantitative sensory testing; and nerve conduction studies of the bilateral sural nerves, right common peroneal, and bilateral posterior tibial nerves.

Utah Early Neuropathy Score
Examination-based measure that includes muscle strength at the great toes; extent of sensory loss to pinprick and vibration in the lower extremities; proprioception at the great toes; muscle jerk reflexes at the ankle joints; and presence of allodynia in the toes or foot.

Screening and assessment scales

Douleur Neuropathique en 4 Questions
Includes questions related to history of seven types of pain, loss of sensation to touch and pinprick, and hyperesthesia.

Leeds Assessment of Neuropathic Symptoms and Signs Pain Scale
Includes five questions related to type of pain and associated signs and examination of decreased sensation to pinprick and hyperesthesia.

Michigan Neuropathy Screening Instrument Questionnaire (MNSI-Q)
Includes 15 questions related to history and neuropathy symptoms.[50]

From Elafros MA, Andersen H, Bennett DL, et al. Towards prevention of diabetic peripheral neuropathy: clinical presentation, pathogenesis, and new treatments. Lancet Neurol. 2022;21(10):922–936.

Treatment Overview of Diabetic Neuropathy

- There is currently no specific treatment that reverses underlying nerve damage in diabetes.
- Treatment strategies focus on prevention, symptom control, and slowing disease progression.
- **Optimal glycemic management** plays a central role in neuropathy prevention and progression.
- Management of modifiable risk factors is essential for comprehensive care.

Glycemic Management and Neuropathy Prevention

- Optimal glycemic control effectively prevents or delays diabetic peripheral neuropathy and cardiovascular autonomic neuropathy in type 1 diabetes.
- In type 2 diabetes, optimal glycemic management modestly slows neuropathy progression but does not reverse neuronal loss.
- Early implementation of glycemic control is critical for long-term benefit.
- Different glucose-lowering strategies may have varying effects on neuropathy outcomes.

Evidence from Major Clinical Trials

- The **BARI 2D trial** showed a lower incidence of distal symmetric polyneuropathy in participants treated with insulin sensitizers.
- This benefit was particularly observed in male participants.
- The **ACCORD trial** demonstrated benefits of intensive glucose and blood pressure management in preventing cardiovascular autonomic neuropathy.
- These findings highlight the importance of comprehensive metabolic control.

Weight Management and Neuropathy

- Obesity is consistently associated with neuropathy in both cross-sectional and longitudinal studies.
- Weight loss may improve neuropathy symptoms, although objective examination findings may not always improve.
- The **Look AHEAD trial** demonstrated symptom improvement with lifestyle-based weight loss.
- Evidence from metabolic surgery suggests potential neuropathy improvement, although randomized trials are limited.

Weight Loss Medications and Neuropathy

- Emerging evidence exists regarding weight loss medications and neuropathy outcomes.
- Study results have been conflicting, and further research is needed.
- The potential benefits of GLP-1 receptor agonists on diabetic peripheral neuropathy remain controversial.
- Altered skin sensation, including allodynia, has been reported with GLP-1–based therapies.

Exercise and Neuropathy

- Exercise may contribute to modest weight loss and improve neuropathy outcomes.
- Systematic reviews indicate improvement in neuropathy symptoms, balance, and functional status.
- The overall strength of evidence supporting exercise interventions is low.
- Exercise should still be encouraged due to its broad metabolic and cardiovascular benefits.

Lipid Management and Neuropathy

- Dyslipidemia is a major contributor to neuropathy development in type 2 diabetes.
- **High triglyceride levels** show the strongest association with neuropathy risk.
- The role of lipid abnormalities in type 1 diabetes is less clear but still relevant.
- Conventional lipid-lowering medications have not shown clear benefit in preventing or treating neuropathy.

Blood Pressure Management and Neuropathy

- **Hypertension** is an independent risk factor for the development of diabetic peripheral neuropathy.
- Meta-analyses show a significantly increased odds of neuropathy in individuals with hypertension.
- Intensive blood pressure control reduces the risk of cardiovascular autonomic neuropathy.
- Blood pressure management should be part of a comprehensive neuropathy prevention strategy.

Neuropathic Pain: Clinical Impact

- Neuropathic pain can be severe and debilitating.
- Pain negatively **affects sleep**, **mobility**, **mood**, and overall quality of life.
- Neuropathic pain contributes to **depression** and **anxiety** in individuals with diabetes.
- Effective pain management is essential for improving patient outcomes.

General Principles of Neuropathic Pain Management

- Glycemic or lifestyle interventions do not reliably relieve neuropathic pain.
- Pharmacologic therapy is the mainstay of treatment for painful diabetic neuropathy.
- Initial management should address comorbid sleep and mood disorders.
- Combination therapy may be required when monotherapy is insufficient.

Recommended Pharmacologic Treatments

- **Gabapentinoids** are recommended as first-line therapy for painful diabetic neuropathy.
- **Serotonin–norepinephrine reuptake inhibitors** are effective for neuropathic pain.
- **Tricyclic antidepressants** are effective but may be limited by side effects.
- **Sodium channel blockers** may be considered in selected patients.

TABLE 38.16 Treatment for Pain Associated With Distal Symmetric Polyneuropathy

Drug Class	Agent[a]	DOSE		NNT Range 30%–50% Improvement[c]	Common Adverse Events	Major Adverse Events
		Initial	Effective			
Anticonvulsants	Pregabalin[b]	25–75 mg, 1–3×/day	300–600 mg/day	3.3–8.3	Somnolence Dizziness Peripheral edema Headache Ataxia Fatigue Xerostomia Weight gain	Angioedema Hepatotoxicity Rhabdomyolysis Suicidal thoughts and behavior Seizures after rapid discontinuation Thrombocytopenia
	Gabapentin	100–300 mg, 1–3×/day	900–3600 mg/day	3.3–7.2	Somnolence Dizziness Ataxia Fatigue	Stevens-Johnson syndrome Suicidal thoughts and behavior Seizures after rapid discontinuation
Antidepressants						
Serotonin-norepinephrine reuptake inhibitors	Duloxetine[b]	20–30 mg/day	60–120 mg/day	3.8–11	Nausea Somnolence Dizziness Constipation Dyspepsia Diarrhea Xerostomia Anorexia Headache Diaphoresis Insomnia Fatigue Decreased libido	Stevens-Johnson syndrome Hepatotoxicity Hypertensive crisis Gastrointestinal hemorrhage Delirium Myocardial infarction Cardiac arrhythmias Glaucoma Suicidal thoughts and behavior Shift to mania in patients with bipolar disorder Seizures Severe hyponatremia Fragility bone fractures Serotonin syndrome Neuroleptic malignant syndrome
	Venlafaxine	37.5 mg/day	75–225 mg/day	5.2–8.4	Nausea Somnolence Dizziness Constipation Dyspepsia Diarrhea Xerostomia Anorexia Headache Diaphoresis Insomnia Fatigue Decreased libido	Same as duloxetine
Tricyclic antidepressants	Amitriptyline	10–25 mg/day	25–100 mg/day	2.1–4.2	Xerostomia Somnolence Fatigue Headache Dizziness Insomnia Orthostatic hypotension Anorexia Nausea Urinary retention Constipation Blurred vision Accommodation Disturbance Mydriasis Weight gain	Delirium Cardiac arrhythmias Conduction abnormalities Myocardial infarction Heart failure exacerbation Stroke Seizures Hepatotoxicity Bone marrow suppression Suicidal thoughts and behavior Shift to mania in bipolar disorder Neuroleptic malignant syndrome Serotonin syndrome Severe hyponatremia Fragility bone fractures

TABLE 38.16 Treatment for Pain Associated With Distal Symmetric Polyneuropathy—cont'd

Drug Class	Agent[a]	DOSE		NNT Range 30%–50% Improvement[c]	Common Adverse Events	Major Adverse Events
		Initial	Effective			
	Desipramine				Same as above	Same as above
	Nortriptyline				Same as above	Same as above
Opioids	Tramadol	50 mg 1–2×/day	210 mg/day	3.1–6.4	Somnolence Nausea Vomiting Constipation Lightheadedness Dizziness Headache	Confusion Seizures Cardiac arrhythmias Hypertension Hypersensitivity reactions Stevens-Johnson syndrome
	Tapentadol[b]	Immediate release: 50–75 mg 4–6×/day	Immediate release: Day 1: 700 mg; after day 1, 600 mg/day	N/A	Somnolence Nausea	Respiratory depression Serotonin syndrome
		Extended release: 50 mg 2×/day	Extended release: 50 mg 2×/day		Vomiting Constipation Dizziness	Seizures Hypertension Neonatal opioid withdrawal syndrome

[a]Refer to source article for specific studies referenced for each agent.

[b]Approved by the U.S. Food and Drug Administration (FDA).

[c]FDA considers 30% to 50% improvement to be significant.

NNT, number needed to treat.

Modified from Pop-Busui R, Boulton AJM, Feldman EL, et al. Diabetic neuropathies: a position statement by the American Diabetes Association. *Diabetes Care.* 2017;40:136–154.

Gabapentinoids in Neuropathic Pain Management

- **Gabapentinoids** are **calcium channel α2-δ subunit ligands** used for neuropathic pain.
- **Pregabalin** is supported by several high-quality and medium-quality clinical studies for painful diabetic peripheral neuropathy.
- **Gabapentin** is supported by one high-quality study and multiple smaller studies.
- **Mirogabalin** has shown a modest effect on pain reduction in diabetic peripheral neuropathy

Adverse Effects of Gabapentinoids

- Adverse effects are more common and severe in older adults.
- Common side effects include **dizziness**, **somnolence**, and **peripheral edema.**
- Starting at low doses and gradual dose titration can reduce adverse effects.
- Careful monitoring is required, particularly in elderly individuals.

Serotonin–Norepinephrine Reuptake Inhibitors (SNRIs)

- SNRIs include **duloxetine**, **venlafaxine**, and **desvenlafaxine**.
- **Duloxetine** is supported by multiple high-quality and medium-quality studies for painful diabetic peripheral neuropathy.
- **Venlafaxine** has demonstrated efficacy in high-quality clinical trials.
- **Desvenlafaxine** has limited evidence supporting its use.

Adverse Effects of SNRIs

- Adverse effects may include **nausea**, **dry mouth**, **dizziness**, and **hypertension**.
- Older adults may experience more pronounced adverse events.
- Lower starting doses and slower titration can improve tolerability.
- **Duloxetine** requires monitoring for blood pressure and hepatic function.

Tricyclic Antidepressants (TCAs)

- Tricyclic antidepressants have been extensively studied for neuropathic pain.
- **Amitriptyline** is the most commonly studied TCA in painful diabetic neuropathy.
- Multiple high-quality and medium-quality studies support its effectiveness.
- TCAs may be limited by their side effect profile.

Adverse Effects of Tricyclic Antidepressants

- **Anticholinergic** side effects include **dry mouth**, **constipation**, **urinary retention**, and **blurred vision**.
- TCAs may cause sedation and orthostatic hypotension.
- These side effects are particularly problematic in individuals aged 65 years or older.
- Dose limitations are often required due to tolerability concerns.

Sodium Channel Blockers

- Sodium channel blockers **reduce neuronal excitability and pain transmission**.
- Agents include **lamotrigine**, **lacosamide**, **carbamazepine**, **oxcarbazepine**, and **valproic acid**.
- Several medium-quality studies support their use in painful diabetic neuropathy.
- These agents may be considered when first-line therapies are ineffective or contraindicated.

Topical Capsaicin Therapy

- Capsaicin 8% patch is approved by the FDA for treatment of painful diabetic peripheral neuropathy.
- High-quality clinical trials support its efficacy.
- Lower-concentration capsaicin cream has moderate evidence of benefit.
- Topical capsaicin is an option for individuals who cannot tolerate oral medications.

Lidocaine 5% Patch

- Lidocaine patches have limited evidence supporting their use in diabetic peripheral neuropathy.
- They may be useful for localized or nocturnal neuropathic foot pain.
- Lidocaine patches are not effective for widespread pain.
- Use should be limited to a maximum of 12 hours within a 24-hour period.

Opioids in Neuropathic Pain

- Randomized controlled trials have shown opioids can reduce neuropathic pain.
- Evidence supporting long-term efficacy of opioids is lacking.
- Long-term opioid use is associated with significant risks including addiction and mortality.
- Opioids are generally not recommended for painful diabetic neuropathy.

Tapentadol and Tramadol

- **Tapentadol** and **tramadol** act through **opioid receptor agonism** and **monoamine reuptake inhibition.**
- These agents demonstrate analgesic effects in painful diabetic neuropathy.
- Their effect size is similar to that of SNRIs.
- Risks associated with opioid therapy outweigh potential benefits in most cases.

Orthostatic Hypotension: Treatment Goals

- The primary goal of treatment is **reduction of postural symptoms**.
- Restoration of normal blood pressure is not the primary objective.
- Management requires a combination of nonpharmacologic and pharmacologic strategies.
- Individualized treatment plans are essential.

Nonpharmacologic Management of Orthostatic Hypotension

- **Adequate salt** and **fluid intake** should be ensured.
- Medications that worsen hypotension should be avoided.
- Compression garments over the legs and abdomen may improve symptoms.
- Physical activity should be encouraged to prevent deconditioning.

Pharmacologic Management of Orthostatic Hypotension

- Supine hypertension may require **bedtime antihypertensive therapy**.
- **Short-acting agents** such as **clonidine** or **guanfacine** may be used.
- **Short-acting calcium channel blockers** or **beta blockers** may be considered.
- **Midodrine** and **droxidopa** are FDA-approved therapies for orthostatic hypotension.

• BOX 38.6 American Diabetes Association Recommendations for Cardiac Autonomic Neuropathy Screening and Diagnosis

- Symptoms and signs of autonomic neuropathy should be assessed in patients with microvascular and neuropathic complications. **E**
- In the presence of symptoms or signs of cardiovascular autonomic neuropathy, tests excluding other comorbidities or drug effects/interactions that could mimic cardiovascular autonomic neuropathy should be performed. **E**
- Consider assessing symptoms and signs of cardiovascular autonomic neuropathy in patients with hypoglycemia unawareness. **C**

ADA recommendations are assigned ratings of A, B, or C depending on the quality of evidence. Expert opinion E is a separate category for recommendations in which there is no evidence from clinical trials, in which clinical trials may be impractical, or in which there is conflicting evidence. From Pop-Busui R, Boulton AJM, Feldman EL, et al. Diabetic neuropathies: a position statement by the American Diabetes Association. Diabetes Care. *2017;40:136–154. Copyright and Material from this publication has been used with the permission of the American Diabetes Association.*

• BOX 38.7 American Diabetes Association Recommendations for Cardiac Autonomic Neuropathy

- Optimize glucose control as early as possible to prevent or delay the development of cardiovascular autonomic neuropathy in people with type 1 diabetes. **A**
- Consider a multifactorial approach targeting glycemia among other risk factors to prevent cardiovascular autonomic neuropathy in people with type 2 diabetes. **C**
- Consider lifestyle modifications to improve cardiovascular autonomic neuropathy in patients with prediabetes. **C**

ADA recommendations are assigned ratings of A, B, or C depending on the quality of evidenc
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Management of Diabetic Gastroparesis

- Dietary modification with small-particle meals may reduce symptoms.
- Foods with smaller particle size improve gastric emptying.
- Medications that impair gastrointestinal motility should be discontinued if possible.
- Risk-benefit assessment is required before discontinuing GLP-1–based therapies.

Pharmacologic Therapy for Gastroparesis

- **Metoclopramide** is the only FDA-approved medication for gastroparesis.
- Evidence supporting its benefit is limited.
- Serious adverse effects include extrapyramidal symptoms and tardive dyskinesia.
- Use beyond 12 weeks is not recommended except in severe refractory cases.

Alternative Therapies for Gastroparesis

- **Domperidone** is available outside the United States.
- **Erythromycin** may be used short term due to tachyphylaxis.
- Gastric electrical stimulation has limited evidence of benefit.
- Current data do not support routine use of gastric stimulation in diabetic gastroparesis.

• BOX 38.8 American Diabetes Association Recommendations for Gastrointestinal Neuropathies

- Evaluate for gastroparesis in people with diabetic neuropathy, retinopathy, and/or nephropathy by assessing for symptoms of unexpected glycemic variability, early satiety, bloating, nausea, and vomiting. **C**
- Exclusion of other causes documented to alter gastric emptying, such as use of opioids or glucagon-like peptide 1 receptor agonists and organic gastric outlet obstruction, is needed before performing specialized testing for gastroparesis. **C**
- To test for gastroparesis, either measure gastric emptying with scintigraphy of digestible solids at 15-min intervals for 4 h after food intake or use a ^{13}C-octanoic acid breath test. **B**

ADA recommendations are assigned ratings of A, B, or C depending on the quality of evidence. From Pop-Busui R, Boulton AJM, Feldman EL, et al. Diabetic neuropathies: a position statement by the American Diabetes Association. Diabetes Care. *2017;40:136–154. Copyright and Material from this publication has been used with the permission of the American Diabetes Association.*

Erectile Dysfunction in Diabetes

- Erectile dysfunction may result from diabetic autonomic neuropathy.
- Treatment includes **phosphodiesterase type 5 inhibitors**.
- Other options include **intracavernosal prostaglandins and vacuum devices.**
- Penile prostheses may be considered in refractory cases.

TABLE 38.15 **Class I and Class II Randomized Controlled Trials From the American Academy of Neurology and European Federation of Neurologic Societies Guidelines on the Treatment of Painful Diabetic Distal Symmetric Polyneuropathy**

Source[c]	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	PATIENTS WITH >50% PAIN REDUCTION: Treatment Effect (%)	Placebo Effect (%)
Lesser et al., 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., 2004	Pregabalin, 300 mg	I	8	76/146	−1.47 (−2.19 to −0.75)	40	14.5	
Lesser et al., 2004	Pregabalin, 600 mg	I	5	82/337	−1.45 (−2.06 to −0.85)	48	18	
Richter et al., 2005	Pregabalin, 600 mg	I	6	72/223	−1.26 (−1.89 to −0.64)	39	15	
Freynhagen et al., 2005	Pregabalin, 300–600 mg	II	12	82/209	Approximately −1.4 to 1.6 ($p = 0.002$)	48-52	24	
Backonja et al., 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., 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, 2001	Gabapentin, 900–3600 mg	II	8	27/54	−1.9 (Not reported; $p < 0.01$)	Not reported; 55.5% treated with gabapentin reported much to moderate improvement vs. 25.9% treated with placebo		
Vrethem et al., 1997	Amitriptyline, 75 mg	I	4	33/99	−1.8 (Not reported; $p < 0.001$)	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., 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., 2005	Duloxetine, 60 mg	I	12	116/348	−0.9 (−1.39 to −0.42)	50	30	Nausea, somnolence, hyperhidrosis, anorexia

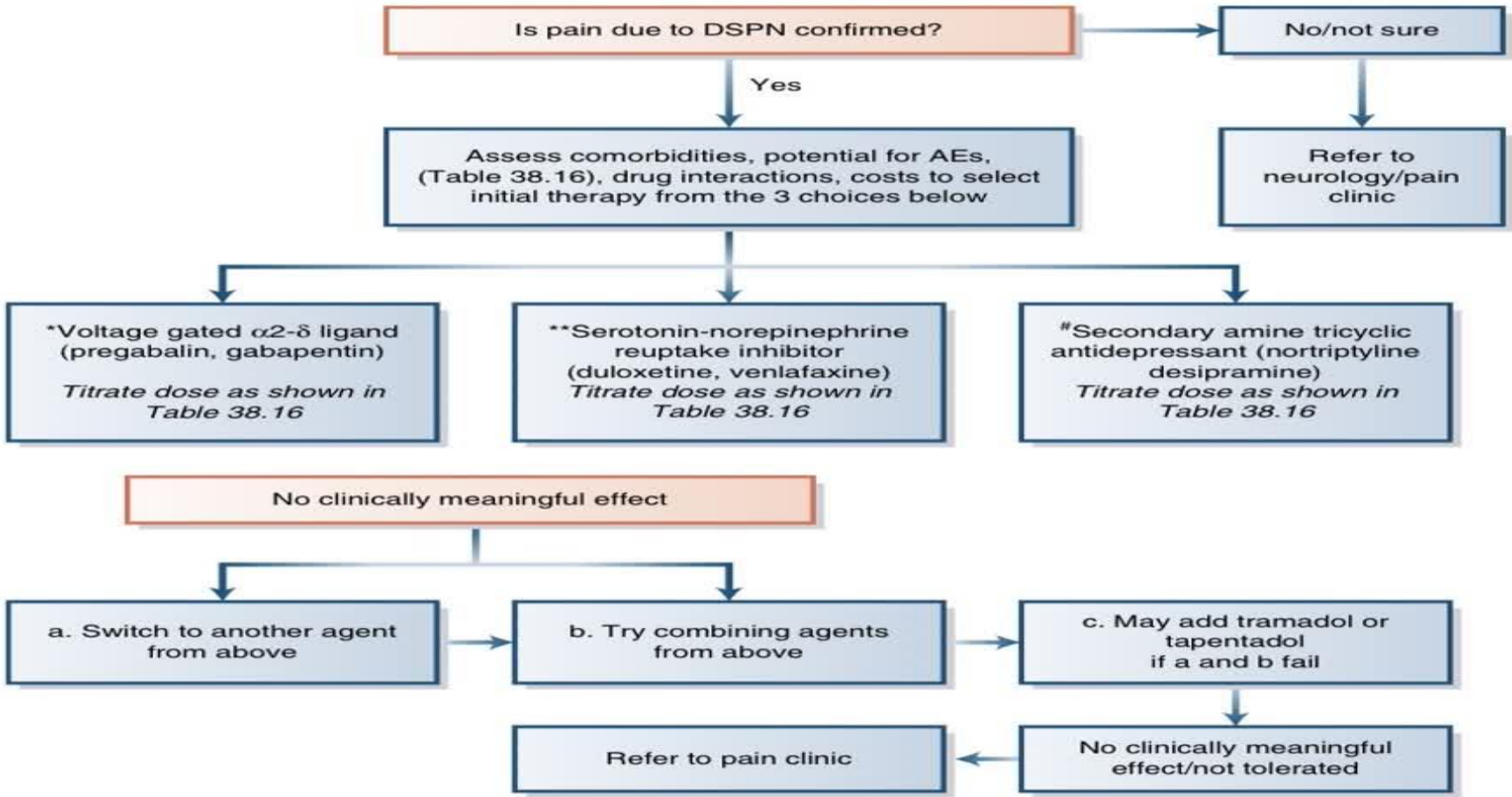
TABLE 38.15 Class I and Class II Randomized Controlled Trials From the American Academy of Neurology and European Federation of Neurologic Societies Guidelines on the Treatment of Painful Diabetic Distal Symmetric Polyneuropathy—cont'd

Source[c]	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 (%)
Goldstein et al., 2005	Duloxetine, 60 mg	II	12	86/344	−1.17 (−1.84 to −0.5)	49	26	
Wernicke et al., 2006	Duloxetine, 60 mg	II	12	85/248	−1.32 (−1.95 to −0.69)	43	27	
Raskin et al., 2005	Duloxetine, 120 mg	I	12	116/348	−0.87 (−1.36 to −0.39)	39	30	
Goldstein et al., 2005	Duloxetine, 120 mg	II	12	80/344	−1.45 (−2.13 to −0.78)	52	26	
Wernicke et al., 2006	Duloxetine, 120 mg	II	12	78/248	−1.44 (−2.08 to −0.81)	53	27	
Rowbotham et al., 2004	Venlafaxine, 150–225 mg	I	6	82/242	−0.7 (Not reported; $p < 0.001$)	56	34	Nausea, dyspepsia, sweating, somnolence, insomnia, blood pressure and cardiac rhythm changes

[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 one 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.

[c]Refer to source article for full reference listings.



• **Fig. 38.50** Algorithm for management of the patient with pain because of distal symmetric polyneuropathy *(DSPN). AE,* adverse events. *Pregabalin is FDA approved for painful DSPN, whereas gabapentin is not. Pharmacokinetic profile, spectrum of AEs, drug interactions, comorbidities, and costs to be considered in selecting the agent of choice. **Duloxetine is FDA approved for painful DSPN, whereas venlafaxine is not. Pharmacokinetic profile, spectrum of AEs, drug interactions, comorbidities, and costs should be considered in selecting the agent of choice. #None is FDA approved for painful DSPN. Spectrum of AEs, drug interactions, and comorbidities need to be considered if selecting these agents. (Modified from Pop-Busui R, Boulton AJ, Feldman EL, et al. Diabetic neuropathy: a position statement by the American Diabetes Association. *Diabetes Care.* 2017;40:136–154.)

Foot Care: Importance in Diabetes

- Foot complications are common and serious in individuals with diabetes.
- Peripheral neuropathy, peripheral artery disease, and foot deformities contribute to risk.
- Foot ulcers and infections are **major causes of morbidity and mortality.**
- Prevention and early intervention are critical.

Foot Care Screening Recommendations

- A comprehensive foot examination should be performed at least annually.
- High-risk individuals should have foot examinations at every clinical visit.
- Screening aims to identify risk factors for ulceration and amputation.
- Early detection can prevent severe outcomes.

Peripheral Artery Disease (PAD) in Diabetes

- Peripheral artery disease commonly coexists with diabetic neuropathy and increases the risk of foot ulcers and amputations.
- Symptoms may be atypical or absent due to coexisting neuropathy.
- Reduced pedal pulses, claudication, and delayed wound healing suggest PAD.
- Early identification of PAD is essential for ulcer prevention.

Evaluation of Peripheral Artery Disease

- Vascular examination should include **palpation of pedal pulses** and **inspection of skin temperature and color.**
- **Ankle–brachial index testing** is recommended when PAD is suspected.
- **Toe–brachial index** may be more accurate in individuals with arterial calcification.
- Vascular imaging is reserved for individuals being considered for revascularization.

Loss of Protective Sensation and Foot Risk Stratification

- Loss of protective sensation is a major risk factor for diabetic foot ulceration.
- Monofilament testing is the primary screening tool.
- Risk stratification guides frequency of follow-up and preventive care.
- Individuals with prior ulcers or amputations are at highest risk.

Patient Education and Preventive Foot Care

- Daily self-inspection of the feet should be strongly encouraged.
- Patients should be educated on proper nail care and skin hygiene.
- Walking barefoot should be avoided at all times.
- Properly fitted footwear reduces the risk of skin breakdown and ulceration.

Management of Diabetic Foot Ulcers (DFU)

- Management of diabetic foot ulcers requires a multidisciplinary approach.
- Pressure offloading is essential for wound healing.
- Sharp debridement improves healing by removing necrotic tissue.
- Infection and ischemia must be promptly identified and treated.

Infection Management in DFU

- Clinical signs of infection include **erythema**, **warmth**, **pain**, and **purulent discharge.**
- Deep tissue cultures are preferred over superficial swabs.
- **Antibiotic therapy** should be guided by severity and culture results.
- Osteomyelitis should be considered in chronic or deep ulcers

Advanced Wound Care Therapies

- Advanced wound therapies may be considered for nonhealing ulcers.
- Options include negative pressure wound therapy and biologic dressings.
- Evidence for hyperbaric oxygen therapy is mixed.
- Advanced therapies should not replace basic wound care principles.

Revascularization in Diabetic Foot Disease

- Revascularization should be considered in individuals with **critical limb ischemia.**
- Both endovascular and surgical approaches may be used.
- Improved blood flow enhances wound healing and limb salvage.
- Decisions should be individualized based on anatomy and comorbidities.

Prevention of Recurrence and Long-Term Care

- Recurrence of foot ulcers is common without preventive strategies.
- Regular podiatric care reduces recurrence risk.
- Custom footwear and orthotics improve pressure distribution.
- Ongoing patient education is essential for long-term success.

Table 12.1—International Working Group on Diabetic Foot risk stratification system and corresponding foot screening frequency

Category	Ulcer risk	Characteristics	Examination frequency*
0	Very low	No LOPS and no PAD	Annually
1	Low	LOPS or PAD	Every 6–12 months
2	Moderate	LOPS + PAD, or LOPS + foot deformity, or PAD + foot deformity	Every 3–6 months
3	High	LOPS or PAD and one or more of the following: • History of foot ulcer • Amputation (minor or major) • Kidney failure	Every 1–3 months

Adapted with permission from Schaper et al. (123). LOPS, loss of protective sensation; PAD, peripheral artery disease. *Examination frequency suggestions are based on expert opinion and person-centered requirements.

Summary and Key Take-Home Messages

- Diabetic neuropathy is a common and serious complication of diabetes.
- Early screening and risk factor modification are essential.
- Symptom management improves quality of life but does not reverse nerve damage.
- Multidisciplinary care is critical for preventing complications and amputations.