



# Diabetic Neuropathy: A Position Statement by the American Diabetes Association

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Diabetic neuropathies are the most prevalent chronic complications of diabetes. This heterogeneous group of conditions affects different parts of the nervous system and presents with diverse clinical manifestations. The early recognition and appropriate management of neuropathy in the patient with diabetes is important for a number of reasons:

1. Diabetic neuropathy is a diagnosis of exclusion. Nondiabetic neuropathies may be present in patients with diabetes and may be treatable by specific measures.
2. A number of treatment options exist for symptomatic diabetic neuropathy.
3. Up to 50% of diabetic peripheral neuropathies may be asymptomatic. If not recognized and if preventive foot care is not implemented, patients are at risk for injuries to their insensate feet.
4. Recognition and treatment of autonomic neuropathy may improve symptoms, reduce sequelae, and improve quality of life.

Among the various forms of diabetic neuropathy, distal symmetric polyneuropathy (DSPN) and diabetic autonomic neuropathies, particularly cardiovascular autonomic neuropathy (CAN), are by far the most studied (1–4). There are several atypical forms of diabetic neuropathy as well (1–4). Patients with prediabetes may also develop neuropathies that are similar to diabetic neuropathies (5–10). Table 1 provides a comprehensive classification scheme for the diabetic neuropathies.

Due to a lack of treatments that target the underlying nerve damage, prevention is the key component of diabetes care. Screening for symptoms and signs of diabetic neuropathy is also critical in clinical practice, as it may detect the earliest stages of neuropathy, enabling early intervention. Although screening for rarer atypical forms of diabetic neuropathy may be warranted, DSPN and autonomic neuropathy are the most common forms encountered in practice. The strongest available evidence regarding treatment pertains to these forms.

This Position Statement is based on several recent technical reviews, to which the reader is referred for detailed discussion and relevant references to the literature (3,4,11–16).

## PREVENTION

Prevention of diabetic neuropathies focuses on glucose control and lifestyle modifications. Available evidence pertains only to DSPN and CAN, and most of the large trials that have evaluated the effect of glucose control on the risk of complications have included DSPN and CAN as secondary outcomes or as post hoc analyses rather than as primary outcomes. In addition, in some of these trials, the outcome measures used to evaluate neuropathy may have limited ability to detect a benefit, if present.

### Recommendations

- Optimize glucose control as early as possible to prevent or delay the development of distal symmetric polyneuropathy and cardiovascular autonomic neuropathy in people with type 1 diabetes. **A**
- Optimize glucose control to prevent or slow the progression of distal symmetric polyneuropathy in people with type 2 diabetes. **B**
- Consider a multifactorial approach targeting glycemia among other risk factors to prevent cardiovascular autonomic neuropathy in people with type 2 diabetes. **C**

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**Table 1—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., CN 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)

**Glucose Control**

Enhanced glucose control in people with type 1 diabetes dramatically reduces the incidence of DSPN (78% relative risk reduction) (17–19). In contrast, enhanced glucose control in people with type 2 diabetes reduces the risk of developing DSPN modestly (5%–9% relative risk reduction) (20,21). In a small trial of Japanese patients with early type 2 diabetes, intensive insulin treatment was associated with improvement in selected DSPN measures (22), and the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial reported a modest but significant DSPN risk reduction with the glycemia intervention in individuals with type 2 diabetes after 5 years of follow-up (21). Yet, no effects are observed in other large trials (20,23–25). This discrepancy highlights the differences between type 1 and type 2 diabetes and emphasizes the point that many

people with type 2 diabetes develop DSPN despite adequate glucose control (20,25). The presence of multiple comorbidities, polypharmacy, hypoglycemia, and weight gain might have attenuated the effects of glucose control in these trials and contributed to inconsistent findings (25). Specific glucose-lowering strategies may also contribute to the discrepancy. For example, participants, particularly men, in the Bypass Angioplasty Revascularization Investigation in Type 2 Diabetes (BARI 2D) study treated with insulin sensitizers had a lower incidence of DSPN over 4 years than those treated with insulin/sulfonylurea (26). This outcome may be a result of less weight gain and less hypoglycemia (26). Last, the fact that many patients have had asymptomatic hyperglycemia for many years prior to the diagnosis of type 2 diabetes may also explain the limited benefit in these patients.

Similar to the findings in DSPN, the most robust evidence for CAN prevention was reported in type 1 diabetes. Intensive glucose control designed to achieve near-normal glycemia reduced the risk of incident CAN during the Diabetes Control and Complications Trial (DCCT) by 45% and by 31% in its follow-up study, the Epidemiology of Diabetes Interventions and Complications (EDIC) study (27). The highly reproducible and sensitive testing protocol, the robust definitions used for CAN, and the large sample size in DCCT/EDIC enhance the validity of the results and support the rationale for implementing and maintaining tight glucose control as early as possible in the course of type 1 diabetes. In contrast, glycemic control in type 2 diabetes has not consistently lowered the risk of CAN (25). However, a multifactorial intervention, including a lifestyle component, targeting glucose and cardiovascular disease risk factors reduced the risk of CAN by 60% in people with type 2 diabetes (28).

**Lifestyle Modifications**

The best models to date regarding parameters for an evidence-based, intensive lifestyle intervention come from the Diabetes Prevention Program (DPP) (29), the Steno-2 Study (28), the Italian supervised treadmill study (30), and the University of Utah type 2 diabetes study (31). The latter study recently reported nerve fiber regeneration in patients with type 2 diabetes engaged in an exercise program compared with loss of nerve fibers in those who only followed standard of care. Overall, such an approach focuses on either exercise alone (supervised aerobic and/or resistance training) (30,31) or combined dietary modification and exercise. There is no consensus regarding dietary regimens, and although the DPP used a low-calorie, low-fat diet, others have championed a Mediterranean diet that is moderately lower in carbohydrate (45%) and higher in fat (35%–40%), with less than 10% of saturated fat.

Although the DPP (32) and the Impaired Glucose Tolerance Neuropathy (IGTN) study (33) reported benefits of lifestyle interventions on measures of CAN and DSPN, respectively, these trials did not include subjects with established diabetes. In addition, in the DPP, indices of CAN improved with the lifestyle intervention and did not change in the other arms (32).

## DSPN

Most common among diabetic neuropathies is chronic DSPN, accounting for about 75% of the diabetic neuropathies (1,3). A simple definition of DSPN for clinical practice is the presence of symptoms and/or signs of peripheral nerve dysfunction in people with diabetes after the exclusion of other causes.

Experimental studies suggest a multifactorial pathogenesis of DSPN (Fig. 1), but the causes remain unknown (34–37). A prevailing view of the pathogenesis is that oxidative and inflammatory stress may, in the context of metabolic dysfunction, damage nerve cells (34–37).

Estimates of the incidence and prevalence of DSPN vary greatly (25,38–40), but evidence from several large observational cohorts (41,42) and the DCCT/EDIC (27,43) suggests that DSPN occurs in at least 20% of people with type 1 diabetes after 20 years of disease duration. DSPN may be present in at least 10%–15% of newly diagnosed patients with type 2 diabetes (44,45), with rates increasing to 50% after 10 years of disease duration (25,26). Rates in youth with type 1 and type 2 diabetes approach those

observed in adult populations (46). DSPN has been associated with glycemia (14,33–35), height (47) (perhaps as a proxy for nerve length), smoking (48), blood pressure, weight, and lipid measures (49,50).

There is emerging evidence that DSPN, especially the painful small-fiber neuropathy subtype, may be present in 10%–30% of subjects with impaired glucose tolerance, also known as prediabetes (5–10) or metabolic syndrome (51).

DSPN is the most important cause of foot ulceration, and it is also a prerequisite in the development of Charcot neuroarthropathy (CN) (52). The reader is referred to several other reviews that cover this topic (52,53). Foot ulceration and CN are both recognized as late complications of DSPN (52,54). These late complications drive amputation risk and economic costs of diabetic neuropathy and are also predictors of mortality.

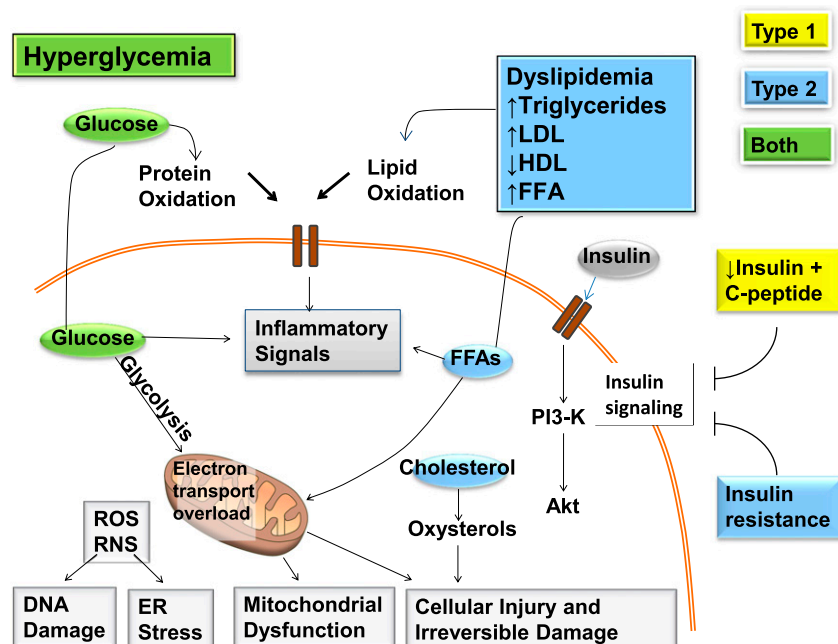
DSPN is also a major contributor to falls and fractures (55–57), through more advanced small- and large-fiber dysfunction, with loss of sensory, proprioception, temperature discrimination, and pain, all ultimately leading to unsteadiness, recurrent minor injuries,

and an increased risk of falls. These recurrent minor injuries may further contribute to the pathogenesis of CN (58).

## Screening and Diagnosis

### Recommendations

- All patients should be assessed for distal symmetric polyneuropathy starting at diagnosis of type 2 diabetes and 5 years after the diagnosis of type 1 diabetes and at least annually thereafter. **B**
- Consider screening patients with prediabetes who have symptoms of peripheral neuropathy. **B**
- Assessment should include a careful history and either temperature or pinprick sensation (small-fiber function) and vibration sensation using a 128-Hz tuning fork (large-fiber function). All patients should have an annual 10-g monofilament testing to assess for feet at risk for ulceration and amputation. **B**
- Electrophysiological testing or referral to a neurologist is rarely needed for screening, except in situations where the clinical features are atypical, the diagnosis is unclear, or a different etiology is suspected. Atypical features include motor greater than sensory neuropathy, rapid onset, or asymmetrical presentation. **B**



**Figure 1**—Mechanisms of diabetic neuropathy. Factors linked to type 1 diabetes (yellow), type 2 diabetes (blue), and both (green) cause DNA damage, endoplasmic reticulum stress, mitochondrial dysfunction, cellular injury, and irreversible damage. The relative importance of the pathways in this network will vary with cell type, disease profile, and time. ER, endoplasmic reticulum; FFA, free fatty acids; PI3-K, phosphatidylinositol-3 kinase; RNS, reactive nitrogen species; ROS, reactive oxygen species. Adapted and reprinted from Callaghan et al. (20), with permission from Elsevier.

Patients with type 1 diabetes for 5 or more years and all patients with type 2 diabetes should be assessed annually for DSPN using medical history and simple clinical tests. Up to 50% of patients may experience symptoms of DSPN (Table 2), whereas the rest are asymptomatic. Patients may not volunteer symptoms but on inquiry may reveal that they are experiencing numbness or other positive symptoms of DSPN.

Symptoms vary according to the class of sensory fibers involved. The most common early symptoms are induced by the involvement of small fibers and include pain and dysesthesias (unpleasant sensations of burning) (1,4,59,60). Neuropathic pain may be the first symptom that prompts patients to seek medical care and is present in up to 25% of individuals with DSPN (61–63). Characteristically, the pain is burning, lancinating, tingling, or shooting (electric shock-like); occurs with paresthesias; presents in

**Table 2—Symptoms and signs of DSPN**

	Large myelinated nerve fibers	Small myelinated nerve fibers
Function	Pressure, balance	Nociception, protective sensation
Symptoms§	Numbness, tingling, poor balance	Pain: burning, electric shocks, stabbing
Examination	Ankle reflexes: reduced/absent	Thermal (cold/hot) discrimination: reduced/absent**
(clinically diagnostic)**	Vibration perception: reduced/absent	Pinprick sensation: reduced/absent**
	10-g monofilament: reduced/absent	
	Proprioception: reduced/absent	

§To document the presence of symptoms for diagnosis; \*\*Documented in symmetrical, distal to proximal pattern.

varying combinations; and is typically worse at night. Neuropathic pain may be accompanied by an exaggerated response to painful stimuli (hyperalgesia) and pain evoked by contact, e.g., with socks, shoes, and bedclothes (allodynia). Neuropathic pain can lead to interference with daily activities, disability, psychosocial impairment, and reduced health-related quality of life (64–66). The direct and indirect economic burden associated with neuropathic pain is substantial (67–69).

The involvement of large fibers may cause numbness, tingling without pain, and loss of protective sensation. Loss of protective sensation indicates the presence of DSPN and is a risk factor for diabetic foot ulceration. Patients can also initially present with an insensate, numb foot due to the loss of large fibers. Patients frequently state that their feet feel like they are wrapped in wool or they are walking on thick socks. It is the loss of the “gift of pain” that permits patients with plantar neuropathic ulcers to walk on the lesions, inducing chronicity, frequently complicated by infection (70).

The following clinical tests may be used to assess small- and large-fiber function distal to proximal (Table 2):

1. Small-fiber function: pinprick and temperature sensation
2. Large-fiber function: vibration perception, proprioception, 10-g monofilament, and ankle reflexes

A 128-Hz tuning fork can be used for the assessment of vibration perception. Assessment of light-touch perception using a 10-g monofilament should include evaluation on the dorsal aspect of the great toe bilaterally as previously validated by Perkins et al. (71). The 10-g monofilament is a useful clinical tool mainly for detecting more advanced neuropathy and identifying patients at increased risk of ulceration and amputation (72).

Assessments should follow the typical DSPN pattern, starting distally (the dorsal aspect of the hallux) on both sides and move proximally until a sensory threshold is identified (72). Combining at least two examinations will increase the sensitivity and specificity of detecting DSPN, as demonstrated in several cohorts of patients with type 1 and type 2 diabetes including children and adolescents (26,46,73–79).

The diagnosis of DSPN is principally a clinical one (Table 2). A combination of typical symptomatology and symmetrical distal sensory loss or typical signs in the absence of symptoms in a patient with diabetes is highly suggestive of DSPN and may not require additional evaluation or referral. As up to half of the patients may be asymptomatic, a diagnosis may only be made on examination or, in some cases, when the patient presents with a painless foot ulcer.

Clinicians should note that the 10-g monofilament test included for the annual DSPN screening and diagnosis is different than the diagnosis of the “high-risk foot” for ulceration, a late DSPN complication that requires that four sites (first, third, and fifth metatarsal heads and plantar surface of distal hallux) be tested on each foot (80).

Consider excluding neuropathy with causes other than diabetes (Table 3) by undertaking a family and medication history and performing relevant investigations (e.g., serum B<sub>12</sub>, folic acid, thyroid function, complete blood count, metabolic panel, and a serum protein immunoelectrophoresis) (81).

Electrophysiological testing or referral to a neurologist is rarely needed for diagnosis, except in situations where the clinical features are atypical, the diagnosis is unclear, or a different etiology is suspected (2,38,40,80). Atypical features that warrant referral include motor greater than sensory neuropathy, asymmetry of symptoms and signs, and rapid progression.

### Foot Complications

The simple yet comprehensive clinical exam is principally designed to identify those at risk for the late complications who need education on preventative foot self-care and regular podiatric foot care. Recently an even simpler

**Table 3—Differential diagnosis of diabetic neuropathies**

Metabolic disease
Thyroid disease (common)
Renal disease
Systemic disease
Systemic vasculitis
Nonsystemic vasculitis
Paraproteinemia (common)
Amyloidosis
Infectious
HIV
Hepatitis B
Lyme
Inflammatory
Chronic inflammatory demyelinating polyradiculoneuropathy
Nutritional
B <sub>12</sub> *
Postgastrectomy
Pyridoxine
Thiamine
Tocopherol
Industrial agents, drugs, and metals
Industrial agents
Acrylamide
Organophosphorous agents
Drugs
Alcohol
Amiodarone
Colchicine
Dapsone
Vinka alkaloids
Platinum
Taxol
Metals
Arsenic
Mercury
Hereditary
Hereditary motor, sensory, and autonomic neuropathies

\*B<sub>12</sub> deficiency is more commonly associated with malabsorption rather than nutritional deficiency.



foot exam, the “3-minute diabetic foot exam,” has been proposed (82). This is intended not only for physicians but also for other health care professionals who may only have 15 min for the entire diabetes annual review; it requires no equipment and provides simple advice on education on preventative foot self-care.

### Management

#### Recommendations

- Tight glucose control targeting near-normal glycemia in patients with type 1 diabetes dramatically reduces the incidence of distal symmetric polyneuropathy and is recommended for distal symmetric polyneuropathy prevention in type 1 diabetes. **A**
- In patients with type 2 diabetes with more advanced disease and multiple risk factors and comorbidities, intensive glucose control alone is modestly effective in preventing distal symmetric polyneuropathy and patient-centered goals should be targeted. **B**
- Lifestyle interventions are recommended for distal symmetric polyneuropathy prevention in patients with prediabetes/metabolic syndrome and type 2 diabetes. **B**

### Prevention

Please refer to PREVENTION on page 136.

### Pathogenetic Therapies

Despite the recent major advances in elucidating the pathogenesis of diabetic neuropathy, there remains a lack of treatment options that effectively target the natural history of DSPN (83) or reverse DSPN once established. Several pathogenetic pharmacotherapies have been investigated (36), but evidence from randomized clinical trials is very limited (81,83,84). Advances in DSPN disease modification need to be confirmed with further robust evidence from clinical trials, together with a better understanding of the mechanisms of action of promising treatments (83).

### Pain Management

#### Recommendations

- Consider either pregabalin or duloxetine as the initial approach in the symptomatic treatment for neuropathic pain in diabetes. **A**

- Gabapentin may also be used as an effective initial approach, taking into account patients' socioeconomic status, comorbidities, and potential drug interactions. **B**
- Although not approved by the U.S. Food and Drug Administration, tricyclic antidepressants are also effective for neuropathic pain in diabetes but should be used with caution given the higher risk of serious side effects. **B**
- Given the high risks of addiction and other complications, the use of opioids, including tapentadol or tramadol, is not recommended as first- or second-line agents for treating the pain associated with DSPN. **E**

No compelling evidence exists in support of glycemic control or lifestyle management as therapies for neuropathic pain in diabetes or prediabetes (33,85), which leaves only pharmaceutical interventions.

At present, pregabalin and duloxetine have received regulatory approval for the treatment of neuropathic pain in diabetes by the U.S. Food and Drug Administration (FDA), Health Canada, and the European Medicines Agency. The opioid, tapentadol, has regulatory approval in the U.S. and Canada, but the evidence of its use is weaker (15).

A large evidence base supports pharmacological treatment of neuropathic pain in diabetic neuropathy using other agents of different classes, as documented by several recent guidelines and systematic reviews (15,16,20,86,87). It is important to mention that only a few trials that targeted pain in peripheral neuropathic pain were carried out in DSPN alone. However, the results of studies performed on peripheral nondiabetic neuropathic pain or mixed neuropathic pain may be applicable to patients with neuropathic pain due to DSPN.

Although there are broad general agreements among the recommendations, there are some inconsistencies that are, in part, a consequence of whether the guidelines are specific for painful DSPN or whether they address neuropathic pain due to all causes (15,16,20,86,87).

Below we summarize the available evidence on the most effective agents for DSPN pain starting with the currently approved drugs and continuing with the

other agents based on mechanism of action and strength of evidence. Evidence levels are assigned based on the strength of the published clinical evidence for the efficacy and safety of the agents for the treatment of DSPN pain, which should be considered in clinical decision making. However, a certain degree of publication bias should be considered, given that many negative trials may not have been published (15).

Additional information on dose titration, adverse effects, number needed to treat, and safety is presented in Table 4.

### Approved Medications

Pregabalin and duloxetine have received regulatory approval for the treatment of neuropathic pain in diabetes in the U.S., Europe, and Canada.

*Pregabalin*, a calcium channel  $\alpha 2\text{-}\delta$  subunit ligand, is an effective treatment for neuropathic pain associated with DSPN. It is the most extensively studied drug by far in DSPN, with the majority of studies being positive regarding the proportion of responders with at least 30%–50% improvement in pain (15,86,88–94). There is also some evidence suggesting a dose response, with a weaker effect with 300 vs. 600 mg/day (88). However, not all trials with pregabalin have been positive (15,86,95,96), especially when treating advanced refractory patients (93). Pregabalin, in contrast to gabapentin (see below), has a linear, dose-proportional absorption in the therapeutic dose range (150–600 mg/day) (88). In addition, pregabalin has a more rapid onset of action and more limited dosage range that requires minimal titration. Adverse effects may be more severe in older patients (97) and may be attenuated by lower starting doses and more gradual titration.

*Duloxetine* is a selective norepinephrine and serotonin reuptake inhibitor. Doses of 60 and 120 mg/day showed efficacy in the treatment of pain associated with DSPN in multicenter randomized trials, although some of these had a rather high drop-out rate (15,86,94,96,98–101). Duloxetine was also suggested to induce improvement in neuropathy-related quality of life (100). In longer-term studies, a small increase in A1C was reported in people with diabetes treated with duloxetine compared with placebo (102). Adverse events may again be more severe in older people but may be attenuated

**Table 4—Treatment for pain associated with DSPN (15,16,20,86,87)**

Drug class	Agent	Dose		NNT range 30–50% improvement**	Common adverse events	Major adverse events
		Initial	Effective			
Anticonvulsants	Pregabalin* (15,86,88–94)	25–75 mg, 1–3×/day	300–600 mg/day	3.3–8.3	<ul style="list-style-type: none"> <li>Somnolence</li> <li>Dizziness</li> <li>Peripheral edema</li> <li>Headache</li> <li>Ataxia</li> <li>Fatigue</li> <li>Xerostomia</li> <li>Weight gain</li> <li>Somnolence</li> <li>Dizziness</li> <li>Ataxia</li> <li>Fatigue</li> </ul>	<ul style="list-style-type: none"> <li>Angioedema</li> <li>Hepatotoxicity</li> <li>Rhabdomyolysis</li> <li>Suicidal thoughts and behavior</li> <li>Seizures after rapid discontinuation</li> <li>Thrombocytopenia</li> </ul>
	Gabapentin (15,86,96,105–111)	100–300 mg, 1–3×/day	900–3,600 mg/day	3.3–7.2	<ul style="list-style-type: none"> <li>Weight gain</li> <li>Somnolence</li> <li>Dizziness</li> <li>Ataxia</li> <li>Fatigue</li> </ul>	<ul style="list-style-type: none"> <li>Stevens-Johnson syndrome</li> <li>Suicidal thoughts and behavior</li> <li>Seizures after rapid discontinuation</li> </ul>
Antidepressants	Serotonin-norepinephrine reuptake inhibitors	Duloxetine* (15,86,94,96,98–101)	20–30 mg/day	3.8–11	<ul style="list-style-type: none"> <li>Nausea</li> <li>Somnolence</li> <li>Dizziness</li> <li>Constipation</li> <li>Dyspepsia</li> <li>Diarrhea</li> <li>Xerostomia</li> <li>Anorexia</li> <li>Headache</li> <li>Diaphoresis</li> <li>Insomnia</li> <li>Fatigue</li> <li>Decreased libido</li> </ul>	<ul style="list-style-type: none"> <li>Stevens-Johnson syndrome</li> <li>Hepatotoxicity</li> <li>Hypertensive crisis</li> <li>Gastrointestinal hemorrhage</li> <li>Delirium</li> <li>Myocardial infarction</li> <li>Cardiac arrhythmias</li> <li>Glaucoma</li> <li>Suicidal thoughts and behavior</li> <li>Shift to mania in patients with bipolar disorder</li> <li>Seizures</li> <li>Severe hyponatremia</li> <li>Fragility bone fractures</li> <li>Serotonin syndrome</li> <li>Neuroleptic malignant syndrome</li> <li>Same as duloxetine</li> </ul>
		Venlafaxine (15,16,20,86,87,126,127)	37.5 mg/day	5.2–8.4	<ul style="list-style-type: none"> <li>Nausea</li> <li>Somnolence</li> <li>Dizziness</li> <li>Constipation</li> <li>Dyspepsia</li> <li>Diarrhea</li> <li>Xerostomia</li> <li>Anorexia</li> </ul>	

Continued on p. 142

Table 4—Continued

Drug class	Agent	Dose		NNT range 30–50% improvement**	Common adverse events	Major adverse events
		Initial	Effective			
Tricyclic antidepressants	Amitriptyline (16,110,112–116)	10–25 mg/day	25–100 mg/day	2.1–4.2	<ul style="list-style-type: none"> <li>• Headache</li> <li>• Diaphoresis</li> <li>• Insomnia</li> <li>• Fatigue</li> <li>• Decreased libido</li> </ul>	<ul style="list-style-type: none"> <li>• Delirium</li> <li>• Cardiac arrhythmias</li> <li>• Conduction abnormalities</li> <li>• Myocardial infarction</li> <li>• Heart failure exacerbation</li> <li>• Stroke</li> <li>• Seizures</li> <li>• Hepatotoxicity</li> <li>• Bone marrow suppression</li> <li>• Suicidal thoughts and behavior</li> <li>• Shift to mania in bipolar disorder</li> <li>• Neuroleptic malignant syndrome</li> <li>• Serotonin syndrome</li> <li>• Severe hyponatremia</li> <li>• Fragility bone fractures</li> </ul>
	Desipramine (113,118–121,122) Nortriptyline (15,16,86,87,113,114,120,121,123)				<ul style="list-style-type: none"> <li>• Xerostomia</li> <li>• Somnolence</li> <li>• Fatigue</li> <li>• Headache</li> <li>• Dizziness</li> <li>• Insomnia</li> <li>• Orthostatic hypotension</li> <li>• Anorexia</li> <li>• Nausea</li> <li>• Urinary retention</li> <li>• Constipation</li> <li>• Blurred vision</li> <li>• Accommodation</li> <li>• Disturbance</li> <li>• Mydriasis</li> <li>• Weight gain</li> <li>• Same as above</li> <li>• Same as above</li> </ul>	<ul style="list-style-type: none"> <li>• Same as above</li> <li>• Same as above</li> </ul>
Opioids	Tramadol (15,16,86,87,109,130)	50 mg, 1–2×/day	210 mg/day	3.1–6.4	<ul style="list-style-type: none"> <li>• Somnolence</li> <li>• Nausea</li> <li>• Vomiting</li> <li>• Constipation</li> <li>• Light-headedness</li> <li>• Dizziness</li> <li>• Headache</li> <li>• Somnolence</li> <li>• Nausea</li> <li>• Vomiting</li> <li>• Constipation</li> <li>• Dizziness</li> </ul>	<ul style="list-style-type: none"> <li>• Confusion</li> <li>• Seizures</li> <li>• Cardiac arrhythmias</li> <li>• Hypertension</li> <li>• Hypersensitivity reactions</li> <li>• Stevens-Johnson syndrome</li> </ul>
	Tapentadol* (103,104,135)	Immediate release: 50–100 mg, 4–6×/day Extended release: 50 mg, 2×/day	Immediate-release: day 1: 700 mg; after day 1, 60 mg/day Extended release: 50 mg, 2×/day	N/A	<ul style="list-style-type: none"> <li>• Respiratory depression</li> <li>• Serotonin syndrome</li> <li>• Seizures</li> <li>• Hypertension</li> <li>• Neonatal opioid withdrawal syndrome</li> </ul>	

NNT, number needed to treat. \*FDA approved. \*\*FDA considers 30–50% improvement to be significant.

with lower doses and progressive titrations of duloxetine.

*Tapentadol extended release* is a novel centrally acting opioid analgesic that exerts its analgesic effects through both  $\mu$ -opioid receptor agonism and noradrenaline reuptake inhibition. Extended-release tapentadol was approved by the FDA for the treatment of neuropathic pain associated with diabetes based on data from two multicenter randomized withdrawal, placebo-controlled phase 3 trials (103,104). However, both used an enriched design and therefore are not generalizable, and a recent systematic review and meta-analysis by the International Association for the Study of Pain Special Interest Group on Neuropathic Pain (NeuPSIG) found the evidence of the effectiveness of tapentadol in reducing neuropathic pain inconclusive (15). Therefore, given the high risk for addiction and safety concerns compared with the relatively modest pain reduction, the use of tapentadol extended release is not recommended as first- or second-line treatment.

#### Anticonvulsants

*Gabapentin*, like pregabalin, also binds the calcium channel  $\alpha 2\text{-}\delta$  subunit and has shown efficacy in a number of clinical trials for treating the pain associated with DSPN (15,86,96,105–111). However, not all painful DSPN studies, some of which are unpublished, have been positive (15,107).

Given its pharmacokinetic profile, gabapentin requires gradual titration and doses up to 1,800–3,600 mg are generally needed to be clinically effective (96,105–107). Adverse effects may be more severe in older patients (97).

#### Monoamine Reuptake Inhibitors

The monoamine reuptake inhibitors—tricyclic antidepressants, selective serotonin reuptake inhibitors, and norepinephrine and serotonin reuptake inhibitors—increase synaptic monoamine levels and directly influence the activity of the descending neurons.

*Amitriptyline*, although not FDA approved, is the most used of the tricyclic agents. Many previous guidelines recommend the medication as a first-line treatment based on few randomized, blinded, placebo-controlled clinical trials that reported significant improvement in neuropathic pain (110,112–116). The effectiveness appeared unrelated to the

antidepressant effect (112). A recent Cochrane Review questioned the quality of evidence on amitriptyline by raising concerns for bias given the small sample size in most and concluded that in fact there is no clear evidence for a beneficial effect for amitriptyline on DSPN pain, especially when balanced against spectrum of side effects (117). However, there was no good evidence of a lack of effect either (117).

The secondary amines, *nortriptyline* and *desipramine*, have a less troublesome side effect profile than the tertiary amines, amitriptyline and *imipramine*, although fewer randomized controlled trials were performed with these agents, and the potential for bias was high given the small size (113,118–123). The use of these agents is preferable, particularly in older and side effect-prone patients (113,118–121).

Several studies have suggested that there is an increased risk of myocardial ischemia and arrhythmogenesis associated with tricyclic agents (124,125). Because of concerns of possible cardiotoxicity, tricyclic antidepressants should be used with caution in patients with known or suspected cardiac disease.

*Venlafaxine*, a selective norepinephrine and serotonin reuptake inhibitor, in doses between 150 and 225 mg/day has shown some effectiveness in the treatment of painful DSPN (126,127). Both venlafaxine and duloxetine (see above) inhibit the reuptake of serotonin and norepinephrine without the muscarinic, histaminic, and adrenergic side effects that accompany the use of the tricyclic agents (98–100,102). However, the level of evidence for pain reduction associated with DSPN is higher with duloxetine (see above). Venlafaxine may lower the seizure threshold, and gradual tapering is recommended to avoid the emergence of adverse events upon discontinuation (126,127).

#### Opioid and Atypical Opioid Analgesics

*Tramadol* is a centrally acting analgesic with pain relief mediated by a weak  $\mu$ -opioid receptor agonist activity and inhibition of norepinephrine and serotonin reuptake (128,129). It is an effective agent in the treatment of painful diabetic peripheral neuropathy compared with placebo as demonstrated by two large multicenter trials (129,130), and it appears to have long-term effects

(131). Although tramadol has a lower potential for abuse compared with other opioids, given these safety concerns, it is not recommended for use as first- or second-line agent.

*Controlled-release oxycodone* improved pain scores in two single-center trials in patients with painful diabetic neuropathy, one of which had a small sample size (132,133). It may provide additional analgesia for patients on  $\alpha 2\text{-}\delta$  ligand treatment (134). As with all opioids, it is not recommended for use as first-, second-, or third-line agent.

#### Warnings on All Opioids

Despite the demonstrated effectiveness of opioids in the treatment of neuropathic pain (15,132,134,135), there is a high risk of addiction, abuse, sedation, and other complications and psychosocial issues even with short-term opioid use. For these reasons, opioids are not recommended in the treatment of painful DSPN before failure of other agents that do not have these associated concerns (136–138).

Although add-on therapy with strong opioids may be required in some patients who do not respond to all other combinations, referral to specialized pain clinics is recommended in these cases to avoid risks.

#### Additional Considerations for Pain

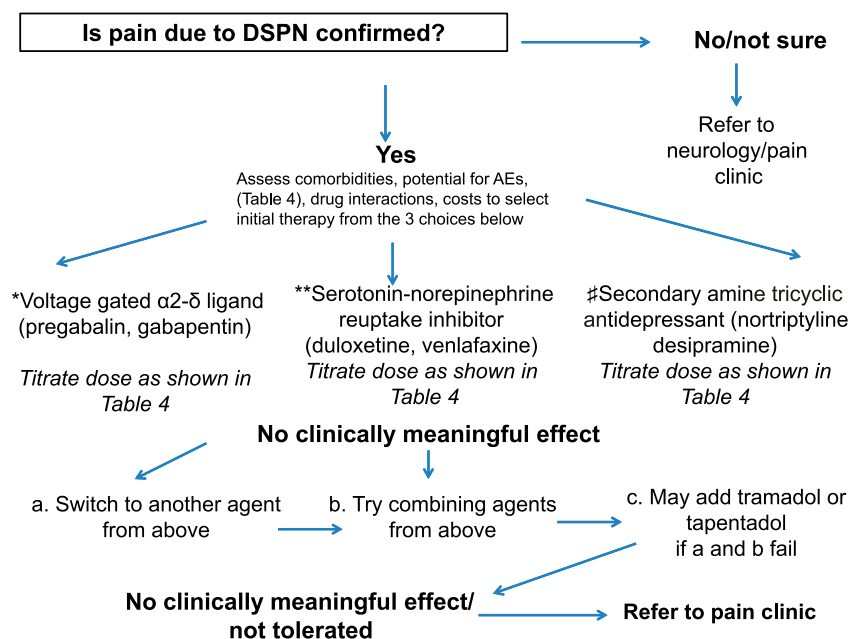
##### Management

Combination therapy, including combinations with opioids, may provide effective treatment for diabetic neuropathic pain at lower doses (94,139). A detailed approach for pain management is amply covered in other literature (15,109), and a simple algorithm for clinical practice use is shown in Fig. 2.

#### Treatment of Foot Complications

Detailed treatment of foot ulceration and CN is beyond the scope of this statement, and the reader is referred to a relevant review (54). Effective off-loading that prevents patients with plantar neuropathic ulcers to walk on the lesions is the key to successful management (52,54). Off-loading, usually with casting, and careful follow-up and repeated investigations are also key components for the management of CN (52,54). Ongoing education and regular podiatry follow-up can reduce the incidence of foot complications in those found to be at “high risk.” Early intervention for foot





**Figure 2**—Algorithm for management of the patient with pain because of 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 to be considered in selecting the agent of choice. #None is FDA approved for painful DSPN. Spectrum of AEs, drug interactions, and comorbidities need be considered if selecting these agents.

lesions and CN or suspected CN can slow or reverse progression.

### Fall Prevention

#### Recommendation

- Tests assessing gait and balance may be considered in people with distal symmetric polyneuropathy to evaluate the risk of falls. **E**

DSPN may also compromise balance in daily activities (58). For instance, progressive loss of proprioception (diminished sensation) and later weakness, superimposed on age-related functional impairments, lead to imbalance and unsteadiness in gait, with increased likelihood of a fall (55,58). A decline in cognitive function, polypharmacy, and neuropathic pain may further contribute. In addition, treatment of neuropathic pain often requires dosages and drug combinations that may further increase the fall risk due to cognitive impairment, drowsiness, dizziness, blurred vision, and gait disturbances (97,109). Older patients are the most susceptible (97,109). Therefore, tests assessing gait and balance may be considered in

clinical practice to evaluate risk of falls in patients at risk (55,58).

### Psychosocial Factors

#### Recommendations

- Consider treatment with duloxetine, pregabalin, and gabapentin to improve quality of life in patients with neuropathic pain. **C**
- Assess the effects of distal symmetric polyneuropathy on quality of life to improve adherence and response to neuropathic pain treatment. **E**

Assessing the effects of DSPN on a patient's quality of life is emerging as a component of patient care and may play an important part in the adherence and the response to therapies in patients with neuropathic pain (140). Some studies report an improvement in quality of life in people with painful DSPN treated with duloxetine (100), pregabalin (141), and gabapentin (106,142). A longitudinal study has shown that DSPN is a risk factor for depression and the strongest symptom associated with depression was unsteadiness. Pain with DSPN may also

give rise to symptoms of anxiety (143). Two research tools that can be used to assess quality of life that are neuropathy specific are the Neuro-QoL (Quality of Life in Neurological Disorders) (144) and QOL-DN (Norfolk Quality of Life-Diabetic Neuropathy) instruments (145).

### DIABETIC AUTONOMIC NEUROPATHIES

Autonomic neuropathies affect the autonomic neurons (parasympathetic, sympathetic, or both) and are associated with a variety of site-specific symptoms. The symptoms and signs of autonomic dysfunction should be elicited carefully during the medical history and physical examination. Major clinical manifestations of diabetic autonomic neuropathy include hypoglycemia unawareness, resting tachycardia, orthostatic hypotension, gastroparesis, constipation, diarrhea, fecal incontinence, erectile dysfunction, neurogenic bladder, and sudomotor dysfunction with either increased or decreased sweating.

Although CAN is the most studied and clinically relevant of the diabetic autonomic neuropathies, gastrointestinal, genitourinary, and sudomotor dysfunction should be considered in the optimal care of patients with diabetes.

#### CAN

Although CAN prevalence is very low in newly diagnosed patients with type 1 diabetes (146), CAN prevalence increases substantially with diabetes duration (13,25), and prevalence rates of at least 30% were observed in the DCCT/EDIC cohort after 20 years of diabetes duration (27,147). In type 2 diabetes, the prevalence of CAN also increases with diabetes duration and may be present in up to 60% of patients with type 2 diabetes after 15 years (13,148,149). CAN may affect youth, especially young women and those with elevated A1C levels, with prevalence rates of at least 20% reported in youth with type 1 or type 2 diabetes (150). In addition, CAN is present in patients with impaired glucose tolerance, insulin resistance, or metabolic syndrome (10,32,151).

A timely diagnosis of CAN may have important clinical implications, as CAN is an independent risk factor for cardiovascular mortality, arrhythmia, silent

ischemia, any major cardiovascular event, and myocardial dysfunction (152–157). Data from two large cardiovascular outcomes trials that included 31,531 patients with stable heart disease and/or diabetes followed for a median of 5 years reported that heart rate, an indirect measure of CAN, analyzed as either categorical (baseline heart rate  $>70$  vs.  $\leq 70$  bpm) or across heart rate quintile, was independently associated with significant increases in cardiovascular disease (CVD) events and all-cause death (158). CAN may also be associated with hemodynamic instability or cardiorespiratory arrest (159). CAN was the strongest risk factor for mortality in a large cohort of patients with type 1 diabetes participating in the EURODIAB Prospective Cohort Study (160), and a meta-analysis of several trials reported higher mortality risk with worse measures of CAN (152).

Conclusive evidence that supports CAN as an independent predictor of mortality was confirmed in more than 8,000 participants with type 2 diabetes in the ACCORD trial (154). Hazard ratios for all-cause and CVD mortality in those with CAN were as high as 2.14 after adjusting for all traditional CVD risk factors

and many other risk factors, including use of various classes of medication use (154).

It was also suggested that intensification of glucose and blood pressure management may increase the risk of a cardiovascular event in people with signs of CAN (161–165). Similarly, emerging evidence demonstrates an association between CAN and glucose variability, especially in the hypoglycemic range (150,164).

In addition, CAN independently predicts the progression of diabetic nephropathy and chronic kidney disease in diabetes (13,166–168).

#### Screening and Diagnosis

##### Recommendations

- 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**

The most common symptoms of CAN occur upon standing and include light-headedness, weakness, palpitations, faintness, and syncope (13,169,170) (Table 5). The patient should be asked about these symptoms when a medical history is taken in the office, although the correlation of symptoms with overall autonomic deficits is weak (149,171). However, these symptoms may occur quite late in the disease course (25,27,147,149). It may be appropriate to screen patients with hypoglycemia unawareness, as this may be associated with CAN (81).

In its early stages, CAN may be completely asymptomatic and detected only by decreased heart rate variability (HRV) with deep breathing (13,169,170). Testing HRV may be done in the office by either 1) taking an electrocardiogram recording as a patient begins to rise from a seated position or 2) taking an electrocardiogram recording during 1–2 min of deep breathing with calculation of HRV (11,81,170).

**Table 5—Symptoms and signs associated with diabetic autonomic neuropathy**

CAN	Gastrointestinal	Urogenital	Sudomotor
Resting tachycardia Abnormal blood pressure regulation <ul style="list-style-type: none"> <li>• Nondipping</li> <li>• Reverse dipping</li> </ul>	Gastroparesis (Gastropathy) <ul style="list-style-type: none"> <li>• Nausea</li> <li>• Bloating</li> <li>• Loss of appetite</li> <li>• Early satiety</li> <li>• Postprandial vomiting</li> <li>• Brittle diabetes</li> </ul>	Bladder dysfunction <ul style="list-style-type: none"> <li>• Frequency</li> <li>• Urgency</li> <li>• Nocturia</li> <li>• Hesitancy</li> <li>• Weak stream</li> <li>• Dribbling</li> <li>• Urinary incontinence</li> <li>• Urinary retention</li> </ul>	Dry skin <ul style="list-style-type: none"> <li>• Anhidrosis</li> <li>• Gustatory sweating</li> </ul>
Orthostatic hypotension (all with standing) <ul style="list-style-type: none"> <li>• Light-headedness</li> <li>• Weakness</li> <li>• Faintness</li> <li>• Visual impairment</li> <li>• Syncope</li> </ul>	Esophageal dysfunction <ul style="list-style-type: none"> <li>• Heartburn</li> <li>• Dysphagia for solids</li> </ul>	Male sexual dysfunction <ul style="list-style-type: none"> <li>• Erectile dysfunction</li> <li>• Decreased libido</li> <li>• Abnormal ejaculation</li> </ul>	
Orthostatic tachycardia or bradycardia and chronotropic incompetence (all with standing) <ul style="list-style-type: none"> <li>• Light-headedness</li> <li>• Weakness</li> <li>• Faintness</li> <li>• Dizziness</li> <li>• Visual impairment</li> <li>• Syncope</li> </ul>	Diabetic diarrhea <ul style="list-style-type: none"> <li>• Profuse and watery diarrhea</li> <li>• Fecal incontinence</li> <li>• May alternate with constipation</li> </ul>	Female sexual dysfunction <ul style="list-style-type: none"> <li>• Decreased sexual desire</li> <li>• Increased pain during intercourse</li> <li>• Decreased sexual arousal</li> <li>• Inadequate lubrication</li> </ul>	
Exercise intolerance	Constipation <ul style="list-style-type: none"> <li>• May alternate with explosive diarrhea</li> </ul>		

In more advanced cases, patients may present with resting tachycardia (>100 bpm) and exercise intolerance (13,170). Advanced disease may also be associated with orthostatic hypotension (a fall in systolic or diastolic blood pressure by >20 mmHg or >10 mmHg, respectively, upon standing without an appropriate increase in heart rate) (172). Orthostatic hypotension is usually easy to document in the office. In most cases of CAN, there is no compensatory increase in the heart rate, despite hypotension (173).

The diagnosis includes documentation of symptoms (Table 5) and signs of CAN, which include impaired HRV, higher resting heart rate, and presence of orthostatic hypotension. In a symptomatic patient presenting with resting tachycardia, with a history of poor glucose control,

or when the diagnosis of CAN is likely, clinicians may not need to perform additional tests given costs and burden.

Exclusion of other comorbidities or drug effects/interactions that may present with the symptoms or signs of CAN and that mimic CAN may be needed (81,174) (Table 6). In addition, polypharmacy may also directly or indirectly impact CAN.

#### Treatment

**Prevention.** Please refer to PREVENTION on page 136.

#### Recommendations

- 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**

As with DSPN, multiple other therapies targeting various pathogenetic mechanisms have failed to reverse established CAN. CAN treatment is generally focused on alleviating symptoms and should be targeted to the specific clinical manifestation.

**Symptomatic Treatment of Orthostatic Hypotension.** Treatment for orthostatic hypotension is challenging and usually

**Table 6—Diagnostic algorithm for CAN**

Symptoms		Signs/diagnostic tests	Differential workup
Resting tachycardia	Palpitations Could be asymptomatic	Clinical exam: resting heart rate >100 bpm	<ul style="list-style-type: none"> <li>• Anemia</li> <li>• Hypothyroidism</li> <li>• Fever</li> <li>• CVD (atrial fibrillation, flutter, other)</li> <li>• Dehydration</li> <li>• Adrenal insufficiency</li> <li>• Medications               <ul style="list-style-type: none"> <li>• Sympathomimetic agents (asthma)</li> <li>• Over-the-counter cold agents containing ephedrine or pseudoephedrine</li> <li>• Dietary supplements (e.g., ephedra alkaloids)</li> </ul> </li> <li>• Smoking, alcohol, caffeine</li> <li>• Recreational drugs (cocaine, amphetamines, methamphetamine, mephedrone)</li> </ul>
Orthostatic hypotension	Light-headedness Weakness Faintness Visual impairment Syncope	Clinical exam: a reduction of >20 mmHg in the systolic blood pressure or >10 mmHg in diastolic blood pressure	<ul style="list-style-type: none"> <li>• Adrenal insufficiency</li> <li>• Intravascular volume depletion               <ul style="list-style-type: none"> <li>• Blood loss/acute anemia</li> </ul> </li> <li>• Dehydration</li> <li>• Pregnancy/postpartum</li> <li>• CVD               <ul style="list-style-type: none"> <li>• Arrhythmias</li> <li>• Heart failure</li> <li>• Myocarditis</li> <li>• Pericarditis</li> <li>• Valvular heart disease</li> </ul> </li> <li>• Alcohol</li> <li>• Medication               <ul style="list-style-type: none"> <li>• Antiadrenergics</li> <li>• Antianginals</li> <li>• Antiarrhythmics</li> <li>• Anticholinergics</li> <li>• Diuretics                   <ul style="list-style-type: none"> <li>• ACE inhibitors/angiotensin receptor blocker</li> </ul> </li> <li>• Narcotics</li> <li>• Neuroleptics</li> <li>• Sedatives</li> </ul> </li> </ul>

involves both pharmacological and non-pharmacological interventions. Physical activity and exercise should be encouraged to avoid deconditioning, which is known to exacerbate orthostatic intolerance. Volume repletion with fluids and salt is central to the management of orthostatic hypotension. Low-dose fludrocortisone may be beneficial in supplementing volume repletion in some patients, although there are growing concerns on risk of supine hypertension.

As neurogenic orthostatic hypotension is in large part a consequence of the failure of norepinephrine release from sympathetic neurons, the administration of sympathomimetic medications is central to the care of patients whose symptoms are not controlled with other measures (173). Midodrine, a peripheral, selective, direct  $\alpha_1$ -adrenoreceptor agonist, is an FDA-approved drug for the treatment of orthostatic hypotension (175). Midodrine should be titrated gradually to efficacy. It should be used only when patients intend to be upright or seated to minimize supine hypertension (173). Recently, droxidopa was approved by the FDA for the treatment of neurogenic orthostatic hypotension but not specifically for patients with orthostatic hypotension due to diabetes (176).

### Gastrointestinal Neuropathies

Gastrointestinal neuropathies may involve any portion of the gastrointestinal tract with manifestations including esophageal dysmotility, gastroparesis (delayed gastric emptying), constipation, diarrhea, and fecal incontinence. The prevalence data on gastroparesis are limited, as most reports were from selected case series rather than larger populations, and there was inconsistency in the outcome measures used (177). In the only community-based study, the cumulative incidence of gastroparesis over 10 years was higher in type 1 diabetes (5%) than in type 2 diabetes (1%) and in control subjects (1%) (178).

Gastroparesis may directly affect glycemic management (e.g., insulin dose or other antidiabetes agents) and may be a cause of glucose variability and unexplained hypoglycemia due to the dissociation between food absorption and the pharmacokinetic profiles of insulin and other agents (12,179–182). Gastroparesis is mainly found in patients with long-standing diabetes (183).

### Screening and Diagnosis

#### Recommendations

- 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  $^{13}\text{C}$ -octanoic acid breath test. **B**

Gastroparesis may manifest with a broad spectrum of symptoms and signs (12,177,179,181). As part of a medical history, providers are encouraged to document symptoms of gastroparesis, such as early satiety, fullness, bloating, nausea, vomiting, dyspepsia, and abdominal pain. However, gastroparesis may be clinically silent in the majority of cases, and symptoms do not necessarily correspond with severity of gastroparesis and are poorly associated with abnormal gastric emptying (184,185). Symptoms such as anorexia, nausea, vomiting, and dyspepsia are nonspecific and resemble many other conditions (186) and may just be associated with the presence of diabetes (181). Importantly, hyperglycemia, hypoglycemia, and acute changes in blood glucose are well documented to alter gastric emptying (182,187,188), as are some medications, especially opioids, other pain management agents, and glucagon-like peptide 1 receptor agonists (189,190). Therefore, all these factors known to affect gastric emptying should always be considered before a firm diagnosis is established.

Exclusion of organic causes of gastric outlet obstruction or peptic ulcer disease (with esophagogastroduodenoscopy or a barium study of the stomach) is needed before considering specialized testing for gastroparesis. The diagnostic

gold standard is the measurement of gastric emptying with scintigraphy of digestible solids at 15-min intervals for 4 h after food intake; the use of  $^{13}\text{C}$ -octanoic acid breath test is emerging as a viable alternative (12,179). Optimization of glucose levels prior to scanning is needed (182,186–188) to avoid false-positive results.

### Treatment

#### Recommendation

- Consider short-term metoclopramide in the treatment of diabetic gastroparesis. **E**

Treatment for diabetic gastroparesis may be very challenging. Dietary changes may be useful, such as eating multiple small meals and decreasing dietary fat and fiber intake. Withdrawing drugs with effects on gastrointestinal motility, such as opioids, anticholinergics, tricyclic antidepressants, glucagon-like peptide 1 receptor agonists, pramlintide, and possibly dipeptidyl peptidase 4 inhibitors, may also improve intestinal motility (180,191). In cases of severe gastroparesis, pharmacological interventions are needed. Only metoclopramide, a prokinetic agent, is approved by the FDA for the treatment of gastroparesis. However, the level of evidence regarding the benefits of metoclopramide for the management of gastroparesis is weak, and given the risk for serious adverse effects (extrapyramidal symptoms, such as acute dystonic reactions; drug-induced parkinsonism; akathisia; and tardive dyskinesia), its use in the treatment of gastroparesis beyond 5 days is no longer recommended by the FDA and the European Medicines Agency. It should be reserved for severe cases that are unresponsive to other therapies (191).

### Urogenital Neuropathies

Diabetic autonomic neuropathy may also cause genitourinary disturbances, including sexual dysfunction and bladder dysfunction. In men, diabetic autonomic neuropathy may cause erectile dysfunction (ED) and/or retrograde ejaculation. ED is three times more common in men with diabetes than those without the disease (192–194). Sexual dysfunction is also more common in women with diabetes (195–199).



### Recommendations

- Consider screening men with other forms of diabetic neuropathy annually for erectile dysfunction with simple questions about a patient's libido and ability to reach and maintain an erection. **C**
- Consider screening patients with other forms of diabetic neuropathy for lower urinary tract symptoms and female sexual dysfunction in the presence of recurrent urinary tract infections using targeted questioning regarding symptoms, such as nocturia, pain during intercourse, and others. **E**

### ED

ED may be a consequence of autonomic neuropathy, as autonomic neurotransmission controls the cavernosal and detrusor smooth muscle tone and function (200). The etiology, however, is multifactorial, and clinicians should also evaluate other vascular risk factors such as hypertension, hyperlipidemia, obesity, endothelial dysfunction, smoking, CVD, concomitant medication, and psychogenic factors (12). There is evidence of associations between ED and other diabetes complications, including CAN (201–203).

A diagnosis should be made after establishing the signs and symptoms of ED and after excluding alternate causes. Clinicians should consider performing hormonal evaluation (luteinizing hormone, testosterone, free testosterone, prolactin) to rule out hypogonadism. In addition, a variety of medications and organic causes should be excluded (12).

Glucose control was associated with a lower incidence of erectile dysfunction in men with type 1 diabetes (204,205). Evidence is less strong for type 2 diabetes. Control of other risk factors such as hypertension and hyperlipidemia may also improve the condition (12). Pharmacological treatment includes phosphodiesterase type 5 inhibitors as first-line therapy and transurethral prostaglandins, intracavernosal injections, vacuum devices, and penile prosthesis in more advanced cases.

### Lower Urinary Tract Symptoms and Female Sexual Dysfunction

Lower urinary tract symptoms manifest as urinary incontinence and bladder dysfunction (nocturia, frequent urination,

urination urgency, weak urinary stream) and is linked to the presence of diabetic neuropathy in both men and women (12,206). Female sexual dysfunction occurs more frequently in women with diabetes than in those without diabetes (196,207) and presents as decreased sexual desire, increased pain during intercourse, decreased sexual arousal, and inadequate lubrication.

Evaluation of bladder function should be performed for individuals with diabetes who have recurrent urinary tract infections, pyelonephritis, incontinence, or a palpable bladder. The medical history should include simple questions to unveil symptoms of lower urinary tract symptoms and female sexual dysfunction (196,207,208).

### Sudomotor Dysfunction

Sudomotor dysfunction may manifest as dry skin, anhidrosis, or heat intolerance (209,210). A rare form of sudomotor dysfunction is gustatory sweating that comprises excessive sweating limited exclusively to the head and neck region triggered by food consumption or, in some cases, the smell of food. Originally described as being solely due to autonomic neuropathy, gustatory sweating is also described in patients with diabetic nephropathy on dialysis (211).

On the basis of the available evidence, the routine screening for sudomotor dysfunction in clinical practice is not recommended at this time. The efficacy of the topical antimuscarinic agent glycopyrrolate in the treatment of gustatory sweating was confirmed in a randomized controlled trial, and daily application attenuates this complication in most patients for at least 24 h (212).

### ATYPICAL NEUROPATHIES

#### Mononeuropathies

Mononeuropathies occur more commonly in patients with diabetes than in those without diabetes (1) and can occur as a result of involvement of the median, ulnar, radial, and common peroneal nerves (213). Cranial neuropathies present acutely and are rare; primarily involve cranial nerves III, IV, VI, and VII; and usually resolve spontaneously over several months (213). Electrophysiological studies are most helpful in identifying nerve conduction slowing or conduction block at the site

of nerve entrapment. Nerve entrapments may require surgical decompression. The improvement in symptom severity and functional status score is no different between patients with and without diabetes (213).

### Diabetic Radiculoplexus Neuropathy

Diabetic radiculoplexus neuropathy, a.k.a. diabetic amyotrophy or diabetic polyradiculoneuropathy, typically involves the lumbosacral plexus (214–216). The complication occurs mostly in men with type 2 diabetes. People with the condition routinely present with extreme unilateral thigh pain and weight loss, followed by motor weakness. Electrophysiological assessment is required to document the extent of disease and alternative etiologies, including degenerative disc disease or neoplastic, infectious, and inflammatory spinal disease (215,216). The disorder is usually self-limiting, and patients improve over time with medical management and physical therapy (214,215). There is presently no evidence from randomized trials to support any recommendation on the use of any immunotherapy treatment in this condition (217).

### Treatment-Induced Neuropathy

Treatment-induced neuropathy in diabetes (also referred to as insulin neuritis) is considered a rare iatrogenic small-fiber neuropathy caused by an abrupt improvement in glycemic control in the setting of chronic hyperglycemia, especially in patients with very poor glucose control (218). The prevalence and risk factors of this disorder are not known but are currently under study.

### NEUROPATHY END POINTS FOR RESEARCH AND CLINICAL TRIALS

There are currently no approved disease-modifying therapies for DSPN, CAN, or other forms of diabetic neuropathy, and multiple clinical trials for these conditions have failed. Important contributing factors include a lack of agreement and uniformity in the use of the most sensitive DSPN measures that capture the natural history of the disease and detect repair in the specific nerve fiber populations, as well as the inclusion of appropriate patient populations. Thus, a valid and careful diagnosis for DSPN in clinical research is critical for correctly identifying the appropriate patient population targeted for either a



specific intervention or for prognostic implications.

The use of validated clinical instruments such as the Michigan Neuropathy Screening Instrument (MNSI) (most widely used in large cohorts of patients with type 1 and type 2 diabetes) (21,26,27,46,74,75), the modified Toronto Clinical Neuropathy Scale (mTCNS) (73), the Utah Early Neuropathy Scale (UENS) (77), or the Neuropathy Disability Score (NDS) (44) are recommended. These may be combined with electrophysiology; measures of small-fiber damage and repair, such as intraepidermal nerve fiber density (219–221) or corneal confocal microscopy (222); and objective measures of patient function in the design of DSPN trials.

The recommended CAN measures for clinical trials targeting either a specific intervention or for prognostic implications include 1) standardized cardiovascular autonomic reflex tests that are simple, sensitive, specific, reproducible, and assess the changes in the R-R interval on electrocardiogram recordings in response to simple clinical maneuvers (deep breathing, Valsalva, and standing) (13,81,191,223); 2) indices of HRV (see above) (11,151,169); and 3) resting heart rate and QTc (154,156,157). Other methods such as baroreflex sensitivity, cardiac sympathetic imaging, and micro-neurography require sophisticated infrastructure and highly trained personnel and are quite expensive and time-consuming (11,13,224).

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