Update on the Management of Diabetic Neuropathy

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IN BRIEF Distal symmetric polyneuropathy (DSPN) and diabetic autonomic neuropathies, particularly cardiovascular autonomic neuropathy (CAN), are prevalent diabetes complications with high morbidity, mortality, and amputation risks. The diagnosis of DSPN is principally a clinical one based on the presence of typical symptoms combined with symmetrical, distal-to-proximal stocking-glove sensory loss. CAN is an independent risk factor for cardiovascular mortality, arrhythmia, silent ischemia, major cardiovascular events, and myocardial dysfunction. Screening for CAN in high-risk patients is recommended. Symptoms of gastroparesis are nonspecific and do not correspond with its severity. Diagnosis of gastroparesis should exclude other factors well documented to affect gastric emptying such as hyperglycemia, hypoglycemia, and certain medications. There is a lack of treatment options targeting the neuropathic disease state. Managing neuropathic pain also remains a challenge. Given the high risk of addiction, abuse, psychosocial issues, and mortality, opioids are not recommended as first-, second-, or third-line agents for treating painful DSPN.

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Diabetic neuropathies (DNs) are serious, chronic complications of diabetes with diverse clinical manifestations (1). Prevalence rates for DNs remain high even with the current standards of care (1). Unfortunately, DNs have been also identified in patients with prediabetes and, more recently, in youths with either type 1 or type 2 diabetes (1–4), thus representing a substantial burden on both patients and society (5).

Distal symmetric polyneuropathy (DSPN) and diabetic autonomic neuropathies, particularly cardiovascular autonomic neuropathy (CAN), are by far the most prevalent of the DNs (1). Despite major advances in diabetes treatment in general, to date, there is a paucity of U.S. Food and Drug Administration–approved therapies that effectively target reversal of the underlying nerve damage (1). Thus, evidence-based measures

to prevent DNs, targeted screening to detect them early, prompt timely interventions to prevent their serious consequences, and treatment of related pain remain the key components of DN management in clinical practice.

The remainder of this article offers a detailed description of the diagnosis and treatment of the various types of DNs.

Distal Symmetric Polyneuropathy

For clinical practice, DSPN is defined as the presence of symptoms or signs of peripheral nerve dysfunction in people with diabetes after the exclusion of other causes (1). Comprehensive family and medication histories, combined with targeted relevant investigations (i.e., serum vitamin B12, folic acid, thyroid function, complete blood count, metabolic panel, and serum protein immunoelectrophoresis) may effectively identify and exclude neuropathy from causes other than diabetes (1).

Contemporary prevalence rates for DSPN remain high, occurring in at least 20% of people with type 1 diabetes of >20 years' duration (1,6,7), 10–15% of people with newly diagnosed type 2 diabetes (1,8,9), and 10–30% of subjects with impaired glucose tolerance (IGT) or metabolic syndrome (1,3,4). The rates increase with disease duration to up to 50% (1,10–12). In addition, recent evidence shows that rates of DSPN and other complications in youths with either type 1 or type 2 diabetes approach those observed in adult populations (2).

Clinical Diagnosis

The most common type of nerve damage is bilateral and symmetric damage to nerves of the lower limb, with a distal-to-proximal gradient of severity known as a "stocking-glove" distribution (5). A similar pattern of injury occurs with prediabetes, supporting the idea that nerve injury secondary to diabetes is a continuum from normal glycemia to varying levels of hyperglycemia (5). DSPN affects primarily the sensory nerves, and the symptoms and signs vary according to the type of sensory fibers involved (1,5).

Symptoms

The earliest symptoms of DSPN are driven by the involvement of the small fibers and include burning, lancinating or shooting (electric shock–like) pain, tingling and prickling sensations (paresthesias), exaggerated response to painful stimuli (hyperalgesia), and pain evoked by contact (e.g., with socks, shoes, and bedclothes; allodynia) (1,5,13). Neuropathic pain may be present in 25–50% of individuals with DSPN and may be the first symptom that prompts patients to seek medical care (1,13,14). This pain can lead to interference with daily activities, disability, psychosocial impairment, reduced health-related quality of life (15,16), and substantial economic burden (1).

In later stages, the damage and loss of the large fibers may cause tingling without pain, loss of protective sensation, and an insensate, numb foot that ultimately may lead to diabetic foot ulcerations (1). In addition, this progressive loss of lower-extremity sensation superimposed on the motor weakness that occurs in later stages of DSPN results in loss of balance, falls, fractures (17,18), and loss of daily function (1,5).

Clinical Signs

The clinical signs of DSPN follow the same distal-to-proximal pattern and are driven by the predominant involvement of the small or large fibers or both (1).

A battery of effective clinical tests performed with simple tools may be used to assess DSPN in clinical practice. These include:

- Tests for small-fiber function: pinprick (push pin) and temperature sensation (1)
- Tests for large-fiber function: vibration perception with a 128-Hz tuning fork, proprioception, light touch to 10-g monofilament on the dorsal aspect of the great toe and bilaterally, and ankle reflexes (1).

The 10-g monofilament test alone is useful for detecting more advanced neuropathy and identifying patients at increased risk of ulceration and amputation (1,19). 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 (1). Combining at least two examinations is associated with higher sensitivity and specificity in detecting DSPN in patients with either type 1 or type 2 diabetes (1,20,21).

Electrophysiological testing or referral to a neurologist is rarely needed for diagnosis, except for situations in which the clinical features are atypical, the diagnosis is unclear, or a different etiology is suspected (1). Atypical features, which warrant referral, include motor greater than sensory neuropathy, asymmetry of symptoms and signs, and rapid progression (1).

The presence of DSPN may compromise balance in daily activities (1,18) due to a progressive loss of sensation, and later weakness, superimposed on age-related functional impairments, decline in cognitive function, polypharmacy, and neuropathic pain, all leading to unsteadiness in gait, with an increased likelihood of falls (17,18). Treatment of neuropathic pain often requires dosages and drug combinations that may further increase patients' fall risk due to cognitive impairment, drowsiness, dizziness, blurred vision, and gait disturbances, particularly in older patients (1,17).

The American Diabetes Association recommends that patients with type 1 diabetes for ≥5 years and all patients with type 2 diabetes should be assessed for DSPN annually, including a medical history to assess for symptoms and a combination of at least two of the examinations described above and

in Table 1. The same assessments should be performed in patients with prediabetes who have symptoms of peripheral neuropathy and in youths with either type 1 or type 2 diabetes (1). Tests assessing gait and balance may be also considered in clinical practice to evaluate the risk of falls in patients who may be at risk, particularly in the elderly (17,18).

Up to 50% of patients may experience symptoms of DSPN, whereas the rest are asymptomatic (1). Thus, targeted inquiries in clinic are recommended because some patients may not volunteer information about symptoms of DSPN (1).

DSPN is the most important cause of foot ulceration and is also a prerequisite in the development of Charcot neuroarthropathy (1). Assessing the effects of DSPN on patients' quality of life is also emerging as an important component of care and may play a part in the adherence and response to therapies of patients with neuropathic pain (1). Two neuropathy-specific research tools that can be used to assess quality of life are the NeuroQol (22) and the Norfolk QOL-DN (23) instruments.

In summary, the diagnosis of DSPN is principally a clinical one. The presence of the typical symptoms described above combined with a symmetrical, distal-to-proximal stocking-glove sensory loss or the presence of 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. Because up to half of patients with DSPN may be asymptomatic, a diagnosis may only be made on examination or, in some cases, when a patient presents with a painless foot ulcer or Charcot neuroarthropathy. These late complications drive the amputation risk and economic costs of diabetic neuropathy and are also predictors of mortality (1). Electrophysiological testing or referral to a neurologist is rarely needed for screening, except in situations where the clinical features are atypical and a different etiology is suspected (1). Tests to assess gait and balance should be considered in older patients with multiple other comorbidities (1). Table 1 provides a summary of key diagnostic steps and management recommendations for DSPN and other neuropathies discussed in this review.

Diabetic Autonomic Neuropathies

Autonomic neuropathies include CAN, which is the most studied, and gastrointestinal, genitourinary, and sudomotor dysfunction and may present with a variety of condition-specific symptoms (1).

Cardiovascular Autonomic Neuropathy

The prevalence of CAN is very low in newly diagnosed patients with type 1 diabetes (24), but increases substantially with diabetes duration (1,10) up to 30% after 20 years of diabetes (7,25); in type 2 diabetes, the prevalence is up to 50% after 15 years of diabetes (1). High prevalence rates for CAN were recently reported in a large cohort of youths with type 1 or type 2 diabetes (2) and in patients with IGT or the metabolic syndrome (4,26).

CAN is an independent risk factor for cardiovascular mortality, arrhythmia, silent ischemia, major cardiovascular events, and myocardial dysfunction, as reported in large cohorts with type 1 or type 2 diabetes (1,27–32). Emerging evidence also demonstrates an association between CAN and glucose variability (33), especially in the hypoglycemic range (34). In addition, CAN independently predicts the progression of diabetic nephropathy and chronic kidney disease in diabetes (1,35–37).

Clinical Diagnosis

Symptoms

In its early stages, CAN may be completely asymptomatic and is detected only by decreased heart rate variability (HRV) (1).

The most common symptoms of CAN occur upon standing and include lightheadedness, weakness, palpitations, faintness, and syncope (1), but unfortunately, these symptoms may occur quite late in the disease course (1,7,10).

As with DSPN, a targeted history with simple questions to elicit these symptoms is often needed in the clinic. The correlation of symptoms with clinical autonomic deficits is weak (1).

Clinical Signs

Signs of CAN include resting tachycardia (>100 bpm), exercise intolerance due to a reduced response in heart rate and blood pressure, blunted increases in cardiac output with exercise, and orthostatic hypotension (a fall in systolic or diastolic blood pressure by >20 or >10 mmHg, respectively, upon standing without an appropriate increase in heart rate) that is usually experienced late in the disease course (1).

Testing for HRV may be done in the clinic as well, by either *1*) taking an electrocardiogram (ECG) recording as a patient begins to rise from a seated position or *2*) taking an ECG recording during 1–2 minutes of deep breathing with calculation of HRV (1).

Diagnosis

Diagnosis includes documentation of the symptoms and signs of CAN, which include impaired HRV, higher resting heart rate, and presence of orthostatic hypotension (1). Orthostatic hypotension and resting heart rate are usually easy to document in the office. 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 the costs and burden of doing so. Differential diagnosis should exclude anemia, hyperthyroidism, dehydration, adrenal insufficiency, and substance abuse, including a variety of prescriptions and over-the-counter medications and supplements (1).

TABLE 1. Diagnostic Steps and Management Recommendations for Diabetic Neuropathy

Type of Neuropathy	Symptoms	Clinical Signs	Diagnosis	Management Recommendations
DSPN	• Burning pain • Lancinating or shooting pain • Paresthesias (tingling and prickling sensation) • Hyperalgesia (exaggerated response to painful stimuli) • Allodynia (pain evoked by light touch) **Note.** Neuropathic pain may be the first symptom that prompts patients to seek medical care.	1. Tests for small-fiber function: • Pinprick (push pin) • Temperature sensation discrimination 2. Tests for large-fiber function: • Vibration perception (128-Hz tuning fork) • Proprioception • Light touch to 10-g monofilament (on dorsal aspect of the great toe bilaterally) • Ankle reflexes **Note.** Electrophysiological testing or referral to a neurologist is rarely needed in clinical practice except for situations in which clinical features are atypical and a different etiology is suspected (i.e., motor greater than sensory neuropathy, asymmetry of symptoms and signs, or rapid progression).	1. Assess symptoms (history taking) 2. Assess clinical signs 3. Confirm pattern for symptoms and signs: • Distal-to-proximal (stocking-glove) • Symmetrical 4. Combine at least two of the small- and large-fiber tests listed in the previous column (e.g., pinprick plus vibration) for higher sensitivity and specificity 5. Differential (as applicable): • Family/medication history • Serum B12 • Folic acid • Thyroid function • Complete blood count • Metabolic panel • Serum protein immunoelectrophoresis	*Prevention* 1. Glucose control targeting near-normal glycemia: strong evidence for type 1 diabetes; modest data for type 2 diabetes 2. Lifestyle modifications: emerging as effective treatment strategies in patients with IGT/metabolic syndrome or type 2 diabetes 3. Prevention of foot complications *Pain treatment (see Figure 1)* 1. Anticonvulsants: • Pregabalin* 150–600 mg/day • Gabapentin 1,800–3,600 mg/day 2. Monoamine reuptake inhibitors: • Selective norepinephrine-serotonin reuptake inhibitors ❍ Duloxetine* 60–120 mg/day ❍ Venlafaxine 150–225 mg/day • Tricyclic antidepressants ❍ Amitriptyline 25–100 mg/day (with titration) ❍ Nortriptyline 25–100 mg/day (with titration) ❍ Desipramine titrate from 12.5 to 100–150 mg/day **Warning.** Opioids are not recommended for DSPN pain as first-, second-, or third-line agents given their high risk of addiction, abuse, and serious adverse events.

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TABLE 1. Diagnostic Steps and Management Recommendations for Diabetic Neuropathy, ***continued from p. 227***

Type of Neuropathy	Symptoms	Clinical Signs	Diagnosis	Management Recommendations
Diabetic autonomic neuropathies				
CAN	• Lightheadedness • Weakness • Faintness • Palpitations • Syncope **Note.** All symptoms occur upon standing.	• Reduced HRV • Resting tachycardia (>100 bpm) • Exercise intolerance • Orthostatic hypotension (a fall in systolic or diastolic blood pressure of >20 or >10 mmHg, respectively, upon standing)	• Document symptoms • Document signs • Consider ECG recordings with deep breathing • Differential (as applicable): ❍ Anemia ❍ Hyperthyroidism ❍ Dehydration ❍ Adrenal insufficiency ❍ Smoking ❍ Alcohol ❍ Caffeine ❍ Medications (e.g., sympathomimetics, over-the-counter cold agents containing ephedrine or pseudoephedrine, recreational drugs, and dietary supplements)	*Prevention* 1. Glucose control targeting near-normal glycemia: strong evidence for type 1 diabetes, controversial data for type 2 diabetes 2. Lifestyle modifications: emerging as effective treatment strategies in patients with impaired glucose tolerance/metabolic syndrome, and type 2 diabetes *Treatment for orthostatic hypotension* 1. Non-pharmacological: • Physical activity • Volume repletion with fluids 2. Pharmacological: • Midodrine* (peripheral, selective, direct α_1-adrenoreceptor agonist); 2.5–10 mg up to 3 times/day, with titration; use lowest effective dose, first dose before arising • Droxidopa** (α/β adrenergic agonist) *Dietary changes* • Eating multiple small meals • Decreasing fat and fiber intake • Withdrawing drugs with effects on motility: opioids, anticholinergics, tricyclic antidepressants, GLP-1 receptor agonists, pramlintide *Medication* • Metoclopramide*** 5–10 mg 3–4 times/day (prokinetic agent, weak evidence, risk of serious adverse effects, tardive dyskinesia)
Gastrointestinal neuropathy (gastroparesis)	• Early satiety • Fullness and bloating • Nausea, vomiting, or dyspepsia • Abdominal pain **Note.** Symptoms are nonspecific and do not correspond with severity of gastroparesis or abnormal gastric emptying	• Clinically silent in the majority of cases • Glucose variability and unexplained hypoglycemia (due to the dissociation between food absorption and the pharmacokinetic profiles of insulin and other agents)	• Careful medication history • Esophagogastroduodenoscopy or barium study to exclude organic causes of gastric outlet obstruction or peptic ulcer disease • Gastric emptying with scintigraphy of digestible solids (gold standard if above tests are negative) • 13C-octanoic acid breath test (emerged as an easier alternative)	

*Adapted from ref. 1. *FDA-approved. **FDA-approved for the treatment of neurogenic orthostatic hypotension but not specifically for orthostatic hypotension due to diabetes. ***FDA-approved for up to 5 days of use.*

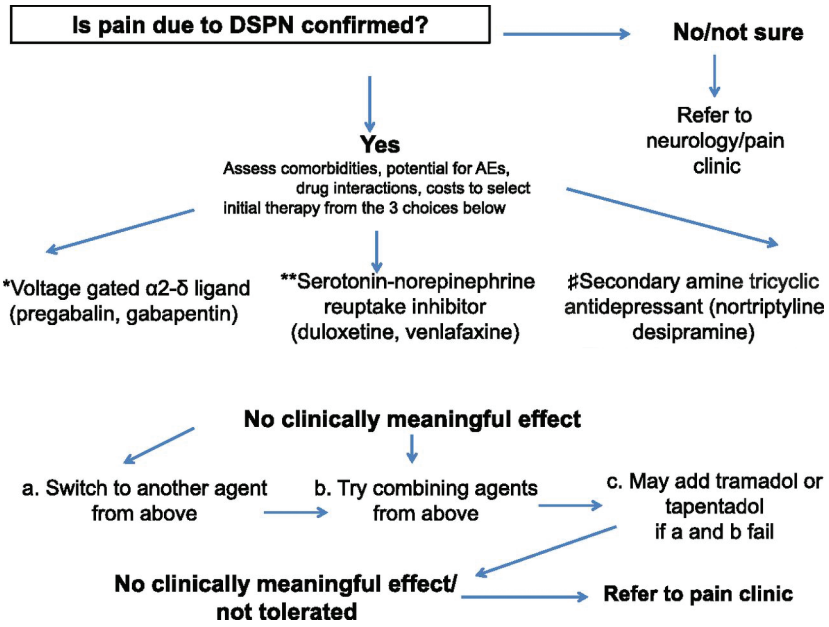

FIGURE 1. Algorithm for management of patients with pain due to DSPN. *Pregabalin is FDA-approved for painful DSPN, whereas gabapentin is not. Pharmacokinetic profile, spectrum of AEs and drug interactions, comorbidities, and costs should be considered in selecting the agent of choice. **Duloxetine is 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 should be considered in selecting these agents. Reprinted with permission from ref. 1.

In summary, all patients should be assessed for CAN starting 10 years after diagnosis or in the presence of other DNs or other diabetes complications (1). Screening for CAN should also be considered in patients with hypoglycemia unawareness and high glucose variability before making insulin dose adjustments and perioperatively (1). Exclusion of other comorbidities, polypharmacy, or drug effects/interactions that may present with the same symptoms or signs and mimic CAN may be needed (1).

Gastrointestinal Neuropathies

Gastrointestinal neuropathies include esophageal dysmotility, gastroparesis (delayed gastric emptying), constipation, diarrhea, and fecal incontinence. Prevalence data on gastroparesis are limited. In the only community-based study, the cumulative incidence of gastroparesis over 10 years was higher in people with type 1 diabetes (5%) than in those with type 2 diabetes (1%) or control subjects (1%) (38).

Symptoms and Clinical Signs

Symptoms of gastroparesis may include early satiety, fullness, bloating, nausea, vomiting, dyspepsia, and abdominal pain. These symptoms are nonspecific and do not correspond with severity of gastroparesis or abnormal gastric emptying (1). Clinical signs are rare because gastroparesis may be clinically silent in the majority of cases (1).

Gastroparesis may directly affect glycemic management (e.g., dosages of insulin or other antidiabetic 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 (1).

Diagnosis

A targeted symptoms assessment as part of the medical history is recommended. A variety of factors are well documented to affect gastric emptying, including hyperglycemia, hypoglycemia, glucose variability, and several classes of medications, especially opioids and glucagon-like peptide 1 (GLP-1) receptor agonists (1). Therefore, all of these factors 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 (1).

The diagnostic gold standard is the measurement of gastric emptying with scintigraphy of digestible solids at 15-minute intervals for 4 hours after food intake, with optimization of glucose levels before scanning to avoid false-positive results (1). The 13C-octanoic acid breath test is emerging as an easier alternative (1).

Management of Diabetic Neuropathies

Prevention

Glucose Control

Enhanced glucose control in people with type 1 diabetes dramatically reduces the incidence of DSPN (78% relative risk reduction) (39,40). In contrast, enhanced glucose control in people with type 2 diabetes reduces the risk of developing DSPN modestly (5–9% relative risk reduction) (41,42) and selectively (10,43). This discrepancy highlights the difference between type 1 and type 2 diabetes and emphasizes the point that many people with type 2 diabetes develop DSPN despite adequate glucose control (10,41), likely because of asymptomatic hyperglycemia for many years before the diagnosis of type 2 diabetes, the presence of multiple other risk factors and comorbidities, polypharmacy, hypoglycemia, obesity, or weight gain (1,5,10,44). Specific glucose-lowering strategies may also contribute to the discrepancy, as reported in the Bypass Angioplasty

Revascularization Investigation 2 Diabetes trial, in which participants treated with insulin sensitizers had a lower incidence of DSPN over 4 years than those treated with insulin/sulfonylurea (11), possibly as a result of less weight gain and less hypoglycemia (1,11).

There is also robust evidence for CAN prevention with intensive glucose control designed to achieve near-normal glycemia in type 1 diabetes (11), as documented by a 45% reduction in the risk of incident CAN, assessed with highly reproducible and sensitive tests in a large sample during the Diabetes Control and Complications Trial and by 31% during its follow-up, the Epidemiology of Diabetes Interventions and Complications study (1,7). This evidence contributes to 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 (1,10). However, a multifactorial intervention that included a lifestyle component and targeted glucose and cardiovascular disease risk factors reduced the risk of CAN by 60% in people with type 2 diabetes (1,45).

Lifestyle Modifications

Intensive lifestyle interventions are emerging as effective treatment strategies for preventing DSPN and CAN (26,45–47). Overall, such an approach focuses on either exercise alone (supervised aerobic exercise with or without resistance training) (46,47), or combined dietary modification and exercise, although the dietary regimens followed varied from low-calorie, low-fat diets to a Mediterranean-type eating plan that is moderately lower in carbohydrate (45%) and higher in fat (35–40%), with <10% from saturated fat (1). The majority of these trials did not include subjects with established diabetes. However, a recent trial in patients with type 2 diabetes engaged in an exercise intervention reported reversal of DSPN as documented by nerve fiber regeneration compared to loss of nerve fibers in those who only followed standard care (47).

In summary, tight glucose control targeting near-normal glycemia in patients with type 1 diabetes dramatically reduces the incidence of DSPN and CAN and is recommended as an effective prevention strategy (1). Intensive glucose control alone is modestly effective in preventing DSPN or CAN in patients with type 2 diabetes; with more advanced disease and multiple risk factors and comorbidities, patient-centered goals should be targeted. Lifestyle interventions are effective for the prevention of DSPN and CAN in patients with IGT/metabolic syndrome or type 2 diabetes.

Disease-Modifying Agents

Despite the recent major advances in elucidating the pathogenesis of DNs, there remains a lack of treatment options that effectively target the natural history of DNs or reverse their course once established (1,5). Several pathogenetic pharmacotherapies have been investigated, but evidence from randomized clinical trials is limited (1,5). Thus, there is an urgent need for robust clinical trials targeting viable mechanisms for human disease to advance promising treatments of DNs (1,5).

Pain Management

The management of neuropathic pain associated with DSPN remains a challenge in clinical care. Although there are multiple published guidelines pertaining to neuropathic pain treatment in general, it is important to note that only few trials that targeted peripheral neuropathic pain were carried out in patients with DSPN alone. This may explain the inconsistencies among the various available guidelines because the majority of these address all-cause neuropathic pain (41,48–50). In addition, publication bias should always be considered given that many trials with negative results may not have been published (1,49).

There are several classes of medications available to treat DSPN pain. Currently, pregabalin and duloxetine have received regulatory approval for the treatment of DSPN pain by the U.S. Food and Drug Administration (FDA), Health Canada, and the European Medicines Agency (EMA). The opioid tapentadol has regulatory approval in the United States and Canada, but the evidence for its use is weaker (1,49).

Anticonvulsants

Pregabalin, a calcium channel $\alpha 2$-δ subunit ligand, is an effective treatment for neuropathic pain. Several randomized, clinical trials reported response rates of 30–50% improvement in neuropathic pain (1,49,51,52). However, not all trials with pregabalin have been positive (49,53), especially when treating advanced refractory patients, and others suggested a progressive response from 300 to 600 mg/day (1,51). Pregabalin, in contrast to gabapentin (discussed below), has a linear and dose-proportional absorption in the therapeutic dose range (150–600 mg/day) and rapid onset of action and requires minimal titration (1,51).

Gabapentin also binds the calcium channel $\alpha 2$-δ subunit, but given its pharmacokinetic profile, gabapentin requires gradual titration (1). Several clinical trials have shown its efficacy in doses of 1,800–3,600 mg for treating the pain associated with DSPN (49,52,54). As with pregabalin, the level of efficacy in reducing DSPN pain was not uniform across these trials, and some trials remained unpublished (1,49).

With either pregabalin or gabapentin, adverse effects (AEs) may be more severe in older patients and may be attenuated by lower starting doses and more gradual titration (1).

Monoamine Reuptake Inhibitors

The monoamine reuptake inhibitors include the selective norepinephrine and serotonin reuptake inhibitors,

tricyclic antidepressants, and selective serotonin reuptake inhibitors. These agents act by increasing the synaptic monoamine levels and directly influencing the activity of the descending neurons. Duloxetine and venlafaxine inhibit reuptake of serotonin and norepinephrine without the muscarinic, histaminic, and adrenergic side effects that accompany the use of the tricyclic agents (1).

Duloxetine is a selective norepinephrine and serotonin reuptake inhibitor. Doses of 60 and 120 mg/day showed efficacy for 30–50% reduction in the pain associated with DSPN in several multicenter randomized trials (1). In longer-term studies, a small deterioration in glucose control was reported in people with diabetes treated with duloxetine compared to placebo (1). AEs may again be more severe in older people but may be attenuated with lower doses and progressive titration (1).

Venlafaxine is also a selective norepinephrine and serotonin reuptake inhibitor. Doses between 150 and 225 mg/day have shown some effectiveness in the treatment of painful DSPN (1). However, the level of evidence for pain reduction associated with DSPN is higher with duloxetine. Venlafaxine may lower the seizure threshold, and gradual tapering is recommended to avoid the emergence of AEs upon discontinuation (1).

Amitriptyline, although not FDA-approved for treating DSPN pain, remains one of the most used of the tricyclic agents in clinical practice (1). Several randomized, blinded, placebo-controlled clinical trials reported significant improvement in neuropathic pain (1), although a recent Cochrane review questioned the quality of evidence, raising concerns about bias given the small sample sizes of most of these trials (55). Pain reduction with amitriptyline needs to be balanced against a spectrum of side effects (1).

The secondary amines nortriptyline and desipramine have a less troublesome side effect profile than amitriptyline and imipramine, although the level of evidence for DSPN pain reduction is lower with these agents (1), and the potential for bias is higher given the small sample size of studies. The use of these agents is preferable, particularly in older patients and those prone to experiencing side effects (1). Several studies have suggested that there is an increased risk of myocardial ischemia and arrhythmogenesis associated with tricyclic agents. Thus, these agents should be used with caution in patients with known or suspected cardiac disease (1).

Opioids and Related Concerns

Extended-release tapentadol, a centrally acting opioid, exerts its analgesic effects through both μ-opioid receptor agonism and noradrenaline reuptake inhibition (1). Two multicenter, randomized-withdrawal, placebo-controlled phase 3 trials reported efficacy in DSPN pain reduction (56,57), leading to FDA approval for the treatment of DSPN pain. However, a recent systematic review and meta-analysis by the Special Interest Group on Neuropathic Pain found some flaws with these trial designs, and thus the evidence of the effectiveness of tapentadol in reducing DSPN pain was deemed inconclusive (49). Given the high risk for addiction and safety concerns compared to the relatively modest pain reduction, the use of extended-release tapentadol is not recommended as a first or second choice (1).

Tramadol and other opioids have also shown some efficacy on DSPN pain in large multicenter trials (1,49,58). However, there is a high risk of addiction, abuse, diversion, sedation, and psychosocial issues even with short-term opioid use (1). Mortality rates associated with overdoses of prescription opioids in the United States have more than quadrupled and have reached the level of a true epidemic (1,59). For these reasons, opioids are not recommended in the treatment of painful DSPN as first-, second-, or third-line agents (1). 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 (1).

In summary, pregabalin and duloxetine have received regulatory approval for the treatment of neuropathic pain in diabetes in the United States, Europe, and Canada. Thus, based on patients' associated comorbidities and medication intake, as well as socioeconomic status, these agents could be considered as the initial approach in the symptomatic treatment of pain associated with DSPN. Gabapentin also may be used as an effective initial approach taking these same patient factors into account. Given the high risks of addiction and other complications, the use of opioids, including tapentadol and tramadol, is not recommended for treating the pain associated with DSPN. No compelling evidence exists in support of glycemic control or lifestyle management as therapies for neuropathic pain in diabetes or prediabetes.

Combination therapy between the various classes of agents discussed above also should be considered because it may provide more effective analgesia for DSPN pain at lower doses of each drug than either offers as monotherapy, thus helping patients avoid some of the most concerning side effects (1). A practical approach algorithm for pain management in clinical practice is shown in Figure 1.

Symptomatic Treatment of CAN

Orthostatic Hypotension

Treatment for orthostatic hypotension is challenging and usually involves both pharmacological and non-pharmacological interventions (1). Non-pharmacological measures include physical activity to avoid deconditioning and volume repletion with fluids and salt (1). Pharmacological therapies include sympathomimetic agents such as midodrine, a peripher-

al, selective, direct α_1-adrenoreceptor agonist that is FDA-approved for the treatment of orthostatic hypotension and should be titrated gradually to efficacy, or droxidopa, which is FDA-approved for the treatment of neurogenic orthostatic hypotension (1). Low-dose fludrocortisone may also be beneficial in supplementing volume repletion in some patients, although there are growing concerns about the risk of supine hypertension (1).

Gastroparesis

Treatment for diabetic gastroparesis is 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, GLP-1 receptor agonists, pramlintide, and possibly dipeptidyl peptidase 4 inhibitors, may also improve intestinal motility (1).

In severe gastroparesis, pharmacological interventions are needed. Metoclopramide, a prokinetic agent, is the only FDA-approved agent for the treatment of gastroparesis. However, the evidence regarding its benefits is weak, and, given the risk for serious AEs (i.e., 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 or the EMA. It should be reserved for severe cases that are unresponsive to other therapies (60).

Duality of Interest

No potential conflicts of interest relevant to this article were reported.

Author Contributions

L.A. and N.C. provided critical input to the manuscript and revised the manuscript. K.M.-S. reviewed and edited the manuscript. R.P.-B. drafted the manuscript. R.P.-B. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity and the accuracy of data presented in this manuscript.

References

1. 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

2. Dabelea D, Stafford JM, Mayer-Davis EJ, et al.; SEARCH for Diabetes in Youth Research Group. Association of type 1 diabetes vs type 2 diabetes diagnosed during childhood and adolescence with complications during teenage years and young adulthood. JAMA 2017;317:825–835

3. Smith AG, Singleton JR. Diabetic neuropathy. Continuum (Minneap Minn) 2012;18:60–84

4. Ziegler D, Rathmann W, Dickhaus T, Meisinger C, Mielck A; KORA Study Group. Prevalence of polyneuropathy in pre-diabetes and diabetes is associated with abdominal obesity and macroangiopathy: the MONICA/KORA Augsburg Surveys S2 and S3. Diabetes Care 2008;31:464–469

5. Feldman EL, Nave KA, Jensen TS, Bennett DLH. New horizons in diabetic neuropathy: mechanisms, bioenergetics, and pain. Neuron 2017;93:1296–1313

6. Tesfaye S, Stevens LK, Stephenson JM, et al. Prevalence of diabetic peripheral neuropathy and its relation to glycaemic control and potential risk factors: the EURODIAB IDDM Complications Study. Diabetologia 1996;39:1377–1384

7. Martin CL, Albers JW, Pop-Busui R. Neuropathy and related findings in the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications study. Diabetes Care 2014;37:31–38

8. Young MJ, Boulton AJ, MacLeod AF, Williams DR, Sonksen PH. A multicentre study of the prevalence of diabetic peripheral neuropathy in the United Kingdom hospital clinic population. Diabetologia 1993;36:150–154

9. UK Prospective Diabetes Study Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). Lancet 1998;352:837–853

10. Ang L, Jaiswal M, Martin C, Pop-Busui R. Glucose control and diabetic neuropathy: lessons from recent large clinical trials. Curr Diab Rep 2014;14:528

11. Pop-Busui R, Lu J, Brooks MM, et al. Impact of glycemic control strategies on the progression of diabetic peripheral neuropathy in the Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) cohort. Diabetes Care 2013;36:3208–3215

12. Ziegler D, Strom A, Lobmann R, Reiners K, Rett K, Schnell O. High prevalence of diagnosed and undiagnosed polyneuropathy in subjects with and without diabetes participating in a nationwide educational initiative (PROTECT study). J Diabetes Complications 2015;29:998–1002

13. Jensen TS, Finnerup NB. Allodynia and hyperalgesia in neuropathic pain: clinical manifestations and mechanisms. Lancet Neurol 2014;13:924–935

14. Abbott CA, Malik RA, van Ross ER, Kulkarni J, Boulton AJ. Prevalence and characteristics of painful diabetic neuropathy in a large community-based diabetic population in the U.K. Diabetes Care 2011;34:2220–2224

15. Vileikyte L, Leventhal H, Gonzalez JS, et al. Diabetic peripheral neuropathy and depressive symptoms: the association revisited. Diabetes Care 2005;28:2378–2383

16. Vinik E, Silva MP, Vinik AI. Measuring the relationship of quality of life and health status, including tumor burden, symptoms, and biochemical measures in patients with neuroendocrine tumors. Endocrinol Metab Clin North Am 2011;40:97–109, viii

17. Morrison S, Colberg SR, Parson HK, Vinik AI. Relation between risk of falling and postural sway complexity in diabetes. Gait Posture 2012;35:662–668

18. Brown SJ, Handsaker JC, Bowling FL, Boulton AJ, Reeves ND. Diabetic peripheral neuropathy compromises balance during daily activities. Diabetes Care 2015;38:1116–1122

19. Tan LS. The clinical use of the 10g monofilament and its limitations: a review. Diabetes Res Clin Pract 2010;90:1–7

20. Martin CL, Albers J, Herman WH, et al. Neuropathy among the Diabetes Control and Complications Trial cohort 8 years after trial completion. Diabetes Care 2006;29:340–344

21. Zilliox LA, Ruby SK, Singh S, Zhan M, Russell JW. Clinical neuropathy scales in neuropathy associated with impaired glucose tolerance. J Diabetes Complications 2015;29:372–377

22. Vileikyte L, Peyrot M, Bundy C, et al. The development and validation of a neuropathy- and foot ulcer-specific quality of life instrument. Diabetes Care 2003;26:2549–2555

23. Vinik EJ, Hayes RP, Oglesby A, et al. The development and validation of the Norfolk QOL-DN, a new measure of patients' perception of the effects of diabetes and diabetic neuropathy. Diabetes Technol Ther 2005;7:497–508

24. DCCT Study Group. The effect of intensive diabetes therapy on measures of autonomic nervous system function in the Diabetes Control and Complications Trial (DCCT). Diabetologia 1998;41:416–423

25. Pop-Busui R, Low PA, Waberski BH, et al. Effects of prior intensive insulin therapy on cardiac autonomic nervous system function in type 1 diabetes mellitus: the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions

and Complications study (DCCT/EDIC). Circulation 2009;119:2886–2893

26. Carnethon MR, Prineas RJ, Temprosa M, Zhang ZM, Uwaifo G, Molitch ME. The association among autonomic nervous system function, incident diabetes, and intervention arm in the diabetes prevention program. Diabetes Care 2006;29:914–919

27. Maser RE, Mitchell BD, Vinik AI, Freeman R. The association between cardiovascular autonomic neuropathy and mortality in individuals with diabetes: a meta-analysis. Diabetes Care 2003;26:1895–1901

28. Pop-Busui R, Cleary PA, Braffett BH, et al. Association between cardiovascular autonomic neuropathy and left ventricular dysfunction: DCCT/EDIC study (Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications). J Am Coll Cardiol 2013;61:447–454

29. Pop-Busui R, Evans GW, Gerstein HC, et al. Effects of cardiac autonomic dysfunction on mortality risk in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial. Diabetes Care 2010;33:1578–1584

30. Ziegler D, Zentai CP, Perz S, et al. Prediction of mortality using measures of cardiac autonomic dysfunction in the diabetic and nondiabetic population: the MONICA/KORA Augsburg Cohort Study. Diabetes Care 2008;31:556–561

31. Soedamah-Muthu SS, Chaturvedi N, Witte DR, Stevens LK, Porta M, Fuller JH. Relationship between risk factors and mortality in type 1 diabetic patients in Europe: the EURODIAB Prospective Complications Study (PCS). Diabetes Care 2008;31:1360–1366

32. Pop-Busui R, Braffett BH, Zinman B, et al.; DCCT/EDIC Research Group. Cardiovascular autonomic neuropathy and cardiovascular outcomes in the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) Study. Diabetes Care 2017;40:94–100

33. Lachin JM, Bebu I, Bergenstal RM, et al.; DCCT/EDIC Research Group. Association of glycemic variability in type 1 diabetes with progression of microvascular outcomes in the Diabetes Control and Complications Trial. Diabetes Care 2017;40:777–783

34. Jaiswal M, Divers J, Isom S, et al. Prevalence and correlates of cardiovascular autonomic neuropathy in youth with type 1 diabetes: SEARCH for Diabetes in Youth Study [Abstract]. Diabetes 2014;63:A145

35. Astrup AS, Tarnow L, Rossing P, Hansen BV, Hilsted J, Parving HH. Cardiac autonomic neuropathy predicts cardiovascular morbidity and mortality in type 1 diabetic patients with diabetic nephropathy. Diabetes Care 2006;29:334–339

36. Orlov S, Cherney DZ, Pop-Busui R, et al. Cardiac autonomic neuropathy and early progressive renal decline in patients with nonmacroalbuminuric type 1 diabetes. Clin J Am Soc Nephrol 2015;10:1136–1144

37. Wheelock KM, Jaiswal M, Martin CL, et al. Cardiovascular autonomic neuropathy associates with nephropathy lesions in American Indians with type 2 diabetes. J Diabetes Complications 2016;30:873–879

38. Choung RS, Locke GR 3rd, Schleck CD, Zinsmeister AR, Melton LJ 3rd, Talley NJ. Risk of gastroparesis in subjects with type 1 and 2 diabetes in the general population. Am J Gastroenterol 2012;107:82–88

39. DCCT Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. N Engl J Med 1993;329:977–986

40. DCCT Research Group. Effect of intensive diabetes treatment on nerve conduction in the Diabetes Control and Complications Trial. Ann Neurol 1995;38:869–880

41. Callaghan BC, Cheng HT, Stables CL, Smith AL, Feldman EL. Diabetic neuropathy: clinical manifestations and current treatments. Lancet Neurol 2012;11:521–534

42. Ismail-Beigi F, Craven T, Banerji MA, et al. Effect of intensive treatment of hyperglycaemia on microvascular outcomes in type 2 diabetes: an analysis of the ACCORD randomised trial. Lancet 2010;376:419–430

43. Charles M, Ejskjaer N, Witte DR, Borch-Johnsen K, Lauritzen T, Sandbaek A. Prevalence of neuropathy and peripheral arterial disease and the impact of treatment in people with screen-detected type 2 diabetes: the ADDITION-Denmark study. Diabetes Care 2011;34:2244–2249

44. Callaghan BC, Xia R, Banerjee M, et al.; Health ABC Study. Metabolic syndrome components are associated with symptomatic polyneuropathy independent of glycemic status. Diabetes Care 2016;39:801–807

45. Gaede P, Vedel P, Larsen N, Jensen GV, Parving HH, Pedersen O. Multifactorial intervention and cardiovascular disease in patients with type 2 diabetes. N Engl J Med 2003;348:383–393

46. Balducci S, Iacobellis G, Parisi L, et al. Exercise training can modify the natural history of diabetic peripheral neuropathy. J Diabetes Complications 2006;20:216–223

47. Singleton JR, Marcus RL, Jackson JE, Lessard MK, Graham TE, Smith AG. Exercise increases cutaneous nerve density in diabetic patients without neuropathy. Ann Clin Transl Neurol 2014;1:844–849

48. Bril V, England JD, Franklin GM, et al. Evidence-based guideline: treatment of painful diabetic neuropathy: report of the American Association of Neuromuscular and Electrodiagnostic Medicine, the American Academy of Neurology, and the American Academy of Physical Medicine & Rehabilitation. Muscle Nerve 2011;43:910–917

49. Finnerup NB, Attal N, Haroutounian S, et al. Pharmacotherapy for neuropathic pain in adults: a systematic review and meta-analysis. Lancet Neurol 2015;14:162–173

50. Moulin D, Boulanger A, Clark AJ, et al. Pharmacological management of chronic neuropathic pain: revised consensus statement from the Canadian Pain Society. Pain Res Manag 2014;19:328–335

51. Freeman R, Durso-Decruz E, Emir B. Efficacy, safety, and tolerability of pregabalin treatment for painful diabetic peripheral neuropathy: findings from seven randomized, controlled trials across a range of doses. Diabetes Care 2008;31:1448–1454

52. Griebeler ML, Morey-Vargas OL, Brito JP, et al. Pharmacologic interventions for painful diabetic neuropathy: an umbrella systematic review and comparative effectiveness network meta-analysis. Ann Intern Med 2014;161:639–649

53. Ziegler D, Duan WR, An G, Thomas JW, Nothaft W. A randomized double-blind, placebo-, and active-controlled study of T-type calcium channel blocker ABT-639 in patients with diabetic peripheral neuropathic pain. Pain 2015;156:2013–2020

54. Quilici S, Chancellor J, Lothgren M, et al. Meta-analysis of duloxetine vs. pregabalin and gabapentin in the treatment of diabetic peripheral neuropathic pain. BMC Neurol 2009;9:6

55. Moore RA, Derry S, Aldington D, Cole P, Wiffen PJ. Amitriptyline for neuropathic pain in adults. Cochrane Database Syst Rev 2015;7:CD008242

56. Schwartz S, Etropolski M, Shapiro DY, et al. Safety and efficacy of tapentadol ER in patients with painful diabetic peripheral neuropathy: results of a randomized-withdrawal, placebo-controlled trial. Curr Med Red Opin 2011;27:151–162

57. Vinik AI, Shapiro DY, Rauschkolb C, et al. A randomized withdrawal, placebo-controlled study evaluating the efficacy and tolerability of tapentadol extended release in patients with chronic painful diabetic peripheral neuropathy. Diabetes Care 2014;37:2302–2309

58. Sommer C, Welsch P, Klose P, Schaefert R, Petzke F, Hauser W. Opioids in chronic neuropathic pain. A systematic review and meta-analysis of efficacy, tolerability and safety in randomized placebo-controlled studies of at least 4 weeks duration. Schmerz 2015;29:35–46 [in German]

59. Jones CM, Einstein EB, Compton WM. Changes in synthetic opioid involvement in drug overdose deaths in the United States, 2010–2016. JAMA 2018;319:1819–1821

60. Pop-Busui R, Stevens M. Autonomic neuropathy in diabetes. In *Therapy for Diabetes Mellitus and Related Disorders*, 6th ed. Umpierrez GE, Ed. Alexandria, Va., American Diabetes Association, 2014, p. 834–863