BMJ Best Practice

Diabetic neuropathy

The right clinical information, right where it's needed

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Summary

- Hyperglycaemia contributes to the pathogenesis of neuropathy in both type 1 and type 2 diabetes. Other metabolic and vascular factors, particularly hypertriglyceridaemia, are important.

- The clinical presentation comprises a broad constellation of symptoms and deficits, involving sensory, motor, and autonomic nerve fibres, and multiple organ systems.

- Diabetic peripheral neuropathy is the most common chronic complication of diabetes, characterised by the presence of peripheral nerve dysfunction, diagnosed after the exclusion of other causes. Pain is the outstanding complaint in most patients, but many patients are completely asymptomatic.

- Treatment has traditionally focused on control of hyperglycaemia as a means of slowing progression or delaying onset, on targeting potential pathogenic mechanisms, and on pain reduction.

- Although pain is generated principally by peripheral nerve injury, the most effective drugs in treating painful diabetic neuropathy are centrally acting. Pregabalin (a voltage-gated calcium channel modulator), duloxetine (a selective dual serotonin-noradrenaline reuptake inhibitor), and tapentadol (an agonist of the mu-opioid receptor and noradrenaline reuptake inhibitor) are the only prescription drugs currently approved for treating painful diabetic neuropathy in some countries.

Definition

Diabetic neuropathy (DN) is a highly prevalent complication of diabetes (type 1 or type 2) and is characterised by the presence of symptoms, and/or signs of peripheral nerve dysfunction, and/or autonomic nerve dysfunction. It is diagnosed after the exclusion of other causes. Frequently, however, people with DN are asymptomatic.

Epidemiology

DN is the most common complication of diabetes. In the US, DN is the primary cause of diabetic foot problems and ulceration, the leading causes of diabetes-related hospital admissions and non-traumatic amputation.[5] Approximately 50% of people with diabetes will develop DN during their lifetime, although estimates vary from 10% to 90%, depending on the diagnostic criteria used.[6] Although there are no major differences in nerve pathology between type 1 and type 2 diabetes, small-fibre neuropathy may be more severe in latent autoimmune diabetes in adults (LADA).[7]

The prevalence of DN is quite low in patients with early type 1 diabetes. However, among participants in the Diabetes Control and Complications Trial (DCCT) who were considered to be non-neuropathic at baseline, the prevalence of an abnormal neurological examination was almost 20% in those on conventional treatment and almost 10% in those on intensive treatment after approximately 5 years of follow-up.[8] The prevalence of both distal symmetric polyneuropathy (DSPN) and cardiovascular autonomic neuropathy (CAN) increased during the observational follow-up of the DCCT cohort, Epidemiology of Diabetes Interventions and Complications (EDIC). At EDIC years 13 to 14, after a mean type 1 diabetes duration of 26 years, reported prevalence rates were 25% and 35% for diabetic peripheral neuropathy (DPN), and 29% and 35% for CAN in the former intensive and conventional control treatment groups, respectively.[9] [10] The EURODIAB IDDM Complications Study found that the prevalence of DN, across randomly selected patients with type 1 diabetes from 16 European countries, was 28%, with no significant geographical differences.[11] In the Pittsburgh Epidemiology of Diabetes Complications Study, in which patients with T1D were followed, the cumulative incidence of DPN over a period of 5.3 years was 29%.[12]

One prospective study of outpatients with type 1 or type 2 diabetes found an increase in the prevalence of DN from 10% (at the time of diagnosis) to 50% after 25 years of diabetes.[13] A similar prevalence was reported in the Rochester Diabetic Study in the US, in which 59% of type 2 and 66% of type 1 diabetic patients had DN.[14] In the UK, in another large cross-sectional study of people with type 1 and type 2 diabetes, the prevalence of DN was 29%.[15] There was no benefit on incidence of DN in people undergoing a multifactorial intervention for screen-detected type 2 diabetes.[16] [17] In one large study that enrolled more than 2300 participants with type 2 diabetes with a mean diabetes duration of approximately 10 years and confirmed coronary artery disease, the prevalence of confirmed DPN was approximately 50%.[18] [19] Among those participants who were free of DPN at baseline, the cumulative incidence of DPN over 4 years of follow-up was 69%.[19] In two longitudinal studies of patients with type 1 diabetes, approximately 18% developed DPN over 3 years.[20] [21] In the NHANES study, the prevalence of painful DPN was found to be 27%.[6]

Longitudinal studies indicate an annual increase in prevalence of CAN of about 6% in type 2 diabetes and of about 2% in type 1 diabetes.[22] Prevalence increases with age (up to 38% in type 1 and 44% in type 2 diabetes patients aged 40-70 years) and diabetes duration (up to 35% in type 1 and 65% in type 2 diabetes patients with longstanding diabetes).[22]

Due to its broad clinical consequences and high morbidity, DN is associated with poor quality of life.[23] [24] Evidence obtained in the SEARCH for Diabetes in Youth study, reported that signs for both cardiac autonomic neuropathy and DPN are found in youth with type 1 diabetes.[25] Studies also show evidence of small-fibre neuropathy in people with impaired glucose tolerance.[26] [27]

Aetiology

DN is a complex consequence of hyperglycaemia-induced alterations in multiple biochemical pathways, associated with other metabolic and vascular factors.

Hyperglycaemia

- The contribution of hyperglycaemia to the pathogenesis of microvascular complications (including DN) in type 1 1[A]Evidence and type 2 2[B]Evidence diabetes is firmly established.[8] [28] [29]
- The Diabetes Control and Complications Trial (DCCT) provided strong evidence for the importance of hyperglycaemia, insulin-deficiency, or both in the pathogenesis of DN in type 1 diabetes.[8]
- The Epidemiology of Diabetes Interventions and Complications (EDIC) study, the prospective observational study of the DCCT cohort, has shown persistent beneficial effects of past glucose control on both DN and cardiovascular autonomic neuropathy in patients with type 1 diabetes,[9] [10] supporting the impact of 'metabolic memory' as previously observed for retinopathy and nephropathy.[30]
- The results of the EDIC study also supported a close association between the severity and/or duration of hyperglycaemia and the development and progression of DN.[31]
- Patients who had received intensive insulin therapy in the DCCT were protected from the development of DN for at least 8 years following completion of the DCCT.[9] [10] [31]
- The ACCORD trial reported that an intensive glucose-lowering strategy, targeting an HbA1c <42 mmol/mol (<6%) delayed the progression of neuropathy in patients with type 2 diabetes at high risk of CVD events.[32] However, in this trial the intensive therapy was stopped before study end because of higher mortality in that group.
- One meta-analysis that included 17 randomised studies of patients with type 1 or type 2 diabetes found high-quality evidence that tight glucose control could prevent the development of DN and reduce the incidence of clinical neuropathy in people with type 1 diabetes.[33] In type 2 diabetes, enhanced glucose control had no impact on vibration perception threshold and failed to significantly reduce the incidence of clinical neuropathy.[33]
- However, in type 2 diabetes, the type of glucose lowering approach may have different effects on DN. Among patients with type 2 diabetes followed for up to 4 years during the BARI 2D study, a glycaemic control therapy with insulin sensitisers significantly reduced the incidence of diabetic peripheral neuropathy compared with insulin provider therapy, especially in men.[19]

Other metabolic and vascular factors

- Data from the United Kingdom Prospective Diabetes Study (UKPDS) suggest that hypertension, obesity, and smoking contribute to the development of DN in type 2 diabetes.[28]
- Cardiovascular risk factors such as hypertension and elevated serum triglycerides are each independently associated with development of DN.[34] [35] [36] The EURODIAB trial found that both hypertension and hyperlipidaemia accelerated the effects of hyperglycaemia on nerve dysfunction in people with type 1 diabetes.[11] [37]

- Elevated triglycerides and lower HDL have been reported to be independently associated with development of DN.[36] [38]

Other general factors

- Age
- Duration of diabetes
- Height
- Body mass index.

Pathophysiology

Research supports the concept that both metabolic and vascular factors are involved in the pathogenesis of DN. Animal and in vitro experiments implicate enzymatic and non-enzymatic pathways of glucose metabolism in the initiation and progression of DN. These include:[39] [40] [41]

- Increased oxidative and nitrosative stress
- Redox imbalance, secondary to enhanced aldose reductase activity
- Non-enzymatic glycation of structural nerve proteins
- Increased chronic inflammation and nuclear factor kappa B (NF-kB) signalling pathways
- Increased protein kinase C-beta activity
- Impaired nitric oxide synthase and endothelial dysfunction
- Cyclo-oxygenase-2 activation
- Hypoxia and ischaemia of nerve trunks and ganglia
- Deficiencies in the neurotrophic support of neurons and deficiencies in C-peptide
- Poly (ADP-ribose) polymerase (PARP) activation
- Alterations in mitogen-activated protein kinases
- Mobilisation of transcription factors
- Oxidised LDL cholesterol-mediated injury.

In nerve tissue, this pattern of metabolic and vascular disturbance impairs mitochondrial function and neurotrophic support, and mediates injury of neurons and Schwann cells, culminating in progressive damage and loss of peripheral nerve fibres and impaired sensory function.[42]

Similar mechanisms may be relevant to the pathogenesis of both micro- and macro-vascular disease in type 2 diabetes. It is likely that endothelial dysfunction, low-grade inflammation, and rheological abnormalities are common mechanistic denominators.[43]

It is now recognised that a major effect of diabetes is on the small unmyelinated or thinly myelinated C and A delta nerve fibres that modulate autonomic function and thermal and pain perception. Small-fibre neuropathy can impact on wound healing and therefore foot ulceration.[44]

Classification

Classification of diabetic neuropathy[1] [2] [3] [4]

1. Distal symmetrical sensorimotor polyneuropathy.
2. Autonomic neuropathy.
3. Focal and multi-focal neuropathies (rarer presenting forms)

- Cranial neuropathies
- Limb mononeuropathies (median, ulnar, radial, femoral, peroneal, lateral femoral cutaneous)
- Trunk mononeuropathy
- Mononeuropathy multiplex
- Lumbosacral plexopathy (amyotrophy).

4. Mixed forms.

The most common forms of DN are chronic sensorimotor polyneuropathy and autonomic neuropathy.

American Diabetes Association (ADA) adapted classification of diabetic neuropathy[2] [3]

Generalised symmetrical polyneuropathies

- Acute sensory
- Chronic sensorimotor
- Autonomic.

Focal and multifocal neuropathies

- Cranial
- Truncal
- Focal limb
- Proximal motor (amyotrophy)
- Co-existing chronic inflammatory demyelinating polyneuropathy (CIDP).

The ADA added that physicians should be alert for treatable neuropathies occurring in patients with diabetes, such as CIDP, monoclonal gammopathy, and vitamin B12 deficiency (particularly in patients taking metformin or a proton pump inhibitor).

Toronto Expert Panel on Diabetic Neuropathy Classification[4]

While this panel endorsed the classifications previously published, it also identified 2 major subgroups:

- Typical diabetic peripheral neuropathy (DPN) - a chronic, symmetrical, length-dependent (longer nerves affected first in the most distal segments) sensorimotor polyneuropathy. It is thought to be the commonest variety of DPN from cohort and population-based epidemiological studies.
- Atypical DPN - may develop at any time during the course of a patient's diabetes mellitus. Onset of symptoms may be acute, subacute, or chronic, but the course is usually monophasic or fluctuating over time, tending to preferentially involve small sensory and autonomic nerve fibres.

Primary prevention

Control of hyperglycaemia has been demonstrated to be the most effective strategy in preventing DN in type 1[1[A]Evidence] and type 2 diabetes.[54] 2[B]Evidence

The effect of intensive multifactorial treatment on incidence of DN in people screened for type 2 diabetes is unclear.[17]

Screening

Screening for peripheral neuropathy should be undertaken in patients with:

- Type 2 diabetes, from diagnosis
- Metabolic syndrome or impaired glucose tolerance, from diagnosis
- Type 1 diabetes, 5 years after diagnosis.

Screening is conducted at least annually thereafter, using symptoms and signs (simple clinical assessments include pinprick sensation, vibration perception [128-Hz tuning fork], light touch perception [10-g monofilament], ankle reflexes).[55] The Michigan Neuropathy Screening Instrument (MNSI) and similar symptom scoring systems are useful in clinical research.[99] [100] [101] [102]

Electrophysiological testing or referral to a neurologist is rarely needed, except in situations where the clinical features are atypical:[55]

- Motor deficits greater than sensory deficits
- Marked asymmetry of the neurological deficits
- Initial symptoms in the upper extremities
- Rapid progression.

The American Diabetes Association recommends screening for signs and symptoms of autonomic neuropathy during history taking and physical exam.[55] Special testing is rarely needed and may not affect management or outcomes.

Screening for cardiovascular autonomic neuropathy (CAN):[22] [58] [59] [80]

- Diagnosis of CAN is based on the use of cardiovascular reflex tests (CARTs) that assess the heart rate (HR) response to deep breathing, standing, and Valsalva manoeuvre, and BP response to standing.
- For the diagnosis and monitoring of CAN, more than one cardiovascular reflex test and BP test are required.
- Performance of CARTs should be standardised and the influence of confounding variables minimised.
- Age-related normal ranges of HR tests are strictly required.

Staging of CAN:

- Stage 1. Possible or early CAN: presence of one abnormal cardiovascular reflex test, to be confirmed over time
- Stage 2. Definite or confirmed CAN: at least two abnormal cardiovascular reflex tests are required
- Stage 3. Severe or advanced CAN: presence of definite CAN plus the presence of orthostatic hypotension (OH)

Progressive stages of CAN are associated with increasingly worse prognosis.
[Fig-3]

[Fig-4]

Secondary prevention

People with DN are particularly at risk of painless foot injuries. Preventing foot ulceration is important, as subsequent wound infection and gangrene can lead to amputation. All patients should be screened for DN at diagnosis of type 2 diabetes or impaired glucose tolerance, and 5 years after diagnosis of type 1 diabetes. Screening should be conducted at least annually thereafter, using simple clinical tests.

Proper care of the foot and prevention of ulceration begins with educating the patient on proper foot care. The feet should be visually examined at each visit. Referral for specialised footwear may be indicated to relieve pressure points and reduce risk of foot trauma. Patients also need to check their feet daily and report any injuries or wounds at an early stage.

One review of 13 randomised clinical trials assessed the benefits and efficacy of various interventions on the prevention of future diabetic foot ulcers. It found that only foot temperature-guided avoidance therapy was beneficial.[264]

Cardiovascular autonomic testing is recommended before a patient with diabetes begins a moderate- or high-intensity exercise programme. People with known cardiovascular autonomic dysfunction should be advised about the need for appropriate hydration when exercising.

Case history

Case history #1

A middle-aged man with type 2 diabetes presents with shooting and burning pain in his feet and lower legs, most severe at night, associated with numbness and allodynia (pain from stimuli that are not normally painful). In the past 6 months, the pain has become much worse and disturbs his sleep. He has been told that his blood glucose is borderline elevated and has been advised to start diet and exercise. He also takes a medication for HTN and recalls that his cholesterol is elevated.

Case history #2

A 54-year-old woman with type 1 diabetes has developed an ulcer on her right foot. She cannot recall any particular injury and has been walking as normal with no pain. Physical examination of the foot reveals a painless ulcer over the metatarsal head. She also complains of feeling tired and has noticed she is particularly dizzy and unsteady on her feet when she stands up. BP measurements in the supine position, repeated after 2 minutes of standing, reveal an abnormal fall in systolic BP, from supine to standing position, of 32 mmHg.

Other presentations

Weakness is less common than pain and is usually minor and occurs later. If weakness is present, it follows a distal pattern, with wasting and weakness of the interossei of the hands and feet. An acute onset of severe sensory neuropathy may occur rarely, but a chronic sensorimotor neuropathy is much more common. Other rare types of neuropathy that may present include cranial neuropathies, mononeuropathies (e.g., carpal tunnel syndrome, or footdrop related to common peroneal neuropathy), truncal radiculopathy (presenting with pain over the thoracic or abdominal wall), or diabetic amyotrophy. Diabetic amyotrophy is more common in older patients with type 2 diabetes, and presents with severe pain, muscle weakness, and muscle atrophy in the thigh unilaterally or bilaterally. Additional symptoms of autonomic neuropathy include nausea, vomiting, and early satiety (gastroparesis); difficulty in emptying the bladder (cystopathy); or erectile dysfunction.

Step-by-step diagnostic approach

The presentation of DN is variable from one patient to another. Up to 50% of patients with DN may be completely asymptomatic.[4] [55] Characteristic history and clinical examination findings are often sufficient to diagnose established DN. There are no distinguishing features unique to DN, so all other possible causes of the neuropathy (e.g., hypothyroidism, vitamin B12 deficiency, uraemia, chronic alcoholism) must be ruled out by careful history, physical examination, and laboratory tests. Some of these conditions occur more frequently in people with diabetes and, therefore, may co-exist.

Many of the symptoms associated with diabetic autonomic neuropathy are common in the general population. The symptoms are frequently non-specific, making confirmation of the cause all the more challenging.

Distinguishing diabetic neuropathies from other polyneuropathies

It is important to exclude other causes of peripheral neuropathy that may be erroneously diagnosed secondary to diabetes. A careful history and examination remains the cornerstone of identifying and differentiating other neuropathies presenting in a similar way. Screening laboratory tests should include thyroid function tests, vitamin B12, immunoglobulin electrophoresis, electrolytes, FBC, and erythrocyte sedimentation rate. An important differential is chronic inflammatory demyelinating polyneuropathy (CIDP). This condition is responsive to immunotherapy and may be more common in patients with diabetes. Patients with CIDP present with tingling, pain, and in particular distal muscle weakness. Nerve conduction studies can specifically identify a reduction in nerve conduction, conduction block, and abnormal temporal dispersion.

History for diabetic peripheral neuropathy

The history may reveal the presence of risk factors strongly associated with DN, including a long duration of diabetes (e.g., >10 years), older age (e.g., >70 years), tall stature, and poorly controlled hyperglycaemia. Intensive blood glucose control is associated with lower rates of DN compared with conventional management.[8] [28] History of dyslipidaemia with elevated triglycerides and hypertension may also be present. In addition, a history of recent falls should be elicited, which may reflect gait and balance disorders.[56]

Symptoms vary according to the class of sensory fibres involved. The most common symptoms are induced by the involvement of small fibres and include:

- Pain
- Dysaesthesias (unpleasant abnormal sensations of burning, tingling, numbness)
- Numbness.

Pain is often the reason why patients with DN seek medical care. Intensity varies from mild discomfort to being disabling, and may be described as:

- Sticking
- Lancinating
- Prickling
- Burning
- Aching
- Boring
- Excessively sensitive.

Pain is often worse at night and may disturb sleep. Involvement of larger fibres may lead patients to complain of a feeling like walking on cotton wool.

The most distal portion of the longest nerves is affected first. Early symptoms typically involve the tips of the toes and fingers. This proceeds proximally, resulting in a 'stocking-glove' pattern of pain and sensory loss.
[Fig-1]

Feeling may also be lost in the feet, with or without pain or dysaesthesias. If nociceptive fibres are involved, loss of sensation may set the stage for painless injuries. An object may become lodged in the shoe and erode through the skin with normal walking and weight-bearing.

[Fig-2]

Weakness is another presenting symptom but is less common, usually minor, and occurs later in the disease process.

Other presentations of DN include:

- Mononeuropathies (e.g., carpal tunnel syndrome [median nerve], foot drop [common peroneal nerve])
- Cranial neuropathies (extremely rare)
- Diabetic truncal radiculoneuropathy (pain over the lower thoracic or abdominal wall)
- Diabetic amyotrophy (severe weakness, pain, and proximal thigh muscle atrophy).

History for diabetic autonomic neuropathy

Symptomatic autonomic neuropathy is infrequent and, in general, occurs later in the course of the disease.[57] [58] [59]

Patients may have exercise intolerance due to a reduced response in heart rate and BP, and blunted increases in cardiac output in response to exercise.[60]

Orthostatic hypotension, defined as a fall in systolic (20 mmHg) or diastolic (10 mmHg) BP within 3 minutes of standing, occurs in diabetes largely as a consequence of efferent sympathetic vasomotor denervation, with reduced vasoconstriction of the splanchnic and other peripheral vascular beds. Symptoms associated with orthostatic hypotension include:

- Light-headedness
- Weakness
- Faintness
- Dizziness
- Visual impairment
- Syncope on standing.

GI symptoms are relatively common among patients with diabetes and often reflect diabetic GI autonomic neuropathy. Some studies have described the presence of delayed gastric emptying in up to 50% of patients with longstanding diabetes, and in severe cases it is associated with significant impairments in both quality of life and glycaemic control.[61] Although GI symptoms are common in diabetes, symptoms are often due to factors other than autonomic dysfunction. While the delay in gastric emptying is not always clinically apparent, the range of symptoms may include:[62]

- Nausea
- Post-prandial vomiting
- Bloating
- Loss of appetite
- Early satiety.

Esophageal dysfunction partly results from vagal dysfunction and may present with symptoms that include heartburn and dysphagia for solids.

Intermittent diarrhoea is evident in 20% of diabetic patients particularly those with known autonomic dysfunction.[57] Profuse watery diarrhoea typically occurs at night, especially in patients with type 1

diabetes. It may alternate with constipation and is extremely difficult to treat. History should rule out other causes of diarrhoea, especially ingestion of lactose, non-absorbable hexitols, or medication.[57]

People with diabetes may also experience faecal incontinence, due to poor sphincter tone.

Bladder dysfunction and impaired ability to void is present in up to 50% people with diabetes and may result in symptoms of:

- Frequency
- Urgency
- Nocturia
- Hesitancy in micturition
- Weak stream
- Dribbling urinary incontinence
- Urine retention.

Erectile dysfunction (ED) is present in 30% to 75% diabetic men and can be the earliest symptom of diabetic autonomic neuropathy. However, it is generally accepted that it is not solely induced by autonomic neuropathy but rather by the co-existence of other multiple vascular risk factors, such as:

- Hypertension
- Hyperlipidaemia
- Obesity (leading to increased aromatase activity and reduced androgens)
- Psychogenic factors.

Women with diabetes may have decreased sexual desire and increased pain during intercourse, and are at risk of decreased sexual arousal and inadequate lubrication.[63]

Sudomotor dysfunction manifests as anhidrosis, heat intolerance, dry skin, or hyperhidrosis.

Hypoglycaemia unawareness may be related to autonomic neuropathy but a study of patients with type 1 diabetes failed to confirm this association.[64]

Assessment of symptoms

Questionnaires have been developed to investigate orthostatic symptoms and their severity. Current validated autonomic scales, include the Autonomic Symptom Profile (ASP)[65] and the Survey of Autonomic Symptoms (SAS).[66]

Physical exam

Physical examination (neurological) may reveal symmetrical distal sensory loss, with reduced or absent ankle reflexes. Sensory loss is defined in terms of extent, distribution, and modality and involves assessment of:

- Pinprick sensation
- Light touch
- Vibration
- Joint position.

A potentially quick, inexpensive, and accurate screening instrument to evaluate high-risk patients in the clinic includes assessment for:[67] [68]

- Loss of vibration sense (using a 128-Hz tuning fork) is tested initially at the big toe. [Fig-3]

  Vibration sensation should be tested bilaterally by placing the tuning fork over the dorsum of the big toe, on the bony prominence of the DIP joint. The patient, whose eyes are closed, should be asked to indicate when he or she can no longer sense the vibration from the vibrating tuning fork. A trial should be conducted when the tuning fork is not vibrating to be certain that the patient is responding to vibration and not pressure.
- Ankle reflexes offer a quick and inexpensive means to identify high-risk patients in the clinic. Ankle reflexes should be examined using an appropriate reflex hammer (e.g., Tromner or Queen square). Ankle reflexes should be elicited in the sitting position with the foot dependent and the patient relaxed. In addition, the foot should be passively positioned and slightly dorsiflexed to obtain optimal stretch of the muscle. The Achilles tendon should be percussed directly. If the reflex is obtained, it is graded as present. If the reflex is absent, the patient should be asked to perform the Jendrassic manouvre (i.e., hooking the fingers together and pulling). Reflexes elicited with the Jendrassic manouvre are designated as present with reinforcement. If the reflex is absent, even with the Jendrassic manouvre, the reflex is considered absent.
- Loss of light touch (using 10-g monofilament) is tested at the dorsal aspects of both big toes. [Fig-4]

  For this examination, it is important that the patient's foot be supported (i.e., allowing the sole of the foot to rest on a flat, warm surface). The filament should initially be pre-stressed (4 to 6 perpendicular applications to the dorsum of the examiner's first finger). The filament is then applied to the dorsum of the big toe midway between the nail fold and the DIP joint. The toe should not be held directly. The filament is applied perpendicularly and briefly (<1 second), with an even pressure. When the filament bends, the force of 10 g has been applied. The patient, whose eyes are closed, should be asked to respond yes if he or she feels the filament. Eight correct responses out of 10 applications is considered normal; 1 to 7 correct responses indicates reduced sensation; no correct answers translates into absent sensation.
- Presence of ulcers, callus, and prior amputations (foot inspection).

Painless injuries may be apparent on exam.
[Fig-5]

These often occur over pressure points on the foot and most commonly over the metatarsal heads. Infection often complicates the situation and can be followed by gangrene if vascular dysfunction is present. Magnetic resonance imaging has emerged as the most accurate means of diagnosing osteomyelitis, but bone biopsy for culture and histopathology remains the criterion standard.[69] [70]

In patients with involvement of large sensory fibres, gait ataxia may develop especially at night or when the patient walks with closed eyes. In patients with severe DN, motor involvement may become clinically apparent with weakness of toe dorsiflexion and intrinsic hand muscles.

Resting tachycardia and a fixed heart rate are characteristic late findings in diabetic patients with vagal impairment. Resting heart rates of 90 to 100 bpm and occasional heart rate increments up to 130 bpm occur.[60] Resting heart rate and heart rate variation (HRV) are easy to measure at the bedside, and can reveal early signs of cardiac autonomic neuropathy.

Measurement of supine and standing BP is important to diagnose orthostatic hypotension.

Bladder dysfunction may ultimately result in urinary retention with evidence of an enlarged bladder on abdominal examination.

Assessment of signs

Resting tachycardia is not a specific sign of cardiovascular autonomic neuropathy (CAN) (class IV). Orthostatic hypotension may be present in advanced CAN but requires prior exclusion of other causes and is an insensitive index (class III). QTi prolongation (class II) and reverse dipping on ambulatory BP monitoring are specific but insensitive indices of CAN (class III).[22]

Investigations

DN is often a clinical diagnosis. Consensus statements from the American Diabetes Association, American Neurological Association, Toronto Consensus Panel on Diabetic Neuropathy, and NEURODIAB recommend that the diagnosis and classification of DN for research and clinical trials be based on at least 1 standardised measure from each of the following categories:[2] [71]

- Clinical symptoms
- Clinical examination
- Electrophysiological testing
- Quantitative sensory testing (QST)
- Autonomic testing
- Skin biopsy and intra-epidermal nerve fibre density[72]
- Corneal confocal microscopy.

There are differences between diagnostic criteria for clinical care and clinical research.[4] [22]

Basic laboratory tests include fasting blood glucose, HbA1c and possibly OGTT, TSH, vitamin B12, serum urea, immunoglobulin electrophoresis, and erythrocyte sedimentation rate. Skin biopsy is a validated technique for determining intra-epidermal nerve fibre density, and may be considered for the diagnosis of DN, particularly small-fibre neuropathy.[73]

Newer non-invasive modalities such as corneal confocal microscopy (CCM), a technique used to image the corneal sub-basal nerve plexus, and laser Doppler imaging flare technique (LDI flare), which assesses the small-fibre axon reflex-mediated neurogenic vasodilatory response to cutaneous heating, have been shown to be comparable to intra-epidermal nerve fibre density.[74] [75]

Electrophysiological testing (nerve conduction tests and EMG) and specialised neurology evaluation are needed in situations where the clinical features are atypical (e.g., where motor deficits exceed sensory deficits; marked asymmetry of the neurological deficits; initial symptoms in the upper extremities; rapid progression).
[Fig-6]

QST quantifies vibration perception threshold (VPT) and thermal perception threshold. A variety of instruments (e.g., Vibratron II, neurothesiometer, CASE IV), using a variety of algorithms, facilitate sensory threshold determination. Two general schemes have emerged: the method of limits and the method of levels. In the method of limits, a patient is required to indicate as soon as they detect an increasingly strong stimulus (ascending ramp) or when they no longer detect a decreasing stimulus (descending ramp). In the method of levels, stimuli of defined intensity levels are tested with the patient indicating whether they detect a specific level; the patient is forced to choose whether they feel a stimulus. Therefore, the method of levels is also referred to as a forced-choice algorithm.[76] QST can be used

when the rest of the examinations are normal, to detect small-fibre neuropathy.[77] 3[B]Evidence An assessment of autonomic neuropathy relies principally on cardiovascular autonomic function testing, which can be complex to perform. CCM has been shown to have an extremely high sensitivity and specificity for diabetic autonomic neuropathy.[79]

Cardiovascular autonomic reflex tests[22]

- Cardiovascular reflex studies should be performed using a battery of validated tests (e.g., R-R response to deep breathing, Valsalva manoeuvre, and response to postural changes), rather than one single test. These provide information mainly on parasympathetic function, whereas the BP response to standing and to Valsalva manoeuvre, and the sustained isometric muscular strain may provide information on sympathetic function.
- The R-R response to deep breathing is the most widely used test of cardiovagal function with approximately 80% specificity.[73]
- The Valsalva manoeuvre needs greater co-operation from patients and cannot be universally performed. HR response depends on the BP response to the manoeuvre; the BP response to sustained handgrip is no longer regarded as an established clinical test but only as an investigational test. The orthostatic hypotension test may still be used in the standard assessment of CAN, despite its low sensitivity.[22]
- These tests are non-invasive, safe, clinically relevant (they correlate with tests of peripheral nervous system function), easy to perform, sensitive, specific, reproducible, and standardised, and, therefore, they are considered consolidated, preferred standard measures of autonomic function.

Heart rate variability (HRV)[58] [59]

- HRV can be assessed either by calculating indices based on statistical analysis of response rate intervals (time-domain analysis) or by spectral analysis (frequency-domain analysis) of an array.[60]
- Time-domain indices of global HRV and total spectral power of HRV represent an index of parasympathetic activity, as well as the HRV spectral power in the high frequency region, while the low frequency relative proportion (not the absolute power) of HRV provides a relative measure of sympathetic modulation. This interpretation should be made with caution if respiratory artifacts (slow breaths) cannot be excluded.[80]
- It is generally accepted that, at this time, the use of HRV should be reserved for clinical research studies.
- QT prolongation is an independent predictor of mortality in diabetic patients and is weakly associated with measures of HRV.[81]
- Presence of CAN, as assessed by impaired HRV, is an important independent predictor of all-cause and cardiovascular mortality.[22] [59] [58]

The following investigations are performed only if the history and physical examination reveal concerns about the possibility of any of these specific autonomic manifestations.

- Gastric emptying studies with double-isotope scintigraphy and, more recently, surface electrogastrography, detect abnormalities in GI pacemaking. This may help in the diagnosis of gastroparesis where the diagnosis is in doubt.
- Hydrogen breath tests using non-radioactive 13C-acetate or -octanoic acid as a label are safe, inexpensive, and correlate well with scintigraphy results.
- A barium meal investigation has a place in evaluating mucosal lesions or obstruction.
- Gastroduodenoscopy is also recommended to exclude pyloric or other mechanical obstructions.

- GI manometry should be considered as a research technique to investigate gastric and intestinal motility.
- For large-volume diarrhoea, faecal fat should be checked and further studied with a 72-hour faecal fat collection and/or the d-xylose test to rule out malabsorptive disorders. If there is significant steatorrhoea, pancreatic function tests should be performed. If coeliac disease is suspected (increased risk in type 1 diabetes), serum levels of coeliac disease antibody profile, including anti-transglutaminase and anti-endomysial antibodies, should be measured.

Patients with erectile dysfunction (ED) should be investigated by:

- Hormonal evaluation (luteinising hormone, testosterone, prolactin), to rule out hypogonadism
- Measurement of nocturnal penile tumescence
- Measurement of penile and brachial BP with Doppler probes
- Calculation of the penile-brachial pressure index (<0.7 suggests penile vascular disease).

Diabetic bladder dysfunction should be evaluated by:

- Urinary culture
- Post-void ultrasound, to assess residual volume and upper-urinary tract dilation
- Cystometry and voiding cystometrogram
- Video-urodynamic studies.[82]

Further investigations mainly used in research

Assessment of sudomotor innervation

- Used mainly for research due to limited data.

Tests of sudomotor function evaluate the extent, distribution, and location of deficits in sympathetic cholinergic function. These tests may include:

- Quantitative sudomotor axon reflex test (QSART)
- Sweat imprint
- Thermoregulatory sweat test (TST)
- Sympathetic skin response: some devices can provide a quantitative assessment of sudomotor function using direct current stimulation and reverse iontophoresis. These devices measure the ability of sweat glands to release chloride ions in response to electrochemical activation by recording local skin conductance.[57] [58] [59] [83]

Quantitative scintigraphic assessment of sympathetic innervation of the human heart is possible using single photon emission computed tomography (SPECT) with 123I-meta-iodobenzylguanidine (MIBG) and positron emission tomography (PET) with 11C-meta-hydroxyephedrine.[84] However, no standardised methods or normative values exist, and the high costs and the available data on the reproducibility limit their use to research only.[59] [58]

Sympathetic outflow, at rest and in response to various physiological perturbations, can be measured directly by microelectrodes inserted into a fascicle of a distal sympathetic nerve to the skin or muscle (muscle sympathetic nerve activity). This is also used for research purposes only.[58] [59] [80]

Cardiac vagal baroreflex sensitivity may also be used in research protocols to assess cardiac vagal and sympathetic baroreflex function.

Additional research investigations include 24-hour BP profile and microneurography. Attenuation (non-dipping) and loss of BP nocturnal fall (reverse dipping) on ambulatory BP monitoring have been associated with cardiovascular autonomic neuropathy and attributed to disruption of circadian variation in sympathovagal activity.[85] In diabetic patients non-dipping or reverse dipping are independent predictors of cardiovascular events and the progression of diabetic nephropathy. Microneurography is based on recording electrical activity emitted by peroneal, tibial, or radial muscle sympathetic nerves and identifying sympathetic bursts. Fully automated sympathetic neurogram techniques provide a rapid and objective method that is minimally affected by signal quality and preserves beat-by-beat sympathetic neurograms.[58] [59] [80] [86]

Pain-related evoked potentials

- Used for research only.

Nerve axon reflex/flare response

- Stimulation of the nociceptive C fibre results in both orthodromic conduction to the spinal cord and antidromic conduction to other axon branches, which stimulates the release of peptides, such as substance P and calcitonin gene related peptide, which causes vasodilation and increased blood flow. This is known as the axon reflex or flare response. An impaired axon reflex indicates small-fibre neuropathy.
- Used for research only. More data are needed before this test can be recommended for clinical use.[87]

Neuropad

- A simple visual indicator test, which uses a colour change to define the integrity of the skin sympathetic cholinergic innervation.
- Neuropad responses have been shown to correlate with the modified neuropathy disability score (NDS), QST, and intra-epidermal nerve fibre (IENF) loss with relatively high sensitivity, but lower specificity for detecting distal symmetric polyneuropathy (DSPN).[88]
- However, the studies had relatively small samples and, therefore, this test requires further validations.

Risk factors

Strong

poorly controlled hyperglycaemia

- The role of hyperglycaemia is supported by strong prospective RCTs and prospective observational studies.[9] [10] [14] [28] [29] [32]
- The annual incidence of DN was approximately 2% in conventionally treated patients with type 1 diabetes, but that rate dropped to 0.6% in intensively treated patients.[8] 1[A]Evidence

prolonged duration of diabetes

- Longer duration of diabetes (e.g., >10 years) increases the risk of DN.[15]
- The association between duration and prevalence of DN may depend, in part, on patient age, which itself is a risk factor.
- The prevalence of DN is estimated to be >50% in people who have had diabetes for >20 years.[2]

older age (e.g., >70 years)

- The incidence and prevalence DN increase with age.[28]
- There is a highly significant correlation between age and prevalence of neuropathy in both type 1 and type 2 diabetes.[15]

tall stature

- Increased height is a risk factor for diabetic peripheral neuropathy, suggesting that longer fibres are more vulnerable to injury.[45] [46] [47]

hypertension

- Studies have shown that HTN amplifies the effects of hyperglycaemia on nerve dysfunction in people with type 1 and type 2 diabetes.[2] [11]

dyslipidaemia with elevated triglycerides

- Epidemiological studies show evidence that therapy with a statin or a fibrate may protect against the development of DN.[48]
- Epidemiological studies also demonstrate a protective role of HDL cholesterol in people with type 1 diabetes.[12] [37]
- Evidence shows that elevated triglycerides are an important predictor of myelinated fibre density loss, independent of disease duration, age, diabetes control, or other variables.[36]

co-existence of multiple CVD risk factors (type 2 diabetes)

- In people with type 2 diabetes, co-existence of multiple CVD risk factors is associated with higher risk for DN.[18] [32]

Weak

obesity

- Prospective observational studies have found that higher BMI is associated with higher DN prevalence.[11]

immune dysregulation

- There is some weak evidence for the role of autoimmunity associated with autonomic neuropathy in type 1 diabetes.
- There are reports of lymphocytic infiltration within autonomic nerve structures in diabetic patients with severe symptomatic autonomic neuropathy.[49] Auto-antibodies to autonomic nerve structures have also been reported.[50] [51] [52] [53]

smoking

- Several epidemiological studies have found that smoking is associated with higher prevalence of DN.[12] [37]

History & examination factors

Key diagnostic factors

presence of risk factors (common)

- All of the following are strongly associated with the development of DN: poorly controlled hyperglycaemia, older age (e.g., >70 years), prolonged duration of diabetes (e.g., >10 years), and tall stature.
- In addition, dyslipidaemia with elevated triglycerides and hypertension are emerging as strong independent risk factors.[34] [35] [36]
- In people with type 2 diabetes, co-existence of several CVD risk factors for cardiovascular disease and the presence of CAD are also associated with DN.[18] [32]

asymptomatic (common)

- Up to 50% patients with DN may be completely asymptomatic.[4] [55]

pain (peripheral) (common)

- Particularly troubling to most patients. Often the reason why patients with DN seek medical care.
- May be described as sticking, lancinating, prickling, burning, aching, boring, or excessively sensitive. It is often worse at night and may disturb sleep.
- Involvement of larger fibres produces a tight, band-like feeling around the extremity, or an electrical tingling sensation. Involvement of small fibres usually produces burning-like pain.

loss of sensation (peripheral) (common)

- Defined in terms of extent, distribution, and modality.
- Assessment includes pinprick sensation, light touch,
  [Fig-4]

  vibration,
  [Fig-3]

  and joint position.
- At an early stage affects tips of toes and/or fingers. Proceeds proximally, causing a symmetrical distal sensory loss in a 'stocking-glove' pattern.
  [Fig-1]
- Among patients who complain only of distal burning, the loss of distal sensation may be very subtle. Feeling may also be lost in the feet, with or without pain. Painless injuries may occur.
- Threshold quantitative sensory testing is probably more reproducible than the subjective assessment by the patient of the strength of stimulus.[2]

dysaesthesia (peripheral) (common)

- Defined as an unpleasant abnormal sensation of burning, tingling, and numbness, associated with peripheral nerve lesions.

reduced or absent ankle reflexes (peripheral) (common)

- Common finding on clinical examination.

painless injuries (peripheral) (common)

- May develop over pressure points, most commonly on the foot, over the metatarsal heads.
  [Fig-5]
- An object may become lodged in the shoe and erode through the skin with normal walking and weight-bearing.
- Infection is a common complication, followed by gangrene if vascular dysfunction is present.

resting tachycardia (autonomic) (common)

- Resting tachycardia and a fixed heart rate are characteristic late findings in diabetic patients with vagal impairment. Resting heart rate is easy to measure at the bedside, but is not specific.
- May be associated with exercise intolerance.

impaired heart rate variability (autonomic) (common)

- Could reveal early signs of cardiac autonomic neuropathy but is challenging to measure correctly in clinical practice and is currently used for clinical research only.

urinary frequency, urgency, nocturia, incontinence, hesitancy, weak stream, or retention (autonomic) (common)

- Associated with incomplete bladder emptying, increased post-void residual, lower peak urinary flow rate, bladder over-distension, and ultimately urinary retention and overflow incontinence.
- Present in up to 50% patients with diabetes.[88]

erectile dysfunction (autonomic) (common)

- Present in 30% to 75% diabetic men.[88] Can be the earliest symptom of diabetic autonomic neuropathy.
- It is generally accepted that it is not solely induced by autonomic neuropathy, but rather by the co-existence of other multiple vascular risk factors, such as hypertension, hyperlipidaemia, obesity, and psychogenic factors.

decreased sexual desire and increased pain during intercourse (autonomic) (common)

- Women may present with these features of sexual dysfunction. They are at risk of decreased sexual arousal and inadequate lubrication.[63]

orthostatic hypotension (autonomic) (uncommon)

- Abnormal fall in systolic/diastolic BP in response to standing.
- Easy to measure at bedside or office. Is usually a late characteristic and has low specificity.
- The postural change in BP is elicited by a supine measurement followed by BP measurements at 1, 2, 3, and sometimes 5 minutes after standing.
- About twice as common in people with type 1 diabetes as in those with type 2 diabetes.
- Consequence of efferent sympathetic vasomotor denervation, causing reduced vasoconstriction of the splanchnic and other peripheral vascular beds.
- May result in light-headedness, weakness, faintness, dizziness, visual impairment, and even syncope on standing.

Other diagnostic factors

constipation (autonomic) (common)

- Can alternate with episodes of diarrhoea.

faecal incontinence (autonomic) (common)

- May occur due to poor sphincter tone.

anhidrosis, heat intolerance, dry skin, or hyperhidrosis (autonomic) (common)

- May be complaints with sudomotor (sweating) dysfunction.

hypoglycaemia unawareness (autonomic) (common)

- May be triggered by autonomic neuropathy, but this relationship is complex.

weakness (peripheral) (uncommon)

- Less common than pain or loss of sensation, and is usually minor and occurs later.
- May become clinically apparent with weakness of toe dorsiflexion and intrinsic hand muscles.

hx of recent falls (peripheral) (uncommon)

- May reflect gait and balance disorders associated with peripheral neuropathy.[56]

gait ataxia (peripheral) (uncommon)

- Present in situations associated with severe peripheral denervation.
- Especially obvious at night or when the patient walks with closed eyes.

nausea, postprandial vomiting, bloating, loss of appetite, early satiety (autonomic) (uncommon)

- Associated with diabetic gastroparesis (delayed gastric emptying of solids or liquids, in the absence of mechanical obstruction).
- Occurs as a consequence of dysfunction of the vagus nerve and intrinsic enteric autonomic nerves.

heartburn and dysphagia for solids (autonomic) (uncommon)

- May be associated with oesophageal dysfunction, which results, at least in part, from vagal dysfunction.

profuse and watery diarrhoea (autonomic) (uncommon)

- May be associated with diabetic gastroparesis. Typically intermittent and may occur at night.
- Extremely difficult to treat.
- Occurs in 20% diabetic people and may alternate with constipation.[88]

specific mononeuropathy (peripheral) (uncommon)

- Rare presentation of DN.
- Presents with specific features depending on the nerve affected (e.g., carpal tunnel syndrome, or footdrop related to common peroneal neuropathy).

cranial neuropathy (peripheral) (uncommon)

- Extremely rare presentation of DN.
- More likely in older patients who have had diabetes for a long time.

pain over lower thoracic or abdominal wall (peripheral) (uncommon)

- Feature of diabetic truncal radiculoneuropathy.
- More common in men and tends to resolve within 4 to 6 months.

thigh muscle atrophy, pain, and weakness (peripheral) (uncommon)

- Features of diabetic amyotrophy.
- More common in type 2 diabetes.

Diagnostic tests

1st test to order

Test	Result
corneal confocal microscopy • A non-invasive ophthalmic technique to image the corneal sub-basal nerve plexus. It has been shown to detect small sensory corneal nerve fibre loss in DN.[89] [90] [91] Studies have found high reproducibility, sensitivity, and specificity.[89] [91]	**corneal nerve fibre damage correlates with intra-epidermal nerve fibre loss and severity of neuropathy**
clinical diagnosis • Routine screening tests may exclude other common conditions.	**diagnosis of peripheral neuropathy is often made on clinical grounds**
fasting blood glucose • Many patients who present with painful neuropathy may have diabetes without knowing it. In this circumstance, a fasting blood glucose may be performed. • The American Diabetes Association recommends any of 3 screening tests to diagnose diabetes: fasting blood glucose, HbA1c, or an oral glucose tolerance test. Two measurements of any of these confirm the diagnosis.[92]	**diagnosis of diabetes mellitus (if not already known to be present)**
HbA1c • Many patients who present with painful neuropathy may have diabetes without knowing it. In this circumstance, HbA1c may be performed. • The American Diabetes Association recommends any of 3 screening tests to diagnose diabetes: fasting blood glucose, HbA1c, or an oral glucose tolerance test. Two measurements of any of these confirm the diagnosis.[92] • Poorly controlled hyperglycaemia is associated with increased risk of neuropathy.	**correlates with degree of glycaemic control**
serum TSH • To exclude thyroid dysfunction.	**normal**
serum vitamin B12 • To exclude deficiency.	**normal**
electrolytes, urea, creatinine • To exclude renal disease.	**normal**
serum lipid profile • To exclude abnormalities in low-density lipoprotein, high-density lipoprotein, triglycerides, and total cholesterol.	**may show lipid abnormalities**
LFTs • To exclude hepatic disease.	**normal**
FBC and erythrocyte sedimentation rate • To exclude anaemia and inflammatory disorders.	**normal**
serum/urine immunoelectrophoresis • To exclude multiple myeloma.	**normal**

Other tests to consider

Test	Result
oral glucose tolerance test • Many patients who present with painful neuropathy may have diabetes without knowing it. In this circumstance, an oral glucose tolerance test may be performed. • The American Diabetes Association recommends any of 3 screening tests to diagnose diabetes: fasting blood glucose, HbA1c, or an oral glucose tolerance test. Two measurements of any of these confirm the diagnosis.[92]	**diagnosis of diabetes mellitus (if not already known to be present)**
nerve conduction studies (nerve conduction velocity, NCV) • Indicated in situations where the clinical features are atypical (such as asymmetrical symptoms and signs or weakness). • Whole nerve electrophysiological procedures (e.g., NCV, F-waves, sensory, and/or motor amplitudes) are performed. [Fig-6] • In very mild or asymptomatic cases, the only change may be distal slowing of conduction or none. • As the neuropathy progressively worsens, findings of axonal degeneration predominate, including decreased amplitude of sensory nerve action potentials (SNAPs); decreased amplitude of compound muscle action potentials; relative preservation of proximal conduction velocities; and evidence of fibrillation potentials. • NCV is usually gradually diminished by DN[93] but may be completely normal in patients with predominantly small-fibre neuropathy. Several prospective clinical trials describe slower worsening of NCV end points in the current standard of care for patients with diabetes.[9] [94] • Longitudinal studies suggest an average loss of SNAP amplitude at a rate of approximately 5% per year over a 10-year period.[93] In patients with type 1 diabetes participating in the Epidemiology of Diabetes Interventions and Complications (EDIC) study, the average loss rate was around 3% per year over a 13- to 14-year period.[9] • Motor nerve studies may demonstrate some slowing, even when patients have no symptoms or signs of neuropathy, with a greater slowing in symptomatic patients. • Motor amplitudes may be decreased in more advanced DN. • A key role for electrophysiological assessment is to rule out other causes of neuropathy (e.g., unilateral conditions, such as entrapments) and to identify neuropathies superimposed on DN.	**reduced sensory nerve conduction velocity and decreased amplitude is the most sensitive and earliest result among the NCV studies**
electromyography (EMG) • Indicated in situations where the clinical features are atypical (such as asymmetrical symptoms and signs, or weakness).	**may be normal in mild or neurologically asymptomatic patients, but demonstrates denervation in more severe DN**

Test	Result
quantitative sensory testing (QST) • Focuses on the vibration perception threshold (VPT) and thermal perception threshold. • Used in people with diabetes in addition to routine clinical examination as a subsequent assessment of loss of protective sensation and axonal pathology when all the other examinations are normal to detect small-fibre neuropathy.[77] • A high sensitivity and specificity for VPT has been confirmed in patients with type 1 diabetes relative to NCV and neurological evaluation.3[B]Evidence • Probably more reproducible than the subjective assessment by the patient of the strength of stimulus.[2] • There is a documented relationship between elevated VPT tested in the 50 to 300 Hz range and DN.[93] • Abnormal thermal thresholds have been reported in 75% of patients with moderate to severe diabetic peripheral neuropathy, and elevated heat pain thresholds were detected in 39% of these patients.[93] • Generally, there is a high correlation between elevated thermal and vibration thresholds, but these measures can be dissociated, suggesting a predominant small or large fibre neuropathy in individual patients.	**may be normal, or deficits in vibration and/or thermal perception threshold may be detected**
skin biopsy • A validated technique for determining intra-epidermal nerve fibre density. May be considered for the diagnosis of DN, particularly small-fibre neuropathy, when electrophysiology does not match clinical presentation.[72]	**may be normal or show abnormalities of intra-epidermal nerve fibre density**
cardiovascular reflex testing • Includes ECG recordings of R-R at rest and several standard clinical challenges. • The following are the ideal standard tests for clinical autonomic testing: HR response to deep breathing, standing, and Valsalva manoeuvre; and BP response to standing.[58] [59] [80] • HR response to deep breathing is measured while the patient is supine and then resting, breathing at 6 breaths per minute. The value of expiration-to-inspiration ratio of the R-R interval varies with age but is decreased compared with normal for the specific age band. • Various mathematical calculations may be used but age-adjusted normative ranges are strictly required for the interpretation of these tests. • The Valsalva manoeuvre is not advisable in the presence of proliferative retinopathy and when there is an increased risk of retinal haemorrhage. • Heart rate response to standing is measured by continuous ECG monitoring. The R-R interval is measured at 15 and 30 beats after standing. • These tests mainly demonstrate impaired parasympathetic tone in people with cardiovascular autonomic neuropathy.	**may be impaired heart rate response to deep breathing, Valsalva manoevre, and/or standing**

Test	Result
heart rate variability (HRV) • HRV can be assessed either by calculating indices based on statistical analysis of R-R intervals (time-domain analysis) or by spectral analysis (frequency-domain analysis) of an array.[58] [59] [60] [80] • QT prolongation is an independent predictor of death in diabetic patients and is weakly associated with measures of HRV.[81] [95]	**may be abnormal; QT prolongation may be present**
gastric emptying studies • Performed with double isotope scintigraphy. • Indicated in people who have symptoms/signs suggesting diabetic gastroparesis where the diagnosis is still in doubt.	**delayed solid phase emptying**
gastroduodenoscopy • Recommended along with other GI investigations (e.g., gastric emptying studies or gastric electrography) to exclude pyloric or other mechanical obstructions in people with suspected diabetic gastroparesis where the diagnosis is in doubt.	**may be normal or may demonstrate solid food residues**
surface electrogastrography • Currently only used as a research tool.	**detects abnormalities in GI pacemaking**
barium meal • Barium meal has a place in evaluating mucosal lesions or obstruction.	**excludes mucosal lesions or obstruction**
GI manometry • Manometry should be considered as a research technique to investigate gastric and intestinal motility.	**may indicate delay in gastric and intestinal motility**
hydrogen breath tests • Diarrhoea is evident in 20% of diabetic patients, particularly those with known autonomic dysfunction.[57] • Diarrhoea in diabetic patients is often due to bacterial overgrowth, which can be diagnosed with hydrogen breath tests. • Using non-radioactive 13C-acetate or -octanoic acid as a label; these are safe, inexpensive tests that correlate well with scintigraphy results.	**may be normal or may suggest bacterial overgrowth**
gastric ultrasonography • A non-invasive diagnostic method. • Two-dimensional ultrasound has been validated for measuring emptying of liquids and semi-solids. However, 3-dimensional ultrasound offers a more comprehensive imaging of the total stomach.	**may demonstrate delayed gastric emptying**
gastric MRI • Has been used to measure gastric emptying and motility with excellent reproducibility, but its use is limited to research purposes.	**may demonstrate delayed gastric emptying**
anorectal manometry • Indicated for evaluating sphincter tone and the rectal-anal-inhibitory reflex. • Distinguishes colonic hypomotility from rectosigmoid dysfunction causing outlet obstructive symptoms.	**may be normal or may suggest hypomotility**

Test	Result
faecal fat • For patients with large-volume diarrhoea, faecal fat should be checked and further studied with a 72-hour collection to rule out malabsorptive disorders. • If significant steatorrhoea, pancreatic function tests should be performed. • If coeliac disease is suspected (e.g., anaemia, chronic diarrhoea, distended abdomen, young age, history of type 1 diabetes), serum levels of coeliac disease antibody profile, including anti-transglutaminase and endomysial, are measured.	**may be normal or elevated (steatorrhoea)**
d-xylose test • Alternative or additional test to the faecal fat measurement that can be used to rule out malabsorptive disorders in people with large-volume diarrhoea.	**normal**
urine culture • Part of the assessment of people with symptoms of bladder dysfunction.	**normal**
cystometry, voiding cystometrogram • Used in addition to post-void urinary tract ultrasound to evaluate diabetic bladder dysfunction. • Residual volume and upper urinary tract dilation are assessed.	**may be normal or may suggest bladder dysfunction**
post-void urinary tract ultrasound • Used in addition to cystometry and voiding cystogram to evaluate diabetic bladder dysfunction. • Residual volume and upper urinary tract dilation are assessed.	**may be normal or may suggest bladder dysfunction**
video-urodynamics • The preferred investigation for invasive urodynamics in patients with neurogenic lower urinary tract dysfunction.[82]	**may be normal or may suggest bladder dysfunction**
measurement of nocturnal penile tumescence and of penile and brachial BP • To evaluate erectile dysfunction and penile vascular disease. • Measured with Doppler probes. • Allows calculation of the penile brachial pressure index.	**normal; penile vascular disease: penile brachial pressure index <0.7**
serum LH, testosterone, free testosterone, prolactin • Indicated in men with erectile dysfunction to rule out hypogonadism.	**normal**
sudomotor function tests • Tests may include quantitative sudomotor axon reflex test; sweat imprint; thermoregulatory sweat test; and sympathetic skin response. • Some devices can provide a quantitative assessment of sudomotor function using direct current stimulation and reverse iontophoresis. These devices measure the ability of sweat glands to release chloride ions in response to electrochemical activation by recording local skin conductance.[83] [96] [97] • These tests evaluate the extent, distribution, and location of deficits in sympathetic cholinergic function.[57] [83] • Performed in specialised units.	**may be normal or impaired**

Test	Result
scintigraphic studies • Quantitative scintigraphic assessment of sympathetic innervation of the human heart is possible using single photon emission computed tomography (SPECT) with 123I-meta-iodobenzylguanidine (MIBG), and positron emission tomography (PET) with 11C-meta-hydroxyephedrine. However, no standardised method or normative values exist, and available data on the reproducibility limits their use to research only.[58] [59] [80]	**may be normal or impaired**
assessment of sympathetic muscle activity • Sympathetic outflow, at rest and in response to various physiological pertubations, can be measured directly by microelectrodes inserted into a fascicle of a distal sympathetic nerve to the skin or muscle (muscle sympathetic nerve activity).[58] [59] [80] Used for research purposes only.	**may be normal or impaired**
cardiac vagal baroreflex sensitivity testing • May be used in research protocols to assess cardiac vagal and sympathetic baroreflex function.	**may be normal or impaired**
24-hour BP profile • Used for research purposes. Attenuation (non-dipping) and loss of BP nocturnal fall (reverse dipping) on ambulatory BP monitoring have been associated with cardiovascular autonomic neuropathy and are attributed to disruption of circadian variation in sympathovagal activity.[85] In diabetic patients, non-dipping and reverse dipping are independent predictors of cardiovascular events and the progression of diabetic nephropathy.	**attenuation (non-dipping) or loss of BP nocturnal fall (reverse dipping) on ambulatory BP monitoring may be present**
microneurography • Used for research purposes. This technique is based on recording electrical activity emitted by peroneal, tibial, or radial muscle sympathetic nerves and identifying sympathetic bursts. Fully automated sympathetic neurogram techniques provide a rapid and objective method that is minimally affected by signal quality and preserves beat-by-beat sympathetic neurograms.[86]	**may be normal or impaired**

Differential diagnosis

Condition	Differentiating signs / symptoms	Differentiating tests
Uraemia	• Various signs associated with the primary cause for end-stage renal disease (ESRD) may be present. • May co-exist with DN.	• Abnormal urea, creatinine, GFR consistent with ESRD.

Condition	Differentiating signs / symptoms	Differentiating tests
Cyanocobalamin deficiency	• Poor nutrition, alcoholism, certain drugs (e.g., trimethoprim, methotrexate, phenytoin), pernicious anaemia, atrophic gastritis, malabsorption, or infection with *Helicobacter pylori* more likely to be present. • Patients are more likely to be older (>65 years).	• FBC reveals macrocytic anaemia. • Reduced serum vitamin B12 levels.
Hypothyroidism	• Fatigue, cold intolerance, weight gain, constipation, myalgia, menstrual irregularities, delayed relaxation of deep tendon reflexes, bradycardia (if severe).	• TSH elevated in primary hypothyroidism. • Free serum T4 may be low.
Acute intermittent porphyria	• Abdominal pain, vomiting, muscle weakness, constipation, fever, diarrhoea, sensory loss, seizures, tachycardia, hypertension may all occur. • Abdominal pain is severe and more typical than in DN.	• Elevated aminolevulinic acid, porphobilinogen.
Chronic high alcohol intake	• Signs of malnutrition, Wernicke encephalopathy, and Korsakoff amnestic syndrome may be present.	• Severe cases present with associated anaemia, thiamine deficiency, and deranged LFTs.
Heavy metal poisoning	• May present with a peripheral neuropathy that frequently manifests with extensor weakness, or wrist/ ankle drop, due to an axonal degeneration, primarily affecting motor nerves. • Abdominal pain ('lead colic'), constipation, joint pains, muscle aches, headache, anorexia, decreased libido, difficulty concentrating and deficits in short-term memory, anaemia, nephropathy, and other symptoms and signs in various combinations.	• Abnormally high blood levels of lead or other metals.

Condition	Differentiating signs / symptoms	Differentiating tests
Drug-induced neuropathy	• Diabetes less likely and drug history likely to include a drug that is known to be a risk for development of neuropathy, such as (in descending order of likelihood of association) antivirals, antibacterials, antineoplastic and immunosuppressants, and cardiovascular, CNS, GI, and metabolism agents. • History may include the following specific drugs suspected of causing neuropathies: stavudine, didanosine, lamivudine, thalidomide, ritonavir, zalcitabine, and amiodarone.	• No differentiating investigations.
Chronic inflammatory demyelinating neuropathy (CIDP)	• People with diabetes may develop features of CIDP. • Severe, predominantly motor neuropathy that is progressive in nature. Features progress despite optimal glycaemic control.	• May be difficult to differentiate. • Nerve conduction studies show a combination of slowed conduction velocities, prolonged distal latencies, prolonged F-wave latencies, and conduction block in ≥1 nerves. • Nerve biopsies demonstrate increased numbers of macrophages. • Unusually high CSF protein.
Sarcoidosis	• Various signs, including fever, skin signs (e.g., erythema nodosum), joint and/or eye lesions.	• Chest x-ray may show bilateral hilar lymphadenopathy and pulmonary reticular opacities. • Biopsies of accessible lesions are diagnostic.
Leprosy	• Travel to or residence in endemic countries. • Nerves commonly involved include the ulnar and median (claw hand), the common peroneal (foot drop), the posterior tibial (claw toes and plantar insensitivity), facial, radial cutaneous, and great auricular.	• Skin smear is positive for acid fast bacilli (AFB). • Biopsy of lesions reveal the presence of AFB plus other associated signs.

Condition	Differentiating signs / symptoms	Differentiating tests
Polyarteritis nodosa (PAN)	• Systemic symptoms (e.g., fatigue, weakness, fever, arthralgias) and signs (e.g., hypertension, renal insufficiency, neurological dysfunction, abdominal pain) of multisystem involvement more likely.	• There is no diagnostic laboratory test for PAN. • Basic laboratory tests help ascertain the extent of organs affected and their degree of involvement.
Amyloidosis	• Muscle weakness and enlargement due to amyloid infiltration (myopathy), disorders of the joints (arthropathy), and lesions of bone (osteopathy) more likely to be present.	• Presence of a paraprotein in the serum (as an M protein on protein immunoelectrophoresis or immunofixation) or urine (as monoclonal light chains) in approximately 90% cases.
Dysproteinaemias and paraproteinaemias	• Possibly no differentiating signs or symptoms.	• Presence of a monoclonal protein in the serum or urine.
Paraneoplastic syndrome	• Varies, based on primary aetiology. • History of a primary neoplastic condition.	• Varies, based on primary aetiology.
Leukaemias and lymphomas	• Symptoms and signs vary but may include anaemia, fever, weight loss, and lymphadenopathy.	• Abnormal blood cell count and bone marrow aspirate. • Specific abnormalities are diverse depending on the type of leukaemia or lymphoma present.
Hereditary neuropathies (e.g., Charcot-Marie-Tooth disease)	• Both motor and sensory nerve manifestations are more common with distal leg weakness, foot deformities (pes cavus, hammer toes), and sensory deficits.	• Genetic testing is diagnostic.
Psychophysiological disorder	• May also present with pains and paraesthesias but without neurological deficit. • There is no sensory loss.	• Specific psychological evaluations help to confirm the diagnosis.
Multiple system atrophy/ Shy-Drager syndrome	• May present with symptoms and signs of autonomic neuropathy, as in DN. • May also have parkinsonism, varying degrees of dysautonomia, cerebellar involvement, and pyramidal signs.	• An excellent response to dopaminergic therapy is an important supportive feature for establishing the diagnosis.

Condition	Differentiating signs / symptoms	Differentiating tests
Riley-Day syndrome	• Progressive sensorimotor neuropathy but sympathetic autonomic dysfunction is responsible for most clinical manifestations (i.e., orthostatic hypotension, swallowing dysfunction, GI motility dysfunction, bladder dysfunction, decreased or absent tearing, pupil dilation, hypohidrosis, and episodic hyperhidrosis).	• Genetic evaluation is sensitive and specific for the diagnosis: a truncated form of I kappa B kinase complex associated protein (IKBKAP) mutation on chromosome 9q31.
Autonomic neuropathy: idiopathic orthostatic hypotension	• Severe postural dizziness and weakness.	• Reduction of systolic BP of at least 20 mmHg, or diastolic BP of at least 10 mmHg, within the first 3 minutes of standing.
Guillain-Barre syndrome	• Progressive, fairly symmetrical muscle weakness accompanied by absent or depressed deep tendon reflexes. • Weakness can vary from mild difficulty with walking to nearly complete paralysis of all extremity, facial, respiratory, and bulbar muscles.	• Albuminocytological dissociation in CSF (i.e., elevated protein with a normal WBC count), present in 80% to 90% patients at 1 week after onset of symptoms.
Myasthenia gravis	• Fluctuating degree and variable combination of weakness in ocular, bulbar, limb, and respiratory muscles.	• Antibodies against acetylcholine receptors or receptor associated proteins are present. • Tensilon test, ice pack test, repetitive nerve stimulation studies, and single-fibre electromyography assist in confirmation of the diagnosis.
Degenerative spinal disc disease	• May present with symptoms and signs of a femoral neuropathy, including asymmetrical pain weakness and sensory loss.	• MRI demonstrates specific vertebral disc pathology.
Femoral neuropathy: intrinsic spinal cord mass lesion	• May present with symptoms and signs of a femoral neuropathy, including asymmetrical pain, weakness, and sensory loss.	• MRI demonstrates the spinal cord mass.

Condition	Differentiating signs / symptoms	Differentiating tests
Cauda equina lesions	• May present with symptoms and signs of a femoral neuropathy, including weakness and sensory loss.	• Diagnosis usually confirmed by MRI.
Carotid aneurysm	• May present with symptoms and signs of a cranial neuropathy, including diplopia and Bell palsy.	• Magnetic resonance angiography and CT angiography confirm diagnosis.
Mononeuropathy multiplex: vasculitis	• May present with symptoms and signs including nerve damage in ≥2 named nerves in separate parts of the body. • Wrist drop, for example, is caused by infarction of the radial nerve, and foot drop by damage to either the sciatic or peroneal nerve.	• Vasculitis and lymphocytic infiltrates on nerve biopsies.
Acromegaly	• Very slow onset over decades. • Typical clinical phenotype, including acral and soft tissue overgrowth; enlargement of jaw, nose, frontal bones, hands, and feet; articular overgrowth.	• Abnormal IGF-1 levels. • Pituitary MRI may reveal pituitary tumour.
Coagulopathies	• May present with haemorrhages or thrombosis.	• Abnormal platelets, prothrombin time, D-dimer, fibrinogen, fibrin degradation products.

Diagnostic criteria

Toronto Expert Panel on Diabetic Neuropathy diagnostic criteria for distal symmetric polyneuropathy (DSPN)[4]

Possible clinical DSPN

- Presence of symptoms or signs of DSPN.
- Symptoms may include:
  - Decreased sensation
  - Positive neuropathic sensory symptoms (e.g., 'asleep numbness', 'prickling' or 'stabbing', 'burning', or 'aching' pain) predominantly in the toes, feet, or legs.
- Signs may include:
  - Symmetrical decrease of distal sensation

- Unequivocally decreased or absent ankle reflexes.

Probable clinical DSPN

- A combination of symptoms and signs of distal sensorimotor polyneuropathy with any 2 or more of the following:
  - Neuropathic symptoms
  - Decreased distal sensation
  - Unequivocally decreased or absent ankle reflexes.

Confirmed clinical DSPN

- An abnormal nerve conduction study, and a symptom or symptoms or a sign or signs of sensorimotor polyneuropathy.

Subclinical DSPN (stage 1a)

- No signs or symptoms of polyneuropathy
- Abnormal nerve conduction.

Toronto Expert Panel on Diabetic Neuropathy definition of small-fibre neuropathy[4]

Possible small-fibre neuropathy

- Presence of distal symmetrical symptoms, and/or clinical signs of small-fibre damage.

Probable small-fibre neuropathy

- Presence of distal symmetrical symptoms, clinical signs of small-fibre damage, and normal or abnormal sural nerve conduction (NC) study.

Definite small-fibre neuropathy

- Presence of length-dependent symptoms, clinical signs of small-fibre damage, normal or abnormal sural NC study, and/or abnormal quantitative sensory testing (QST) thermal thresholds at the foot and reduced intra-epidermal nerve fibre density (IENFD) at the ankle.

Skin biopsy is used for determining IENFD.[14] [72] [73] Nerve biopsy, due to its invasive and highly specialised nature, is not recommended for routine use. Corneal nerve fibre density assessed using corneal confocal microscopy has demonstrated sensitivity and specificity equivalent to IENFD for the diagnosis of diabetic peripheral neuropathy.[74] [98]

Step-by-step treatment approach

Treatment strategies for DN may be divided into those targeting the underlying pathogenic mechanisms, and those targeting the relief of symptoms.

The former is most challenging; the only demonstrated method available is tight glycaemic control in patients with type 1 diabetes. The latter comprises numerous symptomatic approaches. Specific symptomatic therapies are generally recommended, as they can improve the patient's quality of life.

All diabetic patients require regular foot inspection and care. Patients with peripheral neuropathy are particularly at risk of painless injuries so this is especially important. Those with concomitant nephropathy are at much higher risk of foot ulceration.

Patients with longer diabetes duration and more advanced stage of disease may present with a broad spectrum of symptoms and signs consistent with both distal symmetrical polyneuropathy and autonomic neuropathy. Therefore, they may require multiple therapeutic approaches. In such cases the treating physician should decide on the combination of agents that would best address the patient's specific deficits in the safest way, while avoiding most drug interactions.

Glycaemic control

The Diabetes Control and Complications Trial (DCCT) demonstrated that intensive therapy of type 1 diabetes reduced the incidence of neuropathy by 60% over a 5-year period in patients who did not have neuropathy at baseline.[8] [103] 1[A]Evidence Intensive therapy during the DCCT significantly reduced the risk of diabetic peripheral neuropathy (DPN) and cardiovascular autonomic neuropathy (CAN) at the end of the trial, and the prevalence and incidence of DPN and CAN remained significantly lower in the intensive therapy group compared with the conventional therapy group through the observational follow-up study in 2013-2014.[104]

There is some evidence for a reduction in risk of DN with optimal blood glucose control achieved using multiple insulin injections in people with type 2 diabetes, but the evidence is not as strong as that for type 1.4[B]Evidence One meta-analysis that included 17 randomised studies of patients with type 1 or type 2 diabetes found high-quality evidence that tight glucose control could prevent the development of DN and reduce the incidence of clinical neuropathy in people with type 1 diabetes.[33] In type 2 diabetes, enhanced glucose control had no impact on vibration perception threshold and failed to significantly reduce the incidence of clinical neuropathy.[33]

A more recent review that included additional data showed that implementing and maintaining tight glucose control as early as possible in type 1 diabetes prevents early neuropathy development and promotes long-term protection, especially for CAN. For type 2 diabetes the effects of glycaemic control on DPN or CAN are less clear, with earlier data suggesting that glucose control is beneficial in patients with fewer comorbidities if started earlier in the disease course, but later studies not confirming these findings.[54]

The type of glucose lowering approach may also have different effects on DPN. Among more than 2000 patients with type 2 diabetes followed for up to 4 years during the BARI 2D trial, glycaemic control therapy with insulin sensitisers (metformin and/or thiazolidinediones) significantly reduced the incidence of DPN compared with an insulin provider (sulfonylurea and/or insulin) therapy, especially in men.[19] Pancreatic transplantation appears to halt the progression of DN.[106] [107] Two studies have shown an improvement in corneal nerve parameters following simultaneous pancreas and kidney

transplantation.[91] [108] When treating painful neuropathy, maintaining stable blood glucose levels may provide symptom relief.[109]

Foot care

Proper care of the foot begins with educating the patient.[110] A thorough examination should include checking the peripheral pulses, as well as determining reflexes and sensation in the toes and feet.

Minor non-infected wounds can be treated with non-irritating antiseptic solution, daily dressing changes, and foot rest.[111] More serious problems are best handled in consultation with specialists in diabetic foot care.[70] [69]

A multidisciplinary approach and tailored strategies are recommended for individuals with foot ulcers and individuals with high-risk feet, especially those with a history of prior ulcer or amputation, those with Charcot foot, and dialysis patients.[55]

Most diabetic foot infections are polymicrobial; aerobic gram-positive cocci (GPC), most notably staphylococci, are the most common causative organisms. Aerobic gram-negative bacilli are frequent co-pathogens in chronic infections; obligate anaerobes may be co-pathogens in ischaemic or necrotic wounds. Wounds without evidence of soft tissue or bone infection do not require antibiotic therapy. Infected wounds should have a post-debridement specimen (preferably of tissue) sent for aerobic and anaerobic culture. Empiric antibiotic therapy can be targeted at gram-positive cocci in many acutely infected patients. Those at risk for infection with antibiotic-resistant organisms or those with chronic, previously treated, or severe infections usually require broader spectrum regimens.[70] [69]

Reducing plantar pressure by using contact casts and/or specialised footwear accelerates healing.[2] [112]

Lifestyle interventions

An observational study has found that diet and exercise can improve neuropathic symptoms and intra-epidermal nerve fibre density (IENFD) in patients with neuropathy and impaired glucose tolerance.[113] In another longitudinal study in patients with DPN, improvements in IENFD measures were found with a 10-week exercise programme of moderately intense aerobic and resistance training.[114]

Treatment of pain in peripheral neuropathy: initial treatment

Although there are effective treatments for painful DN, many of these therapies have adverse effects, or have only limited evidence for their effect in terms of functional improvement and improvement in quality of life.[115]

The American Academy of Neurology (AAN), the American Association of Neuromuscular and Electrodiagnostic Medicine, and the American Academy of Physical Medicine and Rehabilitation have recommended pregabalin as first-line therapy.[115] Gabapentin, duloxetine, amitriptyline, venlafaxine, opioids (morphine sulfate, tramadol, and oxycodone controlled-release), valproate, and capsaicin were considered to be second-line therapies.[115]

A systematic review and meta-analysis of pharmacotherapy for neuropathic pain by the Neuropathic Pain Special Interest Group (NeuPSIG) resulted in a strong recommendation for first-line treatment with tricyclic antidepressants, serotonin-noradrenaline reuptake inhibitors, pregabalin, and gabapentin; a weak recommendation for lidocaine patches, capsaicin high-concentration patches, and tramadol; and a weak recommendation for strong opioids and botulinum toxin as third-line agents.[116]

Pregabalin

- Is approved for treatment of painful diabetic neuropathy in some countries.
- Binds to and modulates voltage-gated calcium channels.
- Is a more potent regulator of calcium channels than gabapentin (it is this mode of action that may modulate neuropathic pain).
- Has been found to be significantly effective in decreasing mean pain score in people with painful DN compared with placebo.[117] [118] [119] 5[B]Evidence
- Can cause somnolence and pedal oedema.
- Unlike gabapentin, pregabalin may possibly be habit forming.

Gabapentin

- Has been found to improve pain in people with DN in several studies.[121] [122] [123] [124]
- It is not approved in some countries for the treatment of painful diabetic neuropathy, but is widely used.
- May have adverse effects that require discontinuation of therapy. These include somnolence, dizziness, peripheral oedema, and gait disturbance.[124]

Duloxetine

- Is approved in some countries for use in painful DN.
- Clinical studies have shown it to be safe and effective in the management of painful DN.[125] [126] [127] [128] [129] [130] 6[B]Evidence
- Is a selective dual serotonin-noradrenaline reuptake inhibitor, and is relatively balanced in its affinity for reuptake inhibition.
- Nausea can occur but slow-dose titration of the drug and taking it with food can usually reduce or avoid this common adverse effect.
- Somnolence may also occur. [132]

- Pregabalin or gabapentin may be combined with duloxetine if necessary. Few direct head-to-head comparisons have been conducted between drugs for the treatment of DN pain.[133] 7[B]Evidence

Combination treatment

- A multicentre, double-blind, parallel-group study in patients with DPN pain addressed whether, in patients not responding to monotherapy with standard doses of duloxetine or pregabalin, combining both medications was superior to increasing each drug to its maximum recommended dose. In an 8-week combination versus high-dose therapy period, non-responders to monotherapy (n=339) received either maximum dose of duloxetine, a combination of standard doses of duloxetine and pregabalin, or a maximum dose of pregabalin. Both drugs and their combination were well tolerated. Although not significantly superior to high-dose monotherapy, combination therapy was considered to be effective, safe, and well tolerated.[134]
- A combination of imipramine and pregabalin could be considered as an alternative to high-dose monotherapy. In one randomised controlled trial, combination therapy with imipramine and pregabalin significantly lowered pain scores compared with either agent alone, but was associated with a higher dropout rate and a higher rate and severity of side effects.[135]

Tricyclic antidepressants (TCAs)

- Act by blocking neuronal reuptake of noradrenaline and serotonin, thereby potentiating the inhibitory effect of these neurotransmitters in nociceptive pathways.[136]
- Amitriptyline, imipramine, and desipramine all relieved pain more effectively than placebo in small RCTs of patients with DN.8[C]Evidence
- TCA efficacy was demonstrated in a meta-analysis of 21 clinical trials.[142]
- Adverse effects are common with TCAs and may lead to treatment withdrawal. In clinical trials of TCAs, approximately 20% participants withdrew because of intolerable adverse effects, such as sedation, confusion, and anticholinergic adverse effects.
- Commonly used TCAs may be ranked in order of greatest to least risk of anticholinergic effects: amitriptyline; imipramine; nortriptyline; and desipramine.[143]
- Cochrane reviews do not support the use of amitriptyline, nortriptyline, imipramine, or desipramine as first-line treatments for painful diabetic neuropathy.[144] [145] [146] [147] Studies assessing the efficacy of these agents were methodologically flawed and potentially subject to major bias.

Other antidepressants

- Selective serotonin-reuptake inhibitors (SSRIs) may have some efficacy for DN.
- A 2015 Cochrane review found little compelling evidence to support the use of venlafaxine in neuropathic pain.[148]
- Paroxetine has been found to reduce symptoms.9[C]Evidence
- Fluoxetine was effective only in patients who were depressed.[137]
- Sertraline reduced pain from DN in a small open-label study of 8 patients, but a placebo-controlled study has yet to be performed.[150]

Opioid anlagesics

- Used for the treatment of neuropathic pain.[151] [152] [153]
- May be considered either in combination with existing therapies or for use alone.
- Have significant adverse effects with long-term use; dependence may occur.
- Suppress pain by activating mu-receptors present on the pre- and post-synaptic membranes of primary afferent nerve fibres; second-order neurons in the dorsal horn of the spinal cord; and neurons in pain-relevant supraspinal centres.
- Tramadol (a weak opioid) has been found to be effective in treatment of DN pain.10[B]Evidence It may be used to manage breakthrough or refractory pain.
- Tapentadol has been shown to be effective and well tolerated for the management of DPN.[155]
- A Cochrane review of short-term and intermediate-term studies found that the analgesic efficacy of opioids in chronic neuropathic pain is still uncertain.[156]
- One small crossover study found that oxycodone was superior to placebo in the treatment of DN,11[C]Evidence but there is no convincing, unbiased evidence that oxycodone is of value in treating people with painful DN.[157]

Topical capsaicin

- May be used alone or in combination with other therapies for refractory pain.
- Capsaicin stimulates the release and depletion of substance P from sensory nerve fibres.
- Capsaicin cream (0.1 %) has been shown to cause a loss of intra-epidermal nerve fibres and thermal sensation, which does not recover for approximately 150 days.[158] There are no published data on the effect of high concentration topical capsaicin (8% patch) on cutaneous nerve fibres.

It is the opinion of the authors that capsaicin 8 % patches should not be considered for the management of painful diabetic neuropathy.

- A few small studies have demonstrated the efficacy of topical capsaicin in control of pain and improvement in daily activities.[159] [160] [161] [162] [163]
- Poor adherence is common, due to the need for frequent applications, an initial exacerbation of symptoms, and frequent burning and redness at the application site.

Transcutaneous electrical nerve stimulation (TENS), percutaneous electrical nerve stimulation (PENS), or acupuncture

- May be added to existing therapy or used alone, in refractory cases.[164]
- In a controlled study, TENS was more effective than sham treatment in reducing pain in patients with DN.[165]
- In uncontrolled studies of TENS and acupuncture, they decreased pain in >75% patients with DN.[166] [167]
- A report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology, based on a review of the literature up to April 2009, concluded that TENS may have some effectiveness for reducing pain caused by DPN.[164]
- The UK National Institute for Health and Care Excellence found evidence of short-term efficacy of PENS for refractory neuropathic pain with no major safety concerns. Treatment with PENS should involve specialists in pain management.[168]

Spinal cord stimulation

- Should be considered in patients refractory to all other treatment options for severe painful diabetic neuropathy.[169] [170]

Cranial neuropathies, limb mononeuropathies, truncal mononeuropathy, diabetic amyotrophy

There is no specific treatment for cranial neuropathies, although gradual recovery typically occurs. There is also no specific treatment for abrupt limb neuropathies, although some have advocated immunomodulatory therapy when there is multi-nerve involvement.

Once structural abnormalities have been ruled out, treatment for diabetic truncal mononeuropathy consists of pain management. Improvement is generally gradual.

Typically, no treatment is given for diabetic amyotrophy, other than improving glycaemic control. However, patients with inflammatory changes on biopsy may respond to immunomodulation.[171]

Autonomic neuropathy

Control of hyperglycaemia has been shown to delay the onset and progression of autonomic neuropathy in type 1 diabetes and possibly in type 2 diabetes.[8] [103] [172] [173] 12[A]Evidence Studies have shown that implementing tight glucose control as early as possible in the treatment of type 1 diabetes prevents early development of CAN and promotes long-term protection for CAN, but the effects of glycaemic control on CAN are less clear for type 2 diabetes.[54]

The following are various manifestations of autonomic neuropathy and the treatments are discussed.

Management of orthostatic hypotension

Simple lifestyle and supportive measures include:[22] [58] [59]

- Avoiding sudden changes in body posture to the head-up position
- Avoiding medications that aggravate hypotension
- Eating small, frequent meals; avoiding a low-salt diet; adequate fluid intake
- Avoiding activities that involve straining
- Elevating the head of the bed 45 cm (18 inches) at night. This improved symptoms in a small series of patients with orthostatic hypotension from various causes[174]
- Using a compressive garment over the legs and abdomen. Case reports suggest that this approach may be of benefit [175] [176] [177] [178]
- Using an inflatable abdominal band. This was effective in a study of 6 patients with orthostatic hypotension[179]
- Using a low portable chair, as needed for symptoms. This was effective in one study.[180]

Several physical counter-manoeuvres, such as leg crossing, squatting, and muscle pumping, can help maintain BP.[181]

Pharmacological therapy is likely to be required. In some countries, midodrine is the only approved drug for the treatment of orthostatic hypotension, although, in practice, fludrocortisone is frequently used first.

Fludrocortisone

- A synthetic mineralocorticoid, with a long duration of action, which induces plasma expansion. It may also enhance the sensitivity of blood vessels to circulating catecholamines.[182] [183]
- The earliest report described a single patient, and other case reports have followed.[184] [185] [186]
- The effects are not immediate, but occur over a 1- to 2-week period.
- Supine HTN, hypokalaemia, and hypomagnesaemia may occur.
- Caution must be used, particularly in patients with CHF, to avoid fluid overload.[187] [188]

Midodrine[22] [58] [59]

- A peripheral-selective direct alpha-1-adrenoreceptor agonist, and the only agent approved for the treatment of orthostatic hypotension in some countries.
- Activates alpha-1 receptors on arterioles and veins, thereby increasing total peripheral resistance.[189] [190]
- Several double blind, placebo-controlled studies have documented its efficacy in the treatment of orthostatic hypotension.[191] [192] [193]
- Because it does not cross the blood-brain barrier, it has fewer central adverse effects than ephedrine. The main adverse effects are piloerection, pruritus, paraesthesias, urinary retention, and supine HTN.

Mixed alpha-adrenoreceptor agonists, which act directly on the alpha-adrenoreceptor and release noradrenaline from the post-ganglionic sympathetic neuron, include:

- Ephedrine
- Pseudoephedrine.[194]

Severe HTN is an important adverse effect of all sympathomimetic agents. Other adverse effects, which may limit their use, are tremulousness, irritability, insomnia, tachycardia, reduced appetite, and, in men, urinary retention.[195]

Erythropoietin[22] [58] [59]

- Improves standing BP in patients with orthostatic hypotension.[57]
- The mechanism of action for the pressor effect is still unresolved. Possibilities include increase in red cell mass and central blood volume; correction of the normochromic normocytic anaemia that frequently accompanies diabetic autonomic neuropathy; alterations in blood viscosity; and a direct or indirect neurohumoral effect on the vascular wall and vascular tone regulation, which are mediated by the interaction between haemoglobin and the vasodilator nitric oxide.[196] [197] [198]

Clonidine

- An alpha-2 antagonist that usually produces a central sympatholytic effect, and a consequent decrease in BP.
- Patients with severe autonomic failure have little central sympathetic efferent activity, and clonidine may affect venous postsynaptic alpha-2 adrenoreceptors.
- The use of this agent is limited by the inconsistent hypertensive effect, as well as serious adverse effects.
- Clonidine could result in an increase in venous return without a significant increase in peripheral vascular resistance.

Octreotide[22] [58] [59]

- May attenuate the postprandial BP fall and reduce orthostatic hypotension in patients with autonomic failure.
- Mechanisms of action include a local effect on splanchnic vasculature, by inhibiting the release of vasoactive GI peptides; enhanced cardiac output; and an increase in forearm and splanchnic vascular resistance.

Management of diabetic gastroparesis

Some treatments for diabetic gastroparesis are based on commonly accepted clinical practices. These include:[88]

- Eating multiple small meals.
- Changing diet, such as decreasing dietary fat and fibre.[199] [200] [201]

Drug therapy includes:

- Erythromycin
- Metoclopramide
- Domperidone
- Botulinum toxin.

Erythromycin

- Is effective in accelerating gastric emptying.13[B]Evidence
- Is believed to act by stimulating motilin receptors in the gut.[203]

- May be used orally, but intravenous administration has been found to be more effective.[204] [205]

Metoclopramide

- Has anti-emetic properties, stimulates acetylcholine release in the myenteric plexus, and is a dopamine antagonist.[201]
- Open, single-blind, and double-blind trials have shown mild benefit.[202]
- Possible adverse effects include extrapyramidal symptoms, such as acute dystonic reactions; drug-induced parkinsonism; akathisia; and tardive dyskinesia. Galactorrhoea, amenorrhoea, gynaecomastia, and hyperprolactinaemia may also occur.
- Metoclopramide should be used for up to 5 days only in order to minimise the risk of neurological and other adverse effects.[206] Its use in the long-term treatment of gastroparesis is no longer recommended. It should be reserved for short-term use in severe cases that are unresponsive to other therapies.

Domperidone

- Is a peripheral dopamine receptor antagonist.
- Has been shown to stimulate gastric motility and to possess anti-emetic properties. It acts as a prokinetic agent, increasing the number and/or the intensity of gastric contractions, and improves symptoms in patients with diabetic gastroparesis.
- Stimulates both liquid- and solid-phase gastric emptying.[207]
- Its major benefit results from its anti-emetic properties and, to a lesser extent, its motor stimulatory actions.[208]
- A few open trials and double-blind trials have all demonstrated improvement in gastric emptying.[202] [208]
- A systematic review of all studies using oral domperidone for the treatment of diabetic gastroparesis demonstrates the efficacy of domperidone in treating gastroparesis.[209]
- Its role has become controversial due to safety concerns. Following a European review, the Medicines and Healthcare products Regulatory Agency and the European Medicines Agency have issued new recommendations concerning the use of domperidone. The review found the drug was associated with a small increased risk of potentially life-threatening effects on the heart. As a consequence, the agencies recommend that domperidone should only be used for the treatment of symptoms of nausea and vomiting and is no longer recommended for the treatment of conditions such as heartburn, bloating, or stomach discomfort. The risks and benefits should be weighed carefully before using this drug for this off-label indication. It should be used at the lowest effective dose for the shortest possible duration and the maximum treatment duration should not usually exceed 1 week. The new maximum dose recommended in adults is 30 mg/day. Domperidone is contraindicated in patients with severe hepatic impairment or underlying cardiac disease. It should not be administered with other drugs that prolong the QT interval or inhibit CYP3A4.[210] Domperidone is no longer available without a prescription in the UK.

Intrapyloric botulinum toxin injection

- Several case reports of patients with severe diabetic gastroparesis, whose symptoms persisted despite dietary changes and the use of high-dose prokinetic agents, describe significant symptomatic improvement after intrapyloric botulinum toxin injection, performed during upper GI endoscopy.[211] [212] [213]

Non-pharmacological methods have been used to treat diabetic gastroparesis in patients unresponsive to pharmacotherapy.

Gastric pacing (stimulation)

- Short-term studies of gastric pacing in humans have demonstrated that it is possible to entrain gastric slow waves and normalise myoelectrical activity with pacing.[214] [215]
- Uses high-frequency, low-amplitude signals that do not alter gastric myoelectrical or muscular activity
- Improvements in nausea and vomiting with gastric stimulation in people with gastroparesis have been reported.14[C]Evidence

Surgery

- Persistent vomiting may require placement of a feeding jejunostomy to bypass an atonic stomach.[201]
- Radical surgery, consisting of resection of a large portion of the stomach, with performance of a Roux-en-Y loop was successful in a small series of patients.[50]

Management of diabetic diarrhoea

Broad-spectrum antibiotics are commonly used to treat diabetic diarrhoea, either when the hydrogen breath test is positive, or as an empirical trial.[88] An early double-blind study, involving a single patient, found that diarrhoea subsided when the patient was treated with an oral antibiotic preparation, then recurred when placebo was substituted.[217] Several different regimens have been advocated.[199] [200] [201] Caution must be used because long-term use of metronidazole can lead to neuropathy.

Colestyramine can be used in an attempt to chelate bile salts if the hydrogen breath test is normal, or if patients fail an empirical trial of broad-spectrum antibiotics.

Octreotide was effective in a case report of a single patient with diabetic diarrhoea.[218] In healthy volunteers, octreotide improved gastric, small bowel, and colonic transit, and colonic motility and tone.[219] Octreotide may be considered for the management of diabetic diarrhoea when other approaches have failed.

Management of diabetic bladder dysfunction

Bethanechol, a parasympathomimetic agent, may be helpful. Bladder training, such as scheduled voiding, may be used particularly for urge incontinence. The Crede manoeuvre may also be used. This method helps to empty the bladder if it is weak and flaccid. The patient pushes with a hand down on the abdomen from the umbilicus towards the bladder in a smooth even manner.[88]

Management of diabetic erectile dysfunction

The first-line therapy for erectile dysfunction (ED) is a phosphodiesterase-5 (PDE-5) inhibitor.[220] PDE-5 inhibitors revolutionised the management of ED and are efficient and safe. Both sildenafil and tadalafil significantly increase erectile function and are generally well tolerated.[221] [222] However, adverse effects may occur, with headache and flushing the most commonly reported. Flu-like syndromes, dyspepsia, myalgias, abnormal vision, and back pain may occur less frequently.

The second-line option for treatment of ED is intracavernosal injection. The success rate of intracavernosal injections is high, with nearly 90% of patients achieving erection.[223] [224]

Other options that may be considered include vacuum devices and penile prostheses. Several case reports have described the use of vacuum devices, rigid penile implants, and inflatable prostheses for the treatment of erectile dysfunction.[224] [225]

If suspected, hypogonadism should be investigated and treated as necessary. Removal of medication exacerbating erectile dysfunction, management of associated comorbidities, and lifestyle modifications are essential in all patients.

As ED and diabetes can negatively impact male self-esteem and be associated with depression and anxiety, psychological assessment and appropriate treatment of patients affected is also likely to be beneficial.

Treatment details overview

Consult your local pharmaceutical database for comprehensive drug information including contraindications, drug interactions, and alternative dosing. (see Disclaimer)

Ongoing (summary)

Patient group	Tx line	Treatment
without pain	1st	glycaemic control and supportive measures
with pain	1st	pregabalin or gabapentin and/or duloxetine plus glycaemic control and supportive measures
with pain	2nd	antidepressant plus glycaemic control and supportive measures
with pain	3rd	opioid analgesic plus glycaemic control and supportive measures
with pain	4th	topical capsaicin plus glycaemic control and supportive measures
with pain	5th	TENS, PENS, or acupuncture plus glycaemic control and supportive measures
with pain	6th	spinal cord stimulation plus glycaemic control and supportive measures
cranial neuropathies	1st	glycaemic control and supportive measures
limb or truncal mononeuropathies	1st	glycaemic control and supportive measures

Ongoing (summary)

diabetic amyotrophy	1st	glycaemic control and supportive measures
orthostatic hypotension	1st	simple non-pharmacological measures plus midodrine plus glycaemic control and supportive measures
orthostatic hypotension	2nd	simple non-pharmacological measures plus mixed alpha-adrenoreceptor agonist plus glycaemic control and supportive measures
orthostatic hypotension	3rd	simple non-pharmacological measures plus mineralocorticoid plus glycaemic control and supportive measures
orthostatic hypotension	4th	simple non-pharmacological measures plus other pharmacological treatments plus glycaemic control and supportive measures
diabetic gastroparesis	1st	pharmacological methods plus glycaemic control and supportive measures
diabetic gastroparesis	plus	lifestyle measures
diabetic gastroparesis	2nd	non-pharmacological methods plus glycaemic control and supportive measures
diabetic gastroparesis	plus	lifestyle measures
diabetic diarrhoea	1st	broad-spectrum antibiotics plus glycaemic control and supportive measures
diabetic diarrhoea	2nd	colestyramine plus glycaemic control and supportive measures
diabetic diarrhoea	3rd	octreotide plus glycaemic control and supportive measures
bladder dysfunction	1st	bethanechol plus glycaemic control and supportive measures
bladder dysfunction	adjunct	bladder hygiene techniques
erectile dysfunction	1st	PDE-5 inhibitor plus glycaemic control and supportive measures
erectile dysfunction	adjunct	non-pharmacological methods

Treatment options

Ongoing

Patient group	Tx line	Treatment
without pain	1st	**glycaemic control and supportive measures** » There is some evidence for a reduction in risk of DN with optimal blood glucose control achieved using multiple insulin injections in people with type 2 diabetes, but the evidence is not as strong as that for type 1 diabetes.4[B]Evidence » Lifestyle interventions (diet and exercise) are recommended as they may improve neuropathic symptoms and intra-epidermal nerve fibre density in patients with neuropathy and impaired glucose tolerance.[113] [114] » Proper care of the foot begins with educating the patient.[110] Minor non-infected wounds without evidence of soft-tissue or bone infection do not require antibiotic therapy. More serious problems are best handled in consultation with specialists in diabetic foot care.[69] [70]
with pain	1st	**pregabalin or gabapentin and/or duloxetine plus glycaemic control and supportive measures** » Pregabalin has been found to decrease mean pain score in people with painful DN.[117] [118] [119] 5[B]Evidence Unlike gabapentin, pregabalin may possibly be habit forming. » The American Academy of Neurology, the American Association of Neuromuscular and Electrodiagnostic Medicine, and the American Academy of Physical Medicine and Rehabilitation have recommended that pregabalin should be offered for the relief of peripheral DN because its effectiveness has been firmly established.[115] » Gabapentin has been found to improve pain in people with DN in several studies.[121] [122] [123] [124] Adverse effects include somnolence, dizziness, peripheral oedema, and gait disturbance. » Initial clinical studies of duloxetine have found that it is safe and effective in the management of painful DN.[125] [126] [127] [128] [129] [130] 6[B]Evidence Duloxetine may be used alone or added to either pregabalin or gabapentin.[134]

Ongoing

Patient group	Tx line	Treatment
		» Nausea can occur but slow-dose titration and taking the drug with food can usually reduce or avoid this common adverse effect. Somnolence may also occur.[132]
		» There is some evidence for a reduction in risk of DN with optimal blood glucose control achieved using multiple insulin injections in people with type 2 diabetes, but the evidence is not as strong as that for type 1 diabetes.4[B]Evidence
		» Lifestyle interventions (diet and exercise) are recommended as they may improve neuropathic symptoms and intra-epidermal nerve fibre density in patients with neuropathy and impaired glucose tolerance.[113] [114]
		» Proper care of the foot begins with educating the patient.[110] Minor non-infected wounds without evidence of soft-tissue or bone infection do not require antibiotic therapy. More serious problems are best handled in consultation with specialists in diabetic foot care.[69] [70]
		Primary options
		» pregabalin: 50-100 mg orally three times daily initially, increase gradually according to response, maximum 600 mg/day
		OR
		Primary options
		» gabapentin: 300 mg orally three times daily initially, increase by 300 mg/day increments at weekly intervals according to response, maximum 3600 mg/day
		OR
		Primary options
		» duloxetine: 60 mg orally once daily
		OR
		Primary options
		» pregabalin: 50-100 mg orally three times daily initially, increase gradually according to response, maximum 600 mg/day **-and-** » duloxetine: 60 mg orally once daily
		OR

Ongoing

Patient group	Tx line	Treatment
		Secondary options » gabapentin: 300 mg orally three times daily initially, increase by 300 mg/day increments at weekly intervals according to response, maximum 3600 mg/day **-and-** » duloxetine: 60 mg orally once daily
with pain	**2nd**	**antidepressant plus glycaemic control and supportive measures** » Antidepressants may be used if there is no benefit from pregabalin or gabapentin and duloxetine. » They may be used alone or in combination with pregabalin or gabapentin. » Amitriptyline, imipramine, and desipramine all relieved pain more effectively than placebo in small RCTs of patients with DN.8[C]Evidence » Tricyclic antidepressant (TCA) efficacy was demonstrated in a meta-analysis of 21 clinical trials.[142] » In clinical trials of TCAs, approximately 20% participants withdrew because of intolerable adverse effects, such as sedation, confusion, and anticholinergic adverse effects. » Cochrane reviews do not support the use of amitryptyline, nortriptyline, imipramine, or desipramine as first-line treatments for painful DN.[144] [145] [146] [147] Studies assessing the efficacy of these agents were methodologically flawed and potentially subject to major bias. » A 2015 Cochrane review found little compelling evidence to support the use of venlafaxine in neuropathic pain.[148] » Paroxetine has been found to reduce symptoms.9[C]Evidence » There is some evidence for a reduction in risk of DN with optimal blood glucose control achieved using multiple insulin injections in people with type 2 diabetes, but the evidence is not as strong as that for type 1 diabetes.4[B]Evidence » Lifestyle interventions (diet and exercise) are recommended as they may improve neuropathic symptoms and intra-epidermal nerve fibre

Ongoing

Patient group	Tx line	Treatment
		density in patients with neuropathy and impaired glucose tolerance.[113] [114] » Proper care of the foot begins with educating the patient.[110] Minor non-infected wounds without evidence of soft-tissue or bone infection do not require antibiotic therapy. More serious problems are best handled in consultation with specialists in diabetic foot care.[69] [70] **Primary options** » amitriptyline: 10-25 mg orally once daily at bedtime initially, increase according to response, maximum 150 mg/day **OR** **Primary options** » venlafaxine: 75-225 mg orally (extended-release) once daily **OR** **Primary options** » imipramine: 10-25 mg orally once daily at bedtime initially, increase according to response, maximum 150 mg/day **OR** **Primary options** » nortriptyline: 10-25 mg orally once daily at bedtime initially, increase according to response, maximum 150 mg/day **OR** **Primary options** » desipramine: 25-75 mg orally once daily initially, increase dose according to response, maximum 150 mg/day **OR** **Secondary options** » paroxetine: 40 mg orally once daily
with pain	**3rd**	**opioid analgesic plus glycaemic control and supportive measures** » Opioid analgesics may be considered, either in combination with existing therapies or for use alone.

Ongoing

Patient group	Tx line	Treatment
		» They have significant adverse effects with long-term use; dependence may occur. » Tramadol (a weak opioid) has been found to be effective in treatment of pain in DN.10[B]Evidence It may be used to manage breakthrough or refractory pain. » Tapentadol has been shown to be effective and well tolerated for the management of diabetic peripheral neuropathy.[155] » One small crossover study found that oxycodone was superior to placebo in the treatment of DN,11[C]Evidence but there is no convincing, unbiased evidence that oxycodone is of value in treating people with painful diabetic neuropathy.[157] » There is some evidence for a reduction in risk of DN with optimal blood glucose control achieved using multiple insulin injections in people with type 2 diabetes, but the evidence is not as strong as that for type 1 diabetes.4[B]Evidence » Lifestyle interventions (diet and exercise) are recommended as they may improve neuropathic symptoms and intra-epidermal nerve fibre density in patients with neuropathy and impaired glucose tolerance.[113] [114] » Proper care of the foot begins with educating the patient.[110] Minor non-infected wounds without evidence of soft-tissue or bone infection do not require antibiotic therapy. More serious problems are best handled in consultation with specialists in diabetic foot care.[69] [70] **Primary options** » tapentadol: 50-250 mg orally (extended-release) twice daily **OR** **Primary options** » tramadol: 50-100 mg orally every 4-6 hours when required, maximum 400 mg/day **OR** **Primary options** » oxycodone: 10 mg orally (controlled-release) every 12 hours when required

TREATMENT

Ongoing

Patient group	Tx line	Treatment
with pain	4th	**topical capsaicin plus glycaemic control and supportive measures** » Topical capsaicin may be used alone or in combination with other therapies for refractory pain. » A few small studies have demonstrated the effectiveness of topical capsaicin in control of pain and improvement in daily activities.[159] [160] [161] [162] [163] » Poor adherence is common, due to the need for frequent applications, an initial exacerbation of symptoms, and frequent burning and redness at the application site. » There is some evidence for a reduction in risk of DN with optimal blood glucose control achieved using multiple insulin injections in people with type 2 diabetes, but the evidence is not as strong as that for type 1 diabetes.4[B]Evidence » Lifestyle interventions (diet and exercise) are recommended as they may improve neuropathic symptoms and intra-epidermal nerve fibre density in patients with neuropathy and impaired glucose tolerance.[113] [114] » Proper care of the foot begins with educating the patient.[110] Minor non-infected wounds without evidence of soft-tissue or bone infection do not require antibiotic therapy. More serious problems are best handled in consultation with specialists in diabetic foot care.[69] [70] **Primary options** » capsaicin topical: (0.025% or 0.075%) apply to the affected area(s) up to four times daily when required
with pain	5th	**TENS, PENS, or acupuncture plus glycaemic control and supportive measures** » Transcutaneous electrical nerve stimulation (TENS) or acupuncture may be added to existing therapy or used alone in refractory cases.[164] » In a controlled study, TENS was more effective than sham treatment in reducing pain in patients with DN.[165]

Ongoing

Patient group	Tx line	Treatment
		» Uncontrolled studies of TENS and of acupuncture have been reported to decrease pain in >75% patients with DN.[166] [167] » The UK National Institute for Health and Care Excellence found evidence of short-term efficacy of percutaneous electrical nerve stimulation (PENS) for refractory neuropathic pain with no major safety concerns. Treatment with PENS should involve specialists in pain management.[168] » There is some evidence for a reduction in risk of DN with optimal blood glucose control achieved using multiple insulin injections in people with type 2 diabetes, but the evidence is not as strong as that for type 1 diabetes.4[B]Evidence » Lifestyle interventions (diet and exercise) are recommended as they may improve neuropathic symptoms and intra-epidermal nerve fibre density in patients with neuropathy and impaired glucose tolerance.[113] [114] » Proper care of the foot begins with educating the patient.[110] Minor non-infected wounds without evidence of soft-tissue or bone infection do not require antibiotic therapy. More serious problems are best handled in consultation with specialists in diabetic foot care.[69] [70]
with pain	**6th**	**spinal cord stimulation plus glycaemic control and supportive measures** » Should be considered in patients refractory to all other treatment options for severe painful diabetic neuropathy.[169] [170] » There is some evidence for a reduction in risk of DN with optimal blood glucose control achieved using multiple insulin injections in people with type 2 diabetes, but the evidence is not as strong as that for type 1 diabetes.4[B]Evidence » Lifestyle interventions (diet and exercise) are recommended as they may improve neuropathic symptoms and intra-epidermal nerve fibre density in patients with neuropathy and impaired glucose tolerance.[113] [114] » Proper care of the foot begins with educating the patient.[110] Minor non-infected wounds without evidence of soft-tissue or bone infection do not require antibiotic therapy. More serious

Ongoing

Patient group	Tx line	Treatment
		problems are best handled in consultation with specialists in diabetic foot care.[69] [70]
cranial neuropathies	**1st**	**glycaemic control and supportive measures** » There is no specific treatment, although gradual recovery typically occurs. » There is some evidence for a reduction in risk of DN with optimal blood glucose control achieved using multiple insulin injections in people with type 2 diabetes, but the evidence is not as strong as that for type 1 diabetes.4[B]Evidence » Lifestyle interventions (diet and exercise) are recommended as they may improve neuropathic symptoms and intra-epidermal nerve fibre density in patients with neuropathy and impaired glucose tolerance.[113] [114] » Proper care of the foot begins with educating the patient.[110] Minor non-infected wounds without evidence of soft-tissue or bone infection do not require antibiotic therapy. More serious problems are best handled in consultation with specialists in diabetic foot care.[69] [70]
limb or truncal mononeuropathies	**1st**	**glycaemic control and supportive measures** » There is no specific treatment for abrupt limb mononeuropathies, though some have advocated immunomodulatory therapy when there is multi-nerve involvement. » Once structural abnormalities have been ruled out, treatment for diabetic truncal mononeuropathy consists of pain management. Improvement is generally gradual. » There is some evidence for a reduction in risk of DN with optimal blood glucose control achieved using multiple insulin injections in people with type 2 diabetes, but the evidence is not as strong as that for type 1 diabetes.4[B]Evidence » Lifestyle interventions (diet and exercise) are recommended as they may improve neuropathic symptoms and intra-epidermal nerve fibre

Ongoing

Patient group	Tx line	Treatment
		density in patients with neuropathy and impaired glucose tolerance.[113] [114] » Proper care of the foot begins with educating the patient.[110] Minor non-infected wounds without evidence of soft-tissue or bone infection do not require antibiotic therapy. More serious problems are best handled in consultation with specialists in diabetic foot care.[69] [70]
diabetic amyotrophy	**1st**	**glycaemic control and supportive measures** » Typically, no treatment is given for diabetic amyotrophy, other than improving glycaemic control. » However, patients with inflammatory changes on biopsy may respond to immunomodulation.[171] » There is some evidence for a reduction in risk of DN with optimal blood glucose control achieved using multiple insulin injections in people with type 2 diabetes, but the evidence is not as strong as that for type 1 diabetes.4[B]Evidence » Lifestyle interventions (diet and exercise) are recommended as they may improve neuropathic symptoms and intra-epidermal nerve fibre density in patients with neuropathy and impaired glucose tolerance.[113] [114] » Proper care of the foot begins with educating the patient.[110] Minor non-infected wounds without evidence of soft-tissue or bone infection do not require antibiotic therapy. More serious problems are best handled in consultation with specialists in diabetic foot care.[69] [70]
■ **orthostatic hypotension**	**1st**	**simple non-pharmacological measures plus midodrine plus glycaemic control and supportive measures** » Simple measures include avoiding sudden changes in body posture to the head-up position; avoiding medications that aggravate hypotension; eating small, frequent meals; avoiding a low-salt diet; adequate fluid intake; avoiding activities that involve straining.

Ongoing

Patient group	Tx line	Treatment
		» Elevating the head of the bed 45 cm (18 inches) at night improved symptoms in a small series of patients with orthostatic hypotension from various causes.[174] » Case reports suggest that a compressive garment over the legs and abdomen may be of benefit.[175] [176] [177] [178] » An inflatable abdominal band was effective in a study of 6 patients with orthostatic hypotension.[179] » Using a low portable chair as needed for symptoms was found to be effective in one study.[180] » Several physical counter-manoeuvres, such as leg crossing, squatting, and muscle pumping, can help maintain BP.[181] » Midodrine is the only agent approved for the treatment of orthostatic hypotension in some countries. Several double-blind, placebo-controlled studies have documented its efficacy in the treatment of orthostatic hypotension.[191] [192] [193] The main adverse effects are piloerection, pruritus, paraesthesias, urinary retention, and supine HTN. » There is some evidence for a reduction in risk of DN with optimal blood glucose control achieved using multiple insulin injections in people with type 2 diabetes, but the evidence is not as strong as that for type 1 diabetes.4[B]Evidence » Lifestyle interventions (diet and exercise) are recommended as they may improve neuropathic symptoms and intra-epidermal nerve fibre density in patients with neuropathy and impaired glucose tolerance.[113] [114] » Proper care of the foot begins with educating the patient.[110] Minor non-infected wounds without evidence of soft-tissue or bone infection do not require antibiotic therapy. More serious problems are best handled in consultation with specialists in diabetic foot care.[69] [70] **Primary options** » midodrine: 2.5 to 10 mg orally three times daily
orthostatic hypotension	**2nd**	**simple non-pharmacological measures plus mixed alpha-adrenoreceptor agonist**

Ongoing

Patient group	Tx line	Treatment
		plus glycaemic control and supportive measures » Simple measures include avoiding sudden changes in body posture to the head-up position; avoiding medications that aggravate hypotension; eating small, frequent meals; avoiding a low-salt diet; adequate fluid intake; avoiding activities that involve straining. » Elevating the head of the bed 45 cm (18 inches) at night improved symptoms in a small series of patients with orthostatic hypotension from various causes.[174] » Case reports suggest that a compressive garment over the legs and abdomen may be of benefit.[175] [176] [177] [178] » An inflatable abdominal band was effective in a study of 6 patients with orthostatic hypotension.[179] » Using a low portable chair as needed for symptoms was found to be effective in one study.[180] » Several physical counter-manoeuvres, such as leg crossing, squatting, and muscle pumping, can help maintain BP.[181] » Mixed alpha-adrenoreceptor agonists include ephedrine and pseudoephedrine.[194] Severe HTN is an important adverse effect of all sympathomimetic agents. Other adverse effects, which may limit their use, are tremulousness, irritability, insomnia, tachycardia, reduced appetite, and, in men, urinary retention.[195] » There is some evidence for a reduction in risk of DN with optimal blood glucose control achieved using multiple insulin injections in people with type 2 diabetes, but the evidence is not as strong as that for type 1 diabetes.4[B]Evidence » Lifestyle interventions (diet and exercise) are recommended as they may improve neuropathic symptoms and intra-epidermal nerve fibre density in patients with neuropathy and impaired glucose tolerance.[113] [114] » Proper care of the foot begins with educating the patient.[110] Minor non-infected wounds without evidence of soft-tissue or bone infection do not require antibiotic therapy. More serious

Ongoing

Patient group	Tx line	Treatment
		problems are best handled in consultation with specialists in diabetic foot care.[69] [70] **Primary options** » ephedrine: 25-50 mg orally three times daily **OR** **Primary options** » pseudoephedrine: 30-60 mg orally three times daily
orthostatic hypotension	**3rd**	**simple non-pharmacological measures plus mineralocorticoid plus glycaemic control and supportive measures** » Simple measures include avoiding sudden changes in body posture to the head-up position; avoiding medications that aggravate hypotension; eating small, frequent meals; avoiding a low-salt diet; adequate fluid intake; avoiding activities that involve straining. » Elevating the head of the bed 45 cm (18 inches) at night improved symptoms in a small series of patients with orthostatic hypotension from various causes.[174] » Case reports suggest that a compressive garment over the legs and abdomen may be of benefit.[175] [176] [177] [178] » An inflatable abdominal band was effective in a study of 6 patients with orthostatic hypotension.[179] » Using a low portable chair as needed for symptoms was found to be effective in one study.[180] » Several physical counter-manoeuvres, such as leg crossing, squatting, and muscle pumping, can help maintain BP.[181] » The effects of fludrocortisone are not immediate, but occur over a 1- to 2-week period. » Supine HTN, hypokalaemia, and hypomagnesaemia may occur. Caution must be used, particularly in patients with CHF, to avoid fluid overload.[187] [188] » There is some evidence for a reduction in risk of DN with optimal blood glucose control achieved using multiple insulin injections in people with type 2 diabetes, but the

Ongoing

Patient group	Tx line	Treatment
		evidence is not as strong as that for type 1 diabetes.4[B]Evidence » Lifestyle interventions (diet and exercise) are recommended as they may improve neuropathic symptoms and intra-epidermal nerve fibre density in patients with neuropathy and impaired glucose tolerance.[113] [114] » Proper care of the foot begins with educating the patient.[110] Minor non-infected wounds without evidence of soft-tissue or bone infection do not require antibiotic therapy. More serious problems are best handled in consultation with specialists in diabetic foot care.[69] [70] **Primary options** » fludrocortisone: 0.1 to 0.2 mg orally once daily
orthostatic hypotension	**4th**	**simple non-pharmacological measures plus other pharmacological treatments plus glycaemic control and supportive measures** » Simple measures include avoiding sudden changes in body posture to the head-up position; avoiding medications that aggravate hypotension; eating small, frequent meals; avoiding a low-salt diet; adequate fluid intake; avoiding activities that involve straining. » Elevating the head of the bed 45 cm (18 inches) at night improved symptoms in a small series of patients with orthostatic hypotension from various causes.[174] » Case reports suggest that a compressive garment over the legs and abdomen may be of benefit.[175] [176] [177] [178] » An inflatable abdominal band was effective in a study of 6 patients with orthostatic hypotension.[179] » Using a low portable chair as needed for symptoms was found to be effective in one study.[180] » Several physical counter-manoeuvres, such as leg crossing, squatting, and muscle pumping, can help maintain BP.[181] » Erythropoietin (epoetin alfa) improves standing BP in patients with orthostatic hypotension.[57]

Ongoing

Patient group	Tx line	Treatment
		» Octreotide may attenuate the postprandial BP fall and reduce orthostatic hypotension in patients with autonomic failure. A long-acting intramuscular depot may also be used. » There is some evidence for a reduction in risk of DN with optimal blood glucose control achieved using multiple insulin injections in people with type 2 diabetes, but the evidence is not as strong as that for type 1 diabetes.4[B]Evidence » Lifestyle interventions (diet and exercise) are recommended as they may improve neuropathic symptoms and intra-epidermal nerve fibre density in patients with neuropathy and impaired glucose tolerance.[113] [114] » Proper care of the foot begins with educating the patient.[110] Minor non-infected wounds without evidence of soft-tissue or bone infection do not require antibiotic therapy. More serious problems are best handled in consultation with specialists in diabetic foot care.[69] [70] **Primary options** » epoetin alfa: 25-75 units/kg subcutaneously three times weekly initially until haematocrit approaches normal, followed by lower maintenance dose **OR** **Primary options** » octreotide: 25-200 micrograms/day subcutaneously given in divided doses every 8 hours; long-acting depot: 20-30 mg intramuscularly once monthly
diabetic gastroparesis	**1st**	**pharmacological methods plus glycaemic control and supportive measures** » Erythromycin increases gastric emptying in a dose-dependent manner.[203] 13[B]Evidence » Metoclopramide has anti-emetic properties.[201] Possible adverse effects include extrapyramidal symptoms, such as acute dystonic reactions; drug-induced parkinsonism; akathisia; and tardive dyskinesia. Galactorrhoea, amenorrhoea, gynaecomastia, and hyperprolactinaemia may also occur. » Metoclopramide should be used for up to 5 days only in order to minimise the risk of

Ongoing

Patient group	Tx line	Treatment
		neurological and other adverse effects.[206] Its use for the long-term treatment of gastroparesis is no longer recommended. It should be reserved for short-term use in severe cases that are unresponsive to other therapies. Adverse effects should be closely monitored. » Following a European review, the Medicines and Healthcare products Regulatory Agency and the European Medicines Agency have issued new recommendations concerning the use of domperidone. The review found the drug was associated with a small increased risk of potentially life-threatening effects on the heart. As a consequence, the agencies recommend that domperidone should only be used for the treatment of symptoms of nausea and vomiting and is no longer recommended for the treatment of conditions such as heartburn, bloating, or stomach discomfort. The risks and benefits should be weighed carefully before using this drug for this off-label indication. It should be used at the lowest effective dose for the shortest possible duration and the maximum treatment duration should not usually exceed 1 week. The new maximum dose recommended in adults is 30 mg/day. Domperidone is contraindicated in patients with severe hepatic impairment or underlying cardiac disease. It should not be administered with other drugs that prolong the QT interval or inhibit CYP3A4.[210] » There have been several case reports of patients with severe diabetic gastroparesis (whose symptoms persisted despite dietary changes and the use of high-dose prokinetic agents) experiencing significant symptomatic improvement after intrapyloric botulinum toxin injection during upper GI endoscopy.[211] [212] [213] » There is some evidence for a reduction in risk of DN with optimal blood glucose control achieved using multiple insulin injections in people with type 2 diabetes, but the evidence is not as strong as that for type 1 diabetes.4[B]Evidence » Lifestyle interventions (diet and exercise) are recommended as they may improve neuropathic symptoms and intra-epidermal nerve fibre density in patients with neuropathy and impaired glucose tolerance.[113] [114] » Proper care of the foot begins with educating the patient.[110] Minor non-infected wounds

Ongoing

Patient group	Tx line	Treatment
		without evidence of soft-tissue or bone infection do not require antibiotic therapy. More serious problems are best handled in consultation with specialists in diabetic foot care.[69] [70] **Primary options** » erythromycin base: 250 mg orally four times daily 30 minutes before meals and at bedtime **OR** **Secondary options** » metoclopramide: 5-10 mg orally three times daily for a maximum of 5 days, maximum 30 mg/day **OR** **Secondary options** » domperidone: 10 mg orally three times daily for a maximum of 7 days, maximum 30 mg/day **OR** **Secondary options** » botulinum toxin type A: consult specialist for guidance on dose
diabetic gastroparesis	**plus**	**lifestyle measures** » Some lifestyle measures for diabetic gastroparesis are based on commonly accepted clinical practices. » These include the use of multiple small feedings and changes in diet, such as a decrease in dietary fat and fibre.[199] [200] [201]
diabetic gastroparesis	**2nd**	**non-pharmacological methods plus glycaemic control and supportive measures** » Non-pharmacological methods have been used to treat diabetic gastroparesis in patients unresponsive to pharmacotherapy. » Short-term studies of gastric pacing (stimulation) in humans have demonstrated that it is possible to entrain gastric slow waves and normalise myoelectrical activity with pacing.[214] [215]

Ongoing

Patient group	Tx line	Treatment
		» Gastric stimulation uses high-frequency, low-amplitude signals that do not alter gastric myoelectrical or muscular activity. » There have been reports of improvements in nausea and vomiting with gastric stimulation in people with gastroparesis.14[C]Evidence » Persistent vomiting may require placement of a feeding jejunostomy to bypass an atonic stomach.[201] » Radical surgery, consisting of resection of a large portion of the stomach, with performance of a Roux-en-Y loop, was successful in a small series of patients.[50] » There is some evidence for a reduction in risk of DN with optimal blood glucose control achieved using multiple insulin injections in people with type 2 diabetes, but the evidence is not as strong as that for type 1 diabetes.4[B]Evidence » Lifestyle interventions (diet and exercise) are recommended as they may improve neuropathic symptoms and intra-epidermal nerve fibre density in patients with neuropathy and impaired glucose tolerance.[113] [114] » Proper care of the foot begins with educating the patient.[110] Minor non-infected wounds without evidence of soft-tissue or bone infection do not require antibiotic therapy. More serious problems are best handled in consultation with specialists in diabetic foot care.[69] [70]
diabetic gastroparesis	**plus**	**lifestyle measures** » Some lifestyle measures for diabetic gastroparesis are based on commonly accepted clinical practices. » These include the use of multiple small meals and changes in diet, such as a decrease in dietary fat and fibre.[199] [200] [201]
diabetic diarrhoea	**1st**	**broad-spectrum antibiotics plus glycaemic control and supportive measures** » Broad-spectrum antibiotics are commonly used to treat diabetic diarrhoea, either when the hydrogen breath test is positive or as an empirical trial.[88]

Ongoing

Patient group	Tx line	Treatment

» An early double-blind study, involving a single patient, found that diarrhoea subsided when the patient was treated with an oral antibiotic preparation, then recurred when placebo was substituted.[217]

» Several different regimens have been advocated. Caution must be used because long-term use of metronidazole can lead to neuropathy.

» There is some evidence for a reduction in risk of DN with optimal blood glucose control achieved using multiple insulin injections in people with type 2 diabetes, but the evidence is not as strong as that for type 1 diabetes.4[B]Evidence

» Lifestyle interventions (diet and exercise) are recommended as they may improve neuropathic symptoms and intra-epidermal nerve fibre density in patients with neuropathy and impaired glucose tolerance.[113] [114]

» Proper care of the foot begins with educating the patient.[110] Minor non-infected wounds without evidence of soft-tissue or bone infection do not require antibiotic therapy. More serious problems are best handled in consultation with specialists in diabetic foot care.[69] [70]

Primary options

» metronidazole: 500 mg orally every 6 hours for 3 weeks; or 750 mg orally every 8 hours for 3 weeks

OR

Primary options

» ampicillin: 250 mg orally every 6-8 hours for 14 days

OR

Primary options

» tetracycline: 250 mg orally every 6-8 hours for 14 days

OR

Primary options

» amoxicillin/clavulanate: 875 mg orally every 12 hours for 14 days
Dose refers to amoxicillin component.

Ongoing

Patient group	Tx line	Treatment
diabetic diarrhoea	2nd	**colestyramine plus glycaemic control and supportive measures** » Colestyramine can be used in an attempt to chelate bile salts if the hydrogen breath test is normal, or if patients fail an empirical trial of broad-spectrum antibiotics. » There is some evidence for a reduction in risk of DN with optimal blood glucose control achieved using multiple insulin injections in people with type 2 diabetes, but the evidence is not as strong as that for type 1 diabetes.4[B]Evidence » Lifestyle interventions (diet and exercise) are recommended as they may improve neuropathic symptoms and intra-epidermal nerve fibre density in patients with neuropathy and impaired glucose tolerance.[113] [114] » Proper care of the foot begins with educating the patient.[110] Minor non-infected wounds without evidence of soft-tissue or bone infection do not require antibiotic therapy. More serious problems are best handled in consultation with specialists in diabetic foot care.[69] [70] **Primary options** » colestyramine: 2-4 g orally two to four times daily
diabetic diarrhoea	3rd	**octreotide plus glycaemic control and supportive measures** » Octreotide was effective in a case report of a single patient with diabetic diarrhoea.[218] » In healthy volunteers, octreotide improved gastric, small bowel, and colonic transit, and colonic motility and tone.[219] Octreotide may be considered for the management of diabetic diarrhoea when other approaches have failed. » There is some evidence for a reduction in risk of DN with optimal blood glucose control achieved using multiple insulin injections in people with type 2 diabetes, but the evidence is not as strong as that for type 1 diabetes.4[B]Evidence » Lifestyle interventions (diet and exercise) are recommended as they may improve neuropathic symptoms and intra-epidermal nerve fibre density in patients with neuropathy and impaired glucose tolerance.[113] [114]

Ongoing

Patient group	Tx line	Treatment
		» Proper care of the foot begins with educating the patient.[110] Minor non-infected wounds without evidence of soft-tissue or bone infection do not require antibiotic therapy. More serious problems are best handled in consultation with specialists in diabetic foot care.[69] [70] **Primary options** » octreotide: 75-200 micrograms subcutaneously two to three times daily; long-acting depot: 20-30 mg intramuscularly once monthly
bladder dysfunction	1st	**bethanechol plus glycaemic control and supportive measures** » Bethanechol, a parasympathomimetic agent, may be helpful for people with symptoms of bladder dysfunction. » There is some evidence for a reduction in risk of DN with optimal blood glucose control achieved using multiple insulin injections in people with type 2 diabetes, but the evidence is not as strong as that for type 1 diabetes.4[B]Evidence » Lifestyle interventions (diet and exercise) are recommended as they may improve neuropathic symptoms and intra-epidermal nerve fibre density in patients with neuropathy and impaired glucose tolerance.[113] [114] » Proper care of the foot begins with educating the patient.[110] Minor non-infected wounds without evidence of soft-tissue or bone infection do not require antibiotic therapy. More serious problems are best handled in consultation with specialists in diabetic foot care.[69] [70] **Primary options** » bethanechol: 10-30 mg orally three times daily
bladder dysfunction	adjunct	**bladder hygiene techniques** » Bladder training, such as scheduled voiding, may be used particularly for urge incontinence. » The Crede manoeuvre may also be used. This method helps to empty the bladder if it is weak and flaccid. The patient pushes with a hand down on the abdomen from the umbilicus towards the bladder in a smooth, even manner.[88]

Ongoing

Patient group	Tx line	Treatment
erectile dysfunction	1st	**PDE-5 inhibitor plus glycaemic control and supportive measures**

» The first-line therapy for erectile dysfunction (ED) is a phosphodiesterase-5 (PDE-5) inhibitor.

» PDE-5 inhibitors revolutionised the management of ED and are efficient and safe. Both sildenafil and tadalafil significantly increase erectile function and are generally well tolerated.[221] [222] However, adverse effects may occur, with headache and flushing the most commonly reported. Flu-like syndromes, dyspepsia, myalgias, abnormal vision, and back pain may occur less frequently.

» The second-line option for treatment of ED is intracavernosal injection. The success rate of intracavernosal injections is high, with nearly 90% patients achieving erection.[223] [224] Direct injections can be into the corpus cavernosum or by urethral suppository.

» There is some evidence for a reduction in risk of DN with optimal blood glucose control achieved using multiple insulin injections in people with type 2 diabetes, but the evidence is not as strong as that for type 1 diabetes.4[B]Evidence

» Lifestyle interventions (diet and exercise) are recommended as they may improve neuropathic symptoms and intra-epidermal nerve fibre density in patients with neuropathy and impaired glucose tolerance.[113] [114]

» Proper care of the foot begins with educating the patient.[110] Minor non-infected wounds without evidence of soft-tissue or bone infection do not require antibiotic therapy. More serious problems are best handled in consultation with specialists in diabetic foot care.[69] [70]

Primary options

» sildenafil: 25-100 mg orally taken 1 hour before anticipated sexual activity

OR

Primary options

» tadalafil: 5-20 mg orally taken 45 minutes before anticipated sexual activity

OR

Ongoing

Patient group	Tx line	Treatment
erectile dysfunction	adjunct	**Primary options** » vardenafil: 5-20 mg orally taken 45 minutes before anticipated sexual activity **OR** **Secondary options** » papaverine: consult specialist for guidance on dose **OR** **Secondary options** » alprostadil intracavernous: 10-20 micrograms when required, titrate dose according to response, maximum 60 micrograms/dose, maximum 3 doses/week, with at least 24 hours between each dose **OR** **Secondary options** » alprostadil urethral: 125-250 micrograms when required, increase dose according to response, doses of up to 1000 micrograms/day have been reported **non-pharmacological methods** » Several case reports have described the use of vacuum devices, rigid penile implants, and inflatable prostheses for the treatment of erectile dysfunction.[224] [225]

Emerging

Aldose reductase inhibitors (ARIs)

Act by reducing the flux of glucose through the polyol pathway. Earlier studies with ARIs showed inconsistent effects and an unacceptable rate of adverse events.[226] Later studies with the potent ARIs fidarestat, ranirestat, and epalrestat have shown benefit in diabetic patients with peripheral neuropathy.[227] [228] [229] [230] [231] However, a Cochrane review found no difference between ARIs and placebo when treating diabetic polyneuropathy. Therefore, further studies regarding the use of ARIs for treating DN are still required.[232]

Baicalein

The flavonoid baicalein (5,6,7-trihydroxyflavone) has been reported to counteract sorbitol accumulation, activation of 12/15-lipoxygenase, oxidative-nitrosative stress, inflammation, and impaired signalling in models of chronic disease. Animal studies suggest baicalein targets several mechanisms implicated in diabetic peripheral neuropathy (DPN).[233]

Alpha-lipoic acid

A natural cofactor in the pyruvate dehydrogenase complex, where it binds acyl groups and transfers them from one part of the complex to another. It plays a role in the antioxidant network as a thiol-replenishing and redox-modulating agent. Trials in Europe and North America have demonstrated limited effects on neuropathic symptoms after short-term intravenous use and no benefit on electrophysiological testing.[234] [235] [236] [237] [238]

Recombinant nerve growth factor (rNGF)

Two randomised, double-blind, placebo-controlled phase 2 studies of rNGF in the treatment of DN reported improvement in the sensory component of the neurological exam, in quantitative sensory testing, and in a symptom score.[239] However, a large-scale 48-week, phase 3 clinical trial of patients randomised to receive either rNGF or placebo failed to confirm its efficacy.[240]

Acetyl-L-carnitine (ALC)

In preclinical studies, ALC treatment corrected perturbations of neural sodium/potassium-ATPase, myoinositol, nitric oxide, prostaglandins, and lipid peroxidation. Clinical studies have shown modest effects of ALC on painful DN.[241] [242] [243] [244] A large multicentre placebo-controlled phase 3 trial of ALC in patients with mild DN found no improvement in myelinated fibre density in sural nerve biopsies.[245]

Poly (ADP-ribose) polymerase (PARP) inhibitors

Poly (ADP-ribose) polymerase (PARP) activation has been implicated in the pathogenesis of diabetic complications, including nephropathy and peripheral neuropathy. Animal studies support an important role for PARP activation in DPN and kidney hypertrophy associated with type 1 diabetes. These studies provide a rationale for development and further studies of PARP inhibitors, for the prevention and treatment of these complications.[246]

C-peptide

Provides an insulin-like signalling function that translates into beneficial outcomes in early metabolic perturbations of neural Na+/K+-ATPase and nitric oxide with subsequent preventive effects on early nerve dysfunction. Further corrective consequences resulting from this signalling cascade have beneficial effects on gene regulation of early gene responses, neurotrophic factors, their receptors, and the insulin receptor itself. This may lead to preventive and corrective results to nerve fibre degeneration and loss, as well as promotion of nerve fibre regeneration with respect to sensory somatic fibres and small nociceptive nerve fibres. Several small-scale clinical trials confirm these beneficial effects on autonomic and somatic nerve

function and blood flow in a variety of tissues. Therefore, evidence that replacement of C-peptide in patients with type 1 diabetes may retard and prevent chronic complication is real and encouraging. [247] [248] [249] A phase 3 clinical trial evaluating the effects of pegylated C-peptide in patients with type 1 diabetes and mild to moderately severe DPN reported no benefit.[250]

L-methylfolate, methylcobalamin, and pyridoxal-5'-phosphate (LMF-MC-PLP)

Animal studies have suggested a combination of L-methylfolate, methylcobalamin, and pyridoxal-5'-phosphate may be beneficial in DPN. A multicentre, randomised, double-blind, placebo-controlled trial involving 214 patients with type 2 diabetes and neuropathy (baseline vibration perception threshold: 25-45 volts) randomly assigned patients to treatment with either LMF-MC-PLP or placebo. There was no significant improvement in the primary outcome measure (vibration perception threshold) after 24 weeks. However, there was a significant improvement in Neuropathy Total Symptom Score-6 scores at week 16 and week 24.[251]

Neuronal nicotinic receptor (NNR) agonist

Preclinical and clinical studies suggest that neuronal nicotinic receptor (NNR) agonists may be a novel and effective therapy for numerous painful conditions, including DN. Analgesic efficacy and safety of the highly selective alpha-4-beta-2 NNR agonist ABT-894 was evaluated in 2 separate randomised, double-blind, multicentre, placebo-controlled clinical trials in patients with diabetic peripheral neuropathic pain. Disappointingly, in both trials, none of the ABT-894 dose groups showed efficacy compared with placebo, whereas in one study duloxetine achieved a statistically significant improvement over placebo. This suggests that NNR agonists may not be a viable approach to treating neuropathic pain.[252]

Ghrelin

Ghrelin, an endogenous ligand of the growth hormone secretagogue receptor released from the stomach, decreased the cumulative meal-related symptom score and improved liquid emptying in gastroparesis studies.[62] [253] In a double-blind 28-day study, TZP-102 (a novel, macrocyclic, selective, oral ghrelin receptor agonist) had no effect on gastric emptying, but improved symptoms on the patient-reported Gastroparesis Cardinal Symptom Index (GCSI), and improved patient and physician overall treatment evaluation.[254] However, in a subsequent 12-week phase 2b study of 201 patients with diabetic gastroparesis, there was no significant improvement in GCSI or overall treatment evaluation.[255]

Avanafil

This phosphodiesterase-5 (PDE-5) inhibitor received marketing authorisation in Europe in April 2013 for the treatment of erectile dysfunction in adult men, but it is not yet approved in the US.

Topical alprostadil

A topically applied cream formulation of alprostadil has been approved for erectile dysfunction in 10 European countries and in Canada, but is not yet approved in the US.

Treatment for diabetic amyotrophy

In patients with particularly severe amyotrophy, prednisolone, intravenous immunoglobulin (IVIG), and plasmapheresis have shown some promise in open-label, uncontrolled studies. The condition appeared to stop deteriorating and began to improve with these treatments. However, because untreated patients also gradually improve, the efficacy of these treatments is undemonstrated.[256] [257] [258] [259]

Non-pharmacological interventions

A systematic review of physical therapies for managing balance dysfunction in patients with DPN gave a fair recommendation to lower extremity strengthening exercises.[260] Other techniques, including

monochromatic infrared energy therapy, vibrating insoles, and use of a walking stick, had insufficient evidence to recommend them.

Recommendations

Monitoring

General

- Monitoring of blood glucose, BP, and serum lipids, and monitoring for other complications is part of the general management of diabetes in all patients.[263]

Diabetic peripheral neuropathy (DPN)

- All patients should be screened for symptoms and signs of DPN at least annually.[55]
- The most common symptoms include pain, dysaesthesias (unpleasant abnormal sensations of burning and tingling associated with peripheral nerve lesions), and numbness.[55]
- Screening for signs should use simple clinical tests but it is important to note that these tests will only adequately detect moderate to severe neuropathy. Assessment for DPN should start distally on both sides and move proximally until a threshold is detected.[55] In the setting of typical neuropathic symptoms it is important to identify underlying small-fibre deficits.
- Electrophysiological testing is rarely needed, except in situations where the clinical features are atypical (motor deficits greater than sensory deficits; marked asymmetry of the neurological deficits; initial symptoms in the upper extremities; rapid progression).[55]
- Patients with severe or atypical neuropathy should be screened for other causes such as neurotoxic medications, heavy metal poisoning, alcohol abuse, vitamin B12 deficiency (especially in those taking metformin for prolonged periods), advanced renal disease, chronic inflammatory demyelinating neuropathy, inherited neuropathies, and vasculitis.[55]

Diabetic autonomic neuropathy

- Annual monitoring for signs and symptoms of autonomic neuropathy.[55]
- Major clinical signs/symptoms of diabetic autonomic neuropathy include resting tachycardia, exercise intolerance, orthostatic hypotension, constipation, gastroparesis, erectile dysfunction, sudomotor dysfunction, impaired neurovascular function, and unawareness of hypoglycaemia.[55]
- Special testing is rarely needed and may not affect management or outcomes.

Prevention and treatment of neuropathies

- Tight and stable glycaemic control, started as early as possible, has been shown to be effective at preventing the development of DPN and autonomic neuropathy in patients with type 1 diabetes.[55]
- While the evidence is not as strong for type 2 diabetes as for type 1 diabetes, some studies have demonstrated a modest slowing of progression without reversal of neuronal loss.[55] However, all of these studies were undertaken in patients with advanced disease or using end points that are not recommended for clinical trials of DPN.
- Medications for the relief of painful DPN and autonomic neuropathy are recommended because they may reduce pain, improve sleep, and improve quality of life.[55]
- Treatment needs to be monitored regularly in relation to symptoms, adherence, and side effects. The frequency of follow-up will depend on the treatment given and condition.[55]

Foot care

- Visual foot examination should be performed at each visit.
- All patients should be educated about self-care of the feet. Enhanced foot care education should be facilitated and referral for special footwear made as indicated.

Patient instructions

Patients should be advised to:

FOLLOW UP

- Examine their feet daily
- Wear only proper footwear
- Report any symptoms or signs early, including wounds and foot deformities
- Maintain tight glucose control
- Make sure they know what to do if they experience hypoglycaemic episodes
- Keep clinic appointments to check there is tight BP and lipid control.

Complications

Complications	Timeframe	Likelihood
foot wounds/ulcers	**variable**	**high**
Approximately 15% people with diabetes develop a lower extremity ulcer at some point in the course of their condition.[261] [Fig-5] [Fig-7] Minor non-infected wounds can be treated with non-irritating antiseptic solution, daily dressing changes, and foot rest. Reducing plantar pressure using contact casts/specialised footwear accelerates healing.[2]		
wound infection/gangrene	**variable**	**medium**
More serious problems, such as foot deformities, infected lesions, and osteomyelitis, are best handled in consultation with specialists in diabetic foot care. Infected foot ulcers usually require intravenous antibiotics, bed rest with foot elevation, and surgical debridement. Most diabetic foot infections are polymicrobial, with aerobic gram-positive cocci, especially staphylococci, the most common causative organisms. Aerobic gram-negative bacilli are frequent co-pathogens in infections that are chronic or follow antibiotic treatment, and obligate anaerobes may be co-pathogens in ischaemic or necrotic wounds.[69] This is a major cause of diabetic patients being admitted to hospital.		
amputation	**variable**	**medium**
Foot ulceration is a common precursor to amputation. Approximately 7% to 20% of foot ulcers eventually lead to amputation.[261]		
silent MI	**variable**	**medium**
People with impaired heart rate variability (cardiovascular autonomic neuropathy) have an increased risk of silent MI and death.		
death	**variable**	**medium**
The presence of cardiovascular autonomic neuropathy and a self-reported history of neuropathy are predictors of mortality in patients with type 1 and 2 diabetes.[60] [262]		

Complications	Timeframe	Likelihood
depression	**variable**	**medium**
An association between diabetic peripheral neuropathy and depressive symptoms has been demonstrated.[23] Presence of depressive symptoms appears to be influenced by: perceptions of DN symptom unpredictability, the lack of treatment control, restrictions in activities of daily living, and changes in social self-perception.[23]		
Charcot foot	**variable**	**low**
This is an uncommon progressive disorder resulting in severe destruction of the architecture of the foot. [Fig-8] [Fig-7] It is thought to develop because of a combination of factors: loss of protective sensation in the foot; increased blood flow to the foot (due to autonomic neuropathy) leading to bone loss and weak bones susceptible to injury; and unrecognised trauma.		

Prognosis

The prognosis of people with DN depends partly on how well their diabetes is managed. Improvement in blood glucose control may slow the progression of neuropathy, but recovery may be very slow. Foot ulceration and Charcot joints are serious complications of peripheral neuropathy.

There is evidence from observational studies that autonomic neuropathy is associated with increased mortality. This may be partly due to various other complicating factors. However, people with impaired heart rate variability (cardiovascular autonomic neuropathy) have an increased risk of silent MI and death. Symptoms associated with the rarer presentations of cranial neuropathy, mononeuropathies, truncal mononeuropathy, and diabetic amyotrophy tend to gradually improve with time.

Diagnostic guidelines

Europe

Diabetic foot problems: prevention and management

Published by: National Institute for Health and Care Excellence **Last published:** 2016

Summary: Recommendations regarding the management of children and adults with type 1 or type 2 diabetes who have, or are at risk of developing, diabetic foot problems.

Diabetes (type 1 and type 2) in children and young people: diagnosis and management

Published by: National Institute for Health and Care Excellence **Last published:** 2015

Summary: Recommendations regarding the diagnosis of type 1 diabetes in children and young people.

European Federation of Neurological Societies and Peripheral Nerve Society guideline on the use of skin biopsy in the diagnosis of small fiber neuropathy

Published by: European Federation of Neurological Societies; Peripheral Nerve Society **Last published:** 2010

Summary: Revision of previous guidelines on the use of skin biopsy in the diagnosis of peripheral neuropathy.

Management of diabetes: a national clinical guideline

Published by: Scottish Intercollegiate Guidelines Network **Last published:** 2010

International

IWGDF guidance on the prevention and management of foot problems in diabetes

Published by: International Working Group on the Diabetic Foot **Last published:** 2015

Summary: Guidance on foot problems in diabetes.

North America

Standards of medical care in diabetes - 2017

Published by: American Diabetes Association **Last published:** 2017

Summary: Updated annually by the American Diabetes Association. These recommendations cover all aspects of diabetes care, including screening and diagnosis of neuropathy.

Diabetic neuropathy: a position statement by the American Diabetes Association

Published by: American Diabetes Association **Last published:** 2017

Summary: Includes recommendations on screening for and diagnosis of diabetic neuropathies.

North America

Diabetic polyneuropathies: update on research definition, diagnostic criteria and estimation of severity

Published by: Toronto Expert Panel on Diabetic Neuropathy **Last published:** 2011

Summary: Definitions of typical and atypical diabetic peripheral neuropathy, diagnostic criteria, and approaches to diagnose sensorimotor polyneuropathy and to estimate severity.

Cardiovascular autonomic neuropathy in diabetes: clinical impact, assessment, diagnosis, and management

Published by: Toronto Expert Panel on Diabetic Neuropathy **Last published:** 2011

Summary: Includes epidemiology, clinical impact, diagnosis, usefulness of testing, and management of cardiovascular autonomic neuropathy.

Methods of investigation for cardiac autonomic dysfunction in human research studies

Published by: Toronto Expert Panel on Diabetic Neuropathy **Last published:** 2011

Summary: A consensus document providing evidence-based guidelines regarding the evaluation of diabetic cardiovascular autonomic neuropathy for human research studies.

Management strategies for gastrointestinal, erectile, bladder, and sudomotor dysfunction in patients with diabetes

Published by: Toronto Expert Panel on Diabetic Neuropathy **Last published:** 2011

Summary: Covers clinical impact, assessment, diagnosis, and management.

Evaluation of distal symmetric polyneuropathy: role of autonomic testing, nerve biopsy, and skin biopsy (an evidence-based review)

Published by: American Academy of Neurology; American Association of Electrodiagnostic Medicine; American Academy of Physical Medicine and Rehabilitation **Last published:** 2009

Summary: Evidence-based recommendations include the following: Autonomic testing should be considered in the assessment of patients with polyneuropathy to document autonomic nervous system dysfunction. Such testing should be considered especially for assessing suspected autonomic neuropathy and distal small-fibre sensory polyneuropathy. A battery of validated tests is recommended to achieve the highest diagnostic accuracy. Skin biopsy is a validated technique for determining intra-epidermal nerve fibre density and may be considered for the diagnosis of distal symmetrical polyneuropathy, particularly small-fibre sensory neuropathy. The need for additional prospective studies to define more exact guidelines for the assessment of polyneuropathy is noted.

North America

Diabetic foot disorders: a clinical practice guideline

Published by: American College of Foot and Ankle Surgeons **Last published:** 2006

Summary: Makes recommendations concerning the history taking in patients with diabetes, concerning foot problems, and the physical examination. Includes a table of key factors for the lower extremity diabetic foot examination, divided into vascular examination, neurological examination, dermatological examination, musculoskeletal examination, and footwear examination. This document, formerly titled a Clinical Practice Guideline, was retitled a Clinical Consensus Statement in 2012 because it no longer meets the CPG development standards of the Institute of Medicine.

Diabetic neuropathies: a statement by the American Diabetes Association

Published by: American Diabetes Association **Last published:** 2005

Summary: Early recognition and appropriate management of neuropathy in the patient with diabetes is important for several reasons: Non-diabetic neuropathies may be present in patients with diabetes. Several treatment options exist for symptomatic DN. Up to 50% of diabetic peripheral neuropathy may be asymptomatic, and patients are at risk of insensate injury to their feet. Autonomic neuropathy may involve every system in the body. Autonomic neuropathy causes substantial morbidity and increased mortality, particularly if cardiovascular autonomic neuropathy is present.

Distal symmetric polyneuropathy: a definition for clinical research

Published by: American Academy of Neurology; American Association of Electrodiagnostic Medicine; American Academy of Physical Medicine and Rehabilitation **Last published:** 2005

Summary: Formalised consensus process to develop a case definition of distal symmetrical polyneuropathy. Aims to standardise and facilitate clinical research and epidemiological studies. Evidence-based conclusions include the following: Symptoms alone have relatively poor diagnostic accuracy in predicting the presence of polyneuropathy. Multiple neuropathic symptoms are more accurate than single symptoms. Signs are better predictors of polyneuropathy than symptoms and should be weighted more heavily. A single abnormality on examination is less sensitive than multiple abnormalities in predicting polyneuropathy; therefore, an examination should look for a combination of signs. Relatively simple examinations are as accurate in diagnosing polyneuropathy as complex scoring systems. There is too much inconsistency among the studies describing the accuracy of quantitative sensory testing (QST) to incorporate QST in the case definition.

Quantitative sensory testing

Published by: American Academy of Neurology **Last published:** 2003

Summary: QST is a potentially useful tool for measuring sensory impairment for clinical and research studies in identifying small- or large-fibre sensory abnormalities in patients with DN. QST results should not be the sole criteria used to diagnose pathology associated with DN. Well-designed studies comparing different QST devices and methods are still needed and should include patients with abnormalities detected solely by QST. Malingering and other non-organic factors can influence the test results.

Treatment guidelines

Europe

Diabetic foot problems: prevention and management

Published by: National Institute for Health and Care Excellence **Last published:** 2016

Summary: Recommendations regarding the management of diabetic foot problems in children and adults with type 1 or type 2 diabetes.

Type 2 diabetes in adults: management

Published by: National Institute for Health and Care Excellence **Last published:** 2015

Summary: Recommendations regarding the management of adults with type 2 diabetes.

Diabetes (type 1 and type 2) in children and young people: diagnosis and management

Published by: National Institute for Health and Care Excellence **Last published:** 2015

Summary: Recommendations regarding the care of children and young people with type 1 diabetes.

Neuropathic pain in adults: pharmacological management in non-specialist settings

Published by: National Institute for Health and Care Excellence **Last published:** 2014

Summary: Evidence-based recommendations on the pharmacological management of neuropathic pain in non-specialist settings.

Percutaneous electrical nerve stimulation for refractory neuropathic pain

Published by: National Institute for Health and Care Excellence **Last published:** 2013

Summary: Recommendations on the use of percutaneous electrical nerve stimulation (PENS) for refractory neuropathic pain.

Emotional and psychological support and care in diabetes

Published by: NHS Diabetes; Diabetes UK **Last published:** 2010

Summary: Report documenting the findings of a working group established to examine the current challenges in provision of emotional and psychological support and care in diabetes. Makes various recommendations, including in the areas of commissioning, organisation of care, provision of services and workforce.

Management of diabetes: a national clinical guideline

Published by: Scottish Intercollegiate Guidelines Network **Last published:** 2010

International

IWGDF guidance on the prevention and management of foot problems in diabetes

Published by: International Working Group on the Diabetic Foot **Last published:** 2015

Summary: Guidance on the prevention and management of foot problems in diabetes.

North America

Standards of medical care in diabetes - 2017

Published by: American Diabetes Association **Last published:** 2017

Summary: Updated annually by the ADA. These recommendations cover all aspects of diabetes care, including treatment of neuropathy.

Diabetic neuropathy: a position statement by the American Diabetes Association

Published by: American Diabetes Association **Last published:** 2017

Summary: Includes recommendations on treatment and management of diabetic neuropathies.

Canadian Diabetes Association 2013 clinical practice guidelines for the prevention and management of diabetes in Canada: 2016 interim update

Published by: Canadian Diabetes Association **Last published:** 2016

Summary: Recommendations on the care of people with diabetes.

Cardiovascular autonomic neuropathy in diabetes: clinical impact, assessment, diagnosis, and management

Published by: Toronto Expert Panel on Diabetic Neuropathy **Last published:** 2011

Summary: Includes epidemiology, clinical impact, diagnosis, usefulness of testing, and management of cardiovascular autonomic neuropathy.

Management strategies for gastrointestinal, erectile, bladder, and sudomotor dysfunction in patients with diabetes

Published by: Toronto Expert Panel on Diabetic Neuropathy **Last published:** 2011

Summary: Covers clinical impact, assessment, diagnosis, and management.

Evidence-based guideline: treatment of painful diabetic neuropathy

Published by: American Academy of Neurology; American Association of Neuromuscular and Electrodiagnostic Medicine; American Academy of Physical Medicine and Rehabilitation **Last published:** 2011

Summary: Evidence-based guideline for the treatment of painful diabetic neuropathy.

North America

Diabetic foot disorders: a clinical practice guideline

Published by: American College of Foot and Ankle Surgeons **Last published:** 2006

Summary: Makes recommendation concerning the management of foot complications including foot ulcers, foot infections, and diabetic Charcot foot. This document, formerly titled a Clinical Practice Guideline, was retitled a Clinical Consensus Statement in 2012 because it no longer meets the CPG development standards of the Institute of Medicine.

Diabetic neuropathies: a statement by the American Diabetes Association

Published by: American Diabetes Association **Last published:** 2005

Summary: Treatment should be directed at underlying pathogenesis. Effective symptomatic treatments are available for the manifestations of diabetic peripheral neuropathy and autonomic neuropathy.

Oceania

General practice management of type 2 diabetes: 2014 - 2015

Published by: Royal Australian College of General Practitioners **Last published:** 2014

Summary: Recommendations regarding the management of adults with type 2 diabetes.

Evidence scores

1. Development and progression of neurological and microvascular complications: there is good-quality evidence that intensive insulin therapy, with a goal of maintaining blood glucose close to the normal range, effectively delays the onset and progression of DN, nephropathy, and retinopathy in people with type 1 diabetes.[8]
Evidence level A: Systematic reviews (SRs) or randomized controlled trials (RCTs) of >200 participants.

2. Risk of microvascular complications: there is medium-quality evidence that intensive blood glucose control, with either sulfonylureas or insulin, in people with newly diagnosed type 2 diabetes is associated with a substantial decrease in the risk of microvascular complications over 10 years compared with those receiving conventional treatment.[28]
Evidence level B: Randomized controlled trials (RCTs) of <200 participants, methodologically flawed RCTs of >200 participants, methodologically flawed systematic reviews (SRs) or good quality observational (cohort) studies.

3. Sensitivity and specificity of vibration perception threshold (VPT) in type 1 diabetes: there is medium-quality evidence from assessments of peripheral neuropathy (VPT vs standard assessments) in 1177 patients with type 1 diabetes participating in a study of intensive versus conventional diabetes treatment that VPT was a sensitive measure of confirmed clinical neuropathy (87%) and of definite clinical neuropathy (80%) and a specific measure of abnormal nerve conduction (62%).[78]
Evidence level B: Randomized controlled trials (RCTs) of <200 participants, methodologically flawed RCTs of >200 participants, methodologically flawed systematic reviews (SRs) or good quality observational (cohort) studies.

4. Development and progression of DN: there is medium-quality evidence that patients with type 2 diabetes treated with multiple insulin injections have significant improvement in nerve conduction studies over 6 years, whereas median nerve conduction velocities and vibration threshold deteriorate with conventional insulin treatment over 6 years.[105]
Evidence level B: Randomized controlled trials (RCTs) of <200 participants, methodologically flawed RCTs of >200 participants, methodologically flawed systematic reviews (SRs) or good quality observational (cohort) studies.

5. Improvement in diabetic peripheral neuropathic pain: there is medium-quality evidence that pregabalin is associated with significant improvements in pain scores (persisting for 6 to 8 weeks) within 1 week of treatment, compared with placebo. Forty percent of patients receiving pregabalin reported a ≥50% reduction in pain compared with 14.5% of those treated with placebo.[120]
Evidence level B: Randomized controlled trials (RCTs) of <200 participants, methodologically flawed RCTs of >200 participants, methodologically flawed systematic reviews (SRs) or good quality observational (cohort) studies.

6. Improvement in diabetic peripheral neuropathic pain: there is medium-quality evidence that duloxetine 60 mg once daily, or 60 mg twice daily, is associated with significant improvement in the mean score of 24-hour average pain severity after 12 weeks compared with placebo in patients with painful DN and no comorbid depression.[131]
Evidence level B: Randomized controlled trials (RCTs) of <200 participants, methodologically flawed RCTs of >200 participants, methodologically flawed systematic reviews (SRs) or good quality observational (cohort) studies.

7. Symptom improvement: there is medium-quality evidence in the form of an indirect meta-analysis that compared the efficacy and tolerability of duloxetine with pregabalin and gabapentin, using placebo as a common comparator. Duloxetine proved to be of comparable efficacy and tolerability to pregabalin and gabapentin in treating DN.[133]
Evidence level B: Randomized controlled trials (RCTs) of <200 participants, methodologically flawed RCTs of >200 participants, methodologically flawed systematic reviews (SRs) or good quality observational (cohort) studies.

8. Improvement in diabetic peripheral neuropathic pain: there is poor-quality evidence that amitriptyline, imipramine, and desipramine all relieve pain in patients with DN better than placebo in both depressed and non-depressed patients. The efficacy appears to be independent of any antidepressant effect.[137] [138] [139] [140] [141]
Evidence level C: Poor quality observational (cohort) studies or methodologically flawed randomized controlled trials (RCTs) of <200 participants.

9. Improvement in diabetic peripheral neuropathic pain: there is poor-quality evidence that paroxetine 40 mg daily significantly reduces symptoms of neuropathy, but is less effective than imipramine.[149]
Evidence level C: Poor quality observational (cohort) studies or methodologically flawed randomized controlled trials (RCTs) of <200 participants.

10. Improvement in diabetic peripheral neuropathic pain: there is medium-quality evidence that tramadol (average dose 210 mg/day) is significantly more effective than placebo in the treatment of diabetic neuropathic pain. Nausea, constipation, headache, and somnolence were reported adverse effects associated with tramadol.[154]
Evidence level B: Randomized controlled trials (RCTs) of <200 participants, methodologically flawed RCTs of >200 participants, methodologically flawed systematic reviews (SRs) or good quality observational (cohort) studies.

11. Improvement in diabetic peripheral neuropathic pain: there is poor-quality evidence that oxycodone results in significantly lower mean daily pain, steady pain, and total pain and disability over 4 weeks compared with placebo in the treatment of DN pain.[153]
Evidence level C: Poor quality observational (cohort) studies or methodologically flawed randomized controlled trials (RCTs) of <200 participants.

12. Development and progression of abnormal autonomic test results: there is good-quality evidence that conventional insulin therapy in people with type 1 diabetes is associated with a significantly greater slope of decline over time in measurements of R-R variation and Valsalva ratio compared with people receiving intensive insulin treatment.[173]
Evidence level A: Systematic reviews (SRs) or randomized controlled trials (RCTs) of >200 participants.

13. Improvement in gastric emptying with erythromycin use: there is medium-quality evidence in the form of several open trials that found a mean improvement in gastric emptying of >40%.[202] One single-blind trial also demonstrated an improvement in gastric emptying of 50%.[202]
Evidence level B: Randomized controlled trials (RCTs) of <200 participants, methodologically flawed RCTs of >200 participants, methodologically flawed systematic reviews (SRs) or good quality observational (cohort) studies.

14. Improvement in nausea and vomiting symptoms: there is poor-quality evidence that gastric stimulation may significantly reduce self-reported measures for frequency and severity of nausea and vomiting in people with gastroparesis (mostly diabetic) despite not significantly improving gastric emptying.[216]
Evidence level C: Poor quality observational (cohort) studies or methodologically flawed randomized controlled trials (RCTs) of <200 participants.

Key articles

- Boulton AJ, Vinik AI, Arezzo JC, et al. Diabetic neuropathies: a statement by the American Diabetes Association. Diabetes Care. 2005;28:956-962. Full text Abstract
- Dyck PJ, Albers JW, Andersen H, et al; Toronto Expert Panel on Diabetic Neuropathy. Diabetic polyneuropathies: update on research definition, diagnostic criteria and estimation of severity. Diabetes Metab Res Rev. 2011;27:620-628. Full text Abstract
- The Diabetes Control and Complications Trial 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. Full text Abstract
- Albers JW, Herman WH, Pop-Busui R, et al; Diabetes Control and Complications Trial /Epidemiology of Diabetes Interventions and Complications Research Group. Effect of prior intensive insulin treatment during the Diabetes Control and Complications Trial (DCCT) on peripheral neuropathy in type 1 diabetes during the Epidemiology of Diabetes Interventions and Complications (EDIC) Study. Diabetes Care. 2010;33:1090-1096. Full text Abstract
- Pop-Busui R, Low PA, Waberski BH, et al; DCCT/EDIC Research Group. 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. Full text Abstract
- Shichiri M, Kishikawa H, Ohkubo Y, et al. Long-term results of the Kumamoto Study on optimal diabetes control in type 2 diabetic patients. Diabetes Care. 2000;23(Suppl 2):B21-B29. Abstract
- Bernardi L, Spallone V, Stevens M, et al; Toronto Consensus Panel on Diabetic Neuropathy. Methods of investigation for cardiac autonomic function in human research studies. Diabetes Metab Res Rev. 2011;27:654-664. Full text Abstract
- Spallone V, Maiello MR, Morganti R, et al. Usefulness of ambulatory blood pressure monitoring in predicting the presence of autonomic neuropathy in type I diabetic patients. J Hum Hypertens. 2007;21:381-386. Abstract
- Malik R, Veves A, Tesfaye S, et al; Toronto Consensus Panel on Diabetic Neuropathy. Small fiber neuropathy: role in the diagnosis of diabetic sensorimotor polyneuropathy. Diabetes Metab Res Rev. 2011;27:678-684. Full text Abstract
- Kempler P, Amarenco G, Freeman R, et al; Toronto Consensus Panel on Diabetic Neuropathy. Management strategies for gastrointestinal, erectile, bladder, and sudomotor dysfunction in patients with diabetes. Diabetes Metab Res Rev. 2011;27:665-677. Full text Abstract
- Bril V, England J, Franklin GM, et al; American Academy of Neurology; American Association of Neuromuscular and Electrodiagnostic Medicine; American Academy of Physical Medicine and Rehabilitation. Evidence-based guideline: treatment of painful diabetic neuropathy. Neurology. 2011;76:1758-1765. Full text Abstract

REFERENCES

References

1. Porte D Jr, Sherwin R, Rifkin H, eds. Ellenberg and Rifkin's Diabetes Mellitus, 6th ed. Stamford, CT: Appleton and Lange; 2002.

2. Boulton AJ, Vinik AI, Arezzo JC, et al. Diabetic neuropathies: a statement by the American Diabetes Association. Diabetes Care. 2005;28:956-962. Full text Abstract

3. Thomas PK. Classification, differential diagnosis, and staging of diabetic peripheral neuropathy. Diabetes. 1997;46:S54-S57. Abstract

4. Dyck PJ, Albers JW, Andersen H, et al; Toronto Expert Panel on Diabetic Neuropathy. Diabetic polyneuropathies: update on research definition, diagnostic criteria and estimation of severity. Diabetes Metab Res Rev. 2011;27:620-628. Full text Abstract

5. Boulton AJ, Vileikyte L, Ragnarson-Tennvall G, et al. The global burden of diabetic foot disease. Lancet. 2005;366:1719-1724. Abstract

6. Thomas PK, Tomlinson DR. Diabetic and hypoglycemic neuropathy. In: Dyck P, Thomas P, Griffin J, et al, eds. Peripheral Neuropathy. 3rd ed. Philadelphia, PA: WB Saunders; 1993:1219-1250.

7. Alam U, Asghar O, Petropoulos IN, et al. Small fiber neuropathy in patients with latent autoimmune diabetes in adults. Diabetes Care. 2015;38:e102-e103. Abstract

8. The Diabetes Control and Complications Trial 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. Full text Abstract

9. Albers JW, Herman WH, Pop-Busui R, et al; Diabetes Control and Complications Trial /Epidemiology of Diabetes Interventions and Complications Research Group. Effect of prior intensive insulin treatment during the Diabetes Control and Complications Trial (DCCT) on peripheral neuropathy in type 1 diabetes during the Epidemiology of Diabetes Interventions and Complications (EDIC) Study. Diabetes Care. 2010;33:1090-1096. Full text Abstract

10. Pop-Busui R, Low PA, Waberski BH, et al; DCCT/EDIC Research Group. 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. Full text Abstract

11. 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. Abstract

12. Maser RE, Steenkiste AR, Dorman JS, et al. Epidemiological correlates of diabetic neuropathy. Report from Pittsburgh Epidemiology of Diabetes Complications Study. Diabetes. 1989;38:1456-1461. Abstract

13. Pirart J, Lauvaux JP, Rey W. Blood sugar and diabetic complications. N Engl J Med. 1978;298:1149. Abstract

14. Dyck PJ, Kratz KM, Karnes JL, et al. The prevalence by staged severity of various types of diabetic neuropathy, retinopathy, and nephropathy in a population-based cohort: the Rochester Diabetic Neuropathy Study. Neurology. 1993;43:817-824. Abstract

15. Young MJ, Boulton AJ, MacLeod AF, et al. A multicentre study of the prevalence of diabetic peripheral neuropathy in the United Kingdom hospital clinic population. Diabetologia. 1993;36:150-154. Abstract

16. Sandbæk A, Griffin SJ, Sharp SJ, et al. Effect of early multifactorial therapy compared with routine care on microvascular outcomes at 5 years in people with screen-detected diabetes: a randomized controlled trial: the ADDITION-Europe study. Diabetes Care. 2014;37:2015-2023. Full text Abstract

17. Charles M, Ejskjaer N, Witte DR, et al. 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. Full text Abstract

18. Pop-Busui R, Lu J, Lopes N, et al; BARI 2D Investigators. Prevalence of diabetic peripheral neuropathy and relation to glycemic control therapies at baseline in the BARI 2D cohort. J Peripher Nerv Syst. 2009;14:1-13. Full text Abstract

19. Pop-Busui R, Lu J, Brooks MM, et al; BARI 2D Study Group. 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. Full text Abstract

20. Pritchard N, Edwards K, Russell AW, et al. Corneal confocal microscopy predicts 4-year incident peripheral neuropathy in type 1 diabetes. Diabetes Care. 2015;38:671-675. Full text Abstract

21. Lovblom LE, Halpern EM, Wu T, et al. In vivo corneal confocal microscopy and prediction of future-incident neuropathy in type 1 diabetes: a preliminary longitudinal analysis. Can J Diabetes. 2015;39:390-397. Abstract

22. Spallone V, Ziegler D, Freeman R, et al; Toronto Consensus Panel on Diabetic Neuropathy. Cardiovascular autonomic neuropathy in diabetes: clinical impact, assessment, diagnosis, and management. Diabetes Metab Res Rev. 2011;27:639-653. Full text Abstract

23. Vileikyte L, Leventhal H, Gonzalez JS, et al. Diabetic peripheral neuropathy and depressive symptoms: the association revisited. Diabetes Care. 2005;28:2378-2383. Full text Abstract

24. Vileikyte L, Rubin RR, Leventhal H. Psychological aspects of diabetic neuropathic foot complications: an overview. Diabetes Metab Res Rev. 2004;20:S13-18. Abstract

25. Jaiswal M, Urbina EM, Wadwa RP, et al. Reduced heart rate variability among youth with type 1 diabetes: the SEARCH CVD study. Diabetes Care. 2013;36:157-162. Full text Abstract

26. Asghar O, Petropoulos IN, Alam U, et al. Corneal confocal microscopy detects neuropathy in subjects with impaired glucose tolerance. Diabetes Care. 2014;37:2643-2646. Full text Abstract

27. Zilliox LA, Ruby SK, Singh S, et al. Clinical neuropathy scales in neuropathy associated with impaired glucose tolerance. J Diabetes Complications. 2015;29:372-377. Full text Abstract

28. UK Prospective Diabetes Study (UKPDS) 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. Abstract

29. Shichiri M, Kishikawa H, Ohkubo Y, et al. Long-term results of the Kumamoto Study on optimal diabetes control in type 2 diabetic patients. Diabetes Care. 2000;23(Suppl 2):B21-B29. Abstract

30. Pop-Busui R, Herman WH, Feldman EL, et al; DCCT/EDIC Research Group. DCCT and EDIC studies in type 1 diabetes: lessons for diabetic neuropathy regarding metabolic memory and natural history. Curr Diab Rep. 2010;10:276-282. Abstract

31. 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. Full text Abstract

32. Ismail-Beigi F, Craven T, Banerji MA, et al; ACCORD trial group. 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. Erratum in: Lancet. 2010;376:1466. Abstract

33. Callaghan BC, Little AA, Feldman EL, et al. Enhanced glucose control for preventing and treating diabetic neuropathy. Cochrane Database Syst Rev. 2012;(6):CD007543. Full text Abstract

34. Tesfaye S, Chaturvedi N, Eaton SE, et al; EURODIAB Prospective Complications Study Group. Vascular risk factors and diabetic neuropathy. N Engl J Med. 2005;352:341-350. Full text Abstract

35. Stratton IM, Cull CA, Adler AI, et al. Additive effects of glycaemia and blood pressure exposure on risk of complications in type 2 diabetes: a prospective observational study (UKPDS 75). Diabetologia. 2006;49:1761-1769. Full text Abstract

36. Wiggin TD, Sullivan KA, Pop-Busui R, et al. Elevated triglycerides correlate with progression of diabetic neuropathy. Diabetes. 2009;58:1634-1640. Full text Abstract

37. Tesfaye S, Chaturvedi N, Eaton SE, et al. Vascular risk factors and diabetic neuropathy. N Engl J Med. 2005;352:341-350. Full text Abstract

38. Dehghani C, Pritchard N, Edwards K, et al. Risk factors associated with corneal nerve alteration in type 1 diabetes in the absence of neuropathy: a longitudinal in vivo corneal confocal microscopy study. Cornea. 2016;35:847-852. Abstract

39. Pop-Busui R, Sima A, Stevens M. Diabetic neuropathy and oxidative stress. Diabetes Metab Res Rev. 2006;22:257-273. Abstract

40. Stevens MJ, Pop-Busui R, Greene DA, et al. Pathogenesis of Diabetic neuropathy. In Ellenberg and Rifkin's Diabetes Mellitus. Porte DJ, Sherwin R, Rifkin H, eds. Stamford, CT: Appleton and Lange; 2002.

41. Vincent AM, Russell JW, Low P, et al. Oxidative stress in the pathogenesis of diabetic neuropathy. Endocr Rev. 2004;25:612-628. Full text Abstract

42. Sullivan KA, Feldman EL New developments in diabetic neuropathy. Curr Opin Neurol. 2005;18:586-590. Abstract

43. Rosenson RS, Fioretto P, Dodson PM. Does microvascular disease predict macrovascular events in type 2 diabetes? Atherosclerosis. 2011;218:13-18. Abstract

44. Laverdet B, Danigo A, Girard D, et al. Skin innervation: important roles during normal and pathological cutaneous repair. Histol Histopathol. 2015;30:875-892. Abstract

45. Cheng YJ, Gregg EW, Kahn HS, et al. Peripheral insensate neuropathy: a tall problem for US adults? Am J Epidemiol. 2006;164:873-880. Full text Abstract

46. Kote GS, Bhat AN, Thajuddeen K, et al. Peripheral insensate neuropathy: is height a risk factor? J Clin Diagn Res. 2013;7:296-301. Full text Abstract

47. Tseng CH. Prevalence of lower-extremity amputation among patients with diabetes mellitus: is height a factor? CMAJ. 2006;174:319-323. Full text Abstract

48. Davis TM, Yeap BB, Davis WA, et al. Lipid-lowering therapy and peripheral sensory neuropathy in type 2 diabetes: the Fremantle Diabetes Study. Diabetologia. 2008;51:562-566. Abstract

49. Duchen LW, Anjorin A, Watkins PJ, et al. Pathology of autonomic neuropathy in diabetes mellitus. Ann Intern Med. 1980;92:301-303. Abstract

50. Ejskjaer NT, Bradley JL, Buxton-Thomas MS, et al. Novel surgical treatment and gastric pathology in diabetic gastroparesis. Diabet Med. 1999;16:488-495. Abstract

51. Granberg V, Ejskjaer N, Peakman M, et al. Autoantibodies to autonomic nerves associated with cardiac and peripheral autonomic neuropathy. Diabetes Care. 2005;28:1959-1964. Full text Abstract

52. Rabinowe SL, Brown FM, Watts M, et al. Complement-fixing antibodies to sympathetic and parasympathetic tissues in IDDM. Autonomic brake index and heart-rate variation. Diabetes Care. 1990;13:1084-1088. Abstract

53. Stroud CR, Heller SR, Ward JD, et al. Analysis of antibodies against components of the autonomic nervous system in diabetes mellitus. QJM. 1997;90:577-585. Full text Abstract

54. Ang L, Jaiswal M, Martin C, et al. Glucose control and diabetic neuropathy: lessons from recent large clinical trials. Curr Diab Rep. 2014;14:528. Abstract

55. American Diabetes Association. 9. Microvascular complications and foot care. Diabetes Care. 2015;38(suppl 1):S58-S66. Full text Abstract

56. Thurman DJ, Stevens JA, Rao JK; Quality Standards Subcommittee of the American Academy of Neurology. Practice parameter: assessing patients in a neurology practice for risk of falls (an evidence-

based review): report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology. 2008;70:473-479. Full text Abstract

57. Vinik AI, Maser RE, Mitchell BD, et al. Diabetic autonomic neuropathy. Diabetes Care. 2003;26:1553-1579. Full text Abstract

58. Pop-Busui R. What do we know and we do not know about cardiovascular autonomic neuropathy in diabetes. J Cardiovasc Transl Res. 2012;5:463-478. Abstract

59. Pop-Busui R. Cardiac autonomic neuropathy in diabetes: a clinical perspective. Diabetes Care. 2010;33:434-441. Full text Abstract

60. Vinik AI, Ziegler D. Diabetic cardiovascular autonomic neuropathy. Circulation. 2007;115:387-397. Full text Abstract

61. Smith DS, Ferris CD. Current concepts in diabetic gastroparesis. Drugs. 2003;63:1339-1358. Abstract

62. Murray CD, Martin NM, Patterson M, et al. Ghrelin enhances gastric emptying in diabetic gastroparesis: a double blind, placebo controlled, crossover study. Gut. 2005;54:1693-1698. Full text Abstract

63. Enzlin P, Mathieu C, Vanderschueren D, et al. Diabetes mellitus and female sexuality: a review of 25 years' research. Diabet Med. 1998;15:809-815. Abstract

64. Olsen SE, Bjørgaas MR, Åsvold BO, et al. Impaired awareness of hypoglycemia in adults with type 1 diabetes is not associated with autonomic dysfunction or peripheral neuropathy. Diabetes Care. 2016;39:426-433. Full text Abstract

65. Low PA, Benrud-Larson LM, Sletten DM, et al. Autonomic symptoms and diabetic neuropathy: a population-based study. Diabetes Care. 2004;27:2942-2947. Full text Abstract

66. Zilliox L, Peltier AC, Wren PA, et al. Assessing autonomic dysfunction in early diabetic neuropathy: the Survey of Autonomic Symptoms. Neurology. 2011;76:1099-1105. Abstract

67. Armstrong DG, Lavery LA, Vela SA, et al. Choosing a practical screening instrument to identify patients at risk for diabetic foot ulceration. Arch Intern Med. 1998;158:289-292. Abstract

68. Moghtaderi A, Bakhshipour A, Rashidi H. Validation of Michigan neuropathy screening instrument for diabetic peripheral neuropathy. Clin Neurol Neurosurg. 2006;108:477-481. Abstract

69. Lipsky BA, Berendt AR, Cornia PB, et al; Infectious Diseases Society of America. 2012 Infectious Diseases Society of America clinical practice guideline for the diagnosis and treatment of diabetic foot infections. Clin Infect Dis. 2012;54:e132-173. Full text Abstract

70. Lipsky BA, Peters EJ, Senneville E, et al. Expert opinion on the management of infections in the diabetic foot. Diabetes Metab Res Rev. 2012;28 Suppl 1:163-178. Full text Abstract

71. England JD, Gronseth GS, Franklin G, et al. Distal symmetric polyneuropathy: a definition for clinical research: report of the American Academy of Neurology, the American Association of

Electrodiagnostic Medicine, and the American Academy of Physical Medicine and Rehabilitation. Neurology. 2005;64:199-207. Full text Abstract

72. Lauria G, Hsieh ST, Johansson O, et al; European Federation of Neurological Societies; Peripheral Nerve Society. European Federation of Neurological Societies/Peripheral Nerve Society Guideline on the use of skin biopsy in the diagnosis of small fiber neuropathy. Report of a joint task force of the European Federation of Neurological Societies and the Peripheral Nerve Society. Eur J Neurol. 2010;17:903-912. Full text Abstract

73. England JD, Gronseth GS, Franklin G, et al; American Academy of Neurology. Practice parameter: evaluation of distal symmetric polyneuropathy: role of autonomic testing, nerve biopsy, and skin biopsy (an evidence-based review). Report of the American Academy of Neurology, American Association of Neuromuscular and Electrodiagnostic Medicine, and American Academy of Physical Medicine and Rehabilitation. Neurology. 2009;72:177-184. Full text Abstract

74. Chen X, Graham J, Dabbah MA, et al. Small nerve fiber quantification in the diagnosis of diabetic sensorimotor polyneuropathy: comparing corneal confocal microscopy with intraepidermal nerve fiber density. Diabetes Care. 2015;38:1138-1144. Full text Abstract

75. Vas PR, Green AQ, Rayman G. Small fibre dysfunction, microvascular complications and glycaemic control in type 1 diabetes: a case-control study. Diabetologia. 2012;55:795-800. Full text Abstract

76. Shy ME, Frohman EM, So YT, et al. Quantitative sensory testing: report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. Neurology. 2003;60:898-904. Full text Abstract

77. Siao P, Cros DP. Quantitative sensory testing. Phys Med Rehabil Clin N Am. 2003;14:261-286. Abstract

78. Martin CL, Waberski BH, Pop-Busui R, et al; DCCT/EDIC Research Group. Vibration perception threshold as a measure of distal symmetrical peripheral neuropathy in type 1 diabetes: results from the DCCT/EDIC study. Diabetes Care. 2010;33:2635-2641. Full text Abstract

79. Tavakoli M, Begum P, McLaughlin J, et al. Corneal confocal microscopy for the diagnosis of diabetic autonomic neuropathy. Muscle Nerve. 2015;52:363-370. Abstract

80. Bernardi L, Spallone V, Stevens M, et al; Toronto Consensus Panel on Diabetic Neuropathy. Methods of investigation for cardiac autonomic function in human research studies. Diabetes Metab Res Rev. 2011;27:654-664. Full text Abstract

81. Ziegler D, Zentai CP, Perz S, et al; KORA Study Group. 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. Full text Abstract

82. Stöhrer M, Blok B, Castro-Diaz D, et al. EAU guidelines on neurogenic lower urinary tract dysfunction. Eur Urol. 2009;56:81-88. Abstract

83. Mayaudon H, Miloche PO, Bauduceau B. A new simple method for assessing sudomotor function: relevance in type 2 diabetes. Diabetes Metab. 2010;36:450-4. Abstract

84. Asghar O, Arumugam P, Armstrong IS, et al. Individuals with impaired glucose tolerance demonstrate normal cardiac sympathetic innervation using I-123 mIBG scintigraphy. J Nucl Cardiol. 2015;22:1262-1268. Abstract

85. Spallone V, Maiello MR, Morganti R, et al. Usefulness of ambulatory blood pressure monitoring in predicting the presence of autonomic neuropathy in type I diabetic patients. J Hum Hypertens. 2007;21:381-386. Abstract

86. Hamner JW, Taylor JA. Automated quantification of sympathetic beat-by-beat activity, independent of signal quality. J Appl Physiol. 2001;91:1199-1206. Full text Abstract

87. Malik R, Veves A, Tesfaye S, et al; Toronto Consensus Panel on Diabetic Neuropathy. Small fiber neuropathy: role in the diagnosis of diabetic sensorimotor polyneuropathy. Diabetes Metab Res Rev. 2011;27:678-684. Full text Abstract

88. Kempler P, Amarenco G, Freeman R, et al; Toronto Consensus Panel on Diabetic Neuropathy. Management strategies for gastrointestinal, erectile, bladder, and sudomotor dysfunction in patients with diabetes. Diabetes Metab Res Rev. 2011;27:665-677. Full text Abstract

89. Tavakoli M, Quattrini C, Abbott C, et al. Corneal confocal microscopy: a novel noninvasive test to diagnose and stratify the severity of human diabetic neuropathy. Diabetes Care. 2010;33:1792-1797. Full text Abstract

90. Tavakoli M, Marshall A, Thompson L, et al. Corneal confocal microscopy: a novel noninvasive means to diagnose neuropathy in patients with Fabry disease. Muscle Nerve. 2009;40:976-984. Abstract

91. Mehra S, Tavakoli M, Kallinikos PA, et al. Corneal confocal microscopy detects early nerve regeneration after pancreas transplantation in patients with type 1 diabetes. Diabetes Care. 2007;30:2608-2612. Abstract

92. American Diabetes Association. 2. Classification and diagnosis of diabetes. Diabetes Care. 2015;38(suppl 1):S8-S16. Full text Abstract

93. Boulton AJ, Malik RA, Arezzo JC, et al. Diabetic somatic neuropathies. Diabetes Care. 2004;27:1458-1486. Full text Abstract

94. Dyck PJ, Norell JE, Tritschler H, et al. Challenges in design of multicenter trials: end points assessed longitudinally for change and monotonicity. Diabetes Care. 2007;30:2619-2625. Full text Abstract

95. Pop-Busui R, Evans GW, Gerstein HC, et al; Action to Control Cardiovascular Risk in Diabetes Study Group. 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. Full text Abstract

96. Casellini CM, Parson HK, Richardson MS, et al. Sudoscan, a noninvasive tool for detecting diabetic small fiber neuropathy and autonomic dysfunction. Diabetes Technol Ther. 2013;15:948-953. Full text Abstract

97. Eranki VG, Santosh R, Rajitha K, et al. Sudomotor function assessment as a screening tool for microvascular complications in type 2 diabetes. Diabetes Res Clin Pract. 2013;101:e11-e13. Abstract

98. Ziegler D, Papanas N, Zhivov A, et al. Early detection of nerve fiber loss by corneal confocal microscopy and skin biopsy in recently diagnosed type 2 diabetes. Diabetes. 2014;63:2454-2463. Full text Abstract

99. Feldman EL, Stevens MJ, Thomas PK, et al. A practical two-step quantitative clinical and electrophysiological assessment for the diagnosis and staging of diabetic neuropathy. Diabetes Care. 1994;17:1281-1289. Abstract

100. Young MJ, Adams JE, Anderson GF, et al. Medial arterial calcification in the feet of diabetic patients and matched non-diabetic control subjects. Diabetologia. 1993;36:615-621. Abstract

101. Cabezas-Cerrato J. The prevalence of clinical diabetic polyneuropathy in Spain: a study in primary care and hospital clinic groups. Neuropathy Spanish Study Group of the Spanish Diabetes Society (SDS). Diabetologia. 1998;41:1263-1269. Abstract

102. Herman WH, Pop-Busui R, Braffett BH, et al; DCCT/EDIC Research Group. Use of the Michigan Neuropathy Screening Instrument as a measure of distal symmetrical peripheral neuropathy in Type 1 diabetes: results from the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications. Diabet Med. 2012;29:937-944. Abstract

103. Effect of intensive diabetes treatment on nerve conduction in the Diabetes Control and Complications Trial. Ann Neurol. 1995 Dec;38:869-880. Abstract

104. Martin CL, Albers JW, Pop-Busui R; DCCT/EDIC Research Group. Neuropathy and related findings in the diabetes control and complications trial/epidemiology of diabetes interventions and complications study. Diabetes Care. 2014;37:31-38. Full text Abstract

105. Ohkubo Y, Kishikawa H, Araki E, et al. Intensive insulin therapy prevents the progression of diabetic microvascular complications in Japanese patients with non-insulin-dependent diabetes mellitus: a randomized prospective 6-year study. Diabetes Res Clin Pract. 1995;28:103-117. Abstract

106. Kennedy WR, Navarro X, Goetz FC, et al. Effects of pancreatic transplantation on diabetic neuropathy. N Engl J Med. 1990;322:1031-1037. Abstract

107. Navarro X, Sutherland DE, Kennedy WR. Long-term effects of pancreatic transplantation on diabetic neuropathy. Ann Neurol. 1997;42:727-736. Abstract

108. Tavakoli M, Mitu-Pretorian M, Petropoulos IN, et al. Corneal confocal microscopy detects early nerve regeneration in diabetic neuropathy after simultaneous pancreas and kidney transplantation. Diabetes. 2013;62:254-260. Full text Abstract

109. Oyibo SO, Prasad YD, Jackson NJ, et al. The relationship between blood glucose excursions and painful diabetic peripheral neuropathy: a pilot study. Diabet Med. 2002;19:870-873. Abstract

110. Dorresteijn JA, Valk GD. Patient education for preventing diabetic foot ulceration. Diabetes Metab Res Rev. 2012;28(suppl 1):101-106. Full text Abstract

111. Landsman A, Agnew P, Parish L, et al. Diabetic foot ulcers treated with becaplermin and TheraGauze, a moisture-controlling smart dressing: a randomized, multicenter, prospective analysis. J Am Podiatr Med Assoc. 2010;100:155-160. Abstract

112. Roukis TS, Schade VL. Percutaneous flexor tenotomy for treatment of neuropathic toe ulceration secondary to toe contracture in persons with diabetes: a systematic review. J Foot Ankle Surg. 2009;48:684-689. Abstract

113. Smith AG, Russell J, Feldman EL, et al. Lifestyle intervention for pre-diabetic neuropathy. Diabetes Care. 2006;29:1294-1299. Full text Abstract

114. Kluding PM, Pasnoor M, Singh R, et al. The effect of exercise on neuropathic symptoms, nerve function, and cutaneous innervation in people with diabetic peripheral neuropathy. J Diabetes Complications. 2012;26:424-429. Full text Abstract

115. Bril V, England J, Franklin GM, et al; American Academy of Neurology; American Association of Neuromuscular and Electrodiagnostic Medicine; American Academy of Physical Medicine and Rehabilitation. Evidence-based guideline: treatment of painful diabetic neuropathy. Neurology. 2011;76:1758-1765. Full text Abstract

116. 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. Full text Abstract

117. Moore RA, Straube S, Wiffen PJ, et al. Pregabalin for acute and chronic pain in adults. Cochrane Database Syst Rev. 2009;(3):CD007076. Full text Abstract

118. 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. Full text Abstract

119. Raskin P, Huffman C, Toth C, et al. Pregabalin in patients with inadequately treated painful diabetic peripheral neuropathy: a randomized withdrawal trial. Clin J Pain. 2014;30:379-390. Abstract

120. Rosenstock J, Tuchman M, LaMoreaux L, et al. Pregabalin for the treatment of painful diabetic peripheral neuropathy: a double-blind, placebo-controlled trial. Pain. 2004;110:628-638. Abstract

121. Backonja MM. Gabapentin monotherapy for the symptomatic treatment of painful neuropathy: a multicenter, double-blind, placebo-controlled trial in patients with diabetes mellitus. Epilepsia. 1999;40:S57-S59. Abstract

122. Perez HE, Sanchez GF. Gabapentin therapy for diabetic neuropathic pain. Am J Med. 2000;108:689. Abstract

123. Simpson D. Gabapentin and venlafaxine for the treatment of painful diabetic neuropathy. J Clinl Neuromuscul Dis. 2001;3:53-62. Abstract

124. Moore RA, Wiffen PJ, Derry S, et al. Gabapentin for chronic neuropathic pain and fibromyalgia in adults. Cochrane Database Syst Rev. 2014;(4):CD007938. Full text Abstract

125. Goldstein DJ, Lu Y, Detke MJ, et al. Effects of duloxetine on painful physical symptoms associated with depression. Psychosomatics. 2004;45:17-28. Abstract

126. Iyengar S, Bymaster FP, Wong DT, et al. Efficacy of the selective serotonin and norepinephrine reuptake inhibitor, duloxetine, in the formalin model of persistent pain. European Neuropsychopharmacology. 2002;12:215.

127. Goldstein DJ, Lu Y, Detke MJ, et al. Duloxetine vs. placebo in patients with painful diabetic neuropathy. Pain. 2005;116:109-118. Abstract

128. Wernicke JF, Prakash A, Kajdasz DK, et al. Safety and tolerability of duloxetine treatment of diabetic peripheral neuropathic pain between patients with and without cardiovascular conditions. J Diabetes Complications. 2009;23:349-359. Abstract

129. Sultan A, Gaskell H, Derry S, Moore RA. Duloxetine for painful diabetic neuropathy and fibromyalgia pain: systematic review of randomised trials. BMC Neurol. 2008;8:29. Review. Full text Abstract

130. Lunn MP, Hughes RA, Wiffen PJ. Duloxetine for treating painful neuropathy, chronic pain or fibromyalgia. Cochrane Database Syst Rev. 2014;(1):CD007115. Full text Abstract

131. Wernicke JF, Pritchett YL, D'Souza DN, et al. A randomized controlled trial of duloxetine in diabetic peripheral neuropathic pain. Neurology. 2006;67:1411-1420. Abstract

132. Raskin J, Wang F, Pritchett YL, et al. Duloxetine for patients with diabetic peripheral neuropathic pain: a 6-month open-label safety study. Pain Med. 2006;7:373-385. Abstract

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

134. Tesfaye S, Wilhelm S, Lledo A, et al. Duloxetine and pregabalin: high-dose monotherapy or their combination? The "COMBO-DN study" - a multinational, randomized, double-blind, parallel-group study in patients with diabetic peripheral neuropathic pain. Pain. 2013;154:2616-2625. Abstract

135. Holbech JV, Bach FW, Finnerup NB, et al. Imipramine and pregabalin combination for painful polyneuropathy: a randomized controlled trial. Pain. 2015;156:958-966. Abstract

136. Joss JD. Tricyclic antidepressant use in diabetic neuropathy. Ann Pharmacother. 1999;33:996-1000. Abstract

137. Max MB, Lynch SA, Muir J, et al. Effects of desipramine, amitriptyline, and fluoxetine on pain in diabetic neuropathy. N Engl J Med. 1992;326:1250-1256. Abstract

138. Kvinesdal B, Molin J, Froland A, et al. Imipramine treatment of painful diabetic neuropathy. JAMA. 1984;251:1727-1730. Abstract

139. Max MB, Culnane M, Schafer SC, et al. Amitriptyline relieves diabetic neuropathy pain in patients with normal or depressed mood. Neurology. 1987;37:589-596. Abstract

140. Sindrup SH, Ejlertsen B, Froland A, et al. Imipramine treatment in diabetic neuropathy: relief of subjective symptoms without changes in peripheral and autonomic nerve function. Eur J Clin Pharmacol. 1989;37:151-153. Abstract

141. Max MB, Kishore-Kumar R, Schafer SC, et al. Efficacy of desipramine in painful diabetic neuropathy: a placebo-controlled trial. Pain. 1991;45:3-9. Abstract

142. McQuay HJ, Tramèr M, Nye BA, et al. A systematic review of antidepressants in neuropathic pain. Pain. 1996;68:217-227. Abstract

143. Richelson E. Pharmacology of antidepressants--characteristics of the ideal drug. Mayo Clin Proc. 1994;69:1069-1081. Abstract

144. Moore RA, Derry S, Aldington D, et al. Amitriptyline for neuropathic pain in adults. Cochrane Database Syst Rev. 2015;(7):CD008242. Full text Abstract

145. Derry S, Wiffen PJ, Aldington D,et al. Nortriptyline for neuropathic pain in adults. Cochrane Database Syst Rev. 2015;(1):CD011209. Full text Abstract

146. Hearn L, Derry S, Phillips T, et al. Imipramine for neuropathic pain in adults. Cochrane Database Syst Rev. 2014;(5):CD010769. Full text Abstract

147. Hearn L, Moore RA, Derry S, et al. Desipramine for neuropathic pain in adults. Cochrane Database Syst Rev. 2014;(9):CD011003. Full text Abstract

148. Gallagher HC, Gallagher RM, Butler M, et al. Venlafaxine for neuropathic pain in adults. Cochrane Database Syst Rev. 2015;(8):CD011091. Full text Abstract

149. Sindrup SH, Gram LF, Brosen K, et al. The selective serotonin reuptake inhibitor paroxetine is effective in the treatment of diabetic neuropathy symptoms. Pain. 1990;42:135-144. Abstract

150. Goodnick PJ, Jimenez I, Kumar A. Sertraline in diabetic neuropathy: preliminary results. Ann Clin Psychiatry. 1997;9:255-257. Abstract

151. Dellemijn PL, Vanneste JA. Randomised double-blind active-placebo-controlled crossover trial of intravenous fentanyl in neuropathic pain. Lancet. 1997;349:753-758. Abstract

152. Rowbotham MC, Twilling L, Davies PS, et al. Oral opioid therapy for chronic peripheral and central neuropathic pain. N Engl J Med. 2003;348:1223-1232. Abstract

153. Watson CP, Moulin D, Watt-Watson J, et al. Controlled-release oxycodone relieves neuropathic pain: a randomized controlled trial in painful diabetic neuropathy. Pain. 2003;105:71-78. Abstract

154. Harati Y, Gooch C, Swenson M, et al. Double-blind randomized trial of tramadol for the treatment of the pain of diabetic neuropathy. Neurology. 1998;50:1842-1846. Abstract

155. 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. Full text Abstract

156. McNicol ED, Midbari A, Eisenberg E. Opioids for neuropathic pain. Cochrane Database Syst Rev. 2013;(8):CD006146. Full text Abstract

157. Gaskell H, Derry S, Stannard C, et al. Oxycodone for neuropathic pain in adults. Cochrane Database Syst Rev. 2016;(7):CD010692. Full text Abstract

158. Gibbons CH, Wang N, Freeman R. Capsaicin induces degeneration of cutaneous autonomic nerve fibers. Ann Neurol. 2010;68:888-898. Full text Abstract

159. Derry S, Lloyd R, Moore RA, et al. Topical capsaicin for chronic neuropathic pain in adults. Cochrane Database Syst Rev. 2009;(4):CD007393. Full text Abstract

160. Treatment of painful diabetic neuropathy with topical capsaicin. A multicenter, double-blind, vehicle-controlled study. The Capsaicin Study Group. Arch Intern Med. 1991;151:2225-2229. Abstract

161. Effect of treatment with capsaicin on daily activities of patients with painful diabetic neuropathy. Capsaicin Study Group. Diabetes Care. 1992;15:159-165. Abstract

162. Biesbroeck R, Bril V, Hollander P, et al. A double-blind comparison of topical capsaicin and oral amitriptyline in painful diabetic neuropathy. Adv Ther. 1995;12:111-120. Abstract

163. Zhang WY, Li Wan Po A. The effectiveness of topically applied capsaicin. A meta-analysis. Eur J Clin Pharmacol. 1994;46:517-522. Abstract

164. Dubinsky RM, Miyasaki J. Assessment: efficacy of transcutaneous electric nerve stimulation in the treatment of pain in neurologic disorders (an evidence-based review): report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. Neurology. 2010;74:173-176. Full text Abstract

165. Kumar D, Marshall HJ. Diabetic peripheral neuropathy: amelioration of pain with transcutaneous electrostimulation. Diabetes Care. 1997;20:1702-1705. Abstract

166. Julka IS, Alvaro M, Kumar D. Beneficial effects of electrical stimulation on neuropathic symptoms in diabetes patients. J Foot Ankle Surg. 1998;37:191-194. Abstract

167. Abuaisha BB, Costanzi JB, Boulton AJ. Acupuncture for the treatment of chronic painful peripheral diabetic neuropathy: a long-term study. Diabetes Res Clin Pract. 1998;39:115-121. Abstract

168. National Institute for Health and Care Excellence. Percutaneous electrical nerve stimulation for refractory neuropathic pain. March 2013. http://www.nice.org.uk/ (last accessed 16 May 2016). Full text

169. de Vos CC, Meier K, Zaalberg PB, et al. Spinal cord stimulation in patients with painful diabetic neuropathy: a multicentre randomized clinical trial. Pain. 2014;155:2426-2431. Abstract

170. Slangen R, Schaper NC, Faber CG, et al. Spinal cord stimulation and pain relief in painful diabetic peripheral neuropathy: a prospective two-center randomized controlled trial. Diabetes Care. 2014;37:3016-3024. Full text Abstract

REFERENCES

171. Albers JW, Pop-Busui R. Diabetic neuropathy: mechanisms, emerging treatments, and subtypes. Curr Neurol Neurosci Rep. 2014;14:473. Abstract

172. Gaede P, Lund-Andersen H, Parving HH, et al. Effect of a multifactorial intervention on mortality in type 2 diabetes. N Engl J Med. 2008;358:580-591. Full text Abstract

173. 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. Abstract

174. MacLean A, Allen B. Orthostatic hypotension and orthostatic tachycardia. Treatment with "head-up" bed. JAMA. 1940;115:2162-2167.

175. Schatz IJ, Podolsky S, Frame B. Idiopathic orthostatic hypotension. Diagnosis and treatment. JAMA. 1963;186:537-540. Abstract

176. Levin JM, Ravenna P, Weiss M. Idiopathic orthostatic hypotension. Treatment with a commercially available counterpressure suit. Arch Intern Med. 1964;114:145-148. Abstract

177. Lewis HD Jr, Dunn M. Orthostatic hypotension syndrome. A case report. Am Heart J. 1967;74:396-401. Abstract

178. Sheps SG. Use of an elastic garment in the treatment of orthostatic hypotension. Cardiology. 1976;61:271-279. Abstract

179. Tanaka H, Yamaguchi H, Tamai H. Treatment of orthostatic intolerance with inflatable abdominal band. Lancet. 1997:349:175. Abstract

180. Smit AA, Hardjowijono MA, Wieling W. Are portable folding chairs useful to combat orthostatic hypotension? Ann Neurol. 1997:42:975-978. Abstract

181. van Lieshout JJ, ten Harkel AD, Wieling W. Physical manoeuvres for combating orthostatic dizziness in autonomic failure. Lancet. 1992;339:897-898. Abstract

182. Schatz IJ, Miller MJ, Frame B. Corticosteroids in the management of orthostatic hypotension. Cardiology. 1976;61:280-289. Abstract

183. van Lieshout JJ, ten Harkel AD, Wieling W. Fludrocortisone and sleeping in the head-up position limit the postural decrease in cardiac output in autonomic failure. Clin Auton Res. 2000;10:35-42. Abstract

184. Hickler RB, Thompson GR, Fox LM, et al. Successful treatment of orthostatic hypotension with 9-alpha-fluorohydrocortisone. N Engl J Med. 1959;261:788-791. Abstract

185. Bannister R, Ardill L, Fentem P. An assessment of various methods of treatment of idiopathic orthostatic hypotension. Q J Med. 1969;38:377-395. Abstract

186. Campbell IW, Ewing DJ, Clarke BF. Therapeutic experience with fludrocortisone in diabetic postural hypotension. Br Med J. 1976;1:872-874. Full text Abstract

187. Chobanian AV, Volicer L, Tifft CP, et al. Mineralocorticoid-induced hypertension in patients with orthostatic hypotension. N Engl J Med. 1979;301:68-73. Abstract

188. Robertson D, Davis TL. Recent advances in the treatment of orthostatic hypotension. Neurology. 1995;45:S26-32. Abstract

189. Zachariah PK, Bloedow DC, Moyer TP, et al. Pharmacodynamics of midodrine, an antihypotensive agent. Clin Pharmacol Ther. 1986;39:586-591. Abstract

190. McTavish D, Goa KL. Midodrine. A review of its pharmacological properties and therapeutic use in orthostatic hypotension and secondary hypotensive disorders. Drugs. 1989;38:757-777. Abstract

191. Low PA, Gilden JL, Freeman R, et al. Efficacy of midodrine vs placebo in neurogenic orthostatic hypotension. A randomized, double-blind multicenter study. Midodrine Study Group. JAMA. 1997;277:1046-1051. [Erratum in: JAMA. 1997;278:388.] Abstract

192. Kaufmann H, Brannan T, Krakoff L, et al. Treatment of orthostatic hypotension due to autonomic failure with a peripheral alpha-adrenergic agonist (midodrine). Neurology. 1988;38:951-956. Abstract

193. Wright RA, Kaufmann HC, Perera R, et al. A double-blind, dose-response study of midodrine in neurogenic orthostatic hypotension. Neurology. 1998;51:120-124. Abstract

194. Freeman R. Treatment of orthostatic hypotension. Semin Neurol. 2003;23:435-442. Abstract

195. Mathias CJ, Kimber JR. Treatment of postural hypotension. J Neurol Neurosurg Psychiatry. 1998;65:285-289. Full text Abstract

196. Winkler AS, Landau S, Watkins P, et al. Observations on haematological and cardiovascular effects of erythropoietin treatment in multiple system atrophy with sympathetic failure. Clin Auton Res. 2002;12:203-206. Abstract

197. Hoeldtke RD, Streeten DH. Treatment of orthostatic hypotension with erythropoietin. N Engl J Med. 1993;329:611-615. Full text Abstract

198. Perera R, Isola L, Kaufmann H. Effect of recombinant erythropoietin on anemia and orthostatic hypotension in primary autonomic failure. Clin Auton Res. 1995;5:211-213. Abstract

199. Vinik AI. Diabetic neuropathy: pathogenesis and therapy. Am J Med. 1999;107:17S-26S. Abstract

200. Vinik AI. Diagnosis and management of diabetic neuropathy. Clin Geriatr Med. 1999;15:293-320. Abstract

201. Verne GN, Sninsky CA. Diabetes and the gastrointestinal tract. Gastroenterol Clin North Am. 1998;27:861-874, vi-vii. Abstract

202. Sturm A, Holtmann G, Goebell H, et al. Prokinetics in patients with gastroparesis: a systematic analysis. Digestion. 1999;60:422-427. Abstract

203. Peeters T, Matthijs G, Depoortere I, et al. Erythromycin is a motilin receptor agonist. Am J Physiol. 1989;257:G470-474. Abstract

204. Richards RD, Davenport K, McCallum RW. The treatment of idiopathic and diabetic gastroparesis with acute intravenous and chronic oral erythromycin. Am J Gastroenterol. 1993;88:203-207. Abstract

205. DiBaise JK, Quigley EM. Efficacy of prolonged administration of intravenous erythromycin in an ambulatory setting as treatment of severe gastroparesis: one center's experience. J Clin Gastroenterol. 1999;28:131-134. Abstract

206. European Medicines Agency. European Medicines Agency recommends changes to the use of metoclopramide. July 2013. http://www.ema.europa.eu (last accessed 16 May 2016). Full text

207. Horowitz M, Harding PE, Chatterton BE, et al. Acute and chronic effects of domperidone on gastric emptying in diabetic autonomic neuropathy. Dig Dis Sci. 1985;30:1-9. Abstract

208. Patterson D, Abell T, Rothstein R, et al. A double-blind multicenter comparison of domperidone and metoclopramide in the treatment of diabetic patients with symptoms of gastroparesis. Am J Gastroenterol. 1999;94:1230-1234. Abstract

209. Ahmad N, Keith-Ferris J, Gooden E, et al. Making a case for domperidone in the treatment of gastrointestinal motility disorders. Curr Opin Pharmacol. 2006;6:571-576. Abstract

210. European Medicines Agency. CMDh confirms recommendations on restricting use of domperidone-containing medicines. April 2014. http://www.ema.europa.eu/ (last accessed 16 May 2016). Full text

211. Lacy BE, Zayat EN, Crowell MD, et al. Botulinum toxin for the treatment of gastroparesis: a preliminary report. Am J Gastroenterol. 2002;97:1548-1552. Abstract

212. Ezzeddine D, Jit R, Katz N, et al. Pyloric injection of botulinum toxin for treatment of diabetic gastroparesis. Gastrointest Endosc. 2002;55:920-923. Abstract

213. Lacy BE, Crowell MD, Schettler-Duncan A, et al. The treatment of diabetic gastroparesis with botulinum toxin injection of the pylorus. Diabetes Care. 2004;27:2341-2347. Abstract

214. McCallum RW, Chen JD, Lin Z, et al. Gastric pacing improves emptying and symptoms in patients with gastroparesis. Gastroenterology. 1998;114:456-461. Abstract

215. Bellahsene BE, Lind CD, Schirmer BD, et al. Acceleration of gastric emptying with electrical stimulation in a canine model of gastroparesis. Am J Physiol. 1992;262:G826-834. Abstract

216. Forster J, Sarosiek I, Delcore R, et al. Gastric pacing is a new surgical treatment for gastroparesis. Am J Surg. 2001;182:676-681. Abstract

217. Green PA, Berge KG, Sprague RG. Control of diabetic diarrhea with antibiotic therapy. Diabetes. 1968;17:385-387. Abstract

218. Tsai ST, Vinik AI, Brunner JF. Diabetic diarrhea and somatostatin. Ann Intern Med. 1986;104:894. Abstract

219. von der Ohe MR, Camilleri M, Thomforde GM, et al. Differential regional effects of octreotide on human gastrointestinal motor function. Gut. 1995;36:743-748. Full text Abstract

220. Phé V, Rouprêt M. Erectile dysfunction and diabetes: a review of the current evidence-based medicine and a synthesis of the main available therapies. Diabetes Metab. 2012;38:1-13. Abstract

221. Rendell MS, Rajfer J, Wicker PA, et al. Sildenafil for treatment of erectile dysfunction in men with diabetes: a randomized controlled trial. Sildenafil Diabetes Study Group. JAMA. 1999;281:421-426. Full text Abstract

222. Goldstein I, Kim E, Steers WD, et al. Efficacy and safety of tadalafil in men with erectile dysfunction with a high prevalence of comorbid conditions: results from MOMENTUS: multiple observations in men with erectile dysfunction in National Tadalafil Study in the US. J Sex Med. 2007;4:166-175. Abstract

223. Virag R, Frydman D, Legman M, et al. Intracavernous injection of papaverine as a diagnostic and therapeutic method in erectile failure. Angiology. 1984;35:79-87. Abstract

224. Spollett GR. Assessment and management of erectile dysfunction in men with diabetes. Diabetes Educ. 1999;25:65-73. Abstract

225. Saulie BA, Campbell RK. Treating erectile dysfunction in diabetes patients. Diabetes Educ. 1997;23:29-33, 35-26, 38. Abstract

226. Pfeifer MA, Schumer MP, Gelber DA. Aldose reductase inhibitors: the end of an era or the need for different trial designs? Diabetes. 1997;46:S82-89. Abstract

227. Hotta N, Toyota T, Matsuoka K, et al. Clinical efficacy of fidarestat, a novel aldose reductase inhibitor, for diabetic peripheral neuropathy: a 52-week multicenter placebo-controlled double-blind parallel group study. Diabetes Care. 2001;24:1776-1782. Abstract

228. Asano T, Saito Y, Kawakami M, et al. Fidarestat (SNK-860), a potent aldose reductase inhibitor, normalizes the elevated sorbitol accumulation in erythrocytes of diabetic patients. J Diabetes Complications. 2002;16:133-138. Abstract

229. Bril V, Buchanan RA. Long-term effects of ranirestat (AS-3201) on peripheral nerve function in patients with diabetic sensorimotor polyneuropathy. Diabetes Care. 2006;29:68-72. Full text Abstract

230. Bril V, Hirose T, Tomioka S, et al. Ranirestat Study Group. Ranirestat for the management of diabetic sensorimotor polyneuropathy. Diabetes Care. 2009;32:1256-1260. Full text Abstract

231. Hotta N, Kawamori R, Atsumi Y, et al. ADCT Study Group. Stratified analyses for selecting appropriate target patients with diabetic peripheral neuropathy for long-term treatment with an aldose reductase inhibitor, epalrestat. Diabet Med. 2008;25:818-825. Full text Abstract

232. Chalk C, Benstead TJ, Moore F. Aldose reductase inhibitors for the treatment of diabetic polyneuropathy. Cochrane Database Syst Rev. 2007;(4):CD004572. Full text Abstract

233. Stavniichuk R, Drel VR, Shevalye H, et al. Baicalein alleviates diabetic peripheral neuropathy through inhibition of oxidative-nitrosative stress and p38 MAPK activation. Exp Neurol. 2011;230:106-113. Abstract

234. Ziegler D, Hanefeld M, Ruhnau KJ, et al. Treatment of symptomatic diabetic polyneuropathy with the antioxidant alpha-lipoic acid: a 7-month multicenter randomized controlled trial (ALADIN III Study). ALADIN III Study Group. Alpha-Lipoic Acid in Diabetic Neuropathy. Diabetes Care. 1999;2:1296-1301. Abstract

235. Ziegler D, Reljanovic M, Mehnert H, et al. Alpha-lipoic acid in the treatment of diabetic polyneuropathy in Germany: current evidence from clinical trials. Exp Clin Endocrinol Diabetes. 1999;07:421-430. Abstract

236. Ametov AS, Barinov A, Dyck PJ, et al. The sensory symptoms of diabetic polyneuropathy are improved with alpha-lipoic acid: the SYDNEY trial. Diabetes Care. 2003;26:770-776. Full text Abstract

237. Ziegler D, Low PA, Litchy WJ, et al. Efficacy and safety of antioxidant treatment with alpha-lipoic acid over 4 years in diabetic polyneuropathy: the NATHAN 1 trial. Diabetes Care. 2011;34:2054-2060. Abstract

238. Mijnhout GS, Kollen BJ, Alkhalaf A, et al. Alpha lipoic acid for symptomatic peripheral neuropathy in patients with diabetes: a meta-analysis of randomized controlled trials. Int J Endocrinol. 2012:456279. Full text Abstract

239. Apfel SC, Kessler JA, Adornato BT, et al. Recombinant human nerve growth factor in the treatment of diabetic polyneuropathy. NGF Study Group. Neurology. 1998;51:695-702. Abstract

240. Apfel SC. Nerve growth factor for the treatment of diabetic neuropathy: what went wrong, what went right, and what does the future hold? Int Rev Neurobiol. 2002;50:393-413. Abstract

241. Quatraro A, Roca P, Donzella C, et al. Acetyl-L-carnitine for symptomatic diabetic neuropathy. Diabetologia. 1995;38:123. Abstract

242. Onofrj M, Fulgente T, Melchionda D, et al. L-acetylcarnitine as a new therapeutic approach for peripheral neuropathies with pain. Int J Clin Pharmacol Res. 1995:15:9-15. Abstract

243. Scarpini E, Sacilotto G, Baron P, et al. Effect of acetyl-L-carnitine in the treatment of painful peripheral neuropathies in HIV+ patients. J Peripher Nerv Syst. 1997;2:250-252. Abstract

244. Evans JD, Jacobs TF, Evans EW. Role of acetyl-L-carnitine in the treatment of diabetic peripheral neuropathy. Ann Pharmacother. 2008;42:1686-1691. Abstract

245. Sima AA, Calvani M, Mehra M, et al. Acetyl-L-carnitine improves pain, nerve regeneration, and vibratory perception in patients with chronic diabetic neuropathy: an analysis of two randomized placebo-controlled trials.Diabetes Care. 2005;28:89-94. Full text Abstract

246. Drel VR, Pacher P, Stavniichuk R, et al. Poly(ADP-ribose)polymerase inhibition counteracts renal hypertrophy and multiple manifestations of peripheral neuropathy in diabetic Akita mice. Int J Mol Med. 2011;28:629-635. Full text Abstract

247. Sima AA, Kamiya H. Is C-peptide replacement the missing link for successful treatment of neurological complications in type 1 diabetes? Curr Drug Targets. 2008;9:37-46. Review. Abstract

248. Ekberg K, Brismar T, Johansson BL, et al. C-Peptide replacement therapy and sensory nerve function in type 1 diabetic neuropathy. Diabetes Care. 2007;30:71-76. Full text Abstract

249. Ekberg K, Brismar T, Johansson BL, et al. Amelioration of sensory nerve dysfunction by C-Peptide in patients with type 1 diabetes. Diabetes. 2003;52:536-541. Full text Abstract

250. ClinicalTrials.gov. Safety and efficacy of CBX129801 in patients with type 1 diabetes. January 2015. http://clinicaltrials.gov (last accessed 16 May 2016). Full text

251. Fonseca VA, Lavery LA, Thethi TK, et al. Metanx in type 2 diabetes with peripheral neuropathy: a randomized trial. Am J Med. 2013;126:141-149. Full text Abstract

252. Rowbotham MC, Arslanian A, Nothaft W, et al. Efficacy and safety of the α4β2 neuronal nicotinic receptor agonist ABT-894 in patients with diabetic peripheral neuropathic pain. Pain. 2012;153:862-8. Abstract

253. Tack J, Depoortere I, Bisschops R, et al. Influence of ghrelin on gastric emptying and meal-related symptoms in idiopathic gastroparesis. Aliment Pharmacol Ther. 2005;22:847-853. Abstract

254. Ejskjaer N, Wo JM, Esfandyari T, et al. A phase 2a, randomized, double-blind 28-day study of TZP-102 a ghrelin receptor agonist for diabetic gastroparesis. Neurogastroenterol Motil. 2013;25:e140-e150. Full text Abstract

255. McCallum RW, Lembo A, Esfandyari T, et al. Phase 2b, randomized, double-blind 12-week studies of TZP-102, a ghrelin receptor agonist for diabetic gastroparesis. Neurogastroenterol Motil. 2013;25:e705-e717. Full text Abstract

256. Krendel DA, Costigan DA, Hopkins LC. Successful treatment of neuropathies in patients with diabetes mellitus. Arch Neurol. 1995;52:1053-1061. Abstract

257. Krendel DA, Zacharias A, Younger DS: Autoimmune diabetic neuropathy. Neurol Clin. 1997;15:959-971. Abstract

258. Pascoe MK, Low PA, Windebank AJ, et al. Subacute diabetic proximal neuropathy. Mayo Clin Proc. 1997;72:1123-1132. Abstract

259. Jaradeh SS, Prieto TE, Lobeck LJ. Progressive polyradiculoneuropathy in diabetes: correlation of variables and clinical outcome after immunotherapy. J Neurol Neurosurg Psychiatry. 1999;67:607-612. Full text Abstract

260. Ites KI, Anderson EJ, Cahill ML, et al. Balance interventions for diabetic peripheral neuropathy: a systematic review. J Geriatr Phys Ther. 2011;34:109-116. Abstract

261. Frykberg RG, Zgonis T, Armstrong DG, et al. Diabetic foot disorders: a clinical practice guideline (2006 revision). J Foot Ankle Surg. 2006;45(5 suppl):S1-S66. Full text Abstract

REFERENCES

262. Calles-Escandón J, Lovato LC, Simons-Morton DG, et al. Effect of intensive compared with standard glycemia treatment strategies on mortality by baseline subgroup characteristics: the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial. Diabetes Care. 2010;33:721-727. Full text Abstract

263. American Diabetes Association. 1. Strategies for improving care. Diabetes Care. 2015;38(suppl 1):S5-S7. Full text Abstract

264. Arad Y, Fonseca V, Peters A, et al. Beyond the monofilament for the insensate diabetic foot: a systematic review of randomized trials to prevent the occurrence of plantar foot ulcers in patients with diabetes. Diabetes Care. 2011;34:1041-1046. Full text Abstract

Images

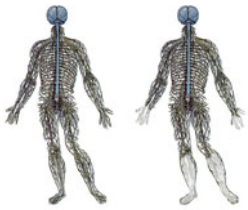

Figure 1: Progressive axonal loss in diabetic peripheral neuropathy

Edwards JL, et al. Pharmacol Ther. 2008;120:1-34; used with permission

Figure 2: Plantar ulcer due to a coin in the shoe of a patient with an insensate foot

From the collection of Dr Rayaz Malik, Weill Cornell Medicine

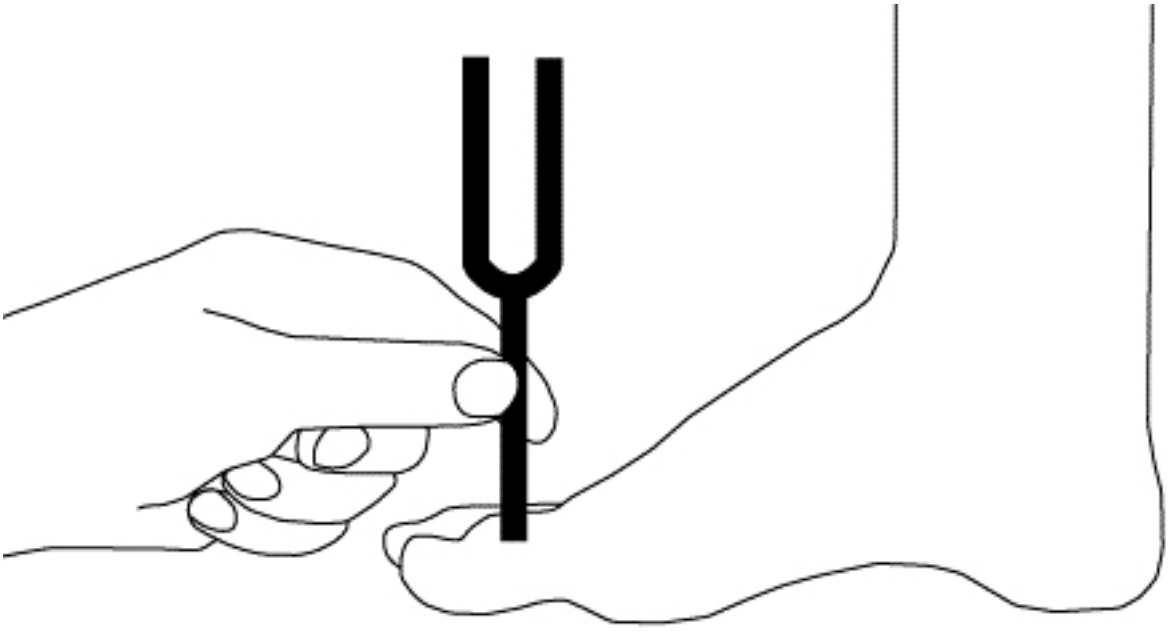

Figure 3: Vibratory testing

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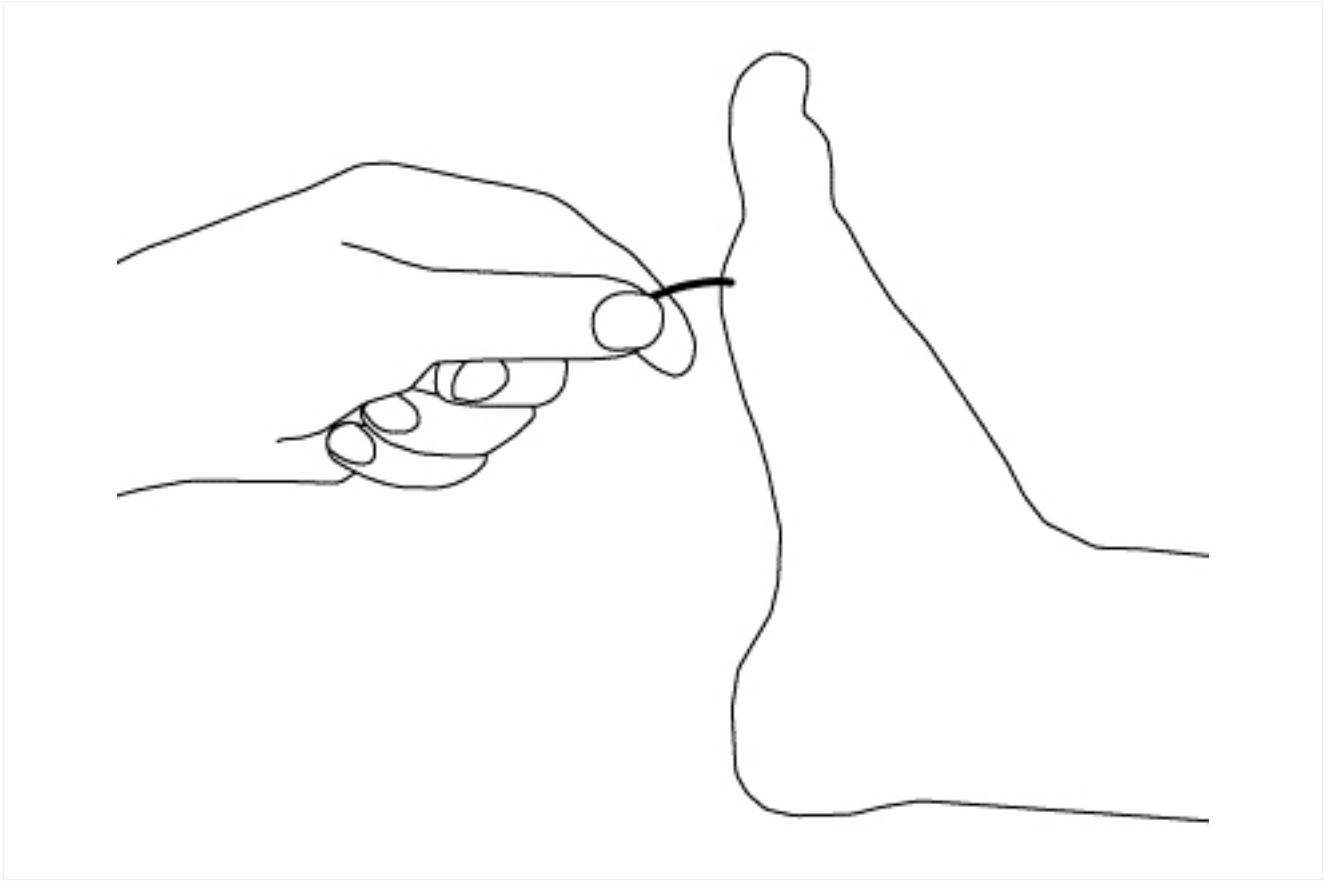

Figure 4: Light touch testing with monofilament

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Figure 5: Plantar ulcer in a patient with type 1 diabetes

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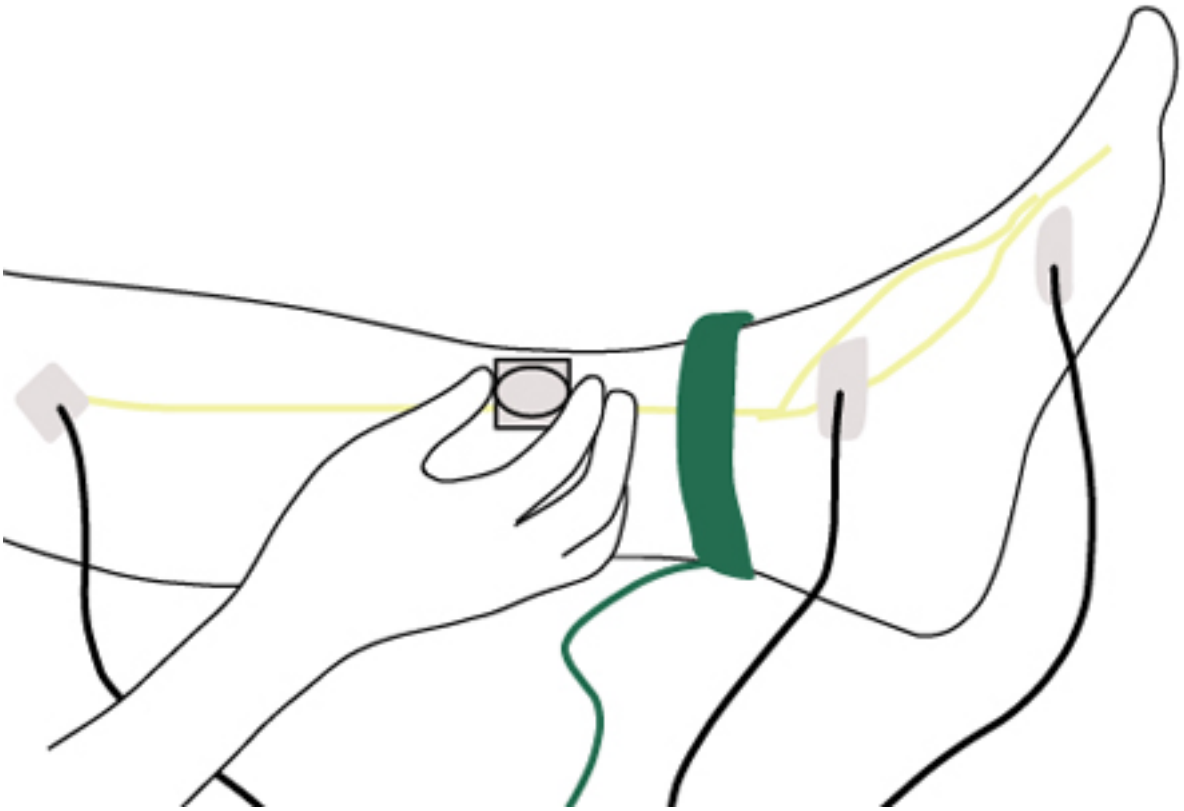

Figure 6: Nerve conduction testing of the lower leg

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Figure 7: Charcot foot with ulcer in a patient with diabetes

From the collection of Dr Rodica Pop-Busui, University of Michigan

Figure 8: Charcot foot in a patient with diabetes

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Contributors:

// Authors:

Rayaz A. Malik, BSc (Hons), MSc, MBChB, FRCP, PhD

Professor of Medicine
Organizational Official for the Human Research Protection Program, Weill Cornell Medicine - Qatar, Doha, Qatar
DISCLOSURES: RAM is on speaker panels for Eli Lilly, Novo Nordisk, and Pfizer; he is on advisory boards for Novo Nordisk and Pfizer. RAM is an author of a number of references cited in this monograph.

Uazman Alam, BSc, MBChB, MPHe, PhD

Speciality Registrar in Diabetes & Endocrinology and General Internal Medicine
University of Manchester, Manchester, UK
DISCLOSURES: UA serves on advisory boards for Eli Lilly.

Shazli Azmi, MBchB, MRCP

SpR Diabetes and Endocrinology
Diabetes and Endocrinology, University of Manchester, Manchester, UK
DISCLOSURES: SA declares that she has no competing interests.

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// Peer Reviewers:

Zachary T. Bloomgarden, MD

Clinical Professor
Department of Medicine, Mount Sinai School of Medicine, New York, NY
DISCLOSURES: ZTB declares that he has no competing interests.

Rajesh K. Garg, MD

Assistant Professor of Medicine
Harvard Medical School, Division of Endocrinology, Diabetes and Hypertension, Brigham and Women's Hospital, Boston, MA
DISCLOSURES: RKG has received consultant fees from Aventis and Novartis, and speaker fees from Novartis.

Edward Jude, MBBS, MD, MRCP, DNB

Consultant and Honorary Senior Lecturer
Tameside General Hospital, Diabetes Centre, Ashton Under Lyne, Lancashire, UK

Contributors:

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