Neuropathy in diabetes

Solomon Tesfaye

Abstract

Diabetic polyneuropathy affects 30–50% of patients with diabetes mellitus. It encompasses several neuropathic syndromes, the most common being distal symmetrical polyneuropathy or 'diabetic peripheral neuropathy' (DPN). Risk factors for DPN include poor glycaemic control and drivers of macrovascular disease including hypertension. Strong evidence in humans and animals implicates nerve ischaemia as the cause of DPN. Despite several well-designed recent trials, no novel approved treatment with unequivocal effects on nerve function decline in DPN has emerged. Painful DPN affects about a quarter of those with diabetes, produces considerable disability and is challenging to assess and manage. First-line therapies are tricyclic antidepressants, serotonin noradrenaline reuptake inhibitors (e.g. duloxetine) and anticonvulsants (e.g. pregabalin, gabapentin). Second-line drugs include opioids. Diabetic autonomic neuropathy also results in considerable morbidity, reduced quality of life and increased mortality. It can involve cardiovascular, gastrointestinal, urogenital, pupillomotor, thermoregulatory and sudomotor function. Although counselling and non-pharmacological interventions are of some use, more severely afflicted patients require pharmacological intervention.

Keywords Autonomic neuropathy; diabetic neuropathy; diabetic peripheral neuropathy; distal symmetrical polyneuropathy; MRCP; painful diabetic neuropathy

Key points

- Diabetic peripheral neuropathy (DPN) is common and results in significant morbidity and mortality. The neuropathic process starts early particularly in type 2 diabetes and early diagnosis at the annual diabetes review is essential in order to prevent further complications. The risk factors for DPN are now known and early management of hyperglycaemia and vascular risk factors including weight management is important
- Painful diabetic neuropathy is often underdiagnosed and hence undertreated. Healthcare professionals should evaluate the presence of neuropathic symptoms at the annual review and start treatment if necessary
- Diabetic autonomic neuropathy also results in considerable morbidity, reduced quality of life and increased mortality. Early diagnosis and multifactorial treatment (glucose and cardiovascular risk management) has been found to be beneficial

Epidemiology and risk factors

Diabetic polyneuropathy is one of the most common complications of diabetes mellitus. It is not one entity but encompasses several neuropathic syndromes (Figure 1), by far the most common being distal symmetrical polyneuropathy, or 'diabetic peripheral neuropathy' (DPN).

Several clinic- and population-based studies have reported similar prevalence rates for DPN – around 30% of individuals with diabetes if clinical peripheral neurological examination is used, rising to around 50% with electrophysiological testing.[1] Prevalence increases with increasing duration of diabetes, with about 50% of both type 1 and type 2 patients affected after 25 years, with no sex difference. Other correlates with DPN include increasing age, poor glycaemic control, hypertension, smoking, obesity and hyperlipidaemia.[2]

Classification of diabetic polyneuropathy

One classification for DPN is based on the natural history of the various syndromes, and outlines three distinct groups (Table 1).

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More recently, the American Diabetes Association (ADA) position statement on diabetic neuropathy[3] has suggested a more detailed classification. This classification divides diabetic neuropathies into diffuse neuropathies that include DPN (small fibre, large fibre and mixed) and autonomic neuropathy (dysfunctions in: cardiovascular, gastrointestinal, urogenital, sudomotor, hypoglycaemic awareness and pupillary function); mononeuropathies including moneuropathy multiplex and atypical forms; radiculopathies including atypical forms; and non-diabetic neuropathies that are more common in diabetes.

Symmetrical neuropathies

DPN

This is by far the most common neuropathic syndrome. The Toronto Consensus Panel defines it as 'a symmetrical, length dependent sensorimotor polyneuropathy attributable to metabolic and microvessel alterations as a result of chronic hyperglycaemia exposure (diabetes) and cardiovascular risk covariates'.[4]

Sensory symptoms start in the toes and extend to involve the feet and legs in a stocking distribution. When lower limb disease is severe, there is often upper limb involvement, with similar progression proximally from the fingers. Exceptionally, nerve damage can extend over the entire body including the head and face. Subclinical autonomic neuropathy detectable by autonomic function tests is usually present, but overt clinical autonomic neuropathy is less common. Motor manifestations can manifest only late in the disease.

The main clinical presentation of DPN is sensory loss. The patient may not be aware of this, or may describe 'numbness' or a 'dead feeling'. Some individuals, however, experience progressive, unpleasant sensory symptoms (Figure 2), including tingling (paraesthesiae), burning pain, paroxysmal shooting pains down the legs, lancinating (knife-like, stabbing) pains,

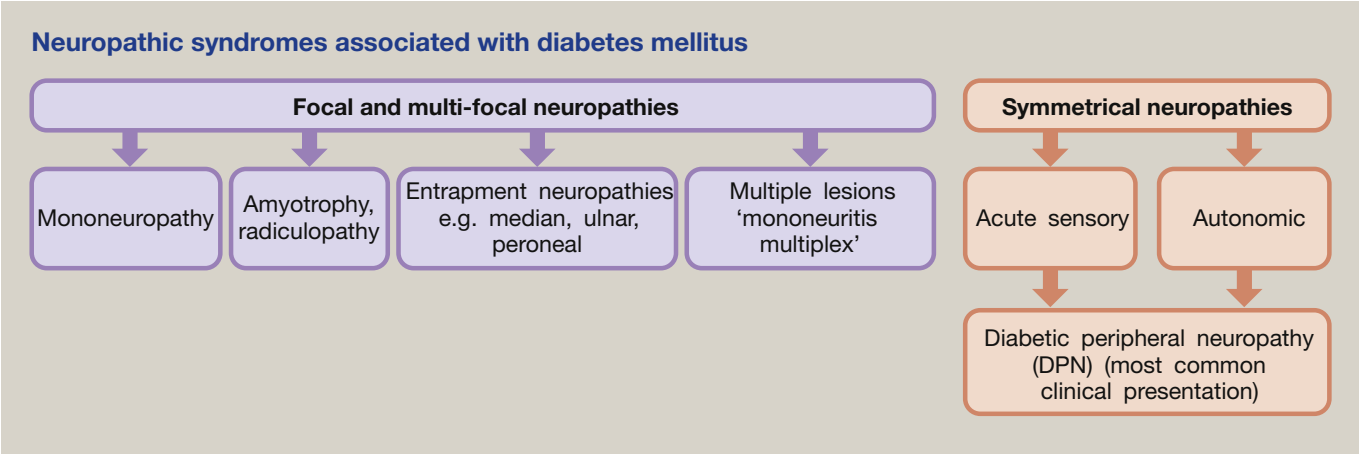


Figure 1

contact pain caused by clothes and bedclothes (i.e. misperception of non-painful stimuli as painful, known as allodynia), exaggerated perception of a slightly painful stimulus (hyperalgesia), pain on walking, often described as 'walking barefoot on marbles/hot sand', sensations of heat or cold in the feet, a persistent ache in the feet, or cramp-like sensations in the legs. Pain occasionally extends to the whole of the legs, in which case upper limb involvement is also usual. There is a wide spectrum of symptom severity, ranging from minor tingling in one or two toes to a numb diabetic foot or severe painful neuropathy refractory to drug therapy.

Classification of diabetic polyneuropathy

Progressive neuropathies

- Onset gradual; no recovery
- Associated with increasing diabetes duration and other microvascular complications
- Sensory disturbance predominates; autonomic involvement common
- Includes DPN, the commonest neuropathy in diabetes, usually with autonomic neuropathy

Reversible neuropathies

- Acute onset; spontaneous recovery
- Often occur at diabetes presentation; not related to diabetes duration or other microvascular complications
- Include acute painful neuropathies ('acute painful neuropathy of poor glycaemic control' and 'treatment induced neuropathy of diabetes – TIND'), cranial nerve palsies and focal neuropathies such as diabetic amyotrophy

Pressure palsies

- Not specific to diabetes, but occur more frequently in diabetes than in general population. No association with diabetes duration or other microvascular complications
- Include carpal tunnel syndrome

Source: Watkins PJ, Edmonds ME. Clinical features of diabetic neuropathy. In Textbook of Diabetes Vol.2. Pickup J, Williams G (Eds.) 1997; pp 50.1–50.20.

Table 1

Painful DPN affects 21–25% of people with diabetes,[5] is characteristically more severe at night, and often prevents sleep. Some patients experience constant tiredness from sleep deprivation, and others are unable to maintain full employment. Severe painful neuropathy occasionally causes a marked reduction in exercise threshold and interferes with daily activities. Not surprisingly, depressive symptoms are frequent.

Importantly, many patients with DPN have none of these symptoms, and their first presentation can be with a foot ulcer. This underlines the need for careful foot examination of all individuals with diabetes to identify those at risk of ulceration. The insensate foot is at risk of mechanical and thermal injury, and patients must be warned about these and given appropriate foot-care advice. Individuals with advanced neuropathy can have sensory ataxia, causing unsteadiness on walking and even falls, particularly if there is associated visual impairment.

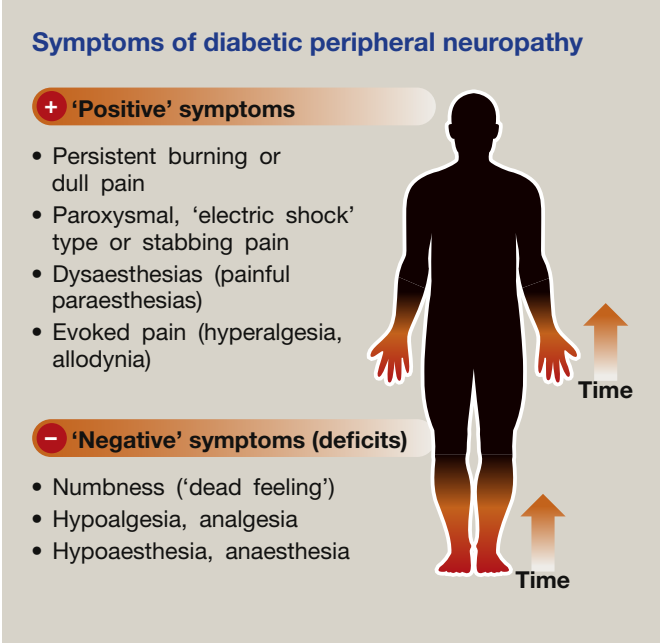


Figure 2

DPN is usually easy to detect clinically. The feet (with shoes and socks removed) should be examined at least annually and more often if neuropathy is present. The most common presenting abnormality is a reduction or absence of vibration sense in the toes, easily detected using a 128 Hz tuning fork. As disease progresses, sensory loss involving all sensory modalities appears in a stocking and sometimes a glove distribution. With severe sensory loss, proprioception can be impaired, leading to a positive Romberg's sign. Ankle tendon reflexes are lost, with knee reflexes also reduced or absent in advanced neuropathy.

Muscle strength is usually normal early over the course of the disease, although mild toe extensor weakness may be found. However, progressive disease is associated with significant generalized muscular wasting, particularly in the small muscles of the hands and feet. Fine movements of the fingers are then affected, with difficulty handling small objects. Wasting of the dorsal interossei is usually caused by entrapment of the ulnar nerve at the elbow. Clawing of the toes, which increases plantar and toe pressures, is believed to be to the result of pulling of the long extensor and flexor tendons that is unopposed because of wasting of the small muscles of the foot. This renders metatarsal heads prone to callus formation and ulceration. Deformities such as bunions can form a focus of ulceration, and with more extreme deformities, for example in Charcot's arthropathy, the risk increases further.

As one of the most common precipitants of foot ulceration is inappropriate footwear, a thorough assessment should also include examination of the shoes for poor fit, abnormal wear, internal pressure areas and foreign bodies. The ADA has recently provided clear recommendations for screening DPN.[3] Peripheral neurological examination should include a large-fibre test (vibration assessment using the 128 Hz tuning fork) and a small-fibre test (either pin-prick sensation or cold sensation assessment). Finally, the 10 g monofilament test can be done to assess feet for foot ulcer risk. Nerve conduction tests or quantitative sensory tests (QST) may be required if there are atypical presentations (e.g. symptoms starting in the hands, severe painful symptoms in the feet whilst clinical exam is normal, focal symptoms or other atypical presentations). In these circumstances, depending on the level of experience of the assessor further advice from a neurologist may be sought.

Recent advances in DPN assessment using novel point-of-care devices (POCDs)

Over the past decade, there have been advances in the development of non-invasive, objective, relatively quick and accurate POCDs that may be able to diagnose DPN before overt clinical signs are apparent. Such devices include: DPNCheck (NeuroMetrix ®), to measure sural nerve conduction velocity and amplitude; Sudoscan (Impeto Medical) and Neuropad (TRIG-Ocare), to measure sudomotor (small fibre) function; and corneal confocal microscopy, to assess corneal small fibres.

A recent study evaluated the use of POCDs in an annual, one-stop diabetes microvascular screening clinic and found that their use reduced clinic visits, unmasked new diagnoses of painful DPN in 25% of patients and identified patients at risk of foot ulceration. However, the long-term impact of such clinics on hard outcomes such as foot ulcers and amputations is yet to be investigated.

Although 95% of neuropathy in patients with diabetes is caused by diabetes, other causes of neuropathy should be excluded by a careful history and investigation (Table 2).

Acute painful neuropathies

These are rare, transient neuropathic syndromes characterized by an acute onset of symmetrical lower limb pain. Pain is invariably present, is usually distressing and can be incapacitating. There are two distinct syndromes, the first occurring in the context of poor glycaemic control, and the second with rapid improvements in metabolic control, often after starting insulin ('insulin neuritis'). Complete resolution of symptoms within 12 months is usual.

Asymmetrical neuropathies

Asymmetrical or focal neuropathies are well recognized in diabetes. They have a relatively rapid onset and usually resolve completely, in contrast to chronic DPN, where there is usually no improvement in symptoms.

Diabetic amyotrophy (proximal motor neuropathy)

Diabetic amyotrophy is a syndrome of progressive asymmetrical proximal leg weakness and atrophy also known as 'proximal motor neuropathy' or 'femoral neuropathy'. It presents as severe pain felt deep in the thigh, sometimes of burning quality and extending below the knee. Pain is usually continuous and often causes insomnia and depression. It is seen in both type 1 and type 2 diabetes in patients >50 years of age. Associated weight

Differential diagnosis of distal symmetrical neuropathy

Metabolic
- Diabetes
- Amyloidosis
- Uraemia
- Myxoedema
- Porphyria
- Vitamin deficiency (thiamine, B_{12}, B_6, pyridoxine)

Drugs and chemicals
- Alcohol
- Cytotoxic drugs, e.g. vincristine
- Chlorambucil
- Nitrofurantoin
- Isoniazid

Neoplastic disorders
- Bronchial or gastric carcinoma
- Lymphoma

Infective or inflammatory
- Leprosy
- Guillain–Barré syndrome
- Lyme borreliosis
- Chronic inflammatory demyelinating polyneuropathy
- Polyarteritis nodosa

Genetic
- Charcot–Marie–Tooth disease
- Hereditary sensory neuropathies

Table 2

loss can sometimes be severe, raising suspicion of occult malignancy.

On examination, there is profound wasting and weakness of the quadriceps, often causing difficulty getting out of a low chair or climbing stairs. Hip flexors and abductors, thigh adductors, glutei and hamstring muscles can also be involved. The knee jerk reflex is usually reduced or absent. Sensory loss is unusual and, if present, indicates coexistent DPN.

It is important to exclude other causes of quadriceps wasting such as nerve root and cauda equina lesions, and the possibility of paraneoplastic polymyositis. An erythrocyte sedimentation rate, lumbar/sacral spine and chest radiographs, and abdominal ultrasonography may be required. Electrophysiological studies may demonstrate increased femoral nerve latency and active denervation of affected muscles. Magnetic resonance imaging (MRI) of the lumbosacral spine may be required to exclude focal nerve root entrapment.

The cause of diabetic amyotrophy is not known. It tends to occur against a background of DPN, and it has been argued that the combination of focal features superimposed on diffuse peripheral neuropathy implicates vascular damage to the femoral nerve roots as a cause. Immune-mediated changes have been shown in microvessels supplying the affected nerves.

As in DPN, prospective studies of the natural history of diabetic amyotrophy are scarce. Pain usually starts to diminish after about 3 months, resolving by 1 year, with the knee jerk reflex restored in 50% of patients after 2 years. Contralateral recurrence is rare. Management is symptomatic and supportive, using similar approaches to those for DPN (see below). Patients should be reassured that the condition is likely to resolve. Whether insulin use influences the natural history of this syndrome remains controversial. Some patients benefit from physiotherapy, including extension exercises to strengthen the quadriceps.

Cranial mononeuropathies

The most common cranial mononeuropathy is a IIIrd cranial nerve palsy, presenting with orbital pain or sometimes frontal headache. Ptosis and ophthalmoplegia, usually with sparing of the pupil, are typical. Recovery usually occurs over 3–6 months. The natural history and focal nature of nerve lesions in post-mortem studies suggest an ischaemic aetiology. Other causes of IIIrd cranial nerve palsy (e.g. aneurysm, tumour) should be sought using imaging if the diagnosis is in doubt. IVth, VIth and VIIth cranial nerve palsies are also seen in people with diabetes, but their association with diabetes is weaker.

Truncal radiculopathy

Truncal radiculopathy, well recognized in diabetes, is characterized by acute onset of pain in a dermatomal distribution over the thorax or the abdomen. The pain is usually asymmetrical and can cause local bulging of the muscle. There can be patchy sensory loss, and other causes of nerve root compression should be excluded. Some patients present with abdominal pain and undergo unnecessary, avoidable investigations including barium enema, colonoscopy and even laparotomy. Recovery is usual within several months, although symptoms can persist for several years.

Pressure palsies

Carpal tunnel syndrome (CTS): CTS typically produces pain and paraesthesiae in the hands, sometimes radiating to the forearm, and particularly marked at night. In severe cases, examination reveals reduced sensation in the median nerve territory and wasting of the thenar eminence. Diagnosis is confirmed by median nerve conduction studies, and treatment involves surgical decompression at the carpel tunnel in the wrist. The response to surgery is generally good, although painful symptoms relapse more commonly than in patients without diabetes.

Ulnar and other nerve entrapments: the ulnar nerve is vulnerable to pressure damage at the elbow in the ulnar groove. This produces wasting of the dorsal interossei, particularly the first. Rarely, patients present with wrist drop from radial nerve palsy after a period of sustained pressure on the radial nerve at the back of the arm; this is usually caused by prolonged sitting or loss of consciousness during hypoglycaemia, sleep or alcohol intoxication.

In the lower limbs, the common peroneal (lateral popliteal) nerve is most commonly affected. Compression at the level of the head of the fibula causes foot drop, which does not usually recover completely. The lateral cutaneous nerve of the thigh is occasionally also affected.

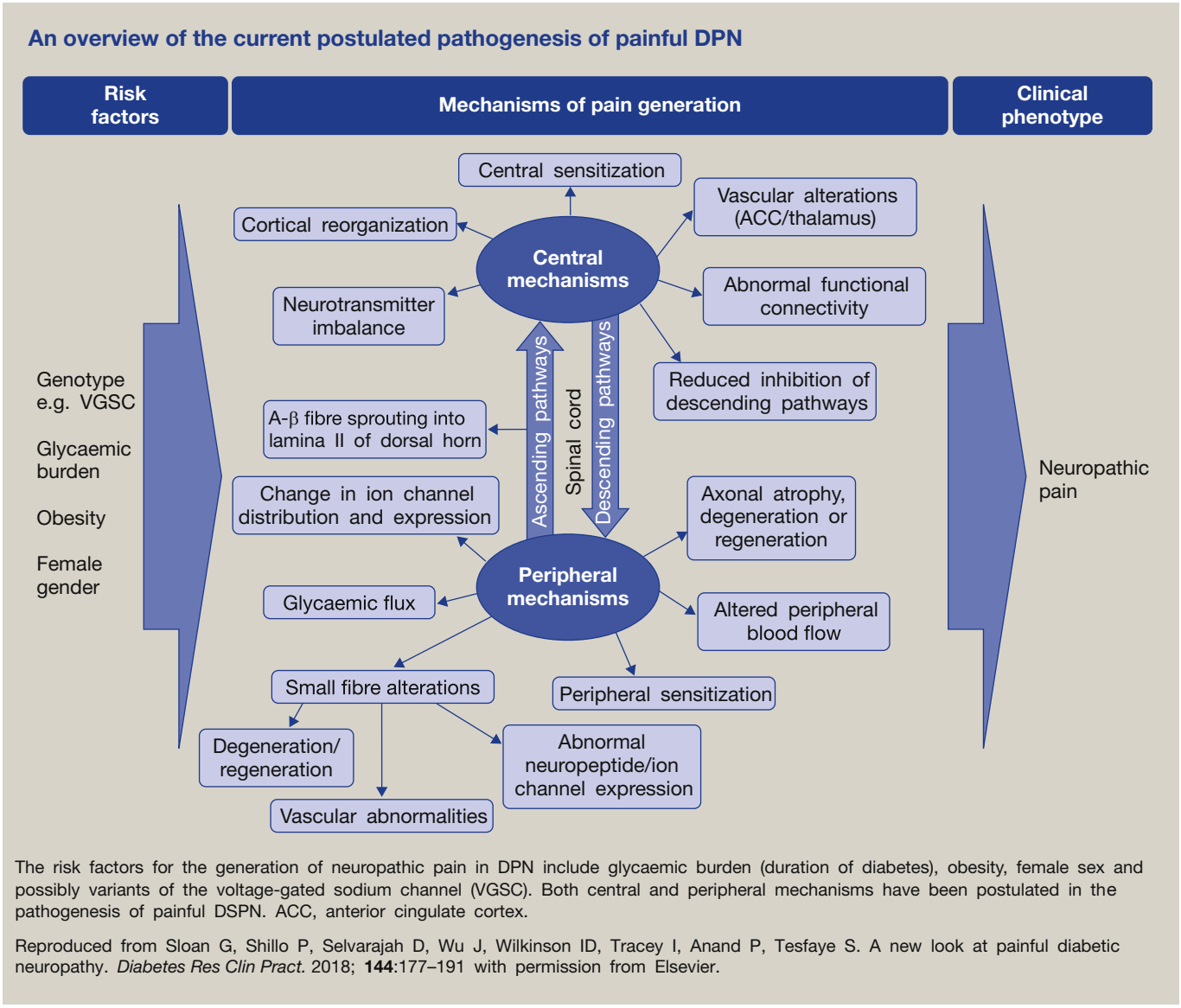
Pathogenesis of DPN

Historically, there were two distinct views regarding the pathogenesis of distal DPN: the first regarded metabolic factors as primarily important, while the second contended that vascular factors were key. However, most authorities now agree that both metabolic and vascular factors are important. Moreover, over the past decade peripheral, central and genetic biomarkers of DPN and painful DPN have emerged (Figure 3). A detailed account of the mechanisms and pathogenesis of pain in DPN is beyond the scope of this article but readers are directed to a recent comprehensive review (see reference, Figure 3).

Management of painful diabetic neuropathy

Painful DPN is often challenging to manage. A careful history and peripheral neurological/vascular examination are essential to exclude other causes of leg pain such as peripheral vascular disease, prolapsed intervertebral discs, spinal canal stenosis and cauda equina lesions. Unilateral leg pain should arouse suspicion of lumbosacral nerve root compression, and can require lumbosacral MRI. The quality and severity of the pain should ideally be assessed using a suitable scale (e.g. numerical rating, visual analogue) to help assess treatment response. An empathetic approach with multidisciplinary support is crucial as psychological dysfunction in diabetic patients is an important factor in increasing the suffering associated with all aspects of the disease.

There is consensus that intensive blood glucose control should be the first step in treatment of any form of diabetic polyneuropathy. Traditional drivers of large vessel disease, including hypertension, obesity, hyperlipidaemia and smoking, are also independent risk factors for neuropathy[2] and should be treated effectively.



The risk factors for the generation of neuropathic pain in DPN include glycaemic burden (duration of diabetes), obesity, female sex and possibly variants of the voltage-gated sodium channel (VGSC). Both central and peripheral mechanisms have been postulated in the pathogenesis of painful DSPN. ACC, anterior cingulate cortex.

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Figure 3

Pharmacotherapy of painful DPN is currently not entirely satisfactory as available drugs are often ineffective and/or cause adverse effects. Tricyclic antidepressants (TCAs) such as amitriptyline and imipramine have been used as first-line agents for many years, but many patients fail to respond and adverse effects are frequent.

The serotonin–noradrenaline reuptake inhibitor (SNRI) duloxetine is also widely used in painful DPN. It relieves pain by increasing synaptic availability of 5-hydroxytryptamine and noradrenaline (norepinephrine) in descending pathways, thus inhibiting pain impulses. The efficacy of duloxetine in painful DPN has been investigated in three identical trials. Their pooled data showed it to be effective in relieving painful symptoms, with benefit starting within a week and lasting the full treatment period of 12 weeks. Nausea, the most common adverse effect, is often self-limiting, resolving after a few days.

The anticonvulsant gabapentin is also effective. In the original trial, dosage was titrated to 3600 mg/day over 4 weeks, although in the UK doses >1800 mg/day are exceptional. In line with the British National Formulary (BNF), the dose can be increased gradually to 3.6 g/day based on careful evaluation of side effects and efficacy. More recently, seven trials of pregabalin have shown clear efficacy in the management of painful DPN. Other drugs include other anticonvulsants, especially carbamazepine, opioids such as tramadol, tapentadol and oxycodone and, for refractory cases, intravenous lidocaine. The antioxidant α-lipoic acid is also an effective treatment and is widely used in Germany, Eastern Europe and China.

The substance-P depletor capsaicin is also used topically, but it initially stings at the site of application and many patients do not persevere with treatment. More recently, a high-concentration capsaicin 8% patch (Qutenza®) has been approved as treatment for chronic neuropathic pain, including painful DPN, in the European Union, and for post-herpetic neuralgia in the USA. Capsaicin acts via cutaneous nerve terminals expressing transient receptor potential cation channel subfamily

V (TRPV)-1 receptor. A single 30-minute application for neuropathic pain can produce effective pain relief for up to 12 weeks. Capsaicin acts in the skin to attenuate cutaneous hypersensitivity and reduce pain by a process best described as 'defunctionalization' of nociceptor fibres. However, the 8% patch treatment is only provided in specialist centres using protective wear.

Table 3 shows the commonly prescribed drugs for painful DPN and their doses, but despite these options, many sufferers have suboptimal pain relief. Non-pharmacological treatments such as acupuncture, transcutaneous electrical nerve stimulation and, for severe resistant cases, electrical spinal cord stimulation can also be used.

The Toronto Consensus Panel evaluated all the published clinical trial data and recommended that first-line therapies for painful DPN be a TCA, duloxetine, pregabalin or gabapentin, taking into account patient co-morbidities and, in resource-limited circumstances, cost (Table 4). Recent UK National Institute for Health and Care Excellence guidance on neuropathic pain also makes a similar recommendation for these agents to serve as fist-line therapies.

Comparative and combination trials

A major deficiency in the treatment of neuropathic pain in diabetes is the relative lack of comparative or combination studies, as emphasized by recent consensus guidelines from international institutions. Virtually all previous trials have been of active agents against placebo, and there is a vital need for more studies comparing drugs with each other or with lower dose combination treatments.

Comparative trials: one small, randomized, double-blind, cross-over trial compared amitriptyline with pregabalin in painful DPN. It found little difference in efficacy, but pregabalin showed a better adverse event profile. However, the study only involved 51 patients, and many participants failed to complete it. Another recent small, cross-over study from the same group compared duloxetine with amitriptyline. Again, the drugs were found to be equally efficacious, although dry mouth was more common with amitriptyline (55% versus 24%; $p < 0.01$).

The lack of direct comparative studies led to an indirect comparison of the efficacy and tolerability of duloxetine compared with pregabalin and gabapentin in painful DPN, using a placebo as a common comparator. No significant differences were found between duloxetine and gabapentin, but pregabalin produced greater overall health improvement than duloxetine, at the expense of increased dizziness. There was no significant difference in 24-hour pain severity between duloxetine and pregabalin.

Combination trials: a randomized trial studied nortriptyline and gabapentin either alone or in combination and confirmed that they were more efficacious when given together. In another cross-over study by the same group, low-dose combination therapy with gabapentin and morphine was also significantly more effective than higher doses of either alone.

COMBO-DN study: this is the largest combination trial in painful DPN to date. It assessed whether combining standard doses of duloxetine and pregabalin was superior to increasing each drug to its maximum recommended dose in patients with incomplete pain relief. No difference in pain or adverse effect profile was found between standard dose combination treatment (duloxetine 120 mg/day and pregabalin 600 mg/day) and maximum dose monotherapy (duloxetine 60 mg/day or pregabalin 300 mg/day).

First-line treatments for painful DPN and treatment algorithm

A simple algorithm was produced by the Toronto International Neuropathy Consensus meeting (Figure 4) to help practitioners manage patients with painful DPN. After excluding other causes

Pharmacological treatment of painful DPN

TCAs
- Amitriptyline 25–150 mg/day
- Imipramine 25–150 mg/day

SNRIs
- Duloxetine[a] 60–120 mg/day

Anticonvulsants
- Pregabalin[a] 300–600 mg/day
- Gabapentin 300–3600 mg/day

Opiates
- Tramadol 200–400 mg/day
- Oxycodone 20–80 mg/day
- Morphine sulphate SR 20–80 mg/day
- Tapentadol ER 100–400 mg/day

Capsaicin cream
- 0.075% applied sparingly 3–4 times per day

Lidocaine
- 5 mg/kg given intravenously over 1 hour with ECG monitoring

[a] Only duloxetine and pregabalin have been approved by both the European Medicines Agency and US Food and Drug Administration for the treatment of painful DPN.

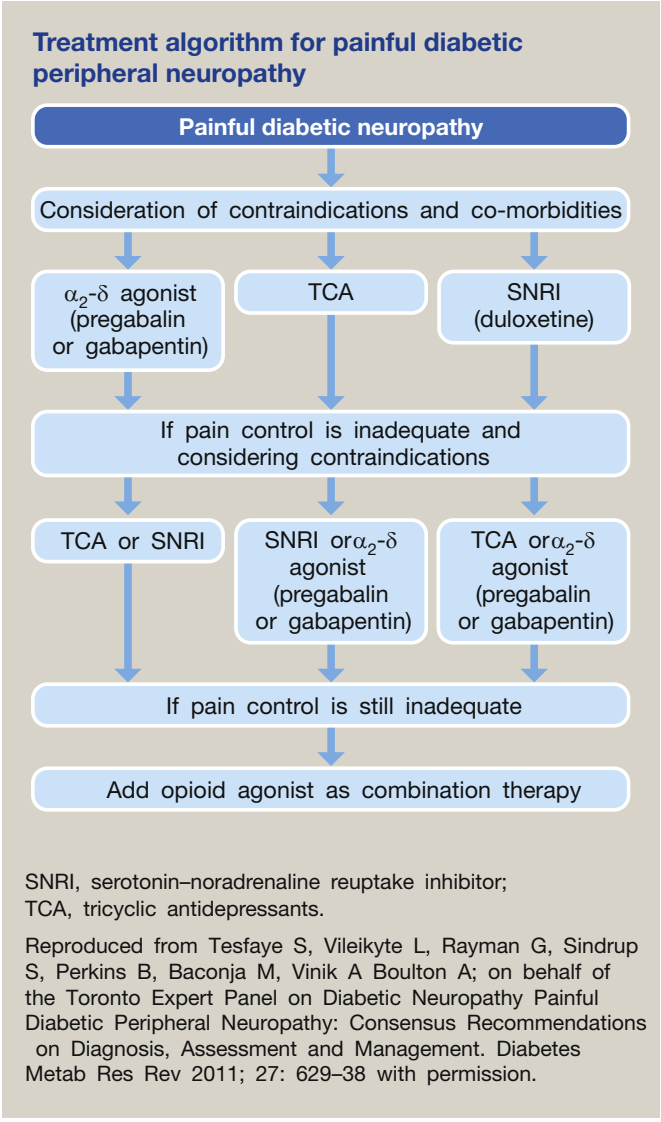
Table 3

Tailoring treatment to the individual patient by taking into account common co-morbidities and cost

Factors	Contraindication
Co-morbidities	
Glaucoma	TCAs
Orthostatic hypotension	TCAs
Cardiovascular disease	TCAs
Hepatic disease	Duloxetine
Oedema	Pregabalin, gabapentin
Unsteadiness and falls	TCAs
Other factors	
Costs	Duloxetine, pregabalin
Weight gain	TCAs, pregabalin, gabapentin

Source: NICE guideline [CG173]. Neuropathic pain in adults: pharmacological management in non-specialist settings. Published November 2013 and last updated April 2018. https://www.nice.org.uk/guidance/cg173/chapter/1-Recommendations (accessed September 2018).

Table 4



SNRI, serotonin–noradrenaline reuptake inhibitor; TCA, tricyclic antidepressants.

Reproduced from Tesfaye S, Vileikyte L, Rayman G, Sindrup S, Perkins B, Baconja M, Vinik A Boulton A; on behalf of the Toronto Expert Panel on Diabetic Neuropathy Painful Diabetic Peripheral Neuropathy: Consensus Recommendations on Diagnosis, Assessment and Management. Diabetes Metab Res Rev 2011; 27: 629–38 with permission.

Figure 4

and optimizing glycaemic control, first-line therapies include either an antidepressant (TCA, duloxetine) or an anticonvulsant (gabapentin, pregabalin). These all have level A evidence of efficacy and a clear pathway of progression if initial therapies fail. Patients with the severest neuropathic pain unresponsive to antidepressant or anticonvulsant therapy may require short-term treatment with opioid or opioid-like drugs such as tramadol or controlled-release oxycodone. All patients with any form of diabetic neuropathy also require education in foot self-care and, if possible, regular podiatry review.

Autonomic neuropathy

Abnormalities of autonomic function are very common in long-standing diabetes, but clinically significant autonomic dysfunction is uncommon. Several systems, including cardiovascular, gastrointestinal and genitourinary, are affected (Table 5). Autonomic neuropathy is of gradual onset and slowly progressive.[3]

Clinical consequences of autonomic neuropathy

CAN
- Sudden death
- Silent ischaemia
- Exercise intolerance
- Orthostatic hypotension
- Foot vein distension/arteriovenous shunting

Gastrointestinal autonomic neuropathy
- Gastroparesis
- Diarrhoea or constipation

Bladder hypomotility
- Urinary incontinence/retention

Erectile dysfunction

Gustatory sweating

Table 5

Cardiovascular autonomic neuropathy (CAN)

CAN is a serious complication of long-standing diabetes and can result in postural hypotension, changes in peripheral blood flow, exercise intolerance, enhanced intraoperative cardiovascular lability, increased incidence of asymptomatic ischaemia/myocardial infarction, decreased likelihood of survival after myocardial infarction and sudden death.

Postural hypotension (orthostatic hypotension): a fall in systolic blood pressure of >20 mmHg on standing is abnormal. The chief symptom is dizziness on standing, which is disabling for some patients, although the severity of dizziness often does not correlate with the measured postural drop in blood pressure. For reasons that are not fully clear, there is increased mortality in those with postural hypotension.

Management of postural hypotension poses major problems, and can ultimately be unsatisfactory. Treatment options include:
- stopping drugs that cause or worsen postural hypotension (e.g. diuretics, β-adrenoceptor blockers, antianginal agents, TCAs)
- advising patients to stand slowly from a sitting or lying position, crossing their legs
- increasing sodium intake to 10 g (185 mmol) per day and fluid intake to 2.0–2.5 litres/day (with caution in heart failure)
- raising the head of the bed by 10–20° to stimulate the renin–angiotensin–aldosterone system and decrease nocturnal diuresis
- drinking approximately 500 ml of water to stimulate a pressor response
- using custom-fitted elastic stockings extending to the waist
- treatment with fludrocortisone, starting at 100 micrograms/day, with monitoring for supine hypertension, ankle oedema and hypokalaemia; potassium supplementation can be required at higher doses
- in severe cases the α_1-adrenoceptor agonist midodrine, a sympathomimetic ephedrine, or occasionally octreotide or erythropoietin (25–75 U/kg three times weekly until a near-normal haematocrit is achieved).

Gastrointestinal autonomic neuropathy

Gastroparesis: autonomic neuropathy can affect the upper gastrointestinal system by reducing oesophageal motility (producing dysphagia and heartburn) and causing gastroparesis (reduced gastric emptying, vomiting, swings in blood glucose). The diagnosis of gastroparesis is often made on clinical grounds, by evaluating symptoms and sometimes by the presence of succussion splash. Barium swallow and follow-through, or gastroscopy, may reveal significant food residue in the stomach, while gastric emptying studies can be performed in some units.

Management of diabetic gastroparesis includes:

- optimization of glycaemic control, as hyperglycaemia can delay gastric emptying
- stopping drugs that can delay gastric emptying, including calcium-channel blockers, exenatide and anticholinergic agents
- antiemetics (metoclopramide, domperidone)
- erythromycin to enhance activity of the gut peptide motilin
- gastric electrical stimulation in drug-refractory gastroparesis.

Severe gastroparesis causes recurrent vomiting and is associated with dehydration, unstable blood glucose and weight loss; it is thus an indication for hospital admission. Adequate intravenous hydration, blood glucose stabilization using intravenous insulin, and antiemetics are important. If the gastroparesis is prolonged, total parenteral nutrition or feeding via a gastrostomy tube may be required.

Autonomic diarrhoea: patients can present with diarrhoea, often worse at night, or constipation. Both respond to conventional treatment. Diarrhoea associated with bacterial overgrowth can respond to broad-spectrum antibiotics, whereas bile acid malabsorption can respond to colestyramine. Antidiarrhoeal opioids (e.g. loperamide, codeine) can improve symptoms by decreasing peristalsis and increasing rectal sphincter tone. Refractory diarrhoea can be treated with the α_2-adrenoceptor agonist clonidine, or the somatostatin analogue octreotide. Octreotide suppresses gastrointestinal motility and inhibits the release of motilin, serotonin and gastrin. It can result in recurrent hypoglycaemia because of impaired counter-regulation.

Abnormalities of bladder function

Bladder dysfunction is a rare complication of autonomic neuropathy involving the sacral nerves. It causes hesitancy and/or increased frequency of micturition and, in serious cases, urinary retention with overflow incontinence. Urinary tract infections are may be required. Treatment includes mechanical bladder emptying using suprapubic pressure or intermittent self-catheterization. Anticholinesterase drugs such as neostigmine or pyridostigmine can be useful. Long-term indwelling catheterization can be required but predisposes to urinary tract infections. Long-term antibiotic prophylaxis may also be needed.

Gustatory sweating

Increased sweating, usually affecting the face and often brought about by eating (gustatory sweating), can be very embarrassing for patients and difficult to treat. Oral anticholinergic agents, such as oxybutinin, propantheline and glycopyrrolate, can improve symptoms; however, adverse reactions, including dry mouth, constipation, worsening of gastroparesis and confusion, limit their use. Clonidine has been used with some success but is also limited by adverse effects including hypotension and dry mouth. Non-systemic approaches include topical glycopyrrolate, a well-tolerated antimuscarinic compound that has been shown to decrease the incidence, severity and frequency of sweating with eating. Botulinum toxin has been used for gustatory sweating, although most reports relate to unilateral, surgery-related cases. ◆

KEY REFERENCES

1 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:** 817–24.

2 Tesfaye S, Chaturvedi N, Eaton SEM, et al. Vascular risk factors and diabetic neuropathy. *New Engl J Med* 2005; **352:** 341–50.

3 Pop-Busui R, Boulton AJ, Feldman EL, et al. Diabetic neuropathy: A position statement by the American Diabetes Association. *Diabetes Care* 2017; **40:** 136–54.

4 Tesfaye S, Boulton AJ, Dyck PJ, et al. on behalf of the toronto diabetic neuropathy Expert Group. Diabetic neuropathies: Update on definitions, diagnostic criteria, estimation of severity and treatments. *Diabetes Care* 2010; **33:** 2285–93.

5 Abbott CA, Malik RA, van Ross ER, et al. Prevalence and characteristics of painful diabetic neuropathy in a large community-based diabetic population in the U.K. *Diabetes Care* 2011; **34:** 2220–4.

FURTHER READING

Tesfaye S, Boulton AJ, Dyck PJ, et al. Valensi P on behalf of the Toronto diabetic neuropathy Expert group. Diabetic neuropathies: update on Definitions, diagnostic Criteria, estimation of severity and treatments. *Diabetes Care* 2010; **33:** 2285–93.

Bönhof GJ, Herder C, Strom A, et al. Emerging biomarkers, tools, and treatments for diabetic polyneuropathy. *Endocr Rev* 2018; **25**. https://doi.org/10.1210/er.2018-00107.

Tesfaye S, Selvarajah D, Gandhi R, et al. Diabetic peripheral neuropathy may not be as its name suggests: evidence from magnetic resonance imaging. *Pain* 2016; **157**(suppl 1)**:** S72–80.

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:** 639–53.

29th Camillo Golgi Lecture: http://www.easdvirtualmeeting.org/resources/19120.