Diabetes is a worldwide epidemic with a global prevalence of 8.3%, and its prevalence is likely to increase in tandem with the global epidemic of obesity. Diabetic neuropathy is the most common complication of diabetes, and risk of developing it increases with the duration of diabetes. On the other hand, even patients with impaired glucose tolerance develop painful neuropathic symptoms and damage to small nerve fibers. Symptoms of diabetic polyneuropathy manifest earlier in type 2 diabetes than in type 1 diabetes. In type 2 diabetes, 8% of patients have neuropathy at the time of diagnosis, and up to 50% of older type 2 diabetic patients have evidence of a distal neuropathy. Poor glycemic control is the most important risk factor for diabetic neuropathy, and according to high-quality evidence, enhanced glucose control significantly prevents the development of clinical neuropathy in type 1 diabetes mellitus.

A meta-analysis showed that enhanced glucose control reduces the incidence of clinical neuropathy, although this finding was not statistically significant. In addition to glucose control, other potentially modifiable cardiovascular risk factors such as higher levels of total and low-density lipoprotein cholesterol and triglycerides, higher body-mass index, smoking, and hypertension also increase the risk of neuropathy.

The clinical features of the diabetic neuropathies vary immensely, and only a minority of patients with neuropathy will experience pain. According to a large community-based study from England, one third of patients with diabetes have painful neuropathy symptoms. Painful diabetic neuropathy was more prevalent in patients with type 2 diabetes and in women. In a recent systematic review of epidemiological studies of neuropathic pain in the general population, the population prevalence of painful diabetic neuropathy was calculated at 0.8%. Incidence rates of painful diabetic polyneuropathy ranged from 15.3/100,000 person-years to 72.3/100,000. The natural history of painful diabetic neuropathy remains unclear, although in a small longitudinal study, one-fourth of the patients experienced remission of pain whereas the rest still had pain after 5 years.

In a small study, dietary management and an exercise program resulted in improvement of painful symptoms and intraepidermal nerve fiber density in patients with impaired glucose fiber density.

Painful diabetic neuropathy is considered to be the cause of considerable morbidity and has a major impact on the ability to function normally, both mentally and physically in terms of the ability to maintain work, mood, and quality of life. In a recent cross-sectional survey, the most common comorbid conditions were sleep disturbance/insomnia, depressive symptoms, and anxiety. Pain is chronic in most patients. Pain is typically burning or aching, but may also have a lancinating component. Patients may also have allodynia (a condition in which normally nonpainful stimuli cause pain); for example, wearing socks during the day or bedclothes at night may...
be painful. At worst, static allodynia of the soles of the feet can make standing and walking intolerable. Patients may also experience uncomfortable tingling (dysesthesia) and peculiar sensations such as feeling as though they are walking on pebbles. Intensity of pain progressively increases throughout the day, reaching its worst at bedtime. In addition to pain and dysesthesia, restless legs, which can be associated with polyneuropathy, may disturb sleep.

**Classification**

Diabetes may affect the peripheral nerves in several ways including cranial mononeuropathies, peripheral mononeuropathies or mononeuropathies multiplex, or symmetrical distal sensorimotor polyneuropathy. The most common presentation of diabetic polyneuropathy is **chronic sensorimotor distal symmetrical polyneuropathy** (DSPN). The Toronto Diabetic Neuropathy Expert Group defined DSPN as “a symmetrical, length-dependent sensorimotor polyneuropathy attributable to metabolic and microvascular alterations as a result of chronic hyperglycemia exposure and cardiovascular risk covariates.” The onset of DSPN is usually gradual or insidious and is heralded by sensory symptoms that start in the toes and then progress proximally to involve the feet and legs in a stocking distribution. When the disease is well established in the lower limbs, in more severe cases, there is upper limb involvement, with a similar progression proximally starting in the fingers. As the disease advances further, motor manifestations, such as wasting of the small muscles of the hands and limb weakness, become apparent. The Toronto consensus panel proposed that patients with possible DSPN should be defined as those with neuropathic symptoms, sensory examination findings, or abnormal reflexes and patients with probable neuropathy as those with two of these three features. Clinical neuropathy was considered to be confirmed in those with either neuropathic symptoms or examination findings, including abnormal reflexes with documented abnormalities on nerve conduction studies or skin biopsy.

**Small-fiber neuropathy** is another phenotype of painful diabetic neuropathy. Small-diameter myelinated and unmyelinated nerve fibers are affected, resulting in burning pain in the feet. The Toronto consensus panel defined “possible” small-fiber neuropathy as symptoms or signs of small-fiber involvement. Probable small-fiber neuropathy requires the addition of normal sural nerve sensory response on nerve conduction studies. Definite small-fiber neuropathy requires the same criteria as for probable small-fiber neuropathy as well as confirmatory tests such as skin biopsy or quantitative sensory testing (QST). Of note, most patients with diabetes and small-fiber neuropathy have concomitant large-fiber neuropathy transitioning to typical DSPN.

**Acute painful diabetic peripheral neuropathy** is a less common variety of symmetrical polyneuropathies. It is characterized by severe sensory symptoms, but with few neurological signs on examination. The overriding symptom reported by all patients is severe pain, and there may be associated weight loss, depression and, in men, erectile dysfunction. This acute neuropathy typically follows some rapid change in glycemic control, which might be either a sudden improvement in control or an episode of very poor glycemic control, typically in young type 1 patients, such as diabetic ketoacidosis, with the symptoms coming on after successful treatment of the acute exacerbation. The prognosis of acute painful diabetic peripheral neuropathy is good, with complete resolution of symptoms usually occurring within a year of onset.

In addition to the above-mentioned polyneuropathies, which have a stocking-and-glove-type location, a variety of **focal and multifocal painful neuroptathes** exist: limb neuropathies, cranial neuropathies, proximal diabetic neuropathy of the lower limbs, and truncal neuropathies. These conditions are relatively uncommon and necessitate referral to a neurologist for differential diagnosis and treatment consideration.

Diabetics can suddenly develop a unilateral third, fourth, sixth, or seventh **cranial nerve palsy**. Retro-orbital pain accompanies about half of the cases. Most patients make a full recovery, with some early evidence of improvement within 2 to 3 months.

**Proximal diabetic neuropathy** (diabetic amyotrophy, diabetic lumbosacral radiculoplexopathy) begins with severe unilateral pain in the back, hip, or thigh that subsequently spreads to the other side within weeks to months. Given the associated weight loss, patients are often suspected to have a pelvic tumor. Within days to weeks of the pain onset, patients develop weakness in the leg muscles, typically the proximal muscles and to a lesser extent the distal ones. The disorder worsens in a gradually progressive or step-wise manner. Eventually, the process stabilizes and gradually improves, although recovery may take many months. In many cases, some degree of permanent weakness may persist.

**Truncal radiculopathy** involves isolated thoracic roots. Patients develop abrupt pain over days to weeks with severe dysesthesias in a dermatomal...
pattern. While the majority of cases are unilateral at onset, symptoms can evolve bilaterally. Weakness of the abdominal musculature may develop, but eventually patients make a partial or full recovery.21

In cases with isolated limb mononeuropathies it is important to perform electrophysiological testing to differentiate diabetic mononeuropathy from compression injury caused by nerve entrapment. Diabetic individuals are more susceptible to compression injuries compared to non-diabetic individuals. Decompressive surgery is needed for recovery in compression neuropathies.

Assessment

History and clinical examination are the cornerstones for diagnostic work-up. Location of pain can be documented with a pain drawing, and intensity of pain can be assessed numerically on a scale of 0–10 (0 = no pain, 10 = worst pain imaginable) or verbally (mild, moderate, severe, or excruciating). To capture both the intensity of pain and how much it interferes with everyday life, a validated questionnaire Brief Pain Inventory for Painful Diabetic Neuropathy (BPI-PDN) can be used in both the clinical and research setting.22 This instrument consists of the four-item pain severity scale (worst pain, least pain, average pain, pain now) and the seven-item pain interference scale (general activity, mood, normal work, walking, relations with others, sleep, and enjoyment of life). The questions specify “due to your diabetes.” The four severity items and the seven interference items can also each be averaged from two composite scores, the Pain Severity Index and the Pain Interference Index. The BPI-PDN is recommended for assessing disability in patients with painful diabetic neuropathy.23

Because diagnosis of DSPN is a diagnosis of exclusion, a careful history and a peripheral neurological and vascular examination of the lower limbs are essential to exclude other causes of neuropathic pain and leg or foot pain. Inspection of the skin, palpation of peripheral pulses, and testing of range of movement of the joints are followed by a sensory examination, which is the most important part of the examination in cases of suspected neuropathic pain. Touch can be assessed by gently applying cotton wool to the skin, pinprick sensation by the response to sharp pinprick stimuli, thermal sensation by warm and cold objects (e.g., water-filled tubes), and vibration sensation by a 128-Hz tuning fork. This examination covers peripheral sensory fibers; touch and vibration are mediated by large fibers, pinprick and cold by small thinly myelinated Aδ fibers, and warmth by small unmyelinated C fibers. The findings in the painful area are compared with the findings in the contralateral area in unilateral pain and in other sites on the proximal-distal axis in bilateral pain. Dynamic mechanical allodynia is tested with a light moving stimulus, static allodynia with gentle compression, and heat and cold allodynias with a warm and cold object, respectively. Deep tendon reflexes and muscle strength are also tested. Standing with the feet together, standing and walking on the toes and heels, walking a straight line, and Romberg’s test are a quick battery of tests for evaluating possible impairment of motor and balance secondary to DSPN.

In cases of focal and multifocal neuropathies, the neurologist will perform a careful neurological examination, and depending on symptoms and findings, he or she will request further examinations to confirm the diagnosis.

If clinical findings are typical for polyneuropathy, electrophysiological testing is not necessarily needed to confirm the condition. However, electromyography (EMG) is helpful in excluding other causes of pain such as entrapment syndromes.29 If clinical findings are compatible with pure small-fiber neuropathy, QST and skin biopsy to measure intraepidermal nerve fiber density (IENFD) can confirm the diagnosis.23 Confocal corneal microscopy is a promising noninvasive method to detect loss of thin nerves at very early stages and to monitor nerve recovery; for both purposes, it is more sensitive than IENFD and, presumably, QST, particularly in diabetic neuropathy.24

Once polyneuropathy is recognized, its cause must be determined. If there is no definite evidence of diabetes mellitus from routine testing of blood glucose, glucose tolerance tests are recommended in distal symmetric sensory polyneuropathy. Screening of kidney, thyroid, and liver function, serum levels of vitamin B₁₂, erythrocyte sedimentation rate, and serum protein electrophoresis are recommended to identify treatable causes of polyneuropathy. If polyneuropathy progresses quickly, the possibility of immune-mediated disorders (e.g., chronic inflammatory demyelinating polyneuropathy) and paraneoplastic polyneuropathy must be taken into account, including the exclusion of underlying malignancies.

Mechanisms of Neuropathic Pain in Diabetes

Mechanisms of Diabetic Neuropathy

The specific pathophysiological mechanisms contributing to diabetic polyneuropathy remain poorly understood, although experts have proposed several interrelated mechanisms and suggested complex interactions between them.
The definition of DSPN by the Toronto Consensus Panel includes two of the most important suggested causes: hyperglycemia and microvascular damage. Actuation of immunological cells and the cytokine network is the newest player in the field of postulated mechanisms.

Observational human studies have given support to the critical role of hyperglycemia in the development of DSPN. Experimental evidence shows that hyperglycemia is able to induce increased mitochondrial production of free radicals. Together with weakened antioxidant defenses, free radicals activate additional damaging pathways or enzymes such as the polyol pathway, nuclear enzyme poly(ADP-ribose) polymerase (PARP), and non-enzymatic glycation of proteins, leading to increased formation of advanced glycation end products (AGE), which in turn have been implicated in the formation of free radicals. Activation of the polyol pathway increases the production of sorbitol, which accumulates in the nerve cells, generating osmotic stress, Schwann cell damage, and also myo-inositol deficiency in the nerves. The reduced myo-inositol concentration leads to dysfunction of an enzyme, renal ATP-ase Na+/K+, which is required for the depolarization of the nerves. All the alterations described above are able to promote structural changes in the nerves, such as Wallerian degeneration and segmental demyelination, resulting in nerve damage and loss of both myelinated and unmyelinated nerve fibers.

Microvascular pathology, causing degeneration and loss of nerve fibers, is an important contributor to the pathogenesis of human diabetic polyneuropathy. Altered peripheral blood flow in vessels supplying the peripheral nerves can lead to endoneurial hypoxia and ischemic nerve injury. Microvascular damage is attributed to the hyalinization of the vessel walls and increased endoneurial vascular resistance. Histopathological changes in endoneurial microvessels correlating with clinical defects include basement membrane thickening, pericyte degeneration, and endothelial cell hyperplasia. Microvascular abnormalities are a consequence of hyperglycemia and related metabolic changes, such as nitric oxide deficit and increased oxygen free radical activity.

Mechanisms of Painful Diabetic Neuropathy

Painful diabetic polyneuropathy is considered a variant of DSPN. There have been attempts to identify possible structural and functional abnormalities or specific diabetes-related mechanisms that may predispose patients to painful diabetic neuropathy. Even though impairment of small-fiber function is considered a prerequisite for neuropathic pain development in diabetes, the available scientific evidence does not support the existence of a link between pain and pure small-fiber neuropathy. The same is true for an association between painful diabetic neuropathy and autonomic neuropathy as well as vascular abnormalities of peripheral nerves. We still lack neurological biomarkers for assessing the risk of development of neuropathic pain in diabetic patients.

Over the past decade, researchers have recognized that the relationship between the principal immune cells of the central nervous system, microglia, and neurons plays a key role in the development of neuropathic pain. Several reports have suggested that spinal microglia become activated in hyperglycemic conditions, leading to the increased release of proinflammatory cytokines that can induce and maintain neuropathic pain.
studies have also shown that high levels of proinflammatory cytokines and tumor necrosis factor-α immunoreactivity of macrophages are associated with painful DSPN and not with nonpainful DSPN.39, 40 The available evidence, however, does not yet allow a definite conclusion about the role of inflammation in painful DSPN.35

Finally, hyperglycemia may also have a direct hyperalgesic effect that is independent of structural damage to the nerves. Methylglyoxal, also known as pyruvaldehyde, is a glycolytic metabolite. Levels of methylglyoxal were significantly elevated in PDNP patients compared with painless DPN in one study.41 Methylglyoxal is able to activate peripheral nerves and modify a nociceptor-specific sodium channel, NaV1.8. Methylglyoxal slows nerve conduction and can cause both thermal and mechanical hyperalgesia. These results indicate that methylglyoxal-dependent modification of NaV1.8 has a specific role in hyperalgesia associated with PDNP.19, 35, 41

**Management**

The aims of management of patients with painful diabetic neuropathy are summarized in Box 1 and the key principles of care (modified from the NICE Clinical Guideline42) in Box 2.

Management should ideally involve a multidisciplinary team that may include a physician (a general practitioner, diabetologist, neurologist, or pain specialist depending on the clinical setting), nurse, physiotherapist, psychologist, podiatrist, occupational therapist, and others. In most clinical settings, such an extensive team is not possible, but the principle of teamwork is useful in any setting. Each team member offers his or her expertise to help the patient achieve optimal quality of life by minimizing discomfort and maximizing functional capacity.

Management of patients with pain is tailored individually. Adherence to treatment is better if the patient’s subjective needs and preferences are taken into account. Management is a stepwise process, and the treatment plan may be modified over time depending on achievement of goals. In addition to pharmacotherapy, nonpharmacological treatment options should be considered. A recent pilot randomized controlled study showed that cognitive-behavioral therapy (CBT) reduced pain severity and interference in patients with painful DSPN, suggesting that CBT may help them acquire skills to become more active and experience less pain.43 A future challenge will be implementing and integrating CBT approaches for pain into the primary care setting so that CBT can be more readily available and accessible to patients who could benefit most from these services.

Maximizing glucose control is a primary goal in patients who already have painful DSPN and in those at risk of developing it. Although controlled trial evidence is lacking, several observational studies suggest that neuropathic symptoms improve not only with optimization of control, but also with the avoidance of extreme blood glucose fluctuations.44 In addition to tight glycemic control, lifestyle modification and management of cardiovascular risk factors are important ways to prevent progression of PDPN.

Pharmacotherapy has a crucial role in treatment of painful PDNP, although it is not entirely satisfactory because currently available drugs are often ineffective and complicated by adverse events. A systematic review and meta-analysis produced by the IASP Special Interest Group on Neuropathic Pain (NeuPSIG) summarized

### Box 1. Targets of management of painful diabetic neuropathy
- Relief of pain and dysesthesia
- Improvement of sleep
- Improvement of mood
- Improvement of functional capacity
- Improvement of quality of life
- Prevention of progression of neuropathy
- Prevention of foot ulceration

### Box 2. Key principles of care (modified from NICE42).
When agreeing on a treatment plan with a patient, take into account his or her concerns and expectations, and discuss:
- the severity of the pain, and its impact on lifestyle, daily activities (including sleep disturbance), and participation in activities
- the benefits and possible adverse effects of pharmacological treatments, taking into account any physical or psychological problems, and concurrent medications
- the importance of dosage titration and the titration process, offering individualized information and advice
- coping strategies for pain and for possible adverse effects of nonpharmacological treatments, for example, physical and psychological therapies (which may be offered through a rehabilitation service) and surgery (which may be offered through specialist services).
inhibitors, 7.7 (6.5–9.4) for pregabalin; 7.2 (5.9–9.21) for gabapentin, including gabapentin extended release and enacarbil, and 3.6 (3.0–4.4) for tricyclic antidepressants.

Lidocaine patches and tramadol were recommended as second line by NeuPSIG. Evidence for lidocaine patches is weak, but because of its excellent safety profile and patient preferences, NeuPSIG proposed lidocaine as a second-line treatment for peripheral neuropathic pain. Tramadol has a moderate quality of evidence (NNT 4.7, 95% CI 3.6–6.7) and a lower potential for misuse, abuse, and dependency than stronger opioids, but owing to potential safety concerns it was recommended as a second-line drug.

Strong opioids (with evidence mainly from oxycodone and morphine) were recommended as third line. Their efficacy (NNT 4.37, 95% CI 3.5–5.8) was balanced against safety concerns (potential risk of abuse, particularly with high doses, and concerns about a recent increase in prescription-opioid-associated overdose mortality, diversion, misuse, and other opioid-related morbidity).

Table 1
First-line drugs for painful diabetic neuropathy

<table>
<thead>
<tr>
<th>Medication</th>
<th>Mechanism of Action</th>
<th>Target dose</th>
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<tr>
<td><strong>TCAs</strong></td>
<td></td>
<td></td>
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<tr>
<td>Nortriptyline, desipramine, (amitriptyline, imipramine)*</td>
<td>Serotonin and norepinephrine reuptake inhibition, sodium channel block, NMDA-receptor antagonist</td>
<td>25–150 mg, once a day or in two divided doses</td>
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<tr>
<td><strong>SNRIs</strong></td>
<td>Serotonin and norepinephrine reuptake inhibition</td>
<td></td>
</tr>
<tr>
<td>Duloxetine</td>
<td>60–120 mg, once a day</td>
<td></td>
</tr>
<tr>
<td>Venlafaxine</td>
<td>150–225 mg, once a day</td>
<td></td>
</tr>
<tr>
<td><strong>Gabapentinoids</strong></td>
<td>A calcium-channel α2δ ligand, which reduces release of presynaptic transmitters</td>
<td></td>
</tr>
<tr>
<td>Gabapentin</td>
<td>1200–3600 mg, in three divided doses</td>
<td></td>
</tr>
<tr>
<td>Pregabalin</td>
<td>300–600 mg, in two divided doses</td>
<td></td>
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</table>

Source: Finnerup et al.45
Abbreviations: SNRIs = serotonin-norepinephrine reuptake inhibitors; TCAs, tricyclic antidepressants.
* Secondary amine TCAs (nortriptyline, desipramine) are preferred owing to better tolerability.
antidepressants can be an alternative option to increasing doses of mono-
thrapy for patients unresponsive to moderate doses of monotherapy.

When selecting the drug, contraindications and possible side effects need to be taken into account. Detailed information is available in a review article. For patients with diabetes, concerns of potential weight gain (a risk with tricyclic antidepressants and gabapentinoids) are important. Regarding tricyclic antidepressants, the risk of falls due to orthostatic hypoten-
sion and major anticholinergic side effects must be considered, especially in the elderly and those with diabetic autonomic neuropathy. An increased risk of sudden cardiac death has been reported with tricyclic antidepressants at doses greater than 100 mg daily. It is also important to remember the risk of hypertension with venlafaxine.

In addition to contraindications and potential risks, comorbid condi-
tions should be taken into account in the selection of treatment. Serotonin-
norepinephrine reuptake inhibitors are a good option for those with depression and pregabalin for those with generalized anxiety disorder. Gabapenti-
noids are recommended for patients with disturbed sleep. A double-blind, placebo-controlled randomized study compared the effect of amitriptyline, duloxetine, and pregabalin on pain, sleep, and daytime functioning. The drugs provided similar pain relief. Pregabalin promoted sleep, whereas duloxetine increased sleep fragmenta-
tion and substantially reduced REM sleep. Daytime function was relatively unaffected by drug treatment.

After prescribing the drug that is presumed to be the best option for the patient, the physician must arrange for follow-up. Each follow-up review should include an assessment of pain control, the drug’s impact on lifestyle, participation in daily activities (including sleep disturbance), physical and psychologi-

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