Painful neuropathy in diabetes

Recognising and relieving

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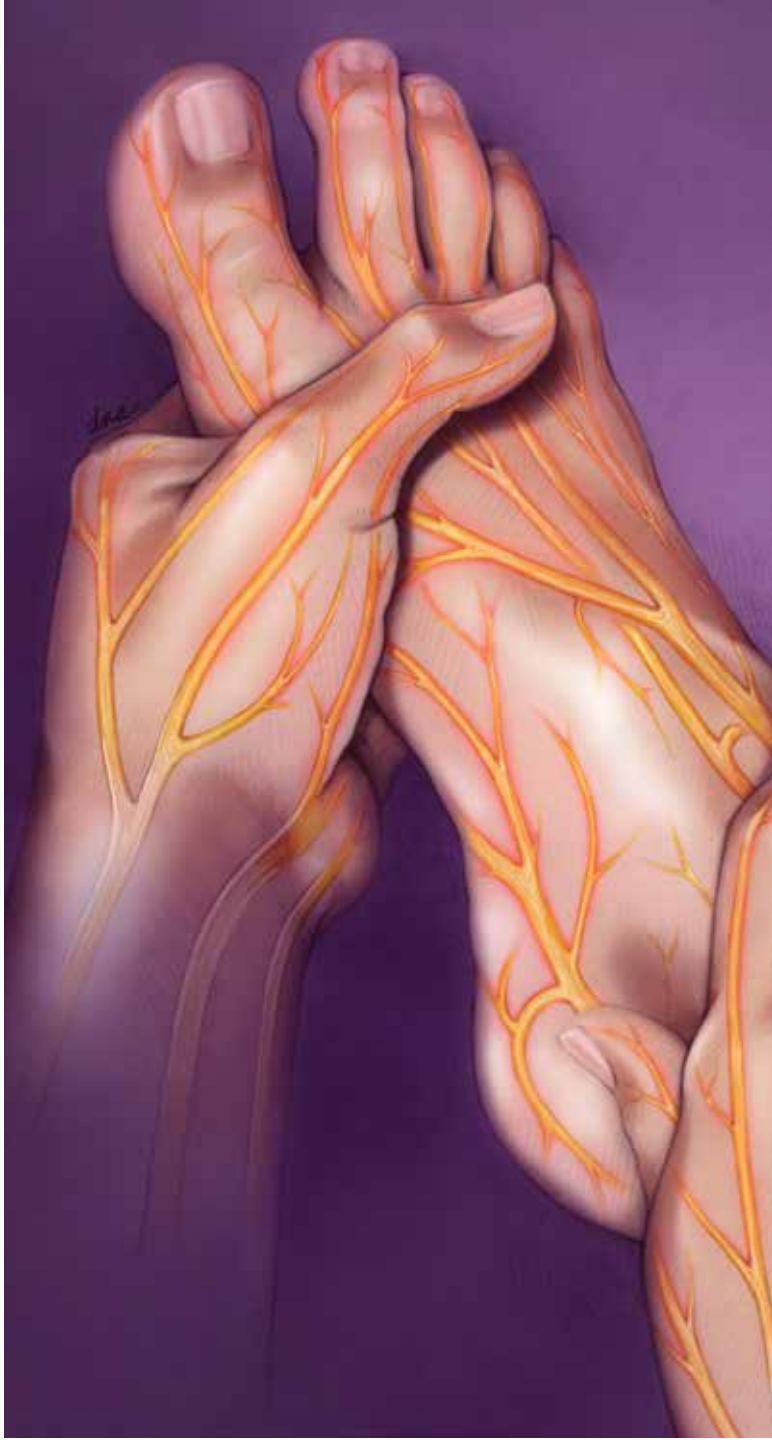
The painful form of diabetic peripheral neuropathy can be severely disabling but is often underappreciated and undertreated. It can occur in the absence of sensory loss and may follow improved glycaemic control or even be the presenting symptom of diabetes. Treatment is symptomatic, aiming to reduce pain and improve function.



Diabetic neuropathy is one of the most common chronic complications of diabetes and can have a major adverse impact on patient's quality of life. Diabetic neuropathy comprises several clinical syndromes, including peripheral neuropathy (a distal and symmetric sensorimotor polyneuropathy), autonomic neuropathy (affecting cardiovascular, gastrointestinal, urogenital and/or sudomotor function), polyradiculopathies (affecting nerve roots), mononeuropathies (affecting individual cranial or peripheral nerves) and mononeuritis multiplex (involving multiple mononeuropathies). Diabetic peripheral neuropathy is the most common neuropathy, affecting up to 50% of people with longstanding diabetes.[1] Symptoms of diabetic peripheral neuropathy can range from none (in up to 50% of cases) to severe pain.[2] This article focuses on the assessment and treatment of patients with painful diabetic peripheral neuropathy.

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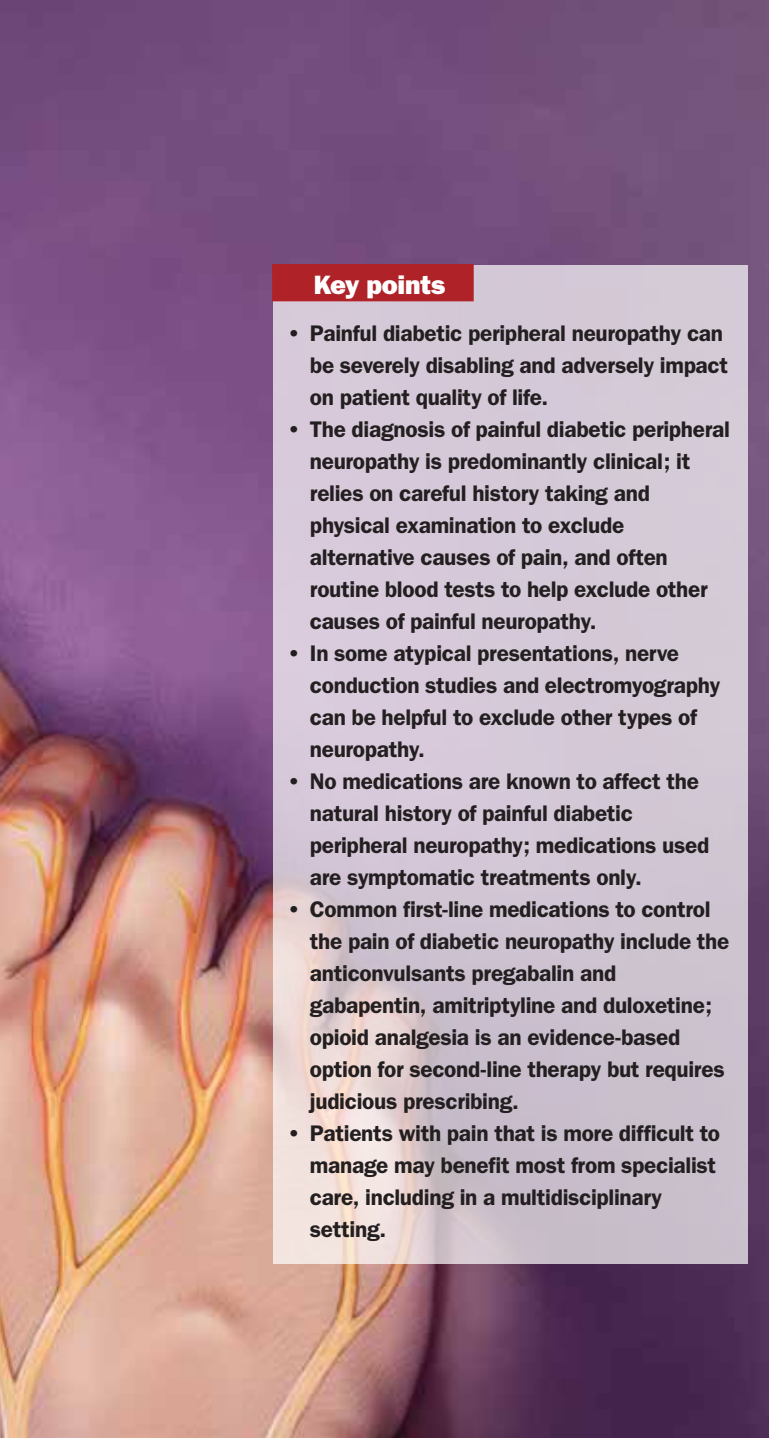
Clinical presentation and assessment

Painful diabetic peripheral neuropathy is diagnosed clinically, based primarily on the patient's description of the pain, and is a diagnosis of exclusion. Painful diabetic peripheral neuropathy can occur with or without detectable sensory loss; in the absence of sensory loss, the risk of foot ulceration due to the neuropathy is not increased at that time.



Key points

- **Painful diabetic peripheral neuropathy can be severely disabling and adversely impact on patient quality of life.**
- **The diagnosis of painful diabetic peripheral neuropathy is predominantly clinical; it relies on careful history taking and physical examination to exclude alternative causes of pain, and often routine blood tests to help exclude other causes of painful neuropathy.**
- **In some atypical presentations, nerve conduction studies and electromyography can be helpful to exclude other types of neuropathy.**
- **No medications are known to affect the natural history of painful diabetic peripheral neuropathy; medications used are symptomatic treatments only.**
- **Common first-line medications to control the pain of diabetic neuropathy include the anticonvulsants pregabalin and gabapentin, amitriptyline and duloxetine; opioid analgesia is an evidence-based option for second-line therapy but requires judicious prescribing.**
- **Patients with pain that is more difficult to manage may benefit most from specialist care, including in a multidisciplinary setting.**

Symptoms

Neuropathic pain in diabetes can be defined as 'pain arising as a direct consequence of abnormalities in the somatosensory system in people with diabetes'.[1] Patients may describe the pain in markedly different ways, including symptom combinations, such as burning, electric shock-like or stabbing sensations, uncomfortable tingling, pain triggered by touching socks or bedsheets at night (allodynia), cold or hot temperature perception, nonspecific aching or cramping in the feet.[1] The pain of diabetic peripheral neuropathy is typically chronic, distal (with feet affected first), bilateral, largely symmetric and paroxysmal. If the pain is unilateral then other differential diagnoses should be considered, such as claudication from peripheral arterial disease, spinal nerve compression or musculoskeletal causes such as arthritis and fasciitis. Neuropathic pain is often worse at night and can be highly disruptive to sleep, leading to fatigue and reduced functioning during the day from sleep deprivation. Pain, unsteadiness and limitation in performing activities of daily living increase the likelihood of associated depression.[3]

Examination signs

Essential components of a diabetic foot examination include dermatological, musculoskeletal, neurological and vascular examinations (summarised in the Box).[4] Painful diabetic peripheral neuropathy can occur with or without evidence of sensory changes on routine physical examination. In some patients with painful diabetic peripheral neuropathy, there are no abnormal clinical examination findings.

Investigations

The diagnosis of painful diabetic peripheral neuropathy is predominantly clinical, based on careful history taking and examination to identify typical symptoms and to exclude alternative differential diagnoses. Investigations may be required to exclude possible differential diagnoses, such as measurement of vitamin B_{12} levels, thyroid function tests, serum protein electrophoresis, lower limb vascular studies and spinal imaging.

Nerve conduction studies are usually not necessary for the diagnosis of painful diabetic peripheral neuropathy but can be useful to help differentiate it from other causes of pain, such as entrapment syndromes. Painful neuropathy can be caused by abnormalities of small nerve fibres alone or a combination of small and large nerve fibres.[5] Because nerve conduction studies assess only large nerve fibres, results of nerve conduction studies may appear normal in some people with painful diabetic peripheral neuropathy.

Tests of small nerve fibre dysfunction have been used in research settings. Quantitative sensory testing of thermal thresholds can detect neuropathy but has not been found to be clinically useful in discriminating between patients with painful and painless diabetic peripheral neuropathy.[5] Skin biopsies have shown that intraepidermal nerve fibre density is lower in patients with painful diabetic neuropathy compared with those without pain.[6] However, loss of intraepidermal nerve fibre cannot explain pain in all cases. This may be because the mechanism of pain in diabetic peripheral neuropathy is likely a combination of altered structure and function in peripheral nerves, enhanced spinal processing and alterations in higher centres.[7] Small-fibre dropout does not always parallel large-fibre function.[6]

Acute presentation

Although painful diabetic peripheral neuropathy presents most commonly as a chronic condition, it can also present acutely with severe pain, which can be associated with weight loss, depression and erectile dysfunction.[1] This acute onset of neuropathic pain is usually associated with a recent rapid improvement in glycaemic control after chronic hyperglycaemia ('treatment-induced neuropathy in diabetes'), or treatment of an episode of diabetic ketoacidosis.[8] In this variant of painful diabetic peripheral neuropathy, there may be few clinical signs on physical examination.[9]

Essential components of a diabetic foot examination*

Neurological
- 10-g monofilament test and one of the following:[4]
  - vibration testing using 128 Hz tuning fork
  - pinprick sensation
  - ankle reflexes
  - vibration perception threshold assessed with biothesiometer

Vascular – arterial
- Foot pulses (posterior tibial and dorsalis pedis pulses)
- Measurement of ankle brachial index if required

Dermatological
- Skin quality (colour, dryness, cracking, calluses, corns, blisters), nail quality, signs of infection

Musculoskeletal
- Deformity of bones or soft tissues, muscle wasting
- Evidence of past amputation

Footwear
- Appropriateness of footwear

Diabetic lumbosacral radiculoplexus neuropathy (diabetic amyotrophy) is another cause of neuropathic limb pain in people with diabetes; however, the presentation is typically subacute and asymmetric, with proximal leg weakness following the onset of the pain, marked hyperglycaemia and weight loss. The condition resolves after 12 to 18 months and requires supportive and symptomatic treatment in the interim.[10] Nerve conduction studies and needle electromyography will assist in the diagnosis.

Risk groups

Diabetic neuropathy is more common with increasing age, duration of diabetes and severity of exposure to hyperglycaemia, and can occur in patients with either type 1 or type 2 diabetes.[9,11,12] However, this relationship is less clear for the painful form of diabetic neuropathy.[7] This can occur in patients with impaired glucose tolerance or recently diagnosed diabetes.[13] Neuropathic pain may even be the presenting symptom of diabetes. Increased neural glucose flux may contribute to pain in people with diabetic neuropathy.[7]

Differential diagnosis

Careful history taking and examination of the neurological and vascular status of the lower limbs are important in determining the diagnosis of painful diabetic peripheral neuropathy, and excluding differential diagnoses such as pain from peripheral vascular disease, arthritis and nerve compression. Up to 10% of people with diabetes may have a nondiabetic cause for peripheral neuropathy.[14] Alternative causes of acquired peripheral neuropathy to be considered include alcohol misuse, thyroid dysfunction, vitamin B_{12} deficiency, monoclonal gammopathy or myeloma, Guillain–Barré syndrome or chronic inflammatory demyelinating polyradiculoneuropathy, malignancy, connective tissue disorders including vasculitis, amyloidosis, sarcoidosis and HIV infection.[15]

When to treat

There is a broad spectrum of symptom severity and associated disability across patients with painful diabetic peripheral neuropathy, and not all patients require pharmacological treatment. Although up to 50% of all patients with diabetic peripheral neuropathy may experience some degree of pain, many do not feel that the pain is sufficiently severe to require pharmacological treatment.[1] Treatment goals for painful diabetic peripheral neuropathy are to reduce pain and improve physical function, quality of life, sleep and mood. A realistic goal would be to achieve 30 to 50% reduction in pain intensity.[7] No medications are known to affect the natural history of neuropathy, and so the evidence-based medications are symptomatic treatments only.

Treatment options

The main classes of medications for first-line treatment of neuropathic pain include anticonvulsants, tricyclic antidepressants (TCAs), and serotonin and noradrenaline reuptake inhibitors (SNRIs) (Table 1).[12] Opioids can be helpful second-line agents, particularly when used in combination therapy. The choice and dose of medication should be guided by effectiveness, side effects and cost. It is also noteworthy that the placebo effect in clinical studies can vary from 0 to 50% pain reduction.[16]

Anticonvulsants

Pregabalin and gabapentin have both been effective in treating neuropathic pain in clinical trials and can be useful first-line treatments.[17] Pregabalin binds to the alpha-2/delta subunit of the calcium channels in the central nervous system to reduce calcium influx, and reduces the release of several neurotransmitters. Common side effects of pregabalin include dizziness, drowsiness, peripheral oedema, headache and weight gain. Common side effects of gabapentin are similar.

Tricyclic antidepressants

The TCA amitriptyline has been effective in improving neuropathic pain, likely through altering central perception of pain.[17] Common side effects include central anticholinergic effects such as drowsiness, dry mouth, constipation, urinary retention, dizziness, orthostatic hypotension and blurred vision. Because of the risk of side effects, amitriptyline should be started at a low dose with careful uptitration depending on efficacy, and should be taken at night (off-label use). Nortriptyline may cause fewer side effects than amitriptyline and has similar efficacy. Particular caution with TCAs is needed in elderly patients at risk of falls, and those with a history of cardiovascular disease.

Serotonin and noradrenaline reuptake inhibitors

SNRIs such as duloxetine and venlafaxine relieve neuropathic pain by increasing synaptic availability of serotonin and noradrenaline in the descending pathways that inhibit pain impulses.[17] Common side effects include nausea, dizziness, drowsiness and fatigue. Duloxetine is not associated with weight gain. Venlafaxine should be used with caution in patients with risk factors for QTc prolongation (off-label use).

Opioids

Opioids are not generally recommended as first-line treatment for painful diabetic peripheral neuropathy but can be helpful as add-on combination therapy if first-line therapy alone

is inadequate to relieve pain. Referral to a pain specialist may be appropriate at this stage. Commonly used opioids with evidence for effectiveness in neuropathic pain include tramadol and controlled-release oxycodone.[1] The mu opioid receptor agonist tapentadol may also be effective in treating symptoms of painful neuropathy. For pain that occurs across the day, the weekly buprenorphine patch with dose uptitration may also be effective as a second-line agent.

Other pharmacological treatments

Topical capsaicin has been effective in clinical trials in patients with painful diabetic peripheral neuropathy.[17] However, its use may be limited by symptoms of burning pain at the application site in more than half of patients. We have found that topical nicoboxil plus nonivamide (0.75%) can also be useful clinically.

Nonpharmacological treatments

Percutaneous electrical nerve stimulation can be considered for treatment of painful diabetic peripheral neuropathy, although studies have shown varying effects on pain relief.[16] Based on currently available evidence, electromagnetic field treatment, low-intensity laser treatment and Reiki therapy are not recommended.[16]

A usual treatment approach

After patients are diagnosed with painful diabetic peripheral neuropathy, they should be assessed for pain frequency and severity and impact on mood, sleep, quality of life and functioning. Simple scales can be used to grade pain, such as an 11-point Likert scale (where 0 = no pain and 10 = maximum pain). Effectiveness of medications can then be assessed and doses uptitrated slowly, based on individual response.

Optimising glycaemic control and managing cardiovascular risk factors (hypertension, dyslipidaemia, overweight) are key components of diabetes care, but there is no clear evidence that these measures improve symptoms of painful neuropathy. Although treatment-induced neuropathy can follow a rapid improvement in glycaemic control, there is insufficient evidence to recommend a glucose threshold target or 'permissive hyperglycaemia' in its treatment.[8] The importance of good general foot self-care should be reinforced, especially if there is loss of protective sensation.

First-line medication choice is from one of the three classes anticonvulsants, TCAs or SNRIs, with the choice influenced by individual patient factors (Table 2). Starting doses should be low, particularly in elderly patients, and uptitration should be slow and progressive, with consideration of side effects. Maximum recommended doses are shown in Table 1. If pain control is inadequate then two first-line agents can be used in combination (although there is limited clinical trial evidence of the efficacy of combining first-line agents), or an opioid can be added.[12]

Table 1. Pharmacological treatment options for painful diabetic peripheral neuropathy

Class of medication	Drug and dose*	Common side effects
First-line options		
Anticonvulsants	• Pregabalin (75 mg twice per day to maximum 300 mg twice per day)† • Gabapentin (300 mg three times per day to maximum 600 mg three times per day)	Drowsiness, dizziness, peripheral oedema, headache, weight gain
Tricyclic antidepressants	• Amitriptyline (25 mg at night to maximum 150 mg at night)†§	Dry mouth, drowsiness, fatigue, headache, dizziness, orthostatic hypotension, nausea, urinary retention, constipation, blurred vision, weight gain
Serotonin and noradrenaline reuptake inhibitors	• Duloxetine (60 mg once daily to maximum 60 mg twice per day)¶ • Venlafaxine (75 mg daily to maximum 225 mg daily)§	Nausea, drowsiness, dizziness, constipation, dyspepsia
Second-line options		
Opioids	• Tramadol (up to maximum 210 mg per day) • Oxycodone (up to maximum 120 mg per day) • Morphine sulfate (up to maximum 120 mg per day) • Buprenorphine patch (titrated, 5, 10 or 20 µg/h) • Tapentadol (50 mg once daily titrated carefully to maximum 600 mg daily)	Drowsiness, nausea, constipation, chronic use leads to tolerance
Other		
Topical analgesic	• Capsaicin cream 0.075% topically, up to three to four times per day	Burning pain at skin application site, which can be temporary

* In the authors' experience, lower doses than those described can be at least partially effective in some patients.
† Pregabalin doses as low as 25 mg once or twice per day can be effective in elderly patients and those who are sensitive to adverse effects.
‡ Amitriptyline doses as low as 10 mg at night can be effective.
§ Use of amitriptyline and venlafaxine for neuropathic pain is off label.
¶ A duloxetine starting dose of 30 mg is available.

Table 2. Patient factors to consider when choosing medication to treat painful diabetic peripheral neuropathy*

Patient factor	Medications to avoid	Medications to prefer
Glaucoma	TCAs	
Orthostatic hypotension	TCAs	
Cardiovascular disease	TCAs	
Unsteadiness or falls	TCAs	
Chronic liver disease	Duloxetine	
Peripheral oedema	Pregabalin, gabapentin	
Weight gain	Pregabalin, gabapentin	
Clinical depression		SNRIs or TCAs

Abbreviations: SNRI = serotonin and noradrenaline reuptake inhibitor; TCA = tricyclic antidepressant.
*Adapted from Tesfaye et al. Painful diabetic peripheral neuropathy: consensus recommendations on diagnosis, assessment and management. Diabetes Metab Res Rev 2011; 27: 629-638.[1]

For pain that is difficult to manage, patients may benefit from specialist care in a multidisciplinary setting, involving the GP together with endocrinologists, a diabetes educator, pain specialists, neurologists, specialist nurses, podiatrists, physiotherapists and psychologists.

Prognosis

Although the natural history of painful diabetic peripheral neuropathy varies, most patients experience a waxing and waning pattern of pain over several years, with the pain eventually becoming less severe as sensory loss worsens with loss of nerve fibres.[1,12] A small prospective case series found spontaneous pain resolution within 12 months for about half of patients, with pain remission being more likely if the neuropathic pain had an acute onset after a sudden improvement in glucose control (such as after treatment for diabetic ketoacidosis) and also in short-duration diabetes, or when neuropathic pain onset followed marked weight loss.[18]

Conclusion

Painful diabetic peripheral neuropathy can be highly disabling for patients and impact severely on quality of life. Recognising the clinical diagnosis of painful diabetic peripheral neuropathy, and excluding alternative causes of pain are essential components of assessment. In the authors' experience, the condition remains underappreciated and undertreated. There are several classes of effective medication available for improving neuropathic pain, although clinical trial evidence supporting a benefit of this therapy for sleep, function and quality of life is sparse. Treatment of intercurrent depression in its own right is another important aspect of care. ET

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