Painful diabetic neuropathy

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Key points
Painful diabetic neuropathy is pain arising as a direct consequence of abnormalities of the somatosensory system in diabetic patients and predominantly affects the feet and legs.

Risk factors for development of diabetic peripheral neuropathy include duration of disease, poor glycaemic control, hypertension, hyperlipidaemia, and smoking, but the specific risk factors for painful neuropathy are less clear.

Patients often find it difficult to clearly describe the pain—up to 40% have never received treatment.

Treatment follows the NICE guidance pathway, with duloxetine and tricyclic antidepressants considered to be first-line agents, but also includes modification of the risk factors for development of neuropathy.

Around 347 million people worldwide are estimated to have diabetes mellitus, making it one of the most common chronic diseases. It is associated with considerable morbidity and mortality because of the primary disease and also secondary complications. The incidence has almost doubled in the last three decades in parallel with an increasing trend in ageing and also in obesity worldwide. It has a huge impact on quality of life, health resources, and economy.

Diabetic neuropathy is the most common long-term complication of the condition and a leading cause of neuropathy in the developed world. Both duration of diabetes and degree of glycaemic control are important predictive factors for the development of neuropathy.

The prevalence of diabetic neuropathy varies considerably among clinical studies because of differences in the study population, design, and diagnostic criteria. Prevalence increases predictably with the duration of diabetes from 10% at diagnosis to as much as 53% after 25 yr of diabetes. There is also a proportional increase with age. It is estimated that around half of the patients with chronic diabetic neuropathy experience pain and the majority of them have features of chronic sensorimotor peripheral neuropathy.

Classification
Diabetic neuropathy is generally classified on the basis of pathophysiology, clinical features, and neurology involved, and also progress of the disease and covariate risk factors involved (Table 1).

Chronic sensorimotor peripheral polyneuropathy is the commonest type of diabetic neuropathy and is estimated to be present in around half of all diabetic patients. Its incidence is ~2% per yr. It is worth noting that the majority of the patients do not volunteer symptoms, and it is not uncommon to accidently uncover abnormal neurology during regular clinical examination. It is also interesting to note that these clinical features are also reported in ~10% of the non-diabetic population. Onset is insidious and if allowed to progress the condition will become chronic. The symptoms typically start in the toes, gradually ascending to the lower limbs. In advanced cases, it spreads to the upper limbs (glove-stocking sensation) and also the abdominal wall.

The clinical features depend on the type of nerve fibre involved. These include sensory symptoms such as paraesthesia, pain, and numbness. The clinical manifestations are generally symmetrical. Patients with motor fibre involvement exhibit clinical features, including difficulty in climbing stairs, handling small objects, and wasting of intrinsic muscles of hands and feet. Neurological examination of advanced cases illustrates impaired touch, proprioception, position and vibration sense, depressed ankle reflex, and an unsteady gait. This naturally accentuates the risks of developing ulcers and amputation of peripheries, which is the leading cause of hospitalization in diabetic patients.

The EURODIAB prospective study identified the following risk factors in the development of diabetic neuropathy:
(a) Duration of diabetes
(b) Poor glycaemic control (glycosylated haemoglobin HbA1c level and change in HbA1c)
(c) Hypertension
(d) Smoking
(e) Hyperlipidaemia
(f) High BMI

Mechanical, inflammatory, ischaemic, and other metabolic causes of neuropathy may also co-exist in diabetic patients and contribute to focal and multifocal types of diabetic neuropathy.

Painful diabetic neuropathy
Based on the definition of neuropathic pain by IASP (International Association for the Study of Pain), painful diabetic neuropathy may be defined as pain arising as a direct consequence of abnormalities in the somato-sensory system in
people with diabetes. The epidemiology of painful diabetic neuropathy has not been studied and also diabetic neuropathy. It is estimated that around half of patients with chronic diabetic neuropathy experience pain and the majority have features of chronic sensorimotor peripheral neuropathy. A community-based population study in the UK reported that around one-third of all diabetic patients have pain. It is also reported that 12% of patients with painful symptoms have never volunteered this to their doctors and ~40% never receive treatment. The prevalence of painful neuropathy in Type 2 diabetes is more than twice that seen in Type 1 diabetes.

Pain is the most distressing amidst all symptoms attributed to diabetic neuropathy. Most patients experience moderate-to-severe pain with the majority of patients finding it difficult to express the character of the pain. The common neuropathic pain descriptors such as ‘burning’, ‘electric shocks’, ‘shooting/stabbing down the leg’, ‘pins and needles and tingling’, and ‘numbness’ can be elicited on further questioning. Patients may also have features of evoked pain such as allodynia (painful response to non-painful stimuli) and hyperalgesia (increased pain from a stimulus that normally provokes pain), which could have a significant impact on everyday activities. Pain is usually present in the feet, and this may ascend to involve the lower limbs and occasionally both hands. Pain typically worsens during the night resulting in sleep disturbance and tiredness.

Pain in combination with physical disability because of other long-standing complications of diabetes substantially impairs the quality of life. Patients with neuropathic pain have markedly lower scores on quality-of-life domains, including enjoyment of life, sleep, physical mobility, self-care, and energy levels. It is not surprising that the majority of patients reporting neuropathic pain suffer from anxiety and depression. The natural history of painful diabetic neuropathy varies from unpredictable fluctuations in pain severity to complete resolution. Pain can develop at any stage of diabetes. Up to one in four patients suffer from pain with no signs of neuropathy.

The risk factors for development of painful diabetic neuropathy are not as well defined as those for neuropathy alone. There is some evidence that age, duration of diabetes, nephropathy, peripheral vascular disease, and waist circumference can be possible predictors for the development of painful neuropathy. However, the risk factors for painful and painless neuropathy overlap, and discrete predictors for the development of painful symptoms are yet to be found.

Clinical assessment

In the pain clinic, comprehensive history and clinical examination are mandatory to make a diagnosis. It is crucial to allocate appropriate time for history taking, as some patients may find it difficult to describe their pain. It is also necessary to find out the duration of diabetes, blood sugar control, and other complications of diabetes, which could assist in the diagnosis and also treatment. Clinicians have to assess the patient’s mood, sleep, physical activities, and social circumstances as part of their examination.

There are a number of neuropathic pain screening tools, such as the Leeds Assessment of Neuropathic Pain Symptoms and Signs (LANSS) and Douleur Neuropathique en 4 questions (DN4), that are validated and available in multiple languages. The self-administered versions of these could be used on first visit to the pain clinic.

As with any other chronic pain condition, quantitative assessment of the following domains is recommended:

- (a) Severity of pain: numeric rating scale or visual analogue scale.
- (b) Physical functioning: for example, brief pain inventory.
- (c) Emotional functioning: for example, Beck Depression Inventory.
- (d) Overall improvement and patient satisfaction: for example, global patient impression of change.

A detailed neurological examination should be performed with particular attention being given to the following:

- (a) Inspection of extremities for dry skin, infection, ulcers, and callouses.
- (b) Sensory modalities: pain sensation with pin, touch with cotton wool, vibration with 128 Hz tuning fork, pressure with 10 g monofilament, and temperature with hot and cold water tubes. Check and demarcate the area of allodynia, hyperalgesia, hypoalgesia, and numbness.
- (c) Muscle wasting, tone, and Achilles reflexes.
- (d) Local autonomic signs such as changes in temperature, colour, and sweating.

Quantitative sensory testing is not commonly used in the UK in the pain clinic. It can be used to accurately quantify the magnitude of sensory deficit for all sensory modalities described above by applying a standard stimulus (e.g. pin-prick for hyperalgesia).

Investigations and diagnosis

Nerve conduction studies can be used to confirm peripheral nerve damage that reflects only large nerve fibre dysfunction. Skin biopsy, a laboratory test to measure the density of intradermal epidermal fibres, can be done to assess small fibres. Laser-evoked potentials may be used to analyse for Aδ fibres. However, the correlation between a type of nerve fibre deficit and painful symptoms is still to be proved. Sometimes, patients with no demonstrable neurological

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**Table 1** Classification of DM neuropathies

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<thead>
<tr>
<th>A. Generalized symmetrical polyneuropathies</th>
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<tr>
<td>1. Chronic sensorimotor polyneuropathy:</td>
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<tr>
<td>• Sensory—thin fibres (C fibres)/thick fibres—Aδ and Aβ fibres</td>
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<tr>
<td>• Mixed nerves</td>
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<td>2. Acute sensory neuropathy (painful)</td>
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<tr>
<td>3. Autonomic neuropathy—gastrointestinal tract, cardiovascular system, and genitourinary system</td>
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<tr>
<td>B. Focal and multifocal</td>
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<tr>
<td>• Mononeuropathies—cranial nerve and peripheral nerve</td>
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<tr>
<td>• Multiple mononeuropathy—mononeuritis multiplex</td>
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<tr>
<td>• Focal limb/trunk involvement—thoracic, lumbosacral, and cervical neuropathy</td>
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<tr>
<td>• Compression neuropathy: for example, carpal tunnel syndrome</td>
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<td>• Inflammatory demyelinating neuropathy</td>
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changes develop painful symptoms. This further highlights that painful diabetic neuropathy is essentially a clinical diagnosis.

It is important to consider other causes of pain such as peripheral vascular disease and other non-diabetic causes of neuropathic pain (e.g. thyroid problems, alcohol, B12 deficiency, spinal stenosis, HIV, cancer, drugs, etc.) that may co-exist in patients with diabetes.

Pathophysiology

In neuropathy

Diabetic neuropathy occurs because of complex interaction between hyperglycaemia-induced metabolic and biochemical changes and inadequate perfusion pertaining to micro-vascular changes (Fig. 1).²

(a) Polyol pathway: hyperglycaemia results in the activation of the polyol pathway resulting in increased production and intracellular accumulation of sorbitol and fructose through the aldose reductase pathway that disrupts neuronal structure and depletes neuronal energy.

(b) Advanced glycation end products: hyperglycaemia increases the glycosylation of amino groups of proteins and lipids of neuronal and vascular cells, which affects their structure and function. An increase in advanced glycation end products is shown to induce cytokines.

(c) Poly (ADP ribose) polymerase (PARP): PARP is a DNA repair enzyme, but its over activation in hyperglycaemia is shown to deplete energy and cause cell death.

(d) Impaired neurotrophic support: it is because of reduction in insulin, nerve growth factor, and neurotrophin.

(e) Abnormal long-chain fatty acid and prostaglandin metabolism: it causes neuronal and microvascular structural changes.

(f) Increase in protein kinase C (PKC): it is formed from diacylglycerol (DAG).

All the above mechanisms induce oxidative stress. This results in the over production of oxygen-free radicals (superoxide), endothelial damage, imbalance between vasoactive factors (nitric oxide and endothelin), and altered expression of neuronal and vascular growth factors. In association with microangiopathy, these pathological changes are postulated to cause neuronal ischaemia, damage, and reduced neuronal regeneration process.

In painful neuropathy

In diabetes, as in any other types of neuropathic pain, a definite causal relationship between a specific pathological finding and pain is yet to be established (Fig. 1). Numerous mechanisms have been proposed for the development of neuropathic pain (Table 1). Irrespective of the cause, pathological changes seem to overlap in the manifestation of symptoms and signs between the diverse types of neuropathic pain. Neuroimaging studies in patients with painful diabetic neuropathy have shown a shrunken spinal cord and increased thalamic vascularity in comparison with painless diabetes, implying the involvement of the central nervous system. Recently, it has been shown that even short-term hyperglycaemia may independently contribute to hyperalgesia in diabetic patients.

Acute painful diabetic neuropathy

This is a relatively uncommon, less established type of painful diabetic neuropathy, characterized by acute onset of severe burning
Painful diabetic neuropathy

Pain with nocturnal exacerbation and weight loss, but often with no or only mild neurological deficits. Sudden fluctuations in blood sugar (e.g. diabetic ketoacidosis) or rapid correction of hyperglycaemia with insulin or other hypoglycaemic agents are postulated to initiate the process. Unlike the chronic variety, symptoms generally disappear within a year when normoglycaemia is achieved.

**Treatment**

**Pathogenetic treatment**

To date, treatments aimed at targeting the natural history of diabetes remain elusive. However, treatments aimed at preventing or modifying underlying pathogenetic changes have evolved over the years.

**Glycaemic control and risk factor management**

Evidence suggests that enhanced glycaemic control decreases the risk of development and also worsening of neuropathy. However, whether better glycaemic control can prevent painful symptoms remains uncertain.

Smaller studies have shown that bigger fluctuations in glycaemic levels are associated with a greater intensity of neuropathic pain. Hence, it is logical to emphasize the importance of stable glycaemic control to patients. It is also necessary to avoid rapid corrections of high blood sugar, as this itself may cause acute neuropathic pain.

It is also important to optimally manage any co-existing co-morbidities, such as hyperlipidaemia, hypertension, etc., which are known risk factors.

**Alpha-lipoic acid**

There is some evidence that alpha-lipoic acid, an anti-oxidant, can improve neuropathy and reduce pain scores. Aldose reductase inhibitors, PKC inhibitors, and inhibitors of glycation are some of the other pathogenetic treatments that have been evaluated.

**Symptomatic treatment**

The management of painful diabetic neuropathy often presents several challenges to the clinician, as painful diabetic neuropathy affects the patient physically, psychologically, and socially. Hence, management should be ideally done by a multi-professional team that comprises diabetologists, neurologists, pain physicians, psychologists, physiotherapists, podiatrists, and nurse specialists. It is essential to empathetically explain the diagnosis and treatment options to the patients. The key components of treatment should include pain reduction, improving physical and emotional aspects and overall quality of life. It is also crucial to provide education on the importance of ‘foot and hand care’ and the need for adequate glycaemic control to prevent ulceration and other complications.

**Pharmacological treatment**

Despite multiple studies on anti-neuropathic medications, choosing an anti-neuropathic drug over others is not necessarily influenced by the aetiology and pathogenesis of the disease. NICE has published guidelines on the pharmacological management of neuropathic pain, with a separate pathway for diabetic neuropathy (http://www.nice.org.uk/guidance/CG96). At the time of writing this article, NICE guidelines were being updated. While choosing an anti-neuropathic agent, the following considerations should be made: safety profile of the drug, co-morbidities, drug interactions, adverse effects, and simplicity in administration.

Simple analgesics such as paracetamol and NSAIDs may not be effective in neuropathic pain.

**Antidepressants**

**Tricyclic antidepressants**

TCAs (e.g. Amitriptyline, Imipramine, and Nortriptyline) act by inhibiting the re-uptake of serotonin and norepinephrine and modulate the descending inhibitory pathways. Other mechanisms have been postulated including antagonism of Na channels, Ca channels, NMDA receptors, and stimulation of opioid receptors. NICE guidelines recommend Amitriptyline as the first-line drug in painful diabetic neuropathy where Duloxetine is contraindicated. Amitriptyline/Nortriptyline should be initiated at low dose (e.g. 10 mg at night) and gradually titrated (e.g. 10 mg week⁻¹) to the maximum dose of 150 mg day⁻¹, and the titration should be balanced between therapeutic and adverse effects. The NNT (at least 50% pain relief) varies between 1.3 and 3.0 for TCAs. NNH (number needed to harm) for minor side-effects is 6 and NNMH (for major adverse events) is 28. The majority of patient withdrawal from Amitriptyline is noted to be because of anti-cholinergic side-effects. TCAs are associated with multiple adverse effects mainly because of α-blocking and anti-cholinergic effects. The common side-effects include sedation, dry mouth, blurred vision, urinary retention, arrhythmias, orthostatic hypotension, and weight gain. Nortriptyline is better tolerated because of fewer anti-cholinergic side-effects.

TCAs are contraindicated in patients with prostatic hypertrophy, closed-angle glaucoma, recent myocardial infarction, and cardiac conduction defects.

**Serotonin—norepinephrine reuptake inhibitors**

Duloxetine is the first-line drug in painful diabetic neuropathy as per the NICE guidelines. It has a balanced action on both serotonin and norepinephrine reuptake from the presynaptic junction. It has both analgesic and antidepressant properties. It is generally started at 30–60 mg day⁻¹ and titrated to the maximum dose of 120 mg day⁻¹ based on the side-effects and tolerance. NNT for 60–120 mg is between 5 and 6 with the higher dose having marginally lower NNT; but with more side-effects. Initial dose titration needs to be slow as the majority of the adverse events occur within the first few weeks. The common adverse effects are nausea, somnolence, sweating, dry mouth, and rarely hepatitis. It also reduces appetite, which can be a useful side-effect in obese patients. It is contraindicated in liver failure, renal failure, and glaucoma. Its use in hypertensive patients needs caution, as it can increase blood pressure.
Venlafaxine, another serotonin–norepinephrine reuptake inhibitor, is shown to have moderate efficacy, but its use is limited because of frequent cardiac side-effects.

**Anticonvulsants**
Gabapentinoids (Gabapentin and Pregabalin) are commonly used anticonvulsants in neuropathic pain. They act by binding with the α-2δ subunit of voltage-gated calcium channels and reduce calcium influx which subsequently reduces the release of calcium-induced excitatory neurotransmitters such as glutamate. The starting dose of Gabapentin is usually 300 mg day<sup>-1</sup>, which is gradually titrated to 1800–3600 mg day<sup>-1</sup> over a few weeks. The initial recommended dose of Pregabalin is 150 mg day<sup>-1</sup> (in two or three divided doses), titrated to the maximum dose of 600 mg day<sup>-1</sup>. NNT described in Cochrane reviews is 5.8 (≥1200 mg day<sup>-1</sup>) for Gabapentin and 5–7 (300–600 mg day<sup>-1</sup>) for Pregabalin. Pregabalin is the recommended second-line agent in NICE after Amitriptyline and Duloxetine. Pregabalin can be titrated to the maximum dose slightly faster than Gabapentin. Gabapentinoids are generally well tolerated. Common adverse effects for both are dry mouth, drowsiness, dizziness, peripheral oedema, weight gain, and diarrhoea. NNH for minor side-effects is 6–7 for either. Both of them are primarily renally excreted, and a reduction in their dosage is necessary in renal impairment.

There are few small sample studies showing some efficacy of Topiramate, Lacosamide, and Lamotrigine, but the results are not consistent.

**Opioids**
Oxycodone and Tramadol are shown to have moderate efficacy in the treatment of painful diabetic neuropathy. However, opioids should be considered only after the failure of other drugs because of their potential risk for drug abuse and long-term endocrine and immunological adverse effects.

Tramadol is a centrally acting opioid agonist that also weakly inhibits serotonin and nor-epinephrine reuptake. It has relatively low abuse potential among opioids. It is advisable to start at 50 mg day<sup>-1</sup>, titrating to the maximum daily dose of 400 mg. A multicentre double-blinded study has demonstrated that the analgesic effects of Tramadol (up to 200 mg day<sup>-1</sup>) were maintained for up to 6 months.<sup>11</sup>

Controlled release oxycodone has been shown to have a favourable outcome in small studies. The common adverse effects of opioids include constipation, nausea, vomiting, drowsiness, and dry mouth.

**Topical treatments**
Capsaicin binds with TRPV<sub>1</sub> (transient receptor potential vanilloid 1) receptors present on terminals of nociceptive nerve fibres. It has been initially postulated to act by depleting substance P; more recent theories describe the mechanism called ‘defunctionalization’, which is demonstrated with repeated application of 0.075% cream and 8% capsaicin. This involves retraction of intra-epidermal axonal endings, hence reducing intra-epidermal nerve fibre density. In painful diabetic neuropathy, capsaicin 0.075% cream was found to be effective in a few studies with NNT of 6–7. It is recommended to be applied 3–4 times a day on an intact skin. Patients should be instructed to wear gloves on application, to avoid contact with mucous membranes and eyes, and to wash hands after application. The role of 8% capsaicin in painful diabetic neuropathy is currently being studied.<sup>12</sup>

The Lidocaine 5% patch has been shown to reduce diabetic pain alone and also in combination with Pregabalin in an RCT. Nitrate topical spray and patch were found to be effective in painful diabetics. It is presumed to be because of the formation of nitric oxide and its effects on microvascular perfusion.

There are very few direct comparison and combination studies of anti-neuropathic drugs. A meta-analysis had concluded that Pregabalin, Gabapentin, and Duloxetine were equally effective.<sup>13</sup> Amitriptyline was shown to be as effective as Pregabalin, but with more side-effects than the latter. Gabapentin, when combined with Morphine at lower doses, was more effective than either drug alone at higher doses. Gabapentin and Nortriptyline combination had also provided better analgesia than single drug in a cross-over trial.<sup>14</sup>

**Other treatments**
Various other non-pharmacological treatments have been trialed for painful diabetic neuropathy, such as TENS, acupuncture, various types of phototherapy, and even spinal cord stimulation. Well-conducted studies are too scarce to make any conclusions.

**Conclusion**
Painful diabetic neuropathy affects around half of patients with diabetic neuropathy. It is not only under diagnosed, but also under treated. The majority of patients experience severe pain, affecting sleep, emotion, and overall quality of life. A comprehensive neurological examination with specific focus on the sensory system is crucial in making the diagnosis as laboratory tests on neurology do not always correlate with pain symptoms. Management should be tailored individually and encompass a multidisciplinary approach. TCAs, Duloxetine, and Gabapentinoids constitute the first-line agents. Drug selection should be based on other co-morbidities, drug interaction, and patient’s tolerance. Capsaicin 0.075% cream, Lidocaine 5% patch, and combination of drugs may be effective in some. Non-pharmacological management including spinal cord stimulation and TENS may be considered for patients who fail conventional treatment, but the evidence for these treatments is poor.

**Declaration of interest**
None declared.

**References**

Please see multiple choice questions 25–28.