Diagnosing and managing chronic painful diabetic neuropathy

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ARTICLE POINTS

1 Chronic painful diabetic neuropathy poses a challenge for health professionals because of difficulties in its recognition and management.

2 Diagnosis is based primarily on eliciting a typical history.

3 Current treatments are aimed at relieving symptoms, and there is no single therapy that will benefit all patients.

4 Currently available therapies should be offered in a stepwise fashion: a treatment algorithm based on the available evidence and the authors' experience is presented.

5 Better understanding of the pathogenic mechanisms involved may lead to more targeted, and hence effective, therapies.

KEY WORDS
- **Diabetic neuropathy**
- **Pain**
- **Diagnosis**
- **Management**

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Introduction

A global epidemic of diabetes has emerged, largely as a result of increasingly sedentary lifestyles and a rising prevalence of obesity. Neuropathy is one of the most common and troublesome complications of diabetes, and the number of people afflicted is likely to increase steadily as the incidence of diabetes in the developed world rises. Although foot ulceration is the most commonly recognised complication of peripheral neuropathy (Boulton, 2000), neuropathic pain can also occur, causing significant morbidity and impairment in quality of life (Benbow et al, 1998). This article reviews the frequency of chronic painful neuropathy, and provides an update on its recognition and management.

Diabetic neuropathy is not a single entity but a heterogeneous group of disorders that encompasses a wide range of abnormalities. One common classification scheme is based on anatomical distribution and includes two main types of diabetic neuropathy: diffuse neuropathies and focal neuropathies (*Table 1*; Thomas, 1997).

The most common diffuse neuropathy in patients with diabetes is chronic distal symmetric sensorimotor polyneuropathy affecting predominantly the feet and lower legs (Boulton, 2000). This can predispose to the development of neuropathic foot ulceration (Boulton, 2000), cause chronic neuropathic pain, or be associated with both.

Neuropathic pain is defined by the International Association for the Study of Pain (IASP) as pain 'initiated or caused by a primary lesion or dysfunction of the nervous system' – in contrast to nociceptive pain (commonly seen in medical practice) which warns the individual of actual or potential tissue damage, e.g. the pain felt when putting your hand into boiling water.

Chronic painful polyneuropathy

This is one of the clinical manifestations of chronic distal sensorimotor polyneuropathy. In some patients with diabetes, painful neuropathic symptoms can be present at the time of diagnosis or may develop insidiously over the following years, eventually becoming debilitating and often impairing the quality of life of those afflicted (Benbow et al, 1998).

The IASP defines chronic pain as pain lasting for more than 3 months. However, in clinical trials, painful symptoms lasting for 12 months or more is a better criterion for distinguishing acute from chronic pain.

Chronic painful neuropathic symptoms may last for many years. Some longitudinal

Table 1. Classification of diabetic neuropathies*

Diffuse neuropathies	Distal symmetric sensorimotor polyneuropathy Autonomic neuropathy Symmetric proximal lower limb motor neuropathy (amyotrophy)
Focal neuropathies	Mononeuropathies Entrapment neuropathies

*Based on Thomas, 1997

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1 Estimates of the prevalence of painful neuropathy vary greatly, depending on the diagnostic criteria used and the populations studied.

2 A recent community-based study, which used well-defined criteria and validated measures of pain severity and quality, estimated the prevalence of chronic (duration >1 year) painful diabetic neuropathy to be 16.2%.

3 The diagnosis of chronic painful diabetic neuropathy is based primarily on a typical history.

4 The contribution of clinical examination and investigations to the diagnosis is probably minimal, although they are necessary to exclude other causes of the pain.

studies of painful diabetic neuropathy have shown a general tendency for painful symptoms to improve (Benbow et al, 1994), whereas others have found no change. The treatment of this chronic form of painful neuropathy presents a real challenge to the physician, and the frequently encountered resistance to various forms of intervention can generate considerable frustration for both patient and doctor.

This article focuses on the chronic form of pain found most commonly in the feet and legs, although severe neuropathic pain can rarely occur in an acute form of lower leg neuropathy, or very occasionally in other sites such as the trunk or thighs.

How common is chronic painful diabetic neuropathy?

Estimates of the prevalence of painful neuropathy vary substantially, depending on the diagnostic criteria used and the populations studied.

- In a hospital clinic population, 25% of patients with diabetes had symptoms of chronic pain and 8% had typical lower limb neuropathic symptoms (Chan et al, 1990).
- One study found that 11% of insulin-treated patients had painful symptoms (Boulton et al, 1985)
- Another study reported that 20% of patients with type 2 diabetes had neuropathic pain after 10 years of diabetes (Partanen et al, 1995).
- More recently a community-based study of patients with type 1 and 2 diabetes (attending either primary or secondary care clinics or both) estimated the prevalence of chronic (duration >1 year) painful diabetic neuropathy to be 16.2% (Daousi et al, 2004). This study is the largest study to date in which well-defined criteria of painful diabetic neuropathy and validated measures of pain severity and quality were used, giving a true and representative picture of the extent of the problem in the population with diabetes in the community.

How is chronic painful diabetic neuropathy diagnosed?

Chronic painful diabetic neuropathy is diagnosed through history and examination.

History

The diagnosis of chronic painful diabetic neuropathy is based primarily on eliciting a typical history. The contribution of clinical examination and elaborate investigations to the diagnosis is probably minimal, although they are necessary to exclude other causes of the pain.

The earliest symptoms, which begin insidiously, typically involve the toes, and then advance proximally up the legs. Hand involvement can occur later, is usually less severe and far less common. There is no relationship between the severity of the neuropathy and the severity of the pain reported by patients.

The character of the pain in diabetic neuropathy can be highly diverse. Patients tend to have a range of symptoms which can also vary over time. Symptoms can develop spontaneously or be brought on by a particular stimulus.

Spontaneous pain can be mainly continuous (although of varying intensity) and

Table 2. Pain terms as defined by the International Association for the Study of Pain*

Pain term	Definition
Allodynia	Pain due to a stimulus that does not normally provoke pain
Analgesia	Absence of pain in response to stimulation that would normally be painful
Hyperalgesia	An increased response to a stimulus that is normally painful
Hyperaesthesia	Increased sensitivity to stimulation, excluding the special senses
Hyperpathia	A painful syndrome characterised by an abnormally painful reaction to a stimulus, especially a repetitive stimulus, as well as an increased threshold
Hypoalgesia	Diminished pain in response to a normally painful stimulus
Hypoaesthesia	Decreased sensitivity to stimulation, excluding the special senses

*From Dworkin, 2002

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1 Patients often find it difficult to describe the pain they have experienced.

2 In such cases, it is important to ask appropriate questions, to elicit various aspects of patients' pain.

3 Painful neuropathy is not the only cause of pain in the lower limbs in patients with diabetes.

4 Health professionals need to be able to distinguish painful diabetic neuropathy from other conditions with which it may be confused, and which may coexist in patients with diabetes.

5 Excessive alcohol intake, vitamin B_{12} deficiency, familial forms of neuropathy, hypothyroidism, malignancy, renal failure and neurotoxic drugs also cause neuropathy, some of which can be painful.

Table 3. Symptoms commonly reported by patients with painful diabetic neuropathy

- Burning pain
- Shooting, lancinating pain
- Pins and needles, tingling
- Hot or cold sensation in the feet
- Aching, cramping pain
- 'Walking on marbles' (metatarsalgia)
- Irritation of feet by bedclothes

includes descriptors such as burning or throbbing, or intermittent or paroxysmal (and usually of short duration) and be described as shooting or stabbing in quality (Dworkin, 2004).

Stimulus-evoked pain includes allodynia and hyperalgesia (*Table 2*), e.g. patients may say that the bedclothes irritate their feet at night, causing them to sleep with their feet out of the bed (allodynia). Patients may also experience abnormal sensations in their feet and legs, e.g. numbness, itching and tingling. *Table 3* lists some of the most commonly reported pain qualities.

Patients often find it difficult to describe the pain they have experienced. It is therefore important to ask the appropriate questions, if necessary, to elicit various aspects of patients' pain, such as:

- Where and when do you get the pain?
- How long have you had it for?
- What does it feel like?
- What makes it worse or better?
- Does it stop you from doing anything?
- Does it affect your sleep?
- Have you tried anything for it?

The severity of pain can be measured using a visual analogue scale (VAS), where patients quantify their pain on a scale of 0 ('no pain') to 10 ('worst pain you can imagine'). The VAS measures pain severity only, whereas both quality and quantity of pain can be formally assessed using the McGill Pain Questionnaire (Melzack, 1975) or the Neuropathic Pain Scale (Galer and Jensen, 1997).

Examination

A detailed general examination of the feet should be performed as normal, and should include examination of peripheral pulses and nervous system. The different types of sensation (heat, cold, pain, vibration, touch etc) are transmitted from the periphery to the brain via two main types of nerve fibres: large and small fibres.

Small fibre function can be assessed by testing sensation to pain and temperature. Large fibre function can be assessed by testing sensation to the 10 g monofilament at multiple sites, measuring vibration (using a 128 Hz tuning fork), testing position sense and eliciting deep tendon reflexes in the lower limbs. Quantitative sensory testing can be used in research settings for more detailed sensory testing.

Classically, in diabetic polyneuropathy the sensory loss, if present, diminishes on testing more proximally, and typically affects both feet. Sensory changes associated with pain that show an asymmetric pattern may be caused by compression of a nerve root or a peripheral nerve, and should not be mistaken for painful polyneuropathy.

Other causes of pain in the feet of people with diabetes

Painful neuropathy is not the only cause of pain in the lower limbs in patients with diabetes. Healthcare professionals must be able to differentiate painful diabetic neuropathy from other conditions with which it may be confused, and which may coexist in patients with diabetes. Other causes of neuropathy include excessive alcohol intake, vitamin B_{12} deficiency, hypothyroidism, familial forms of neuropathy, renal failure, malignancy, and neurotoxic drugs; some of these forms of neuropathy can be painful.

It can sometimes be difficult to distinguish pain due to peripheral vascular disease from painful neuropathy. The intermittent nature of the former pain, which worsens on walking and remits with rest, can prove helpful, as can an examination of the peripheral vascular system. However, more detailed investigation of the vasculature may be needed.

Other causes of pain in the feet of patients with diabetes include plantar fasciitis, tarsal tunnel syndrome, Charcot's neuroarthropathy, neuroma and osteoarthritis.

What causes the pain?

Despite many theories on the potential

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1 The drugs currently used to treat painful diabetic neuropathy do not reverse the nerve damage or halt its progression, but are aimed at relieving the symptoms.

2 There is no single drug therapy that will benefit all patients with painful neuropathy.

3 Patients should be offered the currently available therapies in a stepwise fashion.

4 It is important to explain to patients that the majority of drugs used for pain relief need to be taken regularly and may take some time to have an effect.

5 Patients should be advised of the potential side-effects of prescribed drugs, and regular clinic review should be arranged.

causation of chronic neuropathic pain, it is still unclear how pain is generated and maintained. These theories are beyond the scope of this paper, but have been reviewed elsewhere (Spruce et al, 2003).

A number of mechanisms are undoubtedly involved and may vary over time and between individual patients. Increasing attention is being paid to the possible role of symptoms and signs in identifying the underlying pathophysiological mechanisms involved in pain (Dworkin, 2002). Although this is not yet possible in routine practice, it may lead to more targeted therapies in the future.

Management of neuropathic pain

The drug treatments currently used in the management of painful diabetic neuropathy do not reverse the nerve damage process or halt its progression, but are aimed at relieving the symptoms. There is no single drug therapy that will benefit all patients with painful neuropathy, and there are few data comparing drug classes or examining combinations of drugs.

However, patients should be offered the currently available therapies in a stepwise fashion (Benbow et al, 1999). *Figure 1* shows a treatment algorithm based on the available evidence and the authors' experience. General advice, such as using a bed cradle to prevent allodynia, may be useful (Watkins and Edmonds, 1997).

It is important to spend time with patients explaining the nature of painful diabetic neuropathy. For instance, explain that the majority of drugs used for pain relief need to be taken regularly and may take some time to have an effect. Patients should be advised of the potential side-effects of prescribed drugs, and regular clinic review should be arranged. Regular foot advice and care to prevent ulceration are mandatory.

Metabolic control

Tight blood glucose control undoubtedly delays the development of peripheral neuropathy in diabetes, and has been shown to reduce painful symptoms in some studies (Boulton et al, 1982). Optimal glycaemic control should clearly be aimed for, if only to reduce other complications.

Simple analgesics

Good evidence for the effectiveness of drugs such as aspirin or non-steroidal anti-inflammatory drugs is lacking. Many patients may already have tried them – with little or no effect – before seeking help elsewhere.

Antidepressants

Tricyclic antidepressants (TCAs): Of all the drugs used in the treatment of painful diabetic neuropathy, TCAs are the most extensively studied (Benbow et al, 1999). Amitriptyline and imipramine in particular have been found to relieve symptoms in patients in randomised, double-blind, placebo-controlled trials. A meta-analysis of 21 different clinical trials confirmed their efficacy as first-line agents in the management of pain in diabetic neuropathy (McQuay et al, 1996).

The main side-effects include dry mouth, blurred vision, sedation, constipation, urinary hesitancy, and postural dizziness. Their use requires caution in patients with glaucoma, elderly male patients with possible underlying prostatic hypertrophy and patients with cardiac arrhythmias.

Younger patients are more likely to be able to tolerate these drugs and a reasonable starting dose would be 25 mg/day of imipramine or amitriptyline (10 mg in the elderly), titrating slowly upwards over a few weeks to 75 mg as a single bedtime dose if necessary and tolerated. Occasionally, higher doses are needed.

Patients who suffer from sleep disturbance may find amitriptyline more helpful than imipramine because of its more prominent sedative effect. Nortriptyline is less effective at pain relief but probably causes fewer problems with postural hypotension.

Selective serotonin re-uptake inhibitors: On the whole, there is little evidence for the efficacy of these drugs in clinical trials and they are not particularly useful as analgesics.

Anticonvulsants

Gabapentin is one of the few drugs licensed in the UK for the management of neuropathic pain. It has been shown to be more effective than placebo when used in doses ranging from 900 to 3600 mg/day (Backonja et al, 1998). Our experience has shown that the dosage increments should

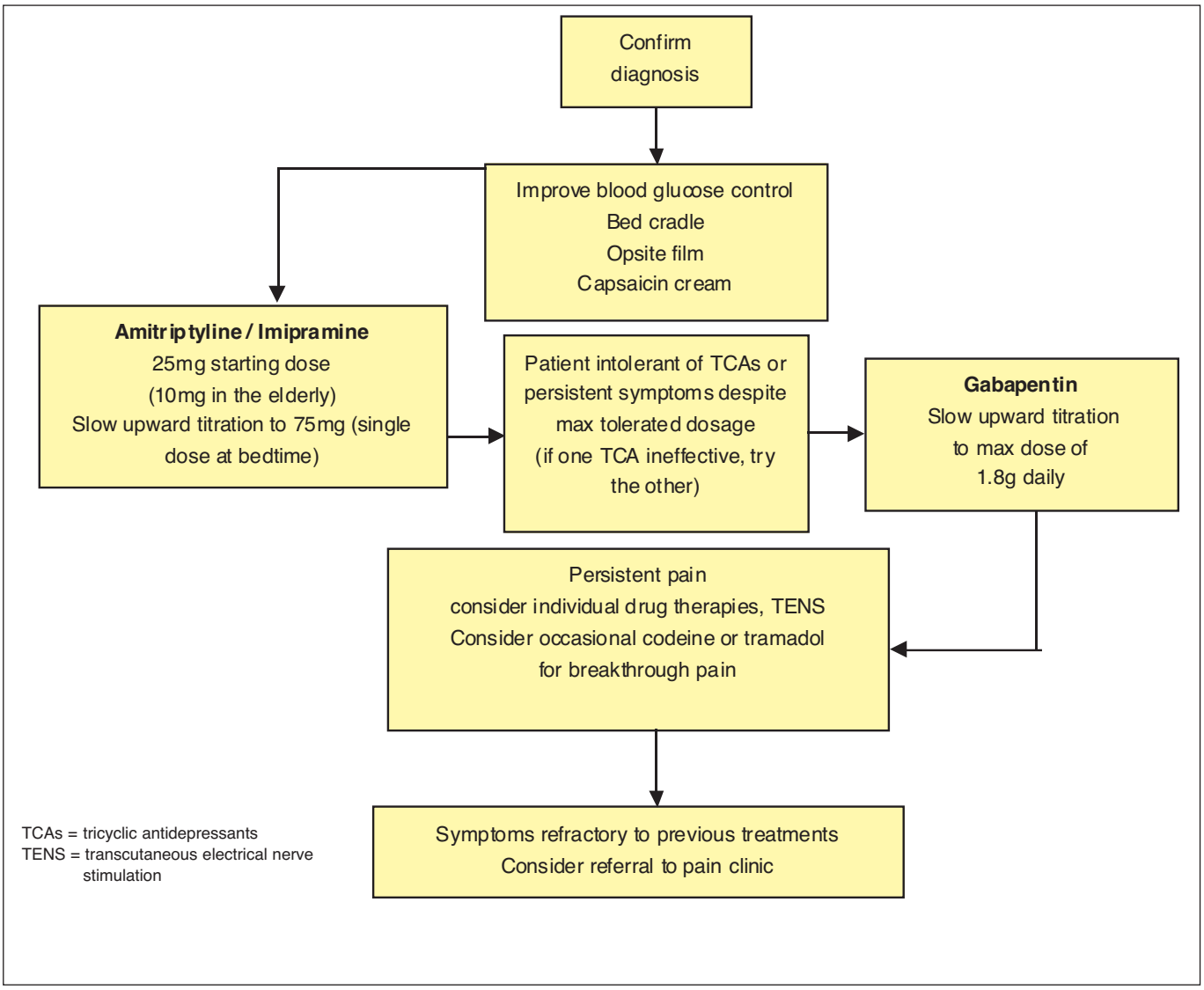

Figure 1. Treatment algorithm for painful diabetic neuropathy.

often be made at a slower rate than formally recommended, to reduce potential side-effects. The dose is therefore typically started at 300 mg once a day for 3 days, increased to 300 mg twice daily for a further 3–4 days, then 300 mg three times a day for another 3–4 days, followed by an increase in steps of 300 mg (usually in three divided doses) according to the response, up to 1.8 g daily – the maximum dose for which the drug is licensed in the UK. In the clinical trials where gabapentin has been used, larger doses have often been necessary to achieve adequate control of patients' pain.

The main side-effects are dizziness, somnolence, diarrhoea, headache and confusion.

Gabapentin appears to be an alternative treatment to TCAs if the patient has persistent symptoms despite maximum tolerated dosage or experiences significant side-effects with TCAs. However, it is increasingly being used by some clinicians as first-line therapy because of its favourable side-effect profile and relative lack of drug interactions. The use of carbamazepine in the treatment of painful diabetic neuropathy is now limited, and phenytoin has not been shown to be effective.

Other new generation anticonvulsants, such as topiramate and lamotrigine, have been shown to reduce the levels of pain in relatively small trials, but larger and longer clinical studies are required to assess the exact role of these agents, particularly as their side-effects may limit usage (Attal, 2000; Spruce et al, 2003). The results of trials of pregabalin are awaited.

Anti-arrhythmic agents

Intravenous lidocaine (lignocaine) has been shown to be beneficial in the relief of neuropathic pain in a few studies, but the lack of an oral agent and the need for ECG monitoring during the infusion render it an unpopular treatment choice.

The efficacy of an oral anti-arrhythmic agent, mexiletine, has been demonstrated to be variable in a small number of studies and the drug is now rarely used in the management of painful diabetic neuropathy.

Opiates

The role of opiates in the treatment of neuropathic pain is controversial. Tramadol was recently found to be effective in the treatment of pain in diabetic neuropathy in a double-blind, placebo-controlled, randomised trial (Harati et al, 1998). It can be used for breakthrough pain on an occasional basis but it is important to avoid regular long-term usage. Side-effects include nausea and vomiting, headaches, constipation, drowsiness and dependence.

Oxycodone was recently reported to be effective in a small study (Watson et al, 2003).

Other drugs

Many other drugs have been tried, with varying degrees of scientific proof of their efficacy (Benbow et al, 1999; Spruce et al, 2003). Interestingly, isosorbide dinitrate spray and glyceryl trinitrate patches appear to have a promising role in the alleviation of burning pain in diabetic neuropathy, but the only data available are from small, double-blind, placebo-controlled, crossover studies (Yuen et al, 2002; Rayman et al, 2003).

Topical therapies

Capsaicin, the main ingredient of the red chilli pepper, acts by depleting the nociceptive C fibres of substance P, which is an important mediator of pain signals. A meta-analysis of four randomised, double-blind, placebo-controlled trials in painful diabetic neuropathy found capsaicin overall to be more effective than placebo (Zhang and Li Wan, 1994). However, the release of large amounts of substance P following application of the cream results in a transient worsening of symptoms during the first week or two of capsaicin use. The burning sensation, time required to achieve pain reduction and the need to apply the cream four times daily to the affected areas can limit its usefulness.

Opsite film has been found to be helpful in reducing pain in some patients.

Neurostimulation techniques

Transcutaneous electrical nerve stimulation (TENS) has been shown, in some trials, to be effective in reducing the severity of pain in diabetic neuropathy, with a concurrent reduction in the use of other conventional analgesic agents (Kumar and Marshall, 1997).

Acupuncture has also been shown to be an effective and safe treatment option in uncontrolled studies (Abuaisha et al, 1998).

Electrical spinal cord stimulation (which involves the delivery of a low-voltage electrical current to the dorsal structures of the spinal cord via an implanted epidural system) has recently been shown to be effective and safe in the long-term treatment of severe, resistant, painful neuropathy. This confirms its place in the contemporary management of chronic intractable pain when other conventional treatment strategies have failed (Tesfaye et al, 1996).

Pain clinics

In refractory cases of chronic painful diabetic neuropathy, a multidisciplinary approach, such as that offered by pain clinics, may be necessary. This allows patients access to a wider variety of possible therapies, as well as potentially helping them to cope more effectively with their pain. Pain clinics can also provide highly sophisticated treatment methods such as neurostimulation techniques or cognitive behavioural therapy or access to pain management programmes.

Conclusion

Chronic painful neuropathy poses a challenge to healthcare professionals because of the difficulties in its recognition and management. A better understanding of the underlying pathogenic mechanisms of pain generation and nerve damage in diabetic neuropathy may lead to mechanism-tailored treatment strategies, which will increase the chances of achieving successful pain relief. ■

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1 Intravenous lidocaine (lignocaine) has provided effective relief of neuropathic pain in a few studies, but the lack of an oral agent and the need for ECG monitoring during the infusion render it an unpopular treatment choice.

2 The role of opiates in the treatment of neuropathic pain is controversial.

3 Tramadol can be used for breakthrough pain on an occasional basis, but it is important to avoid regular long-term usage.

4 Transcutaneous electrical nerve stimulation has been shown, in some trials, to reduce the severity of diabetic neuropathic pain, with a concurrent reduction in the use of other conventional analgesic agents.

5 Isosorbide dinitrate spray and glyceryl trinitrate patches have shown promise in the alleviation of burning pain in diabetic neuropathy in a few small studies.

'Chronic painful neuropathy poses a challenge to healthcare professionals because of the difficulties in its recognition and management.'

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