The neuropathies of diabetes are common, affecting up to 50% of older patients with type 2 diabetes. They have been the subject of several recent reviews. Only a minority of patients experience neuropathic symptoms, so the absence of symptoms must never be equated with the absence of neuropathy. A careful clinical examination of the lower limbs and feet is essential to diagnose neuropathy in any diabetic patient.

Pain and diabetic neuropathy

Pain is a subjective symptom that often motivates patients to seek medical advice. It may be present in several of the somatic neuropathies of diabetes. Two main types of pain have been described.

- **Superficial or dysoesthetic pain** is typically experienced by patients with sensory neuropathies. It is unfamiliar to the patient, who often describes it as burning, shooting, tingling, stabbing or lancinating, or likens it to hot needles or repeated electrical shocks. It is difficult to localise, intermittent and prone to nocturnal exacerbation, with allodynia and bedclothes' hyperaesthesiae. It is thought to be caused by erratic increased firing of sprouting nociceptive fibres.
- **In contrast, nerve trunk pain** is more familiar to the patient, and is described as aching, tender and occasionally knife-like. It may be experienced in spinal root compression, or nerve entrapment syndromes.

**Table 1. Diabetic neuropathies associated with painful symptoms.**

| Predominantly dysoesthetic | Predominantly nerve trunk |
|---------------------------|--------------------------|
| Sensory polyneuropathy:   | Focal:                   |
| acute sensory             | peripheral nerve entrapment |
| chronic sensorimotor      | cranial amyotrophy       |
| Focal:                    |                          |
| amyotrophy                |                          |
| Truncal                   |                          |

The outlook for symptomatic improvement and partial resolution of muscle weakness is good.

Truncal neuropathies. These are usually of abrupt onset, with dysoesthetic symptoms in the truncal region which after improvement of control when starting either insulin or even an oral hypoglycaemic agent. It is characterised by severe dysoesthetic symptoms with few, if any, abnormalities of sensory or motor function on examination. Depression and erectile dysfunction are usually present. Symptomatic treatment is required during the acutely painful phase (see below). Recovery typically occurs within a year with stable glycaemic control.

**Chronic sensorimotor neuropathy.** The chronic sensorimotor variety is common, with up to 30% of diabetic patients affected. The onset is insidious and the course slowly progressive. Painful dysoesthetic symptoms may be intermittently present in some patients, while others never experience any painful or paraesthetic symptoms but develop insensate feet at risk of ulceration.

**Focal neuropathies**

Most focal and multifocal neuropathies are accompanied by painful symptoms, which may be of the nerve trunk or dysoesthetic type. Ocular mononeuropathies are often painful, with a rapid onset of dull, aching pain around or behind the eye accompanied by muscle weakness, depending upon the involved nerve.

**Diabetic amyotrophy.** Pain is invariably a feature of diabetic amyotrophy (also known as femoral neuropathy, proximal motor neuropathy, etc) which typically affects older type 2 male patients and is usually accompanied by a distal sensory neuropathy. The pain may be a combination of dysoesthetic and nerve trunk pain, frequently involving the thighs, buttocks and even the lower back. It is accompanied by proximal motor weakness and is usually asymmetrical, involving predominantly one leg. The outlook for symptomatic improvement and partial resolution of muscle weakness is good.

**Truncal neuropathies.** These are usually of abrupt onset, with dysoesthetic symptoms in the truncal region which
may be severe. They need to be differentiated from pain of cardiac, pulmonary or gastrointestinal origin.

**Treatment of painful neuropathies**

In discussing the treatment of the painful neuropathies, distinction is made between therapies for symptomatic relief and those that might slow the progressive loss of nerve function that represents the natural history of diabetic neuropathy.

**Table 2. Clinical management of symptomatic diabetic neuropathies.**

|   | Exclude non-diabetic causes: | Explain and support |
|---|-------------------------------|---------------------|
| 1 | malignant disease (e.g. bronchogenic carcinoma) |  |
|   | metabolic (e.g. vitamin B<sub>12</sub> deficiency) |  |
|   | toxic (e.g. alcohol) |  |
|   | infective (e.g. HIV infection, leprosy) |  |
|   | iatrogenic (e.g. isoniazid, nitrofurantoin) |  |
| 2 | Explain and support |  |
| 3 | Assess level of metabolic control: |  |
|   | blood glucose profiles |  |
|   | glycated haemoglobin |  |
| 4 | Aim for optimal, stable control |  |
|   | transient symptomatic worsening may occur |  |
| 5 | Consider symptomatic medication |  |

**Table 3. Treatment of diabetic neuropathy.**

| Drug (per day) | Dose |
|---------------|------|
| **Symptomatic relief** |  |
| Oral medications | Tricyclics: |
| | imipramine | 25–150 mg |
| | amitriptyline | 25–150 mg |
| | Gabapentin | 900–3,600 mg |
| | *Tramadol | 50–400 mg |
| | *Mexiteline | up to 450 mg |
| Topical medications | Capsaicin |  |
| | Clonidine |  |
| **Investigational drugs that may slow progression** |  |
| | Aldose reductase inhibitors |  |
| | α-lipoic acid |  |
| | ACE Inhibitors |  |

*Note: drugs in investigational column are not licensed for use in neuropathy. * only short-term usage recommended.

ACE = angiotensin-converting enzyme.

**Glycaemic control**

Two landmark trials, the Diabetes Control and Complications Trial (DCCT) and the UK Prospective Diabetes Study (UKPDS), emphasised the role of chronic hyperglycaemia in the pathogenesis of neuropathy, with a risk reduction of over 50% in those patients with near-normoglycaemia in type 1 diabetes. The role of near-normoglycaemia in preventing and slowing the progression of neuropathy is now confirmed, but its role in the treatment of painful symptoms is less clear. There is some evidence that blood glucose flux may be implicated in the genesis of neuropathic pain but, apart from a few open trials, there is no controlled trial evidence to confirm the role of intensive insulin therapy in the treatment of neuropathic pain. Despite this, it is generally accepted that the first step in the management of neuropathic pain is to aim for stable, optimal glycaemic control, although insulin is not always indicated in patients with type 2 diabetes.

**Symptomatic therapy**

There are several therapies for neuropathic pain whose use has been supported in appropriate randomised trials. A proposed approach to the clinical management of symptomatic neuropathies is provided in Table 2, with options for symptomatic relief and possible slowing of progression listed in Table 3.

**Tricyclic drugs**

Although non-steroidal drugs may provide symptomatic relief in occasional patients, the tricyclic drugs are regarded as first-line therapy for dysaesthetic symptoms. The mechanism of action is believed to involve blockade of norepinephrine reuptake synapses of descending pain control systems. The rapid (in days) onset of symptomatic relief and the observation that these drugs are equally effective in patients with normal or depressed moods suggest that the mode of action is not primarily relief of depression. Amitriptyline and imipramine are most commonly prescribed in doses of 25–150 mg, usually as a single dose before bed. The major – and predictable – problems with tricyclic drugs which limit their usage are the frequent side effects. Drowsiness is common, but the anticholinergic side effects, particularly dry mouth, are troublesome. The combination of tricyclics with major tranquillisers such as fluphenazine or chlorpromazine may be used in more
severe cases only partially responsive to tricyclic monotherapy.

**Anticonvulsant agents**

Phenytoin. Although phenytoin has been used for many years for the treatment of neuropathic pain, there are few data to support its efficacy. Its use for diabetic neuropathy is not therefore recommended.

Carbamazepine. With the exception of one study which demonstrated the efficacy of carbamazepine in patients with mild neuropathic symptoms, there are few adequately designed trials in neuropathy using this drug. Side effects are common, and its use as a first-line agent cannot be recommended.

Gabapentin: This agent is structurally related to the neurotransmitter gamma-aminobutyric acid and was introduced for the management of complex-partial seizures. Its efficacy in painful diabetic neuropathy was confirmed in a large controlled trial, and its safety profile appears to be superior to that of the tricyclics, with dizziness and somnolence reported in less than 25% of patients. Gabapentin is now widely used, and the results of a comparative study with tricyclics are awaited with interest.

Other agents

Mexiletine. The efficacy of a class IB anti-arrhythmic agent, mexiletine, in painful neuropathy has been confirmed in several trials, and was the subject of a recent review. The usual dosage in neuropathy of up to 450 mg daily is not usually associated with any serious adverse events, but regular ECG monitoring is recommended and it should be used only short term.

Traamadol. An opioid-like, centrally acting non-narcotic analgesic, tramadol, has been shown to provide significant pain relief in diabetic neuropathy. Adverse effects (nausea, constipation, headache) may limit its usefulness. It is recommended only for short courses in patients not responding to other agents.

Other symptomatic approaches

Several topical applications have been proposed for the management of neuropathic pain, but they are generally reserved for those with localised pain. Capsaicin, an alkaloid found in red pepper which depletes tissues of substance P, has been shown to be efficacious in treating neuropathic pain. Similarly, clonidine patches have been reported to help sharp or shooting pain.

Two open-label studies have supported the use of acupuncture for distal sensory neuropathy. In severe painful neuropathy unresponsive to conventional therapy, a case series suggested benefit from implanted spinal cord stimulators.

**Therapy that might slow progression of neuropathy**

With the exception of the maintenance of near-normoglycaemia, therapies that might influence the natural history of neuropathy are still in the investigational stage (Table 3). These include the aldose reductase inhibitors, the antioxidant α-lipoic acid and the angiotensin-converting enzyme inhibitor trandolapril.

**General aspects of treatment**

All patients with diabetic neuropathy must be considered as being at risk of insensitive foot ulceration, and should receive appropriate education on foot care and also, if indicated, a podiatry referral.

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Diabetes in African Caribbean, and Indo-Asian ethnic minority people

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This article reviews diabetes in Indo-Asian (IA) people (who came, or whose forefathers came, from the Indian subcontinent), and African-Caribbean (AC) people (who came, or whose forefathers came, from the Caribbean).

Demography

In the 1991 census nearly 840,000 people described themselves as Indian, 500,000 as Black Caribbean and 477,000 as Pakistani, and less than half were born abroad. Compared with their white peers:

- the IA and AC populations were younger
- they were less likely to be in employment – if they had work, it was less well paid and with more arduous physical conditions
- more were poor
- fewer owned their own homes
- they were less able to benefit from social security.

Epidemiology of diabetes

Comparison with whites

Type 1 diabetes was initially uncommon in IA migrants, but the prevalence is now the same as in whites. There are no reliable data for AC people. Type 2 diabetes is commoner in IA, and occurs at an earlier age, with a lifetime risk of approximately one in three. AC have intermediate rates (Table 1). As in all societies, the prevalence of diabetes increases with age, sedentary lifestyle and increase in body weight.

Importantly, the rates in the UK are not different from those recently reported from the Indian subcontinent and the Caribbean. No firm reason for the high rates of diabetes is yet available, but the thrifty gene or phenotype hypotheses are both potential explanations. Insulin resistance is marked in IA, which could explain the onset of diabetes at a young age. Insulin resistance also explains the rapid change from impaired glucose tolerance to overt diabetes and the rapid progression to insulin therapy in this population.

Other risk factors

Hypertension. Hypertension is common in AC and explains the high rate of stroke and renal disease. The rates of hypertension are low in vegetarian Gujarats, but hypertension is common in Punjabi Sikhs. Lipids. AC have lower total cholesterol and triglyceride, but higher high-density lipoprotein than whites or IA. This contributes to the lower rates of coronary heart disease (CHD) seen in AC.

Complications of diabetes

Comparisons here are made with whites as the reference population. Where possible, diabetes-specific prevalence or incidence data have been used.

Renal disease

Renal disease is commoner in IA and AC than in whites. In the former, there are increases in microalbuminuria.