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Improving pain control in diabetic neuropathy

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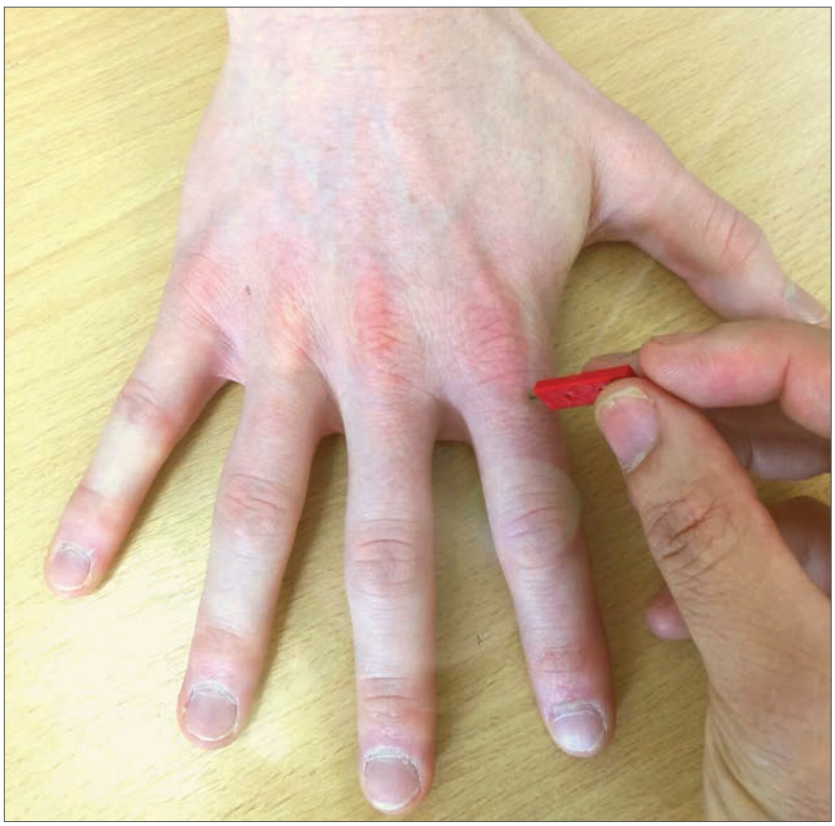

Pinprick testing in a patient with diabetes

What are the risk factors for diabetic neuropathy?

How should pain be assessed?

What are the management options?

DIABETIC NEUROPATHY IS THOUGHT TO AFFECT 1.9% OF THE WORLD POPULATION AND 50% OF PATIENTS with a diagnosis of diabetes mellitus which would equate to 2.25 million people in the UK.[1]

It can affect all nerve types including sensory, motor and autonomic neurones with a wide variety of ensuing consequences and a distinct set of clinical syndromes. With obesity, advanced age and diabetes all on the rise, the prevalence is destined to increase over the next ten years with a massive resultant socio-economic burden.[2] This article will focus on the clinical aspects of the painful sensory neuropathies.

MECHANISMS

Persistent hyperglycaemia creates a cascade of biochemical and metabolic changes that result in disruption to the normal neuronal structure and function. The glycosylation of proteins and lipids impairs the function of both neuronal and vascular cells.[3] This extent of glycosylation correlates well with reduced myelinated nerve fibre density.[4] Accordingly, the duration and extent of hyperglycaemia has been shown to be linked to the likelihood of painful neuropathy clinically.[5]

Other proposed mechanisms of diabetes-related nerve injury include the generation of oxidative free radicals with reduced nerve conduction velocity.[6] Increased polyol flux regulated by aldose reductase, activation of protein kinase C, impaired neurotrophic support, and abnormal prostaglandin metabolism are other mechanisms that have been studied. Indeed, this list is not exhaustive and is beyond the scope of this article. However, the subject is covered in great depth and detail in a review article.[7]

Unfortunately, despite the intense study of multiple mechanisms of injury, there are no novel treatments that have targeted these mechanisms and been incorporated into everyday clinical practice. The exception to this is the aldose reductase inhibitor epalrestat which was approved in Japan after a three-month double blind trial.[8] This has shown further promise in subsequent larger cohorts of more than 2,000 patients and was well tolerated.[9] A recent review has summarised the use of this class of drugs in treating and preventing neuropathy.[10]

CLINICAL SYNDROMES

The term diabetic neuropathy includes multiple distinct clinical entities that have been classified under the broad headings 'focal and multifocal neuropathies', and 'symmetrical neuropathies', see table 1, p24.[11]

Acute mononeuropathy can occur through infarction of the nerve. »

Cranial neuropathies are also possible with acute ophthalmoplegia due to involvement of the oculomotor nerve the most common. This presents with sudden onset of pain above or behind the eye.[12] Peripheral nerves affected most commonly include the ulnar, median, radial, femoral, common peroneal and lateral cutaneous nerve of the thigh,[12] the latter referred to as myalgia paraesthetica.

Diabetic amyotrophy, or Bruns-Garland syndrome, occurs in approximately 1% of patients with diabetes.[13] It presents as an acute progressive asymmetrical painful weakness of the thigh muscles. It can be a presenting symptom of diabetes and the unwary clinician could be misled in search of other diagnoses such as spinal stenosis, cauda equina syndrome or even demyelinating polyneuropathy.[13] Management revolves around tight glycaemic control, aggressive early physiotherapy, and symptomatic relief of pain. Thoracoabdominal radiculopathy is seen in the elderly population with unilateral or bilateral pain.[12] After episodes of ketosis, weight loss, or sudden tight glycaemic control patients can also develop an acute painful neuropathy characterised by the development of paraesthesia, hyperalgesia, or spontaneous nocturnal burning pain.

The specific and individual management of the various aforementioned neuropathies is outside the scope of this article. Instead we will focus on the most common form of diabetic neuropathy that is encountered, namely the chronic symmetrical predominantly sensory neuropathy that affects 50% of patients.[14]

Table 1

Classification of neuropathies

Focal and multifocal neuropathies

- Mononeuropathy
- Asymmetrical radiculopathy and amyotrophy
- Mononeuritis multiplex
- Peripheral nerve entrapment

Symmetrical neuropathies

- Acute sensory neuropathy
- Autonomic neuropathy
- Distal symmetrical polyneuropathy (most common; PDN)

Table 2

Risk factors for diabetic neuropathy

- High BMI
- Hypertension
- Smoking
- Duration of diabetes
- Poor glycaemic control
- Hyperlipidaemia

HISTORY AND EXAMINATION

The majority of these patients describe moderate to severe pain, using neuropathic descriptors such as burning, shooting or electric shocks. Paraesthesia and numbness are also commonly elucidated in the history. The common presentation is of painful symptoms originating in the feet, that then spread to the knees before involving the distal portion of the upper limbs in a 'glove and stocking' distribution.[15] Burning pain that is worse at night can interfere with the patient's sleep pattern causing further reduction in quality of life and pervasive low mood.

Risk factors, as outlined in the EURODIAB study,[16] may be elucidated from the history and examination, see table 2, below left. Many of these are modifiable with diet, medication, and lifestyle changes and strategies to address them should be advocated as appropriate.

The detailed examination of the diabetic foot is not covered in detail in this article however a brief focused examination can help detect the presence of neuropathy. Positive sensory signs may be elicited such as allodynia (pain in response to a non-noxious stimulus such as Von Frey hairs or brush testing) and hyperalgesia (increased and exaggerated pain in response to a noxious stimulus). These phenomena can result in profound disability and discomfort during simple everyday tasks such as getting dressed. More commonly in peripheral diabetic neuropathy (PDN), there is loss of sensory function.

A simple screening tool is the Michigan neuropathy screening instrument, see table 3, below left.[17] The large myelinated A-beta fibres are often considered the first to be affected in diabetic neuropathy,[18] and an early examination finding illustrating this is the loss of vibration sense with a 128 Hz tuning fork.

ASSESSMENT OF PAIN

The three broad categories of pain assessment are self-report measures, observational scales, and physiological variables. Self-report measures are considered to be the most reliable form of assessment given that they detail what is essentially a 'subjective sensory and emotional experience' according to the International Association for the Study of Pain definition.[19]

Unidimensional scales (visual analogue scale, numerical rating scale etc) can quantify acute pain intensity but in the context of chronic pain states such as PDN a full biopsychosocial assessment is useful to assess the impact of the patient's symptoms on their function, mood and quality of life. The brief pain inventory (BPI) is one example of a reliable and validated multidimensional pain scale that is useful in this context.[20]

There are a number of neuropathic specific assessment tools that can be readily used in a non-specialist setting in the community. These include the

Table 3

Michigan neuropathy screening instrument (MNSI)

MNSI items	Description
Appearance of feet*	0 = normal, 1 = abnormal
Ulceration	0 = normal, 1 = abnormal
Ankle reflexes	0 = present, 0.5 = present with reinforcement, 1 = absent
Vibration perception	0 = present, 0.5 = reduced, 1 = absent

*Deformity, dry skin, callus, infection and fissures

Maximum score is 4 for each foot, total = 8

A score ≥ 2 is considered positive (sensitivity 65% and specificity 83%)

Leeds Assessment of Neuropathic Symptoms and Signs (LANSS), Pain DETECT, Id-Pain, Dolouer Neuropathique,[4] and the Neurophysiology of Pain Questionnaire (NPQ).[21]

They vary to some degree but have in common the goal of detecting the presence of a neuropathic component to the patient's presentation. They tend not to grade pain intensity or the impact on function and quality of life that the multidimensional scales address. The LANSS questionnaire comprises five simple questions and two examination findings to give a dimensionless score for the pain out of 24, with a score ≥ 12 suggesting a neuropathic component is likely.[22] The sensitivity and specificity are 82-91% and 80-94% respectively.[21]

There are no specific tools for measuring neuropathic pain in the context of diabetes but in the specialist setting of the chronic pain clinic the above tools, particularly the multidimensional scales, are often used.

MANAGEMENT OF PAIN

Once the diagnosis has been made and a biopsychosocial assessment has indicated the impact on the individual patient, treatment can be tailored accordingly. Naturally, tight glycaemic control should be advocated as it has been implicated in reducing the intensity of pain and preventing further deterioration in symptoms.[23]

First-line medications that can be tried include amitriptyline, gabapentin, pregabalin and duloxetine (see table 4, below). Duloxetine is advocated as the best initial option in the context of diabetic neuropathy. It is the authors' experience that dose escalations are carried out slowly (e.g. 30 mg for one month before increasing) to improve tolerability. Although some patients experience gastrointestinal upset, others experience reduced appetite which may be beneficial in the obese patient.

If treatment fails with first-line therapy, NICE advises careful discontinuation and trying one of the alternative three drugs.[24] In the specialist setting of the pain clinic, when monotherapy with different antineuropathic agents has failed or has not been tolerated at an effective dose, combination therapy will then be explored. This requires gradual titration of the second drug once the first drug dose is optimised. Analgesic efficacy is increased with combination therapy, but side effects are also increased, so it is only an option with patients who tolerate drugs well.

For localised areas of pain, lidocaine 5% plasters (an unlicensed indication) and capsaicin 0.025% cream can be trialled. »

Table 4

Management of pain in diabetic neuropathy

Medication	Initial dose	NNT for 50% pain reduction[28]	Titration	Comments	Duration of trial
Amitriptyline	10 mg nocte	3.6	Increased every 3-7 days as tolerated to maximum 100 mg	Morning sedation/ hangover effect can be negated by taking earlier in the evening e.g. 7pm	6-8 weeks with at least 2 weeks at maximum tolerated dose
Nortriptyline	10 mg nocte	3.6	Increased every 3-7 days as tolerated to 75 mg maximum (50 mg elderly)	Potentially better tolerated in the elderly	6-8 weeks with at least 2 weeks at maximum tolerated dose
Duloxetine	30 mg OD	6.4	Increase weekly to 60 mg BD maximum	GI upset common	4 weeks
Gabapentin	100 mg TDS or 300 mg nocte	7.2	Increased weekly by 300 mg/day to maximum 3600 mg daily	Lower doses required in elderly and renal impairment	3-8 weeks for titration followed by 2 weeks at maximum tolerated dose
Pregabalin	75 mg BD	7.7	Increased weekly by 150 mg/day to 600 mg/day maximum	More linear absorption profile compared with gabapentin. Similar side effects of sedation and weight gain	4 weeks
Carbamazepine	100 mg daily	—	Increase weekly by 200 mg/day. 1600 mg/day total	Leucopaenia (10%), with neutropaenia in 1-10%	6-8 weeks

SPECIAL REPORT
DIABETIC NEUROPATHY

key points

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Diabetic neuropathy is thought to affect 1.9% of the world's population and 50% of patients with a diagnosis of diabetes mellitus which would equate to 2.25 million people in the UK. The term diabetic neuropathy includes multiple distinct clinical entities that have been classified under the broad headings of focal and multifocal neuropathies and symmetrical neuropathies.

Peripheral diabetic neuropathy, a chronic distal symmetrical predominantly sensory neuropathy, is the most common form of diabetic neuropathy. Most patients describe moderate to severe pain, using neuropathic descriptors such as burning, shooting or electric shocks. The common presentation is of painful symptoms originating in the feet, that then spread to the knees before involving the distal portion of the upper limbs in a 'glove and stocking' distribution.

There are a number of specific neuropathic pain assessment tools that can be readily used in a non-specialist setting in the community, such as the Leeds Assessment of Neuropathic Symptoms and Signs (LANSS) questionnaire. This combines five simple questions and two examination findings to give a dimensionless score for the pain out of 24, with a score $\geq$ 12 suggesting a neuropathic component is likely.

Tight glycaemic control should be advocated as it has been implicated in reducing the intensity of pain and preventing further deterioration in symptoms. First-line medications that can be tried for neuropathic pain are amitriptyline, gabapentin, pregabalin and duloxetine. Dose titration should be carried out slowly to improve tolerability. If treatment fails with first-line therapy, NICE advises careful discontinuation before trying one of the three alternative drugs.

In the specialist setting of the pain clinic, when monotherapy with different antineuropathic agents has failed or has not been tolerated at an effective dose, combination therapy will then be explored. For localised areas of pain, capsaicin 0.025% cream can be trialled.

Cases that are difficult to manage warrant specialist input. Options include intravenous lidocaine and ketamine, or the use of the capsaicin 8% patch. In the recent randomised ELEVATE trial of 568 patients with painful diabetic neuropathy, the capsaicin 8% patch was considered to be non-inferior to pregabalin.[25] In the UK, it is administered in the hospital setting under the care of a pain specialist. It can be considered for those in whom systemic analgesia is unsuitable, not tolerated, or inefficacious.

MONITORING AND FOLLOW-UP

Following the initiation of any analgesic intervention, it is imperative to reassess patients for evidence of efficacy and the presence of any side effects. This can prevent worsening of adverse effects, but also ensures that a reasonable dose has been reached before a medication that is well tolerated is discarded for perceived lack of benefit.

The authors have previously described the recommended initial starting doses of the various analgesic options and the recommended trial period to assess efficacy.[26] These recommendations are outlined in table 4, p23.

In the future it is hoped that targeted mechanism based therapies will be available with glycation inhibitors, protein kinase C inhibitors, and alpha lipoic acid being currently evaluated.[27]

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Useful information

Diabetes UK
www.diabetes.org.uk

Diabetes Research and Wellness Foundation
www.drwf.org.uk

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