

## Treatment Options for Neuropathic Pain Associated with Diabetes

a report by

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Diabetic peripheral neuropathy (DPN) is the most common neuropathic syndrome associated with diabetes and has a prevalence rate of approximately 30–50% of all diabetic patients.<sup>1</sup> There are two main clinical consequences of DPN. The first is insensitivity to trauma that results in foot ulceration, sometimes leading to amputation. Paradoxically, the same patients may also have troublesome painful neuropathic symptoms affecting the lower limbs and, in severe cases, the upper limbs. The end result is high patient morbidity, a curtailment of quality of life and remarkable consumption of scarce medical resources.<sup>2</sup> There is now little doubt that glycaemic control and duration of diabetes are major determinants of DPN. In addition, a major European prospective study has demonstrated that potentially modifiable, traditional markers of macrovascular disease such as hyperlipidaemia, hypertension, obesity and tobacco smoking are also independent risk factors for DPN.<sup>3</sup>

### Painful Diabetic Neuropathic Pain

Approximately one-third of patients with DPN have painful diabetic neuropathic pain (DPNP). Pain is the main factor that prompts the patient to seek medical advice and treatment.<sup>4</sup> Indeed, pain may also develop in relation to other neurological syndromes associated with diabetes, including focal and multifocal diabetic neuropathies such as isolated cranial nerve palsies or proximal lower limb motor neuropathy.

The features of pain in DPNP were documented by Pavy in the late 19th

century, who observed that it was of a burning and unremitting quality often with a nocturnal exacerbation.<sup>5</sup> Patients describe their pain in various terms as being of burning, prickling ('pins and needles'), lancinating, shooting ('like electric shock'), cramping, aching and as having contact hypersensitivity (allodynia) and 'dead feeling' (numbness) in their legs.<sup>4</sup> In the EURODIAB prospective study, 'deep burning pain' appeared to be a better discriminator of the presence of painful neuropathy than 'pricking sensation', which was less specific.<sup>6</sup> Further categorisation as to the type and frequency of different pain qualities (spontaneous sensations manifesting as symptoms or elicited in examination as clinical signs e.g. hyperalgesia and allodynia) is necessary.

In general, the patient should be allowed to describe his or her symptoms without too many leading questions. Ordinary walking may be described by some patients as an unusual sensation of walking barefoot on 'pebbles' or 'scalding sand', for example. Others relate odd sensations of their feet being swollen. There is a large spectrum of severity of the many symptoms of DPNP. Some may have mild symptoms in a toe or two; others may have continuous painful symptoms involving both legs and extending to the upper limbs. When the latter is the case, sleep pattern is usually disturbed. Perhaps unsurprisingly, therefore, such patients may be so disabled by the pain as to experience a reduction in their daily activities and may even lose their employment, are profoundly depressed and experience a poor quality of life (QoL).<sup>4</sup> Therefore, the impact of the pain on daily living, work life, recreational activity and QoL must be assessed.

There are very few studies looking at the prevalence of DPNP specifically and these report a prevalence rate of 7–26% reflecting differing criteria used to define neuropathic pain.<sup>7</sup> In the EURODIAB prospective study nearly a quarter developed neuropathic symptoms over a seven-year period.<sup>3</sup> Thus, a significant number of our diabetic patients suffer from neuropathic pain.

Neuropathic pain may present acutely within the context of very poor glycaemic control, typically in type 1 subjects (acute painful neuropathy of poor glycaemic control), or after initiation of treatment (acute painful neuropathy of rapid glycaemic control).<sup>8</sup> These acute syndromes are relatively rare compared with the chronic painful neuropathy associated with DPN. There is a rapid build-up of unpleasant sensory symptoms within weeks leading to persistent lower-limb burning pain, paraesthesiae and allodynia, with nocturnal exacerbation and depression.<sup>8</sup> There may also be marked precipitous weight loss. Sensory loss is often mild or absent, and there are no motor signs. Thankfully, in acute painful neuropathies there is complete resolution of symptoms within a year.<sup>8</sup>



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### Managing Neuropathic Pain

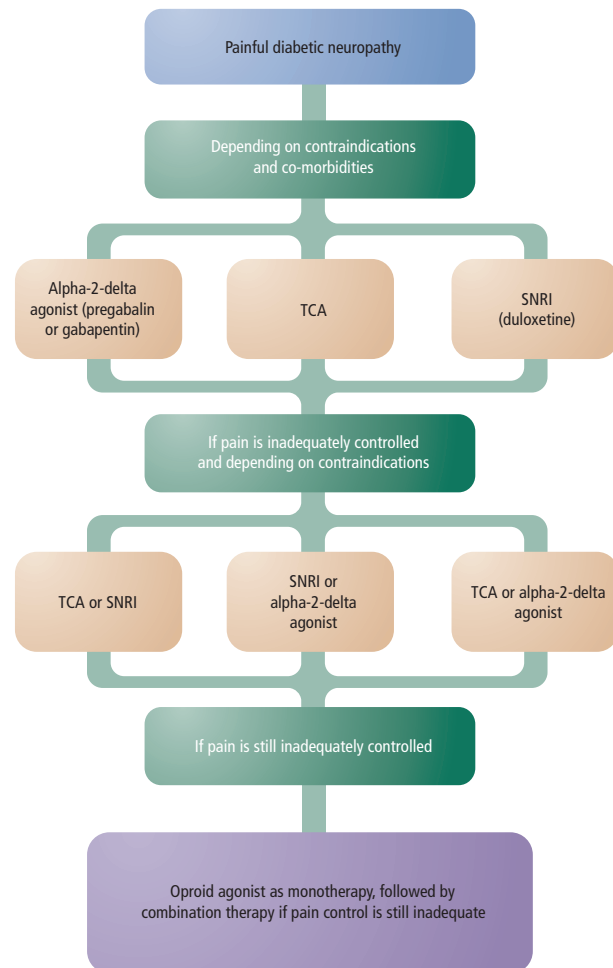
The assessment and management of DPNP continues to pose considerable challenges to clinicians.<sup>4,7</sup> A careful history and peripheral neurological/vascular examination of the patient is essential in order to exclude other possible causes of leg pain such as peripheral vascular disease, prolapsed intervertebral discs, spinal-canal stenosis and corda aquina lesions. Unilateral leg pain should arouse a suspicion that the pain may be due to lumbar-sacral nerve root compression. These patients may well need to be investigated with lumbar-sacral magnetic resonance imaging (MRI). The quality and severity should be assessed, preferably using a suitable scale, so that response to treatment may be evaluated.<sup>4,7</sup> An empathic approach with a multidisciplinary support is essential.<sup>4</sup>

There is now little doubt that good blood-sugar control can prevent/delay the onset of DPN.<sup>9</sup> However, there are no controlled studies that show the efficacy of this intervention in reducing the severity of DPNP. Nevertheless, despite the lack of evidence there is a general consensus that intensive blood glucose control should be the first step in the treatment of any form of diabetic polyneuropathy. Traditional markers of large-vessel disease including hypertension, obesity, hyperlipidaemia and smoking also appear to be independent risk factors for DPN and therefore need to be effectively managed.<sup>3</sup>

Pharmacological treatment of DPNP is not entirely satisfactory as currently available drugs can be ineffective in some patients and may also be complicated by side effects.<sup>7</sup> Tricyclic antidepressants (TCAs) such as amitriptyline (25–150mg/day in divided doses) have been used as first-line agents for many years, but many patients fail to respond to them and side effects are frequent.<sup>7</sup> Serotonin noradrenaline reuptake inhibitors (SNRIs) such as duloxetine effectively block the 5-hydroxytryptamine (5-HT) and noradrenaline transporters, leading to inhibition of excitatory impulse generation and reduced pain perception.<sup>7</sup> The efficacy of duloxetine in DPNP has been investigated in three trials and the 60mg/day and 120mg/day doses appear to be efficacious and well tolerated. The  $\alpha_2\delta$  agonist anticonvulsants gabapentin and, more recently, pregabalin are also effective first-line agents for DPNP. There have been at least three clinical trials that show the efficacy of pregabalin at a dose of 150mg twice/day and 300mg twice/day in DPNP.<sup>7</sup>

Second-line agents include opiates such as tramadol (50–100mg four times/day) and oxycodone 20–40mg/day. Side effects include typical opiate-type adverse events such as constipation and sedation. Refractory cases may be treated with membrane stabilisers including mexiletine and intravenous lignocaine; the antioxidant,  $\alpha$ -lipoic acid and the substance-P depleter, topical capsaicin.<sup>7</sup>

**Figure 1: Proposed Treatment Algorithm for Diabetic Peripheral Neuropathy Including Painful Diabetic Neuropathic Pain**



TCA = antidepressant; SNRI = selective serotonin noradrenaline re-uptake inhibitor. Adapted from Jensen et al., *New perspectives on the management of diabetic peripheral neuropathic pain*, *Diab Vasc Dis Res*, 2006;3(2):108–19. ©Diab Vasc Dis Res

Figure 1 shows an algorithm for the management of DPNP.<sup>7</sup> Though there are newer effective agents available with fewer side effect profiles, treatment must be tailored to the individual patient, taking into account co-morbidities (e.g. if there is cardiovascular disease and/or very old age, do not prescribe TCAs; if there is oedema, do not give gabapentin or pregabalin; if there is liver disease, do not give duloxetine). Treatment must also be carefully titrated to an effective dose in order to reduce the frequency of adverse events.

Lack of response and unwanted side effects of conventional drug treatments force many sufferers to try alternative therapies such as acupuncture, transcutaneous electrical stimulation (TENS) and, as a very last resort, implantation of electrical spinal cord stimulator.<sup>10</sup> ■

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