



Recommendations for the Management of Painful Diabetic Peripheral Neuropathy

The Multidisciplinary Panel on Neuropathic Pain*

I. Pathophysiology, Prevalence and Symptoms

Diabetic neuropathy is a family of progressive, degenerative disorders affecting the sensory, motor or autonomic peripheral nerves. Poor glycaemic control and chronic hyperglycaemia are believed to be responsible for peripheral nerve damage, although the precise mechanism is not known. Abnor-

malities in nerve growth factors, autoimmune disorders, ischaemia and hypoxia may also contribute to loss of nerve fibres.

Risk factors for the development and progression of diabetic neuropathy include:

1. Poor glycaemic control;
2. Increasing age;
3. Undiagnosed type 2 diabetes;
4. Long duration of diabetes;
5. Cardiovascular disease;
6. Peripheral vascular disease;
7. Smoking;
8. High alcohol intake;
9. Low socioeconomic status; and
10. Renal failure.

Approximately 20 to 40% of patients with diabetes develop some form of neuropathy. Autonomic and motor involvement is less common than sensory neuropathy. Autonomic nerve damage can cause cardiovascular abnormalities and systemic symptoms, such as indigestion, diarrhoea or constipation,

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Approximately 20 to 40% of diabetic patients develop some form of neuropathy.

dizziness, bladder infections and erectile dysfunction. Diabetic amyotrophy, predominantly a disorder of motor neurones, is usually seen in elderly patients with poorly controlled type 2 diabetes. Muscles around the pelvis and thigh become weak and painful, and mobility is affected.

The most common form of diabetic neuropathy, distal symmetric polyneuropathy, predominantly affects sensory functions. These polyneuropathies usually involve the peripheral nerves of the feet and legs and, in some cases, the hands and arms. Onset, type and severity of symptoms vary widely among patients, making diagnosis and prognosis imprecise. Early symptoms include numbness, tingling, burning or pain, which may later develop into loss of reflexes, foot deformities (Charcot's joint), muscle weakness or paralysis. Up to 10% of affected patients experience persistent neuropathic pain that may include dysaesthesia. Depression may occur in patients with severe

pain. Diabetic neuropathy may lead to foot ulceration and even the need for amputation. Early diagnosis and management of at-risk patients might prevent at least half of all diabetes-related amputations.

II. Diagnosis

Diagnosis of diabetic neuropathy is based on clinical symptomatology and a comprehensive neurological examination. In addition, other underlying pathologies for neuropathy should be excluded (e.g., vascular disease, HIV, vitamin B₁₂ deficiency, hypothyroidism). Clinical features vary widely, and people with diabetic neuropathy may even be pain-free. However, the classic presentation of advanced polyneuropathy is distal wasting and weakness, absent tendon reflexes, and glove-and-stockings sensory loss or pain. Patients may also experience allodynia. The following history and examinations should be considered in the diagnosis of diabetic neuropathy:

1. Full patient history to determine:
 - Type, duration and level of control of diabetes;
 - Nature of symptoms, if any (intensity, duration, progression, nocturnal exacerbation, recurrent foot problems);
 - Pain characteristics using standard pain questionnaires (chronic or acute pain, bilateral, type of dysaesthesia, hyperaesthesia); and
 - Lifestyle factors that may contribute to progression of neuropathy.
2. Neurological examination:
 - Characterize distal sensory function and reflexes, e.g., pin-prick test, light touch, vibration test, ankle reflex, pressure perception, temperature assessment, monofilament test of two-point discrimination; and
 - Electrophysiological assessment to document neuropathy, if required, e.g., nerve conduction study and electromyography, or Doppler sonography to determine the presence of vascular disease.

III. Management

The goal of treatment for painful diabetic peripheral neuropathy is to relieve painful symptoms, prevent further tissue damage and improve patient education.

Patients without clinical neuropathy should be educated on lifestyle, foot care and the importance of controlling glycaemia to slow disease progression. Refer patients to a diabetes specialist nurse or chiropodist for a yearly foot examination, if necessary.

Patients with suspected diabetic amyotrophy or a decreased quality of life due to clinical symptomatic

neuropathy should be referred to a diabetologist or neurologist for further evaluation. In the interim, treatment for acute or chronic pain should be started.

Patients with peripheral neuropathy and complete or partial loss of sensation should be educated on good glycaemic control and foot care. Refer patients to a diabetes foot specialist.

Trauma, cellulitis or acute ischaemia of the foot require urgent referral to a specialist diabetes foot-care team to prevent new or recurrent lesions and amputation.

In all diabetic patients, the importance of good glycaemic control should be stressed, as this may slow or prevent the development of peripheral neuropathy and other complications, including retinopathy, nephropathy and angiopathy.

IV. Pain Treatments

The mainstay therapeutic agents for managing diabetic neuropathic pain are tricyclic antidepressants (TCAs) and anticonvulsants. Combinations of pharmacological, physical and psychological interventions are likely to attain the optimum level of pain relief for most patients.

For chronic pain, TCAs (e.g., amitriptyline, imipramine, nortriptyline, desipramine) should be considered first-line therapies. Pain relief may not be apparent for up to 3 weeks. TCAs are contraindicated in patients with cardiac and hepatic disease, which include many older patients. Some patients cannot tolerate the side effects of TCAs – drowsiness, anticholinergic effects and postural hypotension – but these can be minimized by starting with a low dose at night and increasing gradually (e.g., for

amitriptyline, start with 10-25 mg daily and increase to 50-100 mg daily). Nortriptyline, imipramine and desipramine are less sedating than amitriptyline.

For acute pain, start with simple analgesics and progress to TCAs or other adjuvant analgesics, if necessary.

If TCAs are contraindicated, ineffective and/or not well tolerated, anticonvulsants (e.g., gabapentin or carbamazepine) should be considered as an alternative first-line choice. Side effects can be common, but are minimized by adopting a slow titration schedule. Gabapentin is generally associated with fewer side effects than TCAs, carbamazepine or phenytoin. Gabapentin should be commenced at 300 mg at bedtime and increased by 300 mg every 3 days up to a dose of 1,800 mg daily after 1 week (given in 3 divided doses). If higher daily doses are required for maintenance, the maximum recommended dose is 3,600 mg daily (a lower dose is recommended in patients with renal impairment). For elderly patients or patients susceptible to side effects, it is recommended to increase gabapentin dosage by 300 mg every week, or to commence with a lower dose (e.g., 100 mg).

Tramadol may be an effective alternative for some patients.

Patients remaining refractory to a reasonable trial of pharmacotherapy (e.g., 2-3 months with 2-3 different agents) should be referred to a multidisciplinary pain clinic for further therapeutic initiatives.

Physical stimulation, such as transcutaneous electrical nerve stimulation (TENS) and acupuncture, may counteract painful sensations. However, acupuncture and topical treatments should be used with cau-

tion in the lower leg in patients with diabetes, as these may aggravate the skin and lead to infection. Pain management programmes and behavioural therapy can also be used with pharmacological approaches to teach patients how to live with pain. Regular walking, warm baths or elastic stockings may also help to relieve leg pain.

V. Appendix on Evidence-Based Management of Painful Diabetic Peripheral Neuropathy

The pharmacological treatments included in these recommendations are based on published clinical evidence in diabetic neuropathy patients and current clinical practice. However, some agents may not be approved for use in neuropathic pain syndromes. Full prescribing information should be consulted before initiating drug therapy.

Pharmacological Management

Tricyclic antidepressants

Several clinical trials have shown that TCAs are effective in treating painful diabetic neuropathy, although they are not licensed for this indication. It has been postulated that TCAs relieve pain independently from their antidepressant action, and dampen sensory nerve function by inhibiting muscarinic and α -adrenergic receptors.

Data from systematic reviews: A recent systematic review of randomized, placebo-controlled trials of antidepressants in diabetic neuropathy pooled data from eight studies using TCAs (amitriptyline, clomipramine, desipramine, imipramine and maprotiline) with a total of 283 patient episodes.¹ The relative benefit of treatment was 1.9 (95% CI: 1.5-2.3) and the number needed to treat

(NNT) for one patient to achieve a 50% reduction in pain was 3.5 (95% CI: 2.5-5.6). This demonstrates the efficacy of TCAs in diabetic neuropathy. Doses were within the low to mid range of those recommended for depression. A similar conclusion was reached by a review completed 4 years earlier.² Furthermore, one review of placebo-controlled trials from 1989 to 1999 reported an NNT of 1.4 for imipramine compared with 2.4 for other TCAs.³

The incidence of adverse events is significantly greater with TCAs than placebo. For minor adverse events, the number needed to harm (NNH) was 3.2 (95% CI: 2.3-5.2) and for major adverse effects (i.e., those necessitating drug withdrawal), the NNH was 14 (95% CI: 8.5-38).¹

Other antidepressants: Pooled data from three trials (162 patient episodes) was used to investigate the effectiveness of the selective serotonin-reuptake inhibitors (SSRIs) citalopram, fluoxetine and paroxetine in treating painful diabetic neuropathy. These agents had a relative benefit of 1.3 (95% CI: 1.0-1.8), demonstrating no significant difference between the SSRIs and placebo.¹ Doses used were two-thirds of the maximum recommended daily dose for depression. Another review reported an NNT for SSRIs of 6.7.³ The efficacy of venlafaxine in painful diabetic neuropathy has not yet been assessed in controlled clinical trials.

Anticonvulsants

Anticonvulsants act as membrane-stabilizing agents and reduce the potential for the transmission of abnormal pain signals. Anticonvulsants are often used to manage chronic neuropathic pain when TCAs

are inappropriate or ineffective.

Data from systematic reviews: A systematic review of anticonvulsants in diabetic neuropathy from all randomized, placebo-controlled trials published up to 1999 has been performed.¹ Four studies investigated anticonvulsants in 247 patients (2 studies on phenytoin, 1 on carbamazepine and 1 on gabapentin). The pooled data showed that anticonvulsants were significantly superior to placebo in the treatment of painful diabetic neuropathy. The relative benefit of treatment was 2.4 (95% CI: 1.8-3.2) and the NNT for one

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patient to achieve a 50% reduction in pain was 2.7 (95% CI: 2.2-3.8). A similar conclusion was reached by a review of trials from 1966 to 1994.^{4,5} From one review of placebo-controlled trials, the specific NNT for carbamazepine was 3.3, and for gabapentin, 3.7.³

Anticonvulsants had a significantly greater incidence of adverse effects than placebo. For minor adverse events, the NNH for all anticonvulsants combined was 2.7 (95% CI: 2.2-3.4) and for phenytoin, the NNH was 3.2 (95% CI: 2.1-6.3).¹ For every eight patients achieving a 50% reduction in pain on an anticonvulsant, one will experience a major adverse event to cause drug withdrawal. An earlier

review calculated that the NNH for major side effects was 20.^{4,5}

Anticonvulsants and antidepressants had comparable efficacy outcomes for painful diabetic neuropathy (NNT for all antidepressants was 3.4 [95% CI: 2.6-4.7] and for all anticonvulsants was 2.7 [95% CI: 2.2-3.8]). There was no significant difference in the incidence of minor adverse events for both drugs; however, more patients required withdrawal from antidepressants than from anticonvulsants because of major side effects.¹

Gabapentin: Gabapentin is the first oral therapy to be licensed for the management of painful diabetic neuropathy as a result of a large, multicentre, double-blind, placebo-controlled trial.⁶ Patients with a 1- to 5-year history of pain attributed to diabetic neuropathy were randomly assigned to gabapentin (n=84; titrated from 900 mg/day to 3,600 mg/day or maximum tolerated dosage) or placebo (n=81). Patients treated with gabapentin had significantly lower mean daily pain scores, at 8 weeks than placebo-treated patients (p<0.001). This improvement was apparent from week 2. Significant improvements with gabapentin were also seen in sleep interference scores, the Short-Form McGill Pain Questionnaire scores, and the Patient and Clinician Global Impression of Change scores. Quality of life, particularly bodily pain, mental health and vitality improved significantly with gabapentin. Eight percent of patients in the gabapentin group withdrew because of adverse events, compared with 6% in the placebo group. Dizziness and somnolence were the only two adverse events that occurred more frequently in gabapentin-treated patients.

With a sound evidence base for efficacy and safety, gabapentin should be considered as an alternative first-line therapy to TCAs for painful diabetic neuropathy.

Lamotrigine: A 6-week, randomized, controlled trial compared lamotrigine (n=29) with placebo (n=30) for the treatment of diabetic neuropathy. Lamotrigine (200-400 mg daily) reduced daily numerical pain scores significantly more than placebo (p<0.001). Global assessment of efficacy was also better with lamotrigine. With an adverse event profile similar to placebo, lamotrigine is an effective therapy for diabetic neuropathy.⁷

Phenytoin: There is little evidence from clinical trials on the efficacy of phenytoin in diabetic neuropathy. Moreover, compared with newer anticonvulsants, both phenytoin and carbamazepine have unfavourable safety profiles, and can cause haematological changes and cardiac arrhythmias.

Tramadol

Tramadol is a synthetic, centrally acting, non-opioid analgesic that may be a useful alternative to TCAs and anticonvulsants. A double-blind, randomized, controlled trial of 6 weeks' duration evaluated 131 patients with painful diabetic neuropathy. Tramadol (average daily dose of 210 mg) provided significantly more effective pain relief (p<0.001) and greater improvement of both physical (p=0.02) and social functioning (p=0.04) than placebo. No benefits were seen in sleep disturbance.⁸ In a 6-month extension of this study, mean pain relief scores were well maintained.⁹

Topical Capsaicin

Several large-scale, placebo-con-

trolled studies have shown that 0.075% capsaicin cream was more beneficial than vehicle-only cream in reducing pain intensity.¹⁰⁻¹² Capsaicin cream allowed greater participation in work and recreational activities, while sleep quality improved significantly.¹¹ Smaller, vehicle-controlled studies report similar benefits for capsaicin.^{13,14} Furthermore, a meta-analysis of efficacy trials reported an odds ratio in favour of capsaicin over placebo of 2.74 (95% CI: 1.73-4.32) for neuropathic pain associated with diabetes.¹⁵ However, local application of topical agents to the lower limbs should only be performed under clinician supervision, as capsaicin and herbal remedies may irritate the skin, leading to infection.

Topical capsaicin has also been compared with oral amitriptyline in a double-blind, multicentre, parallel-group study involving 235 patients. Both agents produced equal and statistically significant improvements in pain over 8 weeks; however, amitriptyline treatment was associated with systemic side effects.¹⁶

Topical capsaicin is not associated with any severe systemic adverse effects. However, stinging and burning, particularly during the first week of therapy, is reported by many patients. Topical capsaicin merits consideration as adjuvant therapy for diabetic neuropathy that is chronically painful and difficult to treat.

Mexiletine

Mexiletine has been evaluated in several randomized, placebo-controlled trials in patients with painful diabetic neuropathy. Visual analogue scale (VAS) pain ratings improved in all studies that used this measure; however, the improvement was significantly greater than placebo in

only two studies.¹⁷ Patients (n=16) receiving mexiletine 10 mg/kg/day for 10 weeks had greater improvements in pain ratings (as measured by VAS) than placebo-treated patients.¹⁸ Nocturnal pain was also reduced in 31 patients receiving mexiletine 675 mg/day for 3 weeks.¹⁹ Patients with stabbing or burning pain, heat sensations or formication were more likely to benefit from mexiletine than patients with other pain sensations.²⁰ In general, mexiletine did not have a significant influence on sleep quality in patients with diabetic neuropathy.¹⁷

Other Agents and Novel Therapies for the Future

Intravenous lignocaine infusion may be useful for providing short-term relief in patients with chronic painful diabetic neuropathy.²¹ Long-term opioid therapy may also be considered if patients remain refractory to other forms of treatment. Supplementation with the vitamins thiamine or pyridoxine was associated with improved diabetic peripheral neuropathy symptoms in an African study.²² Therefore, a balanced diet with vitamin supplementation, if necessary, is important for diabetic patients.

New agents may eventually be available for the treatment of diabetic neuropathy. A recent randomized, placebo-controlled study of 279 patients with diabetic neuropathy compared the aldose reductase inhibitor fidarestat (1 mg daily for 52 weeks) with placebo.²³ Fidarestat treatment improved nerve conduction and subjective symptoms of diabetic neuropathy. Another agent that may improve some aspects of nerve conduction is the antioxidant thiotic acid (alpha-lipoic acid).²⁴ In contrast, a phase III, randomized, placebo-controlled study investigating

recombinant human nerve growth factor in diabetic neuropathy did not demonstrate significant treatment benefit.²⁵ Isosorbide dinitrate spray was assessed in a double-blind, placebo-controlled, cross-over study in 22 patients with diabetic neuropathy.²⁶ The spray was found to reduce overall neuropathic pain and burning sensation, which may be due to increased generation of nitric oxide. Further studies are required to assess the benefit and potential clinical role of these novel agents.

Non-pharmacological Management Physical Stimulation

TENS may be effective in some patients with painful diabetic neuropathy. Transcutaneous electrotherapy may also be combined with a pharmacological agent, such as amitriptyline, to increase symptom relief.²⁷ Further, percutaneous electrical nerve stimulation (PENS) was evaluated in a randomized, cross-over, sham-controlled study in 50 patients with diabetic neuropathy.²⁸ Active PENS treatment reduced pain, improved physical activity and quality of sleep, and was associated with a reduced requirement for non-opioid analgesic medication. More traditional therapies, such as acupuncture, may also provide relief in some patients. However, use of acupuncture, particularly on the lower limbs, may lead to skin aggravation and infection. Therefore, acupuncture in the lower limbs should be avoided.

Psychological Treatment

Multidisciplinary pain management programmes may also provide psychological approaches, such as relaxation and diversion techniques, and behavioural therapy, to help

patients manage pain. Cognitive behavioural therapy can be introduced to help prevent pain behaviours in patients with chronic pain. Referral to a psychiatrist can be considered if the patient is depressed.

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