Recommendations for the Management of Painful Diabetic Peripheral Neuropathy

The Multidisciplinary Panel on Neuropathic Pain

These recommendations from the Multidisciplinary Panel on Neuropathic Pain provide an update of the recommendations first published in 2003.[1] The current recommendations include new data on pharmacological and nonpharmacological strategies for the management of painful diabetic peripheral neuropathy.

The Recommendations for the Management of Painful Diabetic Peripheral Neuropathy are the product of review and appraisal of current evidence in the medical literature. The recommendations serve to assist healthcare professionals in evaluating a patient's condition and deciding on a suitable treatment modality. They are not intended to replace professional judgment in determining the appropriate management of individual patients. While we have taken due care in preparing the recommendations, we cannot warrant the accuracy of the original publications. In selecting good-quality references, a certain degree of judgment based on our professional knowledge in the subject was needed. Such biases are minimized by multidisciplinary discussion and review.

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I. Pathophysiology, Prevalence and Symptoms

Diabetic neuropathy is a family of progressive degenerative disorders affecting the sensory, motor or autonomic peripheral nerves.[2] Poor glycaemic control and chronic hyperglycaemia are believed to be responsible for peripheral nerve damage, although the precise mechanism is not known.[3] Abnormalities 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[4,5]:

- Poor glycaemic control
- Increasing age
- Undiagnosed type 2 diabetes
- Long duration of diabetes
- Cardiovascular disease
- Peripheral vascular disease
- Smoking
- High alcohol intake
- Low socioeconomic status
- Renal failure

Up to 50% of patients with long-standing diabetes develop some form of neuropathy, and painful neuropathy may be present in as many as one third of all diabetic patients.[3] Autonomic and motor involvement is less common than sensory neuropathy.[2] Autonomic nerve damage can cause cardiovascular abnormalities and systemic symptoms, such as indigestion, diarrhoea or constipation, dizziness, bladder infections and erectile dysfunction.[2] Diabetic amyotrophy, predominantly a disorder of motor neurons, is usually seen in elderly patients with poorly controlled type 2 diabetes.[2] Muscles around the pelvis and thigh become weak and painful, and mobility is affected.

The most common form of diabetic neuropathy, distal symmetric polyneuropathy, occurs in about 40% of patients who have had diabetes for 25 years or longer and predominantly affects sensory functions.[2] 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. Depression may occur in patients with severe pain. Diabetic neuropathy may lead to foot ulceration and even the need for amputation.[6] Early diagnosis and management of at-risk patients might prevent at least half of all diabetes-related amputations.[6]

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 (eg, vascular disease, human immunodeficiency virus, vitamin B_{12} deficiency, hypothyroidism).[2,5] 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-stocking sensory loss and/or pain. Patients may also experience allodynia. The following history and examinations should be considered in the diagnosis of diabetic neuropathy.

Full patient history to determine[2,5]:

1. Type, duration and level of control of diabetes;
2. Nature of symptoms, if any (intensity, duration, progression, nocturnal exacerbation, recurrent foot problems);
3. Pain characteristics using standard pain questionnaires (chronic or acute pain, bilateral, type of dysaesthesia, hyperaesthesia);
4. Lifestyle factors that may contribute to progression of neuropathy.

Neurological examination[2,6]:

1. Characterize distal sensory function and reflexes, eg, pin-prick test, light touch, vibration test, ankle reflex, pressure perception, temperature assessment, monofilament test of 2-point discrimination;
2. Electrophysiological assessment to document neuropathy, if required, eg, 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.[2] Refer 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 symptomatic neuropathy should be referred to a diabetologist or neurologist for further evaluation. In the interim, commence treatment for acute or chronic pain.
- 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 the specialist diabetes foot-care team to prevent new or recurrent lesions and reduce the risk of future amputation.
- In all diabetic patients, the importance of good glycaemic control should be stressed,[2] 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.

1. For chronic pain, TCAs (eg, 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 includes 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 (eg, for amitriptyline, start with 10 to 25 mg daily and increase to 50 to 100 mg daily). Nortriptyline, imipramine and desipramine are less sedating than amitriptyline.
2. For acute pain, start with simple analgesics and progress to TCAs or other adjuvant analgesics, if necessary.
3. If TCAs are contraindicated, ineffective and/or not well tolerated, anticonvulsants should be considered as an alternative first-line choice. Side effects may be minimized by slow dosage titration. Gabapentin is generally associated with fewer side effects than TCAs, carbamazepine or phenytoin. Gabapentin should be commenced at 300 mg at bedtime and increased to 1,800 mg daily (maximum recommended daily dose is 3,600 mg).[7] A lower dose should be used in elderly patients and those with renal impairment or poor drug tolerance. Pregabalin may also be given; pregabalin 300 to 600 mg/day effectively relieves pain and improves sleep and overall well-being of patients with painful diabetic neuropathy.[8-10] These effects were observed within 1 week in many patients.
4. Tramadol may be an effective alternative for some patients.[11]
5. Patients remaining refractory to a reasonable trial of pharmacotherapy (eg, 2 to 3 months with two to three different agents) should be referred to a multidisciplinary pain clinic for further therapeutic initiatives.
6. Physical stimulation, such as transcutaneous electrical nerve stimulation (TENS)[12] and acupuncture, may counteract painful sensations. However, acupuncture and topical treatments should be used with caution in the lower leg in patients with diabetes, as these may aggravate the skin and lead to infection. More invasive stimulatory interventions, such as spinal-cord stimulation (SCS), may be considered as a last option.
7. 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.

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.

The proposed treatment algorithm for painful diabetic peripheral neuropathy is presented in the Figure.

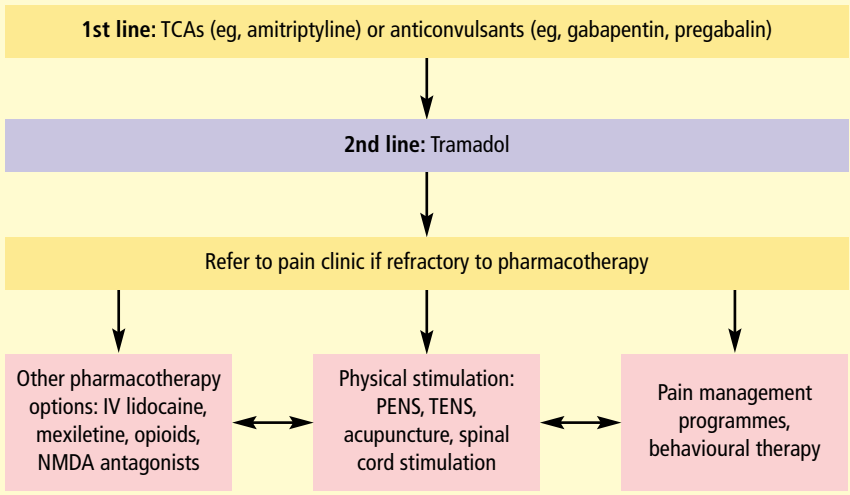
Pharmacological and Nonpharmacological Management

Pharmacological Management

I. TCAs

Several clinical trials have shown that TCAs are effective in treating

Figure. Proposed treatment algorithm for painful diabetic peripheral neuropathy



TCAs, tricyclic antidepressants; IV, intravenous; NMDA, N-methyl-D-aspartate; PENS, percutaneous electrical nerve stimulation; TENS, transcutaneous electrical nerve stimulation

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.

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.[13] 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 at least 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.[14] 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.[15]

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 (ie, those necessitating drug withdrawal), the NNH was 14 (95% CI: 8.5-38).[13]

II. 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.[13] These agents had a relative benefit of 1.3 (95% CI: 1.0-1.8), demonstrating no significant difference between the SSRIs and placebo. Doses used were two thirds of the maximum recommended daily dose for depression. Another review reported an NNT for SSRIs of 6.7.[15] More recently, a multicentre, randomized, double-blind, placebo-controlled study on 244 adult patients demonstrated the efficacy of an extended-release preparation of venlafaxine (75 mg and 150-225 mg) in painful diabetic neuropathy.[16] After 6 weeks, venlafaxine reduced baseline Visual Analogue Pain Intensity by 32% (75 mg) and 50% (150-225 mg; $p<0.001$ vs placebo) compared with 27% by placebo. For the venlafaxine 150-225 mg regimen, the NNT for 50% pain intensity reduction was 4.5, which is similar to the NNTs for TCAs and gabapentin.[16]

III. 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.

A systematic review of anticonvulsants in diabetic neuropathy from all randomized, placebo-controlled trials published up to 1999 has been performed.[13] Four studies investigated anticonvulsants in 247 patients (two studies on phenytoin, one on carbamazepine and one 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 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 published from 1966 to 1999.[17] From one review of placebo-controlled trials, the NNT for carbamazepine was 2.3, and for gabapentin 3.8.[17]

In the systematic review, patients with diabetic neuropathy and postherpetic neuralgia, the incidence of adverse events was significantly greater with anticonvulsants than placebo.[13] 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).[13] For every eight patients achieving a 50% reduction in pain on an anticonvulsant, one will experience a major adverse event to cause drug withdrawal.[13]

Anticonvulsants and antidepressants had comparable efficacy outcomes for painful diabetic neuropathy (the NNT for at least 50% pain relief 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.[13]

Gabapentin

Gabapentin was the first oral drug therapy to be licensed for the management of painful diabetic neuropathy as a result of a large, multicentre, double-blind, placebo-controlled trial.[18] 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 week 8 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 (SF-MPQ) scores and the Patient and Clinician Global Impression of Change (PGIC and CGIC) 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 significantly 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.

Pregabalin

An 8-week, randomized, double-blind, placebo-controlled, parallel-group, multicentre trial compared pregabalin 300 mg/day (n=76) with placebo (n=70) in painful diabetic peripheral neuropathy.[8] Pregabalin-treated patients experienced significant improvements in endpoint mean pain scores ($p<0.0001$ vs placebo), mean sleep interference scores ($p<0.0001$), total SF-MPQ score ($p<0.01$), Short Form-36 (SF-36) Bodily Pain subscale ($p<0.03$), PGIC ($p=0.001$) and Total Mood Disturbance and Tension-Anxiety components of the Profile of Mood States scores ($p<0.03$).

The efficacy of pregabalin was later confirmed in two randomized controlled trials.[9,10] The first trial (n=338), which compared pregabalin 75, 300 and 600 mg/day with placebo, showed that patients treated with pregabalin 300 and 600 mg/day experienced significantly greater improvements in endpoint mean pain score ($p=0.0001$), sleep interference score, PGIC, CGIC, SF-MPQ, and several components of the SF-36 compared with placebo.[9] The second trial (n=246) also demonstrated a significant pain score reduction in patients treated with pregabalin 600 mg/day ($p=0.0002$ vs placebo).[10]

Pain relief and improved sleep were observed as early as 1 week in many patients, and were sustained throughout the study period.[8]

Lamotrigine

A 6-week, randomized, controlled trial compared lamotrigine (n=29) with placebo (n=30) for the treatment of diabetic neuropathy.[19] Lamotrigine (200 to 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.[19]

Topiramate

A 12-week, multicentre, randomized, double-blind trial showed that topiramate (up to 400 mg, depending on tolerance) more effectively reduced pain visual analogue (PVA) scale score than placebo ($p=0.038$).[20] Topiramate-treated patients experienced a 32.1% reduction in PVA score (vs 21.9% with placebo). The topiramate response rate (response defined as >30% PVA reduction from baseline) was also significantly higher than that of placebo (50% vs 34%; $p=0.004$). However, a review

indicated that adverse effects, such as diarrhoea, loss of appetite and somnolence, may limit the use of topiramate.[21]

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.

IV. 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.[11] 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. In a 6-month extension of this study, mean pain relief scores were well maintained.[22]

V. Topical Capsaicin

Several large-scale, placebo-controlled studies have shown that 0.075% capsaicin cream was more beneficial than vehicle-only cream in reducing pain intensity.[23-25] Capsaicin cream allowed greater participation in work and recreational activities, while sleep quality improved significantly.[24] Smaller, vehicle-controlled studies report similar benefits with capsaicin.[26,27] 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.[28] However, local application of topical agents to the lower limb 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.[29] Both agents produced equal and statistically significant improvements in pain over 8 weeks; however, amitriptyline treatment was associated with systemic side effects.

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.

VI. Mexiletine

Mexiletine has been evaluated in several randomized, placebo-controlled trials in patients with painful diabetic neuropathy. A review of such studies revealed that 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.[30] In a randomized, double-blind, crossover study (n=16), patients receiving mexiletine 10 mg/kg/day for 10 weeks had greater improvements in pain ratings (as measured by VAS) than when receiving placebo.[31] Nocturnal pain was also reduced in 31 patients receiving mexiletine 675 mg/day for 3 weeks.[32] Patients with stabbing or burning pain, heat sensations or formication were more likely to benefit from mexiletine than patients with other pain sensations.[33] In general, mexiletine did not have a significant influence on sleep quality in patients with diabetic neuropathy.[30]

VII. Other Agents and Novel Therapies for the Future

Intravenous lidocaine infusion may be useful for providing short-term relief in patients with chronic painful diabetic neuropathy.[34] A 5% lidocaine patch (with a maximum of four patches daily for 18 hours) may also be considered, as suggested by a 3-week open-label trial.[35] Patients showed significant improvements in pain and quality-of-life outcome measures, which were maintained in patients treated for an additional 5 weeks. Long-term opioid therapy may also be considered if patients remain refractory to other forms of treatment.

Another agent that may improve some aspects of nerve conduction is the antioxidant thiotic acid (α-lipoic acid).[36] A meta-analysis of four randomized, double-blind, placebo-controlled, parallel-group trials on α-lipoic acid infusions (600 mg/day) in diabetic patients with polyneuropathy (n=1,258) showed 3 weeks of therapy had a 24.1% relative difference in total symptom score (TSS) in favour of α-lipoic acid compared with placebo.[37] The favourable TSS response was mainly due to improvements in pain, burning and numbness.

A balanced diet with vitamin supplementation, if necessary, is important for diabetic patients. Supplementation with the vitamins thiamine or pyridoxine was associated with improved diabetic peripheral neuropathy symptoms in

an African study.[38] Furthermore, a randomized, double-blind, placebo-controlled pilot study suggested that benfotiamine, a lipid-soluble vitamin B_1 prodrug, may be beneficial.[39] Benfotiamine 50 mg, two tablets qid for 3 weeks significantly improved neuropathy score compared with placebo-treated controls (p=0.023). The most pronounced effect was a decrease in pain (p=0.041).

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.[40] Fidarestat treatment improved nerve conduction and subjective symptoms of diabetic neuropathy. In contrast, a phase III, randomized, placebo-controlled study investigating recombinant human nerve growth factor in diabetic neuropathy did not demonstrate a significant benefit with active treatment.[41] Isosorbide dinitrate spray was assessed in a double-blind, placebo-controlled, crossover study in 22 patients with diabetic neuropathy.[42] The spray was found to reduce overall pain and burning sensation, an effect that 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.

Nonpharmacological 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.[12] Further, percutaneous electrical nerve stimulation (PENS) was evaluated in a randomized, crossover, sham-controlled study in 50 patients with diabetic neuropathy.[43] 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 limb, may lead to skin aggravation and infection. Therefore, acupuncture in the lower limb should be avoided.

SCS is a more invasive technique, but may be useful for long-term therapy. A study with a mean follow-up duration of 3.3 years (n=6) showed SCS reduced median VAS scores for background pain (from 74.5 to 25 mm; p=0.03) and peak pain (from 85 to 19 mm; p=0.03).[44] Among four surviving patients reassessed at 7.5 years (mean), background pain was reduced from 73 to 33 mm, and peak pain from 86 to 42 mm.

Psychotherapy

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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A complete list of references can be obtained upon request to the editor.