In this issue of Challenges in Neuropathic Pain, we present a summary of the Multidisciplinary Panel on Neuropathic Pain (MPNP)’s updated recommendations on the management of painful diabetic peripheral neuropathy. The final in our series of interviews with MPNP members by specialty covers geriatric medicine, with rheumatology and rehabilitation medicine represented by invited non-members. The third in a series on interventional therapies for neuropathic pain is on neurostimulation techniques. Visit www.neuropainhk.org for more resources from the MPNP on neuropathic pain.

Summary of Recommendations for the Management of Painful Diabetic Peripheral Neuropathy: 2013 Update

The Multidisciplinary Panel on Neuropathic Pain has recently updated the Recommendations for the Management of Painful Diabetic Peripheral Neuropathy (DPN); the recommendations were first published in 2003 and revised in 2006. The following is a summary of the updated recommendations, which emphasize the importance of good glycaemic control for diabetics, and include newly published epidemiological studies and clinical evidence for the management of painful DPN.

Pathophysiology, prevalence, symptoms and burden of disease

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. The key risk factors for the development and progression of diabetic neuropathy are:

- 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

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. In a study conducted in China of 556 patients with diabetes of more than 10 years’ duration, 47% were characterized as having diabetic neuropathy. Of these, 38% had mild pain, while 41% reported moderate and 11% severe pain.
Painful DPN is associated with significant burden of disease. In the United States, an observational study of 112 subjects with painful DPN revealed that 44% suffered from sleep disturbance/insomnia, 41% had depressive symptoms and 36% had anxiety. Almost 80% of these subjects reported moderate or severe pain. Healthcare resource utilization was high, and increased with pain severity.

**Diagnosis**

The classic clinical 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:
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 the progression of neuropathy

Neurological examination:
1. Characterize distal sensory function and reflexes, eg, pin-prick test, light touch, vibration test, ankle reflex, pressure perception, temperature assessment, monofilament test of two-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

**Management**

The goals of treatment for DPN are to relieve painful symptoms, prevent further tissue damage and educate patients on their condition.

- The importance of good glycaemic control was demonstrated in a recently published Cochrane review, which revealed that enhanced blood glucose control significantly prevented the development of clinical neuropathy, and reduced nerve conduction and vibration threshold abnormalities in patients with type 1 diabetes mellitus. For patients with type 2 diabetes, there was a trend for a reduction in the incidence of clinical neuropathy with enhanced glucose control (p=0.06), and a significant reduction in nerve conduction and vibration threshold abnormalities.
- Patients without clinical neuropathy should be educated on lifestyle, foot care and the importance of glycaemic control in slowing disease progression. Refer to a diabetes specialist nurse or chiropodist for a yearly foot examination, if necessary.
- Patients with suspected diabetic myoatrophy or a decreased quality of life due to symptomatic neuropathy should be referred to a dietologist 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, as this may slow or prevent the development of peripheral neuropathy and other complications, including retinopathy, nephropathy and angiopathy.

**Pain treatments**

A multidisciplinary approach to management should be taken to maximize pain relief, with pharmacotherapy combined with physical and psychological therapy. The proposed treatment algorithm for painful DPN is presented in the Figure. However, it should be noted that some drugs may not be approved for use in neuropathic pain syndromes; full prescribing information should be consulted before initiating drug therapy.

- **α2-δ ligands** (pregabalin and gabapentin) are considered first-line treatment options due to their efficacy and safety. The most recently published studies with pregabalin indicate that it relieves pain and is well tolerated in Asian populations, effective in the elderly, and improves patient function and quality of life – not only via pain relief, but through a reduction in sleep disturbance and direct effect on patient function. Pregabalin has demonstrated similar pain relief and efficacy outcomes to amitriptyline, but with fewer adverse events.
- **Tricyclic antidepressants** (TCAs; amitriptyline, nortriptyline, desipramine) are also first-line treatment options. TCAs are contraindicated in patients with cardiac and hepatic disease. Some patients cannot tolerate the side effects of TCAs, but these can be minimized by starting with a low dose at night and increasing the dose gradually.
- Another first-line treatment option is the serotonin-norepinephrine reuptake inhibitors (SNRIs). These antidepressants have demonstrated efficacy and safety in painful DPN. Recently published studies have demonstrated that duloxetine and amitriptyline have similar pain relief and efficacy outcomes, but more patients report dry mouth with amitriptyline, and non-inferiority of duloxetine to pregabalin has been established in patients with DPN and inadequate response to gabapentin.
- If a patient does not receive adequate pain relief with a trial of one first-line agent, a referral to pain clinic if refractory to pharmacotherapy can be made. These treatments can be prescribed before starting pharmacological treatment or as an adjunct to pharmacological treatment.

**Figure. Proposed treatment algorithm for painful diabetic peripheral neuropathy**

- **First-line:** α2-δ ligands (pregabalin or gabapentin), TCAs (eg, amitriptyline) or SNRIs
- **Second-line:** Try another first-line drug as appropriate
- **Third-line:** Try a combination of first-line drugs
- **Fourth-line:** Tramadol as an alternative or add-on therapy
- Refer to pain clinic if refractory to pharmacotherapy

**Non-pharmacological treatments:** TENS, PENS, acupuncture; limb exercises. These treatments can be prescribed before starting pharmacological treatment or as an adjunct to pharmacological treatment

**Other pharmacotherapy options:** systemic local anaesthetics; opioids; NMDA antagonists

**Pain interventional treatments:** spinal cord stimulation; sympathetic block

**Pain management programmes:** cognitive behavioural therapy

**Notes:**

- NMMA, N-methyl-D-aspartate; PENS, percutaneous electrical nerve stimulation; SNRI, serotonin-norepinephrine reuptake inhibitor; TCAs, tricyclic antidepressants; TENS, transcutaneous electrical nerve stimulation.
- If a trial of a first-line agent is unsuccessful, consider combination therapy with or switch to another first-line agent.
consider combination therapy with, or switch to, another first-line agent.

- For acute pain, start with simple analgesics and progress to TCAs or other adjuvant analgesics, if necessary.
- **Tramadol** may be an effective alternative or add-on therapy for some patients. Combination therapy with tramadol/acetaminophen has similar efficacy to gabapentin.22

- Patients remaining refractory to a reasonable trial of pharmacotherapy (eg, 2 to 3 months with two or three different agents) should be referred to a multidisciplinary pain clinic for further treatment options.

- Physical stimulation, such as transcutaneous electrical nerve stimulation (TENS)23,24 and acupuncture,25 may counteract painful sensations. However, acupuncture and topical treatments should be used with caution in the lower leg in patients with diabetes, as they may aggravate the skin and lead to infection. More invasive stimulatory interventions, such as spinal cord stimulation, may be considered as a last option.

- Pain management programmes and cognitive behavioural therapy26 can also be used in combination with pharmacological approaches to teach patients how to live with pain. Regular walking, warm baths or use of elastic stockings may also help to relieve leg pain.

- While there is some evidence for effectiveness of acupuncture,27 there is no conclusive evidence to support the use of Chinese herbal medicine for painful DPN.28,29

### Summary

The prevalence of painful DPN in the diabetic population is high, and efforts should be made to diagnose patients with neuropathic pain symptoms early. While a cure for DPN may not be available, this painful condition can be managed with good glycaemic control and pain management techniques. Based on published clinical evidence and international guidelines, first-line agents for painful DPN include α,δ-ligands, TCAs and SNRIs. If a reasonable trial of a first-line agent does not relieve pain effectively, consider combination therapy with or switching to another first-line agent. Tramadol can be considered as an alternative or add-on treatment option. Patients with insufficient pain relief after a trial of first-line agents should be referred to a multidisciplinary pain clinic for further treatment options.

### References


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### INTERVIEW

**Multidisciplinary management of neuropathic pain: Role of specialists in geriatric medicine, rheumatology and rehabilitation medicine**

In the previous two issues of *Challenges in Neuropathic Pain*, we featured interviews with Multidisciplinary Panel on Neuropathic Pain (MPNP) members by specialty. Multidisciplinary management of neuropathic pain is often necessary for effective treatment of neuropathic pain, and can involve a range of specialist physicians and allied health professionals. In this issue, we hear from MPNP member Dr Wong Chun Por, a geriatrician, and from two invited physicians: Dr Gavin Lee Ka Wing, a rheumatologist, and Dr Eddie Chow Siu Lun, a rehabilitation medicine specialist.

Dr Wong and Dr Chow practice in public hospitals, while Dr Lee practices in a private hospital. While none have dedicated multidisciplinary pain clinics within their hospital, Dr Lee points out that there is close coordination between different specialists while Dr Chow indicates that his hospital has a pain clinic run by an anesthesiologist and that they provide interdisciplinary pain rehabilitation for inpatients with concurrent pain and functional issues.

Dr Wong estimates around 5% of his patients have neuropathic pain, with most cases being postherpetic neuralgia (PHN) and occasionally painful diabetic neuropathy or cancer pain. Dr Chow sees many patients with pain, including neuropathic pain, during rehabilitation. The types of neuropathic pain conditions include: central post-stroke pain; acute pain from herpes zoster; chronic pain from PHN and diabetic neuropathy; complex regional pain syndrome, and neuropathic pain related to spinal cord pathology or injury. As a rheumatologist, Dr Lee mainly sees patients with musculoskeletal disorders; his patients with neuropathic pain tend to have primary fibromyalgia or fibromyalgia secondary to existing rheumatic disorders. Dr Lee mentioned that it is not uncommon to see a patient who does not fulfill the formal classification criteria for fibromyalgia, but has definite features to suggest a neuropathic component to their pain.

Patient education and psychosocial support are key to improving patients’ quality of life and encouraging an active lifestyle. Dr Wong points out that psychosocial support is very important in geriatric service settings to ensure that patients seek and continue with the correct treatment, remain positive with support of family members, and hopefully prevent helplessness and depression. Emphasizing patient education, Dr Lee feels that it is essential to encourage patients to accept and participate in a multimodal treatment approach and to motivate patients to live a more active lifestyle. In addition to controlling pain intensity, Dr Chow works also to treat other related pain domains, such as mood and pain behaviours, with the aim of improving patients’ function, activity, participation and quality of life.

Working with other healthcare professionals...
to provide multimodal or multidisciplinary treatment is important. For instance, in the geriatric setting, Dr Wong often engages physiotherapists for pain relieving procedures, such as for acupuncture and transcutaneous electrical nerve stimulation, and social workers, with anaesthesiologists involved in the multidisciplinary pain clinic.

Advances in the field of neuropathic pain management in the past decade have led to the development of interdisciplinary pain management programs and the recognition that collaborative efforts between different specialties are required to improve patient outcomes. In addition to the availability of new medications, better understanding of the underlying pathophysiology of neuropathic pain and chronic pain also provides better explanation to patients on the need for certain medications and the importance of multimodal treatment strategies.

INTERVENTIONAL THERAPIES FOR NEUROPATHIC PAIN

Part 3: Neurostimulation techniques

Continuing this series on interventional therapies for neuropathic pain, we highlight the use of neurostimulation treatments. Neurostimulation therapies may be recommended for patients with neuropathic pain refractory to conventional pharmacological treatments, with a view to improve pain relief, functional capacity and quality of life. However, selection of patients who will derive the most benefit from these therapies remains unclear.

The European Federation of Neurological Societies (EFNS) published recommendations on neurostimulation therapy for neuropathic pain (Table). Neurostimulation therapy for pain commonly includes spinal cord stimulation (SCS), motor cortex stimulation (MCS) and deep brain stimulation (DBS), which will be briefly reviewed herein.

SCS is effective for controlling pain due to failed back surgery syndrome (FBSS) and complex regional pain syndrome (CRPS). A recently published retrospective, long-term study of 23 patients found that cervical SCS may be effective in the treatment of neuropathic upper limb pain. Patients in this study reported an average numerical analog scale pain score of 6.8 without, and 2.8 with, SCS. Adverse effects, including unwanted paresthesia of the trunk and legs as well as changes in paresthesia due to head movement, did not affect SCS effectiveness.

The use of high frequency SCS (HFSCS) may provide analgesia without the associated paresthesia. A randomized double-blind study compared HFSCS (5 kHz, 60 msec pulse width) with sham (no stimulation) in a two-period crossover trial. HFSCS was found to be equivalent to sham in improving Patient’s Global Impression of Change (PGIC) scores, pain and quality of life. A significant ‘period effect’ with improved PGIC scores was observed with the first treatment period (p=0.006), regardless of the treatment administered. The authors concluded that HFSCS and sham are equally effective, with only the order in the sequence rather than the nature of the treatment determining its effect.

Over the past decade, MCS has emerged as a promising treatment for patients with drug-resistant neuropathic pain, showing particular promise in the treatment of trigeminal neuropathic pain and central pain syndromes. DBS has been employed for a number of nociceptive and neuropathic pain states.

A recent literature review found MCS to be safe and efficacious for the treatment of facial chronic neuropathic pain (FCNP). In total, 84% of FCNP patients who used MCS reported good pain control. The most common complication reported was seizure, followed by wound infections.

Two meta-analyses concluded that DBS was more effective for nociceptive than deafferentation pain. Although patients with neuropathic pain of any origin can benefit from DBS, good results are most likely for patients with peripheral, facial or phantom limb pain.

Intracranial haemorrhage is a serious adverse event associated with DBS. Although this rarely occurs (2–4% of procedures), the consequences include neurological deficit and death. Thanks to imaging advances, the risk–benefit ratio for DBS has improved over the years. Nevertheless, MCS is often selected over DBS mainly due to potential risk of complications.

Table. EFNS recommendations on neurostimulation therapy for neuropathic pain

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Condition(s) with shown efficacy</th>
<th>Rating of recommendations</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spinal cord stimulation</td>
<td>FBSS, CRPS Type I</td>
<td>Level B</td>
<td></td>
</tr>
<tr>
<td>Motor cortex stimulation</td>
<td>Central post-stroke and facial pain</td>
<td>Level C</td>
<td>Weak positive evidence requiring further study</td>
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<tr>
<td>Deep brain stimulation</td>
<td>PNP (including pain after amputation and facial pain)</td>
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CRPS, complex regional pain syndrome; FBSS, failed back surgery syndrome; PNP, peripheral neuropathic pain

Rating of Recommendations: Level A (established as effective, ineffective, or harmful) requires at least one convincing class I study or at least two consistent, convincing class II studies; Level B (probably effective, ineffective, or harmful) requires at least one convincing class II study or overwhelming class III evidence; Level C (possibly effective, ineffective, or harmful) requires at least two convincing class III studies.

References

Parts 1 and 2 of this series are available in Challenges in Neuropathic Pain issues 23 and 24, respectively, at www.neuropainhk.org.