

Welcome to the fifth issue of Challenges in Neuropathic Pain, a newsletter brought to you by the members of the Multidisciplinary Panel on Neuropathic Pain. This issue presents the third in a series of treatment recommendations on neuropathic pain. The recommendations aim to provide Hong Kong clinicians with up-to-date information on treatment strategies and assist in everyday clinical practice. Our regular features, including a literature review, Q&A, useful Web sites and a calendar of upcoming conferences, will keep Hong Kong clinicians informed of the latest news on neuropathic pain.



Multidisciplinary Panel on
Neuropathic Pain

神經痛跨學科研究小組

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RECOMMENDATIONS FOR THE MANAGEMENT OF PAINFUL DIABETIC PERIPHERAL NEUROPATHY

One of the key initiatives of the Multidisciplinary Panel on Neuropathic Pain is the development of treatment recommendations for a number of common neuropathic pain syndromes. This issue features a summary of the recommendations for managing painful diabetic peripheral neuropathy. The project leader for developing these recommendations was Dr Lawrence Wong.



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 the peripheral nerve damage, although the precise mechanism is not known.

Approximately 20% to 40% of patients with diabetes develop some form of neuropathy. Risk factors for diabetic neuropathy are outlined in Figure 1. 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, dizziness, bladder infections and erectile dysfunction. Diabetic amyotrophy, predominantly a motor neurone disorder, is usually seen in elderly patients

with poorly controlled type 2 diabetes. In these patients, the muscles around the pelvis and thigh become weak and painful, which affects mobility.

The most common form of diabetic neuropathy – distal symmetric polyneuropathy – predominantly affects sensory functions. The peripheral nerves of the feet, legs and, in some cases, the hands and arms are usually involved. The onset, severity and type of symptoms vary widely between patients. Early symptoms, including numbness, tingling, burning or pain, may progress to 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. Diabetic neuropathy may lead to foot ulceration (Figure 2), and even the need for amputation. Early diagnosis and management of at-risk patients might prevent at least half of all diabetes-related amputations.

Diagnosis

Diagnosis of diabetic neuropathy is based on clinical symptomatology and a comprehensive neurological examination. Other underlying pathologies for neuropathy should be excluded (eg, vascular disease, HIV, vitamin B₁₂ deficiency, hypothyroidism). 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 to diagnose diabetic neuropathy.

Figure 1. Risk factors for the development and progression of diabetic neuropathy

- 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

Full patient history to determine:

- Type, duration and level of diabetes control
- Nature of symptoms (intensity, duration, progression, nocturnal exacerbation, recurrent foot problems)
- Pain characteristics (nature of pain, dysaesthesia, hyperaesthesia)
- Lifestyle factors that may contribute to progression of neuropathy

Neurological examination:

- Distal sensory function and reflexes, eg, pin prick test, light touch, vibration test, ankle reflex, pressure perception, temperature assessment, 2-point discrimination test
- Electrophysiological assessment to document neuropathy, eg, nerve conduction study and electromyography, or Doppler sonography to determine the presence of vascular disease

Figure 2. Ulcers on the feet of a patient with diabetic neuropathy



General management

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

1. For patients without clinical neuropathy, educate on lifestyle, foot care and the importance of controlling glycaemia. Refer to a diabetes specialist nurse or chiropodist for a yearly foot examination, if necessary.
2. Patients with suspected diabetic amyotrophy or symptomatic clinical neuropathy should be referred to a diabetologist or neurologist. Commence treatment for acute or chronic pain.
3. Trauma, cellulitis or acute ischaemia of the foot require urgent referral to the specialist diabetes foot-care team.
4. The importance of good glycaemic control should be stressed to all diabetic patients, as this may slow or prevent the development of peripheral neuropathy and other diabetic complications.

Pharmacological and nonpharmacological treatment

The pharmacological treatments included in these recommendations are based on published clinical evidence in diabetic

neuropathy patients and current clinical practice. The full prescribing information should be consulted before initiating drug therapy.

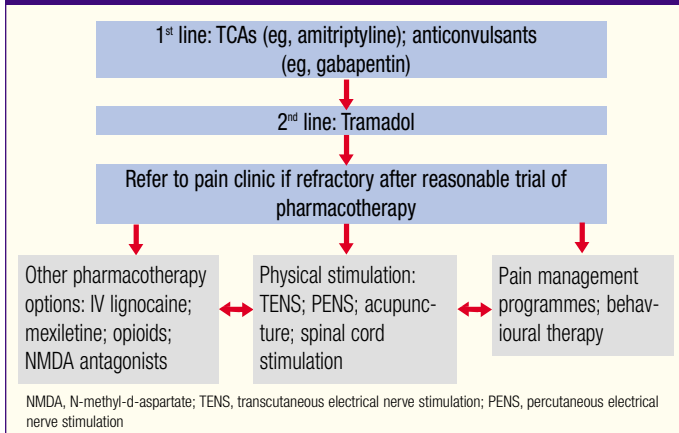
The mainstay therapeutic agents for managing diabetic neuropathic pain are tricyclic antidepressants (TCAs) and anticonvulsants (Figure 3). Combinations of pharmacological, physical and psychological interventions are likely to attain optimum pain relief for most patients.

1. Systematic reviews of randomized, placebo-controlled trials of TCAs in the treatment of diabetic neuropathy have demonstrated the efficacy of these agents.^{1,2} 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 (eg, gabapentin, lamotrigine or carbamazepine) should be considered as an alternative first-line choice. Side effects may 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 is the first oral therapy to be licensed for diabetic neuropathy, based on the results of a large, multicentre, double-blind, placebo-controlled trial.³ 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). The maximum recommended dose is 3,600 mg daily (use a lower dose for patients with renal impairment). For elderly patients or patients susceptible to side effects, increase gabapentin dosage by 300 mg every week, or commence with a lower dose (eg, 100 mg).
4. Tramadol may be an effective alternative in some patients.^{4,5}
5. Refer patients remaining refractory to a reasonable trial of pharmacotherapy (eg, 2 to 3 months with 2 to 3 different agents) to a multidisciplinary pain clinic. Pain relief in intractable painful neuropathy has been previously reported with intravenous lignocaine, oral mexiletine, NMDA-receptor antagonists and opioids.⁶⁻¹⁰
6. Physical stimulation, such as transcutaneous or percutaneous electrical nerve stimulation, acupuncture and spinal cord stimulation, may counteract painful sensations.¹¹⁻¹³ However, acupuncture and topical treatments should be used with caution in the lower leg of diabetic patients, as they may irritate the skin or cause infection.
7. Pain management programmes and behavioural therapy combined with pharmacological approaches teach patients how to live better with pain. Regular walking, warm baths or elastic stockings may help relieve leg pain.

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Figure 3. Treatment options for diabetic neuropathy



CASE PRESENTATION

In each issue, a case study is presented on a relevant neuropathic pain syndrome. Reviewing case studies will help to improve your diagnostic approach to neuropathic pain and increase your understanding of how to select treatment strategies based on presenting symptoms. In this issue, a case of carpal tunnel syndrome in a diabetic patient is discussed.

Carpal Tunnel Syndrome

Presenting Symptoms

A female aged 25 years had been suffering from progressive bilateral hand numbness, pain and weakness for several years. The numbness involved all 5 digits, which differs from the typical radial 3 and a half distribution of carpal tunnel syndrome. She also complained of nocturnal pain and numbness, and mild neck pain.

Medical History

The patient had been diagnosed with insulin-dependent diabetes mellitus as a young child and was using insulin to control her diabetes. A recent blood test revealed a blood glucose level of 12 mmol/dL and glycosylated haemoglobin (HbA_{1c}) of 9.6%. She first presented 6 years previously with bilateral foot and ankle pain. Physical examination revealed metatarsalgia, flat feet and accessory navicular. The patient received conservative treatment with supportive insoles and NSAIDs. In 2000, the patient had a left middle finger infection and was treated with antibiotics; she was prone to infection because of her poor diabetes control.

Clinical Examination

An X-ray of the cervical spine did not reveal any abnormality. Muscle power in both hands and the upper limb was grade 4+ to 5, so the weakness was subjective. A sensory test revealed a slight increase in 2-point discrimination, up to 6 mm, in the right index finger and little finger. As the clinical picture was not typical of carpal tunnel syndrome, a neurophysiological study was performed. The nerve conduction velocity of the motor fibres and the sensory fibres of the median nerve were decreased at the level of the wrist. The right side was affected more severely than the left.

Interpretation

The patient was diagnosed with bilateral carpal tunnel syndrome. The neurophysiological study did not reveal typical features of peripheral neuropathy, although the sensory deficit was a likely complication of poorly controlled diabetes.

Management

A resting wrist splint for wear at night was given for the carpal tunnel syndrome and a course of physiotherapy was given to treat the pain and numbness. However, the patient continued to have symptoms despite conservative treatment, so surgical release of the right median nerve was performed (Figure 4). Postoperatively, the numbness improved slightly, but the patient suffered from new problems. Pain and erythema developed over the surgical scar, for which the patient was treated with a pressure garment, scar massage and oral analgesics. These problems settled, but the patient then developed progressive, bilateral ulnar finger pain. The pain was controlled by acupuncture. A further neurophysiological study was performed (18 months after the initial study) and revealed mild left carpal tunnel syndrome and definite changes associated with peripheral neuropathy. The patient was treated with gabapentin (300 mg nocte) for her neuropathic pain. Although symptoms improved, she suffered from insomnia and switched to diclofenac 100 mg od. However, the neuropathic pain symptoms deteriorated after stopping gabapentin. The patient recommenced gabapentin treatment (900 mg taken in the morning); after 6 weeks the patient is doing well on treatment.

Figure 4. Open surgical release of the median nerve for the treatment of carpal tunnel syndrome



Q&A

Readers are encouraged to send questions to members of the Multidisciplinary Panel on Neuropathic Pain. Please forward your questions concerning any aspect of neuropathic pain and its management to mpnp@medimedia.com.hk or fax to (+852) 2559 6910.

Is acupuncture useful for treating neuropathic pain? What should I tell my patients who want to try acupuncture?

According to the British Medical Acupuncture Society guidelines on referral (www.medical-acupuncture.co.uk/referral.shtml), neuropathic pain is often difficult to treat. However, the guidelines indicate that acupuncture may be effective in some patients with trigeminal neuralgia, postlaminectomy syndromes, phantom leg pain and other neuralgias and neuropathies. The National Center for Complementary and Alternative Medicine of the National Institutes of Health (NIH) provides information on acupuncture (www.nccam.nih.gov/health/acupuncture). The NIH Consensus Statement on Acupuncture states that acupuncture may be useful as an adjunct treatment or acceptable alternative, or be included in a comprehensive management programme in conditions such as low back pain, carpal tunnel syndrome, tennis elbow and stroke rehabilitation. Therefore, acupuncture may be useful in some patients with neuropathic pain. However, as outlined in the recommendations on diabetic neuropathy earlier in this issue (see page 2), acupuncture and topical treatments should be used with caution on the lower leg of diabetics, as these treatments may irritate the skin and cause infection. Despite the recommendations from the various authorities, it should be noted that there is currently no Level 1 evidence supporting the effectiveness of acupuncture therapy in chronic painful neuropathies.

LITERATURE REVIEW

Ang SH, Park HW, Lee BS, et al. Gabapentin effect on neuropathic pain compared among patients with spinal cord injury and different durations of symptoms. *Spine* 2003;28:341-347.

Neuropathic pain is the cause of chronic pain in more than two thirds of patients with spinal cord injury (SCI). This study aimed to compare the effect of gabapentin in patients with SCI who were refractory to treatment with other analgesic agents, including antidepressants, anticonvulsants and opioids. Thirty-one patients with neuropathic pain associated with SCI or cauda equina were included in the study. The duration of pain was less than 6 months in 13 patients (Group 1) and more than 6 months in 18 patients (Group 2). All patients received gabapentin at an initial dose of 300 mg/day, with the dose increased by 300 mg every 3 days for 18 days (the titration period) to a dose of 1,800 mg/day. Patients were maintained at the maximum tolerated dose (up to 3,600 mg/day) for a 5-week maintenance period. Pain and sleep interference scores, measured by a visual analogue scale (VAS), were assessed at baseline and at 2-week intervals during the treatment period.

Twenty-five patients completed the study; the maintenance dose in the majority of these patients (n=20) was 1,800 mg/day. At baseline, the mean pain score was 7.3 ± 0.5 and 7.6 ± 0.4 in Group 1 and Group 2 patients, respectively. A significant reduction in pain score was seen in both groups at the end of the 8-week treatment period, although the score at 8 weeks was lower in Group 1 (3.0 ± 0.6) than Group 2 (5.1 ± 0.6) patients. Furthermore, sleep interference scores improved significantly in both groups. Side effects reported with treatment were mild to moderate in intensity, with the most frequently reported adverse event being somnolence. The authors concluded that gabapentin is effective in patients with neuropathic pain due to SCI who are refractory to other analgesic treatments. However, gabapentin may be more beneficial in patients with a shorter duration (less than 6 months) of symptoms.

WEB SITES ON NEUROPATHIC PAIN

Various Web sites are devoted to neuropathic pain or pain management and provide useful information for clinicians and patients.

The American Chronic Pain Association (www.theacpa.org) aims to create awareness of chronic pain, and offers support and information for sufferers of chronic pain. The site provides information for patients on chronic pain and the role of a multidisciplinary approach to pain management.

The Center for Shingles and Postherpetic Neuralgia (www.shingles.mgh.harvard.edu), which is affiliated with Harvard Medical School, provides patient information on shingles, postherpetic neuralgia (PHN), and ways to reduce the risk of PHN after having shingles. The site includes a calculator for patients with shingles to determine their risk of PHN.

CONFERENCE CALENDAR

MEETING	Hong Kong College of Anaesthesiologists & Asian Oceanic Society of Intravenous Anaesthesia Combined Scientific Meeting in Anaesthesiology	23rd Hong Kong Orthopaedic Association Annual Congress	Hong Kong Neurological Society & Hong Kong Epilepsy Society Scientific Meeting	Hong Kong Neurosurgical Society Annual Scientific Meeting
LOCATION	Hong Kong	Hong Kong	Hong Kong	Hong Kong
DATE	26-28 September, 2003	8-9 November, 2003	8-9 November, 2003	6 December, 2003
CONTACT DETAILS	Secretariat: The Federation of Medical Societies of Hong Kong 4/F, Duke of Windsor Social Service Building 15 Hennessy Road Wanchai, Hong Kong Tel: (+852) 2579 8898 Fax: (+852) 2866 7530 E-mail: cos@fmshk.com.hk Web site: www.hkca.edu.hk	Conference Secretary: Dr KM Siu Room 107, 1/F, Block J Department of Orthopaedics and Traumatology Princess Margaret Hospital Lai Chi Kok, Hong Kong Tel: (+852) 2632 3482 (Miss Terry Leung) Fax: (+852) 2647 7432 E-mail: congress@hkoa.org Web site: www.hkoa.org	Secretariat: The Federation of Medical Societies of Hong Kong 4/F, Duke of Windsor Social Service Building 15 Hennessy Road Wanchai, Hong Kong Tel: (+852) 2579 8898 Fax: (+852) 2866 7530 E-mail: cos@fmshk.com.hk Web site: www.hkns.org	Secretariat: Department of Surgery The Chinese University of Hong Kong Prince of Wales Hospital Shatin, Hong Kong Tel: (+852) 2632 2951 Fax: (+852) 2647 3074 E-mail: asm.ns@surgery.cuhk.edu.hk Web site: www.ns.org.hk

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