

Challenges in Neuropathic Pain

Welcome to the 14th issue of *Challenges in Neuropathic Pain*, a newsletter from the Multidisciplinary Panel on Neuropathic Pain (MPNP). The feature article in this issue summarizes the MPNP's recommendations on the acute and prophylactic management of migraine. The fifth part in the series on drugs for neuropathic pain reviews the role of non-tricyclic antidepressants, and the case presentation is on myofasciitis. Back issues of *Challenges in Neuropathic Pain*, as well as MPNP recommendations on various neuropathic pain conditions and patient education materials, can be found at www.neuropainhk.org.

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PANEL MEMBERS

Dr Chen Phoon Ping
Consultant and Chief of Service
Department of Anaesthesiology and
Operating Services
Alice Ho Miu Ling Nethersole Hospital and
North District Hospital

Dr Josephine Ip
Associate Professor
Division of Hand and Foot Surgery
Department of Orthopaedic Surgery
The University of Hong Kong;
President, Hong Kong Diabetic Limb Society;
Past President
Hong Kong Society for Surgery of the Hand; and
Congress President, 7th Congress of Asian Pacific
Federation of Societies for Surgery of the Hand

Dr Joseph MK Lam
Honorary Consultant and
Honorary Clinical Associate Professor
Division of Neurosurgery
Prince of Wales Hospital
The Chinese University of Hong Kong

Dr Vincent Mok
Associate Professor, Division of Neurology
Department of Medicine and Therapeutics
Prince of Wales Hospital
The Chinese University of Hong Kong

Dr Tsoi Tak Hong
Neurologist and Consultant Physician
Pamela Youde Nethersole Eastern Hospital
President, The Hong Kong Neurological Society

Dr Wong Chun Por
Chief of Integrated Medical Services
Consultant and Head
Department of Geriatrics
Ruttonjee and Tang Shiu Kin Hospitals

Dr Steven Wong
Consultant in Anaesthesiology
Head of Pain Management Team
Department of Anaesthesiology and Operating
Theatre Services
Queen Elizabeth Hospital

Contact the Panel

Forward any comments
on this newsletter to the
Multidisciplinary Panel
on Neuropathic Pain at
mpnp@asia.cmpmedica.com.

Recommendations for the Management of Migraine

This article presents a summary of the Multidisciplinary Panel on Neuropathic Pain (MPNP) recommendations for the acute and prophylactic management of migraine. The full version of these recommendations is available at the MPNP Web site – www.neuropainhk.org.

This recommendation focuses on the management of two migraine subtypes – migraine with and without aura – in adults, for the treatment of acute attacks and for the prophylaxis of migraine. The pharmacological treatments included in this recommendation are based on the published guideline from the European Federation of Neurological Societies (EFNS).¹ However, some agents mentioned may not be approved for use in migraine headache disorders. Full prescribing information should be consulted before initiating drug therapy.

Recommendations for the Acute Treatment of Migraine

Pharmacological Management

Generally, pharmacological treatment is the mainstay of management of acute attacks (Figure).

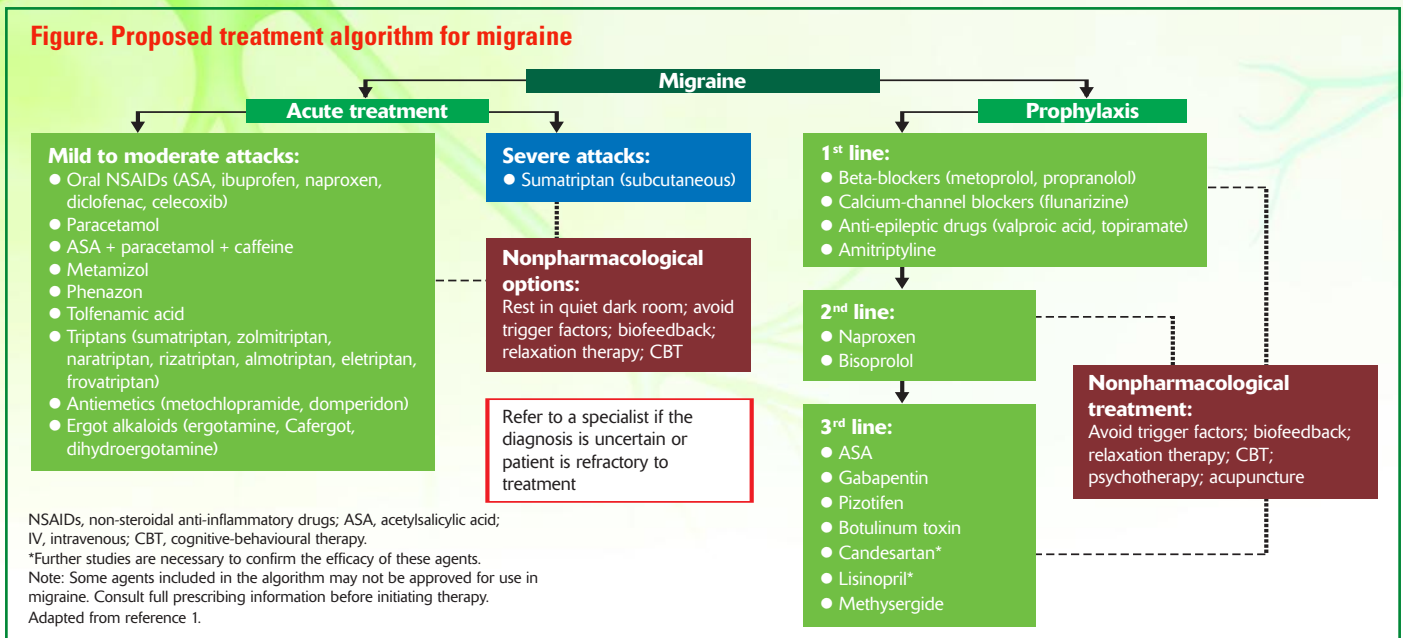
Analgesics

The first-line treatment for mild to moderate attacks of migraine is analgesics, mainly oral non-steroidal anti-inflammatory drugs (NSAIDs),^{1,2} including acetylsalicylic acid (ASA),^{3,5} ibuprofen,^{4,5} and diclofenac.^{6,7} For very severe attacks, the EFNS guideline recommends intravenous ASA;¹ however, this formulation is unavailable in Hong Kong. NSAIDs are usually well tolerated by most patients; the most frequent side effects include gastrointestinal symptoms and bleeding.^{1,8}

A randomized, open-label trial showed that celecoxib 400 mg and naproxen 550 mg caused similar and significant improvements in pain severity in acute migraine attacks.⁹ The incidence of gastric pain was significantly lower in the celecoxib than the naproxen group ($p=0.029$).

Other analgesics with demonstrated efficacy in treating acute migraine attacks include phenazone, metamizole, tolfenamic acid and paracetamol.¹ A fixed combination of ASA, paracetamol and caffeine was shown to be more effective than each drug taken separately.¹⁰

Figure. Proposed treatment algorithm for migraine



One possible complication with the overuse of analgesics in migraine therapy is medication overuse headaches (MOH).^{2,8} To prevent this, it is recommended that simple analgesics should not be taken for more than 15 days/month and combined analgesics for not more than 10 days/month.¹ Patients should be cautioned about the possibility of MOH even when taking analgesics less frequently.

Triptans

Triptans (5-HT₁ receptor-specific agonists) are widely prescribed, migraine-specific medications with well-established efficacy.¹ Usually, these drugs are used to treat moderate to severe migraine or mild to moderate migraine that is unresponsive to analgesics.⁸ For severe attacks, subcutaneously injectable sumatriptan can be administered for more rapid onset of action.⁸ Non-oral forms of triptans are suitable for patients who experience nausea and/or vomiting.

Early intake of triptans (within 1 hour of headache onset) improves efficacy.¹¹ However, triptan use should be restricted to a maximum of 10 days/month because of the risk of MOH.¹ Another concern with triptan use is headache recurrence, which occurs in about 15–40% of patients.¹ Patients who experience headache recurrence may benefit from a second dose of the same triptan.¹ Triptan administration is not recommended during the aura phase of migraine.¹

Data from comparative efficacy trials of triptans and other migraine treatments show that, in general, triptans have comparable efficacy to analgesics, but are superior to ergotamines.^{1,5,7,12,13}

Antiemetics

Adjunctive therapy with antiemetics such as metoclopramide 20 mg or domperidon 20–30 mg is recommended for migraine-associated symptoms such as nausea and impaired gastric motility.^{1,8} These drugs may be administered 20–30 minutes before, or concomitantly with, an analgesic or triptan.

Ergot alkaloids

The ergot alkaloid ergotamine has been used in the treatment of migraine for many years.¹⁴ Other available ergot alkaloid preparations include Cafergot (caffeine and ergotamine) and dihydroergotamine.⁸

Ergotamine is associated with a number of side effects, including nausea, vomiting, paresthesia, leg weakness and ergotism.¹⁴ Use of ergotamine should be restricted to migraine patients with prolonged attacks or regular recurrence.¹⁴ As ergot alkaloids also have the potential to induce MOH, their use should be limited to 10 days/month.^{1,8,15}

Nonpharmacological Management

The nonpharmacological treatment strategies for migraine are mainly behavioural in nature and include biofeedback, relaxation therapy and cognitive-behavioural therapy (CBT). They aim to decrease the emotional impact and disability from headaches and help patients to develop better pain coping techniques. Most of these strategies are based on anecdotal evidence, and very few have been evaluated in clinical studies.

General Supportive Measures

A variety of supportive strategies may also help alleviate symptoms of migraine. These include applying cold or pressure to the head, resting in a quiet, dark room, sleeping and avoiding potential triggers (eg, stress, dietary and environmental factors).^{1,16}

Recommendations for the Prophylaxis of Migraine

Both nonpharmacological and pharmacological treatments play a role in the prophylaxis of migraine attacks (Figure). Drug therapy for prophylactic treatment of migraine may be warranted in patients who experience frequent, severe attacks that cause significant disruption in their daily lives. Generally, preventive treatment for migraine is indicated when¹:

- quality of life, attendance and/or productivity at school/work are severely impaired
- two or more attacks occur each month
- acute drug treatment of migraine attacks is ineffective
- auras are frequent, very long or uncomfortable.

Referral to a specialist may be necessary in special circumstances, such as when the diagnosis is uncertain or medications fail to control symptoms within a reasonable time.

Nonpharmacological Management

The most effective nonpharmacological strategy for preventing migraine is identification and avoidance of trigger factors.¹⁶ Trigger factors can include stress, diet, behavioural changes (missed meals, too much or too little sleep) and environmental factors (loud noises, weather changes, strong odours).^{2,16} Other strategies include biofeedback, relaxation therapy, CBT and psychotherapy (in patients with comorbid psychiatric disorder).^{8,16} Other nonpharmacological

prophylaxes for migraine, which have not been evaluated for long-term safety and efficacy, include aerobic training, chiropractic therapy, osteopathy, naturopathy, homeopathy, transcutaneous electrical nerve stimulation (TENS) and acupuncture.^{8,16}

It may be worth considering these as adjunctive treatments, mainly in patients who have failed to respond to conventional pharmacological treatment.

Pharmacological Management

First-line Treatment

Beta-blockers, specifically metoprolol and propranolol, are one of the first-line treatments for migraine prophylaxis.¹ Generally, beta-blockers are well tolerated; common adverse effects reported in clinical trials include fatigue, depression, nausea, dizziness and insomnia.¹⁷

Another first choice prophylactic therapy is the calcium-channel blocker flunarizine, given at a dose of 5–10 mg/day.¹⁷ The most common side effects include weight gain, somnolence, dry mouth, dizziness, hypotension, depression and extrapyramidal symptoms.^{2,17}

Antiepileptic drugs such as valproic acid and topiramate are also recommended as first-line prophylactic drugs for migraine.¹ Their efficacy rates are comparable to those of metoprolol, propranolol and flunarizine.¹

Second-line Treatment

Despite consistent evidence for efficacy in migraine prevention,^{1,2,18}

central side effects limit amitriptyline (50–150 mg) to use as a second-line treatment in the EFNS guideline.¹ However, in Hong Kong, amitriptyline is one of the most widely prescribed drugs for migraine prophylaxis and has been included in the treatment algorithm (Figure) as an alternative first-line agent. Amitriptyline may be useful in younger patients who may also have tension-type headache; it should be used with caution in the elderly.

Other drugs recommended as second choice for migraine prophylaxis include naproxen 1,000 mg and bisoprolol 5 mg.^{1,18,19}

Third-line Treatment

Potential third-line agents for migraine prophylaxis include ASA 200–300 mg,^{20,21} gabapentin,^{1,22} and methysergide,¹ as well as pizotifen,²³ botulinum toxin, candesartan and lisinopril, although the latter group has limited or conflicting evidence of therapeutic efficacy.

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DRUGS FOR THE TREATMENT OF NEUROPATHIC PAIN

In this issue, we continue our series on drugs for the treatment of neuropathic pain. Part 5 of the series reviews evidence on non-tricyclic antidepressants in neuropathic pain.

Part 5 – Non-tricyclic Antidepressants

Although serotonin specific reuptake inhibitors (SSRIs) are generally thought to be better tolerated than tricyclic antidepressants (TCAs), there is limited evidence to suggest that they are effective for neuropathic pain.^{1,2} As a result, SSRIs do not appear as treatment options in recommendations for management of neuropathic pain syndromes.³⁻⁵ However, studies show that the newer selective serotonin and noradrenaline reuptake inhibitors (SSNRIs) are useful agents in neuropathic pain conditions, particularly painful polyneuropathies like diabetic painful neuropathy (DPN).² In addition, SSNRIs are considered safer than TCAs, particularly in patients with cardiac disease.³ Data for the SSNRIs in other neuropathic pain conditions such as trigeminal neuralgia or postherpetic neuralgia are limited or lacking.

In patients with DPN, duloxetine demonstrated superior pain relief to placebo in three trials, and safety and effectiveness has also been shown with long-term, open-label treatment.⁴ A dose of 60 mg/day appears to be optimal, as higher doses may be associated with more side effects for no efficacy gain.^{3,4} Titration from 30 mg/day to 60 mg/day after 1 week may help to reduce the risk of nausea.

The number needed to treat (NNT) for duloxetine (60–120 mg/day) is 5.2 (95% CI 3.7–8.5).³

Venlafaxine at dosages of 150–225 mg/day has demonstrated efficacy in randomized controlled trials in patients with painful DPN and other painful polyneuropathies.^{3,4} Venlafaxine has an NNT of 3.1 (95% CI 2.2–5.1) based on three studies, which is similar to the NNT for TCAs.¹ Dose titration over 2 to 4 weeks may be required to reach an effective dosage.⁴

Current recommendations from the European Federation of Neurological Societies (EFNS)³ and the Canadian Pain Society⁵ position SSNRIs as second-line drug treatments for painful polyneuropathies, although a recent International Association for the Study of Pain (IASP) consensus meeting⁴ considers SSNRIs a first-line treatment option in these conditions.

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Q & A

Forward any questions on neuropathic pain to the MPNP at mpnp@asia.cmpmedica.com.

What is the role of TENS in the treatment of neuropathic pain?

While there are many controlled studies and meta-analyses of the use of peripheral stimulation techniques such as transcutaneous electrical nerve stimulation (TENS) in nociceptive pain, few controlled trials of

TENS for neuropathic pain syndromes have been published. After performing a comprehensive literature search on this topic, a European Federation of Neurological Societies (EFNS) Task Force

concluded that it was difficult to develop evidence-based recommendations for TENS in neuropathic pain.¹ They found level C evidence that high-frequency TENS may be better than placebo in neuropathic pain syndromes. However, the lack of published controlled trial data does not mean that evidence of benefit does not exist. Case series and clinical experience suggest that some patients with neuropathic pain syndromes will derive benefit from TENS therapy, either as an adjunct to first-line pharmacological treatment or as an alternative treatment in patients who do not respond to

standard therapies. The MPNP consider that TENS may be effective in some patients in relieving pain associated with painful diabetic peripheral neuropathy and postherpetic neuralgia. Importantly, TENS is extremely easy to apply, non-invasive and devoid of risk, which gives a trial of TENS a favourable risk-to-benefit profile in many of the patients who do not obtain acceptable pain relief with medications alone.

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LITERATURE REVIEW

Gilron I. Gabapentin and pregabalin for chronic neuropathic and early postsurgical pain: current evidence and future directions. Curr Opin Anaesthesiol 2007;20:456-472.

This review paper outlines the current evidence base supporting the use of gabapentin and pregabalin for chronic neuropathic and early postsurgical pain. The history of the development of the two drugs, their pharmacological actions and analgesic mechanisms are detailed. Binding of gabapentin and pregabalin to the alpha-2-delta subunit of N-type voltage-gated calcium channels is likely their most important analgesic mechanism. Multiple, often large, high-quality trials have demonstrated the safety and efficacy of gabapentin and pregabalin in neuropathic pain syndromes including painful diabetic peripheral neuropathy, postherpetic neuralgia and other syndromes such as spinal cord injury, complex regional pain syndrome type 1 and cancer-related neuropathic pain. This body of evidence has led to their recommendation as first-line neuropathic pain treatments by

several expert groups. Number needed to treat (NNT) values show that approximately four patients with neuropathic pain need to be treated with gabapentin or pregabalin to achieve one patient with at least 50% pain relief. These data suggest that the efficacy of gabapentin and pregabalin is perhaps slightly less than that of tricyclic antidepressants (NNT=2-3) or morphine (NNT=2.5). Although sedation, dizziness and ataxia are important and relatively common adverse effects of these drugs, their greatest advantages are still considered to be their relative safety, tolerability and ease of use, as well as their lack of adverse interactions with other medications. As both these drugs are relatively new, further research could extend their indications and refine their use to provide even greater benefit in neuropathic and chronic pain conditions.

CASE PRESENTATION

In this issue, a case of a young woman who developed myofasciitis with allodynia following an exercise-related injury is presented.

Myofasciitis

Presenting symptoms and objective findings

A 24-year-old Caucasian female presented complaining of sudden onset of severe right scapular region pain and muscle spasm 3 months earlier. She also noticed severe burning pain when gently touched on the skin of the upper back. Pain limited right upper limb movement. However, no abnormalities or changes in sensation were present in the lower limbs. A cervical spine MRI scan showed mild disk prolapse at the C4/5 and C5/6 level without spinal cord or nerve compression.

Clinical examination revealed tenderness and severe tactile allodynia (severe burning pain upon light touch) over the right lower neck and scapular region, which precluded deep palpation.

Management and outcome

Pregabalin 75 mg bd po, celecoxib 200 mg bd po and nortriptyline 10 mg nocte po were used for initial control of inflammatory and neuropathic pain. Within 48 hours, the allodynia was much reduced. Repeat assessment showed tenderness at the right paraspinal muscle, right upper trapezius and scapular muscle on firm pressure. There were trigger points and taut bands of muscle fibres. The symptoms were localized and did not fulfill the criteria of fibromyalgia.

Pregabalin and nortriptyline were continued while physiotherapy, including soft tissue mobilization, myofascial release and electroacupuncture, was performed. After 3 weeks' treatment, the pain was reduced by 90%. The patient remains on this drug regimen, as the allodynia returned when treatment was discontinued after 3 months. The pain is well controlled and physical activities are not restricted.

Discussion

Inflammation of the muscle and its fascia following injury is often considered the cause of myofasciitis, which can be difficult to treat. In this case, exercise-related injury triggered the onset of pain, which presumably triggered central sensitization and resulted in allodynia with burning sensation, two classic features of neuropathic pain. Low-dose pregabalin and nortriptyline quickly controlled the pain to a manageable level without severe side effects, permitting further treatment.

Source: MPNP members

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CMPMedica Pacific Ltd
Unit 901-903, 9th Floor, AXA Centre, 151 Gloucester Road,
Wan Chai, Hong Kong
Tel: (852) 2559 5888 Fax: (852) 2559 6910
E-mail: enquiry.hk@asia.cmpmedica.com
http://www.cmpmedica.com