

Challenges in

Neuropathic Pain

In this 15th issue of *Challenges in Neuropathic Pain*, the Multidisciplinary Panel on Neuropathic Pain (MPNP) presents a summary of their updated recommendations on the management of central post-stroke pain. Part 6 of the series on drugs for neuropathic pain examines the evidence for use of nonsteroidal anti-inflammatory drugs in neuropathic pain, and the Q&A section discusses physical therapy for neuropathic pain. Also in this issue, the literature review features a paper on pregabalin for central neuropathic pain; an interesting case presentation of neuropathic pain secondary to neuromyelitis optica rounds out the content. Visit www.neuropainhk.org to obtain back issues of *Challenges in Neuropathic Pain*, together with the panel's recommendations on neuropathic pain conditions and patient education materials.

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Updated Recommendations for the Management of Post-Stroke Pain

This article presents a summary of the updated recommendations developed by the Multidisciplinary Panel on Neuropathic Pain (MPNP) for the management of central post-stroke pain (CPSP). The full version of these recommendations is available on the MPNP Web site – www.neuropainhk.org.

INTRODUCTION

CPSP is a neuropathic pain syndrome characterized by constant or intermittent pain following stroke. Pain may be unilateral or only affect small areas, and pain intensity may vary within the affected area. The incidence of CPSP in stroke patients has been reported at 8%; the pain is moderate to severe in 5% of all stroke patients.¹ The onset of pain occurs within 1 month in over half of all CPSP patients; however, in some patients, the pain can take more than 6 months to develop.¹ The following symptoms are typical²:

- Burning or freezing pain sensation.
- Difficulties distinguishing sharp from blunt and warm from cool in the affected area.
- Allodynia (pain sensation from a normally non-painful stimulus).

DIAGNOSIS

The following should be assessed in all stroke patients reporting pain to differentiate CPSP from nociceptive pain²:

- Test the sensation to sharp and blunt objects in the affected area.
- Test the sensation to warmth (eg, touch with a finger) and coolness (eg, a metal instrument) in the affected area.
- If a patient is unable to differentiate between sensations in either or both of the above tests, CPSP is a probable diagnosis.

MANAGEMENT

The key steps in CPSP management are:

1. Record baseline pain intensity, eg, on a visual analogue scale, to allow comparison with post-treatment pain.
2. Counsel patients in relaxation techniques, as stress can exacerbate pain.
3. Commence pharmacological treatment of CPSP with a recommended first-line agent. Early treatment improves outcomes for CPSP patients.
4. Consider referral to a multidisciplinary pain centre if a patient remains refractory to pharmacological treatment.

PAIN TREATMENTS

Relatively few randomized, controlled clinical trials have investigated the effectiveness of treatments for CPSP. The pharmacological treatments in these recommendations are based on the available published clinical evidence and current clinical practice. However, some agents may not be indicated for use in neuropathic pain syndromes. Clinicians should consult the local prescribing information for these treatments. Pharmacological management should be supplemented with physical and psychological interventions.

Pharmacological Management

Antidepressants

The tricyclic antidepressant (TCA) amitriptyline remains one of the first choices in treating CPSP. In a randomized, controlled, cross-over study, amitriptyline was shown to more effectively control pain in CPSP patients than the anticonvulsant carbamazepine, and was better tolerated.³ In addition, a study to test the prophylactic efficacy of amitriptyline in preventing CPSP in 39 patients with thalamic stroke found amitriptyline (10 to 75 mg/day) reduced, but did not completely prevent, the development of CPSP.⁴ Therefore, TCAs such as amitriptyline or nortriptyline should be considered as first-line therapy.

Anticonvulsants

Anticonvulsants are often used as first-line agents in the treatment of neuropathic pain conditions, particularly if antidepressants are contraindicated or ineffective. In particular, lamotrigine and the alpha-2-delta (A2D) ligands gabapentin and pregabalin have demonstrated some benefit in CPSP.

Pregabalin

A 4-week, randomized, double-blind, placebo-controlled trial involving 40 patients with severe central neuropathic pain (including 12 patients with CPSP) showed that pregabalin was well tolerated and produced clinically significant reductions in pain and improvements in health status.⁵ The authors concluded that pregabalin may be proposed as a first-line pharmacological treatment of central neuropathic pain.

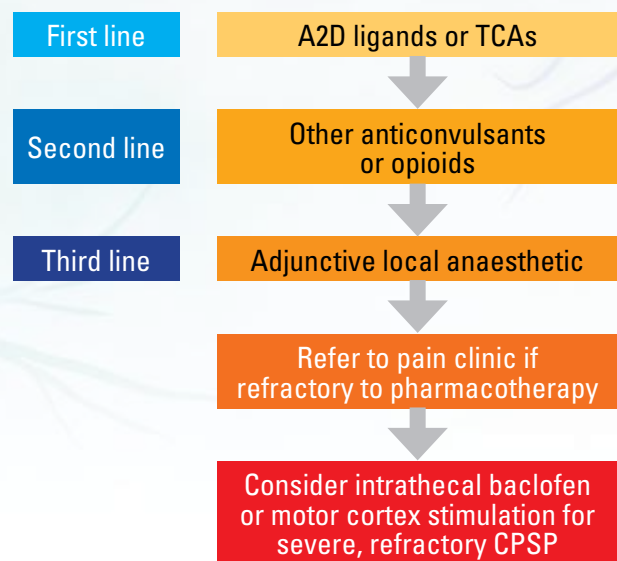
Gabapentin

To date, no randomized, controlled trials with gabapentin have been performed in CPSP patients. A recently published case study does suggest, however, that gabapentin may be beneficial in CPSP.⁶ Furthermore, in a double-blind, placebo-controlled trial, gabapentin reduced pain and improved some quality-of-life measures in patients with a variety of neuropathic pain syndromes, including a small number of patients with post-stroke pain.⁷

Lamotrigine

Lamotrigine may be used as a second-line agent or an alternative first-line treatment to TCAs.⁸ In an 8-week, placebo-controlled, cross-over trial, lamotrigine (maximum dose, 200 mg per day) reduced

Figure. Recommended treatment algorithm for pharmacological management of CPSP



the median pain score relative to placebo, and improved some other outcome measures.⁸ The treatment was generally well tolerated with few transient side effects.

Systemic Use of Local Anaesthetic Agents

In a randomized, placebo-controlled trial of 16 patients (6 with CPSP and 10 with spinal cord injury-related pain), brush-induced allodynia and mechanical hyperalgesia were improved with intravenous (IV) lignocaine (5 mg/kg).⁹ IV lignocaine was also shown to provide some pain relief in a small study of 4 patients with CPSP.¹⁰ One disadvantage of IV lignocaine is its often brief effect; in addition, a positive response does not necessarily predict a favourable response to oral mexiletine.

Mexiletine may have a role as an adjunct to TCAs in selected patients with CPSP when they do not respond to TCAs alone.² In an open-label study, pain improved in 8 of 9 CPSP patients treated with mexiletine 10 mg/kg/day for 4 weeks.¹¹ In general, mexiletine was well tolerated. However, the high doses required for response often give rise to tolerability issues that limit use.¹²

Any antihypertensive therapy should be discontinued 2 days before commencing mexiletine (400 mg orally, followed by 200 mg every 6 hours), but any antidepressants, such as TCAs, should be continued.² Blood pressure should be monitored during mexiletine therapy.

A 2005 review examined all randomized studies comparing lignocaine and mexiletine with placebo or active agents in patients with neuropathic pain of any aetiology.¹³ It found that local anaesthetics were superior to placebo in decreasing the intensity of neuropathic pain. No differences in efficacy or adverse event rates were found between lignocaine and mexiletine and amitriptyline, gabapentin or morphine.¹³

Intrathecal Baclofen

Intrathecal baclofen has been reported to relieve pain and allodynia in a small number of patients with central pain due to brain or spinal lesions.^{12,14} The data are largely limited to case reports and anecdotal evidence; however, intrathecal baclofen may be considered in CPSP patients who fail to respond to other recommended pharmacological therapies.

Opioids

Central pain appears to be poorly responsive, but not totally unresponsive, to opioids.¹⁵ Some pain relief was observed with IV morphine in a randomized, controlled trial involving 15 patients with CPSP (6 patients) or spinal cord injury-related pain (9 patients).¹⁶ Some patients may benefit from opioids when other pharmacological therapy fails, but few will benefit from long-term treatment, particularly in light of the prevalent side effects.

The Figure shows the treatment algorithm recommended by the MPNP to help guide the choice of pharmacological therapy for CPSP.

Non-pharmacological Management Surgery and Physical Stimulation

Surgical interventions can be considered for patients unresponsive to pharmacological therapy; however, these treatments may be associated with morbidity and mortality.

Stereotactic mesencephalic tractotomy has been used for a number of years to treat CPSP. Although a study has shown this intervention to provide long-term relief (67% of 24 patients), the mortality rate was 7.4%.¹⁷

Based on data from 159 cases of central pain secondary to ischaemic or haemorrhagic stroke, motor cortex stimulation (MCS) has a success rate of 52% (83/159 patients).¹⁸ More recently, a task force of the European Federation of Neurological Societies (EFNS)

concluded that there is level C evidence that MCS is useful in 50–60% of patients with CPSP, with low risk of medical complications.¹⁹ Thus, MCS should be considered as an alternative treatment of confirmed efficacy for patients with severe, refractory CPSP.²⁰

Psychological Treatment

Early cognitive behavioural therapy (CBT) and other psychological treatment approaches may be beneficial in many types of chronic pain, including CPSP. CBT can help to modify negative thoughts related to pain and teach coping strategies for residual pain. This can help patients to increase their activity level and functioning which, in turn, can help improve mood, sleep and quality of life. Psychological interventions should be used as part of the multidisciplinary approach to pain management, in concert with pharmacotherapy or surgical treatment.

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DRUGS FOR THE TREATMENT OF NEUROPATHIC PAIN

Continuing our series on drugs for the treatment of neuropathic pain, Part 6 of the series reviews evidence for non-steroidal anti-inflammatory drugs in neuropathic pain.

Part 6 – Non-steroidal anti-inflammatory drugs

Non-steroidal anti-inflammatory drugs (NSAIDs), including cyclooxygenase 2 (COX-2) inhibitors, are well established in the treatment of nociceptive pain. However, NSAIDs are considered of limited use in the treatment of neuropathic pain.^{1,2} Reviews by Galluzzi in 2005, and Gilron and colleagues in 2006, found that NSAIDs are usually ineffective in pure neuropathic pain,^{1,2} but may have a role in treating coexistent nociceptive conditions (eg, sciatica with musculoskeletal low-back pain).²

These review findings are also reflected in the expert consensus of existing neuropathic pain guidelines, none of which include traditional NSAIDs or COX-2 inhibitors in treatment recommendations.³⁻⁵ Despite the availability of these evidence-based guidelines, studies have shown that patients with neuropathic pain are often managed

with conventional analgesics, including NSAIDs, rather than agents recommended for neuropathic pain, such as TCAs.^{6,7} One study found that 1 in 4 neuropathic pain patients had never been prescribed an antineuropathic drug.⁷

NSAIDs are of limited benefit to patients suffering from neuropathic pain, and it appears that awareness of existing evidence-based guidelines needs to be augmented to improve the management of neuropathic pain.

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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 physical therapy in the treatment of neuropathic pain?

Physical therapy plays an adjunctive role to pharmacological treatment in some neuropathic pain conditions, particularly complex regional pain syndrome (CRPS)^{1,2} and fibromyalgia.³ The goals of physical therapy in neuropathic pain include strengthening, increased range of motion and vocational rehabilitation.² Most of the literature on physical therapy in neuropathic pain focuses on CRPS, so this discussion

will be limited to this syndrome.

The MPNP considers an early programme of physical and occupational therapy essential to treat the secondary complications of CRPS, such as decreased joint and tendon movement. This approach will eventually improve pain control and mobility.¹ Immobilization and overprotection of affected limbs can cause or exacerbate a variety

of problems in CRPS patients, including vasomotor changes and oedema.⁴ Loss of muscle tone can lead to back instability and tight, painful joints.⁵ Physical therapy should be introduced gradually beginning with gentle desensitization, including various combinations of heat and cold, and massage; it can then progress, as tolerated, to gentle flexibility and isometric strengthening exercises. With improvement, range-of-motion exercises, stress loading, isotonic strengthening and general aerobic conditioning can be added. It is essential that adequate pain control be maintained throughout.⁶ As patients increase their activity levels, they may initially request more pain

medication. Tailoring pain relief to permit physical therapy and renewed activity will ultimately help achieve the primary purpose of pain treatment, which is the resumption of a more normal lifestyle and restoration of quality of life.⁵

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LITERATURE REVIEW

Vranken JH, Dijkstra MGW, Kruis MR, et al. Pregabalin in patients with central neuropathic pain: a randomized, double-blind, placebo-controlled trial of a flexible-dose regimen. Pain 2008;136:150-157.

Despite a variety of treatment options, including antidepressants, anticonvulsants and opioids, some patients with central neuropathic pain remain inadequately treated, and many patients experience bothersome side effects. Additional effective, well-tolerated treatments are needed. The efficacy of pregabalin in various peripheral neuropathic pain syndromes has been clearly established. Combined with its favourable safety profile, this has led to investigation of its potential in alleviating central neuropathic pain. This trial, conducted in 2006, evaluated the effects of pregabalin on pain relief, tolerability, health status and quality of life in patients with severe central neuropathic pain caused by brain (n=19) or spinal cord injuries (n=21). Patients were randomized to receive placebo or escalating doses of pregabalin (150, 300 and 600

mg/day) for 4 weeks. At the end of the treatment period, there was a statistically significant reduction in mean pain score in the pregabalin group compared with the placebo group (p=0.016). Improvements in health status were also statistically significant in the pregabalin group (p<0.001 vs placebo). Favourable effects on SF36 domain scores were observed in the pregabalin group, although not all improvements reached statistical significance. Pregabalin treatment was generally well tolerated, with a similar incidence of side effects to the placebo group. This study used a dosing strategy that mirrors real-life clinical use, in which the dose is titrated to achieve optimal efficacy and tolerability for each patient. Thus, the study further supports the utility of pregabalin as an effective and well-tolerated treatment for central neuropathic pain.

CASE PRESENTATION

A woman with neuromyelitis optica subsequently develops central neuropathic pain symptoms.

Neuromyelitis optica

History

A 47-year-old Chinese female presented with a 2-day history of progressive weakness and numbness affecting both legs. She had a history of idiopathic left optic neuritis occurring 3 months earlier.

Physical examination and investigations

Examination showed a spastic paraparesis with power grading of 1/5 and bilateral up-going plantars. A sensory level was elicited at the umbilicus. Examinations of the upper limbs, cerebellar system and cranial nerves were unremarkable.

An urgent MRI spine revealed a gadolinium-enhanced T2 hyperintense lesion extending from T4 down to T10. Brain MRI and cerebrospinal fluid analyses were normal. Other investigations, including vitamin B₁₂ level, antinuclear antigen and viral serology, were all normal.

Management and progress

A course of IV steroid pulse therapy was prescribed. Although leg power improved over subsequent weeks, severe "burning" pain developed over the limbs, which was associated with frequent episodes of painful tonic spasms (around 30 seconds duration each). A trial of carbamazepine reduced both central neuropathic pain and spasms, but caused excessive sleepiness. Switching to pregabalin eventually controlled both pain and spasms, with acceptable tolerability.

Discussion

This woman suffered from neuromyelitis optica (or Devic's disease), which is considered a variant of multiple sclerosis and affects more Asians than Caucasians. It preferentially affects the optic nerve and spinal cord. Central neuropathic pain is a common sequelae after spinal cord myelitis. Other related pain syndromes include paroxysmal painful tonic spasm and Lhermitte's symptom (spinal or limb dysaesthesia caused by neck flexion). TCAs or antiepileptic drugs are first-line agents for central neuropathic pain, but if this occurs with painful tonic spasm, antiepileptic drugs may be the drugs of first choice.

Source: MPNP members

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