



Challenges in Neuropathic Pain

The 16th issue of *Challenges in Neuropathic Pain* contains a summary of updated recommendations on the management of complex regional pain syndrome (CRPS) developed by the Multidisciplinary Panel on Neuropathic Pain (MPNP). The role of intravenous drugs in treating neuropathic pain is assessed in Part 7 of the series on drugs for neuropathic pain, and the Q&A looks at whether there is a place for occupational therapy in the management of neuropathic pain. Also in this issue are a short summary of a recent review paper on pregabalin for fibromyalgia, and a case presentation of paroxysmal extreme pain disorder, a rare inherited neuropathic pain condition. 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 complex regional pain syndrome

This article presents a summary of the updated recommendations developed by the Multidisciplinary Panel on Neuropathic Pain (MPNP) for the management of complex regional pain syndrome (CRPS). The full version of these recommendations is available at the MPNP Web site – www.neuropainhk.org.

There is a paucity of published evidence for drug efficacy in CRPS. Where possible, recommendations are based on data from trials in CRPS patients; however, some of the evidence is derived from patients with other neuropathies. Some of the pharmaceutical agents mentioned are not licensed for use in any type of neuropathic pain. Full prescribing information should be consulted before initiating any drug therapy.

INTRODUCTION

CRPS is an uncommon and poorly understood neuropathy that normally affects the limbs. The condition is characterized by pain and altered sensation, motor dysfunction and soft tissue change, vasomotor and autonomic alterations, and psychosocial disturbance.¹

Women are more likely to develop CRPS than men. CRPS most commonly occurs between the ages of 40 and 60 years. It has been suggested that mild CRPS occurs in up to 30–40% of fractures and surgical trauma; severe chronic CRPS, however, is uncommon, with a prevalence of about 2% in most retrospective series.² No precipitating cause can be identified in 10–26% of cases.^{3,4}

CRPS is classified by the International Association for the Study of Pain (IASP) as⁵:

- CRPS type I: occurs after minor injury that may be unnoticed by the patient, and without an obvious associated nerve injury.
- CRPS type II: associated with an identifiable nerve injury, often following trauma or surgery.

Signs and symptoms of CRPS (see Box) progress if left untreated, and the patient may experience debilitating pain, muscle atrophy and permanent joint and skin damage with advanced disease. Psychological disturbances such as anxiety, depression and fear-avoidance often accompany CRPS.

Box. Signs and/or symptoms of CRPS⁵

Pain

Burning or aching pain in the affected limb
Hyperaesthesia, hyperalgesia and allodynia

Autonomic dysfunction

Changes in skin temperature and colour
Changes in sweating patterns
Oedema

Trophic changes

Thin, shiny skin
Thickened nails
Coarse hair
Muscle wasting

Motor dysfunction

Weakness, tremor or dystonia
Exaggerated tendon reflexes
Decreased range of motion

DIAGNOSIS

The diagnosis of CRPS is often complicated by variations in presenting symptoms and the difficulty in identifying causative lesions. CRPS types I and II may or may not be associated with sympathetic-maintained pain (SMP). In 2003, an IASP consensus workgroup endorsed a set of Proposed Clinical Diagnostic Criteria for use in discriminating CRPS from other types of neuropathic pain in a patient management context⁶:

1. Continuing pain that is disproportionate to any inciting event
2. The patient must report at least one symptom in at least three of the four categories below:
 - *Sensory*: Reports of hyperaesthesia
 - *Vasomotor*: Reports of temperature asymmetry and/or skin colour changes and/or skin colour asymmetry
 - *Sudomotor/oedema*: Reports of oedema and/or sweating changes and/or sweating asymmetry
 - *Motor/trophic*: Reports of decreased range of motion and/or motor dysfunction (weakness/tremor/dystonia) and/or trophic changes (hair, nails, skin)
3. The patient must display at least one sign in two or more of the four categories below:
 - *Sensory*: Evidence of hyperalgesia (to pinprick) and/or allodynia (to light touch)
 - *Vasomotor*: Evidence of temperature asymmetry and/or skin colour changes and/or skin colour asymmetry
 - *Sudomotor/oedema*: Evidence of oedema and/or sweating changes and/or sweating asymmetry
 - *Motor/trophic*: Evidence of decreased range of motion and/or motor dysfunction (weakness, tremor, dystonia) and/or trophic changes (hair, nail, skin)

MANAGEMENT

Early identification of at-risk patients may prevent progression of CRPS and worsening of signs and symptoms. The goals of treatment are to relieve pain, promote rehabilitation and restore motor function. Patients should be referred as soon as possible to pain specialists or physicians with experience in managing CRPS; outcome is improved if treatment is started at an earlier stage.

In cases of CRPS associated with trauma, surgical restoration is beneficial (eg, decompression of a compromised neural structure) and, when appropriate, should be performed immediately.

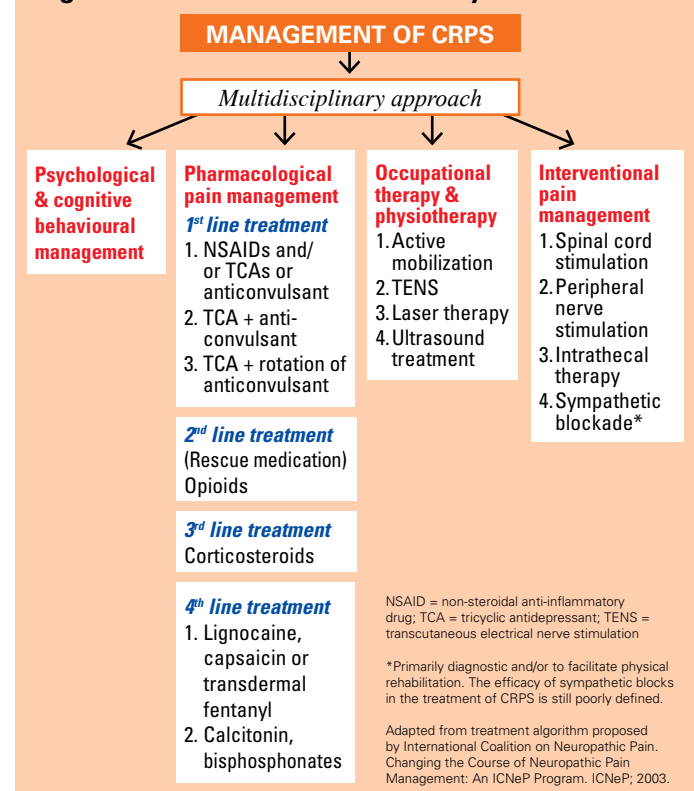
Most children with recent-onset CRPS will improve spontaneously and need conservative management only. In adults, a holistic programme combining both pharmacological and nonpharmacological techniques may achieve remission. The Rehabilitation Pathway

provides a stepwise approach that combines different modalities to optimize CRPS management (Figure).

Treatment guidelines

- An early programme of physical and occupational therapy, especially for at-risk patients, is essential to treat the secondary complications of CRPS, such as decreased joint and tendon movement. This will improve pain control and mobility.
- Psychological support and cognitive behavioural management programmes can help patients manage their pain, and reduce depression and dependence on health care.
- For CRPS patients with SMP, sympathetic blocks are effective pain-relief techniques to facilitate physical rehabilitation. However, the efficacy of sympathetic blocks in the treatment of CRPS remains poorly defined.^{2,7}
- Whenever appropriate, anti-inflammatory medications, including NSAIDs that have significant activity against bradykinin and prostacyclin (eg, ketoprofen), are useful in the acute phase following injury to minimize pain and swelling.^{8,9} Cyclooxygenase-2 selective inhibitors have not been evaluated in CRPS.
- Primary pain management should include tricyclic antidepressants (TCAs, eg, amitriptyline)^{10,11} or anticonvulsants (eg, gabapentin, pregabalin). Side effects from TCAs occur commonly; therefore, TCAs may not be suitable for patients who tolerate them poorly. Trials of gabapentin in CRPS show benefits in terms of pain relief, quality of life and CRPS-associated sensory deficits relative to placebo.^{12,13} Adverse effects of gabapentin are tolerable and mostly transient, occurring during the titration phase.¹² In a recent study, pregabalin produced clinically significant reductions in pain and improvements in health status, and was well tolerated in patients with central neuropathic pain.¹⁴ Slow dosage titration (up to 8 weeks) can help to minimize side effects of both TCAs and anticonvulsants; pain relief may not be apparent for 3 weeks at the maximum tolerated dosage. Older anticonvulsants (eg, phenytoin, carbamazepine) lack convincing evidence of effectiveness in CRPS.¹⁵⁻¹⁷

Figure. The Rehabilitation Pathway



- When the response to TCAs and anticonvulsants is unsatisfactory, a trial of combined TCA and anticonvulsant may be effective.
- Although opioids lack sound evidence of benefit for CRPS, a literature review recommended their addition to ongoing treatment regimens if initial medications do not provide sufficient analgesia, especially if the persistent pain prevents patients from undergoing physical therapy.¹⁸ Use of opioids as rescue therapy should only be short-term.
- The anti-inflammatory effect of corticosteroids can also be particularly useful in the acute phases of CRPS.¹⁹ The efficacy of long-term corticosteroid therapy is also established, but longer courses may have a questionable risk-benefit ratio.^{8,20} In addition to anti-inflammatory effects, corticosteroid therapy may also stimulate the endogenous opioid system and, thus, may further enhance analgesia.²¹
- Fourth-line pharmacological treatments include subcutaneous or intravenous lignocaine infusion,^{22,23} topical capsaicin²⁰ and possibly transdermal fentanyl.²⁴ Calcitonin and bisphosphonates may also help control pain in CRPS.
- For patients remaining refractory to trials of pharmacotherapy and physiotherapy, invasive procedures can be considered. Neurostimulation of the spinal cord^{25,26} or peripheral nerves may

be effective; however, there is no evidence it improves long-term prognosis. Continuous epidural infusions of local anaesthetics, clonidine and opioids have been reported to be effective in patients with intractable CRPS,^{27,28} although their use has been falling.⁷ These interventions should be considered only as a last resort in complicated, resistant CRPS cases.

- Destructive or ablative surgery is not recommended and only has a limited role in providing relief for patients with a short life expectancy.

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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 7 discusses the use of intravenously administered agents in neuropathic pain conditions.

Part 7 – Intravenous agents

Given the chronic nature of neuropathic pain, self-administered oral agents providing effective pain relief over the long term are central to management. Drugs administered intravenously are obviously less convenient and are usually only administered by pain medicine specialists as adjunctive agents when pain is not controlled by first- or second-line oral medications, or when patients are unable to take oral preparations.

Intravenous (IV) lignocaine has been used with some success in painful diabetic neuropathy,¹ complex regional pain syndrome (CRPS)² and central post-stroke pain (CPSP).^{3,4} It may also have an adjunctive role in cancer-related neuropathic pain,⁵ although a systematic review found that IV lignocaine was effective in non-cancer neuropathic pain, but had no effect on cancer-related pain.⁶ However, lignocaine infusions rarely provide relief that persists significantly beyond the duration of infusion.⁷

Another IV agent, ketamine, has shown analgesic effects in clinical

studies of neuropathic pain associated with cancer^{8,9} and spinal cord injury.¹⁰⁻¹² However, ketamine is associated with disturbing side effects and should only be administered by experienced pain management teams under strict monitoring for side effects.⁹

Oral opioids are increasingly appearing as second- or third-line treatment options in neuropathic pain management algorithms, and there are data to suggest that IV opioids (ie, morphine) may help some patients with intractable or breakthrough neuropathic pain associated with CPSP and spinal cord pathologies.¹³

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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 occupational therapy in the treatment of neuropathic pain?

Patients who experience chronic neuropathic pain may often have reduced functional capacity that adversely affects their ability to perform usual activities of daily living. In such patients, treatment needs to achieve both pain management and functional restoration.¹ As medical treatments for neuropathic pain may be only partially successful in eliminating or significantly reducing the degree of pain, multidisciplinary pain management programmes are critical to address

the emotional, social and vocational sequelae of chronic pain.¹

Little published data exist on the use of occupational therapy in neuropathic pain patients; it is most commonly mentioned as part of the multidisciplinary management of complex regional pain syndrome (CRPS).^{1,2} Ghai and Dureja observe that no one therapeutic modality achieves all treatment goals of pain relief, functional recovery and psychological improvement in CRPS.² However, they note that close

collaboration amongst multiple disciplines, including psychologists, physical and occupational therapists, oncologists, neurologists and pain medicine consultants, may help to achieve optimal treatment effects. In a 1998 review, Harden and Cole suggest that occupational therapy should be a primary modality in treating compression-related neuropathies, and have a prominent role in CRPS.¹ Rehabilitation of patients with CRPS with occupational therapy may involve desensitization and stress loading, and gentle active range-of-

motion and stretching exercises to increase flexibility.^{1,3} Occupational therapists can also assess and suggest improvements or modifications to workplace ergonomics, sleep postures and body mechanics to help increase patients' functional capacity at work and at home.¹

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LITERATURE REVIEW

Lyseng-Williamson KA, Siddiqui MAA. Pregabalin: a review of its use in fibromyalgia. Drugs 2008;68:2205-2223.

This Adis drug evaluation reviews the published medical literature on pregabalin in fibromyalgia from 1980 to September 8, 2008. Pregabalin, a calcium channel $\alpha 2\delta$ -subunit ligand with analgesic, anxiolytic and antiepileptic activity, was the first agent to be approved by the US Food and Drug Administration (FDA) for treatment of fibromyalgia.

The review briefly describes fibromyalgia, and provides an overview of the pharmacological properties of pregabalin, including its mechanism of action, pharmacokinetic properties and potential drug interactions. The data presented on the therapeutic efficacy of oral pregabalin in fibromyalgia are largely based on four placebo-controlled trials conducted in the USA: three short-term trials (duration 8 to 14 weeks) and one longer-term study (26 weeks). These data show that, as monotherapy, pregabalin rapidly and effectively

relieves pain in patients with long-standing fibromyalgia and moderate to severe pain levels. In addition, improvements in several sleep parameters and overall health status have been observed. Like other chronic pain conditions, fibromyalgia has been strongly associated with symptoms of anxiety and depression; importantly, pregabalin provides effective pain relief regardless of whether patients have these comorbidities. In clinical trials, adverse events of mostly mild to moderate intensity were frequently reported with pregabalin, but many patients found these tolerable and did not discontinue treatment. The most common adverse events associated with the drug are dizziness and somnolence.

The reviewers conclude that pregabalin is a valuable option in the first-line treatment of patients with fibromyalgia.

CASE PRESENTATION

In this issue, a case of familial neuropathic pain disorder is presented.

Paroxysmal extreme pain disorder

Presenting symptoms

A 46-year-old Chinese male presented from birth with a familial problem of recurrent attacks of pain, swelling and redness over the lower half of the body, triggered by stimulus below the umbilicus. Almost any sensory stimulus, ranging from minor trauma to straining at defecation due to constipation, can provoke an attack upon reaching a certain threshold.

Although the majority of affected members of his family are male, female family members are not untouched. One of the patient's sons has a similar problem.

Management and progress

Investigations, including electroencephalogram and magnetic resonance imaging of the spine, were all normal. He has tried many medications. The painful attacks were controlled by oral midazolam and sublingual buprenorphine, although the onset of action was rather slow. Nasal butorphanol had good effects but is no longer available locally. He has also tried prophylactic anticonvulsants but side effects were intolerable. By taking care to avoid injury and excessive stimulation, he is able to limit the attacks to about one a year.

Discussion

The patient suffers from a familial disorder with autosomal dominant inheritance. First described in 1959,¹ it was initially named 'familial rectal pain'. However, as pain also involves the lower limbs and sometimes the face and eyes, it was renamed 'paroxysmal extreme pain disorder'

(PEPD) in 2005. Genetic linkage studies have shown that PEPD is caused by mutations in the SCN9A gene, which encodes an α -subunit of the voltage-gated sodium channel Na_v1.7. (Paradoxically, a different set of SCN9A mutations causes channelopathy-associated insensitivity to pain [CIP], a congenital inability to perceive any form of pain.)

Treatment of this condition is difficult. A variety of drugs with analgesic or antiepileptic properties have been tried, with inconsistent results. It is hoped that the recognition of sodium channelopathy will lead to development of more targeted pharmacotherapy.²

Source: Dr Steven Wong, MPNP member

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