Recommendations for the Management of Complex Regional Pain Syndrome

The Multidisciplinary Panel on Neuropathic Pain*

I. Pathophysiology, Prevalence and Symptoms

Complex regional pain syndrome (CRPS), previously referred to as reflex sympathetic dystrophy, causalgia, algodystrophy, Sudeck’s atrophy and shoulder-hand syndrome, is an uncommon and poorly understood neuropathy that normally affects the limbs. CRPS 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 can affect all age groups, but most commonly occurs between the ages of 40 and 60 years. It has been reported that CRPS occurs in 1% to 2% of postfracture patients and after peripheral nerve injury in 2% to 5% of patients.2 No precipitating cause can be identified in 10% to 26% of cases.2,3

The International Association for the Study of Pain (IASP) has developed the following classifications for CRPS4:

- CRPS type I occurs after minor injury that may be unnoticed by the patient.
There may not be any obvious associated nerve injury. Type I nerve lesions are undetected because they are partial, or predominantly affect unmyelinated axons.

- CRPS type II is associated with an identifiable nerve injury, often following trauma or surgery.

CRPS is attributed to both peripheral and central mechanisms. Peripherally, \( \alpha \)-receptor upregulation and neurotransmitter release may increase sensitivity to sympathetic stimulation, while persistent inflammation may lead to continuous stimulation and hyperexcitability. Central neuronal sensitization, maintained by N-methyl-D-aspartate (NMDA)-receptor activation, also contributes to post-injury pain hypersensitivity.

The following are signs and/or symptoms of CRPS:
- 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; and
- Motor dysfunction: weakness, tremor or dystonia; decreased range of motion.

Signs and symptoms 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.

II. 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). Patient evaluation should include:

- Review of medical history, including onset of CRPS symptoms, associated injury and details of pain patterns to differentiate the neuropathic features;
- Physical examination of skin, nails, muscles and joints to reveal any trophic and sudomotor changes and to determine the site of pain;
- Neurological examination to assess and exclude reversible neurological pathology; electrodiagnostic testing may be necessary;
- Bone scintigraphy or x-ray to identify any bone changes;
- Thermography, to detect changes in blood flow and skin temperature; and
- Sudomotor evaluation measuring sweat output may be helpful.

In 1994, the International Association for the Study of Pain (IASP) published consensus-based diagnostic criteria for CRPS. The criteria for the diagnosis of CRPS type 1 are as follows:

1. The presence of an initiating noxious event or a cause of immobilization. For CRPS type II, a known nerve injury should be present.
2. Continuing pain, allodynia or hyperalgesia disproportionate to the injury's severity.
3. Evidence at some time of oedema, changes in skin blood flow or abnormal sudomotor activity in the region of pain.
4. CRPS is excluded by the presence of conditions that would otherwise account for the degree of pain or dysfunction.

A validation study of the IASP criteria, however, indicated significant overdiagnosis of CRPS and proposed a set of more specific diagnostic criteria. These modified criteria, set out in Table 1, discriminate between CRPS and other types of neuropathic pain.

### Table 1. Modified diagnostic criteria for CRPS

1. Continuing pain that is disproportionate to any inciting event;
2. The patient must report at least one symptom in each of the four categories below; and
3. The patient must display at least one sign in two or more of the four categories below.

<table>
<thead>
<tr>
<th>Sensory</th>
<th>Hyperalgesia and/or allodynia</th>
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<tbody>
<tr>
<td>Vasomotor</td>
<td>Temperature asymmetry; and/or skin colour changes and/or asymmetry</td>
</tr>
<tr>
<td>Sudomotor/oedema</td>
<td>Oedema and/or sweating changes and/or sweating asymmetry</td>
</tr>
<tr>
<td>Motor/trophic</td>
<td>Decreased range of motion and/or motor dysfunction (weakness, tremor, dystonia) and/or trophic changes (hair, nail, skin)</td>
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III. Management

Early identification of at-risk patients (e.g. injury type, presence of anxiety or depression) can prevent progression of CPRS and worsening of CRPS signs and symptoms. The goals of treatment are to 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 (e.g. 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 in Figure 1 provides a stepwise approach that combines different modalities to optimize CRPS management.

Guidelines for the Management of CRPS

• 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 patients with SMP, sympathetic blocks are effective pain-relief techniques to facilitate physical rehabilitation.
• Whenever appropriate, anti-inflammatory medications are useful in the acute phase following injury to minimize pain and swelling.
• Primary pain management should include tricyclic antidepressants (TCAs, e.g. amitriptyline) or anticonvulsants (e.g. gabapentin, carbamazepine, phenytoin). Slow dosage titration (up to 8 weeks) is necessary to minimize side effects of both TCAs and anticonvulsants; pain relief may not be apparent for 3 weeks at the maximum tolerated dosage.
• When the response to TCAs and anticonvulsants is unsatisfactory, a trial of combined TCA and anticonvulsant may be effective.
• Rescue therapy with opioids may be necessary, but this should only be used for short-term treatment.
• For patients remaining refractory to trials of pharmacotherapy and physiotherapy, invasive procedures can be considered. Neurostimulation of the spinal cord or peripheral nerves may be effective; however, there is no evidence it improves long-term prognosis. Destructive or ablative surgery is not recommended and only has a limited role in providing relief for patients with a short life expectancy.

IV. Appendix on Evidence-based Management of CRPS

Pharmacological Management
Published evidence for drug efficacy in CRPS is lacking; however, the drugs mentioned in these recommendations are effective in a variety of neuropathic pain syndromes. Where appropriate, trials using CRPS patients have been described below; however, some of the evidence is derived from patients with other neuropathies. Some agents are not licensed for use in any type of neuropathic pain. Full prescribing information should be consulted before initiating therapy.

1. Nonsteroidal Anti-inflammatory Drugs
As persistent inflammation is implicated in the development of CRPS, anti-inflammatory drugs may have a role in the early management of CRPS, particularly in cases where there is considerable inflammation. However, clinical trial data on the benefit of NSAIDs for CRPS is lacking. A critical literature review suggested that NSAIDs have significant activity against bradykinin and prostacyclin (e.g. ketoprofen) may be more useful than those with conventional antiprostaglandin effects. Cyclooxygenase-2 selective inhibitors have not been evaluated in CRPS.

2. Gabapentin and Other Anticonvulsants
Gabapentin is approved for use in all neuropathic pain conditions based on evidence from randomized, placebo-controlled trials primarily in patients with painful diabetic neuropathy (PDN) and postherpetic neuralgia (PHN). Patients with painful diabetic neuropathy (PDN) and postherpetic neuralgia (PHN) have also been managed successfully with gabapentin.

To demonstrate further its applicability to other neuropathies, a randomized, double-blind, placebo-controlled study examined the safety and efficacy of gabapentin in a wide variety of neuropathic pain syndromes. Patients were selected on the basis of specific symptoms, rather than specific syndromes, to reflect the realities of clinical practice. Of the 305 patients included in the study, 28% had been diagnosed with CRPS. Gabapentin was administered at 900 mg/day (titrated up over 3 days) for 5 weeks, with escalation to 1,800 or 2,400 mg/day, as required. After 8 weeks, patients...
PAIN MANAGEMENT

MANAGEMENT OF CRPS

Multidisciplinary approach

Psychological and cognitive behavioural management

Pain management

Occupational therapy

Interventional pain management

1. TENS
2. Laser therapy
3. Ultrasound treatment

1st line treatment
1. NSAIDs and/or
2. TCAs or anticonvulsant (e.g. gabapentin)
3. TCA + anticonvulsant
4. TCA + rotation of anticonvulsant

Physiotherapy

2nd line treatment (rescue medication)
Opoids

3rd line treatment
Corticosteroids

4th line treatment
1. Lignocaine, capsaicin or transdermal fentanyl
2. Calcitonin, bisphosphonates

Sympathetic blocks:
1. Ganglion sympathetic block
2. IV sympathetic block
3. IV regional sympathetic block

Neurosurgical management:
1. Spinal cord stimulation
2. Peripheral nerve stimulation
3. Intrathecal therapy

NSAID = nonsteroidal anti-inflammatory drug; SMP = sympathetic-maintained pain; TCA = tricyclic antidepressant; TENS = transcutaneous electrical nerve stimulation
Adapted from Ref. 13.
treated with gabapentin had a 21% decrease in the average daily pain diary score, compared with 14% in the placebo group (p=0.048). Significant improvements with gabapentin were also seen in the Clinician and Patient Global Impression of Change (p<0.05) and in some domains of the Short-Form-36 Health Survey, also improved for patients treated with gabapentin.

In addition, a double-blind, randomized, placebo-controlled crossover trial with two 3-week treatment periods separated by a 2-week washout period examined the efficacy of gabapentin (up-titrated to 600 mg t.i.d.) in CRPS I patients (n=58). Using a visual analogue scale (VAS), there was a significant pain relief in favour of gabapentin in the first period. Using a point-seven scale to determine global perceived effect on pain, significantly more gabapentin-patients experienced pain relief compared with placebo (43% vs. 17%, p=0.002). Gabapentin therapy also significantly reduced CRPS-associated sensory deficits in the affected limb (measured as Von Frey monofilament skin application scores) more effectively than placebo (25.0 vs. 16.8, p=0.027).

Adverse effects of gabapentin are tolerable and mostly transient, occurring during the titration phase. The most commonly reported adverse events are dizziness and somnolence. Gabapentin has a more acceptable side effect profile than the older anticonvulsants, such as phenytoin and carbamazepine.

The theoretical benefit of older anticonvulsants for CRPS has not been demonstrated in clinical trials. Phenytoin was the first anticonvulsant to be used as an antinociceptive agent, but there is no sound evidence for its efficacy in relieving neuropathic pain. Clinical trials support the use of carbamazepine in the treatment of trigeminal neuralgia and PDN, but evidence of its efficacy in CRPS, PHN, phantom limb pain and other neuropathic conditions is limited.

5. Corticosteroids
The anti-inflammatory effect of corticosteroids can also be particularly useful in the acute phases of CRPS. A prospective study on 36 hemiplegic poststroke patients who developed shoulder-hand syndrome revealed low-dose corticosteroid therapy given within 2 to 3 months of the neurologic insult could relieve CRPS. Of the 36 patients, 31 (86.1%) were almost symptom-free after 10 days of oral corticosteroid therapy. The efficacy of long-term corticosteroid therapy is also established, but longer courses may have a questionable risk-benefit ratio. However, a 12-week treatment using oral prednisone 10 mg t.i.d. produced a 75% clinical improvement in patients diagnosed with reflex dystrophy syndrome, according to a small randomized, placebo-controlled study.

Furthermore, plasma metenkephalin levels were increased in CRPS patients after 2 weeks of steroid therapy, suggesting that, in addition to its anti-inflammatory effects, corticosteroid therapy may also have a stimulatory action on the endogenous opioid system and, thus, may further enhance analgesia.

6. Lignocaine, Capsaicin and Topical Fentanyl
A case report on nine CRPS patients treated with continuous 4- to 8-week subcutaneous infusion of 10% lignocaine indicated significant alleviation of pain, dysaesthesia, allodynia, hyperpathia, skin colour and temperature changes, decreased range of motion of involved extremities and ongoing treatment regimens if the initial medications do not provide sufficient analgesia, especially if the persistent pain prevents patients from undergoing physical therapy.
changes in hair and nail growth. However, in many cases, the duration of effect is brief. Moreover, there is no oral preparation for lignocaine. Mexiletine, despite having pharmacological properties similar to lignocaine, has no evidence of efficacy in CRPS.

Capsaicin 5% to 10% may be effective for CRPS - 90% of patients achieved substantial analgesia lasting 1 to 18 weeks in a study on 10 patients with CRPS and other neuropathic pain syndromes. A meta-analysis also showed the pooled odds ratio for benefit from capsaicin was 2.35. However, the use of capsaicin is limited due to its messy application and the associated intolerable burning pain.

According to a 12-month multicentre, open-label trial, transdermal fentanyl (TDF) is effective as long-term treatment for moderate-to-severe chronic noncancer pain, possibly including CRPS. Using a mean dose of 48 to 90 µg/hour, 67% of patients reported substantial pain control with TDF. Forty-two percent reported either good or very good global satisfaction and 86% reported a preference for TDF over their previous treatment (p<0.001, binomial test).

7. Calcitonin and bisphosphonates
Calcitonin and bisphosphonates can control pain in patients with early CRPS, but the mechanism is not yet understood. In a study in which patients were administered 300 IU calcitonin within 8 to 10 weeks of CRPS onset, pain relief and improved range of motion were reported. However, another study did not show any benefit of calcitonin after removal of cases for Colles' fracture. Intravenous pamidronate and clodronate have also demonstrated pain relief in some studies.

Procedures
1. Sympathetic Blocks
The efficacy of sympathetic blocks in the treatment of CRPS is poorly defined. A systematic review of the literature found 29 studies that evaluated 1,144 patients (19 retrospective, 5 prospective case series, 3 randomized and 2 nonrandomized controlled studies). Twenty-nine percent of patients achieved a full response and 41% achieved a partial response, while 32% did not respond. The authors concluded that the evidence supporting the use of sympathetic blocks in CRPS is poor. It is possible that sympathectomy may selectively show more effective pain relief in patients with SMP, thus facilitating physical rehabilitation.

Procedures commonly used for sympathetic blockade are sympathetic ganglion blocks (e.g. stellate ganglion block and lumbar sympathetic block), IV sympathetic blocks (e.g. IV phentolamine and IV lignocaine infusions, IV regional sympathetic block with guanethidine or bretylium and subcutaneous lignocaine). Pain management specialists usually perform these procedures; however, they tend to be used more for diagnosis, as the response is often brief. In some cases, effects may persist for longer periods and provide therapeutic benefit.

2. Spinal-cord Stimulation
When the pain of CRPS is refractory to usual pharmacological treatment and conservative pain management procedures, spinal-cord stimulation (SCS), implantable intrathecal drug delivery systems or peripheral nerve stimulation may also be considered. Severe pain, which may hinder physical rehabilitation and result in long-term functional disability, may be more effectively controlled through these methods and facilitate functional recovery.

A recent literature review showed that SCS is effective in the management of CRPS; most studies reported success rates of between 60% and 91%. However, the review noted that many of the studies on CRPS have poor methodological quality. When considering this procedure, a thorough medical and psychological assessment should be performed to ensure optimal patient selection for favourable outcomes.

3. Intrathecal Drug Administration Systems
Long-term intraspinal morphine administration has been reported to be effective in patients with intractable CRPS. As in SCS, a thorough medical and psychological assessment should be performed to ensure optimal patient selection when considering intrathecal morphine administration.

4. Neuroablation
Neurolytic or surgical sympathectomy may be considered when diagnostic sympathectomy shows a brief but favourable response. However, the role of these procedures is not clear, thus these procedures are not recommended. Although some improvement is often achieved in the short term, the risks associated with...
more invasive and destructive procedures often outweigh their benefits. Ablative and destructive procedures may be more appropriate to relieve pain in patients with terminal cancer who have short life expectancy.

References