Recommendations for the Management of CRPS

The Multidisciplinary Panel on Neuropathic Pain

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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 neuropathy that normally affects the limbs. According to L Turner-Stokes, 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, with a ratio of 2–3:1.² CRPS can affect all age groups, but 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 rare, with a prevalence of about 2% in retrospective series.³ While CRPS can be caused by trauma to the limbs, the condition is most commonly associated with surgery involving the extremities, such as carpal tunnel release, Dupuytren contracture release, knee surgery, amputation, hip
arthroplasty and arthroscopy. CRPS has also been associated with excessively tight casts. In general, the upper limbs are more likely to be involved than the lower limbs. No precipitating cause can be identified in 10% to 26% of cases.

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

- CRPS type 1 occurs after an initiating noxious event, but with no demonstrable nerve lesions.
- CRPS type 2 is associated with an identifiable nerve injury, often following trauma or surgery.

CRPS is attributed to both peripheral and central mechanisms. Peripherally, alpha receptor up-regulation 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.

**Signs and Symptoms of CRPS**

Signs and symptoms (Table 1) 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.

**Diagnosis**

The diagnosis of CRPS is often complicated by variations in presenting symptoms and the difficulty in identifying causative lesions. CRPS types 1 and 2 may or may not be associated with sympathetic maintained pain (SMP). Patient evaluation should include the following:

- 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.
- Sudomotor evaluation measuring sweat output may be helpful.

In 1994, the 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 2, 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 below, discriminate between CRPS and other types of neuropathic pain:

1. Continuing pain, which is disproportionate to any inciting event.
2. Patients must report at least one symptom in three of the four categories below.
   - Sensory: Reports of hyperaesthesia and/or allodynia.
   - 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, nail, skin).

### Table 1. Signs and symptoms of CRPS

<table>
<thead>
<tr>
<th>Symptom Type</th>
<th>Signs and Symptoms</th>
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<tbody>
<tr>
<td>Pain</td>
<td>Burning or aching pain in the affected limb, hyperaesthesia, hyperalgesia and allodynia</td>
</tr>
<tr>
<td>Autonomic dysfunction</td>
<td>Changes in skin temperature and colour, changes in sweating patterns, oedema</td>
</tr>
<tr>
<td>Trophic changes</td>
<td>Thin, shiny skin, thickened nails, coarse hair, muscle wasting</td>
</tr>
<tr>
<td>Motor dysfunction</td>
<td>Weakness, tremor or dystonia, exaggerated tendon reflexes, decreased range of motion</td>
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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 and/or deep somatic pressure and/or joint movement).
- Vasomotor: Evidence of temperature asymmetry and/or skin colour changes and/or asymmetry.
- Sudomotor/Oedema: Evidence of oedema and/or sweating changes and/or asymmetry.
- Motor/Trophic: Evidence of decreased range of motion and/or motor dysfunction (weakness, tremor, dystonia) and/or trophic changes (hair, nail, skin).

In 2003, an IASP consensus workshop group endorsed these criteria as a set of Proposed Research Diagnostic Criteria for use in settings (eg, in clinical trials) in which optimizing specificity (ie, avoiding false positives) is necessary. The group endorsed a separate set of Proposed Clinical Diagnostic Criteria for use in a patient-management context, in which there is a need to optimize sensitivity (ie, avoiding false negatives). The Clinical Diagnostic Criteria differ from the Research Diagnostic Criteria only in the diagnostic decision rules: the clinical diagnosis of CRPS should be made if at least three of four symptom categories and at least two of four sign categories are positive.15

Management of CRPS

Early identification of at-risk patients (eg, injury type, presence of anxiety or depression) may prevent progression of CRPS and worsening of CRPS 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 nerve injury, 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 non-pharmacological techniques may achieve remission. The Rehabilitation Pathway provides a stepwise approach that combines different modalities to optimize CRPS management. (Figure 1)

Appendix on Evidence-based Management of CRPS

Pharmacological Management

There is a paucity of published evidence for drug efficacy in CRPS; 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.

Non-steroidal Anti-inflammatory Drugs (NSAIDs)

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.17,18 However, clinical trial data on the benefit of NSAIDs for CRPS are lacking. A critical literature review suggested NSAIDs that have significant activity against bradykinin and prostacyclin (eg, ketoprofen) may be more useful than those with conventional anti-prostaglandin effects. Cyclo-oxygenase-2 selective inhibitors have not been evaluated in CRPS.

Alpha-2-delta Ligands and Other Anti-convulsants

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)19,20 and post-herpetic neuralgia (PHN).21,22 Phantom limb pain,23 Guillain-Barré syndrome24 and pain from spinal cord injury25 have also been managed successfully with gabapentin.

In a randomized, double-blind, placebo-controlled study of 305 patients with neuropathic pain (28% of whom 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 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), some domains of the Short-Form-McGill Pain Questionnaire, and quality of life measured using the Short-Form-36 Health Survey.

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 thrice daily) in CRPS 1 patients (n=58). Using a Visual analogue scale (VAS), patients in the gabapentin group reported significant pain relief in the first period. 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 vs 16.8, p=0.027).
Adverse effects of gabapentin are tolerable and mostly transient, occurring during the titration phase.26 The most commonly reported adverse events are dizziness and somnolence.26,27 Gabapentin has a more acceptable side-effect profile than the older anticonvulsants, such as phenytoin and carbamazepine.28

In randomized clinical trials, pregabalin has been shown to be effective in various types of chronic neuropathic pain, including postherpetic neuralgia, diabetic peripheral neuropathy and neuropathic pain following spinal cord injury.29,30 A recently published, 4-week, randomized, double-blind, placebo-controlled trial involving 40 patients with severe central neuropathic pain investigated the effects of pregabalin (150–600 mg/day) on pain relief, health status and quality of life.31 After 4 weeks, pregabalin produced clinically significant reductions in pain and improvements in health status, and was well tolerated. The authors concluded that pregabalin may be proposed as a first-line pharmacological treatment of central neuropathic pain.31

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.32 Clinical trials support the use of carbamazepine in the treatment of trigeminal neuralgia33 and PDN,34 but evidence of its efficacy in CRPS, PHN, phantom limb pain and other neuropathic conditions is limited.32

Tricyclic Antidepressants (TCAs)
Antidepressants have been the mainstay of therapy for many types of neuropathic pain. The number needed to treat for antidepressants in neuropathic pain is between 2.3 and 3.35. The efficacy of TCAs, especially amitriptyline, in the treatment of PDN and PHN is well established by numerous clinical trials.36

A randomized, double-blind, crossover trial compared clomipramine with acetylsalicylic acid (ASA) in patients with painful mono- and polyneuropathies, 48 of whom had CRPS.37 The starting dose of clomipramine was 50 mg daily, increasing to thrice daily (n=23), or ASA 500 mg daily, increasing to thrice daily (n=23) for 2 weeks. Patients were crossed over to the alternative group after a 1-week washout period. Patients with dysaesthesia, hyperpathia and CRPS had significant improvements in pain if they were treated with clomipramine (p<0.001). However, adverse events, including hypotension, tachycardia, tremor and sweating, were more pronounced with clomipramine. Side effects from TCAs occur commonly; therefore, TCAs may not be suitable for patients who tolerate them poorly.

It has been suggested that non-selective TCAs may be more effective than those that are relatively selective for noradrenaline uptake.38 In addition, selective serotonin reuptake inhibitors may be less effective than amitriptyline in treating CRPS.2,38

Opioids
Like NSAIDs, opioids lack sound evidence of benefit for CRPS. However, a literature review recommended the addition of opioids to ongoing treatment regimens if the initial medications do not provide sufficient analgesia, especially if the persistent pain prevents patients from undergoing physical therapy.39

Corticosteroids
The anti-inflammatory effect of corticosteroids can also be particularly useful in the acute phases of CRPS. A prospective study on 36 hemiplegic post-stroke patients who developed shoulder–hand syndrome revealed low-dose corticosteroid therapy given within 2 to 3 months of the neurological insult could relieve CRPS.40 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.17,41 However, a 12-week treatment using oral prednisone 10 mg thrice daily produced a 75% clinical improvement in patients diagnosed with reflex dystrophy syndrome, according to a small randomized, placebo-controlled study.42

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.43

Capsaicin and Topical Fentanyl
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.44 A meta-analysis also showed the pooled odds ratio for benefit from capsaicin therapy was 2.35.39 However, the use of capsaicin is limited due to its messy application and the associated intolerable burning pain.16

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.45 Forty-two percent reported either good or very good global satisfaction, and 86% reported a preference for TDF over their former therapy (p<0.001, binomial test).

**Calcitonin and Bisphosphonates**

There is some evidence that calcitonin and bisphosphonates can control pain in patients with early CRPS; by reducing local acceleration of bone remodelling, these agents may alleviate pain by mediating nociceptive primary afferent signalling in bone.2 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, results of a more recent randomized controlled trial did not show any benefit of calcitonin on CRPS type 1 patients.46 Oral alendronate, intravenous (IV) clodronate and IV pamidronate have all been shown in randomized clinical trials to significantly improve CRPS symptoms.47–49

**Procedures**

**Sympathetic Blocks**

Sympathetic blocks are usually performed by pain management specialists more for diagnosis than for therapy, as response to them is often brief. In some cases, however, effects may persist for longer periods and provide therapeutic benefit.

Procedures commonly used for sympathetic blockade are sympathetic ganglion blocks (eg, stellate ganglion block and lumbar sympathetic block) and IV sympathetic blocks (eg, IV phentolamine and IV lignocaine infusions, IV regional sympathetic block with guanethidine or bretylium, and subcutaneous lignocaine).

The efficacy of sympathetic blocks in the treatment of CRPS is still poorly defined.2,50 A systematic review of the literature found 29 studies that evaluated 1,144 patients (19 retrospective, five prospective case series, three randomized and two non-randomized controlled studies). Twenty-nine percent of patients achieved a full response and 41% achieved a partial response, while 32% did not respond.51 The authors concluded then that the evidence supporting the use of sympathetic blocks in CRPS is poor; a 2005 updated review by the same authors yielded the same conclusion.52 It is possible that sympathetic blockade may selectively show more effective pain relief in patients with SMP, thus facilitating physical rehabilitation.

A case report on nine CRPS patients treated with continuous 4- to 8-week subcutaneous infusion of lignocaine 10% indicated significant alleviation of pain, dysaesthesia, allodynia, hyperpathia, skin colour and temperature changes, reduced range of motion in the extremities involved and alterations in hair and nail growth.53 Upon discontinuation of infusion, patients had sustained pain relief. In addition, a randomized, double-blind, placebo-controlled study of CRPS patients with profound allodynia, IV infusion of lignocaine caused a substantial elevation in hot pain thresholds and a lowering of allodynic response to

### 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 healthcare.

- 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 [eg, amitriptyline]) or anticonvulsants (eg, gabapentin, pregabalin). 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.
stoking and cool stimuli, together with a significant drop in pain scores to cool stimuli.54 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.

**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 systematic review reported a statistically significant 2-point mean reduction in VAS pain ratings in CRPS type 1 patients at 24 months’ follow-up in one randomized controlled trial.55,56 The review’s case series studies showed that 67% of type 1 and type 2 CRPS patients reported at least 50% improvement in their pain scores over a median follow-up period of 33 months.55 The authors concluded that SCS appears to be an effective therapy in the management of patients with CRPS type I (Level A evidence) and type II (Level D evidence). When considering this procedure, a thorough medical and psychological assessment should be performed to ensure optimal patient selection for favourable outcomes.

**Intrathecal Drug-Administration Systems**

Continuous epidural infusions of local anaesthetics, clonidine and opioids have been reported to be effective in patients with intractable CRPS.57,58 Use of these agents has significantly decreased over the past decade as other less demanding therapies have become more popular.50 These interventions should be considered only as a last resort in complicated, resistant CRPS cases. As in SCS, a thorough medical and psychological assessment should be performed to ensure optimal patient selection when considering intrathecal drug administration.

**Neuroablation**

Neurolytic or surgical sympathectomy may be considered when diagnostic sympathetic blockade shows a brief but favourable response. However, the role of these procedures is not clear; a recent Cochrane review did not show any evidence of benefit in CRPS patients.59 Moreover, although some improvement may be achieved in the short term, the risks associated with surgical and chemical sympathectomy (eg, compensatory hyperhidrosis, Horner’s syndrome, retrograde ejaculation, wound infection) often outweigh their benefits. Thus, these procedures are not recommended. Ablative and destructive procedures may be more appropriate to relieve pain in patients with terminal cancer who have short life expectancy.

**References**


A complete list of references can be obtained upon request to the editor.