Advances in treatment of complex regional pain syndrome: recent insights on a perplexing disease
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Purpose of review
The paper is a critical appraisal of recent advances in the treatment of complex regional pain syndrome. Rapidly changing concepts related to the pathophysiology of this disease have transformed its current management and necessitate an updated review of the literature.

Recent findings
Complex regional pain syndrome is a perplexing disease that continues to challenge researchers in response to its cause and treatment. Recent improvements in diagnostic entities have advanced our understanding of this disease in a more comprehensive fashion. Emerging data indicate possible dosage optimization in the overall pathophysiology and may have led to treatment with newer anti-inflammatory medications. Certain conventional interventions have been recently scrutinized. A few novel therapeutic options like graded imagery and acupuncture have emerged.

Summary
Enhanced insight into the pathophysiology of chronic regional pain syndrome has modified current clinical practice and the focus of research. Certain standard therapeutic options for chronic regional pain syndrome have failed the test of time while others have prevailed. New options have recently been evaluated and shown promising early results. Knowledge of recent advances in chronic regional pain syndrome will help pain physicians provide optimal care to these patients.

Keywords
chronic regional pain syndrome, neuropathic pain, reflex sympathetic dystrophy, shoulder-hand syndrome, treatment advances

Introduction
Complex regional pain syndrome (CRPS) has been extensively studied over the past few decades and significant insight has been gained into its pathophysiology. More precise diagnostic criteria with improved sensitivity and specificity have also been proposed [1]. These dynamic changes have introduced a new era of clinical research in CRPS. This review provides the reader with a concise update on the treatment of CRPS, highlighting recent reports. Available treatment options can be discussed in three broad categories: pharmacotherapy, interventional techniques, and miscellaneous therapeutic options.

Pharmacotherapy
Innumerable drugs have been tried in CRPS and many are still being investigated. There is a paucity of controlled studies investigating the efficacy of drugs in CRPS patients prior to 1996. This might stem, in part, from the fact that clear diagnostic criteria were proposed by the International Association for the Study of Pain only in 1994. Moreover, the sensitivity and specificity of the initial criteria have been questioned [2].

Anti-inflammatory drugs
Historically, CRPS has been considered as an epitome of neuropathic pain. Certain features characterizing the acute phase of the disease, such as swelling, erythema, and warmth, point towards an inflammatory cause [3]. Numerous clinical and experimental investigations add to the growing consensus that CRPS may have an inflammatory cause, at least during its acute phase [4]. The clinical picture of CRPS may represent an exaggerated local inflammatory response (mediated via cytokines such as interleukins, free oxygen radicals, and tumor necrosis factor-α) [5–7] as well as ‘neurogenic inflammation’ (mediated via neuropeptides such as calcitonin gene-related peptide or substance P) [7–10]. It is not surprising, therefore, that symptomatic improvement is seen in patients with CRPS after treatment with nonsteroidal anti-inflammatory drugs [11], corticosteroids
[12,13], free radical scavengers, [6,14,15] and anti-tumor necrosis factor agents [16].

The efficacy of free radical scavengers such as topical 50% dimethylsulfoxide (DMSO) and N-acetylcysteine (NAC) has been shown in a large multicenter, double-blind trial [15], in which 146 patients were randomly treated with either 50% topical DMSO cream five times a day or given 600-mg NAC tablets three times a day for 17 weeks. Both therapies were generally equally effective in the treatment of CRPS type I.

Neuropathic drugs
Neuropathic medications are commonly used for treating patients with CRPS. Most clinical trials reporting the efficacy of these medications in neuropathic pain have been conducted on patients with painful diabetic neuropathy and postherpetic neuralgia. These results have been extrapolated to patients with CRPS. In a recent evidence-based review, Beniczky et al. [17\textsuperscript{**}] opined that the classification of neuropathic pain medications based on their original therapeutic class is misleading. For instance, medications such as gabapentin, carbamazepine, and pregabalin are categorized as ‘antiepileptic drugs’, possibly giving a false impression that these drugs are effective for all neuropathic pain states, which is clearly not the case. The authors propose four distinct etiologic groups for therapeutic management: peripheral neuropathic pain, CRPS, trigeminal neuralgia, and central neuropathic pain. Furthermore, most ‘standard’ neuropathic pain medications are discussed under the umbrella of ‘peripheral neuropathic pain’. CRPS is, indeed, more complex than merely a peripheral neuropathic pain state, but a lack of evidence for conventional neuropathic medications (such as tricyclic antidepressants) should not be accepted as lack of efficacy. In the past, researchers avoided inclusion of patients with CRPS in the efficacy trials of neuropathic medication due to the lack of precise ‘diagnostic’ criteria for this disease. Other authors have acknowledged the importance of these medications in clinical practice [18].

The neuropathic pain medications that are commonly used in the treatment of patients with CRPS include tricyclic antidepressants, antiseizure medications such as gabapentin and pregabalin, centrally acting medications such as tramadol, opioids, and topical local anesthetics such as lidocaine or clonidine. With the acceptance of the revised diagnostic criteria [1] for CRPS, additional studies need to be conducted to examine the usefulness of these individual drugs for patients with CRPS.

Calcitonin
Calcitonin is a hormone secreted by the parafollicular cells of the thyroid gland. It acts on bone and kidneys causing inhibition of osteoclastic bone resorption that results in reduction in serum calcium and phosphates. Thus, it has been introduced as a useful therapeutic agent in the treatment of Paget's disease, hypercalcemia, and osteoporosis. The antinociceptive effects of calcitonin have not been clearly elucidated. Numerous examples have been proposed including serotonergic and catecholaminergic mechanisms, Ca\textsuperscript{2+} fluxes, protein phosphorylation, endorphin production, cyclooxygenase inhibition [19,20], and possibly actions on opioid receptors [21].

Since salmon calcitonin has a longer half-life and a reduced metabolic clearance in comparison with human calcitonin, it has become a therapeutic agent of choice. It is commercially available in the form of nasal spray. Side effects include rhinitis, nasal itching, headache, epistaxis, and arthralgias. It is metabolized primarily by kidneys and to a certain extent by peripheral tissues. Most of the drug is cleared by the kidneys, with its half life being 43 minutes [22]. Although calcitonin is considered a valuable addition to the existing therapeutic alternatives for patients with CRPS, the results of a few randomized controlled trials have been controversial (Table 1) [23\textsuperscript{-27}].

Bisphosphonates
The bisphosphonates are pyrophosphate analogues that have recently been promoted as effective agents in the treatment of CRPS. Clodronate, pamidronate, and alendronate have specifically been tested in recent randomized controlled clinical trials (Table 2) [28-31] and have shown promising results. The bisphosphonates also selectively inhibit bone resorption and hence are commonly used in the treatment of osteoporosis or Paget's disease. They reduce the formation and dissolution of hydroxyapatite crystals within and outside the skeletal system. Like calcitonin, the exact analgesic mechanism of bisphosphonates in patients with CRPS is unclear. Although patients with CRPS do manifest some degree of regional osteoporosis in the involved extremity, the assumption that the antinociceptive effect of bisphosphonates is primarily due to their capacity to inactivate osteoclasts and antagonize osteoclastogenesis may be simplistic. They inhibit prostaglandin E\textsubscript{2}, proteolytic enzymes, and lactate acid [18,32] but not proinflammatory cytokines [33\textsuperscript{*}] as was previously believed.

Alendronate, given in oral doses of 40mg daily for 8 weeks, has shown benefits in improving pain, pressure tolerance, and joint mobility in patients with CRPS [28]. Bioavailability of most bisphosphonates after oral intake is less than 10\% and is even less when they are taken with food. These drugs are thus often given on an empty stomach or via an intravenous route (pamidronate). Side effects include nausea, dyspepsia, constipation or diarrhea, musculoskeletal pain, fever, and even esophageal erosion or ulcers. Esophageal irritation can be reduced by taking the drug with plenty of water and remaining
Table 1 Randomized controlled trials for efficacy of calcitonin in complex regional pain syndrome

<table>
<thead>
<tr>
<th>Study</th>
<th>Dose</th>
<th>Type of study</th>
<th>Patients (n) and duration of follow-up</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sahin et al., 2006 [23]</td>
<td>Salmon calcitonin, 200IU intranasal per day</td>
<td>RCT, single blind</td>
<td>35 patients (17 paracetamol, 18 drug), 2 months</td>
<td>Pain, allodynia, hyperalgesia, trophic changes, and ROM improved in both groups, with no statistical significance</td>
</tr>
<tr>
<td>Hamenci et al., 1996 [24]</td>
<td>Salmon calcitonin, 100IU intramuscular</td>
<td>Controlled trial</td>
<td>41 patients (16 placebo, 25 drug), 4 weeks</td>
<td>Significant reduction in pain scores and improvement in ROM</td>
</tr>
<tr>
<td>Gobelet et al., 1992 [25]</td>
<td>Salmon calcitonin, 100IU 3 times a day for 3 weeks with or without physical therapy</td>
<td>RCT, double blind</td>
<td>66 patients (33 placebo, 33 drug), 8 weeks</td>
<td>Significant improvement in pain and ROM, significant improvement in ability to work in upper-extremity CRPS patients (81.2% versus 50%), no difference in level of edema, no difference in ability to work in lower-extremity CRPS patients (47% versus 40%)</td>
</tr>
<tr>
<td>Bickerstaff and Kanis, 1991 [26]</td>
<td>Salmon calcitonin, 100IU each nostril twice a day (400IU total) for 4 weeks</td>
<td>RCT, double blind</td>
<td>40 patients, 4 weeks</td>
<td>No difference in improvement in pain scores, stiffness, swelling, and vascular instability</td>
</tr>
<tr>
<td>Gobelet et al., 1986 [27]</td>
<td>Salmon calcitonin, 100IU, 3 times a day for 3 weeks with or without physical therapy</td>
<td>RCT</td>
<td>24 patients, 4 weeks</td>
<td>Improvement in pain scores at 1 week</td>
</tr>
</tbody>
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RCT, randomized controlled trial; ROM, range of motion.

upright for 30 minutes [22]. Contraindications to use of bisphosphonates include decreased renal function, esophageal motility disorders, and peptic ulcer disease. Other bisphosphonates such as residronate and ibandronate can also be administered orally, although they have not yet been explored in the treatment of patients with CRPS.

Interventional therapeutic techniques

The interventional therapies are technically demanding. They can prove beneficial when used in a multidisciplinary setting with a clear understanding that the primary goal of these therapies is to help decrease the pain and facilitate functional rehabilitation.

Intravenous regional sympathetic blockade

In 1908, August Bier described a technique involving injection of a local anesthetic solution in a limb isolated by tourniquet (intravenous regional anesthesia). Hannington-Kiff [34] proposed the use of intravenous regional sympathetic blockade (IRSB) in patients with CRPS, with guanethidine being delivered by a similar method. A host of other medications have been subsequently used, including sympatholytics such as reserpine, bretyllium, and

Table 2 Randomized controlled trials for efficacy of bisphosphonates in patients with complex regional pain syndrome

<table>
<thead>
<tr>
<th>Study</th>
<th>Drug studied</th>
<th>Type of study</th>
<th>Patients (n) and duration of follow-up</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Manicourt et al., 2004 [28]</td>
<td>Alendronate 40mg oral every day for 8 weeks</td>
<td>RCT, double blind, placebo controlled</td>
<td>40 patients 12 weeks</td>
<td>Improvement in spontaneous pain, pressure tolerance, and joint mobility</td>
</tr>
<tr>
<td>Robinson et al., 2004 [29]</td>
<td>Pamidronate 60mg IV, one time</td>
<td>Optional open trial at 12 weeks for 8 weeks</td>
<td>12 patients from each group, 27 patients (13 placebo, 14 drug), 3 months</td>
<td>Improvement in pain score, global assessment of disease severity score, and physical function</td>
</tr>
<tr>
<td>Vareni et al., 2000 [30]</td>
<td>Clodronate 300mg IV for 10 days</td>
<td>RCT, double blind, placebo controlled</td>
<td>32 patients (17 placebo, 15 drug) 40 days</td>
<td>Improvement in pain score and clinical global assessment in clodronate group at 40 days</td>
</tr>
<tr>
<td>Adami et al., 1997 [31]</td>
<td>Alendronate IV infusion (7.5mg in 250ml saline) every day for 3 days</td>
<td>RCT, placebo controlled, Open trial at 40 days</td>
<td>All 32 patients received drug and followed for another 120 days</td>
<td>Significant reduction in spontaneous pain, tenderness, and swelling along with improvement in motion of involved extremity at 2 and 4 weeks</td>
</tr>
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RCT, randomized controlled trial; IV, intravenous; VAS, Visual Analogue Pain Scale.
clonidine; local anesthetics such as prilocaine or lidocaine; and others such as ketanserin (serotonin antagonist), methylprednisolone, and droperidol.

Barring a few isolated studies, the long-term advantages of IRSB in patients with CRPS are questionable. A systematic review of studies on the effects of IRSB with guanethidine in CRPS failed to demonstrate beneficial effects [35]. One study each with ketanserin and bretylium showed potentially beneficial effects [19]. IRSB with lidocaine and steroids have been studied, but the results are inconsistent. Two previous controlled trials [36,37] showed positive long-term benefits (28 and 12 months of follow-up, respectively); however, a more recent study [38] failed to replicate these observations.

Local anesthetic sympathetic blockade
A local anesthetic solution can be injected by placing a needle tip in the proximity of sympathetic structures such as the stellate ganglion or lumbar sympathetic chain (LASB) under fluoroscopic or computed tomographic guidance. Although complications have been reported in the literature, these techniques are safe in experienced hands. For decades these techniques were considered a 'gold standard' in the treatment of patients with CRPS. Unfortunately, only a few controlled trials have been conducted to assess the usefulness of sympathetic blockade in patients with CRPS. Moreover, almost all these trials have been done in mixed CRPS patient populations that include both sympathetically maintained and sympathetically independent states, which may bias the results.

Cepeda et al. [39] attempted a systematic review of randomized controlled trials to examine the benefits of LASB in patients with CRPS (not sympathetically maintained pain). Significant differences in study design precluded sensible pooling of data. The authors then reviewed nonrandomized controlled studies, case series, and randomized controlled trials with acceptable designs, published in English-language peer-reviewed journals from 1916 through 1999. Pooled data from these studies (454 patients) showed that 29% patients undergoing LASB obtained full pain relief (≥75% improvement) while 41% obtained partial relief (25–75% improvement). The authors concluded that a less than one-third positive response ('full' pain relief) is consistent with the placebo effect and that the efficacy of sympathetic blocks for treatment of CRPS is inconclusive. Many of these 14 studies were published prior to 1960 and only two identified technical success of block and pain scores.

Cepeda et al. [40] recently performed another systematic review to assess the short-term (30-minute to 2-hour) and long term (48-hour or later) analgesic effects of LASB. Only two randomized double-blind controlled studies (with a total of 23 subjects) were eventually selected based on the inclusion criteria, but no conclusions could be drawn. The authors called for further trials to address the value of sympathetic blockade with local anesthetic for the treatment of CRPS. At present, short duration of pain relief and reduction in vasomotor symptoms, as often achieved by LASB, should be used to improve mobility, range of motion, and motor strength by physiotherapy. Repeated blocks are beneficial in selected patients to help facilitate participation in physiotherapy, particularly when signs of continued improvement are observed.

Spinal cord stimulation
Spinal cord stimulation (SCS) is the newest therapeutic modality to gain acceptance for a wide variety of neuropathic pain syndromes, including CRPS. The mechanisms of the analgesic effects of neuromodulation are unclear. Neuromodulation may act to restore normal gamma-aminobutyric acid levels in the dorsal horn and affect the release of adenine, thus reducing neuropathic pain [41]. In a recent systematic review of the literature and meta-regression, Taylor et al. [42**] reported a statistically significant 2-point mean reduction in Visual Analogue Pain Scale pain ratings in patients with CRPS type I at 24 months' follow-up along with a lifetime cost saving of approximately US$60,000. The pooled data from case series [42**] showed that almost two-thirds of both type I and type II CRPS patients reported at least 50% improvement in their pain scores over a median follow-up period of 33 months.

Although Taylor et al. [42**] failed to isolate statistically significant predictors of pain relief, studies suggest that patients with good response to sympathetic blocks respond better to neurostimulation [43]. A controlled trial on 29 patients to evaluate the long-term effect of SCS on the improvement of functional status in sympathetically maintained CRPS type I (positive response to sympathetic nerve block) showed that SCS reduced deep pain and allodynia [44]. Considerable improvement in activities of daily living (based on pain disability index) and a reduction in analgesic requirement were observed. Almost 77% (20/26) patients showed a significant improvement in their motor strength over an average follow-up period of about 3 years. In view of the abovementioned clinical and financial benefits, it is not surprising that many pain physicians have started recommending this therapy even in the early phases of the disease.

Neuraxial techniques
Continuous epidural infusions of local anesthetics, clonidine, or opioids have been studied in the management of CRPS. Epidural clonidine has shown some benefit in a randomized trial [45]. Use of these agents has significantly decreased over the past decade, as other less demanding therapies have been explored. Besides, efficacy of intrathecal medications (morphine, bupivacaine,
clonidine, baclofen, or ziconotide) via an implanted pump has shown positive results in case reports and case series. These interventions are considered only as a last resort in complicated and resistant cases of CRPS.

**Sympathetic denervation**

Patients who show good response to initial sympathetic blocks were subjected to the past to radiofrequency denervation, chemical neurolytic destruction of the sympathetic innervation, or surgical sympathectomy in the hope of achieving prolonged benefits. Indeed, almost 90% partial or complete evidence of sympathectomy had been reported even 2 years after these procedures [46], but their analgesic benefits often do not persist that long. Most authors report sustained pain relief in less than two-thirds of patients at 2 years and in about one-third at 5 years. In a systematic review of the effects of percutaneous neurodestructive procedures for neuropathic pain, Malis et al. [47] concluded that the practice of surgical and chemical sympathectomy is based on poor-quality evidence, uncontrolled studies, and personal experience.

Surgical sympathectomy has also been advocated as an alternative in the past for patients who achieve good pain relief with a series of sympathetic block. Videoscopic lumbar sympathectomy has been proven to be as effective as an open surgical intervention [48] and is less aggressive. In a case series with 73 patients with CRPS who underwent video-assisted sympathectomy, Bandyk et al. [49] showed significant improvement (pain severity score <3) in 25% and a moderate improvement in an additional 50% of patients at 1-year follow-up. The most important independent factor in determining a positive outcome of sympathectomy is an interval of less than 12 months between the inciting event and sympathectomy [50].

Complications of all these neurodestructive procedures include postsympathectomy sympathalgia, compensatory hyperhidrosis, Horner’s syndrome, wound infection, and spinal cord injury. Although lower complication rates and postprocedure morbidity are expected following percutaneous techniques, surgical sympathectomy (both videoscopic and open) might achieve better (or more precise) neurodestruction. The accuracy of this presumption remains speculative.

**Miscellaneous therapeutic options**

In a large, prospective, randomized controlled trial [51], physical therapy has been proved to reduce the pain and improve active mobility in patients with CRPS I of less than 1 year’s duration. In addition, the benefits of behavioral and psychological interventions have also been shown in numerous case series. At present, all these modalities should be considered an integral component of any therapeutic plan and their importance cannot be overemphasized.

The discussion of current advances in therapy for CRPS would be incomplete without the mention of certain novel options. Alternatives that are being explored include graded imagery, repetitive transcranial magnetic stimulation [52], hyperbaric oxygen [53], intravenous infusion of iloprost (a prostacyclin analogue) [54] and immunoglobulin [55], as well as subanesthetic infusion of ketamine [56,57]. Of these options, graded motor imagery has shown benefit in a randomized controlled trial [58] consisting of 13 patients with CRPS who were given 2 weeks each of a hand laterality recognition task, imagined hand movements, and mirror therapy. The 12-week follow-up showed an almost 25-point reduction on the neuropathic pain scale. Last but not least, there has been a valuable recent trend to investigate the factors that might prevent the occurrence or recurrence of CRPS. Reuben et al. [59**] have recently shown that the incidence of CRPS is significantly reduced following fasciectomy for Dupuytren’s contracture with preoperative use of axillary block or intravenous regional anesthesia with clonidine (and lidocaine). These encouraging results have added a new dimension to the enduring efforts to minimize the incidence and prevalence of this dreadful disease.

**Conclusion**

Current knowledge about the pathophysiology of CRPS is rapidly expanding. Recent modifications in the diagnostic criteria have improved identification of this disease with more conviction. These ‘winds of change’ have certainly guided researchers in the right direction. Over the past decade or so, many traditional treatment modalities have been scrutinized and some unique therapeutic options have been explored. At present diverse recommendations exist as the ‘treatment of choice’ in a given stage of the disease. Physicians are advised to adopt an individualized, multidisciplinary approach for the optimum care of their patients. Although the dream of conquering this perplexing disease is still far fetched, the future certainly looks bright.

**References and recommended reading**

Papers of particular interest, published within the annual period of review, have been highlighted as: • of special interest •• of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section of this issue (pp. 886–887).


This recent publication from the International Association for the Study of Pain is a state-of-the-art synopsis of the history, present knowledge, and future directions related to CRPS. Most authors are leaders in pain research and have contributed tremendously to current knowledge of CRPS.
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18 An excellent comprehensive review of pharmacologic modalities being used for various neuropathic pain states that have shown benefits in clinical trials.


25 An excellent systemic review confirming the clinical and financial benefits of spinal cord stimulation in the treatment of CRPS-related pain.


27 An excellent systemic review confirming the clinical and functional benefits of spinal cord stimulator implantation in the treatment of CRPS-related pain.

28 An excellent systemic review confirming the clinical and functional benefits of spinal cord stimulator implantation in the treatment of CRPS-related pain.

29 An excellent systemic review confirming the clinical and functional benefits of spinal cord stimulator implantation in the treatment of CRPS-related pain.


A new vision of examining certain modalities that can be used to prevent the incidence or recurrence of CRPS following surgical procedures. Authors showed that axillary block or intravenous regional anesthesia with clonidine offers a significant advantage over either intravenous regional anesthesia with lidocaine alone or general anesthesia for patients undergoing Dupuytren’s surgery.