Complex Regional Pain Syndrome: A Review of Evidence-supported Treatment Options

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Complex regional pain syndrome consists of pain and other symptoms that are unexpectedly severe or protracted after an injury. In type II complex regional pain syndrome, major nerve injury, often with motor involvement, is the cause; in complex regional pain syndrome I, the culprit is a more occult lesion, often a lesser injury that predominantly affects unmyelinated axons. In florid form, disturbances of vasoregulation (eg, edema) and abnormalities of other innervated tissues (skin, muscle, bone) can appear. Because of these various symptoms and the difficulty in identifying causative lesions, complex regional pain syndrome is difficult to treat or cure. Complex regional pain syndrome has not been systematically investigated; there are few controlled treatment trials for established complex regional pain syndrome. This article reviews the existing studies (even if preliminary) to direct clinicians toward the best options. Treatments for other neuropathic pain syndromes that may be efficacious for complex regional pain syndrome also are discussed. Some common treatments (eg, local anesthetic blockade of sympathetic ganglia) are not supported by the aggregate of published studies and should be used less frequently. Other treatments with encouraging published results (eg, neural stimulators) are not used often enough. We hope to encourage clinicians to rely more on evidence-supported treatments for complex regional pain syndrome.

Introduction
In 1872, Mitchell [1••] coined the term “causalgia” to describe a syndrome of persistent burning pain, allodynia, and autonomic changes that he observed in Civil War soldiers with major nerve injuries from saber or bullet wounds. The same features of pain that persist after a wound or trauma heals (usually in an extremity), or pain out of proportion to an injury’s severity, have been described in many different clinical situations.

In 1946, Evans [2] coined the term “reflex sympathetic dystrophy” (RSD) to describe a similar chronic pain syndrome in patients with no obvious nerve damage. Since then, many authors have described the same condition under different names (eg, algodystrophy, Sudeck’s atrophy, shoulder-hand syndrome) and speculated about its pathophysiology, with no clear conclusions.

In 1994, the International Association for the Study of Pain (IASP) authored the descriptive names “complex regional pain syndrome” (CRPS) types I (replaces RSD) and II (replaces causalgia) to replace the misleading terms “reflex,” “sympathetic,” and “dystrophy,” to create uniform diagnostic criteria and to adapt a consensus terminology [3]. According to the IASP guidelines, CRPS type I occurs without a known nerve lesion; however, CRPS type II consists of the same symptoms after an identifiable major nerve lesion. Although Diagnostic Criterion I is an “initiating noxious event,” usually trauma or surgery [4], identical clinical problems occur occasionally without evidence of trauma. It is likely that these patients have had an internal trauma, such as tissue infarction. Criterion II states that there must be “continuing pain, allodynia, or hyperalgesia with which the pain is disproportionate to any inciting event.” Criterion III requires “evidence at some time of edema, changes in skin blood flow, or abnormal sudomotor activity in the region of the pain.” Many clinicians and investigators presume incorrectly that, unless so-called “trophic changes” are present at the time of an examination, a diagnosis of CRPS cannot be made. Criterion IV requires absence of an alternative explanation for the symptoms. The only additional criterion for CRPS II is the presence of a known nerve injury.

The IASP criteria are acknowledged widely to be suboptimal, presumably because of the uncertainty regarding the causes of CRPS, but they are the consensus criteria that should be used to standardize patients who are recruited into research studies. Research into pathophysiology and treatments has been gravely hindered by the loose definitions that have been used; therefore, there have been almost no multicenter, randomized, placebo-controlled trials. Van de Beek et al. [5•] reported that only three of 23
treatment studies published after the introduction of the IASP criteria applied the diagnostic criteria correctly to select patients for study [5••]. There are no medications approved by the US Food and Drug Administration (FDA) for the treatment of CRPS under any name.

Because CRPS I and II have identical clinical symptoms, it seems likely that the cause of CRPS I also is nerve injury, but that the nerve injuries go undetected because they are partial, fascicular, or involve primarily small unmyelinated axons. These specific types of nerve lesions are notoriously difficult to diagnose by examination or electrodiagnostic studies. Many patients are labeled as having "CRPS I" or "RSD" until they are examined by a peripheral nerve specialist who uses detailed knowledge of peripheral neuroanatomy, electrodiagnostic testing, or diagnostic local anesthetic nerve blocks to identify the injured nerve. There is pathologic evidence, from our group [6] and elsewhere [7], that nerve damage, particularly to nociceptive fibers, underlies CRPS I. The excellent outcomes of treatment of CRPS I and II with spinal cord [8••] and peripheral nerve [9] stimulators also testify to the presence of nerve injury in both.

Kingery [10•] has reviewed the controlled clinical trials for CRPS and peripheral neuropathic pain and concluded that the CRPS trials used fewer subjects and were usually of lesser quality (not placebo-controlled, blinded, or analyzed with appropriate statistical tools) than the neuropathic pain trials. It is difficult to make clinical recommendations based primarily on case reports or small open-label trials. For these reasons, this article focuses on medications proven to be effective for other types of neuropathic pain, even if they are not tested specifically on patients with CRPS.

Treatment options are different for adults and children. CRPS in children seems substantially different than in adults. Incidence is highest during the teenage years and is often associated with a sports injury [11]. Most children recover within the first year or so after injury; however, adult cases usually last longer and are less easily treated. The younger the child, the better the prognosis [11]. Pathophysiologic studies of pediatric patients may provide insight into how CRPS could be cured in adults. There also is incentive to avoid medication and invasive treatments in children; therefore, conservative therapies play a larger role in managing pediatric CRPS [12].

Conservative Treatment Options
Physical medicine and rehabilitation
This type of treatment is least likely to cause harm. Its major role seems to be to treat the secondary complications of CRPS, such as decreased joint and tendon range of motion. Increased mobility is likely to have additional general benefits, such as ameliorating depression, weight gain, and pain control. There is no convincing evidence of efficacy against the primary process. A randomized, con-
trolled study demonstrated that physical and, to a lesser extent, occupational therapies reduced pain and improved active mobility in patients with recent-onset CRPS type 1 [13]. Elevation, massage, and contrast bath also have been used [14]. Some patients use surgical stockings or elastic bandages to minimize edema in an affected extremity. For others, dynamic splinting and stress-loading programs of traction can improve range of motion [15]. If contractures are not prevented or treated with physical therapy, orthopedic surgery can become necessary.

Acupuncture and transcutaneous electrical stimulation
There are no convincing data supporting acupuncture in the treatment of CRPS. One small study did not show any statistical differences between acupuncture and sham groups [16]. However, this may have been related to the small number of patients observed or to the therapeutic effect of the sham treatment involving so-called surface stimulation.

Transcutaneous electrical stimulation (TENS) has been found to be effective in 50% to 90% of pediatric patients with CRPS [17]. Because TENS is non-invasive and does not have side effects (with the exception of an occasional skin irritation), it is worth attempting [17].

Psychiatric treatment
Because of the discrepancy between the subjective complaints of pain of patients with CRPS and the limited objective evidence of underlying pathology, some authors in the past have suggested that psychiatric factors are a major cause of CRPS. Although many patients with long-term CRPS battle depression and anxiety, these conditions usually are a consequence, rather than a cause, of their pain [18]. It is clear that experiencing significant ongoing pain is a major adverse life event that will challenge the coping skills of even the most well-adjusted patient. Clinicians should be aware of the high rate of secondary psychiatric problems in CRPS and refer patients for counseling and medical treatment as needed. Some extremely depressed patients will need more aggressive psychiatric treatment, including electroconvulsive therapy [19].

Pharmacologic Treatment

Pharmacologic treatments for early complex regional pain syndrome
Orthopedists and trauma surgeons see patients with CRPS much sooner in the disease course than do pain specialists. Several good-quality trials have evaluated treatments for CRPS symptoms that have been present for only weeks or months. At this subacute stage, in which inflammation and injury from the original event may still exist, there are more options than for established CRPS. It also is likely that some of these patients would recover anyway; therefore, results of treatment are more likely to be favorable.
Unfortunately, there is no evidence that the treatments used for "early" CRPS are effective for chronic CRPS. Not surprisingly, there is evidence for efficacy of corticosteroids, which decrease inflammation, relieve pain, and minimize ectopic electrical activity after nerve injury [20]. In a small, randomized, controlled study, oral prednisone administered to patients with early RSD (average duration, 3 months) decreased pain and edema within 12 weeks [21]. In a placebo-controlled, non-blinded study, methylprednisone administered for 4 weeks reduced the frequency of shoulder-hand syndrome in patients with stroke and hemiparesis [22].

Some (but not all) patients with CRPS develop abnormalities of bone metabolism, including excess bone resorption in the affected area [23], although this likely is a secondary consequence of reduced mobility or loss of innervation to the bone. For this reason, inhibitors of osteoclast activity (e.g., bisphosphonates or regulators of bone metabolism) have been evaluated as treatments for recent-onset CRPS. There also is evidence of direct antihyperalgesic effects of some of these compounds [24]. The mechanisms by which calcitonin and bisphosphonates control pain in early CRPS are unclear. Bisphosphonates hinder the synthesis of prostaglandin E2, proteolytic enzymes, lactic acid, and pro-inflammatory cytokines [25,26]; calcitonin inhibits the synthesis of proteolytic enzymes and lactic acid [25]. None of these agents can be administered orally; calcitonin is available as a nasal spray and bisphosphonates usually are administered intravenously.

In one study [27], 300 IU of calcitonin was administered daily to patients within 8 to 10 weeks of CRPS onset; in another study [28], 400 IU/d was prescribed to patients 2 weeks after removal of casts after Colles' fracture. The first study reported pain relief and improved range of motion; the second did not. The administration of intramuscular 100 IU of calcitonin for patients with hemiplegia secondary to stroke and subsequent RSD was reported to be effective compared with normal saline [29]. Open-label studies suggest that pamidronate can reduce pain and improve range of motion [30]. In a randomized, controlled study, 300 mg of clodronate administered intravenously to patients daily for 10 days resulted in lasting pain relief [31].

**Pharmacologic treatments for chronic complex regional pain syndrome**

Norepinephrine tricyclic antidepressants

The efficacy of tricyclic antidepressants (TCAs) is well demonstrated in neuropathic pain syndromes such as postherpetic neuralgia (PHN) and diabetic neuropathy [32]. Their antihyperalgesic effects seem to be related to several known actions, including enhancement of norepinephrine descending inhibitory pathways and partial sodium-channel blockade. These mechanisms are independent of their antidepressant effects and generally occur at lower doses [33]. Selective serotonin reuptake inhibitors are generally ineffective against neuropathic pain in non-depressed patients [32]. Few patients experience total relief; usage is often limited by side effects, which are worse for amitriptyline than for nortriptyline or desipramine [34]. Wilder et al. [11] evaluated TCA efficacy in an open-label study of treatments for pediatric CRPS. Of 41 patients, two experienced nearly complete pain relief, 21 had substantial improvement, and 18 reported little or no improvement.

**Systemic antiepileptic medications and cation-channel blockers**

Antiepileptic medications also are used to treat CRPS based on trials in other neuropathic pain conditions [10]. Many of these agents block sodium or calcium channels and thus decrease neuronal excitability. Gabapentin has advantages over older agents such as carbamazepine and phenytoin because of its better side-effect profile. Case reports and small series support the efficacy of gabapentin in adult [35] and pediatric [36] CRPS. Newer antiepileptic medications also may be effective, but randomized, placebo-controlled clinical trials are lacking.

There is conflicting evidence regarding whether mexiletine, which is an orally active local anesthetic, is efficacious for neuropathic pain [37]; systemic lidocaine may be more effective, but needs to be administered intravenously or subcutaneously [38].

Many patients with CRPS have disturbances of autonomic control of small blood vessels in the affected area, leaving them with vasodilated, red, warm, swollen extremities (Fig. 1) or cool, pale, vasoconstricted extremities. These vascular changes were once thought to occur consecutively in a sequence, but a study by Veldman et al. [39] of 829 patients (probably the largest to date) did not find evidence for consecutive stages. These clinical features have prompted the evaluation of several modalities with potential vasoactive effects, including calcium-channel blockers, sympatholytic agents, and surgical sympathectomy. One study [40] of combined administration of nifedipine and phenoxybenzamine (an α-blocker) demonstrated some efficacy more so for the patients with recent-onset rather than those with chronic CRPS. Another open-label, uncontrolled study evaluating the use of nifedipine reported efficacy for some patients [41]. Some clinicians have begun to experiment with the use of sildenafile to achieve vasodilation for patients with CRPS, although there are no published studies supporting this use.

**Opioid medications**

To our knowledge, there are no randomized controlled studies that evaluate the effects of opioids in patients with CRPS. However, there is increasing evidence of efficacy and tolerability in various neuropathic pain syndromes [42]. Mitchell [11] remarked that "for the easing of neurotromatic pain...the morphia salts...are invaluable. When continuously used, it is very curious that its hypnotic manifestations lessen, while its power to abolish pain continues, so that the patient who receives a half grain or more..."
anesthetic nerve blocks to identify which specific nerve or nerves have been damaged in patients is underused.

Local anesthetic blockade
of sympathetic and somatic innervation
Despite the lack of large, controlled trials, percutaneous sympathetic blocks were used for many years to treat CRPS. Stellar ganglion and lumbar sympathetic blocks were the most common techniques. The presence or absence of temporary improvement in pain scores was used to categorize patients as having sympathetically maintained or independent pain. However, the response often varied after different attempts were made and did not seem to predict success with oral sympatholytic medications. It became apparent that pain relief after sympathetic blockade also may reflect the inadvertent spread of the anesthetic to nearby somatic ganglia or systemic absorption. The first systematic review of the literature on sympathetic blockade for the treatment of CRPS (29 studies that evaluated 1144 patients) has appeared [57••]. The authors report that the quality of the publications was generally poor, primarily consisting of case series that used varying criteria for enrollment and various ways to define a positive outcome. Most studies had no long-term follow-up. Twenty-nine percent of patients had full response, 41% had partial response, and 32% showed no improvement in their pain. The authors concluded that these results were not significantly different from the expected placebo effect.

In some patients, blockade of somatic ganglia or plexuses is helpful in providing regional anesthesia for procedures. Some patients are administered a continuous infusion of local anesthetics by indwelling catheter for several days, with boluses before physical therapy sessions. These procedures block the sympathetic nerves and somatic axons. There is no evidence of long-lasting effects, so these procedures should be performed rarely and only for an explicit indication (eg, a brief course of intensive physical therapy to treat adhesive capsulitis).

In 1908, German surgeon August Bier reported the first use of regional anesthesia with procaine for pain [58]. In 1974, Hannington-Kiff [59] proposed using intravenous guanethidine after temporary occlusion of limb circulation with a tourniquet to produce prolonged sympathetic block in a limb. Because intravenous guanethidine is unavailable in the United States, different classes of medications (α-adrenergic modulators, nonsteroidal anti-inflammatory agents, local anesthetics, NMDA antagonists) have been used as substitutes, including reserpine [60], bretylium [61], clonidine [17], tenoxicam [62], lidocaine [61], and methylprednisolone [63].

It is well demonstrated that the Bier block does not provide long-term pain relief [64]. However, convincing data demonstrate that guanethidine and bretylium may cause short-term relief (between 3 days and 3 weeks) [61,65]. Again, the main purpose of treatment should be pain relief to facilitate physical therapy.

Treatment options using an indwelling intrathecal catheter and subcutaneous pump
This route of administration was developed to improve the therapeutic ratio of these medications by administering a higher concentration of medication near the spinal cord and less in the brain and periphery. The two most common (and the only FDA-approved) medications delivered this way are morphine and baclofen [66], although various cocktails have been tried in small numbers of patients [67]. There are small case series of efficacy of intrathecal morphine [43]. One small case series found intrathecal bupivacaine to be ineffective [68]. Baclofen is the only intrathecal agent whose efficacy in CRPS is supported significantly in the literature. Baclofen is a γ-aminobutyric acid-receptor (type B) agonist that augments the function of dorsal-horn interneurons that inhibit the output of projection neurons, including those transmitting pain signals through the spinothalamic tracts [69]. It has been used successfully orally and intrathecally for the treatment of neurologic conditions such as dystonia [70]. Some patients with CRPS develop dystonia. Short-term efficacy of intrathecal baclofen for relieving CRPS spasticity has been strongly supported in a double-blind, randomized, crossover trial of bolus intrathecal injections of 25, 50, and 75 μg of baclofen and placebo [71]. Oral and intrathecal baclofen also have been evaluated in preclinical [72] and clinical [73] studies as a treatment for neuropathic pain independent of spasticity. There is some evidence for efficacy in treating CRPS pain, even in patients without dystonia [74]. Seizures are a reported complication [75].

Neurosurgical Treatment Options
Patients who experience CRPS symptoms soon after trauma may benefit from decompression of a compromised neural structure. Some quickly diagnosed nerve injuries can be treated with microsurgical repair. Even some patients with established CRPS may be candidates for neurosurgical procedures. Occasionally, nerves are compressed or compromised by scar tissue and clinical improvement is obtained after neurolysis [76]. When performed on the appropriate patients, neurosurgical procedures provide pain relief that can exceed that obtained from medical treatment. These options should be considered especially when more conservative treatments fail, particularly in the young and otherwise healthy patients, who comprise most of the population suffering from CRPS.

The possibility of improvement must be balanced against the risk of further injury and other complications of surgery. Ablative neurosurgical procedures (eg, cutting nerves), despite a simplistic appeal, are rarely efficacious in the long-term and carry clear risks of further loss of neural function, including worsening of pain after tissue deafferentation. Fortunately, the option of enhancing function of the remaining neurons (neuroaugmentation) is safer and
more efficacious for the treatment of CRPS [77]. Stimulation along the ascending pain pathways has been shown to be helpful in small series. The most common locations for stimulation for CRPS have been the periaqueductal gray [78] and the thalamus (usually nucleus ventralis posterolateralis) [79], but transcortical stimulation by magnetic arrays is a promising, minimally invasive alternative to deep-brain stimulation.

Electrical stimulation of the dorsal columns of the spinal cord
With percutaneous placement of the electrode and subcutaneous placement of the lead and pulse generator, this procedure is minimally invasive and is performed by physicians other than surgeons. The theoretical basis for efficacy was the gate theory of pain [80], but the actual mechanisms have not been defined clearly, perhaps because of the paucity of animal studies. These stimulators activate the central branch of primary afferents ascending in the dorsal horn. Retrograde transmission of these action potentials modulates the physiology of the dorsal horn and neuronal cell body and in the brain stem nuclei in which these axons terminate [81]. In animal models of painful nerve injury, pain-related behaviors and hind-paw hyperalgesia were reduced after stimulator placement [82]. This efficacy may be related to the activation of local GABAergic interneurons in the dorsal horn that inhibit the excitatory amino acids, which activate nociceptive projection neurons [83]. Another explanation may be the enhancement of descending catecholaminergic pathways [84].

In human studies, dorsal column stimulation has been shown to be effective in several clinical trials, although these are difficult to control [85,86]. In one randomized trial that used physical therapy as a control, 36 patients demonstrated improvement in pain and quality of life [87]. One retrospective report found greater efficacy of bilateral than unilateral leads for patients with CRPS I [87]. A limitation is the need to replace batteries, reposition leads, or correct other malfunctions in a significant proportion of patients [88]. It seems critical to have good overlap between the induced paresthesias and the painful area to obtain positive results. A preliminary report suggests that short-term efficacy of sympathetic blockade may predict a positive trial of spinal cord stimulation for patients with CRPS [89].

Electrical stimulation of injured nerves
Stimulation of a painful nerve proximal to the site of injury (Fig. 2) has among the highest success rates of any published treatments for established CRPS [9]. It offers theoretical advantages over dorsal column stimulation because it gives the surgeon the opportunity to inspect and correct any lesions (eg, scars) that may be contributing to the CRPS. Because placement is through an open incision, the position of the electrode can be optimized and secured to prevent migration. However, an experienced neurosurgeon is needed, and patients must be meticulously evaluated preoperatively to ensure that the injured nerve has been identified correctly and the lesions have been restricted to the nerves that are to be stimulated. A prospective trial is under way [90].

Conclusions
Because CRPS is disabling and difficult to treat (at least in adults), guidance from large, randomized, controlled trials is greatly needed. Greater understanding of the causative lesion of CRPS I may encourage more researchers to investigate potential treatments. In the meantime, the literature supports consideration of calcitonin or steroids for acute CRPS symptoms. Most children with recent-onset CRPS will improve spontaneously and should be treated conservatively. Adults with chronic CRPS should receive prompt
and thorough examination, including evaluation by a neurologist if needed, to identify potentially treatable lesions. Comprehensive care by clinicians experienced with CRPS should be instituted and secondary conditions (eg, tendon contractures or reactive depression) should be treated. Pain management should focus on the four classes of medications for which there are randomized, controlled trials in related neuropathic conditions.

A patient who does not achieve significant relief with continued trials of medications is served better by referral for consideration of surgical treatment options. Local anesthetic blocks should be used as a means to an end (eg, localization of a suspected nerve injury) rather than repeated and re-repeated in the hope of achieving long-term pain relief. Among the invasive treatments, neurostimulation is notable for its safety and efficacy. Improvements are needed in reliability and design of better electrodes for nerve stimulation. Destructive or ablative surgical options that can worsen neural damage should rarely be used to provide short-term pain relief (eg, for patients with limited life expectancies). Every attempt should be made to treat patients in ways that improve our knowledge base. In addition to enrolling patients in clinical trials and collecting long-term follow-up data, the importance of obtaining tissue specimens for research when they become available from the operating room or autopsy should not be overlooked. In the authors' experience, most patients with CRPS are eager to help us learn more.

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:
• Of importance
•• Of major importance

1. Mitchell SW: Injuries of Nerves and Their Consequences. New York: Dover Publications; 1965. This book, originally published in 1872 and reprinted in 1965, provided the first accurate description of complex regional pain syndrome II (or as Mitchell called it, causalgia) as it occurred during the American Civil War. His magnificent case descriptions have been validated but never surpassed by any other author. Still relevant today, this book is required reading for any clinician or researcher with a serious interest in complex regional pain syndrome.

This recent article demonstrates how little impact the International Association for the Study of Pain (IASP) criteria of 1994 have had on study design and data analysis. Of 107 studies reviewed, only three used the exact IASP definition of complex regional pain syndrome (CRPS). This level of inconsistency makes it nearly impossible to compare study results. Although the IASP criteria are flawed, they should be used for all studies of CRPS until they are revised or replaced.

This randomized, prospective study of 54 chronic patients with complex regional pain syndrome I compares spinal cord stimulation used in conjunction with physical therapy versus treatment with physical therapy alone. There were 24 patients in the spinal cord stimulation and physical therapy groups and 12 patients in the physical therapy group alone. The data demonstrated large improvement in pain and quality-of-life scores. Twenty-five percent of patients had complications requiring additional procedures, including surgeries. This study is of major importance because it demonstrates the greater improvements achievable with stimulators rather than medication alone.

Reviews 72 articles of controlled trials for complex regional pain syndrome (CRPS) and other types of peripheral neuropathic pain. Of those, 22 discussed CRPS. These studies support efficacy of corticosteroids in CRPS and provide limited or contradictory support for several therapies, including intranasal calcitonin, intravenous phenolamine, epidural clonidine, and Bier blocks with bretylium (but not with guanethidine or reserpine). This search identified no data to evaluate sympathetic ganglion blocks with local anesthetic, surgical sympathectomy, or physical therapy.