Complex Regional Pain Syndrome

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Current Treatment Options in Neurology 2003, 3:xx-xx
Current Science Inc. ISSN 1092-8480
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Opinion statement

Complex regional pain syndrome (CRPS) is a heterogeneous disorder that falls in the spectrum of neuropathic pain disorders. It is maintained by abnormalities throughout the neuraxis (the peripheral, autonomic, and central nervous systems). The pathophysiology of CRPS is not fully known. There are no scientifically well-established treatments. The diagnostic criteria for CRPS at this time are purely clinical; the utility of diagnostic tests has not been demonstrated. The most important element of CRPS treatment is the patient’s persistent efforts at restoration of function through activity combined with the most rational approaches to pain relief based on the neurobiology of the disorder. The most appropriate management of CRPS uses a multidisciplinary approach, including medical and psychologic intervention, and physical and occupational therapy. The key is gradual, persistent functional improvement. The rational use of pain therapies must be grounded in knowledge of pain neurobiology, its endogenous modulation, and the clinical presentation. Potential peripheral pathophysiological targets (and possible treatments) include increased spontaneous firing and responsiveness of peripheral afferent fibers mediated by inflammatory and other algogenic substances (somatosensory blocks, corticosteroids), altered levels of expression and functioning of multiple ion channels (local anesthetics, calcium channel blockers, anticonvulsants), abnormal interneuronal communication, and increased peripheral expression of adrenergic receptors and sympathetic excitation (sympathetic blocks, alpha-adrenergic antagonists, alpha-2 agonists). CRPS is also perpetuated by central mechanisms, with pathophysiological targets (and possible treatments) including reorientation of dorsal horn terminals (desensitization techniques), functional reduction in inhibitory interneuron activity (tricyclic antidepressants, GABA agonists, opioids), central sensitization and increased central excitability (GABA agonists, NMDA receptor antagonists, local anesthetics, alpha-2 agonists, spinal cord stimulation), impaired descending nociceptive inhibition (tricyclic antidepressants, opioids), and adaptive changes in the cortical centers underlying the sensory and affective dimensions of pain (psychologic, physical, and occupational therapies). The treatment choices should be aimed at remodulating, normalizing, disrupting, or preventing the progression of abnormalities in pain processing. Sympathetic nerve blocks should be performed at least once to assess if sympathetically maintained pain is present. To the extent that peripheral somatosensory nerve blocks can diminish nociceptive input to the central nervous system, these techniques may help reduce nociceptive sensitization of spinal neurons. Use of specific peripheral nerve blocks or epidural injections can help block central propagation of abnormal ectopic discharge and resulting central sensitization, and can reduce the size of regions of touch-evoked allodynia and normalize sensation in the involved territory. Pain relief, however it is achieved, is intended to facilitate participation in functional therapies to normalize use and improve motion, strength, and dexterity. Psychologic therapies targeting pain, stress, and mood disorders are valuable adjunctive treatments. Proper patient selection and use as part of a treatment continuum are key to achieving optimal outcomes from spinal cord stimulation. Selection criteria include failure of conservative multidisciplinary therapies, no major psychologic impediments, and successful multiple day trial stimulation to rule out placebo response and establish efficacy.

Introduction

Complex regional pain syndrome (CRPS) is the current diagnostic label for the syndrome formerly known by a variety of names, including reflex sympathetic dystrophy, Causalgia, Sudeck’s atrophy, shoulder-hand syndrome, neuroallogdystrophy, and reflex neurovascular dystrophy. It was originally recognized as a distinct pain syndrome among soldiers during the American Civil War after traumatic nerve injury. It falls within the spectrum of neuropathic pain disorders, and is distinguished by the prominent involvement of the autonomic nervous system. A prototypic presentation of the patient with chronic CRPS includes persistent “burning” dysesthetic pain in a limb with a region of intense
allodynia (pain in response to nonpainful stimuli), hyperalgesia (increased responsiveness to painful stimuli), extreme guarding of the affected limb, diminished strength and range of motion, and objective evidence of local autonomic dysregulation (vasomotor disturbance, sweating abnormalities, edema) and trophic changes (eg, skin, hair, and nail). The syndrome is not limited to the distribution of a single peripheral nerve, and the symptoms are disproportionate to the inciting event. Although reliable epidemiologic data are not available, it is estimated that approximately 5% of patients who experience significant limb trauma will develop CRPS. A small subset of patients may have no known precipitating event. No long-term prospective studies have assessed the natural history of CRPS.

The pathophysiology of CRPS is not fully understood, but recognition of several likely contributors may be useful in guiding treatment. Although the characteristic cool, sweaty extremity seen in patients with CRPS has in the past been assumed to indicate chronic sympathetic hyperactivation, this does not appear to be universally the case. Controlled prospective studies suggest that early acute CRPS is frequently characterized by a warm, dry extremity resulting from reduced sympathetic outflow, presumably related to minor nerve trauma associated with the initiating event [1]. Subsequent upregulation of local adrenoceptors and expression of adrenoceptors on nociceptive fibers after nerve trauma may produce a hypersensitivity to circulating catecholamines, resulting in many of the common features of chronic CRPS [2,3]. In response to persistent nociceptive input, spinal cord central sensitization can occur [4], a state in which a peripheral receptor or central neuron responds to nociceptive stimuli in a manner more intense than it would under normal conditions (hyperalgesia), or responds to a non-nociceptive stimulus to which it would normally be insensitive (allodynia). The key in managing CRPS may be in the recognition that multiple pathophysiologic mechanisms can exist in an individual patient. The patient’s clinical presentation may support the predominance of one of these mechanisms. Although there are few data addressing the issue, it is clinically accepted that early intervention increases the likelihood of successful outcomes. The mechanisms discussed highlight the importance of a treatment rationale that emphasizes response to targeted nerve blocks (sympathetic versus somatic), and the importance of intervening before significant, widespread, and irreversible central changes have occurred.

Well-developed scientifically validated guidelines for management of CRPS derived from large controlled clinical trials are not available, in part because of the historic disagreements over diagnosis of the syndrome. Increasing use of the standardized CRPS diagnostic criteria published in 1994 by the International Association for the Study of Pain (IASP) [5] provides greater opportunity for standardization of research samples and improved comparability across outcome studies (Table 1) [6]. The treatment outcome studies in CRPS published thus far have generally used inconsistent and idiosyncratic diagnostic criteria, thus making it difficult to draw firm conclusions about applicability to patients diagnosed based on the currently accepted IASP criteria. Although the current diagnostic approach distinguishes between CRPS type II (Causalgia; condition associated with defined nerve injury) and CRPS type I (reflex sympathetic dystrophy; no clear nerve injury identified), there is no definitive evidence that this diagnostic distinction has clinical utility with regard to treatment planning.

With these caveats in mind, this review will summarize the available research literature on the management of CRPS. Given the commonly acknowledged difficulties in treating this disorder, it is somewhat surprising that there are few randomized controlled trials (RCTs) of the most widely used treatment approaches. Those clinical trials that are available in CRPS patients are based entirely on small samples of subjects. Furthermore, there are typically mixed results regarding efficacy of the same intervention across studies when multiple controlled trials are available. It is unclear to what extent the negative results may be because of the small sample sizes rather than actual lack of efficacy. Given the limitations, treatment approaches must by necessity be based as much on clinical experience as on controlled outcome studies, although large randomized clinical trials in other neuropathic pain conditions do likely have relevance to CRPS treatment in some cases.

There are a number of treatment options available for CRPS (summarized in Table 2). These approaches can be divided into pharmacologic, interventional, physical/occupational therapy, and psychologic techniques. Although many of these approaches may be effective in certain patients in isolation, most patients will progress only when multiple approaches are integrated simultaneously. Pharmacologic treatment options, such as antidepressants, anticonvulsants, and opioids, are generally considered palliative and can be effective treatments. There is some evidence of a possible inflammatory component to CRPS, particularly in the acute stage. Corticosteroids target this presumed inflammatory component, and in randomized controlled trials have demonstrated significant efficacy in early CRPS. Intervenational approaches are also frequently used in the management of CRPS in conjunction with nonpharmacologic approaches, with one goal being to provide temporary pain relief to permit optimal participation in functional therapies. Intervenational approaches include various sympathetic ganglion blocks (ie, stellate, thoracic, lumbar), intravenous regional sympathetic blocks (Bier blocks), somatic blocks (eg, peripheral nerve blocks, brachial plexus), and epidural blocks. The latter types of blocks can be provided on a continuous basis during inpatient hospital stays or on an
outpatient basis via indwelling catheter with a pump or bolus injections in the clinic. There may be wide variability in responses to sympathetic blockade, with only a subset of CRPS patients exhibiting pain responsive to sympathetic blockade (*i.e.*, sympathetically maintained pain [SMP]). To the extent that interventional blocks diminish nociceptive input to the central nervous system, these techniques could help reduce the nociceptive sensitization of spinal neurons that may contribute to allodynia and hyperalgesia in CRPS and perpetuate the disorder. Although not reviewed here, surgical sympathectomy should only be considered with caution, given its invasiveness, weak evidence for its efficacy, and that it may not fully ablate anomalous pathways, resulting in incomplete disruption of sympathetic outflow to the targeted area. Clinical expert opinion has placed increasing emphasis on functional therapies, including physical and occupational therapy, as being core treatments for CRPS. Within this rehabilitation perspective, interventional and other management approaches are judged largely by their ability to facilitate progress in these functional therapies. Psychologic therapies, including relaxation training with temperature or muscle tension biofeedback, along with cognitive-behavioral techniques, are also commonly believed to be valuable adjunctive treatments for pain control and for facilitating functional improvement.

**Treatment**

**Lifestyle**

- Once CRPS has developed, disuse of the affected extremity in an effort to avoid pain may be a contributor to symptom severity and maintenance of the condition. It is therefore critical that patients be encouraged to maintain, to the extent possible, normal use of the affected extremity.

**Pharmacologic treatment**

- The aims of pharmacotherapy in CRPS are to reduce pain; through decreased pain, improve ability to participate in functional therapies and enhance quality of life; and, for certain drug classes (*e.g.*, corticosteroids, alpha adrenergic antagonists, alpha-2 agonists, and tricyclic antidepressants) address contributing pain pathways and mediators of CRPS pathophysiology.
- The pharmacologic approaches described are generally off-label uses that are not US Food and Drug Administration–approved specifically for CRPS treatment. Examination of the literature indicates that a variety of pharmacologic approaches have been tested for CRPS. However, there are certain core treatments that expert panels have agreed should be considered for management of CRPS [7,8*]. Several less widely-used treatment approaches have also been investigated, although are not considered standard treatments for CRPS. These categories of pharmacologic treatments are summarized herewith.

**Core pharmacologic treatments**

*Corticosteroids (prednisone, methylprednisolone)*

Two prospective RCTs [9, 10, Class I] indicate that a pulse of oral corticosteroids resulted in significant improvements in symptoms compared with placebo in patients with early acute CRPS (mean of 12 weeks duration). Dosages were in the range of 30 mg per day for 2 weeks (but up to 12 weeks), followed by a tapering period [9]. Side effects include weight increase, edema, hypertension, excessive potassium excretion, and psychosis. Contraindications are multiple, and include gastrointestinal problems (*e.g.*, severe ulcerative colitis, diverticulitis, and peptic ulcer), hypertension, congestive heart failure, thromboembolic tendencies, osteoporosis, exanthema, Cushing's syndrome, antibiotic-resistant infections, convulsive disorders, metastatic carcinoma, diabetes mellitus, hypothyroidism, and cirrhosis (enhanced effect of corticosteroids).

*Antidepressants*
Evidence for efficacy of antidepressants is derived from Class I meta-analyses of non-CRPS neuropathic pain RCTs [11–13]. Meta-analytic results from McQuay et al. [12] indicate that for every 100 patients with neuropathic pain receiving antidepressants, 30 will obtain at least 50% pain relief. Although a wide variety of antidepressants may prove effective, meta-analytic reviews support greater efficacy with tricyclic or heterocyclic antidepressants than with serotonin-specific reuptake inhibitors [11,12]. Dosages vary by specific agent used, but the dictum "start low and go slow" is considered appropriate, with upward titration continuing until efficacy is achieved or intolerable side effects occur. Contraindications include cardiac disorders, seizure disorders, hepatic impairment, and pregnancy. Major side effects of tricyclic antidepressants include sedation, anticholinergic effects (eg, dry mouth), rash, and cardiovascular effects (eg, orthostatic hypotension, cardiovascular toxicity).

**Anticonvulsants**

Evidence for efficacy of anticonvulsants is derived from Class I meta-analyses of non-CRPS neuropathic pain RCTs [11,13,14]. The only available Class I RCT specifically in patients with CRPS indicated that carbamazepine (600 mg per day) resulted in significant pain reductions relative to placebo over an 8-day trial [15]. One case series in patients with CRPS (Class III) also suggests the efficacy of gabapentin [16]. In general, dosages should be titrated upward in the same manner as for antidepressant agents. Meta-analysis (Class I) indicates that antidepressants and anticonvulsants display a similar degree of efficacy for neuropathic pain, although through different mechanisms, with anticonvulsants appearing somewhat better tolerated [13]. Contraindications include pregnancy, and cardiac, hepatic, or renal impairment. Gabapentin has few major side effects, although carbamazepine may have major side effects (aplastic anemia, agranulocytosis, severe dermatologic reactions, decreased leukocyte count, hyponatremia, impaired liver function, drowsiness, and dizziness). Monitoring of drug plasma levels is recommended with long-term use of these agents.

**Phenoxybenzamine**

Phenoxybenzamine is an alpha-adrenergic antagonist that has been recommended for use in cases where SMP has been demonstrated by responsiveness to sympathetic ganglion block. Evidence for efficacy of phenoxybenzamine comes solely from case series studies [17,18, Class III], with seemingly greater efficacy in syndromes of less than 3 months in duration [17]. In these studies, treatment was initiated at dosages of 10 mg per day, titrating upward to 120 mg per day. Contraindications include marked cerebral or coronary arteriosclerosis, or renal impairment. Significant side effects included sexual dysfunction (men), orthostatic hypotension, tachycardia, nasal congestion, nausea, and diarrhea.

**Transdermal clonidine**

Clonidine is an alpha-2 adrenergic agonist that may reduce CRPS symptoms through diminution of local norepinephrine release from sympathetic terminals [19]. One small Class III case series indicated that transdermal clonidine applied to the affected extremity reduced or eliminated local CRPS-related hyperalgesia and allodynia [19]. This study sample was restricted to patients with SMP evidenced by responsiveness to sympathetic blockade. In contrast, a larger RCT (Class I) in other neuropathic pain conditions indicated no significant overall efficacy for transdermal clonidine, although approximately 25% of the sample appeared to be clonidine responders (20). Contraindications include coronary insufficiency or cardiac disease. The most common side effects of transdermal clonidine include dry mouth and sedation, with other side effects reported including chest pain, decreased blood pressure, fatigue, headache, insomnia, nervousness, dizziness, irritability, impotence, and localized erythema or contact dermatitis.

**Opioids**

Evidence for efficacy of opioids is derived from Class I studies of neuropathic pain [21–23]. The only available Class I RCT of opioids specifically in CRPS found that sustained-release morphine (90 mg per day) did not significantly reduce pain relative to placebo over an 8-day trial, although this finding may have been impacted by design limitations on upward dose titration allowed [15]. Generally, neuropathic pain appears less responsive to opioids than nociceptive pain [23–25]. This may require use of higher doses in patients with CRPS, and consequently, increased risk of side effects. Daily use of opioids can produce drug tolerance in all patients, and psychologic dependence in susceptible individuals. For patients with a history of substance abuse, concurrent participation in a recovery program or treatment by an addictionologist is strongly advised if opioids are to be used. Side effects include sedation, lightheadedness, dizziness, nausea, vomiting, sweating, hypotension, respiratory depression, euphoria, constipation, weakness, skin rash, dry mouth, and itching.

Less common pharmacologic treatments
Intranasal calcitonin

Calcitonin is a polypeptide hormone produced in the thyroid gland that regulates blood calcium levels and bone calcium metabolism [26]. It has demonstrated some analgesic effects [26]. Meta-analysis (Class I) of the limited available controlled studies indicates significant efficacy for calcitonin in CRPS [27]. Doses for intranasal calcitonin ranged from 100 to 300 U per day [28–30]. Side effects may include nasal congestion, mild nausea, dizziness, facial flushing, and hypoglycemia [28,31,32].

Topical dimethylsulfoxide

Topical dimethylsulfoxide is a potent free-radical scavenger. One small prospective non-randomized trial indicated that topically-applied dimethylsulfoxide resulted in significantly greater pain decreases over 9 weeks than a series of bier blocks with guanethidine [33]. This Class II study included only patients with previously untreated CRPS of brief (less than 3 months) duration. Significant side effects include a strong garlic-taste in the mouth and local skin changes (eg, wrinkling).

Nifedipine

Nifedipine is a calcium channel blocker. Evidence for its efficacy in CRPS comes from Class III case series studies [17,34]. Initial dosages were in the range of 30 mg per day, titrated upward to 60 mg per day [17]. Contraindications include pregnancy, or renal or hepatic impairment. Major side effects include hypotension, vasodilation, headache, flushing, and decreased platelet aggregation. Congestive heart failure (especially in patients also on beta blockers) and cardiac arrhythmias are possible.

Bisphosphonates

Bisphosphonates, such as pamidronate and alendronate, are inhibitors of bone resorption. Evidence for their efficacy in CRPS comes from small Class I RCTs [35,36] and Class III case series [37]. Alendronate (7.5 mg intravenously per day for 3 days) resulted in significant reductions in pain and swelling, and increases in range of motion compared with placebo [35]. Previous trials have administered bisphosphonates as a series of intravenous infusions over 3 to 10 consecutive days [35–37]. Contraindications include pregnancy, renal insufficiency, hypocalcemia, osteomalacia, or serious esophageal disease. Major side effects include gastrointestinal irritation, osteoporosis, and impaired renal function.

Intravenous lidocaine

Lidocaine is a sodium channel blocker. Evidence for its efficacy in CRPS comes from a single Class I RCT [38]. Compared with placebo, lidocaine resulted in significantly reduced cold and tactile allodynia, and decreased spontaneous pain at higher dosages [38]. Infusion dosages (from 329 to 700 mg total dosage) tested were designed to achieve blood levels ranging from 1 to 3 µg/mL at steady state for 20 minutes. Although this study demonstrated short-term efficacy of this treatment, no data are available to indicate its long-term clinical utility. Contraindications include hypersensitivity to amide local anesthetics, congestive heart failure, Stokes-Adams syndrome, Wolff-Parkinson-White syndrome, and severe sinoatrial, atrioventricular or intraventricular block. Significant side effects included lightheadedness, sedation, dry mouth, and increased blood pressure at higher dosages [38], as well as delayed cardiac conduction.

Interventional procedures

- The aims of interventional procedures for CRPS are palliation of pain to facilitate participation in functional therapies and improve quality of life, and to help break the cycle of persistent nociceptive input that may contribute to sensitization of spinal nociceptive neurons.

Sympathetic ganglion block

Only a subset of patients with CRPS display SMP, typically defined as at least a 50% decrease in pain in response to sympathetic blockade, and therefore not all patients will respond clinically to sympathetic blocks. There is some degree of tautology inherent in the distinction between SMP and sympathetic-independent pain (SIP), given that a sympathetic block is being used to diagnose block responsive CRPS. This presumed pathophysiologic distinction may be difficult to determine reliably, given that a negative response to sympathetic block may be because of inaccurate placement rather than lack of SMP, and a positive response may be because of systemic absorption of local anesthetic (as in intravenous lidocaine therapy) or anesthetic spillover to adjacent somatic nerve fibers rather than SMP. What is
clear is that not all patients respond to sympathetic blocks, although a subset may respond quite well. The frequent presence of S1P mechanisms in CRPS makes sample selection for clinical trials of sympathetic blocks problematic, and likely results in an underestimation of the efficacy of such blocks for patients with SMP, and an overestimation of efficacy in patients with S1P. Sympathetic ganglion blocks include stellate ganglion block (SGB) for upper extremity CRPS and lumbar sympathetic block (LSB) for lower extremity CRPS. Fluoroscopic guidance is necessary for LSB, and desirable for SGB. For these approaches, 0.25% to 0.375% marcaine is recommended. For SGBs, a dosage of 5 mL is common, whereas for LSBs, a dosage of 10 mL can be administered.

To the authors' knowledge, there is only one published RCT (n=7 patients; Class I) testing the efficacy of sympathetic ganglion blockade for CRPS [39]. Results indicated that initial pain relief was comparable with placebo, but that relief lasted significantly longer (nearly 4 days) than did relief with saline placebo blockade (less than 1 day). A recent qualitative review of this literature indicates that available Class II and Class III studies (29 studies total, generally poorly controlled) suggest reasonable efficacy of sympathetic ganglion blockade in at least a subgroup of patients with CRPS [40], with 29% of patients achieving total pain relief, and 41% of patients achieving at least 25% pain relief. The studies reviewed as a group did not provide data sufficient to clearly determine the duration of clinical relief achieved [40]. At least two nonrandomized controlled studies (Class III) suggest that the degree of pain relief with sympathetic blockade is not correlated with the degree to which the sympathetic nervous system is blocked [41,42].

Side effects include Horner's syndrome (eg, nasal stuffiness, flushing), as well as cardiac arrest (SGB only) if the block is malpositioned.

**Intravenous regional block**

As with sympathetic ganglion blocks, intravenous regional blocks (IVRB) are likely effective only in patients with SMP. There is therefore wide variability in responsiveness (eg, only 35% of patients in one RCT were responders to guanethidine IVRB [43]. IVRBs are typically given in a series over several days or weeks, and during each, a tourniquet is applied to the affected extremity with the selected agent given intravenously in the affected extremity. The tourniquet is typically maintained for approximately 15 minutes [44,45]. Several agents have been reported to be used in IVRBs, including guanethidine (norepinephrine depleter), bretylium (norepinephrine depleter), ketanserin (serotonin type-2 receptor antagonist), and clonidine (alpha-2 adrenergic agonist).

Evidence for efficacy of IVRB with guanethidine (10 mg in 10 mL saline) is derived from Class I studies [46,47]. One study indicates that pain relief from IVRB with guanethidine may be significantly longer lasting than that observed with sympathetic ganglion blockade (ie, stellate) [48]. Despite positive results reported in these two controlled studies, a meta-analysis (Class I) of all available controlled trials of guanethidine IVRB indicates no significant overall short or long-term efficacy in CRPS [27]. Side effects reported with guanethidine IVRB include severe postural hypotension, bradycardia, dizziness, and chest pain [48].

Evidence for efficacy of bretylium (1.5 mg/kg, combined with 40 to 60 mL of 0.5% lidocaine) comes from a single Class I study [49]. Bretylium in this study resulted in significantly longer lasting pain relief (mean of 20 days) than lidocaine alone (mean of 3 days). Reported side effects include orthostatic hypotension and bradycardia [49].

Evidence for efficacy of ketanserin (10 mg upper extremity, 20 mg lower extremity) also comes from a single Class I study [50]. Side effects of ketanserin included drowsiness, shakiness, and faintness [50].

Evidence for the efficacy of IVRB with clonidine (1 μg/kg in 50 mL 0.5% lidocaine) comes from a single Class III case series [51]. This study reported complete short-term pain relief in four of six patients, all of whom had demonstrated previous responsiveness to sympathetic ganglion blockade. No significant side effects were reported, although hypotension would be an expected side effect.

General side effects of IVRBs include significant acute pain during the procedure because of acute ischemia.

**Somatosensory block**

Somatosensory blocks targeting the presumed peripheral nociceptive generator may include interscalene or axillary brachial plexus blocks for upper extremity, lumbosacral plexus for lower extremity, or selective peripheral nerve blocks such as median, ulnar, or radial nerve blocks [8*]. These blocks may be administered as single blocks, but more frequently are reported as continuous infusions using an indwelling catheter, with the goal being to titrate the dosage to produce sensory blockade without concurrent motor blockade. Given the presumed pathophysiologic role of a continuing nociceptive afferent barrage in development and maintenance of central sensitization in CRPS [4], peripheral sensory blockade theoretically should help interrupt this pathologic process [52]. Clinically, continuous somatosensory blockade is primarily intended to provide sufficient temporary pain relief to allow full participation in functional therapies believed one of the keys to optimal CRPS treatment [8*].

Evidence for efficacy of somatosensory blocks comes solely from Class III case reports or case series studies [52–59]. Agents used in somatosensory blocks vary somewhat, with previous studies reporting use of local anesthetic (typically bupivacaine) [52,56–59], morphine [55], or combinations of local anesthetic and methylprednisolone [54]. For continuous upper extremity somatosensory blockade, local anesthetic dosages have been reported in the range of 4 mL per hour of 0.25% bupivacaine [58], and morphine dosages in the range of 0.16 mg per hour [55].

**Epidural blockade**
Epidural treatment approaches vary, with little published data available to guide treatment. The only published data regarding the epidural treatment approach for CRPS derive from a single Class I study [60]. This placebo-controlled trial examined the efficacy of a single epidural injection of clonidine 300 or 700 μg in 10 mL saline. The doses provided significant reductions in pain relative to placebo, with some evidence for dose-dependent effects. Side effects included hypotension, sedation, dizziness, nausea, mouth sores, and dry mouth.

Continuous epidural blockade using an infusion pump on an inpatient or outpatient basis may also be used. Rauck et al. [60, Class III] examined continuous clonidine infusion via indwelling epidural catheter (10 to 50 μg per hour) for durations of more than 1 month (outpatient) among clonidine responders identified through placebo-controlled trial. Weekly pain ratings were significantly lower than pretreatment ratings across the continuous infusion period [60]. Significant problems with infections at the catheter site were reported in nearly one third of patients.

Other agents may also be used with epidural infusions, although published data on these approaches are extremely limited. Lin et al. [59, Class III] reported two cases in which a lumbar epidural catheter was used to administer three times a day a combination of ketamine (7.5 mg), morphine (0.75 mg), and 0.1% bupivacaine (6 mL). Several courses of such treatment over 3 to 6 months were reported to result in "satisfactory pain relief" for these patients.

It is critical to report that the use of continuous epidural infusions is intended to provide sufficient temporary pain relief to allow full participation in functional therapies [8]. Such treatments should not be viewed as curative, and if not combined with functional therapies, are likely of little lasting value.

**Spinal cord stimulation**

Evidence for the efficacy of spinal cord stimulation (SCS) derives from one Class I RCT [61], and several Class III case series [62]. The only available RCT, which examined highly disabled patients with severe CRPS who had failed less invasive treatments, indicated that SCS plus physical therapy resulted in significant reductions in pain and greater perceived improvement compared with physical therapy alone over a 6 month trial [61]. Qualifications to these results include a failure to demonstrate significant benefits of SCS on functional measures, and the one third of patients who failed to respond to an initial trial of SCS [61]. Additional analyses in this sample indicated only minimal influence of SCS on the hyperalgesia and allodynia components of CRPS [63].

Initial trial implantation and permanent implantation may cost $20,000 in aggregate, and given the level of invasiveness of the procedure, it has been recommended as a treatment only for patients who have failed full trials of less invasive, multidisciplinary treatment approaches [8]. Results of the only existing RCT indicate that SCS alone is unlikely to improve patient functioning, despite an overall benefit with regards to pain. In principal, provision of appropriate physical/occupational therapy in the context of SCS-related analgesia in otherwise treatment-resistant patients may have the potential to lead to functional improvements and improved quality of life. Risks of SCS implantation may include infection at the implantation site, lead migration or fracture, loss of analgesic efficacy, stimulator malfunction, and electromagnetic interference problems.

Contraindications include cognitive problems that would interfere in ability to properly use the stimulator, major psychopathology (e.g., psychosis), current substance abuse, psychologic factors significantly affecting the condition, and brief symptom duration. This latter issue may be important given recent evidence that spontaneous resolutions of CRPS are common in the first 6 months of the disorder [64], a finding that also suggests caution in interpreting the seeming efficacy of CRPS treatments supported solely by uncontrolled case series data. Despite possible spontaneous resolution in some patients with early CRPS, one must take into consideration the patient's suffering no matter what the duration of the condition by providing appropriate pain relief to attempt to abort potential progression to permanent central changes and refractory pain.

**Physical/occupational therapy and exercise**

- Disuse may aggravate central and peripheral sensitization. Therefore, engagement in appropriate physical and occupational therapy is considered a cornerstone in the effective treatment of CRPS [7,8]. Interventions recommended include scrubbing and stress loading protocols as described by Carlson and Watson [65], desensitization training, isometric exercises, aerobic exercise, myofascial release, postural correction, lymphatic massage for edema control, and active range of motion exercises focused on the affected extremity [8]. Passive range of motion exercise must be avoided. As patients improve, specific interventions appropriate to patients' functional status are provided focusing on re-normalizing daily use of the affected extremity. It is critical that the intensity of functionally focused therapy be pain-limited, balancing the desire to increase tolerance and capacity with avoidance of significant and prolonged pain flare-ups [66].

- Evidence for the efficacy of functional therapies comes from one Class I RCT [66] as well as Class III case series studies [65–68]. Results of the only available RCT indicate that physical therapy, and to a lesser extent occupational therapy, resulted in significantly greater improvements in pain, range
of motion, and overall impairment than were achieved using a social work control intervention that emphasized pain avoidance [66]. This study, which also included treatment with topical dimethylsulfoxide and calcium channel blockers, was conducted in patients with CRPS of less than 1 year in duration. Dramatic efficacy has been reported in prospective Class III studies using functional therapy in children, with up to 88% symptom-free at 2-year follow-up [67-68].

**Psychologic and behavioral treatments**

- Complex regional pain syndrome, like all chronic pain, is frequently associated with increased life stress, emotional distress, and interference in ability to carry out daily activities. Some interference in daily activities may be because of learned avoidance of activities that are expected to exacerbate pain, a condition that may be amenable to behavioral treatment approaches. Physiologic arousal accompanying life stress and emotional distress appears to exacerbate CRPS symptoms [69]. The purpose of psychologic treatments for CRPS is therefore to teach psychologic pain and stress management skills that give patients some degree of control over their pain and other symptoms (eg, coldness in affected extremity); and to address maladaptive thoughts, beliefs, and behavior patterns that may contribute to or help maintain functional disability and exacerbate pain.
- Although duration of psychologic treatment will likely vary depending on patient-specific issues, 12 sessions is likely a reasonable time frame for initial exposure to this treatment component if there is sufficient compliance with home practice assignments.

**Biofeedback and relaxation training**

- The goal of relaxation training with biofeedback is to increase patients’ ability to control their pain and decrease emotional arousal that may impact negatively on CRPS. Class III case series studies suggest that breathing-focused relaxation, relaxing imagery, and autogenics all may be effective adjunctive treatments, especially when combined with thermal or surface electromyograph biofeedback [70]. Selection of specific techniques is guided primarily by patient and therapist preference.

**Cognitive-behavioral techniques**

- Cognitive-behavioral techniques include education regarding CRPS and living with the condition, helping patients adopt a self-management perspective emphasizing the need for active involvement in treatment in the clinic and at home, and addressing dysfunctional cognitions that may interfere with treatment. For example, catastrophizing cognitions (eg, “this is terrible,” “I can’t handle this,” “my life is over”) may contribute to elevated distress, which may impact on catecholamines, and thereby aggravate CRPS symptoms. Such cognitions also contribute to adopting a maladaptive passive patient role, and may interfere with functional therapies. It is therefore important to help patients learn to identify their specific dysfunctional cognitions regarding CRPS, and adopt more adaptive ways of thinking about their condition and their treatment. Although RCTs of cognitive-behavioral techniques in the general chronic pain population clearly indicate their efficacy (Class I meta-analyses) [71], there are no studies specifically of this type of intervention in patients with CRPS.

**Pediatric considerations**

- It is desirable in children to minimize the extent to which invasive procedures and medications are required for CRPS treatment. As discussed previously, Class III studies suggest that well-structured functional therapy and exercise programs may provide significant benefits in children [71,72], and should therefore be emphasized. As in adults, it is believed critical for successful outcomes to maintain normalized use of the affected extremity as much as possible. The natural parental reaction to suggest the child avoid any activities that provoke increased pain to decrease the child’s suffering
may work contrary to this treatment goal. Parental education and family therapy may be helpful to prevent these normal protective reactions from interfering with treatment.

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:

- Of importance
- - Of major importance

This article overviews the treatment recommendations of an expert panel of leading CRPS clinicians and researchers, and describes issues related to treatment sequencing and integration of multidisciplinary treatments.


