Prevention and management of complex regional pain syndrome in adults

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INTRODUCTION — Complex regional pain syndrome (CRPS) is a disorder of the extremities that is characterized by pain, swelling, limited range of motion, vasomotor instability, skin changes, and patchy bone demineralization. It frequently begins following an injury, surgery, or vascular event such as a myocardial infarction or stroke.

Alternative names for CRPS in the literature include, reflex sympathetic dystrophy, algodystrophy, causalgia, Sudeck's atrophy, transient osteoporosis, and acute atrophy of bone. Upper extremity involvement following stroke or myocardial infarction is sometimes referred to as the "shoulder-hand syndrome". A consensus development conference in 1995 grouped these disorders under a single heading of complex regional pain syndrome [1].

The prevention and management of CRPS will be reviewed here. The clinical manifestations and diagnosis of CRPS in adults and issues related to CRPS in children are discussed separately, but the following summary may be useful when considering management of CRPS in adults. (See "Etiology, clinical manifestations, and diagnosis of complex regional pain syndrome in adults" and "Complex regional pain syndrome in children".)

A diagnosis of CRPS requires the presence of regional pain and sensory changes, typically following a noxious event. The pain is of a severity greater than that expected from the inciting injury, and is often associated with such findings as abnormal skin color, temperature change, abnormal sudomotor activity, or edema.

TYPES AND STAGES — Two types of CRPS have been recognized:

- Type I corresponds to patients with CRPS without a definable nerve lesion and represents about 90 percent of clinical presentations.
- Type II was formerly termed causalgia and refers to cases where a definable nerve lesion is present.

Three stages can occur during the course of CRPS:

- Stage 1 — Either following an event or without apparent cause, the patient develops pain in a limb. The essential features include burning and sometimes throbbing pain, diffuse uncomfortable aching, sensitivity to touch or cold, and localized edema. Vasomotor disturbances occur with variable intensity, producing altered color and temperature. The radiograph is either normal or shows patchy demineralization.
- Stage 2 — The second stage is marked by progression of the soft tissue edema, thickening of the skin and articular soft tissues, muscle wasting, and the development of brawny skin. This may last for three to six months.
- Stage 3 — The third stage is most severe. It is characterized by limitation of movement, the shoulder-
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hand syndrome (capsular retraction producing a frozen shoulder), contractures of the digits, waxy trophic skin changes, and brittle ridged nails (picture 1). Bone radiography reveals severe demineralization.

**PREVENTION** — The best treatment of CRPS is prevention. Early mobilization may reduce the risk of developing CRPS in patients with stroke or myocardial infarction. Supplementation with vitamin C is another preventive measure that has been used in the setting of fracture management.

**Early mobilization** — Limited data suggest that early mobilization following stroke reduces the risk of CRPS. The following are illustrative:

- Patients with hemiplegia, were randomly assigned to mobilization or ordinary care [2]. The group that received early mobilization had a significantly lower incidence of CRPS (8 versus 27 percent, respectively).

- A comparison of noncontemporaneous cohorts noted lower rates of CRPS in those who received early mobilization versus those who did not [3].

Thus early mobilization after injury, or following a myocardial infarction or stroke should be encouraged. Prolonged use of intravenous therapy should be accompanied by intermittent passive shoulder motion.

**Vitamin C following fracture** — Fracture of the distal radius may lead to CRPS of the upper extremity. The incidence of this complication is uncertain; reported rates range from less than one to 22 percent [4,5]. The prophylactic use of vitamin C after wrist fracture may lower the risk of CRPS.

- In one study of 123 patients with 127 wrist fractures, patients were randomly assigned to receive either vitamin C (500 mg/day) or placebo for 50 days [5]. The incidence of CRPS was significantly decreased in the active therapy group (7 versus 22 percent).

- A larger, multicenter study randomly assigned 416 older women with wrist fractures to receive placebo, or one of three daily doses (200, 500, or 1500 mg) of vitamin C, for 50 days [6]. CRPS was less prevalent in those who received vitamin C (any dose versus placebo, 2.4 versus, 10.1 percent). Each of the three doses was statistically superior to placebo and the higher doses (500 and 1500 mg/day) had greater mean reductions in the relative risk (RR) of CRPS than the lower dose (RR 0.13, 0.17, and 0.41, respectively).

Although the mechanism underlying the beneficial effect of vitamin C is uncertain, there is little risk from use. The optimal dose of vitamin C remains uncertain. Doses of 500 to 1500 mg/day may be more effective than lower doses. There appears to be no clinically significant difference between 500 mg and 1500 mg daily. A dose of 500 mg/day was more efficacious than placebo in both randomized trials for post wrist fracture prophylaxis and is the dose that is currently suggested by the authors of the largest clinical trial [6] and, independently, by others [7].

We recommend early mobilization for stroke patients and use of supplemental vitamin C for those with wrist fractures as preventive measures.

**MANAGEMENT** — A multidisciplinary approach is suggested in a guideline for management of CRPS developed by a consensus of experts [8]. Clinical experience suggests that treatment is more effective when begun in stage 1, as soon as the diagnosis is established and before radiographic changes appear. However, it is uncertain whether immediate referral to a specialist in pain management results in superior outcomes compared to referral to physical or occupational therapy for protective and assisted mobilization of the affected limb within pain limits, supplemented by conservative pharmacologic interventions, to be followed by referral to an expert in pain management if the patient does not improve.

**Patient education** — Patients' participation in physical and occupational therapy may be facilitated by an explanation that neuropathic pain does not indicate tissue damage in the hyperalgesic region but arises from

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nerve damage from a known or unknown cause. Prior to a referral to a specialist in rehabilitation or to a physical or occupational therapist, the clinician should stress the importance of working to regain use of the affected limb while recognizing the difficulty of doing so in the face of ongoing pain.

The patient should be provided with addresses of a support groups; examples include:

- In the United States - The Reflex Sympathetic Dystrophy Syndrome Association, P.O. Box 921, Haddonfield, NJ 08033 or at www.rds.org

- In the United Kingdom - Reflex sympathetic dystrophy - Complex regional pain syndrome UK at www.rsdalert.co.uk/

**Psychologic assessment and counseling** — Job and interpersonal relationships should be evaluated in all patients. Stress-management techniques may reduce the effect of stress on the autonomic and central nervous system.

Patients with later stage CRPS may benefit from assessment by a clinical psychologist and from cognitive behavioral therapy. Although psychologic assessment and therapy have not been formally assessed in patients with CRPS, their usefulness in other chronic painful disorders suggests that this approach can be beneficial to those with CRPS. Graded motor imagery, a psychologic approach that involves having patients with CRPS type I imagine their affected limbs in various positions may be helpful in reducing pain and improving function [9]. A psychologist may also help to identify comorbid mood or other psychiatric disorders and to assist the patient in identifying and coping with ongoing life stresses [10].

We suggest consulting a clinical psychologist if any of the following are present:

- CRPS of more than two months duration at presentation
- No response to treatment
- Suspected comorbid psychologic or psychiatric disorder

**Physical and occupational therapy** — In contrast to the data on the effectiveness of physical and occupational therapy (PT and OT) in prevention of CRPS, randomized and controlled clinical trials of PT and OT for patients with CRPS have produced disparate results as illustrated by the following:

- No advantage of PT and OT over care that did not involve these interventions [11].
- PT and OT better than control [12]
- Less pain with PT and OT but no significant difference in range of motion after one year [13]

Aside from cost and inconvenience there is little downside to arranging for PT and/or OT evaluation and treatment of patients with CRPS. We suggest referral to an appropriate therapist soon after the diagnosis is established. Physical therapy, which can be performed twice daily at home for patients in all stages of disease, should ideally begin before limitation of movement occurs. If physical or occupational therapy is delayed to stage 3, impairment is not likely to improve. Resting splints for the affected limb are sometimes used with a goal of preventing progressive joint contractures. However, the effectiveness of splinting is uncertain.

**Smoking cessation** — Cigarette smoking appears to be a risk factor for CRPS. As an example, a retrospective study of 53 patients with CRPS found that there was a higher incidence of smoking in patients with CRPS compared to controls (68 versus 37 percent) [14]. Although a beneficial effect of smoking cessation has not been assessed for CRPS per se, the possible risk enhancing effect of smoking provides another rationale for advising smoking cessation. (See "Patterns of tobacco use and benefits of smoking cessation" http://www.uptodate.com/online/content/topic.do?topicKey=painrheu/5757&view=print 7/20/2010
Pharmacologic approaches — Only a few pharmacologic agents have been studied in well designed clinical trials in patients with CRPS. Medications that appear to be significantly better than placebo in relieving pain due to CRPS include some agents in the following drug classes [15]:

- Anticonvulsants
- Bisphosphonates
- Oral glucocorticoids
- Nasal calcitonin

Though not specifically studied in CRPS, antidepressant medications are often effective in reducing neuropathic pain. The author's clinical experience suggests that tricyclic antidepressants reduce pain and are a valuable addition to physical therapy for patients with CRPS. (See "Overview of the treatment of chronic pain").

Guidelines developed by a consensus of experts in CRPS suggest beginning treatment for pain due to CRPS with a tricyclic antidepressant (e.g., amitriptyline or nortriptyline), an anticonvulsant (e.g., gabapentin), a nonsteroidal antiinflammatory drug, and, for those with severe pain, with an opioid [8].

Other pharmacologic approaches with some evidence of efficacy require more invasive methods of administration [15]. These include epidural clonidine injections and infusions and intravenous regional sympathetic block with bretylium. Local sympathetic blocks (e.g., stellate ganglion block) with local anesthetic, while of unproven benefit in terms of the long-term outcome, nevertheless may provide a short-term decrease in pain, that can be diagnostically useful and can help with mobilization of the affected limb.

Anticonvulsants are beneficial in chronic pain, particularly with pain that is lancinating, burning, or sharp. Successful use in some cases of CRPS Type I has been reported for gabapentin [16,17]. Newer agents include pregabalin (75 mg twice daily) or lamotrigine (25 mg twice daily). Although unproven in CRPS, these drugs have a good margin of safety and may be useful if NSAIDs and amitriptyline are inadequate for pain management. (See "Overview of the treatment of chronic pain").

Multiple treatment modalities are available to provide pain relief in patients with CRPS. The key to success is to use whatever works quickly. Patients should respond within days; if they do not, move on to the next treatment level. The initial choice of therapy depends upon the stage of disease (table 1).

Topical treatment — Topical application of capsaicin cream is used for treating neuropathic pain. By analogy with treatment of painful diabetic neuropathy, capsaicin (0.075 percent) may be applied topically four times daily over painful areas. Local burning and skin irritation can occur, but this may become less of a problem with continued use. This agent is probably best used in patients with stage 1 CRPS and residual mild to moderate pain despite the use of tricyclic antidepressants and NSAIDs. Three to five days of use may suffice to access effectiveness and tolerability of topical capsaicin.

Bisphosphonates — Bisphosphonates, which have been used to prevent bone resorption in patients with CRPS [18], may also be useful for pain relief. This was illustrated in a trial that randomly assigned 32 patients with stage 1 CRPS to either 300 mg of intravenous clodronate given daily for 10 days or placebo [19]. After 40 days, pain decreased by a mean of 36 mm and 6 mm (on a 100 mm visual analog pain scale) in the clodronate and placebo groups, respectively, a difference that was statistically significant. The only side effect of active therapy was hypocalcemia, which was documented in three patients, none of whom were symptomatic.

Studies of intravenous pamidronate [20] and parenteral or oral alendronate [21,22] have also yielded encouraging results. However, pamidronate may cause symptomatic hypocalcemia, and relapse occurred in 40 percent of those who initially responded to alendronate. Serious adverse effects of bisphosphonates
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Include esophageal ulceration with oral use and osteonecrosis of the jaw.

Patients who have difficulty swallowing, those with disordered esophageal motility, and those who can not sit or stand for 30 minutes should not receive oral bisphosphonate therapy.

Most reported cases of osteonecrosis have been in patients with malignant disease receiving potent intravenous bisphosphonates. However, osteonecrosis has been reported in some patients receiving oral bisphosphonates for benign disorders. (See "Pharmacology of bisphosphonates" and "Risks of bisphosphonate therapy in patients with malignancy", section on 'Osteonecrosis of the jaw'.)

**Glucocorticoids** — Oral glucocorticoids (eg, divided doses of prednisone, 30 to 80 mg/day) may be effective [23]. Data from two small randomised placebo controlled trials in post-traumatic [24] and upper extremity CRPS due to stroke [2] suggest a beneficial effect of a short course of glucocorticoids.

- Among 23 patients with post-traumatic CRPS type I who were randomly assigned to prednisone (10 mg three times daily) or placebo, all 13 patients in the prednisone-treated group showed more than 75 percent clinical improvement within the twelve-week period; of the ten patients who received placebo, only two reported improvement [24].

- Of 36 patients with stroke and CRPS (shoulder hand syndrome) 31 were nearly symptom free following 10 days of low dose steroid treatment [2].

Oral glucocorticoids may be significantly more effective than NSAIDs. This was illustrated in a study that randomly assigned 60 patients with CRPS following stroke to prednisone (40 mg daily) or piroxicam (20 mg daily) [25]. At the end of one month a significantly greater proportion of patients in the prednisolone group than those receiving piroxicam met criteria for improvement (83 percent versus 17 percent, respectively). The mean changes in CRPS score (6.5 versus 0.5) and in a functional index (7.9 versus 4.5) were also significantly different.

Increased activity in the affected limb on technetium-99m bone scan may predict a good response to prednisone [23]. The dose is tapered quickly as the patient responds; continued low-dose corticosteroid treatment may be necessary for a prolonged period in severe cases.

The author's experience with glucocorticoid treatment of reflex sympathetic dystrophy prior to contracture has been excellent, particularly when used in conjunction with a tricyclic antidepressant and physical therapy. However, his experience suggests that patients with stage 3 disease usually do not respond to steroids. Although limited data suggest that glucocorticoids are more effective than NSAIDs, we suggest using NSAIDs first, and reserving use of glucocorticoids for those who do not respond to NSAIDs and antidepressants.

**Calcitonin** — The rationale for use of calcitonin involves the ability of this hormone to retard bone resorption and a putative analgesic effect. The mechanism responsible for analgesia is uncertain. (See "Calcitonin in the prevention and treatment of osteoporosis".)

A systematic review of the treatment of CRPS in 2001 included a meta-analysis of the results of five clinical trials of calcitonin, and concluded that calcitonin "does seem to be effective" in treating pain due to CRPS [26]. This conclusion was principally based on two randomised placebo-controlled trials that included a total of 106 patients [27,28]. Doses used in these latter trials were 300 to 400 IU/day administered by injection or nasal spray. A small decrement in serum calcium may occur, but symptomatic hypocalcemia is unlikely. Cost is an issue.

The optimal dose and duration of calcitonin treatment is uncertain. An initial dose of 200 IU twice daily was
used in one clinical trial [28]. In contrast, the combination of a lower dose (200 IU of salmon calcitonin once daily) plus acetaminophen was no more effective than acetaminophen alone in a subsequent study [29]. If pain and/or function are improved with use, it can be continued and tapered and discontinued as tolerated.

Considering the evidence for efficacy and the low risk associated with its use, we suggest calcitonin for patients with CRPS in combination with physical therapy for patients who have mild or moderate symptoms despite use of NSAIDs and tricyclic antidepressants.

**Sympathetic blockers** — A systematic review and meta-analysis of 12 clinical trials of sympathetic blockers or sympatholytics (ie, propranolol, reserpine, or guanethidine) orally or by intravenous regional sympathetic block concluded that the effect size was not statistically significant for these agents compared to controls [26]. (See 'Regional sympathetic nerve block' below.)

The author's experience suggests that sympathetically maintained pain may respond to addition of an alpha-1 adrenoceptor antagonist. Some experts recommend a trial of terazosin or phenoxybenzamine [8]. The author has used either prazosin (1 to 6 mg/day as tolerated) or phenoxybenzamine (10 to 30 mg/day as tolerated) and noted apparent benefit in some patients. Hypotension is a limiting side-effect of alpha-adrenergic blockers.

**Monitoring response to treatment** — Patients with stage 1 disease are seen on a weekly basis and the treatment is changed if the response is suboptimal. Decreased pain, improved mobility, and better function are goals of therapy. (See 'Types and stages' above.)

Patients in stage 1 who are not improving despite two weeks of the oral treatments discussed above combined with physical therapy should be considered for invasive forms of treatment. Stage 2 and stage 3 CRPS patients are also candidates for invasive therapies if pain and function are not rapidly improved (see below).

**Invasive therapies** — Patients receiving noninvasive therapy who are not improving are offered increasingly invasive interventions, allowing two weeks for improvement before moving on to the next type of treatment. In tertiary centers, consideration for spinal cord stimulation, arguably the most invasive therapy, would be considered by 12 to 16 weeks from the time therapy for CRPS is initiated [30].

**Tender point injections** — Tender points may be found about the shoulder girdle when CRPS is limited to the upper limb. These tender points (trigger points) points are located in the trapezius, and supraspinal muscles in most patients. If unilateral involvement occurs the other side can be used for comparison. The author's clinical experience suggests that tender point injections are sometimes effective and are safer than other invasive forms of treatment. Injection of each tender point with 40 mg methylprednisolone or an equivalent glucocorticoid, combined with a local anesthetic is used for patients with stage 1 disease, before proceeding to more invasive and risky procedures.

**Nerve stimulation** — Electrical nerve stimulation may be helpful in some patients who do not respond to other treatments. Observational data suggest that transcutaneous electrical nerve stimulation (TENS unit) can be helpful in selected patients (eg, children and those with recent onset of lower limb CRPS) [31]. Long-term peripheral nerve stimulation with implanted programmable generators and plate-like electrodes are under investigation for the treatment of pain that is in the distribution of one major peripheral nerve [31].

**Epidural clonidine** — Clonidine administered by epidural injection or infusion may reduce the pain of CRPS, but side effects such as hypotension and sedation frequently occur [32,33]. Transdermal clonidine may reduce pain but the effect is localized to the skin beneath the patch, suggesting a local rather than a central nervous system effect [32]. Potential complications of epidural injection have limited study of this treatment to patients with severe refractory CRPS; 26 such patients were randomly assigned to epidural clonidine (300 or 700 microgram bolus injection) or placebo and assessed for up to six hours [33]. Epidural clonidine provided significantly greater pain relief than placebo injections in patients with severe refractory
We suggest that epidural clonidine be used only for patients refractory to other less invasive approaches. We suggest not using topical clonidine for CRPS.

**Regional sympathetic nerve block** — Temporary sympathetic nerve block can be accomplished by infiltration of a local anesthetic into the region of the sympathetic ganglia or by intravenous regional infusion of a sympathetic blocker, typically in combination with a local anesthetic. A systematic review in 2005 identified two randomized double-blind trials that included a total of 23 patients [34]. Regional sympathetic blockade did not produce a significantly greater short-term improvement in pain that did a sham intervention (relative risk of achieving a 50 percent reduction in pain of 1.17, 95% CI 0.80-1.72). The authors of the systematic review cautioned that the small number of subjects precluded a conclusion on the effectiveness of regional sympathetic block for CRPS.

Patients with objective cutaneous changes or any persistent loss of motion may be candidates for sympathetic nerve blocks. The clinician should consider referral to a regional pain center unless an experienced anesthesiologist is available.

- Ganglion blocks — Sympathetic ganglion block with local anesthetic injection produces more and longer lived pain relief than placebo injection; duration of analgesic effect were 3.5 versus 1.0 days in one controlled study [35]. Patients who respond to stellate ganglion blocks are said to have sympathetically-dependent pain; these patients are typically in the first stage of disease.

Some centers use an infusion of 40 mg phentolamine with concurrent cardiovascular monitoring as a test for those who are likely to have sympathetically-dependent pain. However, there is a risk of severe hypotension associated with this procedure; autonomic testing as described elsewhere is a safer alternative. (See "Etiology, clinical manifestations, and diagnosis of complex regional pain syndrome in adults", section on 'Autonomic testing'.)

Stellate ganglion blocks may be performed at intervals of one to four days, repeated six to twelve times. This treatment is abandoned if an immediate response (eg, improved temperature and decreased pain) does not occur following the first or second nerve block.

- Intravenous regional blocks — The efficacy of intravenous regional blocks (Bier blocks) is uncertain, since a 2001 meta-analysis of nine randomized trials in patients with CRPS type 1 found no significant analgesic effect [26]. Nevertheless, this approach is still being used in some centers for patients with upper limb involvement, and can be tried before sympathetic nerve block. Tourniquets placed above and below the site of injury allow perfusion of the drug in the affected area at 48 to 72 hour intervals. The agents used include ketorolac (30 to 60 mg), methylprednisolone (80 to 120 mg), or bretylium (1.5 mg/kg).

Oral medications and intensive mobilizing physical therapy should continue in patients who receive sympathetic or Bier blocks. Each block should result in a longer duration of pain relief.

**Dorsal column spinal cord stimulation** — Dorsal column spinal cord stimulation may be helpful if traditional therapeutic modalities fail, particularly in patients with disease limited to one extremity. In a randomized study of 36 patients and 18 controls, electrical stimulation and physical therapy reduced pain and improved health-related quality of life more than physical therapy alone for up to two years, however, the addition of spinal cord stimulation did not change functional outcome measures [36,37]. It may be significant that the controls did not undergo a sham intervention. No significant difference in pain was present during the period from three to five years following implantation [38]. Complications of this technique are common, and mostly associated with improper positioning of the electrode.

**Sympathectomy** — Sympathectomy has not been compared to sham surgery. Chemical or surgical
sympathectomy may be considered when the disease progresses despite less invasive measures discuss above. A study of 35 patients referred to a surgical clinic for sympathectomy found excellent results in 26 (74 percent) [39]. However, a systematic review concluded that the evidence for the effectiveness was poor and noted high rates of adverse effects that included increased pain, new neuropathic pain, and bothersome sweating [40].

Patients with stage 3 disease (eg, significant skin disease and contractures) may benefit from sympathectomy. However, in the author’s experience, aggressive physical therapy, pain management, and encouraging the patient to work beyond the pain typically obviated the need for this type of treatment. Sympathectomy should only be used in patients who have shown a previous response to nerve blockade (eg, have sympathetically-dependent pain) and are fully informed about the potential complications of the procedure.

Other modalities — Intrathecal baclofen may relieve dystonia in patients with CRPS [41]. Case reports and personal experience, suggest that a skilled hypnotherapist can be helpful for patients with heightened arousal, manifested by features of fear, anxiety, excessive sweating, and weakness, in whom exercise is otherwise impossible [42,43]. Hypnosis allowed physical therapy to progress in some patients with otherwise intractable disease.

Experimental approaches — Several different approaches have been of interest for the treatment of longstanding or refractory CRPS, including Intravenous ketamine, intravenous magnesium, tadalafil, and intravenous immunoglobulin [44].

- Intravenous immunoglobulin — A randomized crossover trial involving 13 patients refractory to standard treatment found that treatment with intravenous immunoglobulin (IVIG), can reduce pain at 6 to 19 days following infusion, by a statistically significant but modest degree, compared with normal saline (1.6 units in a 0 to 10 pain score, 95% CI 1.3-1.8) [45]. The authors and an editorialist note the multiple limitations of the study design and the need for further trials to assess the efficacy of this intervention and its role relative to other therapeutic options [44].

Treatment of relapse — Individual episodes of CRPS may last six to nine months, followed by spontaneous resolution or successful therapy. However, sequelae may persist, and recurrences can occur. We have seen patients have an exacerbation several months after treatment due to exposure to cold or emotional trauma. Small doses of tricyclic antidepressants (eg, amitriptyline) and oral guanethidine have been helpful in treating recurrences.

PROGNOSIS — The prognosis of CRPS type I, which accounts for more than 90 percent of cases of CRPS, is generally favorable. This was illustrated in a population-based study in which 74 percent of patients reported resolution of symptoms, some spontaneously [46]. Litigation and work-related compensation issues are involved in a substantial proportion of cases of CRPS cared for in tertiary pain-management clinics, present in 17 and 54 percent respectively in one study in the United States [47].

SUMMARY AND RECOMMENDATIONS

- Complex regional pain syndrome (CRPS) is a disorder of the extremities that is characterized by pain that is distributed in a pattern that is not explained by a single nerve, trunk, or root injury. Pain is accompanied by swelling, limited range of motion, vasomotor instability, skin changes, and in later stages by patchy bone demineralization. It frequently begins following an injury, surgery, or a vascular event such as a myocardial infarction or stroke. (See "Etiology, clinical manifestations, and diagnosis of complex regional pain syndrome in adults".)

Preventive measures

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To prevent CRPS following stroke we recommend early mobilization (Grade 1B). We also suggest early mobilization as a preventive strategy for those with CRPS due to injuries and myocardial infarction (MI), with the recognition that casting for fractures and activity limitations following MI may be unavoidable. (See 'Early mobilization' above.)

For patients with wrist fractures, we recommend supplemental vitamin C (Grade 1B). A typical dose is 500 mg daily and the duration is 50 days. (See 'Vitamin C following fracture' above.)

**Treatment**

- Some interventions that are appropriate for all patients include:
  - Patient education, including contact information for patient support groups (see 'Patient education' above).
  - Assessing job and Interpersonal relationships (see 'Psychologic assessment and counseling' above).
  - Physical therapy and/or occupational therapy assessment and treatment are initiated as quickly as practicable following diagnosis of CRPS. (See 'Physical and occupational therapy' above.)
  - Patient who smoke are encouraged to stop. (See 'Smoking cessation' above.)

- Pharmacologic and invasive procedures are utilized in an escalating fashion beginning with those that are relatively safe and for which there is some evidence of effectiveness and progressing to more risky interventions if a desired response is not achieved after a two week therapeutic trial. Our suggested approach is based on the clinical stage at presentation (see 'Types and stages' above).

- Regardless of the clinical stage, the goal of pain management is to allow active participation in a rehabilitation regimen an to restore movement and strength of the affected limb. The clinician must emphasize this, particularly to reluctant patients.

  **Clinical stage 1** — For patients with clinical stage I (eg, with burning and sometimes throbbing pain, diffuse uncomfortable aching, sensitivity to touch or cold, and localized edema, vasomotor disturbances of variable intensity that produce altered color and temperature and a radiograph that is either normal or shows patchy demineralization) the following approach is suggested.

We suggest starting a combination of agents that includes the following (Grade 2C):

- Topical capsaicin cream (0.075 percent), which may be discontinued if it is too irritating or there is no benefit after three to five days of use.

- An antidepressant that is effective for neuropathic pain. We typically start with amitriptyline 25 mg at bedtime and increase the dose, as tolerated, to 150 mg. Other tricyclic antidepressants and dual uptake inhibitors that are indicated for treatment of neuropathic pain are alternatives to amitriptyline. (See "Overview of the treatment of chronic pain", section on 'Tricyclic antidepressants' and "Overview of the treatment of chronic pain", section on 'Other antidepressants'.)

- A nonsteroidal antiinflammatory drug. A typical initial regimen is naproxen 250 to 500 mg twice daily.

For patients who do not have a satisfactory response to initial therapy after one to two weeks, one or more of the following may be tried sequentially:

- If there are muscular tender points, we suggest injecting with a mixture of local anesthetic and long
acting glucocorticoids (Grade 2C). (See 'Tender point injections' above.) A typical dose is 40 mg of methylprednisolone acetate and 1-2 cc of 1 percent lidocaine. Equivalent doses of other injectable glucocorticoids and local anesthetics may be used depending upon availability and clinician preference.

- In the absence of tender "trigger" points, or if pain persists three to five days following local injections of steroids, we suggest adding an anticonvulsant (Grade 2C). Gabapentin, pregabalin, or lamotrigine are alternatives. (See "Overview of the treatment of chronic pain", section on 'Anticonvulsants'.)

- If pain persists despite the addition of an anticonvulsant to the regimen, we suggest the addition of either calcitonin or a bisphosphate (Grade 2A). If cost is not an overriding issue, we suggest use of calcitonin nasal spray; a typical dose would be 400 mg/day (eg, 200 IU twice daily). If the cost of calcitonin is prohibitive, we suggest use of a bisphosphate. Intravenously administered bisphosphonates (eg, clodronate 300 mg or pamidronate 1 mg/kg) or oral agents (eg, alendronate 70 mg weekly) may be used (see 'Bisphosphonates' above).

- For patients with CRPS Type I and clinical stage 1 who remain symptomatic despite the interventions described above, or are evolving signs of having clinical stage 2 we recommend use of an oral glucocorticoid (Grade 1A). (See 'Glucocorticoids' above.) A typical regimen is a therapeutic trial of prednisone 1 mg/kg daily for three days. If effective, prednisone is continued and tapered over the ensuing three weeks.

Clinical stage 2 — For patients with clinical stage 2 CRPS (eg, persistent soft tissue edema, accompanied by thickening of the skin and periarticular soft tissues, muscle wasting, and the development of brawny skin changes), we suggest the same initial combination described above plus glucocorticoids either by soft tissue injection or orally (Grade 2C). (See 'Clinical stage 1' above.)

Referral to a pain management specialist with experience in management of CRPS is appropriate for patients with clinical stage 2 CRPS. Depending on the expertise of the specialist, regional sympathetic block or sympathetic ganglion block may be the preferred initial intervention. Other invasive treatments that are typically reserved for those with severe and refractory disease include epidural clonidine, implantable peripheral nerve stimulators, and electrical spinal cord stimulators. (See 'Invasive therapies' above.)

An alternative approach, suitable for patients who are unwilling to consider invasive therapies, is the sequential addition of calcitonin or a bisphosphate to an ongoing regimen consisting of an antidepressant, an anticonvulsant, an NSAID, and, if necessary to control severe pain, an opioid analgesic. (See 'Clinical stage 1' above.)

Clinical stage 3 — Patients with clinical stage 3 CRPS should be referred to an experienced pain management specialist at a tertiary care center.

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REFERENCES


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GRAPHICS
Claw limb in reflex sympathetic dystrophy

A delay in the comprehensive treatment of RSD may result in progression to a useless claw-like limb. In this case, the patient ultimately recovered full use of the extremity.

### Management of reflex sympathetic dystrophy

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<th>Medication</th>
<th>Other</th>
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<td>Physical therapy</td>
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<td></td>
<td>Tricyclic antidepressants: Amytriptyline 25 to 150 mg or doxepin 5 to 20 mg</td>
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<td>Ketorolac (30 to 60 mg)</td>
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<td></td>
<td>Guanethidine or phenoxybenzamine 10 to 30 mg/day or prazosin 1 to 6 mg/day</td>
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<td>Failure or stage II</td>
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<td>Prednisone 80 mg/day, decrease 10 mg q 4 days to 20mg/day, then taper slowly</td>
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<td>Tricyclic antidepressants</td>
<td></td>
</tr>
<tr>
<td>Failure or stage III</td>
<td>Tricyclic antidepressants</td>
<td>Physical therapy</td>
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<tr>
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<td>Sympathetic ganglion blocks</td>
</tr>
<tr>
<td>Failure</td>
<td></td>
<td>Referral to tertiary center, or if patient has had good response to sympathetic blocks consider sympathectomy</td>
</tr>
</tbody>
</table>

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