

and codeine are second choices, whereas NSAIDs for 1 to 2 weeks and strong opioids are third choices. Muscle spasms and pain related to spasticity are best treated with spasmolytics. For neuropathic pain, gabapentin and pregabalin are the first drug choices, followed by antidepressants and drug combinations, and finally, by tramadol, opioids, cannabinoids, and lamotrigine.

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# Chapter 39

## COMPLEX REGIONAL PAIN SYNDROME: TREATMENT APPROACHES

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## INTRODUCTION

The physiologic response to an injury includes pain and inflammation that is typically proportional to the severity of tissue damage. Tissue injury activates peripheral pain fibers,  $\alpha\gamma$ - and C-fibers. Acute-phase reactants such as cytokines and free radicals cause local swelling (tumor), redness (rubor), pain (dolor), and increase in temperature (calor). This normal physiologic process serves as a protective mechanism to prevent ongoing insult to an injured area of the body. As the affected area heals, pain and swelling improve and full function is restored.

However, inappropriate or abnormal activation of this pain pathway can produce a disease state that can lead to debilitating

and painful conditions in patients who were previously highly functional. The manifestations of this pathophysiologic process have been described in many ways, but the name was ultimately changed to *complex regional pain syndrome* (CRPS) at a consensus workshop in 1995.

## TAXONOMY

CRPS was probably first described by Dr. Silas Mitchell as severe burning pain after gunshot wounds sustained by soldiers during the American Civil War. Many other names—such as reflex sympathetic dystrophy (RSD), causalgia, algodystrophy mineures, mimocausalgia, sympathalgia, and post-traumatic spreading syndrome—have been attached to this syndrome. The name commonly used for this syndrome, reflex sympathetic dystrophy, is actually a misnomer in that it implies a reflex mechanism associated with a hyperactive sympathetic nervous system. However, animal models have suggested that altered neuromodulation, nerve hyperexcitability, and central sensitization may all contribute to this complicated disease process known as CRPS. In order to incorporate new research findings and create uniform terminology and diagnostic criteria, the International Association for the Study of Pain (IASP) proposed taxonomy that grouped the disorders under the term “complex regional pain syndromes.” The term CRPS is broad and nonspecific and incorporates the array of signs and symptoms that this syndrome exhibits in patients. Two subtypes exist: CRPS I (RSD) and CRPS II (causalgia). CRPS I refers to a post-traumatic syndrome causing spontaneous pain not limited to the distribution

of a single nerve and disproportionate to the inciting event. CRPS II represents a pain syndrome occurring after evidence of a specific nerve injury and not necessarily limited to the territory of the injured nerve.

## EPIDEMIOLOGY

CRPS occurs more frequently in young adults and more often in women than in men. The disease may be triggered by any number of insults including major or minor trauma, surgery, inflammation, stroke, nerve injury, myocardial infarction, certain neoplasms, and immobilization. No correlation exists between severity of injury and subsequent severity of CRPS. Psychological stressors and poor coping skills can influence the natural history and severity of CRPS.

## PATHOPHYSIOLOGY

Like many neuropathic syndromes, the pathophysiologic mechanisms of CRPS are ill defined. Animal studies have demonstrated that acute-phase inflammatory reactants and free radicals can cause signs and symptoms similar to those of CRPS in the acute setting. Further, animal models have shown sprouting of sympathetic nerve fibers around sensory neurons in the dorsal root ganglia (DRG) after peripheral nerve injury. In fact, abnormal nerve sprouting and C-fiber (pain fiber) excitation by the sympathetic nervous system may explain abnormal discharges seen in peripheral nerves after nerve damage. Human studies, however, have implicated the sympathetic nervous system less directly. For instance, there is variable response to sympathetic blockade with high rates of relapse among patients receiving these injections. Researchers have hypothesized that changes in the dorsal horn of the spinal cord may lead to the hyperexcitable state of CRPS. Central sensitization and continual activation of *N*-methyl-D-aspartate (NMDA) receptors in the central nervous system may maintain this state of neural hyperarousability after nerve injury.

## CLINICAL FEATURES

Patients with CRPS exhibit a diversity of symptoms. Manifestations of CRPS reflect pathologic changes in the autonomic, sensory, and motor systems (Fig. 39-1). Patients often report “stinging” and “burning” pain, although they may describe “aching,” “shooting,” “squeezing,” and “throbbing” sensations. Many patients describe hyperesthesia (increased sensitivity to stimulation) to common mechanical stimuli such as clothing touching an affected region or even cool breezes blowing on an extremity. Alterations in environmental temperature may also provoke or exacerbate the pain.

The IASP differentiates only between two general subtypes of CRPS: type I and type II.<sup>1-4</sup> Type I refers to a syndrome that lacks a specific nerve lesion (see Fig. 39-1), whereas type II reflects clear evidence of nerve injury. The somatosensory symptoms of CRPS II extend beyond the course of the affected peripheral nerve and thus distinguish it from isolated peripheral mononeuropathies. Both types can manifest the same symptoms and signs, and clinicians may use both the IASP diagnostic criteria and the proposed modified research diagnostic criteria to aid in formulating a diagnosis (Boxes 39-1 and 39-2). The literature notes a series of sequential stages of untreated CRPS beginning with stage I (early, acute, and marked by sensory/vasomotor, sudomotor disturbances), stage II (increased pain, vasomotor disturbance, and substantial motor/trophic changes), and stage III (diminished pain, significantly increased motor/trophic changes, and continued vasomotor changes).<sup>5</sup> In practice, the distinction between these stages may not be appreciated, and the importance of making such distinctions for treatment purposes has yet to be discovered. A retrospective analysis



**Figure 39-1. Complex regional pain syndrome (CRPS) I of the left ankle.** (Symptoms and signs include edema, skin discoloration, dryness, shiny skin, dystonia, atrophy, and contracture.)

of patients with CRPS, type I describes three patterns of spread from the initial area of presentation: *contiguous spread* noted in all patients and characterized by an enlargement of the affected area; *independent spread* noted in 70% of patients and described as the appearance of symptoms in a distant and non-contiguous location; and *mirror-image spread* noted in 15% of patients and highlighted by symptoms on the opposite side of the affected region that mimicked the site of initial presentation.<sup>6</sup>

### Box 39-1 CURRENT DIAGNOSIS\*

1. A neuropathic pain syndrome that displays sudomotor and vasomotor disturbances.
2. Previous descriptors include RSD and causalgia.
3. Severity and duration are highly variable and stages of the disease may not be evident.
4. Two subtypes exist: CRPS I (RSD) and CRPS II (causalgia).
5. CRPS I: Post-traumatic syndrome causing spontaneous pain not limited to the distribution of a single nerve and disproportionate to the inciting event.
6. CRPS II: Pain syndrome occurring after evidence of a specific nerve injury and not necessarily limited to the territory of the injured nerve.
7. Regional, spontaneous pain, allodynia, or hyperalgesia not limited to the territory of a single peripheral nerve and disproportionate to a known inciting event.
8. Evidence of edema, changes in skin blood flow, or abnormal sudomotor activity in the painful region.
9. Presence of a noxious event or cause or immobilization (may be absent in 5%–10% of patients).
10. No other condition can otherwise account for the degree of pain and dysfunction.

\*Nos. 7–10 represent the IAPS Diagnostic Criteria for CRPS.

CRPS, complex regional pain syndrome; IASP, International Association for the Study of Pain; RSD, reflex sympathetic dystrophy.

### Box 39–2 PROPOSED MODIFIED RESEARCH DIAGNOSTIC CRITERIA FOR CRPS

Diagnostic criteria for CRPS in scientific settings (clinical trials):

1. Continuing pain that is out of proportion to the inciting event.
2. Patient reports at least **one symptom** in each of the **four** categories:
  - a. **Sensory:** Reports of hyperesthesia, allodynia, or hyperalgesia.
  - b. **Vasomotor:** Reports of temperature asymmetry or skin color changes.
  - c. **Sudomotor:** Reports of hyperhidrosis, dryness, edema, or shiny skin.
  - d. **Motor:** Reports of spasm, tremor, weakness, decreased range of motion, atrophy, dystonia, contractures, or dystrophic changes to hair, nails, or skin.
3. Displays at least **one sign** in **two or more** of the following four categories:
  - a. **Sensory:** Evidence of hyperesthesia, allodynia, or hyperalgesia.
  - b. **Vasomotor:** Evidence of temperature asymmetry or skin color changes.
  - c. **Sudomotor:** Evidence of dryness, sweating, edema, or shiny skin.
  - d. **Motor:** Evidence of spasm, tremor, weakness, decreased range of motion, atrophy, dystonia, contractures, or dystrophic changes to hair, nails, or skin.

CRPS, complex regional pain syndrome; IASP, International Association for the Study of Pain.

Patients typically report pain caused from stimuli that ordinarily do not provoke pain (allodynia) and/or describe exaggerated responses to stimuli that are normally painful (hyperalgesia). Certain patients may even protect the affected part from mechanical or thermal stimulation by wearing a glove or a boot or assuming defensive postures. Other common CRPS symptoms include vasomotor disturbances such as temperature asymmetry and/or skin color changes. For instance, patients may complain that a limb feels warm and appears red or feels cool and looks dusky or bluish. Further, patients may report sudomotor changes in the form of asymmetry of hyperhidrosis (sweating), dryness, edema, or skin in the affected region. Motor dysfunction may manifest as spasm, tremor, dystonia, weakness, atrophy, or contracture in the affected extremity. Patients often refer to symptoms of myofascial pain in the proximal joint as well. Trophic disturbances may present as changes in skin, nails, or hair pattern.

Selective sympathetic blockage to the affected limb may be performed for both diagnostic and therapeutic purposes. If the block reduces pain, the patient is regarded as having a sympathetically mediated pain (SMP) component associated with the CRPS. However, no pain relief probably suggests sympathetically independent pain. Results of the sympathetic blockade should be viewed with caution, given the potential for false-positive and false-negative outcomes.

CRPS, like many chronic pain conditions, may be viewed as a biopsychosocial disturbance. Patients frequently experience depression, anxiety, fear, progressive disuse of the affected part, and social withdrawal. No well-controlled studies have linked these symptoms to a cause of CRPS or a result of the syndrome; however, clinicians should recognize the psychological/behavioral factors associated with CRPS-related pain and disability.

## EVALUATION

The hallmark of CRPS diagnosis remains a thorough clinical evaluation of symptoms and signs. The literature suggests that some quantitative testing may aid in confirmation, however. The IASP criteria for diagnosis (see Box 39–1) are broad and quite sensitive and can lead to overdiagnosis. Consequently, a separate set of criteria have been proposed to the IASP that retain much of the diagnostic sensitivity of the current criteria while almost doubling the specificity (reducing false positives). In effect, the Proposed Modified Research Diagnostic

Criteria for CRPS attempt to standardize the diagnosis and aid in more homogenous research investigations (see Box 39–2).

Current IASP diagnostic criteria for CRPS include (1) the presence of an initiating noxious event or a cause of immobilization, (2) continuing pain, allodynia, or hyperalgesia in which the pain is disproportionate to any known inciting event, (3) evidence at some time of edema, changes in skin blood flow, or abnormal sudomotor activity in the region of pain (can be a sign or symptom), and (4) this diagnosis is excluded by the existence of other conditions that would otherwise account for the degree of pain and dysfunction. Although the current diagnostic criteria (see Box 39–1) do not require that a patient display or a clinician observe a specific number of symptoms or signs before diagnosing CRPS, the Proposed Modified Diagnostic Criteria (see Box 39–2) do make that distinction. For instance, patients should report pain that is disproportionate to any inciting event, describe at least one symptom in each of the four categories (sensory, vasomotor, sudomotor/edema, and motor/trophic), and display at least one sign in two or more of the following categories: sensory, vasomotor, sudomotor/edema, and motor/trophic.

Laboratory testing may clarify the existence of SMP and autonomic disturbance or may exclude conditions that resemble CRPS. That is, vascular studies can help exclude deep vein thrombosis (DVT); electromyography testing/nerve conduction testing (EMG/NCT) can help exclude peripheral neuropathy; magnetic resonance imaging (MRI) and radiographs can help exclude soft tissue or disk disease, central canal stenosis, neuroforaminal stenosis, or bone disease; and blood testing can help exclude infection, cellulitis, or rheumatologic disease.

Other tests may reinforce the diagnosis of CRPS by detecting abnormalities in sympathetic activity or disturbances in blood flow in affected regions. Outcome studies fail to support the diagnostic or therapeutic value of any of the following tests:

**Thermography:** An infrared thermometer measures thermal differences in the skin of two extremities.

**Quantitative Sensory Tests:** These assess differences required to produce light touch, vibration, heat, cold, and thermal pain thresholds.

**Radiographs:** X-rays image areas of CRPS that may display a range of patchy osteopenia as soon as 2 weeks after onset to generalized osteopenia and cortical erosions.

**Three-phase bone scan:** Bone scan demonstrates increased uptake into joints of the affected limb during the third phase (bony uptake of  $^{99m}\text{Tc}$ -labeled phosphates). This is frequently ordered and its utility is questionable.

**Sudomotor Testing:** Sudomotor testing compares resting and provoked sweat output in the painful limb compared with the unaffected limb.

**Sympathetic blocks (stellate ganglion (SG) or lumbar sympathetic) or pharmacologic sympathetic block via phentolamine (generic) intravenous infusion:** These aid in assessing an SMP component and in facilitating pain relief for functional restoration (physical therapy [PT], occupational therapy [OT]).

## MANAGEMENT

Treatment of CRPS should consist of an early, aggressive, multimodal approach. Goals of therapy should be threefold: pain relief, functional restoration, and psychological stabilization (Box 39–3). Pain control is important in order to facilitate active participation in physical rehabilitation. Clinicians should consider several modalities for the treatment of CRPS such as pharmacotherapeutic agents; nerve blocks; occupational, physical, vocational, and recreational therapy; psychological/behavioral therapy; and neuromodulation (Fig. 39–2). Patients and clinicians alike should understand that a multidisciplinary approach reflects the best method of improving symptoms and function and enhancing quality of life.

**Box 39–3 CURRENT THERAPY**

Therapy is achieved via a multimodal approach. The overarching goal is functional restoration.

1. **Pharmacologic:** TCAs, anticonvulsants, opioids, bisphosphonates, steroids, topical therapy.
2. **Functional restoration:** Physical therapy, occupational therapy, recreational therapy, vocational therapy.
3. **Interventional procedures:** Sympathetic nerve blockade (stellate ganglion/lumbar), spinal cord stimulation, peripheral nerve stimulation, intraspinal infusion therapies.
4. **Psychosocial elements:** Assessment and treatment of psychiatric diagnoses (axis I), assess patient and family response to CRPS, assess significant ongoing life stressors, relaxation/biofeedback training, coping skills, cognitive-behavioral interventions.

CRPS, complex regional pain syndrome; TCAs, tricyclic antidepressants.

In the absence of any uniformly efficacious medical or surgical treatment, a multimodal strategy represents a “best practice” for the successful management of CRPS.

### Pharmacotherapy

Several classes of medications are used to treat CRPS patients despite the paucity of randomized, controlled studies to support their efficacy in this disease. Some medications (gabapentin, pregabalin, tricyclic antidepressants [TCAs], opioids, transdermal lidocaine) have been adequately studied in patients with painful diabetic neuropathy and/or postherpetic neuralgia, and the results extrapolated to the treatment of CRPS (Table 39–1).

#### TCAs

TCAs have been used for many years in the treatment of neuropathic pain. Randomized, controlled trials have documented their analgesic properties aside from their antidepressant effects. These medications can ease pain, alleviate depression, and promote sleep (often disrupted because of pain and limb immobility) in patients with CRPS. TCAs inhibit reuptake of serotonin and norepinephrine

at presynaptic nerve terminals and facilitate the descending antinociceptive (pain-relieving) pathway in the central nervous system. They may confer further benefit to CRPS patients through their sedative effects (antihistaminergic) and anxiolytic actions. Both the tertiary amines (amitriptyline, doxepin) and the secondary amines (nortriptyline, desipramine) are used clinically. Adverse effects are more common with tertiary amines; therefore, the secondary amines should be strongly considered for initial treatment. A reasonable dosing regimen consists of 25 mg by mouth before bedtime, gradually increasing by 25 mg every week until reaching a target dose of 100 mg by mouth at bedtime. If patients experience insufficient pain relief and do not develop intolerable adverse effects, the dose can be escalated in 25-mg increments until a maximum dose of 150 mg at bedtime is reached.

Adverse effects may include conduction abnormalities (sodium channel antagonism), anticholinergic side effects (fatigue, xerostomia, constipation, imbalance, urinary retention, and palpitations), orthostatic hypotension ( $\alpha_1$ -adrenergic antagonism), weight gain (antihistaminergic effect), and sedation (antihistaminergic effect). Often, adverse effects are dose-related and less pronounced when low doses are increased gradually. Relevant contraindications to TCAs include recent heart attack, epilepsy, narrow-angle glaucoma, heart block, urinary retention, and use of monoamine oxidase inhibitors. Prescribe cautiously in patients with congenital QT syndrome, cardiovascular disease, or hypokalemia. Clinicians should consider tapering TCAs over 1 to 2 weeks to avoid the discontinuation syndrome (malaise, chills, myalgias, nasal discharge). More conservative doses should be used in older persons such as 10 mg by mouth before bedtime then escalating in increments of 10 mg weekly to a maximum dose of 150 mg at bedtime. Note that overdose of TCAs can be lethal; therefore, avoid using these medications in patients who are actively suicidal.

Selective serotonin reuptake inhibitors (SSRIs) are less effective in treating neuropathic pain, although venlafaxine (Effexor), duloxetine (Cymbalta), and other antidepressants that block both serotonin and norepinephrine reuptake (SNRIs) may be more effective.

#### Anticonvulsants

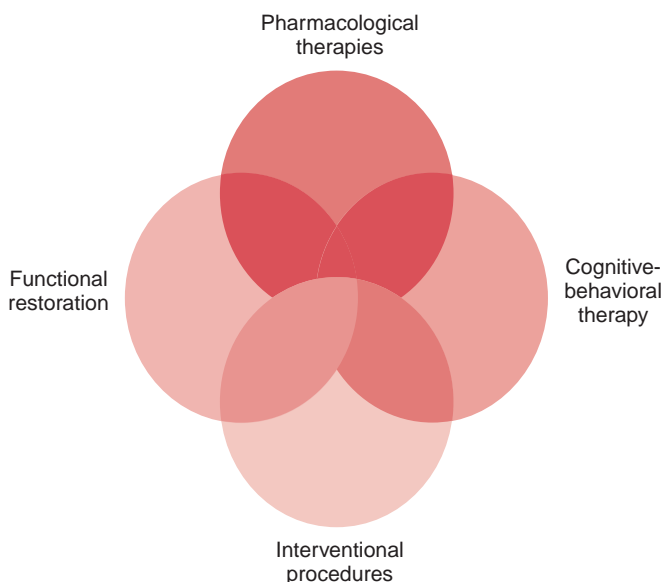
Anticonvulsants are effective in treating neuropathic pain associated with trigeminal neuralgia, postherpetic neuralgia, and diabetic neuropathy. Only case series suggest that gabapentin (Neurontin) may be effective in treating CRPS.<sup>7</sup> Most anticonvulsants have been used in individual patients, but none have been properly studied to determine their efficacy in CRPS. Commonly used medications include gabapentin, pregabalin (Lyrica), phenytoin (Dilantin), and carbamazepine (Tegretol). Other agents incorporated into CRPS treatment may include lamotrigine (Lamictal), oxcarbazepine (Trileptal), topiramate (Topamax), and tiagabine (Gabitril).

A rational dosing structure for gabapentin may be 300 mg three times daily with 100- to 300-mg increments every 5 days or so until a maximum dose of 3600 mg/day is obtained if patients fail to achieve adequate relief at lower doses. Dose adjustment is necessary for patients with renal insufficiency. Frequently reported adverse effects are somnolence and dizziness, and sometimes, ataxia and fatigue. These effects often resolve within 2 weeks of initiation of treatment.

Typical pregabalin dosing begins at 75 mg twice daily and increasing to 150 mg twice daily within 1 week if patients are tolerating the medication. Adverse events (dizziness, somnolence) are similar to those of gabapentin.

Less often used, phenytoin and carbamazepine may follow similar dosing schedules for treating trigeminal neuralgia and diabetic neuropathy. Serum levels of both should be assessed for toxicity. Theoretically, carbamazepine (sodium channel blocking capacity) may be effective for CRPS II because injury to the peripheral nerve changes the expression and distribution of sodium channels on axons.

Dosing of other anticonvulsants for CRPS is speculative, given the dearth of evidence for their utility in neuropathic pain.



**Figure 39–2.** Functional restoration of CRPS is achieved by a multimodal approach.

**Table 39–I. Proposed Pharmacotherapeutic Agents for the Treatment of Complex Regional Pain Syndrome**

Drug	Dose	Comments
<b>Antidepressants (Oral):</b>		
<b>TCA</b>		
Nortriptyline (Pamelor)	10–25 mg qhs initial dose and titrate up to max of 150 mg qhs over several wks.	Caution in elderly, pts. with suicidal ideation, and pts. with recent cardiac events.
Desipramine (Norpramin)		Consider tapering over 1–2 wk to avoid malaise, chills, myalgias, nasal D/C.
Amitriptyline (Elavil)		
Doxepin (Sinequan)		
Venlafaxine (Effexor)	37.5 mg bid initially. Maximum dose 225 mg. Titrate up over several wks.	Similar to TCA precautions.
<b>Anticonvulsants (Oral)</b>		
Gabapentin (Neurontin)	300 mg day 1, bid day 2, tid day 3. Max 3600 mg/day. Titrated up over several wks.	D/C taper over 7 days.
Pregabalin (Lyrica)	75 mg bid for 1 wk, then 150 mg bid	D/C taper over 7 days.
Phenytoin (Dilantin)	150 mg bid	Must follow serum levels.
Carbamazepine (Tegretol)	100 mg bid initially. Titrate over several days. Maximum 600 mg/day	Must follow serum levels. Useful especially for CRPS II.
<b>Opioids</b>		
	<i>Initial dosages:</i>	
Methadone (Methadose)	5 mg tid	Increase while balancing analgesia and adverse effects.
Fentanyl patch (Duragesic)	12.0 mcg/hr	
Morphine (MS Contin)	15 mg q 12 hr.	Do not crush or chew.
Oxycodone (OxyContin)	10 mg q 12 hr.	Do not crush or chew.
Tramadol (Ultram)	50–100 mg q 4–6 hr.	Can cause N/V, dizziness, HA, somnolence, constipation.
Oxymorphone (Opana ER)	Titrate to 400 mg/day maximum 5 mg q 12 hr.	
<b>Bisphosphonates</b>		
Intranasal calcitonin (Miacalcin Nasal)	100 IU/spray tid x 3 wk.	Common adverse effects: Flushing, N/V, backache, rhinitis. Rare: MI, anemia, anaphylaxis, CVA, bronchospasm.
Intravenous clodronate	300 mg daily for 10 days.	
Intravenous alendronate	7.5 mg daily for 3 days.	
<b>Steroids</b>		
Prednisone	30 mg/day; max 12 wk.	Taper slowly.
<b>Topical Agents</b>		
Lidocaine patch (Lidoderm)	5%; apply 12 hr/day	Usage longer than 12 hr/day may lead to tolerance; skin irritation.
Capsaicin (Zostrix)	0.025% apply tid	Induces cutaneous burning.
50% DMSO (Rimso-50)	Apply daily for 8 wk.	

CRPS, complex regional pain syndrome; D/C, discontinuation; DMSO, dimethyl sulfoxide; HA, headache; TCA, tricyclic antidepressants.

Clinicians may consider tapering anticonvulsants over 7 days to avoid the unlikely potential of withdrawal seizures in CRPS patients.

### Corticosteroids

Corticosteroids have been reported in studies to be effective treatment for CRPS. They may suppress ectopic neural discharges and reduce the inflammatory component of CRPS. Chronic steroid use is not recommended owing to an unfavorable risk-to-benefit profile. However, some evidence indicates that prednisone 30 mg per day for 12 weeks may be helpful.

### Topical Agents

Topical agents for CRPS may be useful. For instance, lidocaine (Lidoderm) patches 5%, applied for 12 hours per day can help treat focal, allodynic areas of pain.<sup>8</sup> Capsaicin (Zostrix) cream 0.025% applied two or three times a day produces analgesia in CRPS through release and reuptake inhibition of substance P. Unfortunately, most patients cannot tolerate the cutaneous burning sensation associated with capsaicin application. Some studies suggest that topical 50% dimethyl sulfoxide (DMSO [Rimso-50]) may be beneficial as well.

## Opioids

Opioids are gaining favor for the treatment of chronic neuropathic pain through prospective and some randomized, controlled studies.<sup>9-12</sup> Because opioids can produce significant adverse effects as well as tolerance, physical dependence, and addiction, they are often reserved for CRPS-related pain that responds inadequately to other medical or procedural therapies. When opioids are incorporated, patients should develop specific goals of treatment such as more active participation in functional restoration and/or engagement in social activities. Long-acting or sustained-release opioids provide continuous medication with fewer fluctuations in serum levels, better compliance with dosing regimen, and consequently, better pain control. Reasonable starting doses of typical opioids include methadone (Methadose) 5 mg by mouth three times daily, sustained-release morphine (MS Contin) 15 mg by mouth every 12 hours, sustained-release oxycodone (Oxycontin) 10 mg by mouth every 12 hours, extended-release oxymorphone (Opana ER) 5 mg by mouth every 12 hours, or transdermal fentanyl (Duragesic) 12 mcg/hour every 3 days. Because NMDA receptor antagonists may more effectively treat neuropathic pain and methadone displays NMDA receptor blocking capacity, clinicians may consider methadone as an initial opioid for CRPS. The goal of opioid therapy consists of achieving a balance between analgesia and intolerable adverse effects; therefore, no maximal dose can be recommended. The dose should be customized for each patient.

Bear in mind that opioids are often associated with adverse effects such as nausea, constipation, sedation, hormonal changes, immunologic alterations, hyperalgesia, and impaired cognitive function. Tolerance to the constipative effects of opioids rarely develops; hence, concurrent laxative therapy is critical. Comprehensive and ongoing assessment of opioid responsiveness, adverse effects, and aberrant behavior (diversion, self-escalation) should be integral to treatment.

Tramadol (Ultram), a synthetic derivative of codeine acts as a weak  $\mu$ -receptor agonist, inhibits reuptake of serotonin and norepinephrine (similar to TCAs), and facilitates neuronal serotonin release. Randomized, controlled trials demonstrate tramadol's effectiveness for peripheral neuropathy,<sup>13,14</sup> and may be useful for patients with CRPS. The usual dosing consists of 50 to 100 mg by mouth every 4 to 6 hours and gradually escalating by 50-mg increments every 3 to 4 days to diminish the onset of adverse events. The maximum dose is 400 mg/day. An extended-release formulation is available. Common adverse effects may include nausea, vomiting, dizziness, vertigo, constipation, somnolence, and headache. Clinicians should be mindful of the potential for increased risk of seizures or serotonin syndrome in patients concurrently using tramadol with SSRIs, selective monoamine oxidase inhibitors, or TCAs.

## Bisphosphonates

Bisphosphonates may represent the most thoroughly studied therapy for CRPS to date. They act as powerful inhibitors of bone resorption and may help interfere with local production of cytokines. In effect, their use may help combat the development of patchy osteoporosis associated with CRPS. Placebo-controlled studies have documented the benefit of three bisphosphonate compounds: intranasal calcitonin (Miacalcin), intravenous clodronate, and intravenous alendronate. The doses of each are listed in Table 39-1 and reflect the doses used in the respective studies. In practice, few clinicians have adopted these agents for the treatment of CRPS.

## Sympatholytic Agents

Sympatholytic agents are often used as a treatment for CRPS, despite the lack of randomized, controlled trials. These medications

include clonidine (oral and transdermal), reserpine (Resa), phenox-ybenzamine (Dibenzylamine), and prazosin (Minipress). Phentolamine (Regitine) infusion tests are sometimes used as an adjunctive tool in determining the presence of adrenergic mechanisms associated with CRPS.

## Other Medications

Other medications have been tried in the treatment of CRPS, but no randomized, controlled trials can confirm their efficacy. These agents include calcium channel blockers, thalidomide (Thalomid), benzodiazepines, ketamine (Ketalar), clonidine (Catapres), and muscle relaxants. Intrathecal baclofen (Lioresal) may aid in alleviating dystonia or exaggerated flexor reflexes in select patients with CRPS.

## Procedures

### Sympathetic Nerve Blocks

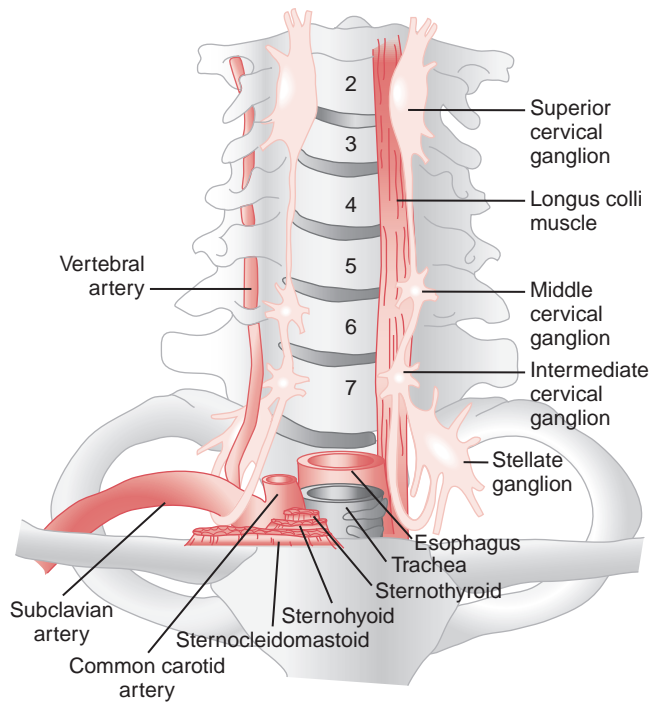
Sympathetic blockade with local anesthetics have been performed for both diagnostic and therapeutic purposes in the management of CRPS. Despite widespread use, there is weak evidence for sympathetic blockade as a beneficial therapy, and no guidelines for selecting patients or drugs for sympathetic blocks (SG or lumbar sympathetic) currently exist. A subset of CRPS patients may display SMP, and those patients are more likely to derive pain relief from sympathetic blocks. Furthermore, anecdotal reports coupled with the literature suggest that patients with mechanical allodynia and burning pain along with temperature and color changes may represent good candidates for sympathetic blockade. A positive response (pain relief) may not be diagnostic of the SMP subset of CRPS patients, given the risk of false-positive and false-negative outcomes associated with these procedures. For instance, improper needle placement may result in no block or in pain relief from partial or total sensory/motor block (somatic nerve block). Consequently, some clinicians use pharmacologic sympathetic block with phentolamine to help confirm the involvement of a sympathetically maintained component in CRPS patients. Patients who report pain reduction, increased range of motion, and greater participation in functional restorative techniques (PT, OT) may benefit from an extended series of repeat blocks. PT should be coordinated after the blocks to maximize the analgesic benefit of the procedure.

CRPS of the upper extremity can be treated with cervicothoracic (SG) blocks, and that of the lower extremity can be treated by lumbar sympathetic blocks. Both blocks of the sympathetic chain should preserve sensory and motor function, thereby allowing full engagement in PT and rehabilitation strategies. Sympathetic blockade is assessed by thermography, observing a rise in skin temperature to core body temperature in the blocked extremity. In the upper extremity and head, clinicians will further note evidence of Horner's syndrome (ptosis, myosis, enophthalmos, conjunctival injection, nasal congestion, and facial anhidrosis) as well as engorgement of veins of the back of the hand and forearm. In the lower extremity, practitioners will typically notice warmth along with a temperature rise. Informed consent must be obtained prior to all procedures. Prudent clinicians initial the operative side prior to performing the injection. All injections should be preceded by proper sterile technique.

### Cervicothoracic (SG) Block

#### Anatomy

Preganglionic axons to the head and neck join the sympathetic chain and synapse at the SG (fusion of the inferior cervical and first thoracic ganglion), middle cervical ganglion, or superior



**Figure 39-3.** Anatomy of the stellate ganglion. (From Loeser JD [ed]: *Bonica's Management of Pain*. Philadelphia: Lippincott Williams & Wilkins, 2001, with permission.)

cervical ganglion (Fig. 39-3). Postganglionic fibers either follow the carotid arteries to the head or merge with the gray communicating rami to join the cervical plexus or upper cervical nerves that innervate the neck and upper extremity. Therefore, to successfully block the sympathetic innervation to the head and neck, one needs to block the SG. This ganglion receives all preganglionic nerves that are traveling to more superior ganglia. The SG supplies sympathetic innervation to the upper extremities through C7–T1. Some contributions derive from T2 and T3, which do not pass through the SG; these are termed *Kuntz's nerves*. They join the brachial plexus and innervate distal structures of the upper extremity. If the SG block fails to track sufficiently inferior, Kuntz's nerves can cause persistent pain in an upper limb.

The SG lies in the anterior neck and in front of the first rib. It extends to the interspace between C7 and T1, is bounded medially by the longus colli muscle, laterally by the scalene muscles, anteriorly by the subclavian artery, posteriorly by the transverse process, and inferiorly by the posterior aspect of the pleura. The SG is positioned posterior to the vertebral artery, but the vertebral artery lies behind the transverse process of C6 (Chassaignac's tubercle). Classic teaching of the SG block requires needle positioning at the level of C6, which safely places the needle anterior to the artery. However, needle positioning at the level of the C7 vertebral body is also performed.

### Technique

Patients are positioned supine with the neck in slight extension. An intravenous catheter should be strongly considered as a conduit for resuscitative medications or for sedation. Immediate access to resuscitative drugs, suction, oxygen, defibrillator, and an endotracheal tube should be available. The level is identified under anteroposterior (AP) fluoroscopy or by palpation of the C6 transverse process (Chassaignac's tubercle). Anatomic landmarks include the trachea, sternocleidomastoid muscle, cricoid cartilage, and transverse process of C6. The SG lies just anterior to the transverse process of C7. A 22- to 27-gauge, 3.5-inch beveled needle is typically advanced slightly inferiorly to contact the periosteum of C6 or C7



**Figure 39-4.** Cervicothoracic (stellate ganglion) block in anteroposterior (AP) view at C7. Cervicothoracic (stellate ganglion) block under fluoroscopy. Needle is positioned at the left C7 transverse process.

at the junction of the vertebral body and transverse process. Avoid puncture of the carotid sheath by retracting it laterally with the sternocleidomastoid muscle. Once the periosteum is encountered, the needle is withdrawn about 2 mm. Intermittent fluoroscopic guidance can be used to verify appropriate needle trajectory and to confirm correct needle placement in relation to the C6 or C7 transverse process (Fig. 39-4). The needle tip should align medial to the vertebral artery, superior to the subclavian artery, and anterior to the epidural space in this position. Note that the vertebral artery is more exposed and less protected by the transverse process at the level of C7. Before injection, careful aspiration is performed to rule out the presence of blood or cerebrospinal fluid. If aspiration is negative, 1 ml of contrast is injected to verify proper spread along the cervicothoracic ganglia and to exclude intravascular or intrathecal injection (Fig. 39-5). Next, a 1-ml test dose of local anesthetic should be injected to exclude signs of central nervous system toxicity (intravascular injection) or spinal anesthesia (intrathecal or epidural injection). Finally, a total of 10 mL of local anesthetic is injected with intermittent aspiration after each 3 to 4 ml of solution. This volume of local anesthetic should block the sympathetic innervation to the upper extremity even if Kuntz's nerves are present.

### Complications

Complications include infection; tracheal or esophageal puncture; thoracic duct trauma (left side); hematoma; pneumothorax; intravascular, subarachnoid, or epidural injection; brachial plexus block; recurrent laryngeal nerve paresis with hoarseness; phrenic nerve block with temporary diaphragmatic paralysis; cardiovascular instability; seizure; coma; or death. A small volume of local anesthetic (< 1 ml) injected intravascularly, especially into the vertebral artery, can induce unconsciousness, respiratory paralysis, seizures, and severe hypotension. If less than 2 ml of solution is injected intravascularly, these sequelae are typically short lived. There is a higher risk of pneumothorax if the C7 transverse process is used as a landmark and the needle is inserted too caudally. The needle can puncture the dome of the lung (located around the C7–



**Figure 39-5.** AP fluoroscopic view of needle positioned at C7 and proper spread of contrast along the stellate ganglion and cervicothoracic region.

T1 interspace), especially in thin, tall patients because the dome of the lung is positioned more cephalad.

#### Absolute contraindications

Absolute contraindications include patient refusal, coagulopathy, pneumothorax, or pneumonectomy on the contralateral side (risk of additional pneumothorax), recent myocardial infarction (SG blockade interrupts the cardiac accelerator nerves), overlying skin infection, and systemic infection.

#### Relative contraindications

Relative contraindications include previous cervical surgery in the region, pregnancy if incorporating fluoroscopy, glaucoma (repeated SG blocks may exacerbate glaucoma), and marked atrioventricular heart block (SG block interrupts upper thoracic sympathetic ganglia which may produce bradycardia).

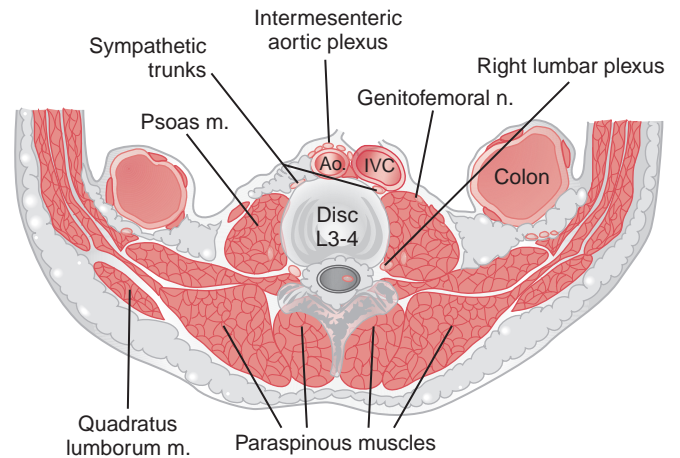
#### Lumbar Sympathetic Block

##### Anatomy

Preganglionic sympathetic fibers arise from the dorsolateral aspect of the spinal cord (typically T11, T12, L1, and L2) and then synapse with the lumbar sympathetic ganglia located on the anterolateral aspect of the L2–4 vertebral bodies. The lumbar sympathetic ganglia lie anterior to the psoas muscle (Fig. 39–6). Most postganglionic sympathetic fibers follow spinal nerves of the lumbar and lumbosacral plexuses to join all major nerves and corresponding vessels of the lower extremities. Because the majority of fibers pass through the L2 and L3 sympathetic ganglia, blockade of these two structures produces nearly complete denervation of the lower extremity.

##### Technique

The patient is positioned prone with one or two pillows placed across the anterior iliac crest to permit flexion of the lumbar spine and to open the transverse process interspaces. The clinician obtains an oblique fluoroscopic image of the targeted lumbar



**Figure 39-6.** Transverse image of lumbar sympathetic ganglia. (From Brown DL [ed]: *Atlas of Regional Anesthesia*, 2nd ed. Philadelphia: WB Saunders, 1999, with permission.)

vertebra (L2 or L3, typically) to the point at which the tip of the transverse process can be viewed just lateral to the vertebral body (Fig. 39–7). Local anesthetic can be used to anesthetize the skin and subcutaneous tissue at the anticipated needle entry point. A 22- to 25-gauge, 5- to 7-inch spinal needle is then inserted in oblique view to the anterolateral aspect of the vertebral body, verified with both AP and lateral fluoroscopic imaging (see Figs. 39–7 to 39–9). The needle may pass lateral or caudad to the lumbar transverse process. If the needle tip contacts the vertebral body too posteriorly, it may be slightly withdrawn and advanced more anteriorly. If the approach is too lateral, the needle may pierce the kidney, and an overly medial approach may access the epidural or intrathecal space. Contrast injection (2–3 ml) should confirm proper spread anterior to the vertebral body (on lateral imaging) and lateral to midline of the vertebral body (on AP imaging) (Figs. 39–10 and 39–11). Further, both contrast injection and needle aspiration should be performed prior to local anesthetic injection to ensure the absence of intravascular communication (aorta on the left side and inferior vena cava on the right side). Approximately 15 ml of



**Figure 39-7.** Lumbar sympathetic block. Needle position at L3 in oblique view.



**Figure 39-8. Lumbar sympathetic block.** Needle positioned at L3 vertebral body and viewed under lateral fluoroscopic guidance.

local anesthetic is then injected with intermittent aspiration to provide proper cephalad and caudad spread of solution along the sympathetic chain.

### Complications

Complications include infection, hematoma, intravascular injection, epidural or intrathecal injection, lumbar plexus block (causing quadriceps paresis), nerve root injury, disk trauma, renal injury (hematuria), hypotension, paraplegia, ureteral injury, and visceral perforation.



**Figure 39-10. Lumbar sympathetic block.** Contrast spread on AP fluoroscopic imaging.

### Contraindications

Contraindications include patient refusal, overlying skin infection, systemic infection, pregnancy (radiation exposure from fluoroscopy), and coagulopathy.

Chemical (phenol or alcohol), surgical, and radiofrequency sympatholytic procedures of the SG and lumbar sympathetic chain have been performed to more permanently interrupt the pain associated with the sympathetic nervous system. To date, only poor-quality evidence supports the use of these neurolytic interventions. Given the occurrence of bothersome side effects, clinicians should



**Figure 39-9. Lumbar sympathetic block.** Needle verification of proper position under AP fluoroscopy.



**Figure 39-11. Lumbar sympathetic block.** Contrast spread on lateral fluoroscopic imaging.

seriously consider the value of performing neurolysis until higher-quality evidence defines their effectiveness.

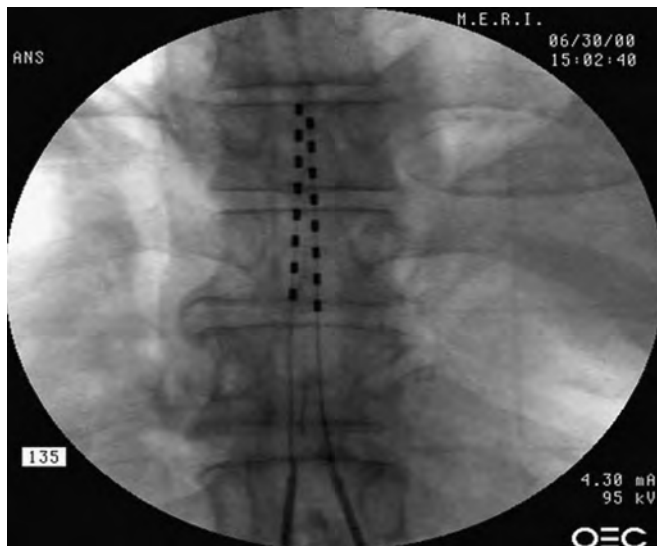
## Neuromodulation

### Spinal cord stimulation

The mechanism of action of dorsal column stimulation remains vague, although the goal remains clear: relieve pain by applying electrical stimulation to a degree that paresthesias cover the painful region without discomfort or motor dysfunction. Current theory suggests that large fiber stimulation may “close the gate” to painful input from small, unmyelinated  $\alpha\delta$ -, C-fibers. Further, spinal cord stimulation (SCS) may inhibit sympathetic outflow by stimulating  $\alpha$ - and  $\beta$ -fibers in the dorsal column of the spinal cord. The entire process of SCS may trigger the descending modulatory pain system and promote changes in spinal or supraspinal  $\gamma$ -aminobutyric acid (GABA)-mediated neurochemistry.

The use of SCS for CRPS is controversial, though growing in its application. In select patients who require facilitation of their treatment goals or who are achieving limited benefit with conservative therapies, SCS may improve health-related quality of life. For instance, one randomized, controlled trial showed a significant decrease in pain intensity with SCS in CRPS patients, but no improvement in functional status.<sup>15,16</sup> Other, more recent studies support SCS therapy in carefully screened patients who respond favorably to a SCS trial.

**Technique.** Psychiatric comorbidities, substance use disorders, and issues of secondary gain should be assessed prior to implementation, usually by a licensed psychologist. Test stimulation with temporary lead placement is performed under fluoroscopic guidance followed by a 3 to 7 day trial period on an outpatient basis. Clinicians should offer a permanent implant to patients who report approximately a 50% reduction in pain and demonstrate stable medical regimens. SCS trials are performed on an outpatient basis, and implantations require either outpatient or short inpatient stays. Patients are typically placed prone and lightly sedated in order to communicate the sensation of paresthesias in the appropriate anatomic region. Coverage of lower extremity pain requires lead placement in the lower thoracic region, whereas capturing pain in the upper extremities demands lead placement in the lower cervical region. Dual leads may best cover bilateral symptoms (Fig. 39–12).



**Figure 39–12. Spinal cord stimulator implantation.** Two leads located in the dorsal epidural space are viewed under fluoroscopy.

The three SCS manufacturers (Advanced Neuromodulation Systems, Medtronic, and Boston Scientific) offer rechargeable implanted batteries and sophisticated systems that permit multiple programming options to maximize coverage and subsequent pain relief.

**Complications.** Complications include spinal cord injury or nerve injury, cerebrospinal leak, infection, bleeding, lead migration/malposition, lead fracture, epidural hematoma, epidural abscess, and generator (battery) failure.

**Contraindications.** Contraindications include patient refusal, sepsis, coagulopathy, pregnancy, untreated psychiatric comorbidities (anxiety, depression), substance use disorder, inability to cooperate, secondary gain, demand cardiac pacemaker (need to change to a fixed rate), and specific needs for MRIs (SCS equipment is incompatible with MRI).

### Peripheral nerve stimulation

Peripheral nerve stimulation may be effective for CRPS II, in which patients have a well-defined nerve injury. Current literature is scant on the benefit of peripheral nerve stimulation in CRPS, however.

### Deep brain stimulation

There are minimal data to support the use of deep brain stimulation for CRPS. This should be considered in refractory cases when the potential for enhanced quality of life or functional restoration is likely.<sup>17</sup>

### Intrathecal infusion devices

Most data citing the benefit of intrathecal infusion therapies consist of case reports. Little evidence supports the use of intrathecal medications for the treatment of CRPS; however, case reports suggest that morphine may ease intractable pain and one RCT demonstrates the effectiveness of baclofen in reducing dystonic postures.<sup>18</sup> The role of clonidine, ziconotide (Prialt), and other opioids for CRPS has yet to be discovered.

## Psychological/Behavioral Approaches

Pain-related psychological distress resulting from CRPS may exacerbate pain intensity and promote disuse of the affected extremity. Although confirmative studies are lacking, experts have proposed that psychological treatments for CRPS focus on interrupting learned disuse and stress/distress and offering coping skills that will facilitate function and quality of life. Several case series suggest that specific techniques such as guided imagery, thermal biofeedback, hypnosis, progressive muscle relaxation, and autogenic training may diminish the pain of CRPS. Other studies highlight the benefit of integrating psychological approaches with multidisciplinary treatment (medications, physical restoration, procedural interventions) in a broad effort to help patients manage CRPS.

Specifically, cognitive-behavioral therapy may help patients identify and develop constructive pain coping mechanisms that will make their condition more tolerable and minimize the dramatic impact on their daily life. Psychological assistance with kinesophobia, or the fear of pain from movement of an affected limb, can aid in improving physical rehabilitation. Clinicians should request psychological evaluation in four areas: (1) Axis I psychiatric disorders (anxiety disorder, depression, panic disorder, post-traumatic stress disorder), (2) a patient's cognitive, behavioral, and emotional response to CRPS, (3) a patient's ongoing life stressors, and (4) response of significant others to the patient's CRPS. Similar to other chronic pain conditions, CRPS is considered a biopsychosocial disorder. Accordingly, the most successful treatments will target

the biologic, psychological, and social elements of this syndrome. All psychological hindrances to physical rehabilitation should be addressed and treated in the context of a comprehensive multidisciplinary treatment program.

## Functional Restoration

OT, PT, recreational, and later, vocational rehabilitation therapy should be considered soon after diagnosis. In many instances, CRPS patients will require concomitant pain-specific medications, psychological intervention, and perhaps specific injections before, during, and after functional rehabilitation. Consensus-based treatment guidelines recommend that clinicians and patients view functional restoration as primary treatment and all other interventions as adjunctive and supportive of the primary treatment.<sup>19</sup>

The role of the occupational therapists entails designing a rehabilitation strategy that controls pain and edema while maximizing function of the affected extremity. Physical therapists educate CRPS patients on achieving a balance between underutilizing the extremity (inactivity) and overstrengthening the limb. They develop a gradual and progressive weight-bearing program that improves strength and flexibility. Recreational therapists work with other disciplines (OT, PT) to help patients reengage in the community and practice new leisure skills. Most importantly, recreational therapists help minimize kinesophobia by encouraging patients to increase movement in creative ways. Finally, many patients may require vocational counseling to assist them with the transition back to employment as quickly as possible without risk to their health. Vocational specialists decide whether patients can return to work, will require modifications of their job, need a different job with the same employer, or simply need a new employment opportunity.

Either occupational or physical therapists will begin their program with desensitization techniques. The affected limb is exposed to heat, cold, vibration, massage, and contrast baths with progressive duration and intensity. After desensitization, isometric strengthening is introduced. This assists in halting the progression of atrophy that results from disuse of the limb. If the patient tolerates isometric exercise, then range of motion, aerobic conditioning, and isotonic exercise are initiated. These activities mobilize the patient and reintroduce the affected region to daily activity. In upper extremity CRPS, the use of “scrub and carry” exercises are utilized by some therapists. Although disuse is detrimental, overuse is equally harmful, so therapists educate patients on the appropriate limits of activity.

The restorative process may require months to complete. Practitioners should write an order, referral, or prescription for desensitization followed by isometric exercise and then range of motion and isotonic conditioning plus aerobic strengthening. This intense regimen should ideally be performed by therapists who are familiar with treating CRPS patients, and clinicians may wish to discuss treatment goals directly with the consulting therapists. Patients will benefit from knowing in advance that functional rehabilitation may transiently exacerbate their pain and edema.

## CONCLUSIONS

Like many chronic pain syndromes, a specific etiology has not been identified for CRPS. It may likely have several contributing factors. There is no single diagnostic test and no constellation of symptoms that occur in every patient that is pathognomonic for CRPS.

Similarly, there is no single therapy or combination of therapies that is universally effective for all CRPS patients. Currently, treatment of CRPS focuses on an early, aggressive multimodal approach that targets pain reduction and functional rehabilitation. Interventions aimed toward the attainment of these goals include specific pain-relieving medications, sympathetic nerve blockade, neuromodulation, functional restorative approaches (PT, OT, recreational therapy, vocational counseling), and psychological/behavioral treatments.

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