Complex Regional Pain Syndrome (Reflex Sympathetic Dystrophy)

Author(s):
Dennis D. Dey, MD, PhD;
Robert J. Schwartzman, MD

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The preponderance of data supporting this statement is derived from:

A level 1 studies, which meet all of the evidence criteria for that study type

B level 2 studies, which meet at least one of the evidence criteria for that study type

C level 3 studies, which meet none of the evidence criteria for that study type or are derived from expert opinion, commentary or consensus

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[1] Has no financial relationships with pharmaceutical companies, biomedical device manufacturers, or health-care related organizations.

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1. Prevention: Treat posttraumatic pain early and effectively to help prevent CRPS. C

1.1 Pay particular attention to pain control in patients at risk for CRPS. C

Specific recommendation:

- Consider all patients with trauma to a major nerve or plexus, soft tissue, bone, or joint to be at risk for CRPS.
- Consider CRPS particularly after:
  - Flexion extension trauma to the neck
  - Carpal tunnel median nerve release procedures
  - Sciatic nerve injury from trauma, spondylosis, or spine surgery
  - Trimalleolar fracture of the ankle
  - Colles fracture of the wrist or femoral head fracture
  - Soft tissue ligamentous injuries
  - Knee trauma followed by arthroscopy and immobilization
  - Prolonged casting
  - Repetitive nerve injuries
  - Surgery
- Maintain pain control in the healing period and avoid additional nerve or soft tissue injury through casting.

Rationale:

- CRPS can occur after any trauma, but certain injuries are believed to be more strongly associated.
- Central and peripheral sensitization are likely key mechanisms in the pathophysiology of CRPS.
- At the level of the peripheral nerve, the spinal cord, and the brain, repetitive and chronic pain can lead to a remodeling of ascending pain pathways and descending inhibitory systems; this leads to increased pain sensitivity and is probably a major mechanism in the development of chronic pain.
- Careful pain control may help to avoid sensitization.

Evidence:

- The symptoms of CRPS have been described after specific injuries (1).
- Peripheral and central sensitization are well recognized and described phenomena in chronic pain states leading to hypersensitivity, mechanoallodynia, thermal allodynia, and motor phenomena (2).
- A marked inflammatory response after fracture may indicate that the patient is at higher risk for developing CRPS (3).

Comments:

- A population-based study in Olmsted County, Minnesota, found the prevalence of CRPS to be 20.57 per 100,000. The female-to-male ratio was 4:1 (4).
- An epidemiologic study from the Netherlands found the estimated overall incidence rate of CRPS to be 26.2 per 100,000 person-years, four times higher than in the Olmsted County study, likely due to methodologic

differences. Females were affected at least three times more often than males (5).

1.2 Consider the use of vitamin C to prevent development of CRPS. B

Specific recommendation:
- Consider the use of vitamin C, 500 mg/d for 50 days following fractures to prevent development of CRPS.

Rationale:
- Inflammation and increased vascular permeability due to free radical damage of endothelium may play a role in the development of CRPS after injury. Vitamin C reduces lipid peroxidation, scavenges hydroxyl radicals, protects the capillary endothelium, and inhibits vascular permeability.

Evidence:
- In a prospective, double-blind study of 123 adults with 127 conservatively treated wrist fractures, patients were randomly given 500 mg of vitamin C or placebo daily for 50 days. The study found that patients taking vitamin C had a lower risk for developing CRPS (6).
- Another double-blind, prospective, multicenter trial of 416 patients with 427 wrist fractures also concluded that vitamin C reduced the prevalence of CRPS after wrist fractures (7).
- A quasi-experimental study of two groups of patients who had foot and ankle surgery showed that vitamin C supplementation helped prevent CRPS I of the foot and ankle (8).

Comments:
- Certain patients may be at higher risk for developing CRPS after injury. These include patients with multiple sclerosis (9) and those with family members affected by CRPS (10).

2. Screening: Not applicable to this module.

3. Diagnosis: Consider the diagnosis of CRPS in all patients with a history of trauma; characteristic, persistent, regional pain out of proportion to the injury; vasomotor or sudomotor instability in the affected region at presentation or by history; and no alternative diagnosis to explain their symptoms. C

3.1 Use clinical evaluation to diagnose CRPS, which requires the onset of pain after injury, persistence of pain beyond the expected healing period, and at least two of the following: neuropathic pain, autonomic dysfunction, swelling, dystrophy, and movement disorder. C

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- Ask about duration of pain beyond the expected period of normal healing or severity of pain out of proportion to the initial injury.
- Determine if at least two of the following are present:
  - Neuropathic qualities of pain (allodynia, hyperalgesia, or hyperpathia)
  - Autonomic dysfunction of the affected extremity
  - Swelling
  - Dystrophy
  - Movement disorder
- Exclude other conditions that can explain the symptoms.

Rationale:

- Required for the diagnosis of CRPS is the onset of pain after injury, its persistence beyond the expected period of normal healing, and at least two associated symptoms or signs.
- Application of diagnostic criteria helps to distinguish CRPS and other painful conditions associated with trauma.

Evidence:

- Diagnostic criteria for complex regional pain syndrome were proposed by the International Association for the Study of Pain in 1994 based on clinical symptoms and signs. A literature study has found that these criteria are not uniformly applied in published studies (11)
- A study exploring the external validity of the International Association for the Study of Pain criteria in 160 patients with pain of different etiologies found that the criteria had good sensitivity but low specificity, leading to overdiagnosis unless modifications were made (12).
- A study comparing three different sets of criteria for CRPS showed a significant lack of agreement, which may lead to different results in various studies and, thus, prevent scientific advances in this field (13).
- In a cohort study of 43 patients with CRPS, motor disorders including focal dystonia, weakness, spasms, tremor, difficulty initiating movement, and increased tone and reflexes were observed. In some cases these symptoms preceded other symptoms and signs by weeks to months (14).
- Comprehensive descriptions of CRPS are found in other reviews (1; 15; 16).

Comments:

- The diagnosis of CRPS is often missed, particularly early in the disease. A high index of suspicion in patients with chronic, burning pain after an injury typically associated with CRPS will lead to earlier detection of the disease, earlier treatment, and possibly better outcome.
- CRPS in children may present differently than in adults, making it more difficult to diagnose (17).

3.2 Identify the characteristic properties of the pain in CRPS, looking for a burning quality, regional distribution, spread, and the presence of dynamic allodynia and hyperalgesia. B

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- Ask about:
  - Duration of the pain beyond the period of normal healing
  - Spread of the pain to contiguous and distant body areas
  - History of pain in body areas other than those directly affected by the injury
- Define the painful area and compare to plexus, root, and nerve territories.
- Explore the quality of the pain to determine if it is of “burning” quality.
- Understand that CRPS pain does not respect neurologic territories.
- Examine for dynamic allodynia by applying a normally nonpainful mechanical or thermal stimulus and determining if the stimulus (e.g., lightly touching the patient's skin or applying mild pressure) provokes pain.
- Examine for hyperalgesia by applying a normally painful stimulus (e.g., applying a pinprick) and determining if it is felt as too painful and the pain spreads beyond the point of the stimulus.

Rationale:

- Pain in CRPS is regional pain; it does not respect root or nerve territories, distinguishing it from mononeuropathy and radicular pain syndromes.
- The most common description is that of burning, but other descriptors (squeezing, throbbing, aching, shooting) may coexist or be used instead.
- Spontaneous joint pain and joint sensitivity to pressure is also characteristic.
- Mechanoallodynia is present in almost all cases.
- Thermoallodynia to cold, hyperalgesia, and hyperpathia are often found.
- The duration of the pain is beyond the period of normal healing, and its severity is commonly out of proportion to the initial injury.
- The origin of the pain corresponds to the initial structural injury, and spread commonly occurs, frequently to a distant site, but can be contiguous or in mirror distribution.

Evidence:

- The character of the pain in CRPS has been described in multiple publications (16; 18; 19).
- The spread of CRPS is a unique but well-documented phenomenon. The patterns of spread have been described in a retrospective study in 27 CRPS patients as contiguous with the initial painful area (19%), independently occurring at distant body sites (70%), and in a mirror distribution (4%) (20).

Comments:

- The intensity of the pain fluctuates spontaneously. Additional injury of the same or of other body areas and emotional stress can provoke exacerbations and accelerate spread. Pain from conditions that were present before the onset of CRPS and had become asymptomatic may become reactivated.
- Mechanoallodynia is often the single most disabling component. It can be so severe that the patient does not allow the area to be touched by

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anything. Dynamic mechanoallodynia from a moving stimulus is more common than static allodynia. When occurring at a distance the spread is most often in a mirror distribution, involving the contralateral extremity. CRPS in its extreme form can spread to involve the whole body.

3.3 Look for autonomic dysfunction and edema in the affected part of the body and elsewhere. C

Specific recommendation:

- Look for:
  - Edema of the painful area
  - Color and temperature changes and abnormal sweating of the painful area
- Ask about voiding difficulties, urge and stress incontinence.
- Be aware that the severity of these symptoms typically fluctuates in individual patients.
- Pay attention to these signs also in body areas not affected by the initial injury.

Rationale:

- The autonomic dysfunction manifests as abnormal sweating with color and temperature abnormalities due to alterations in blood flow.
- Piloerection, increased hair and nail growth, and livedo reticularis may be seen.
- The severity of the autonomic changes fluctuates, particularly in the early stages of CRPS, and can be observed in nonpainful body areas, remote from the original injury.
- Bladder dysfunction (detrusor hyperreflexia, detrusor areflexia, sensory urgency, and detrusor sphincter dyssynergia) has been described as a consequence of CRPS.

Evidence:

- The autonomic symptoms of CRPS are well described (16; 18).
- Evidence is accumulating for central autonomic dysregulation as an explanation for autonomic symptoms remote from the site of injury (21).
- A retrospective study found voiding difficulties in 20 patients that occurred in the course of CRPS. Urodynamic studies revealed detrusor hyperreflexia (8 patients), detrusor areflexia (8 patients), sensory urgency (3 patients), and detrusor sphincter dyssynergia (1 patient) (22).

Comments:

- Early in the course of the disease increased sweating, swelling, and hyperperfusion with increased temperature and decreased capillary refill time are typical. Later, the involved area is most often cool and cyanotic. The fluctuation of symptoms often leads to considerable confusion, particularly when only reported by the patient and not present at the time of examination. This is also true for the spread of symptoms.

3.4 Determine if the movement disorder of CRPS, which can include difficulty initiating movements, tremor, dystonia, muscle

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spasm, decreased reflexes, or weakness, is present. B

Specific recommendation:
- Look for:
  - Difficulty in initiating movements by having the patient perform rapid finger and foot tapping, and count the number of movements in a 30-second period
  - Dystonia manifested as plantar flexion and inversion of the foot or flexion and inversion of the hand
  - Tremor
  - Weakness independent of or out of proportion to pain
  - Muscle spasm
  - Increased reflexes
- Recognize that although usually experienced in the painful extremity, these findings can also occur in the contralateral extremity.

Rationale:
- In longstanding CRPS, motor activity is impaired beyond the limitations expected from pain and inactivity.
- The movement disorder of CRPS consists of hypokinesia with difficulty initiating movement, dystonia, muscle spasms, weakness, exaggeration of physiologic tremor, increased reflexes, and rarely, myoclonus; any one or a combination of these symptoms may be seen.
- The movement disorder is almost invariably present in long-term CRPS patients but may be seen early in the disease.
- The movement disorder can occur in the contralateral extremity, often in a mirror fashion, and therefore the involved extremity may not be the painful extremity.

Evidence:
- The movement disorder of CRPS is well described and recognized (21; 23; 24). It has been part of the early description of the syndrome (25), but the first systematic description was a retrospective review of 43 cases describing focal dystonia, spasms, tremor, and difficulty initiating movement (14).
- A retrospective study of 185 patients found that 121 had a movement disorder, with dystonia being the most prevalent manifestation (91%) (26).
- Functional imaging studies also showed central reorganization of motor circuits, which may contribute to motor disorders in patients with CRPS (27).

Comments:
- The movement disorder adds significantly to the disability caused by CRPS, and recognition of it is important because it is treatable.

3.5 Look for dystrophy in the late stage of CRPS. C

Specific recommendation:
- Look for:
  - Hair loss

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- Brittle nails
- Skin atrophy
- Gum atrophy
- Early cataracts
- Skin ulcerations
- Poor healing of infections

• Consider plain radiographs, bone scan, and bone densitometry of the affected area.

Rationale:

• In the late stages of the disease hair loss, brittle nails, atrophic and cyanotic skin occur in the affected extremity.
• Osteoporosis can be shown by plain radiography or bone densitometry, and these findings are more pronounced distally than proximally.
• In single, severe cases, gum atrophy with loosening of the teeth as well as early formation of cataracts and skin ulcerations have been observed.

Evidence:

• The dystrophic changes of skin and bone are well described and widely recognized. They have been part of the description of CRPS/RSD since the introduction of the term in 1937 (1; 15; 28; 29).
• Reports of gum atrophy, loosening of the teeth, and early formation of cataracts are anecdotal.

Comments:

• The dystrophy is speculated to be due to compromised blood flow secondary to central autonomic dysregulation.

3.6 Determine the level of psychological functioning in patients with CRPS. C

Specific recommendation:

• Ask about:
- Mood, energy, and sleep
- Appetite
- Guilt and suicide potential
- Ability to function at home and work
- Effect of CRPS on the relationship to others and in social interactions
- Effect of CRPS on sexual functioning

• Show empathy for the severe effects the disease has on the patient's personal and social life.

Rationale:

• Depression develops commonly in patients with CRPS but is not more frequent or severe than in other types of chronic pain; the CRPS population, however, does not have a specific psychiatric profile.
• CRPS patients are commonly puzzled by the difficult-to-understand symptoms of their disease.
• The impact of CRPS on the patient's occupational and personal life is usually devastating, causing severe emotional, social, and financial distress to the patient.

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Evidence:

- In a retrospective review, illness behavior, symptom reporting, and level of psychological distress, as well as history of psychological childhood trauma, were compared among three groups: 44 patients with low-back pain, 21 patients with neuropathy, and 25 patients with CRPS. The CRPS patients were found to be psychologically no different from the neuropathy group, whose pain was secondary to a widely accepted organic cause (30).
- A retrospective study of 25 consecutive CRPS patients found that a major depressive disorder occurs in 20% of patients (31).

Comments:

- Physical findings and disability are usually out of proportion to the initial injury. Their nature and severity are puzzling and may lead to confusion even among experienced physicians. This can lead to the misdiagnosis of CRPS patients as having a primary psychiatric disorder or being malingerers. Patients may react with frustration, anger, and mistrust.
- No high-quality study has provided clear-cut evidence to support the suggestion that psychological factors predispose to CRPS or have an impact on its course, and available studies yield contradictory or inconclusive results (32; 33; 34).

3.7 Consider the use of diagnostic testing to support the diagnosis of CRPS and rule out other conditions. C

Specific recommendation:

- Use diagnostic tests to support the diagnosis and to exclude other conditions:
  - Bone scan
  - Quantitative sensory testing
  - Autonomic sensory testing
  - Thermography
  - Sweat testing
  - Plain radiograph
  - MRI
  - EMG/NCS
  - Vascular studies if vascular or venous thrombotic disease are suspected
  - Sedimentation rate
  - Blood cell count
  - Rheumatologic testing
- See table Laboratory and Other Studies for CRPS.

Rationale:

- Diagnostic tests are not needed for the diagnosis but usually are required to exclude underlying pathology that may maintain the chronic pain or exacerbate CRPS, or to provide an alternative explanation for the encountered symptoms.
- Demonstration of abnormal bone metabolism and osteoporosis by bone scan, bone densitometry, MRI, or plain X-ray supports the diagnosis.

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- Thermography, sweat testing, and quantitative sensory testing can also support the diagnosis.
- MRI, EMG/NCS, vascular studies, and laboratory studies are helpful in excluding other conditions.

Evidence:
- The value of supportive testing has been reviewed. There is no gold standard test, and the mainstay of the diagnosis is the clinical picture (19; 35; 36).

Comments:
- None.

3.8 Include all conditions for which chronic pain is a prominent symptom in the differential diagnosis of CRPS. C

Specific recommendation:
- Consider an alternative diagnosis if:
  - There is no history of trauma
  - Allodynia is not present
  - Patients do not complain of pain
  - There is edema or abnormal sweating or blood flow to the affected area
  - Pain is confined to an anatomic territory (hemibody, plexus, root or nerve territory)
  - Sensory loss or weakness is prominent at onset
  - Signs or symptoms of systemic disease are prominent at onset
- See table Differential Diagnosis of CRPS.

Rationale:
- Painful sensory neuropathy; lesions involving the thalamus, the dorsal root ganglion, or the spinothalamic tract; and neoplastic, rheumatic, and vascular disease may have symptoms seen in CRPS.

Evidence:
- Due to their complexity, the symptoms of CRPS may be confused with those of other conditions (23; 29).

Comments:
- The diagnosis of CRPS requires the absence of a concomitant condition that could account for the pain. However, structural lesions may coexist and should be sought because they can both compound and exacerbate the disease. Altered body mechanics in the chronic pain state increase the risk for disc herniation, nerve entrapment, and osteoarthritis. Use of crutches commonly leads to brachial plexus traction injury.
- It is important to recognize that the symptoms of CRPS naturally fluctuate substantially. It may take several visits to make a diagnosis. The lability of the symptoms is characteristic, often distressing to the patient, and can be confusing for the physician who does not see many cases of CRPS.

4. Consultation for Diagnosis: Consider consulting an

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appropriate specialist for help in diagnosing CRPS. C

4.1 Consider consulting a pain specialist, neurologist, psychiatrist, or rheumatologist if the diagnosis is unclear or if specialized testing is needed. C

Specific recommendation:
- Obtain a consultation with an appropriate specialist if the diagnosis cannot be established unequivocally or if superimposed or coexisting neurologic or rheumatologic disease is a possibility.

Rationale:
- The complex symptoms of CRPS and their significant overlap with neurologic and rheumatologic conditions justify a neurologic and possibly rheumatologic evaluation in most cases to help distinguish CRPS from neuropathy, radiculopathy, plexopathy, or central post-stroke pain and from rheumatic or collagen vascular disease.
- Factitious disorders, malingering, and somatoform disorders should also be excluded.

Evidence:
- A 2010 Cochrane Review evaluating the effect of sympathectomy and other interventions for chronic pain syndromes, including CRPS, found only one study meeting inclusion criteria and none evaluating sympathectomy (38).
- A retrospective study found more patient-reported benefit from early compared with late treatment with sympathectomy (39).

Comments:
- Chances of therapeutic success are higher with early diagnosis and early treatment.
- Proper identification of underlying psychiatric conditions will prevent inappropriate treatment and improve outcomes.

5. Hospitalization: Consider inpatient treatment for patients with severe symptoms of CRPS. C

5.1 Consider hospitalizing patients with CRPS if symptom control is unsatisfactory on an outpatient basis. C

Specific recommendation:
- Refer patients with severe symptoms unresponsive to outpatient therapy to an inpatient pain service for infusion of iv lidocaine and intrapleural or lumbar epidural bupivacaine as a last resort.
- Provide cardiac monitoring and frequent monitoring of vital signs and neurologic status for patients treated with iv lidocaine, and check lidocaine levels daily.
- Monitor neurologic status frequently in patients treated with intrapleural or lumbar epidural bupivacaine.
- Consider administering ketamine in an anesthetic dosage over 5 days.

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Rationale:
- Outpatient management sometimes fails to control the patient's symptoms; poorly controlled symptoms may promote central sensitization, and effective pain control during a period of inpatient treatment may mitigate this process.
- Monitoring is necessary because iv lidocaine can lead to arrhythmias and seizures, hypotension can occur, and indwelling catheters can become infected; leg weakness and urinary retention can occur from treatment with lumbar epidural bupivacaine.

Evidence:
- Based on the mechanism of central sensitization, even temporary pain relief or sympathetic blockade through a course of inpatient treatment may have a lasting effect (2).
- An open-label trial found some improvement in pain reduction, CRPS symptoms, and quality of life with ketamine in an anesthetic dosage in patients with previously refractory CRPS, but randomized, controlled trials are needed (40).

Comments:
- None.

6. Therapy: Use drug treatment to target neuropathic pain, the sympathetic pain generator if present, the mechanisms of central sensitization, and dystonia. Recognize the importance of non-drug modalities in the treatment of CRPS. A B

6.1 Prescribe physical therapy for all patients with CRPS. A

Specific recommendation:
- Provide adequate analgesia before physical therapy is started.
- Begin with isometric strengthening and gentle flexibility exercise.
- Proceed to more challenging exercises as the patient's condition improves.
- Avoid exercises that induce pain.
- See figure Clinical Pathway for Complex Regional Pain Syndrome (CRPS).

Rationale:
- Physical therapy is an essential part of treatment for CRPS.
- Preservation of joint mobility and prevention of contractures and osteoporosis cannot be accomplished without physical therapy.

Evidence:
- A randomized, controlled trial in 135 patients showed significant reduction in pain and improvement in active range of motion at 1-year follow-up with physical therapy compared to social work alone (41).
- A systematic literature review also showed that graded motor imagery is effective in reducing pain in patients with CRPS (42).

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Comments:

- It must be emphasized that the exercises be associated with as little pain as possible because pain may maintain the chronic pain state through central sensitization. Central sensitization requires nociceptive input for its maintenance and is characterized by plastic changes in the nervous system on an anatomic and molecular level; therefore, repetitive painful stimuli may exacerbate the disease process and maintain the chronic pain state.
- A physical therapist experienced in working with CRPS patients is crucial to success, as is good communication between physical therapy and the treating physician.

6.2 Use anticonvulsants, tricyclic antidepressants, NSAIDs, lidocaine, opioids, alendronate, calcitonin, and corticosteroids to treat pain. A

Specific recommendation:

- Consider use of corticosteroids at onset of CRPS.
  - Institute a trial of oral prednisone, 10 mg tid per day for up to 12 weeks (or until remission, if it occurs before 12 weeks), or methylprednisolone, 32 mg/d by mouth for 2 weeks followed by a 2-week taper as soon as possible after diagnosis
- For the treatment of chronic pain symptoms, start with either gabapentin or a tricyclic antidepressant.
  - Start gabapentin at 100 to 200 mg tid, and increase the dose to 600 mg tid over 2 weeks
  - Note that higher doses are frequently required; although the standard maximum dose is a total of 3600 mg/d, doses of 6 g/d and higher have been used
  - When using a tricyclic antidepressant, consider nortriptyline or amitriptyline
- Use NSAIDs for pain control either alone or in conjunction with another agent.
- Add topical lidocaine in the form of a patch, 12 hours on, 12 hours off.
- Use alendronate, 40 mg/d, even if osteoporosis is not present.
- Use calcitonin, 300 to 400 IU/d, given by nasal spray or injection.
- Use oxycodone/acetaminophen combination, 5 mg/325 mg every 4 to 6 hours, for physical therapy breakthrough pain.
- Use slow-release oxycodone, morphine, or methadone if oxycodone/acetaminophen is needed daily.
- Use iv lidocaine in an inpatient setting to alleviate severe symptoms in generalized CRPS that do not respond to combinations of other agents.
- See table Drug Treatment for CRPS.
- See figure Clinical Pathway for Complex Regional Pain Syndrome (CRPS).

Rationale:

- Steroids are potent anti-inflammatory agents and may abort CRPS/RSD evolution if started early enough after symptom development. The

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analgesic effect of steroids may also aid in symptom control.

- Gabapentin is widely used due to its favorable safety profile for neuropathic conditions such as postherpetic neuralgia and diabetic neuropathy; its mechanism of action in chronic pain may be exerted by blockade of N-type voltage-dependant calcium channels in the dorsal root ganglion.
- The efficacy of various tricyclic antidepressants has been shown in many neuropathic pain conditions, such as diabetic neuropathy, postherpetic neuralgia, and neuropathic pain after breast surgery, and in central post-stroke pain. The effect relies on descending modulation of pain transmission in the dorsal horn through stimulation of both 5-HT and α-2 adrenoreceptors. The effect on the α-2 receptor is the likely reason for their superiority over SSRIs.
- Lidocaine is an Na^+ channel blocker that has high affinity to TTX-sensitive Na^+ channels. These channels have been shown to be upregulated in the dorsal horn of the spinal cord after nerve injury, and their blockade has led to reduced allodynia in animal models of neuropathic pain. Significant decrease of mechanical and thermal allodynia has been shown in patients with CRPS treated with iv lidocaine.
- Alendronate, a bisphosphonate, has been shown to be effective in relieving pain in patients with CRPS even if no osteoporosis is present.
- Oxycodone (slow release) is widely used. Methadone may be superior to other opioids in the treatment of neuropathic pain due to its NMDA-receptor antagonist properties.

Evidence:

- Twenty-three patients with CRPS were randomly allocated to medication with oral prednisone or placebo. All 13 patients in the prednisone-treated group showed more than 75% clinical improvement within the 12-week period. Of the 10 patients who received placebo, only 2 reported improvement (43).
- In a placebo-controlled, non-blind trial, 31 of 36 patients became almost symptom-free within 10 days' treatment with low doses of oral corticosteroids (44).
- Alendronate has been shown to alleviate pain and improve joint mobility and pressure tolerance in a randomized, controlled, double-blind study in 40 patients with posttraumatic CRPS (45).
- A review of studies testing the value of bisphosphonates in patients with CRPS showed a trend in favor of these medications, but the data are limited, particularly in regard to adverse effects (46).
- The efficacy of gabapentin for neuropathic pain has been shown in large-scale placebo-controlled trials for postherpetic neuralgia (47) and painful diabetic neuropathy (48).
- The efficacy for amitriptyline has been shown in double-blind, placebo-controlled, randomized trials (49; 50).
- A 2001 systematic review and meta-analysis of treatments for RSD found that guanethidine or IV regional sympathetic blocks did not improve symptoms but that calcitonin did result in symptom

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improvements (51).
- The blockade of TTX-sensitive Na^+ channels has led to reduced allodynia in animal models of neuropathic pain (52).
- Significant decrease of mechanical and thermal allodynia has been shown in patients with CRPS treated with iv lidocaine in a double-blind, randomized, placebo-controlled trial (53).
- Doses required for relief of neuropathic pain have been shown to be twice as high as in nociceptive pain in a double-blind, randomized, placebo-controlled trial (54).
- Methadone has been effective in a patient with treatment-resistant, chronic neuropathic pain from burns resistant to gabapentin, amitriptyline, and other opioids (55).
- A double-blind, randomized, placebo-controlled study on patients suffering from CRPS compared treatment with morphine and an NMDA-receptor antagonist with morphine and placebo on functional MRI images representing cerebral pain. The study found a larger MRI effect in the combination group but did not measure clinical outcomes (56).
- Intrathecal glycine is ineffective for treating pain in CRPS, according to a 2009 randomized, double-blind, placebo-controlled crossover study involving 19 patients (57).
- A 2012 systematic review determined that there is insufficient data to justify the use of immunotherapy in CRPS (58).
- An expert panel has recommended treatment strategies for CRPS (59).

Comments:
- The studies on steroid treatment were small, but the results were encouraging. Steroids have significant side effects, but the doses used were fairly small and the duration of treatment was limited. In the acute phase of CRPS/RSD, when the inflammation is still quite prominent, a trial of steroids appears to be a reasonable option but not so in the chronic, dystrophic, or “burnt out” stages.
- Although free radical scavenging therapy with vitamin C appears to be effective in CRPS prevention, intravenous free radical scavenging therapy with 10% mannitol proved to be no better than placebo in patients with established CRPS (60).
- Anticonvulsants other than gabapentin, such as carbamazepine, phenytoin, lamotrigine, topiramate, and felbamate, have also been used for neuropathic pain conditions, but are less widely used due to their higher risk for serious side effects than gabapentin (61).
- SSRIs are less effective than tricyclic antidepressants for neuropathic pain.
- Pathologic activation of the NMDA-receptor plays a role in the development of opioid tolerance as well as in the maintenance of neuropathic central pain (2; 62). Due to its NMDA-receptor antagonist properties, methadone may be more suited than other opioids to treat neuropathic pain (63).

6.3 Treat dystonia in CRPS with oral muscle relaxants or, in severe cases in patients resistant to oral drugs, intrathecal baclofen. B

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Dennis D. Dey, MD, PhD;
Robert J. Schwartzman, MD

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Specific recommendation:

- Use muscle relaxants in early dystonia, starting one of the following:
  - Tizanidine at 2 mg qhs and titrating slowly to a maximum dose of 8 mg tid
  - Baclofen at 5 mg tid and titrating up every 3 days to a maximum of 80 mg/d divided tid or qid
- Consider referral to an interventional pain center for intrathecal baclofen in patients with severe dystonia intractable by oral agents.
- See table Drug Treatment for CRPS.
- See figure Clinical Pathway for Complex Regional Pain Syndrome (CRPS).

Rationale:

- Tizanidine is an agonist at α-2 receptors that decreases sympathetic outflow facilitation from caerulospinal pathways and presynaptically inhibits motor neuron output in the spinal cord.
- Baclofen is a GABA-B receptor agonist that leads to inhibition of sensory input into the motor neurons of the spinal cord; continuous intrathecal administration at 350 to 850 µg/d has been used successfully to treat severe dystonia in CRPS.

Evidence:

- In a double-blind, placebo-controlled, crossover trial, baclofen bolus injections, 50 to 75 µg intrathecally, and subsequent continuous infusion with a baclofen pump led to alleviation of dystonia and pain in six of seven RSD patients. Hyperhidrosis, skin discoloration, and increased nail growth were also reduced (64). Bladder atony occurred in two of the seven patients treated with intrathecal baclofen and required self-catheterization.
- A single-blind, placebo-run-in, dose-escalation study in 42 patients with CRPS found improvement in dystonia, pain, disability, and quality of life following treatment with intrathecal baclofen (65).
- A randomized trial comparing intrathecal glycine to placebo in 19 patients showed that glycine is ineffective for treating dystonia in CRPS (57).

Comments:

- Tizanidine is structurally related to the antihypertensive clonidine, and slow titration is recommended because hypotension can occur, although less commonly than with clonidine. Based on its pharmacodynamic properties, tizanidine is likely to have an effect on the pathophysiologic process in RSD on several levels (66).

6.4 Use calcitonin or sympathetic blockade to prevent exacerbation of CRPS by invasive procedures. B

Specific recommendation:

- Use calcitonin prophylaxis, 100 IU sc, 4 days before and 3 weeks after any invasive intervention.
- Alternatively, consider sympathetic blockade before invasive procedures.
- See table Drug Treatment for CRPS.

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Dennis D. Dey, MD, PhD;
Robert J. Schwartzman, MD

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- See figure Clinical Pathway for Complex Regional Pain Syndrome (CRPS).

Rationale:
- Any invasive procedure in a CRPS patient, including therapeutic blocks, has the potential to exacerbate the disease.
- The risk is particularly high in the case of surgery in the painful area but can occur with intervention at any site; calcitonin may reduce this risk.

Evidence:
- A retrospective study of 100 patients showed that perioperative use of sympathetic blockade in CRPS patients reduced the risk for recurrence from 72% to 10% after reoperation of the affected extremity (67).
- In a series of 10 cases, prophylaxis with calcitonin, 100 IU sc or as a nasal spray, 4 days before surgery and 23 days after surgery reduced the risk for recurrence of RSD from 28% (based on historic controls) to 3% (68).
- In a case series it was found that the use of perioperative calcitonin prophylaxis in patients undergoing a second intervention at the site of previous surgery was helpful in avoiding a recurrence of RSD (69).

Comments:
- None.

6.5 Consider drug treatment with calcitonin, alendronate, or clodronate in patients with CRPS and pain, with or without osteoporosis. C

Specific recommendation:
- For treatment of osteoporosis in patients with CRPS:
  - Ensure calcium intake of 1500 mg/d
  - Begin calcitonin, 200 IU intranasally qd (alternating nostrils), or oral alendronate, 10 mg/d or 70 mg weekly
  - Consider a course of clodronate, 300 mg/d iv, for 10 days
- Consider these treatments in the absence of osteoporosis to reduce pain.
- See table Drug Treatment for CRPS.
- See figure Clinical Pathway for Complex Regional Pain Syndrome (CRPS).

Rationale:
- Osteoporosis is common in CRPS, at least in part due to inactivity.
- Inhibition of osteoclastic activity may help reduce pain.

Evidence:
- A randomized, double-blind, controlled trial of 32 patients with RSD found clinical improvement after a 10-day course of clodronate, 300 mg/d iv (70).

Comments:
- A randomized trial of clodronate compared with placebo in 32 patients with RSD showed more pain relief in the clodronate group (70).

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- A randomized trial of alendronate compared to placebo in patients with CRPS found more pain relief in the alendronate group for the 12 weeks of the study (45).

6.6 Consider placement of a spinal cord stimulator in patients with CRPS who do not respond to physical therapy and medication. B

Specific recommendation:

- Consider a dorsal column stimulator implant in patients with symptoms limited to one limb and with poor response to drug management and physical therapy.
- Avoid treating patients with serious psychiatric disorders such as psychosis or substance abuse with a dorsal column stimulator, but do not exclude those with pseudoaddiction because of undertreated pain or opioid dependence as a result of chronic pain.
- Consider other modalities of neuromodulation, such as motor cortex stimulation and deep brain stimulation.
- See figure Clinical Pathway for Complex Regional Pain Syndrome (CRPS).

Rationale:

- The mechanism of dorsal column stimulation is poorly understood.

Evidence:

- A 2004 Cochrane Review of the effectiveness of spinal cord stimulation for chronic pain found only one study of CRPS meeting inclusion criteria, although that study did demonstrate symptom relief from the treatment (71).
- A 2006 systematic review of spinal cord stimulation for CRPS found mostly observational data supporting its effectiveness compared to placebo (72).
- A randomized, controlled trial of 24 patients found that dorsal column stimulation plus physical therapy alleviated pain and improved health-related quality of life compared to treatment with physical therapy alone. CRPS was limited to one extremity in all patients. Patients considered by a psychiatrist to have serious psychiatric disorders or substance abuse were excluded. There was no improvement in functional status (73). Complications occurred in 6 of 24 patients (25%) treated with spinal cord stimulation and included unsatisfactory electrode placement, infection (1 patient), and electrode malfunction.
- A review of the literature identified one randomized, controlled trial, two prospective observational studies, and 12 retrospective observational studies. The authors concluded that the available evidence suggests the efficacy of spinal cord stimulation in CRPS (74).
- In an analysis of patients randomly assigned to spinal cord stimulation in a randomized controlled trial of 36 patients with CRPS, the presence of brush-evoked allodynia was found to be a negative prognostic factor for success with spinal cord stimulation therapy (sensitivity, 75%, and specificity, 81%) (75).
- Only a few studies of the use of motor cortex stimulation and deep brain

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Dennis D. Dey, MD, PhD;
Robert J. Schwartzman, MD

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stimulation in the management of neuropathic pain are available (76).

Comments:
- Efficacy of spinal cord stimulation appears to decrease over time. At 5 years after implantation of a permanent spinal cord stimulator, spinal cord stimulation was found to produce similar pain relief to physical therapy alone (77). Life-threatening complications are rare, but less serious complications occur in about one third of patients. These included need for stimulator revision (23%), equipment failure (10%), and pain in the area of implanted components (5.8%); 11% of patients had their stimulator removed completely (78).

6.7 Consider sympathetic blockade in CRPS. C

Specific recommendation:
- If conservative treatment is unsuccessful within the first 3 months of therapy, assess the effect of sympathetic blockade by paravertebral ganglion block or bretylium Bier block.
- If sympathetic blockade reduces the patient's pain, consider spinal cord stimulation or prolonged sympathetic blockade with bupivacaine (a local anesthetic) either through infusion of intrapleural bupivacaine or lumbar epidural bupivacaine on an inpatient basis.
- Alternatively, treat the patient's sympathetically maintained pain in CRPS with repeated sympathetic blockade on an outpatient basis.
- See table Drug Treatment for CRPS.
- See figure Clinical Pathway for Complex Regional Pain Syndrome (CRPS).

Rationale:
- Early sympathetic blockade may be more effective than late.

Evidence:
- A 2005 Cochrane Review assessed the effectiveness of sympathetic blockade with local anesthetics in patients with CRPS and found few studies and no evidence of pain improvement (79).
- Pooled data from 29 studies involving a total of 1144 patients found that local anesthetic sympathetic blockade was effective in 29% of patients, partially effective in 41%, and not or only minimally effective in 32% (80).
- In a retrospective study of 23 patients with RSD who were treated with spinal cord simulation, a history of pain relief from sympathetic blockade correlated strongly with the success of spinal cord stimulation (81).

Comments:
- For intensive inpatient treatment, five to six daily injections of 0.5% bupivacaine, 20 mL, into the pleural space via an intrapleural catheter can lead to alleviation of upper extremity symptoms. After the injection, the patient is put into the Trendelenburg position to allow infiltration of the anesthetic from the pleural space to the cervical part of the sympathetic nervous system. Treatment duration is usually 5 to 7 days.
- Continuous epidural analgesia with 0.1% bupivacaine for 5 to 7 days can be used for the treatment of lower extremity symptoms. Both modalities

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Robert J. Schwartzman, MD

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require frequent monitoring of vital signs and neurologic status.

6.8 Consider sympathectomy for refractory cases of CRPS. B

Specific recommendation:
- If a sympathetic block has a substantial but transient effect on CRPS symptoms, consider surgical sympathectomy if other modalities have failed and the symptoms are severe.

Rationale:
- The longer CRPS persists, the greater the chance that the patient's pain becomes sympathetically independent.
- The chance for a successful outcome is higher if sympathectomy is performed early in the disease course, and it is less than 50% after 2 years.

Evidence:
- A retrospective study of 29 patients with CRPS who had responded to pharmacologic sympathetic blockade showed that duration of symptoms significantly influences the likelihood of sustained pain relief. All (7 of 7) of the patients undergoing sympathectomy within 12 months of symptom onset had sustained pain relief. Pain relief was sustained in 69% (9 of 13) of patients who had a symptom duration of up to 24 months and in 44% (4 of 9) after that (39).
- A Cochrane review found that there is little high-quality evidence in support of surgical or chemical sympathectomy for neuropathic pain and CRPS (38).

Comments:
- Pain in early CRPS is believed to be sympathetically maintained, possibly through expression of α-2 adrenoreceptors on C-fiber nerve terminals and intraspinal connections between afferent pathways and sympathetic neurons.
- A population-based study found resolution of CRPS in up to 74% of cases (4). Irreversible treatment such as surgical sympathectomy should therefore be reserved for severe, disabling, and otherwise intractable cases that have not responded to physical therapy, medication, and spinal cord stimulation. On the other hand, if surgical sympathectomy is performed, the likelihood of success is greatest in the first 2 years of symptoms.

6.9 Consider noninvasive brain stimulation techniques, particularly repetitive transcranial magnetic stimulation, as add-on therapy for refractory patients. C

Specific recommendation:
- Consider noninvasive brain stimulation techniques, particularly rTMS, as add-on therapy to physical therapy and analgesia for refractory CRPS.
- See figure Clinical Pathway for Complex Regional Pain Syndrome.

Rationale:
- rTMS can be efficacious as add-on therapy in refractory CRPS during

Author(s):
Dennis D. Dey, MD, PhD;
Robert J. Schwartzman, MD

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active treatment and it may have a beneficial effect on depression.

Evidence:
- A randomized trial in 23 patients with CRPS type 1 compared optimal medical therapy plus rTMS to optimal medical therapy plus sham TMS. Patients were assessed daily, after 1 week, and after 3 months using the Visual Analogical Scale, McGill Pain Questionnaire, Health Survey-36, and Hamilton Depression Scale. While patients receiving rTMS had reduction in pain during treatment compared with placebo, the difference between active and sham treatment was not apparent either 1 week or 3 months after completion of treatment (82).
- A 2010 Cochrane review included 33 randomized and quasi-randomized studies of three noninvasive brain stimulation techniques for chronic pain: rTMS (19 studies), cranial electrotherapy stimulation (8 studies), and transcranial direct current stimulation (6 studies). There was risk of bias with many of the included studies, and none clearly reduced chronic pain. Only 1 included study enrolled patients with CRPS (83).

Comments:
- The evidence for mirror therapy for CRPS of the upper limb is weak, although a positive trend has been noted for the treatment of CRPS following stroke (84; 85).
- A systematic review of the literature was inconclusive in determining if mirror therapy is useful in the rehabilitation of CRPS (86).

6.10 Treat bladder problems symptomatically. C

Specific recommendation:
- Treat urge incontinence with oxybutynin, 2.5 to 5 mg bid to qid, or long-acting oxybutynin, 5 to 15 mg qd.
- Treat voiding difficulties with bethanechol, 10 mg to 30 mg tid.
- See table Drug Treatment for CRPS.
- See figure Clinical Pathway for Complex Regional Pain Syndrome (CRPS).

Rationale:
- Bladder dysfunction can be associated with CRPS.

Evidence:
- A retrospective study found voiding difficulties in 20 patients that occurred in the course of RSD. Urodynamic studies revealed detrusor hyperreflexia (8 patients), detrusor areflexia (8 patients), sensory urgency (3 patients), and detrusor sphincter dyssynergia (1 patient) (22).

Comments:
- None.

6.11 Consider experimental use of high-dose ketamine in refractory cases of CRPS. C

Specific recommendation:
- Consider informing patients of the experimental use of high-dose iv

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Dennis D. Dey, MD, PhD;
Robert J. Schwartzman, MD

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ketamine in severe cases resistant to the established treatment methods.
- See table Drug Treatment for CRPS.
- See figure Clinical Pathway for Complex Regional Pain Syndrome (CRPS).

Rationale:
- Treatment with anesthetic dose ketamine in an intensive care setting has shown dramatic improvement in refractory CRPS patients.

Evidence:
- Ketamine has been shown to relieve neuropathic pain in randomized, controlled trials and case studies for post-herpetic neuralgia, peripheral nerve injuries, phantom pain, and acute and chronic orofacial pain (87; 88; 89; 90).
- A dramatic improvement was seen in 10 refractory CRPS patients with anesthetic dose ketamine for 5 days. All patients were pain-free immediately after the treatment. Five of the patients had sustained pain relief for more than 1 year (91).
- Two small randomized trials suggest that multiple intravenous ketamine infusions are overall well-tolerated and effective in patients with CRPS (92; 93).

Comments:
- Treatment with NMDA-receptor blockers such as ketamine, memantine, amantadine, and dextromethorphan is in its experimental stages. The crucial role of the NMDA receptor in dorsal root ganglion cells, neurons of the dorsal horn, and central pain projecting neurons for the maintenance and transmission of chronic neuropathic pain is well established (2; 94); however, the use of NMDA blockade to treat chronic neuropathic pain has been limited by psychomimetic side effects, including hallucinations, unpleasant dreams, visual disturbances, and delirium. In subsequent studies these side effects were minimal when midazolam or lorazepam were coadministered.
- This treatment is being conducted in Europe on an experimental basis, and a referral to a specialized pain center should be made.

6. Patient Education: Ensure that patients understand the importance of long-term collaborative care in treating CRPS. C

7.1 Ensure that the patient understands the nature of the disease, available treatments, and available support. C

Specific recommendation:
- Discuss what is known and what is not known about CRPS with your patient.
- Explain the multi-level and stepwise therapeutic approach, providing hope for alleviation of symptoms.
- Prepare the patient for temporary setbacks due to the chronic nature and

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Dennis D. Dey, MD, PhD;
Robert J. Schwartzman, MD

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the fluctuating course of the disease and the possibility of exacerbation by surgery, minor injury, or emotional distress.

Rationale:
- An open discussion acknowledging the serious disruption of the patient's social and occupational lives, the emotional burden of chronic pain, and the need for intensive therapeutic efforts is often helpful.
- Although there is not yet a curative treatment established for CRPS, effective treatment is possible and this should be emphasized.

Evidence:
- Consensus.

Comments:
- Discussion of CRPS can be time consuming but offers an invaluable opportunity to strengthen the physician-patient relationship. It is common for CRPS patients to consult multiple physicians because they feel that their condition is not being managed properly.

7. Consultation for Management: Use a multidisciplinary approach that includes physical therapy, interventional pain management, psychiatry, and neurosurgery as indicated. B

8.1 Consider consulting a physical therapist as an essential part of management of CRPS. A

Specific recommendation:
- Consult a physical therapist for all patients and ensure that exercises are designed not to exacerbate pain.

Rationale:
- Physical therapy is an essential part of the management of CRPS.
- Preservation of joint mobility and prevention of contractures and osteoporosis cannot be accomplished without physical therapy.

Evidence:
- A randomized, controlled trial with 135 patients showed significant reduction in pain and improvement in active range of motion at 1-year follow-up with physical therapy compared to social work alone. Occupational therapy was also effective but less so (41).

Comments:
- Therapist and patient should be instructed to avoid exercises that exacerbate the pain.

8.2 Consult an interventional pain specialist if conservative therapy is insufficient. C

Specific recommendation:
- Consult a pain specialist early in the course of the disease for sympathetic blockade.
- Consult for other specific body area blocks if necessary.

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Dennis D. Dey, MD, PhD;
Robert J. Schwartzman, MD

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- Consider prophylaxis with calcitonin, 100 IU sc, 4 days before and 3 weeks after the intervention.

Rationale:
- Sympathetic blockade is particularly useful early in CRPS.
- Because it is well recognized that any intervention in CRPS patients bears an increased risk for disease exacerbation, the expected benefits and the risk for disease intensification need to be carefully weighed against each other and discussed with the patient.
- Calcitonin prophylaxis has been used successfully to reduce the risk for exacerbation of CRPS through surgical procedures.

Evidence:
- A retrospective study of 29 patients with RSD who had sympathectomy after paravertebral sympathetic blockade showed that the duration of symptoms significantly influences the likelihood of sustained pain relief by sympathetic blockade (39).
- In a series of 10 cases, prophylaxis with calcitonin, 100 IU sc, or as a nasal spray 4 days before surgery and 23 days after surgery reduced the risk for recurrence of RSD from 28% (based on historic controls) to 3% (68).

Comments:
- None.

8.3 Consider consulting a psychiatrist for help in managing depression in patients with CRPS. B

Specific recommendation:
- Obtain psychiatry consultation if the patient is depressed.

Rationale:
- Major depression develops commonly in CRPS; however, it is not more common than in other chronic pain conditions.

Evidence:
- A retrospective study of 25 consecutive RSD patients found that a major depressive disorder occurs in 20% of patients, obsessive-compulsive personality in 28%, and self-defeating personality in 20% (31).

Comments:
- There is considerable controversy in the older literature on CRPS about the extent of premorbid psychiatric disease and personality disorder. The concept of CRPS as a primary psychiatric or psychological disorder is no longer tenable. No difference has been shown in premorbid personality profile and likelihood of developing CRPS (96).
- No high-quality study has provided clear-cut evidence to support the suggestion that psychological factors predispose to CRPS or have an impact on its course, and available studies yield contradictory or inconclusive results (32; 33; 34).

8.4 Consult neurosurgery, an interventional pain specialist, or

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Dennis D. Dey, MD, PhD;
Robert J. Schwartzman, MD

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thoracic surgery in patients who are candidates for a dorsal column stimulator or baclofen pump implantation. B

Specific recommendation:
- Consider referral for placement of a dorsal column stimulator if the symptoms are limited to one limb and have responded poorly to drug management and physical therapy, except in patients with serious psychiatric disorders such as psychosis or substance abuse (see also placement of a dorsal column stimulator).
- Consider consulting for an intrathecal baclofen pump if dystonia cannot be managed with oral agents (see also intrathecal baclofen).

Rationale:
- Conservative therapy is often not adequate to treat CRPS.

Evidence:
- A randomized, controlled trial found that dorsal column stimulation is effective in RSD (73).
- A review of the literature concluded that the available evidence suggests the efficacy of spinal cord stimulation in RSD (74).
- In a double-blind, placebo-controlled, crossover study, continuous infusion of baclofen via pump led to reductions of dystonia and pain in 6 out of 7 CRPS patients (64).
- A single-blind, placebo-run-in, dose-escalation study in 42 patients with CRPS found improvement in dystonia, pain, disability, and quality of life following treatment with intrathecal baclofen (65).

Comments:
- None.

8. Follow-up: Ensure longitudinal follow-up of patients with CRPS to adjust therapy and treat complications. C

9.1 Schedule frequent follow-up to calibrate medication dose. See patients every 2 to 4 weeks while titrating medication for chronic pain and approximately every 6 months thereafter. C

Specific recommendation:
- Follow the patient closely while medication doses are titrated to achieve optimal effect with an initial interval of 2 to 4 weeks.
- Reassure the patient who experiences nuisance side effects.
- Monitor closely for serious side effects.
- See table Drug Treatment for CRPS.

Rationale:
- Frequent initial follow-up is recommended to titrate dose and ensure compliance.
- Serious side effects can occur and warrant discontinuation of the offending drug.
- Nuisance side effects are common, and patients often need

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Dennis D. Dey, MD, PhD;
Robert J. Schwartzman, MD

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reassurance.

Evidence:
- A systematic review of the literature revealed that higher doses of gabapentin are more effective but rapid-dose escalation leads to a frequent occurrence of CNS side effects (95).

Comments:
- Drugs for neuropathic pain should be titrated slowly to minimize side effects.

9.2 Watch for development of the known complications of CRPS including depression, movement disorders, urinary symptoms, and osteoporosis. C

Specific recommendation:
- Ask about symptoms of depression at every visit and refer to a psychiatrist as needed.
- Watch for development of a movement disorder.
- Perform bone densitometry initially, then every year if there is no osteoporosis.
- Ask about urgency, voiding difficulties, and incontinence.
- See figure Clinical Pathway for Complex Regional Pain Syndrome (CRPS).

Rationale:
- Depression is common in CRPS.
- The complications of CRPS, in particular depression, movement disorder, and bladder dysfunction, add substantially to the patient's disability and discomfort. Movement disorder occurs in almost all patients with CRPS.

Evidence:
- A retrospective study of 25 consecutive CRPS patients found that a major depressive disorder occurs in 20% of patients (31).
- The movement disorder of RSD is well described and recognized (21; 23; 24). A case series reported 43 patients with RSD who manifested abnormalities of movement. These patients had focal dystonia, weakness, spasms, tremor, difficulty initiating movement, and increased tone and reflexes (14).
- Osteoporosis is commonly part of the clinical picture in CRPS (19).
- A retrospective study found voiding difficulties in 20 patients that occurred in the course of RSD. Urodynamic studies revealed detrusor hyperreflexia (8 patients), detrusor areflexia (8 patients), sensory urgency (3 patients) and detrusor sphincter dyssynergia (1 patient) (22).

Comments:
- None.

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Dennis D. Dey, MD, PhD;
Robert J. Schwartzman, MD

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Dennis D. Dey, MD, PhD;
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1 Studies that meet all of the evidence criteria for that study type

2 Studies that meet at least one of the criteria for that study type

3 Studies that meet none of the evidence criteria for that study type or are derived from expert opinion, commentary, or consensus

Study types and evidence criteria are defined at http://pier.acponline.org/criteria.html

The number in parentheses at the end of the reference citations identify PubMed abstracts, which can be found on the National Library of Medicine's web site http://www.ncbi.nlm.nih.gov/entrez.

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Complex Regional Pain Syndrome (Reflex Sympathetic Dystrophy)

Author(s):
Dennis D. Dey, MD, PhD;
Robert J. Schwartzman, MD

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Glossary

^{99m}Tc	^{99m}technetium
ANA	antinuclear antibody
bid	twice daily
BP	blood pressure
CAD	coronary artery disease
CHF	congestive heart failure
CNS	central nervous system
COX-1	cyclo-oxygenase 1
COX-2	cyclo-oxygenase 2
CRP	C-reactive protein
CRPS	complex regional pain syndrome
CVD	cerebrovascular disease
DEXA	dual-energy X-ray absorptiometry
DVT	deep venous thrombosis
ECG	electrocardiography
EMG	electromyography
ESR	erythrocyte sedimentation rate
GABA	γ-aminobutyric acid
GI	gastrointestinal
HIV	human immunodeficiency virus
HLA-B27	human leukocyte antigen B27
IU	international units
iv	intravenous
MRI	magnetic resonance imaging
NCS	nerve conduction study
NMDA	*N*-methyl-D-aspartate
NSAID	nonsteroidal anti-inflammatory drug
PAN	polyarteritis nodosa
po	oral
PPI	proton-pump inhibitor
prn	as needed
PVD	peripheral vascular disease
qd	every day
qhs	every night
qid	four times daily
RA	rheumatoid arthritis
RSD	reflex sympathetic dystrophy
rTMS	repetitive transcranial magnetic stimulation
sc	subcutaneous
SLE	systemic lupus erythematosus
SSRI	selective serotonin reuptake inhibitor
tid	three times daily
T1	spin-lattice or longitudinal relaxation time (MRI scan)
T2	spin-spin or transverse relaxation time (MRI scan)

Terms

Allodynia	A normally nonpainful stimulus evokes pain. Allodynia can be mechanical or thermal.
Autonomic sensory testing (AST)	Maps abnormality in regional blood flow.
Bier block	Type of nerve block named after August Bier, Professor of Surgery in Berlin, Germany, where he first used this method in 1908.
Central sensitization	Amplification of pain perception at the level of the spinal cord and brain in chronic pain states.
Cold allodynia	A normally nonpainful, cold stimulus is perceived as painful (pain in response to cold at higher temperatures).
Complex regional pain syndrome	See *Reflex sympathetic dystrophy*.
Dissociated sensory loss	Sensory loss to pain and temperature (mediated by the spinothalamic tract) and preservation of touch and proprioception (mediated by the dorsal column system).
Dynamic mechanoallodynia	A moving mechanical stimulus provokes pain (for example, lightly brushing the skin).
Dystonia	Sustained abnormal posture.

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Heat allodynia	A normally nonpainful, warm stimulus is perceived as painful (pain in response to heat at lower temperatures).
Hyperalgesia	A normally painful stimulus evokes pain that is more painful than expected, spreads, and is nonstimulus bound.
Hyperpathia	Pain threshold is increased, but once exceeded pain reaches maximal intensity faster, is more severe and nonstimulus bound.
Mechanoallodynia	A normally nonpainful mechanical stimulus provokes pain. Mechanical allodynia can be further divided into static (nonmoving stimulus) and dynamic (moving stimulus).
Mononeuropathy	Distribution of symptoms in area of a single peripheral nerve.
Movement disorder	Abnormal pattern of movement despite intact strength and coordination.
Myoclonus	Irregular, asymmetric, spontaneous muscle activity large enough to move a joint.
Neuropathic pain	Pain that is characterized by allodynia and hyperalgesia and is often burning in nature.
Peripheral sensitization	Amplification of pain transmission at the level of the nociceptor.
Plexopathy	Distribution of symptoms in a plexus or partial plexus territory.
Polyneuropathy	Distribution of symptoms distal and symmetric at onset.
Quantitative sensory testing (QST)	Test to determine the pain threshold in response to heat and cold stimuli. The test gives a quantitative result but is based on the patients subjective response.
Radiculopathy	Distribution of symptoms in one or two nerve root territories.
Reflex sympathetic dystrophy	The name was changed in 1994 to CRPS (complex regional pain syndrome). A distinction between CRPS I (no nerve injury can be demonstrated) and CRPS II (nerve injury can be shown) was introduced.
Static mechanoallodynia	A nonmoving mechanical stimulus provokes pain (for example, pressing lightly on the skin).
Sudomotor	Related to sweat gland function.
Sweat testing	Maps sweat pattern.
Thermal allodynia	A normally nonpainful thermal stimulus provokes pain. Thermal allodynia can be divided into heat and cold allodynia.
Thermography	Maps temperature of body surface.
Vasomotor	Related to vascular tone.

Laboratory and Other Studies for CRPS

Test	Notes
Quantitative sensory testing	Quantitative sensory testing is used to determine the temperature threshold for heat and cold allodynia. Patients are presented with an increasingly warm or cold temperature stimulus and report when pain is evoked. A study comparing 16 CRPS patients and 16 age- and sex-matched controls found a difference of 10°C (18°F) in cold allodynia threshold and 4.5°C (8.1°F) for heat allodynia (15)
Autonomic sensory testing	Abnormality in regional blood flow in affected extremity and contralaterally. Not corresponding to plexus, root, or nerve territory
Thermography	Thermography measures temperature at several symmetrical points of the affected and contralateral extremity. Greater than 1°C (1.8°F) difference between ipsilateral and contralateral extremity is significant and supports the diagnosis. The predictive value of the test increases with increasing number of sites with significant temperature differences. Symmetric responses do not rule out the diagnosis (19)
Sweat testing	Sweat output can be measured by applying an indicator starch powder that changes color when the limb sweats. Abnormal resting sweat output and abnormal response to a cholinergic challenge with acetylcholine or methacholine (quantitative sudomotor axon reflex) are seen in CRPS and support the diagnosis (19)
Plain radiograph	Plain radiographs can show patchy osteoporosis early in the course of CRPS. Immobilization and disuse may contribute to this finding. Later in the course, bony structures may have a “ground glass” appearance, and cortical erosions may be seen (19)
^{99m}Tc triple-phase bone scan	A three-phase bone scan with ^{99m}Tc-labeled bisphosphonates is sensitive but relatively nonspecific. Typical findings in CRPS are increased periarticular uptake throughout the three phases (blood pool, blood phase, scan phase) (19)
Bone densitometry	Patients with CRPS may be at increased risk for osteoporosis, in part correlating with the patient's activity level (19)
MRI	MRI is essential to rule out or show underlying bone or soft-tissue pathology. One uncontrolled series of 51 cases of RSD in all stages found skin thickening and contrast enhancement in 31 of 35 patients with early RSD when the affected limb was studied with T1, T2 and T1-weighted images with fat suppression and contrast material (37)
EMG/NCS	May be helpful in distinguishing CRPS from painful sensory neuropathy, sensorimotor neuropathy, nerve entrapment, mononeuropathy, radiculopathy, myotonia, and myopathy. May show nerve injury associated with CRPS II
Vascular studies	Venous and arterial Doppler ultrasound help to distinguish CRPS from arterial peripheral vascular disease and venous thrombosis
Autoimmune serologies and related studies	Sedimentation rate, blood count, ANA, rheumatoid factor, antidouble-stranded DNA antibodies, Sjögren antibodies, anticardiolipin antibodies and other rheumatologic laboratory studies may help to exclude rheumatic and collagen vascular disease

Table Continued...

ANA = antinuclear antibody; CRPS = complex regional pain syndrome; EMG = electromyography; MRI = magnetic resonance imaging; NCS = nerve conduction study; RSD = reflex sympathetic dystrophy; T1 = spin-lattice or longitudinal relaxation time (MRI scan); T2 = spin-spin or transverse relaxation time (MRI scan).

Differential Diagnosis of CRPS

Disease	Characteristics	Notes
CRPS	Persistent pain after an injury, across neurologic boundaries, with associated symptoms	Must exclude other causes of pain before making the diagnosis
Osteomyelitis	Acute or chronic infection of the bone and associated structures, usually bacterial. May occur after trauma or surgery with inoculation of microorganisms or after hematogenous spread of organisms. Older adults are typically affected but also children and infants, particularly in cases of hematogenous osteomyelitis. Systemic signs such as fever and leukocytosis can be absent in chronic cases or immunosuppressed individuals. ESR and CRP are usually elevated. MRI scan of the affected area is the preferred imaging test	It may be impossible to distinguish osteomyelitis from early CRPS on the basis of clinical exam alone. Onset of CRPS is not acute
Cellulitis	Acute, spreading infection of the dermis and subcutaneous tissues characterized by swelling, erythema, and pain and tenderness. May follow minor trauma or surgery. A delayed onset may be seen, for example, after saphenous venectomy for coronary bypass when cellulitis may arise months to years later. Fever, elevated ESR, and leukocytosis are generally present	It may be impossible to distinguish cellulitis from early CRPS on the basis of clinical exam alone. Onset of CRPS is not acute
Postherpetic neuralgia	History of painful vesicular rash, no history of trauma, commonly allodynia and spontaneous burning pain in thoracic dermatome or first division of fifth cranial nerve. Treatment with antiviral therapy is indicated as long as blisters are present and reduces incidence and severity of postherpetic neuralgia. Pain in postherpetic neuralgia should be treated early and aggressively to blunt central sensitization. If trigeminal nerve distribution, ophthalmologic consultation is mandatory to exclude corneal involvement	Postherpetic neuralgia has no association with trauma, no prominent changes in skin perfusion, and no edema. CRPS usually starts in a limb following trauma. No history of vesicular rash in CRPS
Painful peripheral neuropathy (neuropathy with small fiber involvement)	Characteristically has neuropathic pain in a distal and symmetric distribution. May have sensory loss. May be idiopathic but frequently is associated with underlying disease such as diabetes, uremia, alcoholism, HIV, SLE, cancer, hepatitis, primary biliary cirrhosis, and others. If sensory loss is present, a reduced sensory nerve action potential on EMG may be seen. Small fiber neuropathy often has an autonomic component, and orthostatic hypotension, impotence, and constipation may be seen	Painful peripheral neuropathy has no association with trauma. CRPS usually starts unilaterally. In CRPS sensory loss is not prominent at onset. EMG is normal in CRPS except in the case of CRPS type II where CRPS is associated with a peripheral nerve injury
PVD	Characterized by intermittent claudication provoked by walking. Usually associated with history of CAD or CVD	PVD has no allodynia and no association with trauma. Resting relieves the pain. Distal pulses are not compromised in CRPS

Table Continued...

Differential Diagnosis of CRPS

Disease	Characteristics	Notes
Acute occlusion of peripheral artery	Characterized by acute onset of pain and pallor in a limb usually associated with history of vascular disease or atrial fibrillation. Rarely may occur from artery dissection due to trauma	Onset of CRPS is not as acute. Acute occlusion of a peripheral artery has no allodynia. Distal pulses are not compromised in CRPS
DVT	Asymptomatic or associated with swelling, sinus tachycardia, and may have some dull pain	The pain in DVT is less prominent than in CRPS. There is no allodynia in DVT
Mononeuropathy multiplex	Characterized by defects in the territory of several major nerves in more than one limb. Underlying causes include diabetes, PAN, RA, SLE, hereditary liability to pressure palsies, HIV, and lymphoma	In mononeuropathy multiplex, weakness, sensory loss, or both of these symptoms are prominent at onset, but pain can be the chief complaint, and allodynia may be present. The symptoms occur in the territory of multiple peripheral nerves. There is no association with trauma, no prominent change in skin color and perfusion, and no edema
Polyradicular syndrome	Characterized by involvement of multiple nerve roots. Underlying causes include diabetes, SLE, meningeal carcinomatosis, and lymphoma	In a polyradicular syndrome the symptoms occur in the distribution of multiple nerve roots. Pain can be the chief complaint but usually sensory loss or motor deficits are present early. No association with trauma, no prominent changes in skin color and perfusion, and no edema
Meralgia paresthetica	Entrapment neuropathy of the lateral cutaneous femoral nerve. Burning pain in the femoral nerve distribution is characteristic. Predisposed are heavy individuals with tight-fitting clothes or heavy belts	Pain is not confined to the territory of a single nerve in CRPS. No trauma history in meralgia paresthetica
Multiple sclerosis	Generally optic neuritis, intranuclear ophthalmoplegia, sensorimotor or cerebellar symptoms before pain, but pain can be the presenting symptom. If present, lancinating pain, often in thoracic dermatome. Commonly, abnormal brain or spinal cord MRI result. Usually no allodynia, no association with trauma	CRPS follows trauma; pain is prominent at onset and is the overwhelming symptom. Deficits in sensation are uncommon. Weakness develops late in the course and is associated with dystonia and other symptoms of the movement disorder
Central post-stroke pain	Usually occurs after an infarction involving the thalamus, the parietal lobule, the brainstem, or the cerebellum. Confined to a hemibody distribution and has characteristic qualities, including spontaneous pain of burning quality difficult to localize for the patient and hyperalgesia. Incidence has been reported to be as high as 8% of all stroke patients	CRPS pain usually starts in a limb and then may spread to involve other areas. Usually the spread occurs in a mirror distribution and does not stay confined to one side of the body. Swelling is not seen as a result of post-stroke pain. There is no association with trauma to the initially painful area in stroke
Syringomyelia	Sensory loss involving pain and temperature but sparing touch and vibration (dissociated sensory loss) in a bilateral, frequently shawl-like distribution. Sometimes associated with trauma to neck or spine. Syrinx shown on MRI	CRPS usually starts unilaterally. Sensory loss in CRPS is not prominent at onset, and if present, it is not dissociated. MRI does not show a syrinx in CRPS

Table Continued...

Differential Diagnosis of CRPS

Disease	Characteristics	Notes
Brachial plexus injury	Often following flexion extension injury of the neck. No autonomic dysfunction in limb; may have Horner's syndrome; sensory loss is usually present. EMG result is negative unless injury is extensive	Brachial plexus injury is a common underlying cause for CRPS and often coexists. Chronic pain from brachial plexus injury becomes CRPS once additional, CRPS-defining symptoms develop
Lumbar disc herniation	Pain is in the distribution of a radicular dermatome, and no allodynia is present initially but may develop if the pain is longstanding	CRPS pain is not confined to a radicular dermatomal distribution. Edema and changes in skin perfusion are not seen in lumbar disc herniation, which may coexist due to its frequency in the general population. It may also develop due to changed body mechanics in severely affected CRPS patients
Cervical disc herniation	Pain is in the distribution of a radicular dermatome. Motor symptoms correspond to the myotome of the affected root	CRPS pain does not respect radicular territory and usually has allodynia and skin perfusion changes
Erythromelalgia	Acral erythematous skin changes with burning pain provoked by skin warming may occur after chemotherapy or in the course of small fiber neuropathy. Usually symmetric	CRPS is usually initially asymmetric; there is a history of trauma and usually no history of chemotherapy. Patients with erythromelalgia classically obtain relief from cold application to the affected limbs, while patients with CRPS/RSD avoid cold exposure due to worsening of pain intensity
Rheumatoid arthritis	Symptoms or laboratory results are consistent with the criteria of the American College of Rheumatology (http://www.rheumatology.org/practice/clinical/classification/ra/2010_revised_criteria_classification_ra.pdf), including a combination of morning stiffness, polyarthritis of three or more joints, involvement of proximal interphalangeal joints, symmetric involvement, positive rheumatoid factor, typical changes of hand X-ray, and rheumatic nodules. Onset generally occurs in the third to sixth decade	CRPS has a history of trauma and initially is asymmetric. In CRPS, allodynia is prominent at onset
SLE	Polyarthritis; systemic symptoms; skin changes, typically in the face with photosensitivity. SLE often affects multiple organs. It may have neuropathy, including painful sensory neuropathy. Laboratory: 95% ANA positive, also frequently anti-dsDNA antibodies	CRPS has a history of trauma. The multisystem involvement and characteristic laboratory findings should allow ready differentiation
Raynaud's phenomenon	Intermittent attacks of bilateral pallor, usually of the fingers, provoked by cold followed by redness, vasodilation, swelling, and pain. Resolves with warming	In contrast to CRPS, no trauma history, and no allodynia. Raynaud's phenomenon resolves with warming and occurs bilaterally, whereas CRPS is usually asymmetric at onset
Ankylosing spondylitis	Characterized by sacroiliac joint pain, spinal pain, occasionally arthritis of peripheral joints, typically in a young man. Often positive for HLA-B27. As disease progresses, increasing ankylosis of spine with characteristic bamboo spine on X-ray	In ankylosing spondylitis there is no association with trauma, and pain is not of a neuropathic type. Pain in CRPS starts typically in a limb

Table Continued...

Differential Diagnosis of CRPS

Disease	Characteristics	Notes
Scleroderma	Typically starts with swelling of hands and induration of skin in patients 30-50 years old. Patients eventually may develop microstomia, sclerosed frenulum, swallowing difficulty, and Raynaud's phenomenon. Laboratory: 90% ANA positive, may have anti-Scl-70 and other antibodies associated with collagen vascular disease	In scleroderma pain is not prominent except during an attack of Raynaud's phenomenon. There is no association with trauma, and pain is not of a neuropathic type
Polymyalgia rheumatica	Characterized by pain and stiffness in the proximal musculature in a patient older than age 50 years. ESR is usually elevated, and the symptoms readily respond to corticosteroids	In CRPS there is a history of trauma and the onset is usually asymmetric in the distal part of a limb. ESR is not elevated in CRPS, and the pain usually does not respond to corticosteroids
Osteoarthritis	Joint pain secondary to progressive loss of articular cartilage, usually affecting the knees bilaterally or joints with unphysiologic mechanical stress. May be due to underlying disease, including Wilson's disease, hemochromatosis, Paget's disease, acromegaly, hemophilia, hyperparathyroidism, and joint denervation from neuropathy	In osteoarthritis there is no association with trauma, and pain is not of a neuropathic type. Changes of skin perfusion and edema are not associated. In CRPS joint pain may be present but is not the most prominent pain complaint
Vitamin B_{12} deficiency	Characteristically has sensory ataxia with symmetric loss of position and vibration sense. May also have dementia and lancinating pain. Can be associated with underlying disease of the gastrointestinal tract (loss of terminal ileum, pernicious anemia) and may be precipitated by use of nitrous oxide in anesthesia induction	CRPS is usually asymmetric initially, and there is a history of trauma. In vitamin B_{12} deficiency there is no association with trauma, and pain is not of a neuropathic type. Changes of skin perfusion and edema are not associated
Rotator cuff injury	Characterized by pain and abduction deficit after shoulder injury. Injury can usually be shown on MRI	Pain after rotator cuff injury is not of a neuropathic type; change in skin perfusion and edema are not seen. Pain in CRPS starts typically more distally in a limb
Frozen shoulder	Pain and limited active and passive range of motion in a shoulder. Frozen shoulder may occur without trauma and is believed to be secondary to adhesive capsulitis. Decreased joint volume can be shown by arthrography. If surgery is performed, a fibrous band traversing the glenohumeral space and adhesions may be found. Clinically, frozen shoulder is difficult to distinguish from brachial plexus injury, and most clinically diagnosed cases may be secondary to brachial plexus injury	Pain in frozen shoulder is not of a neuropathic type. Change in skin perfusion and edema is not seen. Pain in CRPS starts typically more distally in a limb
Gout	Acute, spontaneous pain, most commonly in first metatarsophalangeal joint but can affect other joints (ankle >knee >wrist). The joint is swollen and warm. Usually elevated uric acid. Usually subsides after 3-10 days	CRPS does not usually subside

Table Continued...

ANA = antinuclear antibody; CAD = coronary artery disease; CRP = C-reactive protein; CRPS = complex regional pain syndrome; CVD = cerebrovascular disease; DVT = deep venous thrombosis; EMG = electromyography; ESR = erythrocyte sedimentation rate; HIV = human immunodeficiency virus; HLA-B27 = human leukocyte antigen B27; MRI = magnetic resonance imaging; PAN = polyarteritis nodosa; PVD = peripheral vascular disease; RA = rheumatoid arthritis; RSD = reflex sympathetic dystrophy; SLE = systemic lupus erythematosus.

Drug Treatment for CRPS

Agent	Mechanism of Action	Dosage	Benefits	Side Effects	Notes
Corticosteroids (prednisone , methylprednisolone)	Reduction of inflammation and vascular permeability	Prednisone, 10 mg tid per day for up to 12 weeks, or methylprednisolone, 32 mg/d for 2 weeks followed by a 2-week taper, oral administration	Reduced inflammation	Hypertension, impaired healing, fluid retention, hypernatremia, GI tract ulceration, increased risk of infections, osteoporosis, hyperglycemia, mood disturbance	Prescribe gastroprotectant, monitor for side effects
Gabapentin	Blockade of N-type voltage-dependant calcium channels in the dorsal root ganglion and enhancement of GABA-effect among other possible mechanisms	100-1200 mg po tid Higher doses (as high as 6 g/d) may be required	Active against peripheral and central mechanisms of neuropathic pain. Mood stabilizing effect	Somnolence, fatigue, poor concentration, anorexia, nausea, ataxia, dizziness, rash, peripheral edema, stuttering, anxiety, paresthesias, arthralgias, twitching, tremor, visual disturbances, headache	13% of patients do not tolerate the side effects, but serious side effects are rare. Dose adjustment is necessary in patients with limited renal function. Gabapentin is commonly underdosed (95)
Amitriptyline	Blockade of noradrenalin and serotonin reuptake, NMDA-antagonist-like effect, inhibition of Na^+-channels	10-300 mg; usual initial dose: 10-25 mg qhs (general effective dose: 75-100 mg qhs)	Active against peripheral and central mechanisms of neuropathic pain	Anticholinergic side effects: dry mouth, blurry vision, constipation, and difficulty with urination. Orthostatic hypotension, AV-block, sexual dysfunction, restlessness, jitteriness, anxiety. Antihistaminergic side effects: sedation and carbohydrate craving with weight gain	Initial dosing should be low because restlessness and anxiety occurs in some patients in the induction phase. The therapeutic response usually has a ceiling effect at a daily dose of 100 mg. Efficacy against pain is expected 4 days to 1 week after reaching the appropriate dose. Increase dose to efficacy or until side effects become limiting. Avoid in patients with bifascicular heart block, left bundle-branch block or a prolonged QT interval. An ECG should be checked before the start of therapy if clinical suspicion for cardiac disease exists

Table Continued...

Drug Treatment for CRPS

Agent	Mechanism of Action	Dosage	Benefits	Side Effects	Notes
Nortriptyline	Blockade of noradrenalin and serotonin reuptake, NMDA-antagonist-like effect, inhibition of Na^+-channels	12.5-150 mg po qd (general effective dose: 40-100 mg qd)	Active against peripheral and central mechanisms of neuropathic pain	Anticholinergic side effects: dry mouth, blurry vision, constipation, and difficulty with urination. AV-block, sexual dysfunction, restlessness, jitteriness, anxiety. Antihistaminergic side effects: sedation and carbohydrate craving with weight gain	Initial dosing should be low because restlessness and anxiety occurs in some patients in the induction phase. The therapeutic response usually has a ceiling effect at a daily dose of 100 mg. Efficacy against pain is expected 4 days to 1 week after reaching the appropriate dose. Increase dose to efficacy or until side effects become limiting. Avoid in patients with bifascicular heart block, left bundle-branch block, or a prolonged QT interval. An ECG should be checked before the start of therapy if clinical suspicion for cardiac disease exists
Lidocaine (topical)	Blockade of TTX-sensitive Na^+ channels	5% patch, 12 hours on, 12 hours off	Active against peripheral mechanisms of neuropathic pain. Can be applied at home	Local irritation, allergic reaction	Risk of systemic side effects is low if only one patch is used and the instructions regarding on-off time are followed

Table Continued...

Drug Treatment for CRPS

Agent	Mechanism of Action	Dosage	Benefits	Side Effects	Notes
Lidocaine	Blockade of TTX-sensitive Na^+ channels	Infusion at 0.1-0.4 mg/min	Active against peripheral mechanisms of neuropathic pain	Nausea, lightheadedness, somnolence, sustained bradycardia and other cardiac arrhythmias, hypotension, hallucinations, seizures, tremor, dysarthria, nystagmus	Administer only under cardiac monitoring, frequent BP checks, and assessment of mental status. The dose is titrated to effect or limitation through side effects. Even if no side effects are observed, a plasma level of 5 µg/mL should not be exceeded. The duration of pain relief is variable and is usually in the range of weeks. Pain relief is rarely complete. If treatment with iv lidocaine is efficacious, the duration of relief can be prolonged up to 3-5 months by the use of its oral congener mexiletine at up to 300 mg/d. Lidocaine and mexiletine are contraindicated in patients with heart block and CHF
Oxycodone/acetaminophen (combination product)	Oxycodone: µ-opioid receptor agonist Acetaminophen: unknown	5 mg/325 mg, q 4-6 h prn	May help with breakthrough pain	Hepatotoxic, nephrotoxic, agranulocytosis, thrombopenia, pancreatitis, angioedema, rash, urticaria, nausea	Widely used for many different pain conditions
Oxycodone (slow release)	µ-opioid receptor agonist	10-160 mg q 12 h	Quicker onset of analgesia and less plasma level variation than morphine	Respiratory depression, respiratory arrest, dependency, cardiovascular depression, paralytic ileus, seizures, nausea, somnolence, confusion, rash, constipation, pruritus, headache, fever	Widely used for many different pain conditions
Methadone	µ-opioid receptor agonist, NMDA-receptor antagonist	2.5-20 mg po q 12 h	Opioid with less potential for promoting central sensitization	Nausea, vomiting, sedation, urinary retention, pruritus, respiratory depression	Due to its NMDA receptor antagonist properties, methadone may be more suited than other opioids to treat neuropathic pain (62; 63)

Table Continued...

Drug Treatment for CRPS

Agent	Mechanism of Action	Dosage	Benefits	Side Effects	Notes
Bupivacaine (intrapleural)	Blockade of voltage-gated sodium channels	Five to six daily injections of 20 mL of 0.5% bupivacaine into the pleural space for 5 to 7 days	Active against peripheral mechanisms of neuropathic pain	Hypotension, bradycardia, heart block, cardiac arrhythmias, cardiac arrest, myocardial depression, seizures, nausea, paresthesias, burning at catheter site, pruritus, restlessness	Inpatient treatment, frequent assessment of vital signs and neurologic status necessary
Bupivacaine (epidural)	Blockade of voltage-gated sodium channels	Continuous epidural analgesia with 0.1% bupivacaine for 5 to 7 days	Active against peripheral mechanisms of neuropathic pain	Hypotension, bradycardia, heart block, cardiac arrhythmias, cardiac arrest, myocardial depression, seizures, nausea, paresthesias, burning at catheter site, pruritus, restlessness	Inpatient treatment, frequent assessment of vital signs and neurologic status necessary
Baclofen	GABA B-agonist	15-80 mg po divided tid	Decrease in muscle spasm, dystonia, and pain	Drowsiness, psychiatric disturbances, urinary frequency, retention, constipation, vomiting, hypersensitivity reactions	Continuous intrathecal administration (baclofen pump) at daily doses of 350 µg to 850 µg has been used successfully to treat severe dystonia in RSD (64; 65)
Tizanidine	Presynaptic α-2 receptor agonist	Initial dose: 2 mg po qhs. Titrate slowly up to 8 mg tid	Decrease in muscle spasm, dystonia, and pain	Sedation, dry mouth, dizziness, fatigue, hypotension	Tizanidine is structurally related to the antihypertensive clonidine, and slow titration is recommended because hypotension can occur, although less commonly than with clonidine (66). Based on its pharmacodynamic properties, tizanidine is likely to have effect on the pathophysiologic process in RSD on several levels (66)

Table Continued...

Drug Treatment for CRPS

Agent	Mechanism of Action	Dosage	Benefits	Side Effects	Notes
Calcitonin	Unknown	100 IU sc or intranasally 4 d before and 23 d after intervention to prevent exacerbation of CRPS. 200 IU intranasally qd (alternating nostrils) for treatment of CRPS-associated osteoporosis	May help prevent or limit the risk of invasive procedures	Anaphylaxis, bronchospasm, epistaxis, headache, back pain	Adequate pain control for invasive procedures may be more important than calcitonin. Even with calcitonin prophylaxis, the risk of exacerbating CRPS by invasive procedures is high
Alendronate	Inhibits osteoclastic activity	40 mg po qd for pain 10 mg qd or 70 mg/wk for associated osteoporosis	May reduce bone remodeling	Esophageal ulcer, esophagitis, gastroduodenal ulcer, angioedema, skin reactions, uveitis, scleritis, nausea	Take with water 30 minutes before first meal; avoid supine position for 30 minutes
Clodronate	Inhibits osteoclastic activity	300 mg/d iv for 10 days for associated osteoporosis	Unclear reason for effect on pain	Abdominal and muscle cramps, bone pain	
Oxybutynin	Acetylcholine receptor antagonist	2.5-5 mg bid to qid; 5-15 mg qd if long-acting preparation	Better control of urinary symptoms	Palpitations, tachycardia, decreased sweating, constipation, dry mouth, urinary retention, cycloplegia, dizziness, hallucinations, restlessness, mydriasis, impotence, suppression of lactation	Widely used for control of urgency from various conditions
Bethanechol	Stimulates acetylcholine receptors	10-30 mg tid	Better control of urinary symptoms	Bronchospasm, diarrhea, abdominal pain, flushing, headache, malaise, hypotension, lacrimation, miosis, nausea, urinary urgency, diaphoresis, tachycardia	Used for control of hesitancy from various conditions
Ketamine	NMDA-receptor antagonist	Depends on experimental protocol	May be able to break severe chronic, centrally maintained neuropathic pain	Hallucinations, unpleasant dreams, visual disturbances, delirium, hepatic damage	In studies, the psychomimetic side effects of ketamine were minimal when midazolam or lorazepam were coadministered (91)

Table Continued...

Drug Treatment for CRPS

Agent	Mechanism of Action	Dosage	Benefits	Side Effects	Notes
Vitamin C	Reduces lipid peroxidation, scavenges hydroxyl radicals, protects the capillary endothelium, and inhibits vascular permeability	500 mg orally for 50 days after injury	Reduced inflammation	Diarrhea	Widely used as a supplement. Used following injury to prevent CRPS

bid = twice daily; BP = blood pressure; CHF = congestive heart failure; COX-1 = cyclo-oxygenase 1; COX-2 = cyclo-oxygenase 2; CRPS = complex regional pain syndrome; ECG = electrocardiography; GABA = γ-aminobutyric acid; GI = gastrointestinal; IU = international units; iv = intravenous; NMDA = *N*-methyl-D-aspartate; po = oral; PPI = proton-pump inhibitor; prn = as needed; qd = every day; qhs = every night; qid = four times daily; RSD = reflex sympathetic dystrophy; sc = subcutaneous; tid = three times daily.