Chapter 9
Complex Regional Pain Syndrome and Interventions

Helen Gharaei

Introduction

Complex Regional Pain Syndrome (CRPS) is outlined as a painful and disabling condition accompanied by physical changes within the affected extremity, characterized by allodynia, edema, baldness, and sudomotor and dilatation dysfunction. The CRPS is a life-altering condition that generally affects the extremities after a trauma or nerve injury. The physiologic changes that follow as a result of the inciting injury are complex. In CRPS type I (reflex sympathetic dystrophy), small injuries or fractures initiate the onset of symptoms without evidence of nerve damage in the affected limb while CRPS type II (causalgia) develops once an injury to a large supplemental nerve happened with evidence of nerve damage in the affected limb. CRPS type 1 accounts for about 90% of CRPS [1]. However, some research has identified evidence of nerve damage in CRPS-I which puts into question as to whether the disorder is always divided into two types. Nevertheless, the treatment is similar [2].

Unfortunately, pain and disability related to CRPS frequently result in comorbidities that produce a vicious cycle of pain and depression. It is distinct from other pain syndromes due to the presence of autonomic dysfunction, inflammatory changes, and a scarcity of dermatomal distribution. This condition is ambiguous in nature. It has been historically challenging to diagnose, laborious to treat, and the pathophysiology behind it has not been fully defined.

H. Gharaei (✉)
ASA Pain Clinic, Tehran, Iran

J. de Castro, Y. El Miedany (eds.), *Advances in Chronic and Neuropathic Pain*, Contemporary Rheumatology, https://doi.org/10.1007/978-3-031-10687-3_9

History

Ambroise Paré (1510–1590), the father of modern surgery, was the first to describe a disorder that could be related to the current concept of CRPS. He successfully treated a severe and persistent pain syndrome that occurred to King Charles IX of France after a phlebotomy [3]. The first written description of CRPS was made by Denmark who published a case report of a soldier wounded by a bullet that passed over his arm during the siege of Badajuz (1812) [4].

In 1864, Silas Weir Mitchell, in collaboration with George Morehouse and William Keen, published a monograph entitled "Bullet Wounds and Other Injuries," which soon became the benchmark for diagnosing and treating nerve damage until World War I. A syndrome characterized by a typical chronic burning pain that is located at the end of the peripheral nerve injury site and is associated with skin disorders was described by the author and was highly suggestive of this disease and now became the hallmarks of what we now call CRPS. This clinical condition was later named "causalgia" in "Nerve Injuries and Their Consequences", which is the second book published by Mitchell in 1872. It was later coined by Ruble Danglison in the first edition of the Medical Dictionary in 1874 [5, 6].

Another milestone in the history of the CRPS is made by Paul Sudek. In 1900, at the 29th Congress of the German Surgical Association, Sudeck presented an article entitled "Acute Inflammatory Bone Atrophy" which describes the results of his experiments on patients undergoing X-ray examinations which he was called "Sudeck atrophy" and is still a common term to define algodystrophy [7].

Another turning point in the history of CRPS was the hypothesis that the sympathetic nervous system plays a major role in the signs and symptoms of the disease. This hypothesis was accepted by Rene Leriche (1917) who described a patient with chronic hand pain and numbness after a bullet wound to the right arm. He performed the first sympathectomy on the patient and noted complete resolution of the pain syndrome within 2 weeks [8]. James E. Evans, then emphasized the term "sympathetic reflex dystrophy" (RSD) [9]. Philip S. Foisie, also described a persistent but low-grade arterial spasm after a soft tissue injury, which can lead to severe pain syndrome characterized by allodynia, edema, muscle atrophy, osteoporosis, joint stiffness, and decreased mobility. He argued that RSD might be better defined as a "traumatic arterial vasospasm" [10].

In the 1950s, Algology, a new field of medicine, was born as a branch of anesthesia. John Bonica (1953) was the first to propose the stages for RSD with three types of clinical imaginations [11] and these stages were used as the basis for the next diagnostic criteria (Table 9.1).

John Bonica also found the first scientific association dedicated to the study of pain in 1973: The International Association for the Study of Pain (IASP). One of the several goals of the society was to standardize the classification of chronic pain. The first IASP conference was held in 1988 and the second one was in 1993 where they formulated and described the distinct characteristics of CRPS type I and CRPS type II [12]. Other diagnostic criteria for CRPS have been proposed by Peter Veldmann

Table 9.1 Bonica three stages of the RSD

Stage 1 (acute) from the moment of the trauma to 3 months after	• Erythema	Negative X-ray examination, but a positive scintigraphy showing hyperaccumulation
	• Calor	
	• Edema	
	• Marked hyperhidrosis a distribution of the pain not related to root nor nerve involvement	
	• Limited range of motion and reduced muscle strength	
Stage 2 (dystrophic)	• Severe pain	
	• Edematous skin	
	• Decreased hair growth	
	• Discoloration with cyanotic areas	
	• Persistent hyperhidrosis	
	• Muscle weakness and limited range of motion of the affected joint or joints	
Stage 3 (atrophic) from 6 weeks onwards	• Decreased but still disabling pain that improves with rest and worsens with passive movements	Radiographic examination shows inhomogeneous regional osteoporosis (Sudeck's atrophy)
	• The skin could be atrophic, thin, dry, sometimes ulcerated, cold, mottled or cyanotic	
	• There could be loss of joint range of motion and muscle strength with tendon atrophy, contractures, tremors and dystonia determining a significant motor impairment of the affected limb	

(1993) who criticized the subset in the steps suggested by IASP experts, and identified less common cold forms, and the more common hot forms [13]. Norman Harden and Stephen Bruehlc conducted two papers in 1999 in a multicenter study to test the internal validity and external validity of IASP criteria [14, 15]. A new classification system was proposed during the Consensus Conference in Budapest in 2003. This study supports the validity of the Budapest diagnostic criteria for CRPS and demonstrates their superiority over current IASP criteria. The results of this study support suggestions for accepting the Budapest criteria as a standard for diagnosing clinical CRPS [16].

Epidemiology

Many epidemiological studies have been performed, and there appears to be regional variations in terms of presentation. The diversity in these studies highlights the challenges of diagnosing CRPS. Because this is a clinical diagnosis, physicians will often have different results using different criteria.

An epidemiological study in USA by Sandroni et al. (2003) showed an incidence rate of 5.46 per 100,000 and a prevalence of 20.57 per 100,000. The female to male ratio was 4:1 with a mean age of 46 years and the upper/lower limb ratio was 2:1. All cases reported an inciting event and fracture was the most common stimulus (46%). An excellent correlation was observed between signs and symptoms, with vasomotor symptoms being the most common. Three-phase bone scan and autonomic testing diagnosed the disease in more than 80% of cases. Seventy-four percent of patients treated spontaneously recovered. These results suggest that invasive treatment of CRPS may not be necessary in most cases [17].

Another study in Netherlands by De Mos et al. (2007) estimated the overall incidence of CRPS at 26.2 per 100,000. Women were affected at least three times more often than men. The highest incidence occurred in women between 61 to 70 years old. The upper limb was more affected than the lower limb and fracture was the most common cause (44%). Menopausal women appear to be at the highest risk for CRPS [18].

The German epidemiological study by Ott and Maihofner (2018) reported an incidence of 71% and 29% between men and women, respectively. They also showed that the upper limb was more prone to CRPS (70% of patients), with CRPS I occuring more frequently than CRPS II (88% and 12%, respectively) [19].

Korean epidemiological study by Kim et al. (2018) showed that the difference between men and women was much narrower and the age with the highest incidence was much higher than the previous report. They also found that the pelvis, thighs, and lower limbs were more likely to be affected than the upper limbs in their patient population [20].

Denmark epidemiological study by Petersen et al. (2018), risk factors for CRPS were determined and the following ratios were found: women: men was 4:1, initial diagnosis of upper extremity: lower extremity was 2.5:, and surgical treatment: non-surgical was 3:1. The mean age was 47.5 ± 13.7 years and no gender differences were observed. Antebrachial fractures (23%) and CTS (9%) were the most common initial conditions [21].

According to UK study, CRPS is not a common disease. It has an incidence rate of 6.28 per 100,000 people per year for both types 1 and 2. According to the National Institute of Neurological Disorders and Stroke, the disease can occur at any age, is rare in the elderly and children under 10, and peaks at the age of 40 [22].

Pathophysiology

It is unlikely that a unique linear mechanism will be discovered behind the development of CRPS. According to the most common pathology model, CRPS is a detailed combination of various factors.

For example, peripheral mechanisms explain how hypoxia due to vasoconstriction and endothelial dysfunction leads to a decrease in nitric oxide levels and an

increase in endothelin-1 levels in the affected limb. There is a sterile inflammation caused by an elevated levels of proinflammatory cytokines such as interleukin-6 and tumor necrosis factor-alpha. A neurogenic inflammation by the excretion of neuropeptides from C-fibers and a high level of substance P, bradykinin, and calcitonin gene peptide were also observed. Neurosensitivity is caused by the peripheral degeneration of small fiber neurons in the skin of damaged limbs, leading to improper nerve firing [23–25] and catecholamine sensitivity after injury [26]. The researchers reported significant degeneration of large motor Aα nerve fibers, while Aδ nerve fibers survived. They hypothesized that neural signaling imbalance may occur peripherally, increasing Aδ activity and increasing pain. Nevertheless, long-term changes in the peripheral nervous system appear to play an important role [27]. There is also an increase in the expression of α1-adrenoceptors in CRPS-affected organs [28]. Changes in circulating catecholamines can explain clinical development of warm-to-cold limb. In the acute phase, studies show a decrease in circulating norepinephrine, which potentially leads to vasodilation, edema, and warmness. It is believed that over time, this leads to an increase in peripheral catecholamine sensitivity, which in turn leads to excessive vasoconstriction and hyperhidrosis, leading to cooling limb in the chronic phase of the disease [22]. Clinically, an increase in the number of alpha-1 receptors in the affected limb, increased sensitivity of peripheral alpha adrenergic receptors, and chemical coupling between sympathetic neurons and CRPS-induced limb pain caused sympathetic dysfunction and lead to variable vasoconstriction, hypoxia, and sweating abnormalities and involuntary movements characterized by dystonia, and decreased range of motion [29].

Continuous activation of the peripheral nerve after injury has been shown to increase the firing effect of synaptic pain in the dorsal horn and lead to central sensitization [30]. Central mechanisms, such as (super) spinal sensitization via *N*-methyl-D-aspartate and neurokinin-1 receptors have also been described [31]. CRPS patients due to damaged limbs experience a smaller view of the sensorimotor cortex than the normal limbs [32]. There is cortical reorganization characterized by the significant contraction of the extension of the cortical view of the hand at the injured side, shifting of the hand to the cortical area of the lip, and the reorganization of the opposite side of the S1 cortex. These reorganization are associated with CRPS pain, mechanical hyperalgesia, and neuropathic pain [33]. Recent study showed that S1 representation of the CRPS hand is comparable between affected and unaffected hand map [34].

There is also an evidence of autoimmune-mediated reaction in the development of CRPS. Autoantibodies are believed to be produced against the structures of the autonomic nervous system causing exacerbation of inflammation and symptoms [35]. The mast cells were shown to decrease around atrophied cutaneous nerve fibers in the affected limbs. The researchers hypothesized that abnormal nerve-mast cell interaction occurs, leading to long-term inflammation and delayed tissue repair in CRPS [36]. Research studies have shown that up to 70% of these patients have anti-autonomic antibodies to immunoglobulin G in their serum [37].

The genetic impact on the development of CRPS is currently under investigation and showed that family relationships were associated with early-onset and increased

incidence of multi-member involvement [38]. Discovering specific microRNA signatures (miRNAs) is another interesting way to study genetics. These small non-coding fragments of RNA have been shown to directly alter gene expression [37, 39] However, the genetic link is not definitive. A paradoxical study in 2016 examined more than 200,000 single nucleotide polymorphisms between CRPS patients and control groups and found no significant difference in expression between the two [40].

There is evidence that certain mental states can predispose a patient to illness. Patients with post-traumatic stress disorder (PTSD) significantly showed increased CRPS compared with controls [41]. In many of these patients, PTSD precedes the onset of CRPS as indicated by their medical history. In fact, psychological stress seems to affect the progression of the disease. Patients with higher levels of anxiety, disability perception, and fear of pain have been shown to worsen the course of the disease [42].

Clinical Presentation

CRPS describes an array of painful conditions that are characterized by a continuing (spontaneous and/or evoked) pain that is seemingly disproportionate to a given trauma or any inciting event. To wit, an unexpected prolongation of recovery of an uncomplicated fracture characterized this disease. Pain may vacillate between allodynia, signs of autonomic instability, and sensory dysfunction of the skin which include hyperalgesia and mechanical allodynia and hypoalgesia and mechanical hypoesthesia. There are also motor dysfunction which include a reduction in the "range of motion" of affected joints and/or weakness, tremor, involuntary movements, bradykinesia, and dystonia along with an abnormality of cerebral motor processing which are unusually associated with a peripheral process and deep tendon reflex findings. A fracture, or crushing injury or a forceful trauma to the arm is the most common initial event when it occurs in the upper extremity. It usually starts in the limb as an extreme pain, swelling, limited range of motion, and trophic changes in the skin and bones with nearly all patients showing sweating abnormalities (hypohydrosis or hyperhydrosis). It may initially affects one limb (asymmetrical distal extremity pain) and then spreads throughout the body with sensory abnormalities affecting the most distal part of the extremities ("stocking-glove" pattern). Furthermore, the affected area usually manifest symptoms beyond the site of the original injury with varying degrees of pain over time such that pain and other symptoms are often exacerbated with exertion of the affected extremity [43].

To quantify the severity of the disease, Harden et al. (2010) developed the CRPS Severity Score (CSS) . Higher scores were not only positively associated with increased pain and functional limitations, but were also used as a measure to detect the disease and to monitor response to a given treatment (Table 9.2) [16, 44].

Table 9.2 CRPS severity score

Symptoms that were self-reported	Symptoms observed at the time of examination
Allodynia	Hyperpathia to pinprick
Temperature asymmetry	Allodynia
Skin color asymmetry	Temperature asymmetry to palpation
Sweating asymmetry	Skin color asymmetry
Trophic changes	Sweating asymmetry
Motor changes	Asymmetric edema
Decreased range of motion	Trophic changes
Asymmetric edema	Motor changes
	Decreased active range of motion

The clinical progression of the disease can usually be divided into three stages:

1. An acute early stage, with inflammatory symptoms
2. Dystrophic stage characterized by a gradual decrease in edema
3. An atrophic stage can then be seen in which atrophy and skin contractions become common

The first symptoms usually appear within a few weeks after the injury and the affected limb is very painful, erythematous, swollen, and warm. Allodynia, hyperalgesia, trophic changes in the skin and nail growth, and muscle weakness may be present. The affected area is limited and does not have a specific nerve distribution. As the disorder progresses, the pain exacerbates and spreads. Voluntary motor control decreases, negative sensory symptoms (hypostasis, hypoalgesia, and hypothermia) develop, and the limbs become cold, dark, and sweaty. Myoclonus, tremor and dystonia may also occur. Over time, the clinical symptoms can spread to other parts of the body even affecting the contralateral or bilateral sides. A subset of patients with CRPS becomes chronic, and after a long period of illness (>5 years) develop other features such as urological symptoms, syncope, and even mild cognitive impairments. The acute phase and dystrophy are reversible, while the form of atrophy is irreversible [45].

Three distinct vascular regulation patterns related to the duration of the disorder were also identified:

1. In the “warm” (acute) pattern, the affected limb was warmer and the amount of perfusion was greater in CRPS limb.
2. In the “moderate” pattern, the limbs were either warmer or colder.
3. In the “cold” (chronic) pattern, skin temperature and perfusion were lower.

It is suggested that in CRPS I, unilateral inhibition of sympathetic vasoconstrictor neurons leads to warmer limb in the acute phase. Secondary changes in neurovascular transmission may lead to vascular contraction and cold skin in chronic CRPS I, while sympathetic activity is still depressed [46].

Three possible subtypes of CRPS is also described that is useful clinically:

1. Relatively limited syndrome with predominant vasomotor symptoms,
2. Relatively limited syndrome with predominant neuropathic pain/sensory abnormalities,
3. Florid CRPS syndrome, described as "classic RSD"

Subgroup 3 showed the highest levels of motor/trophic symptoms and possible changes due to osteopenia in bone scans, despite the shortest duration of pain in the three groups. The EMG/NCV test indicates that subgroup 2 may reflect CRPS-Type 2 [2].

Diagnosis

The diagnosis and treatment of CRPS has been a challenge to health care providers. Diagnosis is based upon criteria obtained from the medical history and physical examination. Due to the great clinical diversity and heterogeneity of the cause, the diagnosis is not easy. There are many non-standard diagnostic benchmark systems. The new diagnostic criteria were developed by the International Association for the Study of Pain (IASP) based on classification in the consensus workshop in 1994. Subsequent validation research using these criteria have encountered problems differentiating the disease with the possibility of over-diagnosis. In the fall of 2003, diagnostic criteria were reviewed in Budapest which were adopted in 2012 as a new international standard for the diagnosis of CRPS by the IASP and could reduce the CRPS diagnosis by about 50%. The most commonly used criteria are the main IASP criteria and the modified Harden and Bruehl's diagnostic criteria. The criteria described by Veldman are often used in the Netherlands (Table 9.3). All criteria are essentially empirically determined and have overlapping parameters to some extent. However, the IASP criteria is the most sensitive, while the modified criteria according to Harden and Bruehl is the most specific [16, 42, 47].

No diagnostic test is considered definitive for CRPS, there are no laboratory tests to diagnose or eliminate it completely. However, other methods can help with the diagnosis. Thermography may be the most common and the most basic diagnostic method used wherein changes of 1 °C or more are considered diagnostic [48].

Standard radiographs can be normal in the early stages (bone mineral depletion occurred within 3–6 weeks of the onset of symptoms, and this change may continue for up to 2 years after the symptoms have resolved). In the absence of clinical signs (autonomic changes and dystrophy) and radiographic examination findings, further tests such as MRI and scintigraphy are done for accurate evaluation. MRI imaging scans show low signal intensity in T1-w images and high signal intensity in STIR or T2-w fat suppression images. These changes indicate an increase in the intracellular and extracellular fluid of the bone marrow, which results from the formation and repair of bone (differential diagnosis on MRI should be made for infection, osteonecrosis, and post-traumatic brain edema). A three-stage bone scan may be

Table 9.3 Different diagnostic criteria for CRPS

Dutch criteria (Veldman 1993)	IASP criteria (Merskey 1994)	Budapest clinical diagnostic criteria for CRPS (2003)	Modified diagnostic criteria (Harden 2007)
1. 4 or 5 of the following symptoms:	1. Develops after tissue damage (CRPS type—1) or nerve damage (CRPS type—2)	1. Continuing pain, which is disproportionate to any inciting event	1. Continuous pain, disproportionate to the inciting event.
(a) Inexplicable diffuse pain	2. Continuous pain, allodynia or hyperalgesia disproportional to the inciting event.	2. Must report at least one symptom in three of the four following categories:	2. Patients should have at least 1 symptom in each of the following categories and 1 sign in 2 or more categories.
(b) Difference in skin color between affected and contralateral extremity	3. Evidence at some time of edema, abnormal skin blood flow and sudomotor abnormalities in the region of pain.	(a) Sensory: reports of hyperesthesia and/or allodynia	Categories:
(c) Diffuse edema	4. Other causes of pain or dysfunction are excluded.	(b) Vasomotor: reports of temperature asymmetry and/or skin color changes and/or skin color asymmetry	1. Sensory (allodynia, hyperalgesia, hypoesthesia)
(d) Difference in skin temperature between affected and contralateral extremity	Criteria 2, 3, and 4 must be fulfilled	(c) Sudomotor/edema: reports of edema and/or sweating changes and/or sweating asymmetry	2. Vasomotor (temperature or skin color abnormalities)
(e) Limited "active range of motion"		(d) Motor/trophic: reports of decreased range of motion and/or motor dysfunction (weakness, tremor, dystonia) and/or trophic changes (hair, nail, skin)	3. Sudomotor (edema or sweating abnormalities)
2. The occurrence or increase of above—mentioned symptoms with use of the involved extremity.		3. Must display at least one sign at time of evaluation in two or more of the following categories:	4. Motor/trophic (muscle weakness, tremor, hair, nail, skin abnormalities)

(continued)

Table 9.3 (continued)

Dutch criteria (Veldman 1993)	IASP criteria (Merskey 1994)	Budapest clinical diagnostic criteria for CRPS (2003)	Modified diagnostic criteria (Harden 2007)
3. Above—mentioned symptoms are present in an area that is greater than the area of original trauma or surgery and distal to this area.		(a) Sensory: evidence of hyperalgesia (to pinprick) and/or allodynia (to light touch and/or deep somatic pressure and/or joint movement)	
		(b) Vasomotor: evidence of temperature asymmetry and/or skin color changes and/or asymmetry	
		(c) Sudomotor/edema: evidence of edema and/or sweating changes and/or sweating asymmetry	
		(d) Motor/trophic: evidence of decreased range of motion and/or motor dysfunction (weakness, tremor, dystonia) and/or trophic changes (hair, nail, skin)	
		There is no other diagnosis that better explains the signs and symptoms	

positive a few days after the onset of symptoms. Tc99m-MDP increases uptake, indicating a focal increase in capillary permeability, hyperemia, and osteoblastic activity [49]. Three-phase bone scan may show increased absorption of technetium Tc99m bisphosphonate due to increased bone metabolism, although it has no benefit in the management of CRPS and should not be used as a confirmatory measure [50, 51].

Electromyography has shown some validity in some specific patients. Myoclonus, which occurs in CRPS patients, is thought to be distinct from other types of myoclonus and may be detected by electromyography. However, only 11–36% of patients showed myoclonus, greatly limiting its sensitivity as a diagnostic tool [52].

Musculoskeletal ultrasound can also be used to describe physical differences in muscle tissue in CRPS patients, CRPS-affected muscles have significant

myoglobular deviation, whereas muscles affected by chronic neuropathic pain have a normal structure [53].

Painful hypersensitivity in persistent CRPS is maintained by autoantibodies, which act by sensitizing pain receptors A and C. Twenty-seven (33%) of the 82 CRPS patients whose serum was available tested positive for ANA, indicating that autoantibodies may be associated with the pathophysiology of CRPS, at least in a subset of patients [54, 55].

Treatment

CRPS treatment guidelines recommend a multidisciplinary approach including physiotherapy, occupational therapy, and psychotherapy (with coping mechanisms for pain, relaxation training, thermal biofeedback, and graded exposure therapy) to improve movement, mobility, quality of life, and the patient ability to manage pain [56]. The graded motor imagery and mirror therapy have the best available data that could improve pain and function in CRPS I patients [57].

Intense exercise therapy is critical to the effective treatment of CRPS and the reduction in the reported high incidence of recurrence in patients treated with physiotherapy alone and cognitive-behavioral therapy. Electrical nerve stimulation (TENS) reduces CRPS 2 pain and when delivered contralateral to a nerve injury best reduces allodynia in a combination of high- and low-frequency [58]. Many CRPS 1 patients receiving neurofeedback training report a significant short-term reduction in their pain experience as well as improvement of symptoms [59].

Pharmacologic Therapy

Based on overlapping pathophysiologic mechanisms of CRPS different pharmacological treatment is recommended. Commonly used drugs are nonsteroidal anti-inflammatory drugs (NSAIDs) such as naproxen or ibuprofen, tramadol, antidepressants such as amitriptyline, doxepin or trazodone; anticonvulsants (e.g. gabapentin), clonidine, clonazepam, baclofen, topical capsaicin cream, lidocaine 5 patch [60].

The effect of NSAIDs in reducing pain in some neuropathic conditions have not been well demonstrated. However, inflammation is involved in CRPS, especially in the early months of the syndrome and may respond effectively to NSAID. Systemic corticosteroids have been studied in various trials and have generally had positive results [61, 62]. A short course of steroids may be indicated in early CRPS with prominent inflammation, but contraindicated for a long course [56].

Neuropathic pain medications for CRPS have not been extensively studied. The use of neuropathic pain medications to treat CRPS is based on their usefulness in the treatment of other neuropathic diseases. Evidence of their use in CRPS is limited; some of these medications include amitriptyline, doxepin, nortriptyline, desipramine, imipramine, and trazodone, serotonin-norepinephrine reuptake inhibitors

(SNRIs) duloxetine and venlafaxine. The use of other neuropathic pain medications by pain physicians to treat CRPS is experimental and is based on the preference and experience of each provider [63, 64]. Gabapentin and amitriptyline were effective in reducing pain intensity and improving sleep [65]. Carbamazepine, another anticonvulsant also showed pain relief [66].

Bisphosphonates (e.g., pamidronate, clodronate, alendronate) are one of the most widely used drugs for the treatment of osteoporosis, but as a treatment for CRPS the mechanism of pain relief is unclear. Some theories include the ability of bisphosphonates to modulate inflammation, inhibit the growth and migration of bone marrow cells, and reduce bone marrow acidity [67, 68]. In patients with acute CRPS-1, Neridronate was associated with clinical benefits compared with placebo control group [69].

Anesthetic doses of ketamine, an NMDA receptor antagonist, were used in patients with severe refractory CRPS that was spreading [70]. Intranasal calcitonin showed improvement in pain intensity, but not in all studies [71].

One possible mechanism of CRPS is that it is triggered by an exaggerated inflammatory response to tissue damage caused by the overproduction of oxygen-mediated radicals, so free-radical scavengers (alpha lipoic acid, dimethyl sulfoxide [DMSO], *N*-acetylcysteine [NAC], and vitamin C) have been studied with some success for the treatment of CRPS [72, 73]. There is also the possibility that vitamin C may be effective in preventing CRPS but due to the varied results and the overall quality of evidence, it is unclear whether vitamin C is generally effective in reducing the prevalence of CRPS after fractures and limb surgeries [74, 75].

Alpha-adrenoceptor antagonists (such as phentolamine, phenoxybenzamine, clonidine, and reserpine) have been used clinically to treat CRPS without good results from prospective randomized trials. Patients who have symptoms of vasomotor hyperactivity leading to cold (intermittent) CRPS may respond to alpha-1 adrenergic blockers such as phenoxybenzamine and trazosine or calcium channel blockers such as nifedipine [43]. Oral clonidine has not been shown to be significantly effective in neuropathic pain and its use is challenging due to its characteristic side effects. It is mostly used as an intrathecal agent [76–78]. The transdermal clonidine patch in four CRPS patients with sympathetic pain has shown some benefits. It is also suggested that oral terazosin may be effective in treating sympathetically maintained pain in patients with CRPS. Oral nifedipine or oral phenoxybenzamine was useful for controlling severe vasoconstriction in two uncontrolled cases of patients with CRPS. Intravenous phentolamine has been used to assess pain maintained by the sympathetic, and is not commonly used clinically, however, it may be used to make a diagnosis [77–83].

Transdermal clonidine and the fentanyl patch, lidocaine patch 5%, eutectic mixture of local anesthetics (EMLA) cream, dimethyl sulfoxide (DMSO), and capsaicin introduced based on their effect on neuropathic pain, but none of which has been directly studied in CRPS. Intravenous lidocaine is used both therapeutically and diagnostically to assess the responsiveness to a subsequent oral sodium channel blocker (e.g., mexiletine, oxcarbazepine, and carbamazepine) [60, 64, 84–86]. Bier block with methylprednisolone and lidocaine in CRPS type I does not provide long-term benefit in CRPS. While its short-term benefit is not superior to placebo [87].

There is considerable controversy about the use of opiates to treat chronic noncancerous pain, and this is especially true in CRPS. Opioids are generally thought to be less effective in chronic neuropathic pain conditions than in acute and subacute pain conditions. However, there is good evidence that opiates can reduce pain and improve quality of life in patients with neuropathic pain. However, there are no controlled studies showing long-term improvement in opioid-treated neuropathic pain [88–90].

The auto-antigenicity of KRT16 in a murine CRPS model and CRPS patients further reinforce the idea of autoimmune involvement in CRPS, suggesting that new diagnostic tests and treatment strategies may be developed to follow these findings [90]. The use of new immunomodulatory and anti-inflammatory drugs such as thalidomide and lenalidomide (an alpha tumor necrosis factor inhibitor) may offer a new approach to treating CRPS [91]. Low dose naltrexone has unique properties to specifically help the disease cascade of CRPS including attenuation of microglial cells involved in pain transmission, decreased proinflammatory cytokines and toll-like receptor antagonism 4 (TLR4), and stimulation of endorphin secretion. Naltrexone is currently approved for the management of alcohol and opioid disorders. Previous reports have shown that about one-tenth of the dose used for these approved indications may be beneficial for patients with CRPS. A company is developing a new low-dose naltrexone formulation which is due for evaluation [92, 93]. Treatment with low-dose intravenous immunoglobulin (IVIG) may significantly reduce pain in refractory CRPS [94]. Although a trial in 2016 showed that it was "not effective in relieving pain in patients with moderate to severe CRPS between 1 and 5 years of age" [95]. Plasma replacement therapy is also effective in a subset of patients with severe and long-term CRPS [96].

Interventional Therapy

Botulinum toxin type A (BTA) prevents release of acetylcholine from cholinergic nerve terminals, and therefore, intradermal injection of BTX-A has direct analgesic effects in patients with focal chronic neuropathic pain associated with allodynia [97]. BTA-enhanced sympathetic blocks for the treatment of CRPS [98].

CRPS is a very painful condition where patients are unable to move the affected limb much. Because ligaments are very sensitive to immobility, also called stress deprivation, they never heal, although other injuries, such as bone fractures, heal. This unhealed ligament injury continues to activate the sympathetic nervous system, and the patient continues with chronic symptoms, including severe burning pain from CRPS. Ligament relaxation often activates the sympathetic nervous system, and prolotherapy not only relieves pain by stimulating ligament regeneration, but also relieves sympathetic hyperactivity and CRPS-related symptoms [99]. Nerve stimulation which occur through repetitive muscle contractions and a sudden change in the direction of the sensory nerves move between the muscular and facial layers. Cutaneous nerve trauma may cause nerve edema in the proximal and distal regions of the lesion. With perineural prolotherapy, dextrose binds to presynaptic calcium channels and prevents the release of nerve-damaging peptides, thereby reducing

nerve inflammation, restoring the normal flow of nerve growth factors, and facilitating nerve repair and produces an almost immediate analgesic effect from hours to days [100]. Stem cell therapy is a new type of regeneration therapy and really an advanced type of prolotherapy. It also has the ability to increase blood flow to damaged tissue and help heal the injured area at the same time. It is a good alternative to RSD treatment and its effect could be monitored by neuro-musculoskeletal thermology [101].

Part of the pathophysiology of CRPS is thought to be related to an autoimmune disorder in the affected limb with an exaggerated response to catecholamines which subsequently causes pain. Sympathetic blocks may facilitate the ratio of sympathetic pain at that point and be of therapeutic benefit, but they cannot exclude or rule out the diagnosis of CRPS. Stellate ganglion blocks and thoracic sympathetic block (T2–T3) are useful in the treatment of sympathetic block of upper extremity pain and lumbar sympathetic block for the lower extremity. Also, a catheter with a stationary sympathetic chain provides continuous pain relief, while it has no motor or sensory dysfunction and may be very effective in allowing the PT to continue working. Single-shot sympathetic blocks must be coordinated with PT sessions, so the patient is painless in all sessions. The successful block is usually controlled by increasing the temperature of the lower part [102–104] (Figs. 9.1 and 9.2).

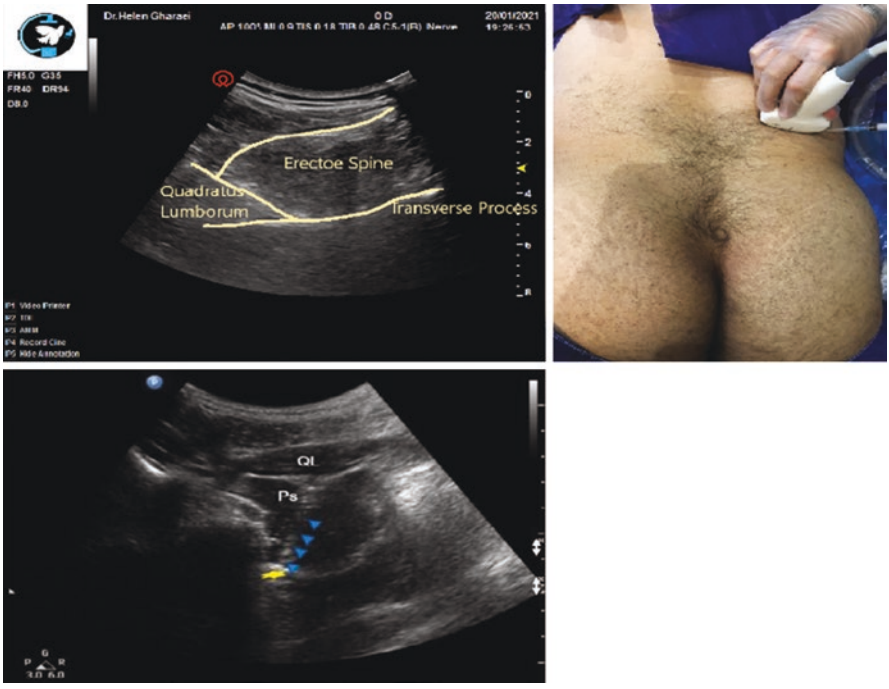

Fig. 9.1 Ultrasound-guided lumbar sympathetic block at L3 inter-transverse space. After visualization of the transverse process by turning the medial side of the probe clock-wise in order to see the anterior border of the vertebral body and psoas muscle. Arrow heads point to a needle shaft and a yellow star shows the anterior fascia of the psoas major muscle. *Ps* psoas major muscle, *QL* quadratus lumborum muscle

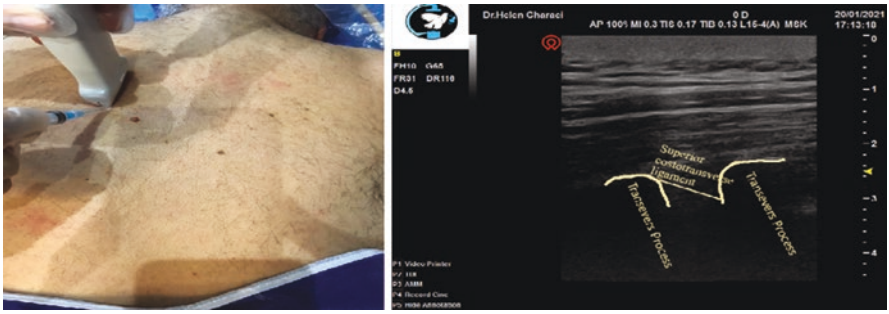

Fig. 9.2 Ultrasound-guided thoracic paravertebral (between the T2 and T3). After passing the ligament, inject drug

Brachial plexus block is used to treat the somatic part of the CRPS-affected upper limb pain. Different approaches to the current block exist including the supraclavicular block, interscalene block, axillary block and the infraclavicular block with the latter being the most common. Continuous popliteal blocks, sciatic peripheral nerve block and saphenous peripheral nerve blockade are of use in treating the somatic part of CRPS lower extremity pain. Continuous epidural analgesia allows a similar level of pain management for PT. Continuous peripheral nerve catheters reduce pain and facilitate intensive physiotherapy and practical rehabilitation, they resulted in resolution of physical changes associated with CRPS and a decrease need for pharmacological drugs, including opioids. Peripheral nerve blockade treats the symptoms. However, it cannot suppress activity at the dorsal root ganglion and it does not address the chronic sensitization within the disease process. Peripheral nerve catheters have the advantage of continuous epidural infusion and can be used in upper extremity disease, provide unilateral analgesia, provide limited and localized sympathetic blockade, and have no effect on bladder or bowel function. However, continuous peripheral nerve block should be more comfortable at home than continuous epidural analgesia. The use of disposable pumps reduces hospitalization such that this treatment can be continued at home. Stationary epidural catheters, although usually effective in relieving pain, cause additional motor block and/or sensation that the patient cannot participate in PT effectively. This may be harmful because any limb immobilization appears to worsen CRPS [105–109].

For patients with upper extremity CRPS type 1 who experience incurable neuropathic pain that is largely limited to the distribution of a peripheral nerve may benefit from implantation of a percutaneous PNS when other options have failed and thus provide pain relief. Peripheral nerve stimulation to the left ulnar nerve may be used for the treatment of patients with complex type 1 pain syndrome following injury to the left fifth finger [110]. Peripheral nerve stimulation is a useful way to improve function and reduce long-term pain in patients who suffer from CRPS types I and II [111]. Wireless peripheral nerve stimulation (WPNS) has unique properties due to its minimally invasive technique. This system does not involve implanting a battery or its connections. In the case of CRPS I, which affects the

upper extremities, a WPNS with radial and median nerve coverage provides good pain relief [112]. The plexus stimulation, such as brachial plexus stimulation, has long been used in the treatment of complex regional pain syndrome of the upper extremities [113]. In refractory cases, neuromodulatory option such as SCS stimulation or DRG stimulation may be considered, in very elite cases. Sympathectomy is also useful for this condition [105, 108] (Figs. 9.3, 9.4, and 9.5).

Neuropathic pain is defined as "pain from a lesion or disease of the somatosensory system." Deep brain stimulation (DBS) has been the central implantable nerve stimulation of choice for chronic pain. Some neurosurgeons advocate DBS and its newer target, the anterior cingulate cortex (ACC), while stimulating the motor cortex as "the hall's last chance" [114]. There are good evidences for interventional therapy of CRPS (Table 9.4) [43, 115].

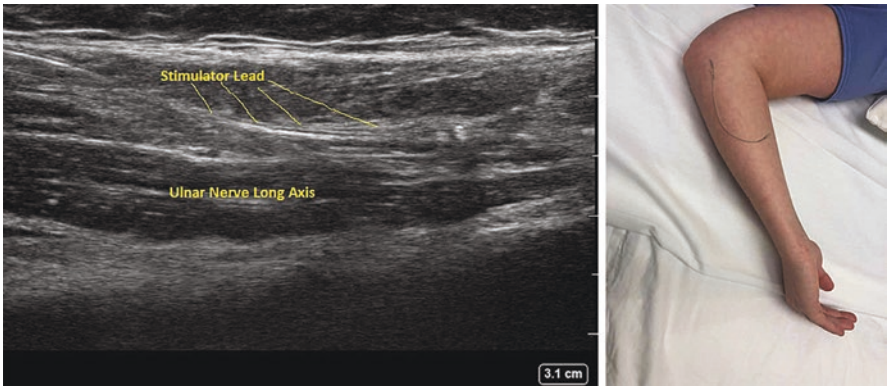

Fig. 9.3 Administration of percutaneous peripheral nerve stimulation in CRPS Type 1 following a crush injury to the fifth digit

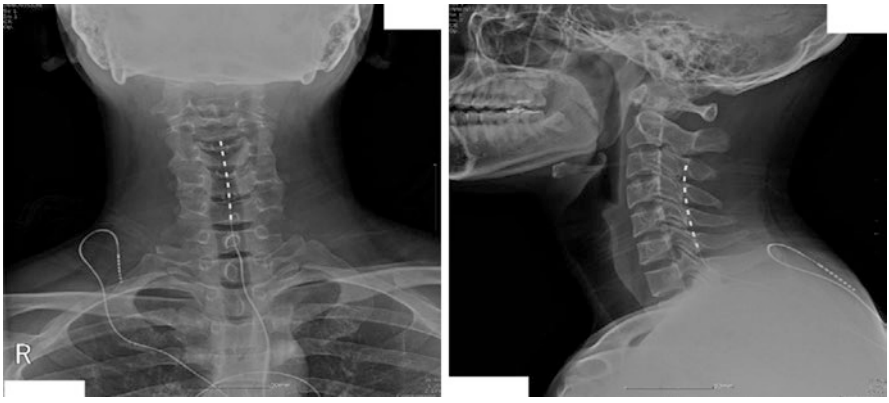

Fig. 9.4 SCS lead position; the catheter enter from T6 and 7 interspaces with final position at the right side of the C3 body in a refractory case of right arm CRPS

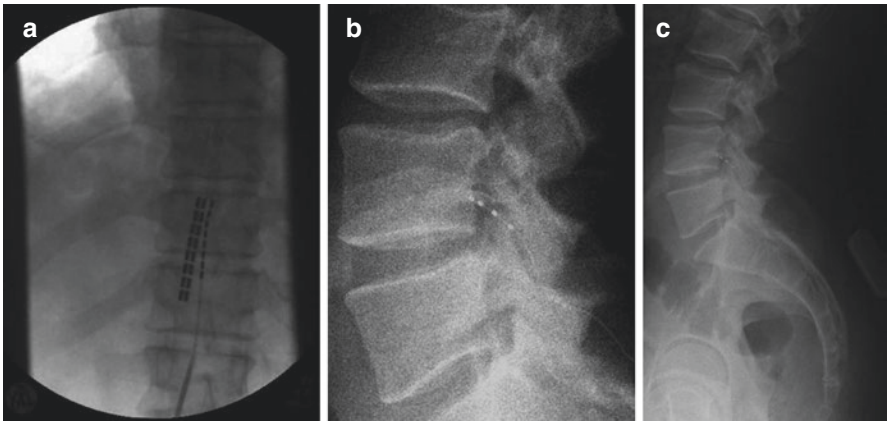

Fig. 9.5 CRPS recurrence 2 years after midtibial amputation, L4 dorsal root ganglion stimulation achieved substantial pain relief after a failed trial of SCS

Table 9.4 Evidence based medicine for interventional pain management in CRPS

Treatment	Recommendations in 2010	Grade level of evidence in 2015	Recommendations in 2018
• Sympathetic blocks with local anesthetics (sympathetic blocks of the ganglion stellatum for CRPS in the arm)	2B+	Moderate	Moderate against
• Thoracic block (T2–T3) with ropivacaine and triamcinolone	2A−	Low	Weak
• IV regional blocks with guanethidine	2B+	Moderate	Moderate against
• Spinal cord stimulation	2C+	Moderate	Moderate
• DRG stimulation (for lower extremity CRPS)		Moderate	Moderate
• Peripheral nerve stimulation		Very low	Very weak
• Low-dose IV ketamine		Moderate	Weak

Algorithmic Approach to CRPS Pain Management

The primary treatment of CRPS consists of early active mobilization by physical therapy combined with pharmacological pain treatment. An early diagnosis is mandatory for therapeutic success and functional outcome. The therapeutic approach with more possibilities of success in the early stages is primarily pharmacological. When conservative treatment with physical and medical treatment fail, multidisciplinary evaluation should be considered. Physical therapy with active mobilization and graded motor imagery treatment, together with a symptom oriented pharmacological treatment, is the best initial approach of CRPS. When there is no

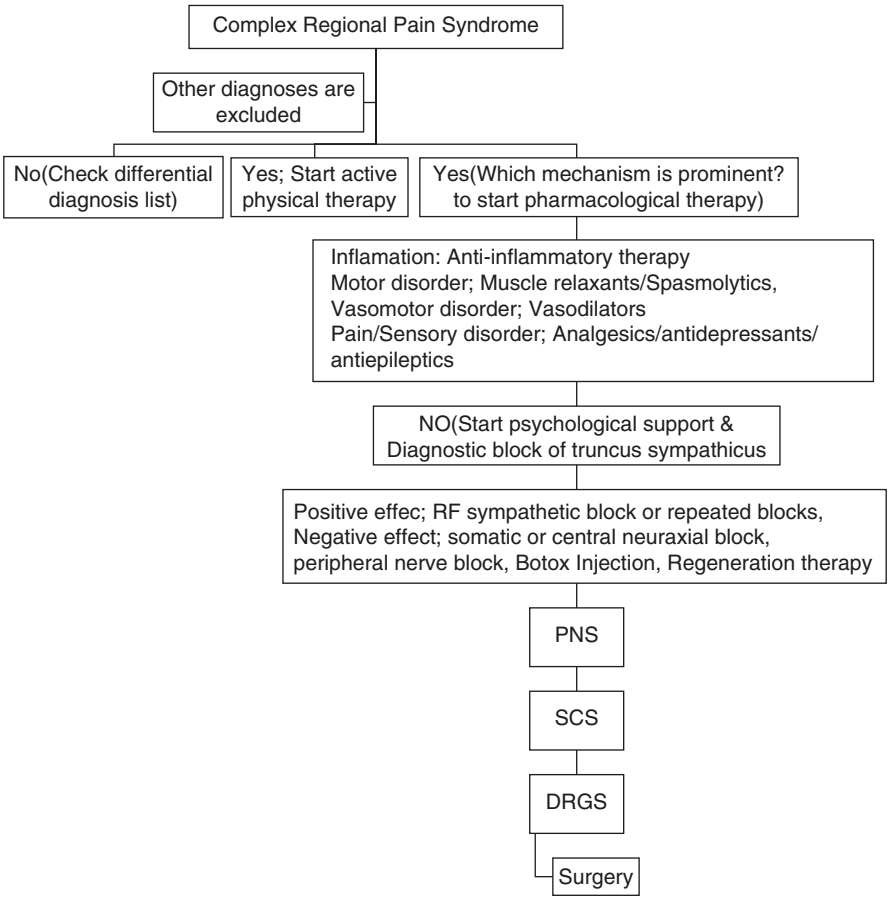

Fig. 9.6 Algorithmic approach to CRPS pain management

improvement in pain and dysfunction, interventional pain management including sympathetic blockade may be performed. If this block is effective, it may be followed by repeated injections or RF treatment. If symptoms persist, a continuous epidural infusion, intermittent or continuous plexus brachialis block in combination with exercise therapy may be useful. And in refractory cases, SCS after a successful trial stimulation period may yield positive results [43] (Fig. 9.6).

Conclusion

Currently, there are no drugs approved by FDA specifically for the treatment of CRPS. Early diagnosis is still the key in the success of therapeutic intervention. Interventional pain management in CRPS is a great chance given to us to resolve these difficult cases in the early stages while patients with CRPS have negative bone

scans. Chronic CRPS, or a predominantly cold illness are less likely to respond to any treatment modalities [67, 68]. I recommend to start with less invasive and less expensive intervention especially in low income country and a judicious use of any intervention regardless of the country of origin as soon as possible without leaving these cases unsolved.

References

1. National Institute of Neurological Disorders and Stroke. Complex regional pain syndrome. https://www.ninds.nih.gov/Disorders/Patient-Caregiver-Education/Fact-Sheets/Complex-Regional-Pain-Syndrome-FactSheet#:~:text=Complex%20regional%20pain%20syndrome%20(CRPS,peripheral%20and%20central%20nervous%20systems. Accessed 14 Dec 2020.
2. Bruehl S, Harden RN, Galer BS, Saltz S, Backonja M, Stanton-Hicks M. Complex regional pain syndrome: are there distinct subtypes and sequential stages of the syndrome? Pain. 2002;95:119–24.
3. Paré A. Of the cure of wounds of the nervous system. The collected works of Ambroise Pare. New York: Milford House; 1634.
4. Denmark A. An example of symptoms resembling tic Douleureux, produced by a wound in the radial nerve. Med Chir Trans. 1813;4:48–52.
5. Mitchell SW. Injuries of nerves and their consequences. Philadelphia: JB Lippincott; 1872.
6. Dunglison R. A dictionary of medical science. Philadelphia: Blanchard & Lea; 1874.
7. Sudeck P. Über die akute entzündliche Knochenatrophie. Arch Klin Chir. 1900;62:147–56.
8. De la Leriche R. causalgie envisagee comme une nevrite due sympathique et de son traitment par la denudation et l'excision des plexus nerveux peri-arteriels. Presse Med. 1916;24:178–80.
9. Evans JA. Reflex sympathetic dystrophy. Surg Clin N Am. 1946;26:780–90.
10. Foisie PS. Traumatic arterial vasospasm. N Engl J Med. 1947;237:295–302.
11. Bonica JJ. The management of pain. Philadelphia: Lea & Febiger; 1953.
12. Merskey H, Bogduk N. International Association for the Study of Pain Task Force on Taxonomy: classification of chronic pain: descriptions of chronic pain syndromes and definitions of pain terms. 2nd ed. Seattle, WA: IASP Press; 1994.
13. Veldman PH, Reynen HM, Arntz IE, Goris RJ. Signs and symptoms of reflex sympathetic dystrophy: prospective study of 829 patients. Lancet. 1993;342(8878):1012–6.
14. Harden RN, Bruehl S, Galer BS, Saltz S, Bertram M, Backonja M, Gayles R, Rudin N, Bhugra MK, Stanton-Hicks M. Complex regional pain syndrome: are the IASP diagnostic criteria valid and sufficiently comprehensive? Pain. 1999;83(2):211–9.
15. Bruehl S, Harden RN, Galer BS, Saltz S, Bertram M, Backonja M, Gayles R, Rudin N, Bhugra MK, Stanton-Hicks M. External validation of IASP diagnostic criteria for complex regional pain syndrome and proposed research diagnostic criteria. International Association for the Study of Pain. Pain. 1999;81(1–2):147–54.
16. Harden RN, Bruehl S, Perez RS, Birklein F, Marinus J, Maihofner C, Lubenow T, Buvanendran A, Mackey S, Graciosa J, Mogilevski M, Ramsden C, Chont M, Vatine JJ. Validation of proposed diagnostic criteria (the "Budapest criteria") for complex regional pain syndrome. Pain. 2010;150(2):268–74.
17. Sandroni P, Benrud-Larson LM, RL MC, Low PA. Complex regional pain syndrome type I: incidence and prevalence in Olmsted county, a population-based study. Pain. 2003;103:199–207.
18. de Mos M, de Bruijn AG, Huygen FJ, Dieleman JP, Stricker BH, Sturkenboom MC. The incidence of complex regional pain syndrome: a population-based study. Pain. 2007;129:12–20.

19. Ott S, Maihofner C. Signs and symptoms in 1,043 patients with complex regional pain syndrome. J Pain. 2018;19:599–611.
20. Kim H, Lee CH, Kim SH, Kim YD. Epidemiology of complex regional pain syndrome in Korea: an electronic population health data study. PLoS One. 2018;13:e0198147.
21. Petersen PB, Mikkelsen KL, Lauritzen JB, Krogsgaard MR. Risk factors for post-treatment complex regional pain syndrome (CRPS): an analysis of 647 cases of CRPS from the Danish Patient Compensation Association. Pain Pract. 2018;18:341–9.
22. Goh EL, Chidambaram S, Ma D. Complex regional pain syndrome: a recent update. Burns Trauma. 2017;5:2.
23. Groeneweg JG, Huygen FJ, Heijmans-Antonissen C, Niehof S, Zijlstra FJ. Increased endothelin-1 and diminished nitric oxide levels in blister fluids of patients with intermediate cold type complex regional pain syndrome type 1. BMC Musculoskelet Disord. 2006;7:91.
24. Birklein F, Schmelz M. Neuropeptides, neurogenic inflammation and complex regional pain syndrome (CRPS). Neurosci Lett. 2008;437:199–202.
25. Oaklander AL, Fields HL. Is reflex sympathetic dystrophy/complex regional pain syndrome type Ia small-fiber neuropathy? Ann Neurol. 2009;65:629–38.
26. Janig W, Baron R. Complex regional pain syndrome: mystery explained? Lancet Neurol. 2003;2:687–97.
27. Yvon A, Faroni A, Reid AJ, Lees VC. Selective fiber degeneration in the peripheral nerve of a patient with severe complex regional pain syndrome. Front Neurosci. 2018;12:207.
28. Finch PM, Drummond ES, Dawson LF, Phillips JK, Drummond PD. Up-regulation of cutaneous alpha1-adrenoceptors in complex regional pain syndrome type I. Pain Med. 2014;15:1945–56.
29. Gibbs GF, Drummond PD, Finch PM, Phillips JK. Unravelling the pathophysiology of complex regional pain syndrome: focus on sympathetically. Clin Exp Pharmacol Physiol. 2008;35(7):717–24.
30. Woolf CJ. Central sensitization: implications for the diagnosis and treatment of pain. Pain. 2011;152:S2–S15.
31. de Mos M, Sturkenboom MC, Huygen FJ. Current understandings on complex regional pain syndrome. Pain Pract. 2009;9:86–99.
32. Di Pietro F, McAuley JH, Parkitny L. Primary somatosensory cortex function in complex regional pain syndrome: a systematic review and meta-analysis. J Pain. 2013;14:1001–18.
33. Maihöfner C, Handwerker HO, Neundörfer B, Birklein F. Patterns of cortical reorganization in complex regional pain syndrome. Neurology. 2003;61(12):1707–15.
34. Mancini F, Wang AP, Schira MM, Isherwood ZJ, McAuley JH, Iannetti GD, Sereno MI, Moseley GL, Rae CD. Fine-grained mapping of cortical somatotopies in chronic complex regional pain syndrome. J Neurosci. 2019;39(46):9185–96.
35. Blaes F, Schmitz K, Tschernatsch M. Autoimmune etiology of complex regional pain syndrome (M. Sudeck). Neurology. 2004;63:1734–6.
36. Morellini N, Finch PM, Goebel A, Drummond PD. Dermal nerve fibre and mast cell density, and proximity of mast cells to nerve fibres in the skin of patients with complex regional pain syndrome. Pain. 2018;159:2021–9.
37. Birklein F, Ajit SK, Goebel A, Perez R, Sommer C. Complex regional pain syndrome - phenotypic characteristics and potential biomarkers. Nat Rev Neurol. 2018;14:272–84.
38. de Rooij AM, de Mos M, Sturkenboom MC, Marinus J, van den Maagdenberg AM, van Hilten JJ. Familial occurrence of complex regional pain syndrome. Eur J Pain. 2009;13:171–7.
39. Orlova IA, Alexander GM, Qureshi RA. MicroRNA modulation in complex regional pain syndrome. J Transl Med. 2011;9:195.
40. Janicki PK, Alexander GM, Eckert J, Postula M, Schwartzman RJ. Analysis of common single nucleotide polymorphisms in complex regional pain syndrome: genome wide association study approach and pooled DNA strategy. Pain Med. 2016;17:2344–52.
41. Speck V, Schlereth T, Birklein F, Maihofner C. Increased prevalence of posttraumatic stress disorder in CRPS. Eur J Pain. 2017;21:466–73.

42. Urits I, Shen AH, Jones MR, Viswanath O, Kaye AD. Complex regional pain syndrome, current concepts and treatment options. Curr Pain Headache Rep. 2018;22:10.
43. van Eijs F, Stanton-Hicks M, Van Zundert J, Faber CG, Lubenow TR, Mekhail N, van Kleef M, Huygen F. Evidence-based interventional pain medicine according to clinical diagnoses. 16. Complex regional pain syndrome. Pain Pract. 2011;11(1):70–87.
44. Harden RN, Bruehl S, Perez RS. Development of a severity score for CRPS. Pain. 2010;151:870–6.
45. Giannotti S, Bottai V, Dell'Osso G, Bugelli G, Celli F, Cazzella N, Guido G. Algodystrophy: complex regional pain syndrome and incomplete forms. Clin Cases Miner Bone Metab. 2016;13(1):11–4.
46. Wasner G, Schattschneider J, Heckmann K, Maier C, Baron R. Vascular abnormalities in reflex sympathetic dystrophy (CRPS I): mechanisms and diagnostic value. Brain. 2001;124(Pt 3):587–99.
47. Harden RN, Maihofner C, Abousaad E. A prospective, multisite, international validation of the complex regional pain syndrome severity score. Pain. 2017;158:1430–6.
48. Jeon SG, Choi EJ, Lee PB. Do severity score and skin temperature asymmetry correlate with the subjective pain score in the patients with complex regional pain syndrome? Korean J Pain. 2014;27:339–44.
49. Korompilias AV, Karantanas AH, Lykissas MG, Beris AE. Bone marrow edema syndrome. Skelet Radiol. 2009;38(5):425–36.
50. Wertli MM, Brunner F, Steurer J, Held U. Usefulness of bone scintigraphy for the diagnosis of complex regional pain syndrome 1: a systematic review and Bayesian meta-analysis. PLoS One. 2017;12(3):e0173688.
51. Ringer R, Wertli M, Bachmann LM, Buck FM, Brunner F. Concordance of qualitative bone scintigraphy results with presence of clinical complex regional pain syndrome 1: meta-analysis of test accuracy studies. Eur J Pain. 2012;16:1347–56.
52. Munts AG, Van Rootselaar AF, Van Der Meer JN, Koelman JH, Van Hilten JJ, Tijssen MA. Clinical and neurophysiological characterization of myoclonus in complex regional pain syndrome. Mov Disord. 2008;23:581–7.
53. Vas L, Pai R. Musculoskeletal ultrasonography to distinguish muscle changes in complex regional pain syndrome type 1 from those of neuropathic pain: an observational study. Pain Pract. 2016;16:E1–3.
54. Cuhadar U, Gentry C, Vastani N, Sensi S, Bevan S, Goebel A, Andersson DA. Autoantibodies produce pain in complex regional pain syndrome by sensitizing nociceptors. Pain. 2019;160(12):2855–65.
55. Dirckx M, Schreurs MWJ, de Mos M, Stronks DL, Huygen FJPM. The prevalence of autoantibodies in complex regional pain syndrome type I. Mediat Inflamm. 2015;2015:718201.
56. Harden RN, Oaklander AL, Burton AW. Complex regional pain syndrome: practical diagnostic and treatment guidelines, 4th edition. Pain Med. 2013;14:180–229.
57. Smart KM, Wand BM, O'Connell NE. Physiotherapy for pain and disability in adults with complex regional pain syndrome (CRPS) types I and II. Cochrane Database Syst Rev. 2016;2:CD010853.
58. Somers DL, Clemente FR. Transcutaneous electrical nerve stimulation for the management of neuropathic pain: the effects of frequency and electrode position on prevention of allodynia in a rat model of complex regional pain syndrome type II. Phys Ther. 2006;86(5):698–709.
59. Jensen MP, Caroline Grierson RN, Tracy-Smitm V, Bacigalupi SC, Othmer S. Neurofeedback treatment for pain associated with complex regional pain syndrome type I. J Neurother. 2008;8:45–53.
60. Clinical practice guidelines–third edition. International Research Foundation for RSD/CRPS. www.rsdfoundation.org/en/en_ clinical_practice_guidelines.html. Accessed 1 Apr 2009.
61. Breuer AJ, Mainka T, Hansel N, Maier C, Krumova EK. Short-term treatment with parecoxib for complex regional pain syndrome: a randomized, placebo-controlled double-blind trial. Pain Physician. 2014;17:127–37.

62. Eckmann MS, Ramamurthy S, Griffin JG. Intravenous regional ketorolac and lidocaine in the treatment of complex regional pain syndrome of the lower extremity: a randomized, double-blinded, crossover study. Clin J Pain. 2011;27:203–6.
63. Collins SL, Moore RA, McQuay H, et al. Antidepressants and anticonvulsants for diabetic neuropathy and postherpetic neuralgia: a quantitative systematic review. J Pain Symptom Manag. 2000;20:449–58.
64. Dworkin RH, O'Connor AB, Backonja M, et al. Pharmacologic management of neuropathic pain: evidence-based recommendations. Pain. 2007;132:237–51.
65. Brown S, Johnston B, Amaria K. A randomized controlled trial of amitriptyline versus gabapentin for complex regional pain syndrome type I and neuropathic pain in children. Scand J Pain. 2016;13:156–63.
66. Harke H, Gretenkort P, Ladleif HU, Rahman S, Harke O. The response of neuropathic pain and pain in complex regional pain syndrome I to carbamazepine and sustained-release morphine in patients pretreated with spinal cord stimulation: a double-blinded randomized study. Anesth Analg. 2001;92:488–95.
67. Varenna M, Adami S, Sinigaglia L. Bisphosphonates in complex regional pain syndrome type I: how do they work? Clin Exp Rheumatol. 2014;32:451–4.
68. Chevreau M, Romand X, Gaudin P, Juvin R, Baillet A. Bisphosphonates for treatment of complex regional pain syndrome type 1: a systematic literature review and meta-analysis of randomized controlled trials versus placebo. Joint Bone Spine. 2017;84:393–9.
69. Varenna M, Braga V, Gatti D, et al. Intramuscular neridronate for the treatment of complex regional pain syndrome type 1: a randomized, double-blind, placebo-controlled study. Ther Adv Musculoskelet Dis. 2021;13:1759720X211014020.
70. Kiefer RT, Rohr P, Ploppa A, et al. Efficacy of ketamine in anesthetic dosage for the treatment of refractory complex regional pain syndrome: an open-label phase II study. Pain Med. 2008;9:1173–201.
71. Perez R, Kwakkel G, Zuurmond W, et al. Treatment of reflex sympathetic dystrophy (CPRS type I): a research synthesis of 21 randomized clinical trials. J Pain Symptom Manage. 2001;21:511–26.
72. Zuurmond WW, Langendijk PN, Bezemer PD, et al. Treatment of acute reflex sympathetic dystrophy with DMSO 50% in a fatty cream. Acta Anaesthesiol Scand. 1996;40:364–7.
73. Zollinger PE, Tuinebreijer WE, Kreis RW, Breederveld RS. Effect of vitamin C on frequency of reflex sympathetic dystrophy in wrist fractures: a randomised trial. Lancet. 1999;354:2025–8.
74. Besse JL, Gadeyne S, Galand-Desme S, Lerat JL, Moyen B. Effect of vitamin C on prevention of complex regional pain syndrome type I in foot and ankle surgery. Foot Ankle Surg. 2009;15:179–82.
75. Lichtman DM, Bindra RR, Boyer MI. American Academy of Orthopaedic Surgeons clinical practice guideline on: the treatment of distal radius fractures. J Bone Jt Surg Am. 2011;93:775–8.
76. Te AE. A modern rationale for the use of phenoxybenzamine in urinary tract disorders and other conditions. Clin Ther. 2002;24:851–61.
77. Muizelaar JP, Kleyer M, Hertogs IA, DeLange DC. Complex regional pain syndrome (reflex sympathetic dystrophy and causalgia): management with the calcium channel blocker nifedipine and/or the alpha-sympathetic blocker phenoxybenzamine in 59 patients. Clin Neurol Neurosurg. 1997;99:26–30.
78. Raja SN, Turnquist JL, Meleka S, Campbell JN. Monitoring adequacy of alpha-adrenoceptor blockade following systemic phentolamine administration. Pain. 1996;64:197–204.
79. Davis KD, Treede RD, Raja SN, et al. Topical application of clonidine relieves hyperalgesia in patients with sympathetically maintained pain. Pain. 1991;47:309–17.
80. Stevens DS, Robins VF, Price HM. Treatment of sympathetically maintained pain with terazosin. Reg Anesth. 1993;18:318–21.

81. Prough DS, McLeskey CH, Poehling GG, et al. Efficacy of oral nifedipine in the treatment of reflex sympathetic dystrophy. Anesthesiology. 1985;62:796–9.
82. Inchiosa MA, Kizelshteyn G. Treatment of complex regional pain syndrome type 1 with oral phenoxybenzamine: rationale and case reports. Pain Pract. 2008;8:125–32.
83. Raja SN, Treede RD, Davis KD, et al. Systemic alpha-adrenergic blockage with phentolamine: a diagnostic test for sympathetically maintained pain. Anesthesiology. 1991;74:691–8.
84. Mackey S, Feinberg S. Pharmacologic therapies for complex regional pain syndrome. Curr Pain Headache Rep. 2007;11(1):38–43.
85. Mao J, Chen LL. Systemic lidocaine for neuropathic pain relief. Pain. 2000;87:7–17.
86. Attal N, Brasseur L, Chauvin M, et al. Effects of single and repeated applications of a eutectic mixture of local anaesthetics (EMLA) cream on spontaneous and evoked pain in postherpetic neuralgia. Pain. 1999;81:203–9.
87. Taskaynatan MA, Ozgul A, Tan AK, Dincer K, Kalyon TA. Bier block with methylprednisolone and lidocaine in CRPS type I: a randomized, double-blinded, placebo-controlled study. Reg Anesth Pain Med. 2004;29(5):408–12.
88. Dellemijn P. Are opioids effective in relieving neuropathic pain? Pain. 1999;80:453–62.
89. Watson CP, Babul N. Efficacy of oxycodone in neuropathic pain: a randomized trial in postherpetic neuralgia. Neurology. 1998;50:1837–41.
90. Tajerian M, Hung V, Khan H, et al. Identification of KRT16 as a target of an autoantibody response in complex regional pain syndrome. Exp Neurol. 2017;287:14–20.
91. Asher C, Furnish T. Lenalidomide and thalidomide in the treatment of chronic pain. Expert Opin Drug Saf. 2013;12(3):367–74.
92. FDA grants Orphan Drug status to Soin Therapeutics for low dose naltrexone (LDN) to treat complex regional pain syndrome (CRPS). News release. September 9, 2021.
93. Taylor SS, Noor N, Urits I, et al. Complex regional pain syndrome: a comprehensive review. Pain Ther. Published online June 24, 2021.
94. Goebel A, Baranowski A, Maurer K, Ambler G. Intravenous immunoglobulin treatment of the complex regional pain syndrome: a randomized trial. Ann Intern Med. 2010;3:152–8.
95. Hopes dwindle for new CRPS treatment. BLB Chronic Pain Solicitors Dec 21st, 2016. https://www.blbchronicpain.co.uk/news/hopes-dwindle-for-new-crps-treatment/.
96. Aradillas E, Schwartzman RJ, Grothusen JR, Goebel A, Alexander GM. Plasma exchange therapy in patients with complex regional pain syndrome. Pain Physician. 2015;18:383–94.
97. Ranoux D, Attal N, Morain F, Bouhassira D. Botulinum toxin type a induces direct analgesic effects in chronic neuropathic pain. Ann Neurol. 2008;64:274–83.
98. Ian Carroll J, Clark D, Mackey S. Sympathetic block with botulinum toxin to treat complex regional pain syndrome. Ann Neurol. 2009;65(3):348–51.
99. Hauser RA, Debra K, Brinker RN. The theoretical basis for and treatment of complex regional pain syndrome with prolotherapy. J Prolother. 2010;2(2):356–70.
100. Thor JA, Hanapi NHM, Halil H, Suhaimi A. Perineural injection therapy in the management of complex regional pain syndrome: a sweet solution to pain. Pain Med. 2017;18(10):2041–5.
101. Schwartz RG. Stem cells for the treatment of complex regional pain syndrome (CRPS)/reflex sympathetic dystrophy (RSD): a case study. Pan Am J Med Thermol. 2014;1(2):89–92.
102. O'Connell NE, Wand BM, Gibson W, Carr DB, Birklein F, Stanton TR. Local anaesthetic sympathetic blockade for complex regional pain syndrome. Cochrane Database Syst Rev. 2016;7(7):CD004598.
103. Moon JY, Choi JK, Shin JY, Chon SW, Dev S. A brief report on a technical description of ultrasound-guided lumbar sympathetic block. Korean J Pain. 2017;30(1):66–70.
104. Kim J, Lee HJ, Lee YJ, Lee CS, Yoo Y, Moon JY. Ultrasound-guided thoracic paravertebral block as a sympathetic blockade for upper extremity neuropathic pain: a prospective pilot study. J Pain Res. 2020;13:3395–403.
105. Martin DP, Bhalla T, Rehman S, Tobias JD. Successive multisite peripheral nerve catheters for treatment of complex regional pain syndrome type I. Pediatrics. 2013;131(1):e323–6.

106. Margic K, Pirc J. The treatment of complex regional pain syndrome (CRPS) involving upper extremity with continuous sensory analgesia. Eur J Pain. 2003;7(1):43–7.
107. Dadure C, Motais F, Ricard C, Raux O, Troncin R, Capdevila X. Continuous peripheral nerve blocks at home for treatment of recurrent complex regional pain syndrome I in children. Anesthesiology. 2005;102(2):387–91.
108. Goebel A, Lewis S, Phillip R, Sharma M. Dorsal root ganglion stimulation for complex regional pain syndrome (CRPS) recurrence after amputation for CRPS, and failure of conventional spinal cord stimulation. Pain Pract. 2018;18(1):104–8.
109. Gharaei H. Continuous peripheral nerve catheters in pediatric complex regional pain syndrome. Anesth Pain Med. 2015;5(1):e23414.
110. Fritz AV, Ferreira-Dos-Santos G, Hurdle M, et al. Ultrasound-guided percutaneous peripheral nerve stimulation for the treatment of complex regional pain syndrome type 1 following a crush injury to the fifth digit: a rare case report. Cureus. 2019;11(12):e6506.
111. Chmiela MA, Hendrickson M, Hale J, Liang C, Telefus P, Sagir A, Stanton-Hicks M. Direct peripheral nerve stimulation for the treatment of complex regional pain syndrome: a 30-year review. Neuromodulation. 2021;24(6):971–82.
112. Herschkowitz D, Kubias J. Wireless peripheral nerve stimulation for complex regional pain syndrome type I of the upper extremity: a case illustration introducing a novel technology. Scand J Pain. 2018;18(3):555–60.
113. Frederico TN, Freitas TS. Peripheral nerve stimulation of the brachial plexus for chronic refractory CRPS pain of the upper limb: description of a new technique and case series. Pain Med. 2020;21(1):S18–26.
114. Farrell SM, Green A, Aziz T. The current state of deep brain stimulation for chronic pain and its context in other forms of neuromodulation. Brain Sci. 2018;8(8):158.
115. Huygen F, Kallewaard JW, Tulder MV, Boxem KV, Vissers K, van Kleef M, Van Zundert J. “Evidence-based interventional pain medicine according to clinical diagnoses”: update 2019. Pain Pract. 2019;19(6):664–75.