Curr Pain Headache Rep (2012) 16:139–146
DOI 10.1007/s11916-012-0253-3

PSYCHIATRIC MANAGEMENT OF PAIN (MR CLARK, SECTION EDITOR)

Chronic Regional Pain Syndrome: What Specialized Rehabilitation Services Do Patients Require?

I. Elias Veizi · Thomas C. Chelimsky · Jeffrey W. Janata

Published online: 15 March 2012

Abstract Chronic regional pain syndrome (CRPS) is a complex disorder, the optimal treatment of which requires an interdisciplinary approach encompassing medical, interventional, psychological, and rehabilitation services that emphasize the role of physical and occupational therapies. The central focus of treatment is the restoration of function, utilizing a systematic, coordinated, and progressive set of therapeutic strategies. The poorly delineated pathophysiology and variable course of CRPS suggest that individualized strategies are required for optimal management, but also mean that carefully controlled trials of physiotherapy are difficult to conduct. This article presents a brief review of the nature and pathophysiology of CRPS, the medical and psychological approaches that have been found to be effective, and a review of the current trends in rehabilitation.

Keywords Chronic regional pain syndrome · CRPS · Rehabilitation · Physical therapy · Physiotherapy · Interdisciplinary management

I. E. Veizi · J. W. Janata (✉)
Departments of Psychiatry and Anesthesiology, University Hospitals Case Medical Center,
11100 Euclid Avenue,
Cleveland, OH 44106, USA
e-mail: jeffrey.janata@case.edu

T. C. Chelimsky
Department of Neurology, Medical College of Wisconsin,
9200 West Wisconsin Avenue,
Milwaukee, WI 53226, USA

Introduction

Complex Regional Pain Syndrome History and Nomenclature

Complex regional pain syndrome (CRPS) is the newer nomenclature encompassing the clinical entities of reflex sympathetic dystrophy (RSD) and causalgia [1]. CRPS is characterized by intractable pain usually affecting one or more extremities. Even though it was originally described over 100 years ago, debate lingers over the clinical and basic pathophysiological characteristics of this condition. Named causalgia (from Greek, *kausos* [heat], *algos* [pain]), it was initially described in 1864 during the American Civil War by Silas Weir Mitchell based on medical observation of soldiers who developed chronic pain following traumatic nerve injuries [2]. Since its original description, it has variously been labeled algodystrophy, posttraumatic dystrophy, sympathetic-maintained pain syndrome, hand–shoulder syndrome, and Sudeck atrophy. Early in the 20th century, Paul Sudeck described a syndrome with predominantly trophic symptoms that developed following distal bone fractures not directly affecting peripheral nerves [3]. Patients experienced significant pain relief by sympathetic block, thus suggesting the central role of the autonomic nervous system in the pathophysiology of the condition and the term reflex sympathetic dystrophy (RSD), coined by Evans in 1946, was adopted to label syndromes characterized by persistent and extreme chronic pain following injury, responsive to sympathetic blocks, and, as such, implicating the role of the sympathetic system [4]. As understanding of the condition evolved, it was clear that sympathetically maintained pain

was not specific to RSD but common in other neuropathic pain disorders as well. In addition, dystrophic changes were not always observed, and there was no evidence that the condition was reflexive.

As such, a working group of the International Association for the Study of Pain (IASP) developed a consensus definition in 1994 and proposed a new terminology reflecting a more accurate description of the condition. The term CRPS type I replaces RSD; and the term CRPS type II, which requires demonstrable peripheral nerve injury, replaces the term causalgia [1]. Various diagnostic tests have been proposed (without much success) to confirm the diagnosis of CRPS, including, among others, radiological studies, triple-phase bone scans, quantitative sensory testing, quantitative sudomotor axon reflex test (QSART), and limb thermography with or without sympathetic block. Thus, the diagnosis of CRPS remains a clinical process relying mostly on history and physical examination. The current IASP diagnostic criteria define CRPS type I as a syndrome that usually develops following a trauma, fracture, surgery, or immobilization, with pain that is disproportionate to the inciting event in a regional/nondermatome pattern; that is, the pain is not limited to the distribution of a single peripheral nerve or nerve root. CRPS II requires the same set of descriptive criteria; however, an identifiable nerve injury is required for diagnosis. Although these diagnostic criteria had a high sensitivity (98%), their specificity was poor (36%); resulting in a correct diagnosis in as few as 40% of patients [5]. The lack of an objective test that serves as a gold standard for diagnosis has led to extensive efforts to validate a set of bedside diagnostic criteria to improve the accuracy of CRPS diagnosis. The diagnostic criteria do not implicate a particular pathogenesis of the disease, but rather supply a set of descriptive signs and symptoms that demonstrate adequate sensitivity and specificity [6].

Patient Demographics and Risk Factors

There are only two population-based epidemiological studies of CRPS in the general population. One reported the population-based incidence rate in North America [8] and the other in Europe [9], with differing estimates of incidence. The North America study reported an incidence of 5.6 per 100,000 person-years, while the more recent European study reported a rate of 26.2. The inclusion criteria for the studies differed, which could be one of the factors accounting for the discrepancy. CRPS affects females more than males, at a ratio almost 4:1 [10], and most CRPS cases in females occur in the postmenopausal stage of life. Mean patient age at diagnosis is 52.7 years [8, 9, 11], higher than generally expected based on clinical samples [12]. Before the mid-1980s there were only scattered case reports of RSD in children. However, over the past 10 to 15 years, it has become apparent that CRPS does occur in children, with a mean age of onset of about 12.5 years [13], particularly following sports injuries.

No single causal factor has been identified in the development of this complex disorder, but an inciting event frequently precedes the onset of CRPS. Initial observations correlated CRPS with wounds and crushing limb injuries. Fractures are the most common trigger, wrist fractures in particular [14], and cast immobilization also appears to be associated [15], with increased pressure and early complaints of tightness as predictive risk factors. On the other hand, CRPS has also been known to develop as a consequence of nonperipheral processes such as stroke [16], spinal cord injury, and myocardial infarction [17]. The risk for developing CRPS may depend on susceptibility to an amplified response to a triggering event by fundamental pain-related mechanisms such as inflammation and sensitization. This theory has led to a search for gene polymorphisms that could predict development of CRPS. For example, Herlyn and colleagues [18] identified a single nucleotide polymorphism within the α-adrenoceptor that appears to be a risk factor for the development of CRPS I after distal radius fracture. Polymorphisms in the human leukocyte antigen (HLA) system have been studied, and loci from all three HLA classes reportedly have been associated with CRPS onset [19]. Studies on the co-occurrence of CRPS with disorders such as migraine, osteoporosis, menstrual dysregulation, and neuropathies [20, 21] provide clues to potential common etiologic factors.

Pathophysiology

The pathophysiology of CRPS is not fully understood; however, based on animal and human studies, several hypothesized mechanisms appear to play an important role. In the acute (early) stage, as described by Veldman and associates [12], CRPS presents with skin discoloration, edema, increased nail or hair growth, temperature difference, limited movement, or reported sweating. Traditional sequential staging of CRPS into acute inflammatory, subacute dystrophic, and chronic atrophic stages has been largely supplanted by classifying the condition based on limb appearance and warmth. Thus, CRPS has been more recently subdivided into a "warm and a cold form" [12, 22]. The difference in temperature between affected and unaffected extremities has led to the diagnostic use of thermography, albeit with low specificity for either diagnosis or prognosis [23, 24]. Symptoms such as edema, trophic changes, sweating, and vasomotor-related changes are signs of autonomic system dysregulation, and pain that responds favorably to sympathetic blocks is thought to be sympathetically

maintained. However, the role of the sympathetic system in CRPS has been debated because the vasomotor instability can be explained by other mechanisms [25–27] such as abnormal sensitivity of adrenergic receptors to normal sympathetic outflow [28]. Moreover, α-adrenoceptors appear to be overexpressed in hyperalgesic skin from CRPS-affected limbs [29]. The reverse hypothesis of diminished sympathetic stimulation has been postulated as an underlying cause of adrenergic receptor upregulation and sensitization in CRPS patients [30]. A generally acknowledged view today is that sympathetic dysregulation is a significant but not obligatory component of CRPS.

Aseptic neuroinflammation may be an early mechanism in the acute stage of CRPS [31]. Trauma-related events are posited to activate and sensitize primary neuronal afferents to cytokines and neuropeptides released in the affected body region, mainly substance P and calcitonin gene–related peptide (CGRP) [31]. Evidence of a neuroinflammatory process is also obtained from analysis of cytokines in fluid derived from artificially produced blisters on CRPS-affected extremities revealing a strong proinflammatory expression profile [32, 33]. However, there is a lack of correlation between cytokine expression and severity and duration of CRPS, suggesting that neuroinflammation is only partly involved in the pathophysiology of CRPS [34].

Pain and hyperalgesia are the predominant symptoms in CRPS. Persistent peripheral nociceptive input in CRPS results in spinal cord central sensitization with features of mechanical hyperalgesia and allodynia [35, 36]. A hallmark of central sensitization is spreading of hyperalgesia, which goes far beyond the initial site of injury. This expansion of nociceptive receptive fields occurs as a result of neuroplasticity changes in the central nervous system (CNS) between the dorsal horn (DH) of the spinal cord and the somatosensory cortex. At the spinal level, DH central pain-projecting neurons are pathologically activated by *N*-methyl-D-aspartate (NMDA) receptor–mediated processes, which leads to hyperexcitability and central sensitization [37]. Furthermore, changes in central representation of somatosensory input in the thalamus and cortex have been found [38, 39]. This cortical reorganization correlates linearly with the amount of CRPS pain and is reversed following pain relief as confirmed by magnetoencephalography (MEG) studies [39].

Recently, the hypothesis of progressive small-fiber degeneration as the basis for CRPS has gained some ground. This has primarily resulted from the work of Oaklander and Fields [40]. Oaklander and colleagues [41] demonstrated for the first time, through a morphometric analysis performed on skin biopsies, that CRPS I is associated with small-fiber axonal degeneration.

Because CRPS is a heterogeneous disorder, multiple mechanisms, including inflammatory and neuropathic, are likely involved in complex interactions, resulting in this chronic painful and potentially debilitating disorder.

Interdisciplinary Management of Complex Regional Pain Syndrome

Medical Approaches

Treatment approaches for CRPS can be categorized as pharmacological, interventional, psychological, and rehabilitative. Restoration of function is the primary goal of interdisciplinary treatment and, as such, physical (PT) and occupational therapies (OT) are emphasized in the management of CRPS. However, physical activity of any kind is often limited by the pain itself, and pain-control interventions can be employed to enable full patient participation in the rehabilitative activity [42, 43]. Interventional approaches can be very useful, particularly when used to relieve pain enough to enhance patient compliance with PT. Sympathetic blocks, intravenous regional blocks, and epidural blocks can be useful in limiting pain to permit greater levels of activity. However, response to sympathetic blocks is inconsistent and may only be more effective than placebo in the duration but not in the magnitude of pain relief [44]. In general, pharmacological pain treatment rests on the same strategies used in the management of neuropathic pain and can include antidepressants (particularly tricyclics and serotonin–noradrenalin reuptake inhibitors), antiepileptics (e.g., gabapentin), and, less frequently, antispasmodics and topical analgesics [36]. Opioids may have a limited role in treating refractory CRPS, but generally only as a short-term strategy to allow aggressive physical activation. Steroids, given their anti-inflammatory action, may be effective, especially early in treatment [45]. Antioxidants and free radical scavengers may have a role given that hypoxic phenomena in the affected limb can enhance the production of free radicals. Finally, bisphosphonates have shown promise in randomized clinical trials [46, 47] and may alleviate pain by acting on nociceptive primary afferents in bone.

Surgical Approaches

A proportion of CRPS patients have “sympathetically maintained pain,” characterized as pain maintained by sympathetic efferent innervation, the mechanism of which has prompted attempts to destroy sympathetic nervous system pathways surgically or chemically. Minimally invasive radiofrequency ablation results only in occasional temporary relief because regeneration of the sympathetic chain does occur. Surgical dissection performed openly (historically) or laparoscopically (more recently) has not resulted in improved outcomes and is accompanied by unacceptable risk.

Reviews of the available evidence suggest that the practice of sympathectomy (both surgical and chemical) for CRPS is based on quite minimal quality evidence [48].

Psychological Approaches

Psychological treatment in CRPS typically emphasizes the use of cognitive-behavioral therapy (CBT) based on demonstrated efficacy in the management of chronic pain in general [36] and the role of psychological processes in the development of CRPS in particular [5]. CBT treatment emphasizes the development of pain coping strategies, particularly derived from helping the patient realize that CRPS pain accompanying physical activity does not signify tissue damage. Patients frequently experience pain catastrophization, which serves to impede rehabilitative progress; CBT helps systematically reconceptualize these exaggerated cognitions as the benign accompaniments to increases in activity levels. Reactivation of the affected extremity and reduced avoidance of feared activity in turn helps prevent gradually increasing dysfunction and facilitates improved function. Comorbid psychopathology, especially depression (which is frequently consequential of chronic pain [49]) and generalized anxiety (which can serve to increase physiologic arousal and contribute to the severity of pain), are effectively treated with CBT [50], particularly with relaxation training and cognitive coping strategies. Ultimately, CBT emphasizes the active role that the patient must play in ameliorating CRPS pain when learned pain avoidance serves to seduce patients into the gradual assumption of a passive role in their treatment and encourages them to await a cure.

Additionally, though, psychological interventions also may have a direct effect on the pathophysiologic mechanisms that accompany CRPS. For example, catecholamine-mediated nociceptor activation can contribute to central nervous system sensitization through persistent nociceptive input. This central sensitization may contribute to increased pain via the hyperalgesia and allodynia associated with CRPS. Psychological strategies, which address negative affect and stress and thus reduce the release of catecholamines, may presumably directly influence the pathophysiologic substrate of CRPS [25].

Rehabilitation Strategies

Physiotherapy is widely advocated as the essential strategy in the treatment of CRPS and is used in the context of the aforementioned interdisciplinary treatment paradigms with medical, interventional, and behavioral components. Rigorous controlled trials of rehabilitative strategies are lacking, hampered by the variability in presentation and course of CRPS, but expert consensus suggests that PT is the central strategy in CRPS treatment [5], designed to guide the patient systematically through the process of resumption of function. Treatment content is flexible and utilizes strategies appropriate to patient status, complexity, and rate of progress. Research is hampered by inconsistent application of diagnostic criteria, heterogeneity of the syndrome presentation, late diagnosis, and lack of standardization of control treatments presenting a barrier in evaluating the evidence for PT outcomes. Furthermore, the scope, complexity, and application of practice are variable.

Rehabilitative strategies, applied sequentially both by physical and occupational therapists include education, emphasizing helping patients recognize the role of avoidance of activity in maintaining fear of pain; reflecting the fear-avoidance model of pain; graded exposure in vivo to activity, movements, and light touch [51]; sensorimotor treatment with pain adapted exercises and desensitization activities [52]; exercise with stretching and active range of motion [53]; water therapy [54]; and stress loading [55]. Mirror visual feedback involves using a mirror placed between the affected and unaffected limb, obscuring the affected limb, and exercises are performed while the participant looks at the image of the unaffected limb [56]. Graded motor imagery is a motor imagery program (MIP) where the patient recognizes the laterality of a photograph of a hand or foot, followed by imagining moving their painful limb into the position in the photograph, progressing to mirror feedback [57–59]. Pain management techniques include improving pain control, optimizing coping, relaxation, connective tissue massage, and developing compensatory skills [43]. Additionally, transcutaneous electrical nerve stimulation has been employed with success [60], as has electromagnetic field treatment [53].

Oerlemans and colleagues [61] compared PT to OT in patients with CRPS I. They enrolled 135 patients with recent diagnosis of CRPS I of the upper extremity in a prospective randomized clinical trial. These patients were not previously treated by sympathectomy. Outcomes selected included pain assessment (visual analogue scale and McGill questionnaire) as well as changes in active range of motion (AROM; measured relative to contralateral side). Patients were assigned randomly to PT, OT, or to a control group. Outcomes were assessed at baseline, 6 weeks, and 3, 6, and 12 months. The authors found out that PT is superior to OT and control in improving pain, particularly at 12 months. PT and OT (to a lesser degree) resulted in better functional outcome compared to control as assessed by changes in AROM. They concluded that PT and OT are helpful in reducing pain and improving function in patients with unilateral CRPS I of the upper extremity of less than 1 year duration.

Subsequently, Oerlemans et al. [62] calculated impairment rating in all three groups 1 year after inclusion in the

study. The impairment rating was performed according to the American Medical Association's Guides to the Evaluation of Permanent Impairment and included AROM, two-point discrimination, and grip strength. No significant differences were found between the three groups. These authors then followed up [63] with an analysis of the same data but with an emphasis on impairment level sum-scores (ISS) over 1 year. A difference of five ISS points was considered clinically significant. They concluded that both PT and OT resulted in rapid improvement of disability level compared to the control group; however, no differences were observed on level of handicap. Furthermore, they found that PT was more cost effective than OT.

The optimal frequency of PT sessions was examined by Lee et al. [7]. The authors recruited 28 children, aged 8 to 17 years, suffering from lower extremity CRPS, who had not received sympathetic blocks or more than two sessions of physiotherapy. CBT (relaxation training, deep breathing exercises, biofeedback, and guided imagery) was provided to all patients, who were randomly assigned to receive PT at a frequency of one or three times a week for 6 weeks. The PT program was individualized and included transcutaneous electrical nerve stimulation, progressive weight bearing, tactile desensitization, massage, and contrast baths. At short-term (6 weeks to 3 months after treatment) and long-term follow-ups (6 to 12 months after treatment), no inter-group differences were noted in terms of outcomes related to pain and function. Furthermore, a phone interview conducted at a mean of 133 weeks post-treatment revealed no difference between groups in pain, function (ambulation), CRPS recurrence, activity level (participation in exercise), and school attendance.

Moseley [57] recruited 13 patients who developed CRPS after a wrist fracture and randomly assigned them to a motor imagery program (MIP) or to continuation of their ongoing (conventional) treatment. The MIP incorporated recognition of hand laterality (patients were presented with pictures of right and left hands and asked to identify the correct side), imagined hand movement (patients were presented pictures of a hand in different positions and asked to imagine moving their own hand to adopt the posture shown), as well as mirror movements (patients placed both hands into a box with a mirror separating the two compartments and, while moving both hands, were asked to watch the reflection of the unaffected hand in the mirror). Each stage lasted 2 weeks, and patients were required to perform the tasks hourly from 8 am to 8 pm. No restrictions were placed on the conventional treatment. Patients in the MIP group reported significantly less pain and decreased swelling 6 and 12 weeks after the completion of treatment. The beneficial effects of treatment were replicated when the controls crossed over to the MIP group.

In a follow-up study, Moseley et al. [19] randomly assigned 20 patients to receive MIP in three different application sequences of recognition of laterality (Rec), imagined movements (Im), and mirror movements (Mir). At 12 weeks, the author found that the RecImMir sequence provided a significantly greater decrease in pain and an increase in functionality compared with the other two groups.

Ek and colleagues [64•] examined whether treatment of longstanding CRPS type 1, focusing only on functional improvement while neglecting pain, results in clinical improvement of this syndrome. This prospective case series evaluated 106 patients in an outpatient rehabilitation clinic. Physical therapy of the affected limb focused exclusively on functional improvement while treating therapists did not allow report of pain to factor into treatment decisions. Normal use of the limb between the treatments was encouraged despite pain. A maximum of five of these sessions were performed in 3 months. Outcomes measured included monitoring functional improvement in the arms, as well as walking speed and distance. They found that the function in the affected arm or leg was significantly improved. Full functional recovery was experienced in 49 (46%) patients, with pain reduction in 75 (71%). Full function was recovered in 23 patients (22%), despite an increase in pain, and only 4 patients dropped out of the due to increased pain. The authors concluded that "pain exposure physical therapy" is effective and safe for patients who are unresponsive to accepted standard therapies. Avoiding the use of a limb due to pain will result in loss of function, while forced use restores function and allows patients to regain control with a reduction of pain in most cases.

The concept of whether pain exposure physical therapy (PEPT), consisting of a progressive-loading exercise program and management of pain-avoidance behavior, could be applied safely was examined by van de Meent and colleagues [65]. In their study, 20 patients with CRPS type 1 were enrolled. The diagnosis of CRPS type 1 was defined using the Bruehl and Harden/IASP diagnostic criteria and the diagnosis had been made between 3 and 18 months after the inciting event (trauma). Using a multiple single-case design (baseline [A1], treatment [B], follow-up [A2]), multiple baseline and follow-up measurements evaluated changes in CRPS signs and symptoms and assessed functional parameters. When comparing the baseline with the follow-up phase, patients improved significantly with respect to pain (57% improvement), pain intensity (48%), muscle strength (52%), arm/shoulder/hand disability (36%), 10-m walking speed (29%), pain disability index (60%), kinesiophobia (18%), and the domains of perceived health change in the Short Form-36 survey (269%). Three patients initially showed increased vegetative signs but improved in all other CRPS parameters and showed good functional recovery at follow-up. The authors concluded that a progressive-loading exercise program and management of

pain-avoidance behavior without the use of specific medication (pain exposure physical therapy) is safe and effective for patients with CRPS.

Conclusions

Caution should be exercised when interpreting the limited data available on CRPS in the rehabilitation literature. The complexities of diagnosis, pathophysiology, and variable progression of the syndrome make firm conclusions difficult. The physiotherapy strategies employed in these studies require continued elucidation through well-designed and meticulously conducted randomized controlled trials. Future trials would benefit from the use of uniform diagnostic criteria for CRPS, and blinded assessment ideally would be employed. Furthermore, the duration of CRPS before enrollment and the length of follow-up need to be rigorously controlled. Study endpoints should include pain relief, reversal of trophic changes, and, particularly, measures of improvement of function. Finally, most research has focused on individual therapeutic modalities employed in the context of interdisciplinary treatment whose specific contributions are difficult to quantify.

These limitations notwithstanding, the clear direction of the available evidence and the consensus opinions of expert panels reinforce the strategic importance of a central role for physical and occupational therapies in the amelioration of CRPS symptoms and the resumption of patient function. Recent strategies, such as pain exposure physical therapy, employ physical therapy approaches in psychologically informed ways and show promise in enhancing patient function as well as demonstrating the effectiveness of interdisciplinary collaboration.

Disclosures No potential conflicts of interest relevant to this article were reported.

References

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

- Of Importance

1. Stanton-Hicks M, Baron R, Boas R, Gordh T, Harden N, Hendler N, Koltzenburg M, Raj P, Wilder R. Complex Regional Pain Syndromes: guidelines for therapy. Clin J Pain. 1998;14(2):155–66.
2. Oerlemans HM, Oostendorp RA, de Boo T, Goris RJ. Evaluation of three methods to rate impairment in patients with complex regional pain syndrome I of one upper extremity. Clin Rehabil. 2000;14(3):331–9.
3. Kemler MA, Schouten HJ, Gracely RH. Diagnosing sensory abnormalities with either normal values or values from contralateral skin: comparison of two approaches in complex regional pain syndrome I. Anesthesiology. 2000;93(3):718–27.
4. Kemler MA, Barendse GA, van Kleef M, Egbrink MG. Pain relief in complex regional pain syndrome due to spinal cord stimulation does not depend on vasodilation. Anesthesiology. 2000;92(6):1653–60.
5. Stanton-Hicks MD, Burton AW, Bruehl SP, Carr DB, Harden RN, Hassenbusch SJ, Lubenow TR, Oakley JC, Racz GB, Raj PP, et al. An updated interdisciplinary clinical pathway for CRPS: report of an expert panel. Pain Pract. 2002;2(1):1–16.
6. 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(1–2):119–24.
7. Lee BH, Scharff L, Sethna NF, McCarthy CF, Scott-Sutherland J, Shea AM, Sullivan P, Meier P, Zurakowski D, Masek BJ, et al. Physical therapy and cognitive-behavioral treatment for complex regional pain syndromes. J Pediatr. 2002;141(1):135–40.
8. Harden RN, Rudin NJ, Bruehl S, Kee W, Parikh DK, Kooch J, Duc T, Gracely RH. Increased systemic catecholamines in complex regional pain syndrome and relationship to psychological factors: a pilot study. Anesth Analg. 2004;99(5):1478–85. table of contents.
9. Apkarian AV, Sosa Y, Krauss BR, Thomas PS, Fredrickson BE, Levy RE, Harden RN, Chialvo DR. Chronic pain patients are impaired on an emotional decision-making task. Pain. 2004;108(1–2):129–36.
10. Bruehl S, Chung OY. Psychological and behavioral aspects of complex regional pain syndrome management. Clin J Pain. 2006;22(5):430–7.
11. Harden RN, Bruehl SP. Diagnosis of complex regional pain syndrome: signs, symptoms, and new empirically derived diagnostic criteria. Clin J Pain. 2006;22(5):415–9.
12. Mogilevsky M, Janig W, Baron R, Harden RN. Complex regional pain syndrome-a multifaceted disorder requiring multidimensional care: case study. J Pain. 2007;8(9):677–81.
13. Harden RN, Bruehl S, Stanton-Hicks M, Wilson PR. Proposed new diagnostic criteria for complex regional pain syndrome. Pain Med. 2007;8(4):326–31.
14. Blaes F, Tschernatsch M, Braeu ME, Matz O, Schmitz K, Nascimento D, Kaps M, Birklein F. Autoimmunity in complex-regional pain syndrome. Ann N Y Acad Sci. 2007;1107:168–73.
15. Maihofner C, Baron R, DeCol R, Binder A, Birklein F, Deuschl G, Handwerker HO, Schattschneider J. The motor system shows adaptive changes in complex regional pain syndrome. Brain. 2007;130(Pt 10):2671–87.
16. Vladimir Tichelaar YI, Geertzen JH, Keizer D, Paul van Wilgen C. Mirror box therapy added to cognitive behavioural therapy in three chronic complex regional pain syndrome type I patients: a pilot study. Int J Rehabil Res. 2007;30(2):181–8.
17. Geha PY, Baliki MN, Harden RN, Bauer WR, Parrish TB, Apkarian AV. The brain in chronic CRPS pain: abnormal gray-white matter interactions in emotional and autonomic regions. Neuron. 2008;60(4):570–81.
18. Kemler MA, de Vet HC, Barendse GA, van den Wildenberg FA, van Kleef M. Effect of spinal cord stimulation for chronic complex regional pain syndrome Type I: five-year final follow-up of patients in a randomized controlled trial. J Neurosurg. 2008;108(2):292–8.
19. Moseley GL, Zalucki N, Birklein F, Marinus J, van Hilten JJ, Luomajoki H. Thinking about movement hurts: the effect of motor imagery on pain and swelling in people with chronic arm pain. Arthritis Rheum. 2008;59(5):623–31.

20. Selles RW, Schreuders TA, Stam HJ. Mirror therapy in patients with causalgia (complex regional pain syndrome type II) following peripheral nerve injury: two cases. J Rehabil Med. 2008;40(4):312–4.
21. Cacchio A, De Blasis E, Necozione S, di Orio F, Santilli V. Mirror therapy for chronic complex regional pain syndrome type 1 and stroke. N Engl J Med. 2009;361(6):634–6.
22. Harden RN, Bruehl S, Perez RS, Birklein F, Marinus J, Maihofner C, Lubenow T, Buvanendran A, Mackey S, Graciosa J, et al. Development of a severity score for CRPS. Pain. 2010;151(3):870–6.
23. Harden RN. Objectification of the diagnostic criteria for CRPS. Pain Med. 2010;11(8):1212–5.
24. van Eijs F, Smits H, Geurts JW, Kessels AG, Kemler MA, van Kleef M, Joosten EA, Faber CG. Brush-evoked allodynia predicts outcome of spinal cord stimulation in complex regional pain syndrome type 1. Eur J Pain. 2010;14(2):164–9.
25. Bruehl S. An update on the pathophysiology of complex regional pain syndrome. Anesthesiology. 2010;113(3):713–25.
26. Klega A, Eberle T, Buchholz HG, Maus S, Maihofner C, Schreckenberger M, Birklein F. Central opioidergic neurotransmission in complex regional pain syndrome. Neurology. 2010;75(2):129–36.
27. Sato K, Fukumori S, Matsusaki T, Maruo T, Ishikawa S, Nishie H, Takata K, Mizuhara H, Mizobuchi S, Nakatsuka H, et al. Nonimmersive virtual reality mirror visual feedback therapy and its application for the treatment of complex regional pain syndrome: an open-label pilot study. Pain Med. 2010;11(4):622–9.
28. Oerlemans HM, Oostendorp RA, de Boo T, van der Laan L, Severens JL, Goris JA. Adjuvant physical therapy versus occupational therapy in patients with reflex sympathetic dystrophy/complex regional pain syndrome type I. Arch Phys Med Rehabil. 2000;81(1):49–56.
29. Harden RN, Swan M, King A, Costa B, Barthel J. Treatment of complex regional pain syndrome: functional restoration. Clin J Pain. 2006;22(5):420–4.
30. Collins CK. Physical therapy management of complex regional pain syndrome I in a 14-year-old patient using strain counterstrain: a case report. J Man Manip Ther. 2007;15(1):25–41.
31. Celik D, Demirhan M. Physical therapy and rehabilitation of complex regional pain syndrome in shoulder prosthesis. Korean J Pain. 2010;23(4):258–61.
32. van de Meent H, Oerlemans M, Bruggeman A, Klomp F, van Dongen R, Oostendorp R, Frolke JP. Safety of "pain exposure" physical therapy in patients with complex regional pain syndrome type 1. Pain. 2011;152(6):1431–8.
33. Rothgangel AS, Braun SM, Beurskens AJ, Seitz RJ, Wade DT. The clinical aspects of mirror therapy in rehabilitation: a systematic review of the literature. Int J Rehabil Res. 2011;34(1):1–13.
34. Oerlemans HM, Oostendorp RA, de Boo T, Goris RJ. Pain and reduced mobility in complex regional pain syndrome I: outcome of a prospective randomised controlled clinical trial of adjuvant physical therapy versus occupational therapy. Pain. 1999;83(1):77–83.
35. Phillips ME, Katz JA, Harden RN. The use of nerve blocks in conjunction with occupational therapy for complex regional pain syndrome type I. Am J Occup Ther. 2000;54(5):544–9.
36. Galer BS, Bruehl S, Harden RN. IASP diagnostic criteria for complex regional pain syndrome: a preliminary empirical validation study. International Association for the Study of Pain. Clin J Pain. 1998;14(1):48–54.
37. Aronoff GM, Harden N, Stanton-Hicks M, Dorto AJ, Ensalada LH, Klimek EH, Mandel S, Williams JM. American Academy of Disability Evaluating Physicians (AADEP) position paper: complex regional pain syndrome I (RSD): impairment and disability issues. Pain Med. 2002;3(3):274–88.
38. Ramsden C, Gagnon C, Graciosa J, Faurot K, David R, Bralley JA, Harden RN. Do omega-6 and trans fatty acids play a role in complex regional pain syndrome? A pilot study. Pain Med. 2010;11(7):1115–25.
39. Maihofner C, et al. Cortical processing of mechanical hyperalgesia: a MEG study. Eur J Pain. 2010;14:64–70.
40. Oaklander AL, Fields HL. Is reflex sympathetic dystrophy/complex regional pain syndrome type I a small-fiber neuropathy? Ann Neurol. 2009;65:629–38.
41. Oaklander AL, et al. Evidence of focal small-fiber axonal degeneration in complex regional pain syndrome-I (reflex sympathetic dystrophy). Pain. 2006;120:235–43.
42. Oerlemans HM, et al. Adjuvant physical therapy versus occupational therapy in patients with reflex sympathetic dystrophy/complex regional pain syndrome type I. Arch Phys Med Rehabil. 2000;81:49–56.
43. Oerlemans HM, et al. Do physical therapy and occupational therapy reduce the impairment percentage in reflex sympathetic dystrophy? Am J Phys Med Rehabil. 1999;78:533–9.
44. Price DD, et al. Analysis of peak magnitude and duration of analgesia produced by local anesthetics injected into sympathetic ganglia of complex regional pain syndrome patients. Clin J Pain. 1998;14:216–26.
45. Christensen K, Jensen EM, Noer I. The reflex dystrophy syndrome response to treatment with systemic corticosteroids. Acta Chir Scand. 1982;148:653–5.
46. Robinson JN, Sandom J, Chapman PT. Efficacy of pamidronate in complex regional pain syndrome type I. Pain Med. 2004;5:276–80.
47. Varenna M, et al. Intravenous clodronate in the treatment of reflex sympathetic dystrophy syndrome. a randomized, double blind, placebo controlled study. J Rheumatol. 2000;27:1477–83.
48. Straube S, Derry S, Moore RA, McQuay HJ. Cervico-thoracic or lumbar sympathectomy for neuropathic pain and complex regional pain syndrome. Cochrane Database Syst Rev. 2010 Jul7;(7): CD002918.
49. Romano J, Turner J. Chronic pain and depression: does the evidence support a relationship? Psychol Bull. 1985;97:18–34.
50. Keefe FJ. Cognitive behavioral therapy for managing pain. Clin Psychol. 1996;49(3):4–5.
51. de Jong J, Vlaeyen J, Onghena P, Cuypers C, den Hollander M, Ruijgrok J. Reduction of pain related fear in Complex Regional Pain Syndrome Type One: the application of graded exposure in vivo. Pain. 2005;116:264–75.
52. Pleger B, Tegenthoff M, Ragert P, Forster A, Dinse H, Schweinkreis P, et al. Sensorimotor returning in Complex Regional Pain Syndrome parallels pain reduction. Ann Neurol. 2005;57:425–9.
53. Durmus A, Cakmak A, Disci R, Muslumanoglu L. The efficiency of electromagnetic field treatment in Complex Regional Pain Syndrome Type One. Disabil Rehab. 2004;26:537–45.
54. Singh G, Willen S, Boswell M, Janta J, Chelimsky T. The value of interdisciplinary pain management in Complex Regional Pain Syndrome Type One: A prospective outcome study. Pain Physician. 2004;7:203–9.
55. Watson H, Carlson L. Treatment of Reflex Sympathetic Dystrophy of the hand with an active “stress loading” program. J Hand Surg (Am). 1987;12A5:779–85.
56. McCabe C, Haigh R, Ring E, Halligan P, Wall P, Blake D. A controlled pilot study of the utility of mirror visual feedback in the treatment of Complex Regional Pain Syndrome Type One. Rheumatology. 2003;42:97–101.
57. Moseley G. Graded motor imagery is effective for long standing Complex Regional Pain Syndrome: A randomized controlled trial. Pain. 2004;108:192–8.
58. Moseley G. Is successful rehabilitation of Complex Regional Pain Syndrome due to sustained attention to the affected limb? A randomized clinical trial. Pain. 2005;114:54–6.
59. Moseley G. Graded motor imagery for pathologic pain: A randomised controlled trial. Neurology. 2006;67:2129–34.

60. Robaina F, Rodriguez J, de Vera J, Martin M. Transcutaneous electrical nerve stimulation and spinal cord stimulation for pain relief in Reflex Sympathetic Dystrophy. StereotactFunctNeurosurg. 1989;52:53–62.
61. Oerlemans H, Goris R, de Boo T, Oostendorp R. Do physical therapy and occupational therapy reduce the impairment percentage in Reflex Sympathetic Dystrophy? Am J Phys Med Rehabil. 1999;78:533–9.
62. Oerlemans H, Oostendorp R, de Boo T, Goris R. Pain and reduced mobility in Complex Regional Pain Syndrome type one: Outcome of a prospective randomized controlled trial of adjuvant physical therapy versus occupational therapy. Pain. 1999;83:77–83.
63. Oerlemans H, Oostendorp R, de Boo T, Laan L, Severens J, Goris R. Adjuvant physical therapy versus occupational therapy in patients with Reflex Sympathetic Dystrophy/Complex Regional Pain Syndrome Type One. Arch Phys Med Rehabil. 2000;81:49–56.
64. • Ek JW, van Gijn JC, Samwel H, van Egmond J, Klomp FP, van Dongen RT. Pain exposure physical therapy may be a safe and effective treatment for longstanding complex regional pain syndrome type 1: a case series. Clin Rehabil. 2009;23(12):1059–66. *This study examines a noteworthy rehabilitation strategy that directs effort solely at functional improvement, using a psychologically informed physical therapy approach. Patient report of pain did not drive treatment decisions and full functional recovery was obtained in 49% of patients*.
65. van de Meent H, Oerlemans M, Bruggeman A, et al. Safety of "pain exposure" physical therapy in patients with complex regional pain syndrome type 1. Pain. 2011;152(6):1431–8.