



Pharmacologic Therapies and Functional Restoration Techniques for CRPS

By Steven P. Stanos, DO

COMPLEX REGIONAL PAIN SYNDROME (CRPS) is a neurological syndrome characterized by pain disproportionate to the initiating event, allodynia, hyperalgesia, swelling, temperature and color changes, vasomotor changes, and/or trophic changes. Recent pathophysiologic hypotheses include afferent (neurogenic inflammation), efferent (autonomic disturbances), and central nervous system (cerebral plasticity) mechanisms. Others have suggested possible osteoclastic activity, where osteoclasts are stimulated by substance P and TNF-alpha in response to injury.

There has also been increasing evidence of cortical changes in patients with CRPS. Ongoing pain alters somatosensory processing, causing cortical hyperexcitability¹ and cortical reorganization. Susceptibility to cortical reorganization postinjury may also be a prerequisite for CRPS.² These changes serve as ideal targets for pharmacologic, nonpharmacologic, and interventional therapies.

Movement Disorders

Alterations in central nervous system (CNS) processing may be responsible for the movement disorders and related motor impairment seen in some CRPS patients, including weakness, bradykinesia, dystonia, myoclonus, and tremor.

To test for motor neglect, have patients flick their fingers repeatedly, first by looking at the affected hand, and then with their eyes turned away to eliminate visual feedback. The clinician may find a stroke-like change seen in these patients, where fluid movements are lost, clumsy, or less coordinated. Normal “wiring” and nervous system function is altered—treatment goals will include retraining this abnormal nervous system dysfunction, potentially decreasing pain, and improving somatosensory processing.

Hand Dystonia

A 2001 van Hilten study³ examined patients with CRPS presenting with hand dystonia, many of whom demonstrated a relative sparing of the first 2 digits. The researchers theorized that with human dexterity there is a large portion of corticomotoneuronal connections in the first 2 flexors of the digits, whereas flexors III and IV are more characterized by interneuronal-motoneuronal connections that may be more susceptible to cortical reorganization and dysfunction.

Hand Recognition

A 2004 Moseley study⁴ discussed a delayed recognition of hand laterality—the ability to quickly distinguish whether a pictorial representation of a hand was the

right or left limb—and how it correlates to the duration of symptoms, evoked pain, and impaired movement. Laterality deficits are thought to be related to cortical reorganization. Specialized treatment involves retraining the brain to recognize this laterality, by decreasing plasticity and hopefully facilitating motor recovery and improved hand function.

Immobilization

Immobility of the affected limb, commonly prescribed to patients early in treatment, may lead to altered sensory processing. A 2008 study involved 27 healthy subjects with no pain, who were casted from the elbow to hand for 28 days.⁵ After cast removal, sensory testing demonstrated transient cold hyperalgesia, skin temperature changes, and movement-induced pain for up to 3 weeks in selected patients. These findings underscore the importance of restoring motion and limiting immobility as a key goal in CRPS therapy.

Pharmacologic Options

The study of pharmacotherapy for CRPS is limited by a paucity of literature and randomized controlled trials. Since no medication is FDA approved for CRPS, treatment is based on a mechanistic approach characterized by rational polypharmacy that targets the multiple mechanisms

of action along the CNS. A literature review of CRPS primarily includes a limited number of placebo-controlled clinical trials, case reports, and case series. Like other chronic pain conditions, pharmacotherapy for CRPS consists primarily of off-label use of antidepressants, anticonvulsants, opioids, topical preparations, and anti-inflammatory compounds.

Dimethyl Sulfoxide (DMSO) and N-acetylcysteine (NAC)

The antioxidant DMSO has shown improvement in CRPS symptoms,⁶ and NAC has decreased soft tissue damage in an animal model of inflammatory pain.⁷ The effects of these 2 free radical scavengers, topical DMSO 50% (applied 5 times daily) and oral NAC (600 mg twice per day), were examined in a 17- to 52-week randomized controlled study in subacute CRPS patients.⁸ Although no significant differences were found between DMSO and NAC, a subgroup analysis of “warm” or “cold” CRPS patients did show differences. DMSO showed more favorable benefit in warm CRPS patients, while NAC demonstrated more benefit in cold CRPS patients.

Gabapentin

Gabapentin, a commonly used medication in many neuropathic pain conditions, was discussed in CRPS through a case series by Mellick and Mellick in the late 1990s.⁹ A 2007 Tan and colleagues study¹⁰ included a cohort of primarily acute posttraumatic CRPS patients. Treatment involved an inpatient-based 3-week program that included active physical therapy. Subjects were prescribed 600 mg gabapentin up to 3 times daily within the first week, and demonstrated decreases in spontaneous pain and allodynia.

A 2004 van de Vusse study¹¹ involved chronic CRPS patients, with an average diagnosis period of 3 years, divided into 2 groups. Group 1 was prescribed gabapentin at 1800 mg titrated for 3 weeks,

followed by a 2-week washout and then placebo. Group 2 received placebo first for 3 weeks, followed by the 2-week washout and then gabapentin. Gabapentin only showed efficacy in the first 3 weeks; on the longer 8-week measurement, there was no difference in pain.

Antihypertensive Medication Use as a Predictor of Developing CRPS

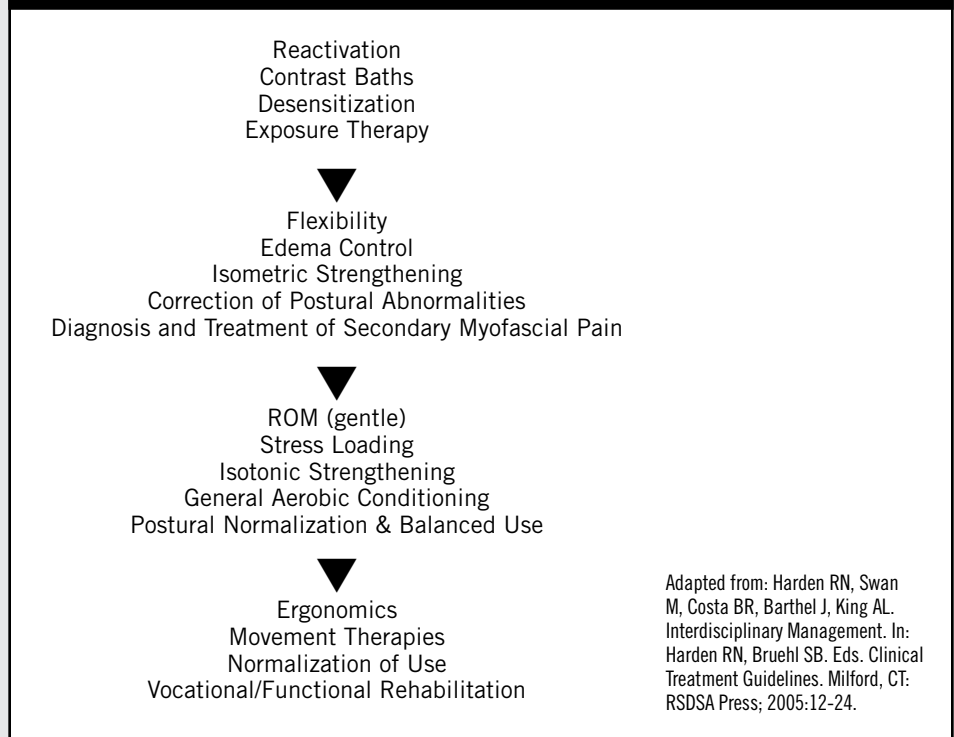
A 2009 de Mos and colleagues study¹² examined antihypertensive medications, including calcium channel blockers and ACE inhibitors, that could increase the risk of developing CRPS. Patients were considered users of the medication if they were taking it 7 days before the CRPS-causing incident. From a pain standpoint, ACE inhibition blocks the degradation of substance P and bradykinin; thus its loss could lead to an accumulation of substance P and bradykinin that could result in an up-regulation of the bradykinin receptors. The researchers were able to show that being on an ACE inhibitor could be a predictor of developing CRPS (odds ratio, 1.8:2.3).

Functional Restoration

The basic model of functional restoration uses a stepwise approach (Table 1) that reflects the complex pathophysiology and impairments related to CRPS. This collaborative approach incorporates many disciplines, including physical and occupational therapy, pain psychology, relaxation therapy, exercise, pain medicine, and vocational rehabilitation.

This model is best delivered in an interdisciplinary environment, where therapists and clinicians can work together in one setting. Nonpharmacologic therapies within this model include education-based graded exposure programs, sensory motor treatment that includes desensitization and stress loading, mirror therapy, graded motor imagery, and electromagnetic therapies. Movement-based therapies are also commonly incorporated, such as yoga, tai chi, Feldenkrais method, Alexander technique, Pilates, and aquatic therapy.¹³ The general treatment goals are based on improving movement, decreasing central

Table 1: A Sample, Stepwise, Functional Restoration Algorithm



Adapted from: Harden RN, Swan M, Costa BR, Barthel J, King AL. Interdisciplinary Management. In: Harden RN, Bruhl SB. Eds. Clinical Treatment Guidelines. Milford, CT: RSDSA Press; 2005:12-24.

and peripheral sensitization, and decreasing psychosocial distress.

Physical Therapy and Graded Imagery

De Jong and colleagues¹⁴ described an education and graded exposure program that focused on fear-avoidance models in CRPS patients. The therapist then talks the patients through recreating these activities. Slowly, the patients break through their fear of movement and progress to moving and using the affected limb. At the end of the treatment process in this study, subjects experienced decreased pain-related fear, disability, and intensity.

Mirror Therapy

The basic treatment approach in mirror therapy can be summarized as SEE IT, IMAGINE IT, and MOVE IT. Patients see their affected limb, imagine it moving, then are eventually able to move it. Many patients do not want to look at their limb; they talk about how it is not a part of them. These patients have a stroke-like neglect associated with their limb. McCabe and colleagues¹⁵ used standard physical therapy and mirror therapy exercises to facilitate decreased pain in patients with early CRPS (less than 8 weeks) and reduced stiffness in subacute CRPS (5 to 12 weeks). Outcomes were less favorable for patients with chronic CRPS (more than 2 years).

Summary

Pharmacologic therapies for CRPS are based on a mechanistic approach characterized by targeting medications at multiple mechanisms of action along the CNS. A review of the literature primarily includes a small number of placebo-controlled clinical trials and more case reports and case series. Like other chronic pain conditions, pharmacotherapy for CRPS includes primarily of off-label use of antidepressants, anticonvulsants, opioids, top-

ical preparations, and anti-inflammatory compounds. Nonpharmacologic methods include an interdisciplinary approach incorporating, in a step-wise manner, reactivation, exposure-based therapy, and desensitization, followed by strengthening and range of motion, myofascial pain and postural correction, stress loading, and isometric strengthening, and finally, more higher-level movement-based therapy, and ergonomic and functional restoration. New nonpharmacologic treatments include graded motor imagery, mirror virtual feedback exercises, and desensitization, all focused on restoring normal nervous system function, assessing both peripheral and central sensitization.

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