

Comprehensive Mechanisms and Non-Invasive Treatment for Complex Regional Pain Syndrome: A Narrative Review

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Abstract: Complex Regional Pain Syndrome (CRPS) is a chronic pain condition characterized by an exaggerated response to an initial stimulus, accompanied by autonomic, sensory, motor, and sudomotor dysfunctions. Recognized as a systemic disorder, CRPS involves complex interactions among inflammatory, immunologic, neurogenic, genetic, and psychological factors. The primary mechanisms include peripheral and central sensitization, sympathetic nervous system dysregulation, and altered somatosensory processing. However, the exact pathophysiology remains unclear, contributing to ongoing debate about optimal treatment approaches. Management typically involves a multimodal approach. Pharmacologic options such as corticosteroids, ketamine, and bisphosphonates have demonstrated relative safety and efficacy in clinical practice. Moreover, rehabilitation therapies—including cortically directed sensorimotor rehabilitation, range-of-motion or aerobic exercises, exposure therapy, transcutaneous electrical nerve stimulation, and thermal therapy—serve as valuable nonpharmacologic interventions. No consensus currently exists on standardized treatment protocols for CRPS, particularly regarding the choice of non-invasive approaches. In this context, a comprehensive understanding of the underlying pathophysiological mechanisms is essential for guiding appropriate management strategies. This review provides updated insights into the pathophysiological mechanisms of the disease, alongside a synthesis of evidence-based non-invasive treatment, to support mechanism-driven clinical decision-making, potentially improving treatment outcomes.

Keywords: complex regional pain syndrome, pathophysiology, neuroinflammation, pharmacological therapy, rehabilitation

Introduction

Complex Regional Pain Syndrome (CRPS) is a chronic and debilitating pain condition that typically develops following trauma, operation, or limb immobilization, with a reported prevalence of 5.46 to 26.2 per 100,000 individuals annually.^{1,2} CRPS occurs more commonly in females than in males, with reported female-to-male ratios ranging from 2:1 to 4:1.^{3,4} Patients with CRPS often experience substantial socioeconomic challenges. Approximately 30%–40% of affected patients with CRPS are unable to return to their jobs, and 27%–35% require workplace adaptations.⁵ At diagnosis, total healthcare and pain medication prescription costs are 2.17 and 2.56 times higher than baseline, respectively, peaking within the first year and gradually decreasing over time.⁶ Overall, their healthcare costs are approximately 20% higher than those of non-CRPS patients.⁷ Consequently, CRPS is associated with significantly reduced quality of life and represents a notable societal burden.^{7,8}

It is characterized by disproportionate pain not confined to a single peripheral nerve distribution, accompanied by varying combinations of sensory, vasomotor, sudomotor, trophic, and motor abnormalities. CRPS has previously been referred to by several names, including reflex sympathetic dystrophy, causalgia, Sudeck's atrophy, algoneurodystrophy, and shoulder-hand syndrome.^{1,2} In 1994, a consensus conference in Orlando standardized the terminology as CRPS. The diagnosis of CRPS lacks specific confirmatory tests and is primarily clinical, based on patient history and symptomatology. In 2003, the Budapest criteria were introduced by the International Association for the Study of Pain (IASP)⁹ to

improve diagnostic consistency and were revised in 2012.¹⁰ In 2019, the IASP CRPS Special Interest Group convened a workshop in Valencia and proposed pragmatic updates to diagnostic instructions and taxonomy (Table 1). These revisions refined the definitions of CRPS type II (CRPS II) and CRPS Not Otherwise Specified (NOS), added a third CRPS subtype—CRPS with Remission of Some Features, and clarified symptom assessment procedures, while retaining the original phrasing to preserve criterion validity.¹¹

Many patients with CRPS experience refractory pain that significantly restricts their daily activities. Although a range of therapeutic interventions, including pharmacological, procedural, and rehabilitative therapy, have been explored, pain management is often suboptimal. Effective management requires a comprehensive understanding of CRPS pathophysiology and the available treatment modalities.

This review explores the underlying mechanisms of CRPS and highlights non-invasive treatment approaches—pharmacological and rehabilitative—aiming to support clinical decision-making and improve symptom management. The following sections present the pathophysiological mechanisms of CRPS, pharmacological treatments, and rehabilitative treatment approaches for managing the condition.

Mechanisms of Complex Regional Pain Syndrome

CRPS is a multifactorial syndrome involving an interplay of nociceptive, neuropathic, and nociplastic mechanisms.⁹ The specific mechanisms of CRPS are illustrated in Figure 1. Understanding these mechanisms enables a shift from symptom-based to mechanism-targeted treatment approaches.¹²

Peripheral Inflammation and Neuroinflammation

Peripheral inflammation represents the biological response to tissue injury and infection, characterized by immune cell activation and the release of inflammatory mediators. Neuroinflammation, occurring in both the peripheral and central nervous systems, involves immune cell infiltration, glial cell activation, and mediator release, contributing to peripheral and central sensitization.^{13,14} Neuroinflammation is essential in the onset and maintenance of CRPS-related chronic pain.^{14,15}

Trauma is a common precursor to CRPS, with fractures accounting for approximately 44%, sprains for 18%, and elective surgeries for approximately 12% of cases.¹⁶ Additional risk factors include limb immobilization, disuse, and tissue hypoxia. Following injury, both innate and adaptive immune cells—including mast cells,^{17–19} macrophages, monocytes,^{20,21} and T cells,^{21,22}—the non-immune cells such as keratinocytes^{23–26} and dendritic cells²⁷ are recruited to the site. These cells release inflammatory mediators, including serotonin, histamine, prostaglandin E2 (PGE2), bradykinin, adenosine triphosphate (ATP), protons (H⁺), nerve growth factors (NGF), and various cytokines,^{28,29} which cause vasodilation and increased vascular permeability, manifesting as clinical signs such as warmth, erythema, and edema.

Studies in CRPS have demonstrated a cytokine imbalance characterized by elevated levels of proinflammatory cytokines [tumor necrosis factor- α (TNF- α), interleukin-1 beta (IL-1 β), and IL-6] and decreased anti-inflammatory cytokines (IL-4 and IL-10) in local blister fluid,³⁰ skin,³¹ plasma,³² and cerebrospinal fluid.³³ These mediators interact with receptors and ion channels on nociceptive peripheral nerve terminals, sensitizing and exciting primary afferent nociceptors (particularly C-fibers), lowering activation thresholds, and inducing ectopic discharges;²⁹ this process constitutes a key mechanism of peripheral sensitization. Therapeutic agents that promote the metabolism of these mediators or inhibit their nociceptor interactions may reduce inflammation and represent a promising avenue for drug development. As multiple mediators and diverse receptors are involved (Figure 2), targeting a single mediator may be insufficient.

The interaction between immune cells and nociceptors is bidirectional and central to CRPS pathogenesis.³⁴ Upon activation, primary afferent nociceptors in the dorsal root ganglion (DRG) release neurotransmitters both centrally and peripherally. Among these, neuropeptides such as calcitonin gene-related peptide (CGRP) and substance P (SP) are pivotal mediators of both peripheral and central sensitization in CRPS.^{35–37} At peripheral nerve endings, CGRP induces vasodilation,^{38,39} enhances sweat gland activity,^{40,41} and stimulates hair follicles,⁴⁰ resulting in clinical signs such as elevated skin temperature, erythema, excessive sweating, and enhanced hair growth. CGRP-mediated vasodilation also

Table 1 Diagnostic Procedures, Budapest Criteria, and Taxonomy of Complex Regional Pain Syndrome (CRPS)^a

Diagnostic procedures	<ul style="list-style-type: none"> • All symptoms listed in the criteria should be assessed at each formal diagnostic evaluation. • For unilateral CRPS, asymmetry should be assessed by comparison with the contralateral extremity; for bilateral or symmetrical CRPS, by comparison with an unaffected extremity or with healthy individuals. Asymmetry is determined by clinical judgment rather than by prespecified criteria. • Full diagnostic criteria must be applied to each extremity. • Hyperalgesia, defined as increased pain in response to a normally painful stimulus, should be assessed by comparing a single pinprick at the center of the most affected area with the corresponding site on the unaffected limb or a control site in bilateral CRPS. The test is positive if the pain is more intense or prolonged on the affected side. • Allodynia is defined as pain evoked by a normally nonpainful stimulus, assessed by light touch, vibration, temperature, deep tissue or joint pressure, or joint movement. The presence of allodynia is confirmed if any modality elicits pain. Light touch can be assessed manually or with a brush; tissue pressure, by finger pressure sufficient to blanch the evaluator's nail bed (below 100 g/cm², maximum 500 g load); vibration, by a tuning fork over a bony prominence; and temperature, by application of cool or warm stimuli. • Temperature asymmetry is assessed by comparing the affected area with the contralateral side or a control site, and should be detectable by palpation with the dorsum of the examiner's hand. • Obvious regional color asymmetry (eg, hand, foot, knee) should be documented, specifying the nature of the change (eg, red, blue, pale, or mottled). • If a sign is observed without a corresponding reported symptom, a "signs override symptoms" approach cannot be automatically applied.^b
Budapest criteria	<p>All criteria (A, B, C, and D) must be met:</p> <p>A. Patient has continuing pain that is disproportionate to any inciting event.</p> <p>B. Patient reports of at least 1 symptom in at least 3 of the 4 categories.</p> <p>C. At least 1 sign in at least 2 of the 4 categories observed by the physician during the examination.</p> <p>D. No other diagnosis better explains the described symptoms and signs.</p> <p>The 4 categories are:</p> <ol style="list-style-type: none"> 1. Sensory^c <ol style="list-style-type: none"> a. Allodynia b. Hyperalgesia 2. Vasomotor <ol style="list-style-type: none"> a. Temperature asymmetry b. Skin color changes c. Skin color asymmetry 3. Edema/sudomotor <ol style="list-style-type: none"> a. Edema b. Changes in sweating c. Sweating asymmetry 4. Motor/trophic <ol style="list-style-type: none"> a. Decreased range of motion b. Motor dysfunction (weakness, tremor, dystonia) c. Trophic changes in hair, nails, or skin
Taxonomy	<p>CRPS Type I: Criteria are met at the time of evaluation with no known nerve lesion in the affected area.</p> <p>CRPS Type II: Criteria are met at the time of evaluation in an anatomic region extending beyond the territory of an identified nerve injury.</p> <p>CRPS With Remission of Some Features: Criteria were previously met but are not met at the time of evaluation.</p> <p>CRPS Not Otherwise Specified: Criteria have never been fully met, but no alternative diagnosis better explains the clinical presentation.</p>

Notes: ^aGoebel et al¹¹ ^bA rare limitation of the CRPS diagnostic criteria is that objective signs, such as color or temperature asymmetry, may be observed without the patient reporting corresponding symptoms. This discrepancy can reduce the symptom count below the required threshold for diagnosis, even when clinical features are present. Although a "sign overriding a symptom" approach (ie, a sign automatically generates a tick also as a symptom) seems logical, it cannot be automatically applied due to the statistical validation of the criteria. A pragmatic solution may be needed in rare cases, such as patients with impaired vision.¹¹ ^cReported hyperesthesia is considered a symptom within the sensory category.¹¹ Data from Goebel A, Birklein F, Brunner F, et al. The Valencia consensus-based adaptation of the IASP complex regional pain syndrome diagnostic criteria. *Pain*. 2021;162(9):2346–2348.¹¹

Abbreviation: CRPS, complex regional pain syndrome.

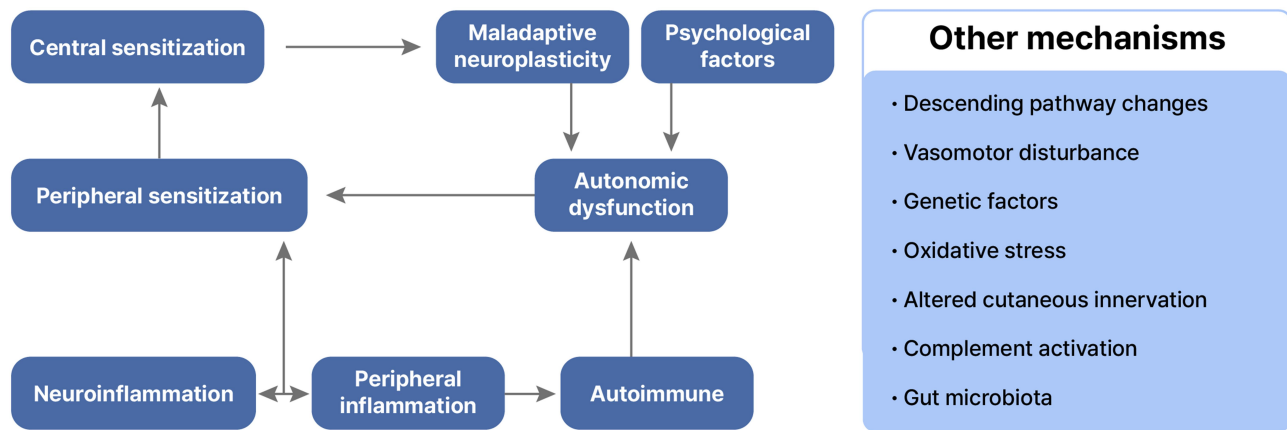


Figure 1 Summary of mechanisms of complex regional pain syndrome (CRPS).

Notes: Following an inciting event (such as trauma, immobilization, disuse, or hypoxia), peripheral inflammation and neuroinflammation occur, leading to peripheral sensitization and subsequently central sensitization. Central sensitization affects the brain, resulting in maladaptive neuroplasticity. Evidence suggests that autoimmune dysfunction and autonomic disturbances contribute to the pathogenesis of CRPS. Maladaptive plasticity, autoimmune factors, and psychological influences are believed to contribute to autonomic dysfunction. Moreover, factors such as vasomotor disturbances; changes in descending pathways; genetic factors; oxidative stress; altered cutaneous innervation; complement activation; and gut microbiota may play a role in CRPS pathophysiology.

contributes to edema formation.⁴² SP increases capillary permeability, promoting plasma extravasation and edema.⁴³ Moreover, CGRP and SP activate and recruit immune cells, exacerbating inflammation.^{38,42,44}

At the dorsal horn of the spinal cord, primary afferent nociceptors release neurotransmitters that interact with dorsal horn neurons and activate glial cells, promoting central sensitization. Neurotransmitters such as brain-derived neurotrophic factor (BDNF), SP, and glutamate heighten neural excitability in dorsal horn neurons, marking the onset of central sensitization. Glial cell activation, particularly of microglia and astrocytes, further amplifies this process^{45–47} and contributes to the chronicity of CRPS.⁴⁸ Microglia are the first glial cells to respond to peripheral nerve injury, typically activating within 24 hours in the spinal cord and usually subsiding within 3 months.⁴⁵ Upon activation, microglia express specific markers such as Toll-like receptor 4 (TLR4), regulate immune responses, proliferate, and release proinflammatory mediators. This release creates a proinflammatory milieu in the dorsal horn that sensitizes peripheral afferents and dorsal horn neurons, leading to pain hypersensitivity and persistence.^{45,48} TLR4 activation enhances proinflammatory cytokine release within the central nervous system, making it a therapeutic target for mitigating neuroinflammation.⁴⁹ Astrocytes become activated around the third day after injury and may remain active for up to 3 months.^{45,50} Beyond releasing inflammatory mediators that sensitize secondary neurons in the spinal cord, astrocytes modulate microglial activity and contribute to pain processing in higher-order central nervous system structures.^{50–52}

Peripheral Sensitization

Peripheral sensitization refers to the process by which primary afferent nociceptors lower their activation threshold, become hyperexcitable, and generate spontaneous ectopic discharges.^{28,53} Inflammation and neuroinflammation are key contributors to this process. Following nerve injury, alterations in ion channel expression further enhance sensitization.²⁹ Increased expression and aberrant distribution of voltage-gated sodium channels (VGSC), including Nav1.3, Nav1.7, and Nav1.8, lowers the activation threshold and promotes ectopic discharges (Figure 2).⁵⁴ Certain calcium channels (N-type, T-type, and L-type) and potassium channels (hyperpolarization-activated cyclic nucleotide-gated channels) contribute to heightened neuronal excitability.²⁹ Sympathetic sprouting, discussed in Section 2.4, is implicated in developing peripheral sensitization.²⁸

As a result of these mechanisms, primary afferent nociceptors exhibit heightened excitability and spontaneous discharges, contributing to hallmark CRPS symptoms. These include spontaneous pain (from ectopic nociceptor activity), allodynia (due to lowered stimulation thresholds), and primary hyperalgesia (localized to the site of tissue injury due to peripheral sensitization).²⁹

Central Sensitization

Central sensitization refers to a prolonged but reversible increase in the excitability and synaptic efficacy of neurons in the central nervous system. Clinically, it manifests as dynamic tactile allodynia, secondary punctate hyperalgesia, aftersensations, and enhanced temporal summation,^{46,47,55} which are commonly observed in CRPS. This process is considered a key mechanism underlying chronic pain,^{47,55} including that seen in CRPS. As previously described, primary afferent nociceptors release neurotransmitters (including SP and glutamate), which activate their respective postsynaptic receptors on second-order neurons in the spinal cord (Figure 3). SP binds to the neurokinin-1 receptor (NK1R), increasing intracellular calcium levels, while glutamate stimulates alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors, leading to further calcium influx and depolarization of postsynaptic neurons. When this depolarization reaches sufficient amplitude and duration, it removes the Mg²⁺ block on N-methyl-D-aspartate (NMDA) channels, permitting additional calcium entry and further enhancing neuronal excitability.^{56,57}

The activation of NMDA receptors is central to the phenomenon of “wind-up”, which refers to a progressive increase in dorsal horn neuron firing following repeated C-fiber activation, ultimately causing long-term neuroplastic changes in the spinal cord).²⁹ Moreover, glial cell activation (as mentioned in “Peripheral Inflammation and Neuroinflammation” Section) significantly contributes to central sensitization and the persistence of chronic pain.

Autonomic Dysfunction

Sympathetic nervous system dysfunction is a major contributor to CRPS pathogenesis and is frequently referred to as sympathetically maintained pain. In the early stage of CRPS, plasma norepinephrine levels in the affected limb are significantly reduced, indicating diminished sympathetic outflow.^{58,59} Clinically, this phenomenon presents as vasodilation, redness, warmth, and edema. However, the decreased norepinephrine release may trigger a compensatory upregulation of vascular α 1-adrenoceptors, leading to vasoconstriction and the characteristic cold, bluish appearance of the limb

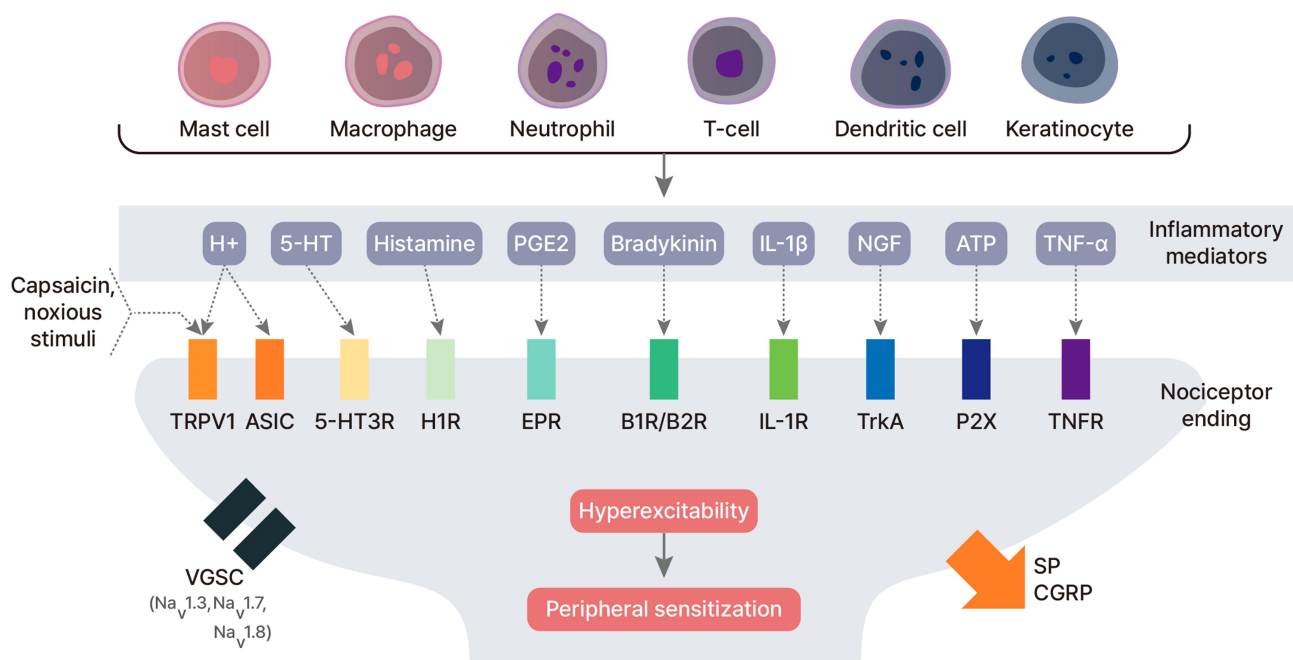


Figure 2 Peripheral sensitization in complex regional pain syndrome (CRPS).

Notes: In CRPS, local production and release of inflammatory mediators occur around the primary afferent nociceptor endings due to the activation of both immune and non-immune cells. These mediators interact with their corresponding receptors, resulting in neuronal hyperexcitability and peripheral sensitization. Furthermore, the upregulation of VGSC, including Na_v1.3, Na_v1.7, and Na_v1.8, contributes to the sensitization of primary afferent nociceptors. Activated nociceptors also release SP and CGRP, leading to vasodilation and increased vascular permeability in CRPS.

Abbreviations: TRPV-1, transient receptor potential vanilloid 1; ASIC, acid-sensing ion channel; 5-HT, 5-hydroxytryptamine; 5-HT₃R, 5-hydroxytryptamine 3 receptor; H₁R, histamine receptor; PGE₂, prostaglandin E₂; EPR, E prostanoid receptor; B₁R/B₂R, bradykinin 1 receptor/bradykinin 2 receptor; IL-1 β , interleukin-1 beta; IL-1R, interleukin 1 receptor; NGF, nerve growth factor; TrkA, tyrosine kinase A; ATP, adenosine triphosphate; P₂X, purinergic receptor of ATP; TNF- α , tumor necrosis factor alpha; TNFR, tumor necrosis factor receptor; VGSC, voltage-gated sodium channels; SP, substance P; CGRP, calcitonin gene-related peptide.

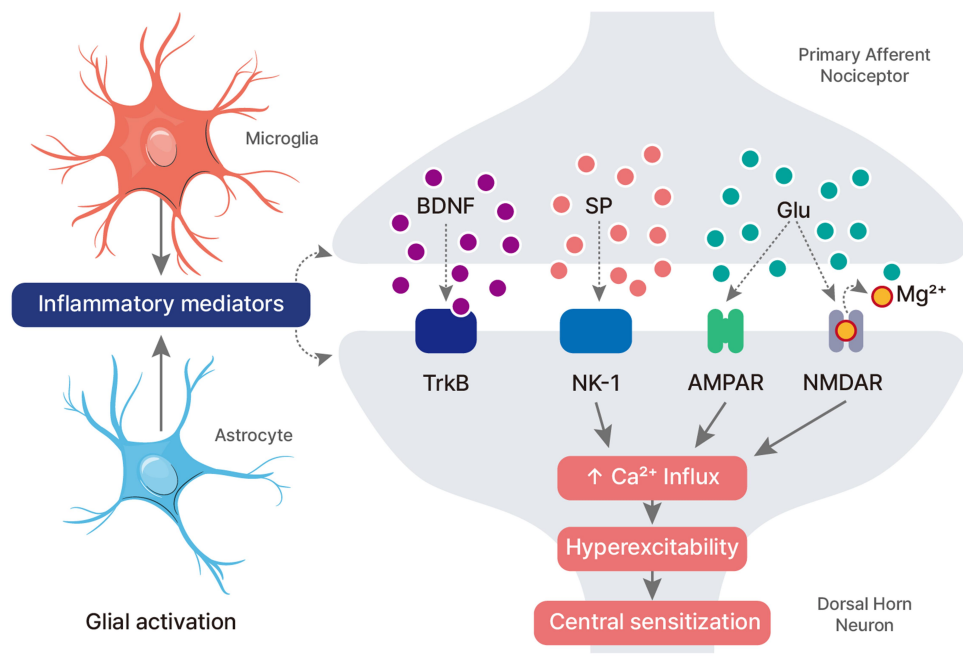


Figure 3 Central sensitization in complex regional pain syndrome (CRPS).

Notes: In CRPS, afferent nociceptor terminals release BDNF, SP, and glutamate. SP acts on NK1 receptors, while glutamate stimulates AMPA receptors, leading to Ca²⁺ influx into dorsal horn neurons and depolarization. When this depolarization reaches sufficient amplitude and duration, the Mg²⁺ block on NMDA channels is removed, and in combination with the action of glutamate, this facilitates additional Ca²⁺ influx, ultimately leading to neuronal hyperexcitability and central sensitization. Activation of glial cells (microglia and astrocytes) further sensitizes both primary afferent nociceptors and dorsal horn neurons in the spinal cord, contributing to peripheral and central sensitization.

Abbreviations: BDNF, brain-derived neurotrophic factor; SP, substance P; Glu, glutamate; TrkB, tropomyosin receptor kinase B; NK1, neurokinin 1; AMPAR, α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; NMDAR, N-methyl-D-aspartate receptor.

during the chronic “cold” phase of CRPS.⁶⁰ In patients with CRPS, increased expression and density of α -adrenoceptors have been observed in epidermal cells and nociceptors on the affected and unaffected sides compared to healthy controls.⁶¹ Epidermal cells expressing α -adrenoceptors, such as keratinocytes, under norepinephrine stimulation, may release proinflammatory mediators that stimulate nociceptors and contribute to peripheral pain. Moreover, sympathetic-afferent coupling, the interactions between sympathetic and sensory nerves that heighten pain sensitivity, plays a significant role in peripheral and central sensitization in CRPS.²⁸ Structural brain changes have also been reported in CRPS, including atrophy in regions associated with autonomic regulation, such as the ventromedial frontal cortex and the right anterior insula, indicating central involvement in autonomic dysfunction.⁶² Moreover, psychological factors and autoimmune mechanisms are believed to influence autonomic dysfunction and will be discussed in subsequent sections.

Autoimmune Mechanisms

Growing evidence supports an autoimmune component in CRPS pathogenesis. Serological studies have identified previous infections—such as *Chlamydia*, *Parvovirus*, and *Campylobacter*—in patients with CRPS,^{63–65} prompting Goebel et al to investigate the presence of pathogen-specific antibodies. Their findings revealed significantly elevated immunoglobulin M (IgM) and immunoglobulin G (IgG) titers against specific bacterial and viral surface epitopes in patients with CRPS compared to healthy controls, suggesting abnormal immune responses may lead to cross-reactive autoantibody production.⁶⁶ Furthermore, CRPS patient sera contain IgG targeting autonomic nervous system components, including β 2-adrenergic and muscarinic M2 receptors,⁶⁷ providing additional evidence for autoimmunity’s contribution to autonomic dysfunction in CRPS. Dharmalingam et al demonstrated that antibodies from patients with CRPS can bind to endothelial cells in vitro, inducing proinflammatory and cytotoxic effects that may contribute to CRPS development.⁶⁸ Similarly, Dubuis et al found that serum IgG from patients with chronic CRPS targets α -1a adrenergic receptors, modulating cardiomyocyte excitability and supporting an autoimmune mechanism.⁶⁹ Tékus et al demonstrated that transferring IgG from patients with chronic CRPS into trauma-inflicted mice induced mechanical hyperalgesia,

edema, and increased proinflammatory markers, mimicking human CRPS symptoms.⁷⁰ Guo et al highlighted the role of IgM antibodies in a CRPS mouse model, where bone fractures led to the expression of neoantigens in the limb skin, sciatic nerve, and spinal cord. This antigen expression triggered B-cell production of IgM antibodies bound to these antigens, eliciting a pronociceptive immune response.⁷¹ Additionally, the female-to-male ratio in CRPS, ranging from 2:1 to 4:1,^{2,3} corresponds with the female predominance commonly observed in many autoimmune diseases.⁷² Given growing evidence for autoimmune mechanisms in CRPS, intravenous immunoglobulin (IVIG) therapy has emerged as a promising treatment option. However, clinical outcomes with IVIG are variable and inconsistent across studies.^{73,74} This issue will be discussed in greater detail in the treatment section concerning immunoglobulin therapy. The inconsistent findings regarding the efficacy of IVIG limit the strength of the evidence supporting the autoimmune hypothesis in CRPS. Nevertheless, autoimmunity remains a plausible contributing mechanism in the pathogenesis of this condition.

Maladaptive Neuroplasticity

Neuroplasticity, also called neural or brain plasticity, refers to the nervous system's ability to reorganize its structure, functions, or connections in response to internal or external stimuli.⁷⁵ In CRPS, neuroplastic changes associated with central sensitization contribute to sensory and motor dysfunctions.

Alterations in the primary somatosensory cortex (S1) have been well-documented in CRPS and are associated with sensory disturbances.^{76,77} The reorganization of the S1 region representing the affected hand, including a marked reduction in size and a shift toward the cortical representation of the lips, has been correlated with pain severity and mechanical hyperalgesia.⁷⁸ Importantly, this somatotopic reorganization has been shown to reverse alongside pain reduction.⁷⁶ The S1 processes tactile input and integrates proprioceptive, vestibular, and visual cues to construct a central somatosensory representation of the body—called the body schema. Disruptions to this neural map have been hypothesized to contribute to body perception disturbances (BPD) in CRPS.⁷⁷ Pleger et al demonstrated that reorganization in S1 and the secondary somatosensory cortex (S2) is associated with impaired tactile discrimination.⁷⁹

Neuroimaging studies have linked brain alterations to motor dysfunction in CRPS. Using functional magnetic resonance imaging (fMRI) during finger tapping tasks involving the affected limb, Maihöfner et al reported increased activation in the contralateral primary motor cortex (M1) and supplementary motor area (SMA), both of which were correlated with motor impairment severity.⁸⁰ Similarly, Freund et al observed heightened activation in the posterior cingulate cortex during painful stimulation, suggesting enhanced motor inhibition. They also observed reduced activity in the opercular region, indicating impaired sensory-discriminative processing compared to healthy controls.⁸¹ Furthermore, Azqueta-Gavaldon et al identified abnormalities in M1, SMA, the posterior parietal cortex, and basal ganglia, potentially underlying motor symptoms such as dystonia and reduced range of motion (ROM) in patients with CRPS.⁸²

Visual input is believed to significantly influence pain perception.^{83,84} Viewing one's body has been shown to reduce neural responses to pain and lower perceived pain intensity—a phenomenon known as visually induced analgesia.⁸⁴ However, in some patients with CRPS, ambiguous visual input can trigger pain, sensory disturbances, peripheral vasomotor responses, and even dystonia.⁸⁵ Hall et al demonstrated that observing a bistable spatial image increased pain intensity and evoked additional symptoms in patients with CRPS.⁸⁶ Moreover, distorted body perception and cortical reorganization can alter motor and sensory maps, impairing sensorimotor integration and promoting pain development.^{87–89} In McCabe et al's study, healthy individuals experienced pain and sensory disturbances, temperature changes, and altered limb perception when performing incongruent limb movements while viewing a mirror reflection, creating a sensory-motor mismatch. These symptoms were reported in the limb hidden behind the mirror, suggesting that visual-proprioceptive incongruence alone can induce pain-like sensations.⁹⁰

Dysfunction of Descending Inhibitory Pathways

Dysfunction of descending modulatory pathways significantly contributes to CRPS-related pain. Under normal conditions, descending pathways from regions such as the periaqueductal gray-rostral ventromedial medulla system and the dorsal reticular nucleus–ventrolateral medulla exert inhibitory control over spinal nociceptive transmission through

neurotransmitters such as serotonin, norepinephrine, dopamine, and endogenous opioids.^{29,91} However, the balance between descending inhibition and facilitation is disrupted in chronic pain conditions. Reducing noradrenergic inhibitory tone and shifting serotonergic signaling from inhibitory to facilitatory enhances spinal cord excitability and promotes pain transmission.⁹² The interplay between pain and comorbidities such as sleep disturbances, anxiety, and depression is attributed to the shared involvement of norepinephrine and serotonin in regulating both pain and mood.⁹³ Consequently, monoamine reuptake inhibitors, such as tricyclic antidepressants (TCAs) and selective serotonin-norepinephrine reuptake inhibitors (SNRIs), are effective in alleviating both pain and psychiatric symptoms in patients with CRPS.

Genetic Factors

Increasing evidence implicates genetic predisposition in CRPS pathogenesis. Studies have identified associations between CRPS and several major histocompatibility complex (MHC) alleles, including human leukocyte antigen (HLA)-DR6, HLA-DR13, HLA-DR2, HLA-DQ1, HLA-B62, and HLA-DQ8, as well as a promoter polymorphism in the TNF- α gene.⁹⁴ Notably, HLA-B62 and HLA-DQ8 have been associated with CRPS with fixed dystonia, while HLA-DQ8 alone is associated with CRPS without dystonia.^{95,96} The presence of these alleles in affected individuals supports the hypothesis that autoimmune mechanisms may contribute to CRPS pathogenesis.⁷² Moreover, patients with CRPS exhibit significantly elevated expression of the matrix metalloproteinase 9 (MMP9) gene compared to healthy controls, suggesting a role in pain progression.⁹⁷ Recent research has also identified several hub genes, including MMP9, Prostaglandin-Endoperoxide Synthase 2 (PTGS2), C-X-C Motif Chemokine Ligand 8 (CXCL8), Oncostatin M (OSM), and Talin 1 (TLN1), as being associated with CRPS, providing novel insights into potential therapeutic targets.⁹⁸

Psychological Factors

Psychological factors are both potential risk factors and consequences of CRPS.⁹⁹ The CRPS is associated with adverse psychological outcomes such as depression and anxiety, as well as psychosocial challenges, including reduced quality of life and impaired occupational functioning. Children with CRPS report experiencing more stressful life events than those with other chronic pain conditions, such as headaches or abdominal pain.¹⁰⁰ Furthermore, the prevalence of posttraumatic stress disorder (PTSD) is significantly higher in individuals with CRPS than in the general population.¹⁰¹ According to Levit-Binnun et al, disturbances in sensory, motor, and regulatory functions may serve as behavioral indicators of increased vulnerability to future psychological challenges.¹⁰²

The influence of psychological factors in the development of CRPS has been well-documented. A higher number of stressful life events is associated with an increased risk of developing CRPS type I.¹⁰³ In an extensive retrospective cohort study, Pereira et al found that those with preexisting anxiety or mood disorders had a significantly elevated risk of CRPS I following fractures (hazard ratio, upper limb: 1.8; lower limb: 2.2).¹⁰⁴ Similarly, a meta-analysis on risk factors for CRPS after radius fractures showed that psychiatric conditions significantly increased CRPS incidence (relative risk: 2.04; 95% confidence interval: 1.83–2.28).¹⁰⁵

One proposed mechanism linking psychological and psychiatric conditions to CRPS involves chronic stress-induced elevations in systemic catecholamine levels.¹⁰⁶ Elevated catecholamine levels may sustain autonomic dysfunction, contributing to CRPS pathogenesis. Moreover, psychological stress is associated with increased production of proinflammatory mediators, potentially exacerbating CRPS-related inflammation.²

Other Mechanisms

Vasomotor Disturbance

In patients with CRPS, the affected limb often exhibits an imbalance between vasoconstrictive and vasodilatory mediators, with elevated endothelin-1 (a potent vasoconstrictor) and reduced nitric oxide (a powerful vasodilator) compared to the unaffected limb.¹⁰⁷ This imbalance results in vasoconstriction and tissue hypoxia, promoting acidosis and free radical production. These metabolic changes activate nociceptors and contribute to peripheral sensitization.

Oxidative Stress

Oxidative stress results from an excess of reactive oxygen species (ROS) overwhelming the body's antioxidant defenses. Free radicals generated via the mitochondrial respiratory chain are hypothesized to contribute to the pathophysiology of CRPS I. Taha et al reported evidence of mitochondrial dysfunction in muscle tissue from patients with CRPS I. However, it remains unclear whether oxidative stress and mitochondrial dysfunction are causative factors or secondary effects of CRPS I.¹⁰⁸ Therapeutic strategies targeting mitochondrial dysfunction have included compounds that activate endogenous antioxidant enzymes through nuclear transcription factors such as nuclear factor erythroid 2-related factor 2 (Nrf2) and mitochondria-targeted antioxidants including Mito-Vitamin E and Mito-Coenzyme Q.¹⁰⁸

Altered Cutaneous Innervation

Multiple studies have demonstrated altered cutaneous innervation in CRPS. Histopathological analyses of CRPS I-affected limbs have revealed degeneration of small nerve fibers, specifically C and A-delta (A δ) fibers.^{109,110} Morellini et al hypothesized that reduced cutaneous nerve fiber density increases the distance between nerve endings and dermal mast cells, weakening chemotactic signaling. Given the critical role of mast cells in immune responses and wound healing, this disruption may prolong inflammation and impair tissue repair.¹¹¹ Moreover, the upregulation of α 1-adrenoceptors in CRPS-affected skin may suppress nerve growth factor production, impairing neurite outgrowth and further disrupting nerve-mast cell communication.¹¹¹ Conversely, Yvon et al analyzed peripheral nerves in a patient with CRPS; they found selective degeneration of only A α fibers (responsible for motor function and proprioception) and C fibers (pain perception), while A δ fibers (nociceptive) remained intact. The loss of A α fibers may disrupt nerve signaling, leading to aberrant activation of intact A δ fibers, which mediate pain and autonomic responses.¹¹² Further research is needed to elucidate the precise role of altered cutaneous innervation in CRPS pathophysiology.

Complement Activation

The complement system is a cascade of plasma proteins that, upon activation, initiate enzymatic reactions resulting in cell lysis. Emerging evidence supports the role of complement activation in the pathogenesis of CRPS. In animal models of neuropathic pain following peripheral nerve injury, microglial cells become strongly activated and stimulate various complement components.⁴⁵ In a study by Shi et al, intraplantar injection of CRPS-derived IgM elevated C5a levels in wild-type mice and increased C1q levels in B-cell-deficient mice. These IgM-induced effects were attenuated by a C5a receptor antagonist (PMX53) or a broad-spectrum cytokine inhibitor (pentoxifylline).¹¹³ Further research is needed to clarify the role of the complement system in CRPS and to inform the development of novel therapeutic strategies.

Gut Microbiota

The microbiota-gut-brain axis is believed to contribute to CRPS pathophysiology; however, its role remains unclear. Gut microbiota can interact with immune cells and macrophages through TLRs, triggering the release of proinflammatory mediators. They can also secrete factors that influence nociceptor excitability by targeting receptors on the DRG neurons and modulate glial activity directly or through intermediary pathways.¹¹⁴ Crock et al proposed that gut microbiota influence metabolic pathways, immune responses, and microglial activation, contributing to CRPS development and persistence.¹¹⁵ Reichenberger et al analyzed the gut microbiome of 16 patients with CRPS (including five with intestinal discomfort) and 16 healthy controls using deoxyribonucleic acid (DNA) and ribosomal ribonucleic acid (RNA) sequencing. Patients with CRPS showed significantly more diverse lower gut microbiota and elevated Proteobacteria levels. These alterations were associated with heightened inflammation and microglial activation, potentially contributing to CRPS pathogenesis.¹¹⁶ Further research is needed to clarify the role of microbiota, which may provide a foundation for novel therapeutic strategies in CRPS.

Pharmacological Treatment

The CRPS is a complex disorder with no single causative mechanism. Multiple intricate pathophysiological processes are believed to contribute to its diverse clinical presentations. This complexity presents significant challenges in establishing standardized, evidence-based treatment protocols. Although several therapeutic algorithms using various medications have been proposed, no universal regimen for CRPS treatment currently exists. The key pharmacologic options currently

Table 2 Mechanisms of Action and Pharmacologic Interventions for Complex Regional Pain Syndrome (CRPS)

Drugs	Mechanism of Action
NSAIDs	Inhibit COX enzymes, reducing prostaglandin synthesis and inflammation
Corticosteroids	Reduce inflammation by inhibiting cytokine production and immune response
Free oxygen radical scavengers	Neutralize ROS, reduce oxidative stress and inflammation
Bisphosphonates	Modulate the acidic microenvironment and immune response
Gabapentin	Modulate calcium channels, reducing neuronal excitability
Carbamazepine	Block sodium channels, reducing neuronal excitability
TCA's	Inhibit serotonin and norepinephrine reuptake, enhancing pain inhibition
SNRIs	
Opioids	Bind to opioid receptors in the CNS, modulate pain perception
NMDA receptor antagonists	Block NMDA receptors and reduce NMDA receptor activity in the CNS, resulting in decreased central sensitization
IVIg therapy	Reduce inflammation, neutralize pathogenic autoantibodies, suppress B-cell-mediated autoantibody production, and inhibit cytotoxic T-cell activity
PE	Reduce autoantibodies and proinflammatory cytokines in serum
Cytokine modulation	Inhibit proinflammatory cytokines (such as TNF- α antagonist, IL-1 receptor antagonist) or promote anti-inflammatory effects (such as recombinant IL-10)
LDN	Block TLR4 receptor, regulate glial cell activation to reduce cytokine release in the CNS
α -adrenergic antagonists	Block α -adrenergic receptors, reduce vasoconstriction and sympathetic overactivity
α -adrenergic agonists	Reduce sympathetic outflow, modulate pain and vasodilation
Capsaicin	Act on TRPV1, reducing pain sensation
BTX-A	Inhibit neurotransmitter release related to pain transmission
Calcitonin	Inhibit inflammatory processes, providing central analgesic effects

Abbreviations: NSAIDs, nonsteroidal anti-inflammatory drugs; COX, cyclooxygenase; ROS, reactive oxygen species; TCAs, tricyclic antidepressants; SNRIs, serotonin-norepinephrine reuptake inhibitors; CNS, central nervous system; NMDA, N-methyl-D-aspartate; IVIG, intravenous immunoglobulin; PE, plasma exchange; TNF- α , tumor necrosis factor alpha; IL, interleukin; LDN, low-dose naltrexone; TLR4, toll-like receptor 4; TRPV1, transient receptor potential vanilloid 1; BTX-A, botulinum toxin A.

employed in CRPS management are summarized in [Table 2](#) to support clinicians in selecting appropriate pharmacologic interventions tailored to individual patients.

Prevention of CRPS

ROS are known contributors to CRPS development. Vitamin C (ascorbic acid), an antioxidant, neutralizes ROS, protects cell membranes, maintains microcirculatory integrity, reduces vascular permeability and edema, and has been shown to prevent CRPS I following orthopedic surgery or trauma.¹¹⁷ Multiple systematic reviews and meta-analyses have demonstrated that high-dose Vitamin C (ascorbic acid) (500–1000 mg/day for 45–50 days) significantly reduces the incidence of CRPS I following orthopedic procedures.^{117–121} In these studies, vitamin C was consistently more effective than placebo in preventing CRPS I.¹¹⁸ However, a meta-analysis by Evaniew et al examining patients with distal fractures reported unclear efficacy and low-quality evidence regarding the use of vitamin C for CRPS prevention before

surgery.¹²² Thus, although high-dose vitamin C has demonstrated efficacy in some studies, its routine use for CRPS prevention before surgery remains controversial.

Anti-Inflammatory Drugs

An exaggerated inflammatory response is a central feature of CRPS pathophysiology. Accordingly, anti-inflammatory agents offer a targeted, mechanism-based therapeutic approach. Standard options include nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids, and free radical scavengers.

Nonsteroidal Anti-Inflammatory Drugs (NSAIDs)

The NSAIDs exert their effects by inhibiting cyclooxygenase (COX), an enzyme essential for prostaglandin synthesis—key mediators of inflammation and pain.¹²³ Despite their widespread use, evidence supporting the efficacy of selective COX-2 inhibitors (such as celecoxib) in CRPS is limited. A recent meta-analysis by Zhu et al reported no significant difference in therapeutic outcomes between NSAIDs and placebo.¹²⁴ Furthermore, NSAIDs carry risks of cardiovascular and gastrointestinal side effects, warranting cautious use in clinical practice.¹²⁵

Corticosteroids

Corticosteroids are frequently employed in CRPS management due to their potent anti-inflammatory properties. They suppress the expression of multiple inflammation-related genes activated during chronic inflammation, thereby alleviating swelling, pain, and immune responses.¹²⁶ Moreover, corticosteroids may inhibit microglial activation in the central nervous system, thereby reducing central sensitization and promoting pain relief.¹²⁷ The efficacy of oral corticosteroids in controlling inflammatory symptoms, such as edema, localized warmth, and erythema, in patients with CRPS has been demonstrated in several studies. However, evidence supporting their analgesic effects remains limited.^{124,128,129} A systematic narrative review by Kwak et al suggests that prednisolone may help alleviate various CRPS symptoms, including pain, sensory and motor disturbances, edema, and limited range of motion.¹²⁸ A scoping review by Her et al indicates that systemic corticosteroids provide effective short-term pain relief but do not lead to improved functional outcomes.¹²⁹ However, a meta-analysis by Zhu et al reveals that corticosteroids did not produce significant analgesic effects in the short or long term. Moreover, the study reports that glucocorticoids are safe, exhibiting no significant difference in adverse events compared to that of a placebo.¹²⁴ Overall, while evidence regarding the analgesic efficacy of systemic corticosteroids in CRPS remains inconsistent, their safety profile appears to be well-established. Regarding dosage, earlier studies administered 30 to 100 mg/day of prednisolone. Conversely, several reports suggest that even 30 mg/day can yield significant clinical benefits, suggesting it is an optimal dose. Moreover, a comparative study found no significant difference in efficacy between low-dose (30 mg/day) and high-dose (60 mg/day) regimens, supporting the lower dose's effectiveness and safety. While typical treatment duration ranges from 1 to 3 months, shorter courses of 1–2 weeks have shown effectiveness. Approximately 30% of patients may experience mild, reversible side effects, including gastrointestinal discomfort, mood changes, and weight gain.¹²⁸

Free Radical Scavengers

Antioxidants such as dimethyl sulfoxide (DMSO) and N-acetylcysteine (NAC) have also demonstrated efficacy in CRPS treatment. A 2003 randomized, double-dummy controlled, double-blind trial involving 146 participants revealed that both topical 50% DMSO (applied five times daily) and oral NAC (600 mg, three times daily) administered over 17 weeks were effective in treating CRPS I. DMSO was preferred for warm CRPS I, while NAC appeared to be favored for cold CRPS I. However, the therapeutic efficacy of both agents diminished with longer disease duration.¹³⁰ A meta-analysis by Zhu et al later reported that DMSO was ineffective for short-term pain relief,¹²⁴ and the evidence supporting NAC's benefits in CRPS remains insufficient. Overall, the effectiveness of DMSO and NAC in CRPS management remains controversial.¹³¹

Bisphosphonates

Bisphosphonates, primarily known for their anti-osteoclastic properties, have demonstrated analgesic efficacy in treating CRPS.¹³² However, the exact mechanism underlying their pain-relieving effects remains unclear. A recent study reported

elevated osteoblastic activity in acute CRPS, while osteoclastic activity was not elevated. This finding suggests that bisphosphonates work through mechanisms beyond osteoclast inhibition.¹³³ One proposed mechanism involves modulation of the acidic microenvironment characteristic of CRPS. Bisphosphonates may reduce proton concentration in bone tissue, thereby decreasing activation of acid-sensing nociceptors and alleviating pain.¹³⁴ Moreover, bisphosphonates exhibit immunomodulatory effects, by inhibiting the production of proinflammatory mediators.^{135–137} Their analgesic benefit may also relate to the clinical presence of osteopenia or osteoporosis in patients with CRPS, conditions that reflect altered bone metabolism and heightened nociceptor sensitivity to mechanical or chemical stimuli. By stabilizing bone turnover and improving bone density, bisphosphonates help alleviate pain in this patient population. A scoping review by Her et al also suggested that oral and intravenous bisphosphonates are effective in reducing pain and improving function in patients with CRPS.¹²⁹ A meta-analysis by Chevreau et al, incorporating four randomized controlled trials (RCTs) (n=181), found that bisphosphonates significantly reduced pain in the short term (within 40 days) and mid-term (months 2–3) in patients with CRPS I, without serious adverse events.¹³⁴ In contrast, another meta-analysis by Zhu et al reported no significant pain reduction during the first month but demonstrated meaningful pain relief thereafter, also with a favorable safety profile.¹²⁴ Despite differences in the timing of therapeutic effects, both meta-analyses support bisphosphonates as an effective and safe treatment option for pain management in patients with CRPS.

Anticonvulsants

Gabapentin, a first-line agent for neuropathic pain,¹³⁸ exerts its effect by inhibiting the $\alpha_2\delta$ subunit of voltage-dependent calcium channels, thereby reducing neuronal excitability. However, studies evaluating gabapentin's role in CRPS are limited. Van de Vusse et al conducted a randomized, double-blind, placebo-controlled crossover study in 58 patients with CRPS I. They found that gabapentin produced mild pain relief and significantly improved sensory deficits in the affected limb.¹³⁹ In a prospective study by Tan et al, 22 patients with CRPS received an initial gabapentin dose of 600 mg/day, which was titrated until adequate pain control was achieved. The results confirmed gabapentin's efficacy in pain reduction, although it did not affect other CRPS symptoms.¹⁴⁰ Pregabalin, sharing a mechanism similar to gabapentin, is widely used in clinical settings; however, its effectiveness in CRPS is supported only by case reports.^{141,142}

Carbamazepine, a first-line treatment for trigeminal neuralgia, inhibits voltage-gated sodium channels to prevent repetitive neuronal firing.¹⁴³ In an RCT by Harke et al, 22 patients with CRPS I who had previously responded to spinal cord stimulation were administered 600 mg/day of carbamazepine for 8 days while stimulation was paused. The results suggested modest analgesic benefits.¹⁴⁴ Oxcarbazepine, a derivative of carbamazepine with a similar mechanism but fewer adverse effects, has not yet been evaluated in patients with CRPS.²

Clinical evidence supporting the use of anticonvulsants in CRPS remains limited, underscoring the need for further robust research to establish their efficacy.

Drugs Enhancing Descending Inhibitory Activity

Antidepressants, including TCAs and SNRIs, enhance descending inhibitory pain pathways by inhibiting norepinephrine reuptake at the presynaptic membrane. However, research on their effectiveness in CRPS is limited. Brown et al conducted an RCT including 34 patients aged 7–18 years with CRPS I or neuropathic pain, randomly assigning them to receive either 10 mg amitriptyline or 300 mg gabapentin. Both drugs significantly reduced pain intensity and improved sleep, with no significant difference between them in pain relief or sleep outcomes.¹⁴⁵ TCAs and SNRIs are established agents in neuropathic pain management.¹⁴⁶ Moreover, antidepressants can offer dual benefits in CRPS, as psychiatric comorbidities are common in these patients. The α_2 -adrenergic agonists, such as clonidine, enhance descending inhibition by stimulating presynaptic α_2 -receptors in the central nervous system. This inhibitory action reduces excitatory neurotransmitter release and attenuates pain signal transmission at the spinal cord level.

Opioids

Opioids relieve pain in CRPS by binding to mu(μ)-opioid receptors in the central and peripheral nervous systems, inhibiting nociceptive neurotransmission.¹⁴⁷ Although they may be effective for short-term pain control in early-stage CRPS, prolonged use is discouraged. Repeated opioid administration can activate glial cells, potentially worsening

neuropathic pain.¹⁴⁸ While low-dose opioids can be considered as second- or third-line treatment options, dose escalation should be avoided due to the risks of overdose and opioid-induced hyperalgesia. Evidence on the effectiveness of opioids in treating CRPS is very limited. In the two available RCTs,^{144,149} opioids (morphine) were used in combination with other drugs, making it difficult to isolate their specific therapeutic effect.

NMDA Receptor Antagonists

The activation and upregulation of NMDA receptors in the dorsal horn of the spinal cord play a crucial role in the “wind-up” phenomenon. Increased excitability of primary afferent nociceptors amplifies incoming pain signals, contributing to the development of central sensitization. The NMDA antagonists exert their effects by blocking NMDA receptors, thereby reducing receptor activity in the central nervous system¹⁵⁰ and attenuating central sensitization.

Ketamine

Ketamine is a well-known NMDA receptor antagonist. Several studies have highlighted its efficacy in treating CRPS. Sigtermans et al conducted a randomized, double-blind, placebo-controlled trial involving 60 patients with chronic CRPS I; 30 received a 4-day intravenous low-dose ketamine infusion (max 0.43 mg/kg/h), and the other 30 received a placebo. Ketamine significantly reduced pain for up to 11 weeks, although it did not improve functional outcomes. Psychomimetic side effects, such as hallucinations, dysphoria, and derealization, were common but generally tolerable and transient.¹⁵¹ In another randomized, double-blind, placebo-controlled trial, Schwartzman et al studied 19 patients with severe CRPS. Nine received low-dose intravenous ketamine (up to 0.35mg/kg/hour for 4 hours daily over 10 days) and ten received a placebo. The ketamine group experienced significant pain relief lasting up to 12 weeks, with no significant psychomimetic side effects reported.¹⁵² According to a meta-analysis by Zhu et al, ketamine provides adequate short-term analgesia in CRPS with moderate certainty and without severe adverse effects.¹²⁴

Magnesium

Magnesium is a naturally occurring element vital for various cellular processes, including enzyme activation and DNA synthesis. In the nervous system, it functions as a competitive NMDA receptor antagonist, helping modulate abnormal neural activity. However, findings on the effectiveness of magnesium sulfate (MgSO₄) in those with CRPS I have been inconsistent. Collins et al conducted an RCT involving 10 patients with CRPS I, where one group (eight patients) received intravenous MgSO₄ (70 mg/kg), and the other two received 0.9% NaCl over 4 hours daily for 5 days. Results showed significant improvements in pain, function, and quality of life with MgSO₄, which was well tolerated.¹⁵³ Conversely, Fischer et al replicated this design in a larger RCT, with 29 patients receiving MgSO₄ and 27 receiving a placebo. They concluded that the MgSO₄ offered no significant benefit in chronic CRPS compared to the placebo.¹⁵⁴ A recent meta-analysis by Zhu et al also reported that MgSO₄ did not provide substantial short- or long-term pain relief compared to placebo.¹²⁴

Immune Modulation

Intravenous Immunoglobulin

The mechanism by which IVIG exerts therapeutic effects in CRPS remains unclear. It is believed to work by reducing inflammation, neutralizing pathogenic autoantibodies, suppressing B-cell-mediated autoantibody production, and inhibiting cytotoxic T-cell activity.¹⁵⁵ However, RCTs investigating IVIG's efficacy in CRPS have shown inconsistent results. An RCT by Goebel et al conducted in 2010 reported that low-dose IVIG (0.5 g/kg) reduced pain in patients with refractory CRPS.⁷³ Conversely, a subsequent multicenter, Phase III randomized, placebo-controlled trial by the same group, conducted in 2017, found no significant benefit.⁷⁴ The discrepancy between these two studies may be attributed to differences in sample size and disease duration.¹⁵⁶ In the 2010 study, Goebel et al⁷³ enrolled only 13 patients with CRPS, while the study⁷⁴ in 2017 included a significantly larger sample of 111 patients. The average duration of CRPS was 1.6 ± 0.7 years and 2.4 ± 0.9 years, respectively, in 2010⁷³ and 2017⁷⁴ studies. Therefore, one possible explanation for the greater efficacy of IVIG in the study by Goebel et al in 2010⁷³ compared to 2017⁷⁴ is that patients were enrolled at

a comparatively earlier stage of the disease. Nevertheless, given these conflicting results and the high cost of IVIG, larger, well-designed studies are needed to determine its actual therapeutic value.

Plasma Exchange

Plasma exchange (PE) therapy, or plasmapheresis, is a promising treatment option for CRPS, particularly due to its presumed autoimmune basis. However, current evidence is limited, primarily comprising retrospective studies,¹⁵⁷ case reports,¹⁵⁸ and case series.¹⁵⁹ In a retrospective study of 33 patients with CRPS, Aradillas et al¹⁵⁷ reported significant pain relief in 30 patients with long-standing disease. Sustained improvement was achieved with ongoing maintenance therapy using weekly PE, IVIG, or other immunomodulatory agents.¹⁵⁷ Notably, six patients who did not receive maintenance therapy experienced a recurrence of pain to baseline levels. However, evidence supporting the efficacy of PE therapy in CRPS remains limited, as most studies are case reports, case series, or retrospective analyses. Therefore, well-designed prospective studies are needed to verify the therapeutic value of PE.

Cytokine Modulation

Cytokine modulation represents a novel therapeutic approach in CRPS management. Immunomodulatory agents inhibiting proinflammatory cytokines (such as TNF- α antagonists and IL-1 receptor antagonists) or exerting anti-inflammatory effects (such as recombinant IL-10) can reduce peripheral sensitization and relieve pain. The potential of TNF- α antagonists in CRPS has been demonstrated in case reports and one RCT. Huygen et al reported two CRPS I cases successfully treated with infliximab, demonstrating clinical improvement and marked reductions in local TNF- α and IL-6 levels, suggesting a role for anti-TNF therapy.¹⁶⁰ In a preliminary double-blind RCT, Dirckx et al studied 13 patients with CRPS (six in the infliximab group and seven in the placebo group). They observed that although infliximab did not yield significant clinical improvement, a trend toward TNF- α reduction indicated potential anti-inflammatory effects.¹⁶¹ In a pilot case series, Eisenberg et al treated 10 patients with CRPS I with subcutaneous adalimumab injections, reporting variable individual responses—some with notable relief and functional improvement—although no significant overall effect was noted.¹⁶² Given the low level of evidence, potential cost, and adverse effects—including injection site reactions, infusion reactions, neutropenia, and increased risk of severe infections,¹⁶³ TNF- α antagonist therapy in CRPS should be approached cautiously and further investigated through higher-quality studies. In CRPS animal models, recombinant IL-10¹⁶⁴ and IL-1 receptor antagonists (such as anakinra)¹⁶⁵ have shown promising results, warranting additional clinical research to assess their potential in human treatment.

Glial Modulation

Low-Dose Naltrexone

Low-dose naltrexone (LDN) involves administering naltrexone at subtherapeutic doses—typically 1–5 mg per day—much lower than Food and Drug Administration (FDA)-approved levels for opioid or alcohol dependence. LDN has been shown to suppress glial inflammation via TLR4 signaling and enhance endogenous opioid activity through transient opioid receptor blockade.^{166,167} Chopra et al reported significant clinical improvement in two patients with severe, long-standing CRPS following 2 months of LDN and reduced ketamine usage.¹⁶⁶ Similarly, Weinstock et al described a case of chronic CRPS in a patient with Ehlers–Danlos syndrome achieving sustained remission following a multimodal treatment regimen—including LDN—targeting small intestinal bacterial overgrowth, obstructive sleep apnea, and neuroinflammation.¹⁶⁸ The LDN is cost-effective, well tolerated, and has no known abuse potential. However, data on optimal dosing and long-term safety remain limited.¹⁶⁹ Moreover, as naloxone is an opioid antagonist, it may diminish opioid efficacy if used concurrently. Therefore, the effectiveness and safety of LDN in CRPS should be validated through rigorous, high-quality clinical trials.

Potential Glial Activation Inhibitors

Glial activation inhibitors, such as ibudilast and propentofylline, offer therapeutic effects by acting on glial cells. Ibudilast inhibits TLR4 signaling,¹⁷⁰ whereas propentofylline suppresses proinflammatory cytokine production.¹⁷¹ Both ibudilast^{172–174} and propentofylline^{173,175} have demonstrated analgesic and anti-allodynia effects in animal models

of neuropathic pain, suggesting their potential role in treating CRPS. However, further research is needed to validate their efficacy and safety in clinical settings.

Alpha-Adrenergic Modulators

Alpha-Adrenergic Agonists

Alpha(α)-adrenergic agonists reduce sympathetic activity by mimicking the inhibitory effects of norepinephrine, thereby suppressing preganglionic sympathetic neurons. These agents effectively treat CRPS-related pain, which involves heightened sympathetic nervous system activity.¹⁷⁶ Clonidine, the most commonly used α -adrenergic agonist, can be administered orally, transdermally, intravenously, or epidurally.^{177–179} Epidural clonidine administration provides pain relief for up to six hours in severe CRPS cases, though it is associated with significant side effects, including sedation and hypotension.¹⁸⁰ While clonidine is effective in alleviating pain, its systemic use is limited by centrally mediated side effects.

Alpha-Adrenergic Antagonists

Alpha(α)-adrenergic antagonists are used when an overactive sympathetic system causes pain. Phenoxybenzamine and phentolamine, both α -adrenergic antagonists, are occasionally considered third-line treatments for CRPS. However, minimal clinical evidence supports their efficacy, with only a few studies available.² Furthermore, their use is often limited in practice due to a high incidence of adverse effects, including hypotension, tachycardia, vomiting, dizziness, and headache.⁴⁹

Topical Treatment

Topical medications act locally by targeting dermal nerve endings, blood vessels, and skin cells. Their primary advantage is a low risk of systemic side effects, with skin irritation and allergic reactions being the primary concerns. Potential topical treatments for CRPS include 5% lidocaine patches, 8-methyl-N-vanillyl-noneamide (capsaicin), and DMSO. The lidocaine 5% patch, commonly used for postherpetic neuralgia,¹⁸¹ may also provide analgesia in CRPS. Capsaicin, a selective transient receptor potential vanilloid 1 (TRPV1) agonist, has demonstrated efficacy in specific neuropathic pain conditions, though evidence for its use in CRPS is limited to a few case reports.^{182,183} A retrospective study of 12 patients with CRPS suggested capsaicin may help reduce pain intensity and the affected area size.¹⁸⁴ However, its application is often limited by intense local burning sensations. The DMSO 50% cream has shown therapeutic benefit in CRPS I.¹³⁰ Moreover, Russo et al conducted a retrospective study involving 13 patients with CRPS treated with a compound analgesic cream (CAC) containing ketamine 10%, pentoxifylline 6%, clonidine 0.2%, and DMSO 6%–10%, reporting symptom relief in nine patients.¹⁸⁵ These findings suggest that this topical combination could be a valuable addition to multimodal therapy for CRPS patients. Previous studies on topical treatment for CRPS are limited; most have a very low level of evidence.

Other Drugs

Botulinum Toxin-A

Botulinum toxin-A (BTX-A), widely used for treating movement disorders and spasticity, modulates neuronal exocytosis and temporarily blocks the presynaptic release of neurotransmitters—primarily acetylcholine and SP—at the neuromuscular junction.¹⁸⁶ It also inhibits the release of pain-related neurotransmitters, making it a potential therapy for neuropathic pain.¹⁸⁷ However, research on BTX-A for CRPS remains limited and yields mixed outcomes. Carroll et al conducted a randomized, double-blind, crossover trial involving nine patients with refractory CRPS I. They found that adding BTX-A to a lumbar sympathetic block substantially prolonged the anesthesia compared to the block alone (median 71 vs <10 days). The treatment was well tolerated, with minimal adverse events, and considerably reduced the pain intensity over time. These results suggest that sympathetic block combined with BTX-A may offer a promising non-destructive approach to CRPS pain management.¹⁸⁸ Similarly, Yoo et al reported in an RCT that lumbar sympathetic block with BTX-A raised the affected foot's temperature for three months and alleviated pain without severe adverse events.¹⁸⁹ Conversely, Safarpour et al conducted a pilot study using intradermal and subcutaneous BTX-A in 14 patients

with CRPS-related allodynia and observed no significant pain relief. Most patients discontinued treatment due to poor tolerability and injection-related discomfort.¹⁹⁰ In summary, sympathetic ganglion block with BTX-A shows potential as a safe and effective option for CRPS pain relief.^{186,191} However, further well-designed studies are necessary to support widespread clinical adoption.

Calcitonin

Calcitonin treats CRPS because it inhibits inflammatory processes and provides central analgesic effects.^{192,193} Gobelet et al conducted a double-blind, randomized study, involving 66 patients with CRPS, dividing them into two groups of 33 each. Group I received 300 IU/day of salmon calcitonin via intranasal spray, while group II received three sprays of a placebo. Both groups received conventional rehabilitative treatment. Their study found that salmon calcitonin significantly improved pain relief and ROM.¹⁹⁴ Bickerstaff et al conducted an RCT including 40 patients with CRPS randomized into two groups of 20 for 4 weeks. The intervention group received 400 IU of nasal calcitonin, while the control group received saline. No additional treatments were administered during the study. Results showed no substantial differences in pain reduction, swelling, stiffness, vascular instability, or strength between the calcitonin and placebo groups.¹⁹⁵ Sahin et al studied 35 patients with CRPS I in an RCT, dividing them into two groups: one group of 17 patients received paracetamol (1500 mg/day), and the other group of 18 patients received 200 IU/day of salmon calcitonin for 2 months, along with conventional physical therapy. Both groups showed considerable improvement in symptoms such as hyperalgesia, tropic changes, and allodynia, with no significant difference between treatments.¹⁹⁶ Due to conflicting results from previous studies, using calcitonin in CRPS remains limited in clinical practice.

Summary of Pharmacological Treatment

Currently, no universally accepted pharmacological treatment is considered optimal for CRPS. However, current evidence allows a tentative ranking of available pharmacological treatments according to their efficacy and the quality of supporting research findings.

Bisphosphonates and ketamine demonstrate the most consistent analgesic efficacy in meta-analyses, reporting no serious adverse events, therefore making them preferred treatment options. Systemic corticosteroids are widely used in clinical practice and are generally regarded as safe; however, their analgesic effectiveness remains controversial across studies.

Neuropathic pain medications—including anticonvulsants (eg, gabapentin, pregabalin), TCAs, and SNRIs—are commonly prescribed for CRPS, but evidence supporting their use in CRPS is limited and is primarily extrapolated from studies on broader neuropathic pain conditions.

Opioids are occasionally prescribed for CRPS, and the evidence supporting their effectiveness is sparse and insufficient to recommend routine use.

Meta-analyses show that NSAIDs, magnesium sulfate, and free radical scavengers (eg, DMSO and NAC) lack significant analgesic benefit and are therefore not recommended as core treatment options.

BTX-A, particularly when administered to the stellate ganglion or other sympathetic regions, demonstrates efficacy and safety in a limited number of studies. However, supporting evidence remains scarce. Calcitonin has yielded conflicting results across studies and is infrequently used in clinical practice. Similarly, alpha-adrenergic modulators are not routinely recommended owing to limited research and a higher risk of adverse effects.

Topical agents, including ketamine cream and lidocaine, remain under-investigated but may offer localized symptom relief.

Finally, emerging therapies, such as immunomodulatory approaches (eg, IVIG and PE) and cytokine or glial cell modulation (eg, TNF- α antagonists and LDN), show preliminary promise in small studies and case reports, but high-quality clinical trials are needed to validate their efficacy and safety.

Future pharmacological research in CRPS should prioritize high-quality RCTs to confirm the efficacy and safety of promising agents such as bisphosphonates and ketamine. Additionally, further studies are needed to better define the role of routinely used medications such as systemic corticosteroids and neuropathic pain medications (anticonvulsants, TCAs, and SNRIs). Emerging therapies—including immunomodulatory agents (eg, IVIG and PE) and cytokine or glial

modulators (eg, TNF- α antagonists and LDN)—also warrant further investigation. Future trials should also be designed to account for different CRPS subtypes and disease stages, facilitating the identification of patient groups most likely to benefit from targeted treatment approaches. Additionally, greater attention should be given to evaluating the long-term efficacy of pharmacological treatments.

Rehabilitation

Rehabilitation is considered one of the primary treatment options for patients with CRPS,¹⁹⁷ as it has been reported to be effective in managing symptoms. This approach emphasizes an interdisciplinary or multidisciplinary strategy focused on pain reduction and functional restoration.

Cortically Directed Sensory-Motor Rehabilitation

Patients with CRPS may experience neglect-like symptoms, where the affected limb feels foreign (“cognitive neglect”), and directed mental and visual attention is required to move it (“motor neglect”).¹⁹⁸ As described in the mechanism of CRPS section, cortical reorganization is thought to cause disturbances in body perception. This reorganization correlates with pain intensity and mechanical hyperalgesia,⁷⁸ and it can reverse in parallel with clinical improvements in CRPS.⁷⁶ Furthermore, incongruence between motor intention, proprioception, and vision in patients with CRPS is hypothesized to contribute to the affective sensation of pain. The goal of cortically directed sensory-motor rehabilitation is to reverse cortical reorganization, restore the integrity of sensorimotor cortical information processing, or both.^{198–200} This training includes mirror therapy (MT), graded motor imagery (GMI), and virtual reality (VR).

Mirror Therapy

Mirror therapy (MT) involves the movement of the extremities within a mirror box, where the visual feedback of the affected hand is replaced with that of the unaffected hand reflected in the mirror (Figure 4). MT is believed to aid in reversing cortical changes and restoring accurate sensorimotor processing in the brain.¹⁹⁸ Several studies have investigated the effectiveness of MT in treating CRPS. Cacchio et al conducted an RCT involving 48 patients with CRPS I with upper extremity involvement, dividing them into two groups: the MT group (n=24) and the control group (n=24). Both groups participated in a 4-week standard stroke rehabilitation program consisting of five 1-hour sessions weekly, including neurorehabilitation, occupational therapy, and optional speech therapy.²⁰¹ The MT group received additional MT, starting with 30 minutes per session in the first 2 weeks and 1 hour per session in the final 2 weeks. At the 6-month follow-up, the MT group showed significant improvements in pain relief, functional ability, and mean performance time, while the control group exhibited no notable changes. Considerable differences were observed in the MT group compared to the control group, after treatment and at the 6-month follow-up. Pervane Vural et al conducted an RCT on 30 patients with CRPS I with upper limb involvement following a stroke, randomly assigning them to the MT group (n=15) or the control group (n=15). Both groups participated in a 4-week conventional stroke rehabilitation program (5 days/week, 2–4 hours/day), which included neurodevelopmental facilitation techniques, occupational therapy,

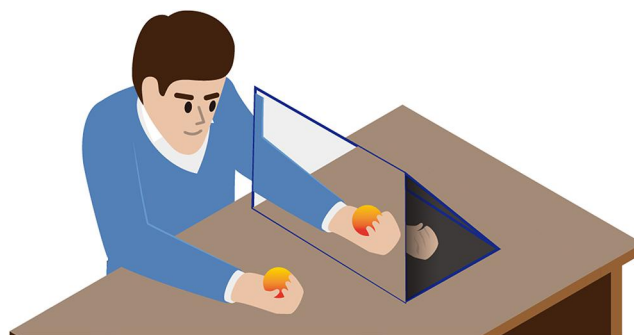


Figure 4 Mirror therapy for complex regional pain syndrome (CRPS). This figure illustrates a patient with CRPS affecting the left hand. The patient positions the left hand behind a mirror, and the therapist demonstrates a simple hand movement. The patient is instructed to replicate the movement with both hands, focusing on the reflection of the right (unaffected) hand in the mirror.

physiotherapy, and speech therapy (if required).²⁰² The MT group also received 30 minutes of daily MT. Both groups showed significant improvements in pain relief and independent motor function, with the MT group demonstrating more substantial gains, including significant improvements in hand and arm motor recovery and hand function. In an RCT involving 38 patients with CRPS with upper limb involvement following a stroke, Saha et al reported that MT significantly improved edema, pain, and hand function, with significant differences compared to the control group.²⁰³ Shafiee et al conducted a meta-analysis and demonstrated that adding MT to conventional stroke rehabilitation results in substantial improvements in pain [standardized mean difference (SMD): 1.88, 95% CI: 0.73 to 3.02] and disability (SMD: 1.3, 95% CI: 0.11 to 2.49) in patients with CRPS I after stroke, with effects lasting up to 6 months.²⁰⁴ More extensive studies involving patients with various CRPS classifications are needed to more accurately assess the effectiveness of MT.

Graded Motor Imagery

Graded motor imagery (GMI) is known to help reverse cortical alterations and restore precise sensorimotor processing in patients with CRPS.²⁰⁰ GMI comprises hand laterality recognition, imagined hand movements, and MT (Figure 5). Moseley et al conducted an RCT with 13 patients with chronic CRPS, dividing them into two groups: an intervention group (received GMI and conventional treatment, n=7) and a control group (received conventional treatment only, n=6).²⁰⁰ Each component was conducted over 2 weeks. The study found that GMI significantly reduced pain compared to the control group after 12 weeks of follow-up. In the meta-analysis by Shafiee et al, GMI was shown to lead to significant improvements in pain (SMD 1.36, 95% CI 0.75 to 1.96) and disability (SMD 1.64, 95% CI: 0.53 to 2.74) in patients with CRPS.²⁰⁴

Virtual Reality

Virtual reality (VR) therapy has been developed to treat chronic pain and has shown promising outcomes for various conditions, including CRPS.²⁰⁵ The VR therapy aims to replace real sensory experiences with a simulated, computer-generated environment.²⁰⁶ It is hypothesized that VR therapy can promote brain reorganization, which can help relieve pain in patients with CRPS.²⁰⁷ Moreover, VR therapy assists in developing coping skills, supports daily activities, boosts mood, and reduces the fear of movement, all of which positively impact CRPS treatment. Lewis et al conducted an RCT involving 45 patients with refractory upper-limb CRPS and BPD. In the intervention group (n=23), patients viewed a digital image of their affected hand for one minute, which was modified based on their description of how they wanted it to appear. The control group (n=22) viewed the unaltered image.²⁰⁸ Lewis et al found that visual body illusion improved pain and BPD in those with chronic CRPS, with pain reduction lasting at least 2 weeks.²⁰⁸ Several other studies also reported the positive effects of VR therapy on pain relief or BPD improvement in CRPS.^{209–212} However, further high-quality studies are needed to draw definitive conclusions about the effectiveness of VR therapy in CRPS treatment.

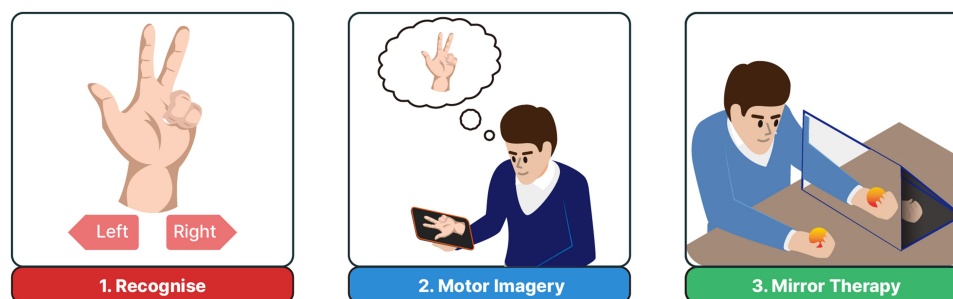


Figure 5 Graded motor imagery program for complex regional pain syndrome (CRPS). The graded motor imagery program consists of three sequential components, each typically lasting about two weeks: (1) recognition of hand laterality, (2) imagined hand movements, and (3) mirror therapy. (1) Patients with CRPS are asked to determine whether the pictured limbs are left or right. (2) Patients view images of the affected limb (in this case, the left hand) performing simple activities and are instructed to mentally simulate these movements. (3) For mirror therapy, the affected hand is placed behind a mirror, and patients focus on the reflection of the unaffected hand while replicating movements with both hands.

Exercise

Exercise is increasingly recognized for its potential to alleviate pain and improve physical function in CRPS. Exercise benefits CRPS treatment through mechanisms such as central and peripheral nervous system remodeling, vasodilation regulation, adrenaline level modulation, endogenous opioid release, and increased anti-inflammatory cytokines.²¹³ Exercise in CRPS should follow a gradual progression, starting with passive ROM exercises, then transitioning to active ROM exercises, followed by stress loading, aerobic training, and eventually load-bearing exercises.²

Oh et al reported a case of CRPS I in which the patient showed reduced pain and swelling, along with functional improvement, after 20 days of passive ROM exercises administered under sedation.²¹⁴

Topcuoglu et al conducted a 4-week prospective RCT involving 40 patients with post-stroke CRPS I with affected upper limbs, randomly assigned to an intervention group (n=20) receiving arm crank ergometry (5 W/min, 5 days a week, for 30 minutes per session) combined with conventional physiotherapy, and a control group (n = 20) receiving only conventional physiotherapy.²¹⁵ The intervention group reported significantly greater pain relief compared to controls. Shafiee et al, in a meta-analysis, demonstrated that incorporating aerobic exercise into conventional treatment significantly improved CRPS-related pain (SMD 0.86, 95% CI 0.23 to 1.5).²⁰⁴

Additional exercise approaches, including strength training, proprioception exercises, functional task practice, postural training, and hydrotherapy, are also used in CRPS management,²¹⁶ though further studies are needed to confirm their effectiveness.

Exposure Therapy

Exposure therapy involves gradually confronting situations or activities that provoke fear. In CRPS, it can help reduce kinesiophobia and fear of skin contact, alleviating psychological symptoms and promoting greater engagement in rehabilitation. Consequently, exposure therapy may contribute to pain reduction in patients with CRPS.

Pain exposure physical therapy (PEPT) is a commonly used exposure therapy technique for patients with CRPS. The PEPT combines physical exercise with the management of pain-avoidance behaviors to treat chronic pain. Ek et al reported a case series of 106 patients with CRPS I treated with PEPT. In their study, 95 patients (90%) showed functional improvement in the affected limbs, and 49 (46%) achieved full functional recovery after 3 months of treatment. Moreover, 75 patients (71%) experienced pain reduction, and only four discontinued due to increased pain. The authors concluded that PEPT is effective and safe for CRPS management.²¹⁷ Similarly, Van de Meent et al evaluated PEPT in 20 patients with CRPS I in a multiple single-case design study and supported its safety and effectiveness.²¹⁸ Barnhoorn et al conducted an RCT involving 56 patients with CRPS I, with 28 receiving PEPT and 28 receiving conventional treatment. The PEPT group demonstrated greater pain relief and improved active ROM.²¹⁹ Den Hollander et al conducted another RCT involving 46 patients with CRPS I, where 23 patients receiving pain exposure (including daily activity training and education) showed significantly more pain reduction than those receiving conventional pain-reducing therapy (n=23).²²⁰ Based on the studies by Barnhoorn et al and den Hollander et al, a meta-analysis by Shafiee et al also confirmed that pain exposure therapy leads to significant pain reduction (SMD 0.81, 95% CI 0.12 to 1.49), with effects lasting up to six months post-treatment.²⁰⁴

Moreover, tactile and thermal desensitization techniques are frequently used in clinical CRPS management; however, no clinical trials have evaluated their efficacy.

Transcutaneous Electrical Nerve Stimulation

Transcutaneous electrical nerve stimulation (TENS) delivers electrical currents to stimulate nerves and modulate pain perception.²²¹ It is widely used in clinical settings for pain management. Although its precise mechanisms remain unclear, TENS is believed to work via the gate control theory of pain,²²¹ the release of endogenous opioids,²²² reduction in central excitability, and peripheral α -adrenergic receptor blockade.²²² Bilgili et al conducted an RCT involving 30 patients with upper-extremity CRPS I, randomly assigned to two groups. The experimental group (n=15) received 20 minutes of active TENS, while the control group (n=15) received sham TENS. Patients in the experimental group

showed significantly greater improvements in pain, edema, and ROM in the second and third fingers compared with controls.²²³

Thermal Therapy

Thermal therapy, including the application of heat or cold, is another approach used in CRPS management. Fluidotherapy circulates warm, dry air and fine solid particles to deliver heat and tactile stimulation to affected limbs, thereby alleviating pain.²²⁴ Sezgin Ozcan et al in an RCT administered 15 sessions of fluidotherapy (five sessions/week in 3 weeks) alongside conventional stroke rehabilitation to 15 patients with post-stroke CRPS I. Outcomes were compared with another 15 patients with post-stroke CRPS I who received only conventional stroke rehabilitation. The group receiving fluidotherapy demonstrated greater reductions in neuropathic pain and edema.²²⁴ Sethy et al in an RCT compared fluidotherapy combined with stress-loading exercises (n=11) to routine occupational therapy (n=11), and reported significantly greater improvements in pain, arm function, and disability in patients receiving the combined intervention.²²⁵

Contrast bath therapy, another commonly used thermal intervention in clinical practice, involves alternating immersion of the affected limb in warm and cold water. Protocols vary in temperature ranges, immersion times, and overall duration. Cold water typically ranges from 7.2°C to 22°C, and warm water from 26.7°C to 45°C. A standard protocol begins with 10 minutes in warm water, alternated with a 1-minute dip in cold water, followed by alternating 4 minutes in warm water and 1 minute in cold water for 3–4 cycles over 30 minutes. Some protocols omit the initial warm phase and use a 4:1 or 3:1 warm-to-cold ratio.²²⁶ Although the exact mechanism remains unclear, contrast bath therapy is believed to induce cycles of vasodilation and vasoconstriction, producing a vascular pumping effect that enhances tissue perfusion and oxygenation, thereby reducing edema and pain.²²⁷ Furthermore, it has been shown to significantly reduce sympathetic activity on the affected side in patients with post-stroke CRPS.²²⁸

Summary of Rehabilitation

Rehabilitation plays a key role in the multidisciplinary management of CRPS, aiming to alleviate pain, restore limb function, and prevent chronic disability. Although studies remain limited, approaches such as MT, GMI, and PEPT show promising analgesic effects and are considered potential therapeutic options. Other physiotherapeutic interventions may also offer benefits; however, given the limited available evidence, their effectiveness should be interpreted with caution. Moreover, most rehabilitation studies for patients with CRPS have small sample sizes and are primarily focused on individuals with CRPS type I. Therefore, to establish more comprehensive evidence on rehabilitation strategies for CRPS, future studies should prioritize high-quality RCTs involving patients with different CRPS subtypes. Additionally, greater emphasis should be placed on evaluating the long-term effectiveness of rehabilitation interventions.

Conclusion

CRPS is a multifactorial condition involving a complex interplay of immune and neuroimmune responses, peripheral and central sensitization, autonomic dysregulation, and maladaptive neuroplasticity. Nonetheless, a comprehensive understanding of CRPS pathophysiology has remained necessary, especially to resolve ongoing controversies related to mechanisms such as autoimmunity. The involvement of various mechanisms in CRPS highlights the need for individualized, multidisciplinary therapeutic strategies. Although several pharmacological options have been proposed, there is insufficient evidence to fully support their effectiveness and safety. Corticosteroids, ketamine, and bisphosphonates appear to be relatively safe and effective options for clinical use. Moreover, rehabilitation approaches, including cortically directed sensory-motor rehabilitation, ROM or aerobic exercises, exposure therapy, TENS, and thermal therapy, should be considered integral components of CRPS treatment. Currently, no universally accepted pharmacological or rehabilitative “best treatment” approach exists for CRPS, forcing clinicians to base their therapeutic decisions on the best available evidence. Therefore, future research should prioritize high-quality, large-scale, and long-term clinical trials to help establish standardized treatment protocols, ultimately improving prognosis and quality of life for patients with CRPS.

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Disclosure

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