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STATE OF THE ART REVIEW

Complex regional pain syndrome

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ABSTRACT

Complex regional pain syndrome is a chronic pain condition characterized by autonomic and inflammatory features. It occurs acutely in about 7% of patients who have limb fractures, limb surgery, or other injuries. Many cases resolve within the first year, with a smaller subset progressing to the chronic form. This transition is often paralleled by a change from "warm complex regional pain syndrome," with inflammatory characteristics dominant, to "cold complex regional pain syndrome" in which autonomic features dominate. Multiple peripheral and central mechanisms seem to be involved, the relative contributions of which may differ between individuals and over time. Possible contributors include peripheral and central sensitization, autonomic changes and sympatho-afferent coupling, inflammatory and immune alterations, brain changes, and genetic and psychological factors. The syndrome is diagnosed purely on the basis of clinical signs and symptoms. Effective management of the chronic form of the syndrome is often challenging. Few high quality randomized controlled trials are available to support the efficacy of the most commonly used interventions. Reviews of available randomized trials suggest that physical and occupational therapy (including graded motor imagery and mirror therapy), bisphosphonates, calcitonin, subanesthetic intravenous ketamine, free radical scavengers, oral corticosteroids, and spinal cord stimulation may be effective treatments. Multidisciplinary clinical care, which centers around functionally focused therapies is recommended. Other interventions are used to facilitate engagement in functional therapies and to improve quality of life.

Introduction

Complex regional pain syndrome (CRPS) is a chronic pain condition characterized by spontaneous and evoked regional pain, usually beginning in a distal extremity, that is disproportionate in magnitude or duration to the typical course of pain after similar tissue trauma.[1]

CRPS is distinguished from other chronic pain conditions by the presence of signs indicating prominent autonomic and inflammatory changes in the region of pain. In its most severe form, patients present with a limb displaying extreme hyperalgesia and allodynia (normally non-painful stimuli such as touch or cold are experienced as painful); obvious changes to skin color, skin temperature, and sweating relative to the unaffected side; edema and altered patterns of hair, skin, or nail growth in the affected region; reduced strength; tremors; and dystonia.[2] Altered body perception and proprioception may also be present, reflected in reduced limb positioning accuracy, delays in recognizing limb laterality, abnormal referred sensations and tactile perception, and altered subjective mental representations of the affected limb.[3-8] The syndrome is often associated with serious impairments in activities of daily living and ability to function.[9-12]

First recognized as a distinct pain condition during the American civil war,[13] CRPS has been known since that time by various names, including reflex neurovascular dystrophy, neuroalgodystrophy, shoulder-hand syndrome, reflex sympathetic dystrophy, and causalgia.

The dramatic nature of its presentation, limited understanding of its mechanisms, and frequent lack of response to intervention has led to clinical confusion and misunderstanding in the past. Research into CRPS and consequently understanding of the condition have grown extensively in the past 20 years, although understanding remains incomplete. Even now, the simple question of whether complex regional pain syndrome should be classified as a neuropathic pain condition remains a subject of debate among experts in the area.[14 15]

As currently conceptualized, CRPS is subdivided into type I and type II on the basis of absence or presence, respectively, of clinical signs of major peripheral nerve injury (such as nerve conduction study abnormalities). Despite this clinical distinction, core diagnostic features are identical across both subtypes, which adds to the confusion about the role of neuropathic mechanisms.

This review summarizes the current state of knowledge about CRPS, including its epidemiology, pathophysiological mechanisms, diagnosis, natural course, prevention, and treatment. Although complete understanding of the syndrome remains a work in progress, this review aims

HOW PATIENTS WERE INVOLVED IN THE CREATION OF THIS ARTICLE

The perspective of patients with complex regional pain syndrome (CRPS) was incorporated into the final article on the basis of comments made on an initial draft by a patient with CRPS and James Broatch, executive vice president/director of the Reflex Sympathetic Dystrophy Syndrome Association (RSDSA). The RSDSA is the primary CRPS patient advocacy organization in the United States.

Box 1 | Current International Association for the Study of Pain clinical diagnostic criteria for complex regional pain syndrome[1]

- Continuing pain, which is disproportionate to any inciting event
- Must report at least one symptom in three of the four following categories*:
  - Sensory: Reports of hyperalgesia and/or allodynia
  - Vasomotor: Reports of temperature asymmetry and/or skin color changes and/or skin color asymmetry
  - Sudomotor/edema: Reports of edema and/or sweating changes and/or sweating asymmetry
  - Motor/trophic: Reports of decreased range of motion and/or motor dysfunction (weakness, tremor, dystonia) and/or trophic changes (hair, nails, skin)
- Must display at least one sign at time of evaluation in two or more of the following categories*:
  - Sensory: Evidence of hyperalgesia (to pinprick) and/or allodynia (to light touch or deep somatic pressure, or joint movement)
  - Vasomotor: Evidence of temperature asymmetry and/or skin color changes and/or asymmetry
  - Sudomotor/edema: Evidence of edema and/or sweating changes and/or sweating asymmetry
  - Motor/trophic: Evidence of decreased range of motion and/or motor dysfunction (weakness, tremor, dystonia) and/or trophic changes (hair, nails, skin)
- There is no other diagnosis that better explains the signs and symptoms

*For research settings in which it is desirable to maximize specificity, a more stringent research diagnostic decision rule requires all four of the symptom categories and at least two of the sign categories to be positive for diagnostic criteria to be met.

to dispel some misunderstandings that have continued despite recent advances.

Incidence

Two questions about the incidence of CRPS are of interest. The first is how commonly the condition occurs in the general population, and the second is how commonly it occurs after injuries that are known to trigger it.

Incidence in the general population

Two retrospective population based studies have assessed the incidence of CRPS in the general population. Both found that it is three to four times more common in women than in men, more commonly affects the upper limbs, and peaks in incidence at 50-70 years of age.[16 17] Estimates from both studies reflect the 1994 International Association for the Study of Pain (IASP) diagnostic criteria for CRPS.[18] In a study conducted in the United States, incidence rates of CRPS type I and CRPS type II were reported as 5.46 per 100 000 person years and 0.82 per 100 000 person years, respectively.[16] A population study in the Netherlands reported an incidence of CRPS type I and type II combined (based on clinician diagnoses of CRPS confirmed against 1994 IASP criteria in 93% of cases) of 26.2 cases per 100 000 person years[17]—more than four times higher than that noted in the US sample.

More specific diagnostic criteria were adopted in 2012 as the new international standard for the diagnosis of CRPS by the IASP (box 1),[1] and these criteria have been shown to reduce CRPS diagnostic rates by about 50%.[17 19 20] The earlier estimates may therefore provide an upper limit of the incidence of CRPS as currently defined in the general population. The US Food and Drug Administration and the European Medicines Agency have granted CRPS an orphan disease designation on the basis of their determination that fewer than 200 000 people in the US and fewer than 154 000 people in the European Union are affected each year.[21 22]

Incidence after injury

In the general population, CRPS seems to occur most often after fracture (>40% of CRPS cases in two population based studies[16 17]), although sprains, contusions, crush injuries, and surgery are also known triggers.[2] The best information on the incidence of CRPS after injury comes from two large prospective studies of fracture patients (n=596; n=1549).[23 24] Using the most restrictive research version of the 2012 IASP criteria,[25] the incidence of CRPS was 3.8-7.0% within four months of fracture.[23 24]

A slightly higher incidence (8.3%) was reported in a large (n=301) prospective study of patients undergoing carpal tunnel release.[26] In summary, only a minority of people develop CRPS even after the most common precipitating event—fracture. The fact that some people develop CRPS and others with similar injuries do not underlies the importance of understanding the pathophysiological mechanisms of CRPS.

Sources and selection criteria

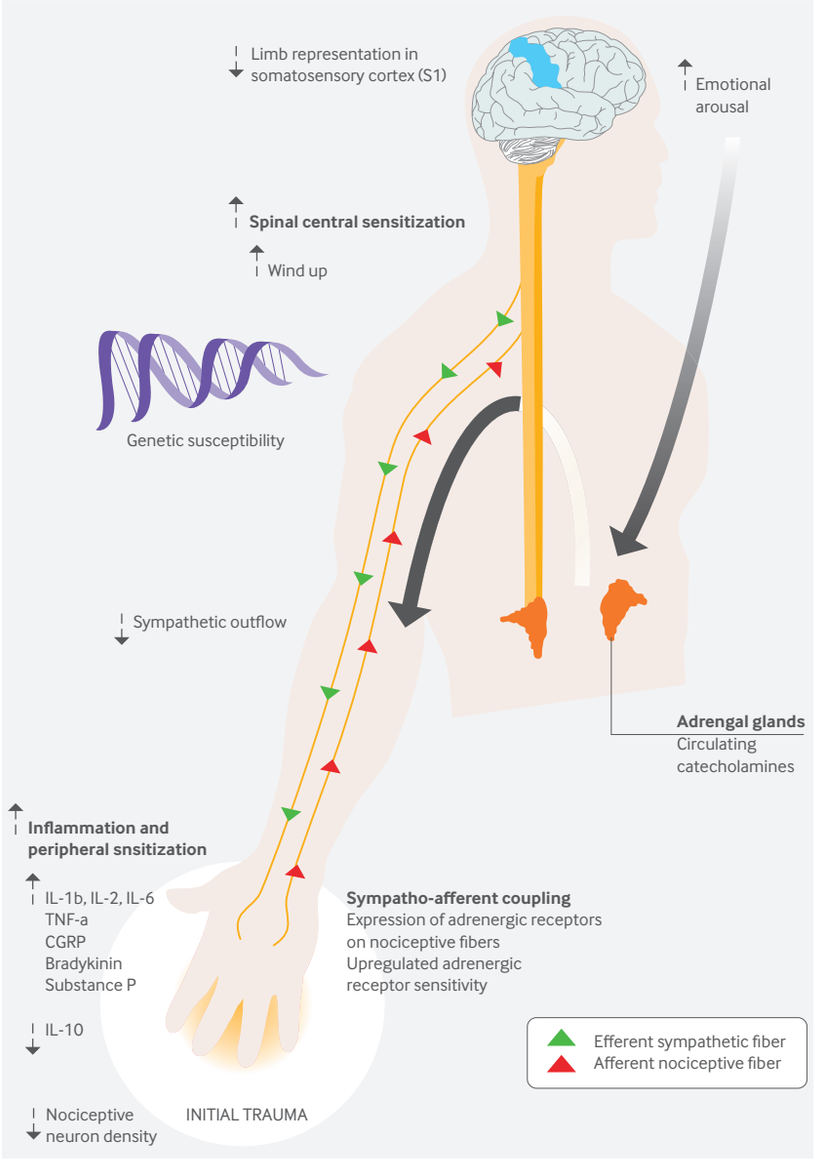
The PubMed database was searched from 1985 to 1 October 2014 using the terms "complex regional pain syndrome", "reflex sympathetic dystrophy", "causalgia", "CRPS", and "RSD". Bibliographies of articles were also searched for other relevant studies. A selective narrative review is provided below that does not incorporate a systematic quality assessment of the literature. Studies presented below are those that the author judged to be representative of the highest methodological quality (for example, prospective studies) or most relevant to the topics discussed.

Pathophysiology

In contrast to past attempts to reduce CRPS to a single mechanism (such as sympathetically maintained pain),[27] it is now generally agreed that the syndrome is caused by a multifactorial process involving both peripheral and central mechanisms.[28 29] Although there is evidence for a role of each of the mechanisms below in the development or expression of CRPS (box 2), little is known experimentally about how these mechanisms might interact to produce CRPS. Given the diversity of presentations seen in CRPS, the relative contributions of different mechanisms probably differ across individual patients and even within patients over time. The figure provides a speculative model of interacting mechanisms involved in the development of CRPS.

Box 2 | Possible mechanisms involved in complex regional pain syndrome

- Nerve injury[31-34]
- Ischemic reperfusion injury or oxidative stress[35-40]
- Central sensitization[41-43]
- Peripheral sensitization[44 45]
- Altered sympathetic nervous system function or sympathoafferent coupling[46-52]
- Inflammatory and immune related factors[53-77]
- Brain changes[78-89]
- Genetic factors[90-92]
- Psychological factors and disuse[93-103]



Speculative model of interacting mechanisms involved in the development of complex regional pain syndrome. CGRP=calcitonin gene related peptide; CRPS=complex regional pain syndrome; IL=interleukin; SNS=sympathetic nervous system; TNF=tumor necrosis factor. Adapted, with permission, from Bruehl[30]

Factors related to the initiating injury

Although CRPS is reported to occur without clear antecedent injury (or no specific injury that is recalled by the patient) in a small number of cases, most cases occur after known tissue injury. One key mechanistic question that is still debated is: what aspects of the initiating injury trigger the development of CRPS?

One important trigger seems to be the extent to which a proinflammatory and immunological response is elicited by the initiating injury. Evidence from animal fracture models of CRPS type I suggest that changes after injury, such as B cell activation and increased interleukin 1β (IL-1β) and substance P signaling, are crucial for the development of CRPS.[53-55]

A recent human study suggests that after injury persistently raised concentrations of osteoprotegerin, an osteoclastogenesis inhibitory factor, may also have a role in determining whether tissue injury resolves normally or evolves into CRPS.[104] On the basis of findings in a different animal model of CRPS type I,[35] ischemic reperfusion injury and related microvascular disease in deep tissues after injury have also been suggested as triggers for the onset of CRPS.[36] These processes have been shown to produce similar inflammatory responses and clinical characteristics (allodynia, hyperalgesia, edema, and altered vasoconstriction) to those seen in acute CRPS.[35 37]

It has also been suggested that nerve injury itself may trigger CRPS. A clinical distinction is made between CRPS type I and CRPS type II, with CRPS type II being distinguished by evidence of peripheral nerve injury. Nonetheless, similar injuries can trigger both CRPS subtypes, and the nature of these injuries (for example, fractures, crush injuries, and surgery) could all plausibly be associated with some degree of nerve injury. Some studies report decreased C-fiber and A-δ fiber density in the affected limbs of patients with CRPS type I,[31-33] although others report that such changes were seen in only a subset (20%) of these patients.[34] These last findings suggest that such changes may reflect an occasional consequence or correlate of CRPS type I rather than a consistent cause.

Central and peripheral nociceptive sensitization

After tissue or nerve injury, the nervous system adapts in a manner that enhances responsiveness to pain and increases inflammation; this protects the injured area and leads to avoidance of activities that might cause further injury. These changes occur in both the peripheral and central nervous systems. Within the central nervous system, ongoing noxious input after tissue injury triggers central sensitization—an increase in the excitability of nociceptive neurons in the spinal cord that increase responsiveness to pain.[41] A role for central sensitization in CRPS is indicated by findings that the limb affected by CRPS (relative to unaffected limbs) exhibits increased temporal summation—a laboratory derived objective index believed to reflect central sensitization.[42 43] In the periphery, injury produces local changes to primary afferent fibers that increase background firing of nociceptors, increase firing in response to normally painful stimuli, and decrease the nociceptive firing threshold for thermal and mechanical stimuli.[44 45] Peripheral and central sensitization are mediated by the release of inflammatory mediators (such as bradykinin) and pronociceptive neuropeptides (such as substance P). In addition, proinflammatory cytokines also contribute to peripheral sensitization,[44] and the excitatory amino acid glutamate has a role in central sensitization through its activation of spinal N-methyl-D-aspartate (NMDA) receptors.[41 105] Both peripheral and central sensitization can contribute to some of the characteristic features of CRPS, including spontaneous pain, hyperalgesia, and allodynia.[41 44]

Altered sympathetic nervous system function and sympatho-afferent coupling

Other nervous system changes after injury that may also contribute to CRPS are altered function of the sympathetic nervous system and possible sympatho-afferent coupling. It has long been assumed that the sympathetic nervous system plays a key role in CRPS—the most common older label for CRPS type I was "reflex sympathetic dystrophy." Because patients with chronic CRPS commonly present

with a cold and sweaty limb, it was assumed that excessive sympathetic nervous system outflow was involved, and this was the rationale for using sympathetic ganglion blocks to reduce the symptoms of CRPS. However, a prospective study in patients early after fracture indicates that patients with reduced sympathetic nervous system outflow after injury are the ones at greatest risk of developing subsequent CRPS symptoms, with these changes noted to be bilateral despite unilateral injury.[46]

Other relevant nervous system changes after injury are more localized. One study found that within days after nerve injury, nociceptive fibers in the affected area, even when not directly injured, displayed increased firing in the presence of sympathetic nervous system activity.[106] Similar injuries have been shown to result in the expression of catecholamine receptors on nociceptive fibers,[47 48] leading to a situation in which sympathetic nervous system outflow or circulating catecholamines (released in response to pain or stress) might directly trigger firing of nociceptors (thus producing pain). This phenomenon is referred to as sympatho-afferent coupling.

Although this phenomenon has been directly observed in humans (through single nerve fiber recordings) in only a single case report,[49] it has been indirectly observed in several well controlled CRPS studies, suggesting it may play a role in the syndrome at least with regard to determining its severity.[50-52] Mechanisms by which reductions in function of the sympathetic nervous system after injury might eventually transform in many patients into a clinical picture more consistent with exaggerated sympathetic responses (reduced skin temperature, dusky skin color, increased sweating) are incompletely understood.

Inflammatory and immune related factors

Recent research has focused on the role of inflammatory and immune related mechanisms in CRPS, and animal models of CRPS type I also support a role for inflammatory mechanisms.[53 55] Evidence of the involvement of inflammatory mechanisms, especially in the acute phase, comes from studies documenting raised concentrations of proinflammatory neuropeptides and mediators (substance P, calcitonin gene related peptide, bradykinin) and cytokines (IL-1β, IL-2, and IL-6, and tumor necrosis factor α (TNF- α) in the systemic circulation, cerebrospinal fluid, and affected limbs of patients with CRPS.[56-65] These substances increase plasma extravasation (leading to edema), can produce vasodilation (leading to a warm red appearance in the affected area), and may increase hair growth and sweating.[66 67] Thus inflammatory mechanisms can induce several key clinical features of CRPS. There is evidence that the sympathetic nervous system is involved in facilitating inflammation after injury.[107 108] These findings show in principle that the various mechanisms that independently contribute to CRPS may interact.

Inflammation can be elicited not only enzymatically through the cyclo-oxygenase pathway, but also non-enzymatically through an oxidative stress pathway.[109 110] The ischemic reperfusion injury animal model described previously that reproduces many features of CRPS type I activates this oxidative stress pathway,[35 37] and pharmacological interventions that reduce oxidative stress in this model also reduce CRPS related symptoms.[35 38 39] Consistent with these animal data, at least one study indicates that indirect markers of oxidative stress are raised in patients with CRPS relative to healthy controls,[40] and this mechanism is the target of some CRPS interventions.

Although they did not specifically assess CRPS, several studies in patients undergoing limb surgery indicate that the use of a tourniquet (versus no tourniquet use) is associated with significantly greater pain and edema (up to six weeks after surgery); both of these features are characteristic of early CRPS.[111-113] Extended tourniquet use is known to be associated with ischemic reperfusion injury and raised oxidative stress.[35 114]

Immune related mechanisms are also probably involved in CRPS. For example, in a mouse model of CRPS type I, CRPS-like features including hyperalgesia and skin temperature changes emerge after limb fracture, but depletion of CD20+ B cells limits the development of these changes.[54] In humans, increased numbers of pro-inflammatory monocytes (CD14+ CD16+) and mast cells have been reported in patients with CRPS compared with healthy controls.[68-70] Altered innate immune responses (impaired neutrophil activity) have also been reported in patients with CRPS.[71]

Recent work suggests that antibodies from people with CRPS may be capable of transferring the condition to previously unaffected individuals, also supporting a role for immune mechanisms. IgG from patients with CRPS and a comparison group of healthy controls was given to mice that underwent a mild tissue injury.[72] Mice that received IgG from patients with CRPS, but not those that received IgG from controls, developed significant hyperalgesia and edema, both of which are characteristic of CRPS. Similar work found that IgG from patients with CRPS when injected into mice in the absence of any injury induced motor changes, another key characteristic of CRPS.[73] Data such as these have led to the suggestion that in some patients CRPS might be an expression of autoimmune processes.[74] This autoimmune model is further supported by the presence of autoantibodies directed against autonomic nervous system structures, including β_2 adrenergic and muscarinic type 2 receptors, in a subset of patients with CRPS.[75-77]

Brain changes

Brain imaging studies over the past decade suggest that several brain changes are associated with CRPS. Two studies indicate that endogenous pain inhibitory pathways (opioid mediated) in the brain are impaired in patients with CRPS, with greater impairments associated with greater severity of pain.[78 79] For CRPS of the upper limb, reduced representation of the affected limb in both primary and secondary somatosensory cortices has also been consistently noted,[80-83] a finding supported by a recent meta-analysis.[84] However, new data suggest a surprising source for these effects—an increase in the somatosensory representation of the *unaffected* limb in patients with CRPS.[85]

Meta-analysis indicates that not only are there somatosensory changes in CRPS, but also motor changes, specifically disinhibition of the primary motor cortex.[86] Beyond changes in brain function, structural changes

have also been noted—patients with CRPS showed reduced gray matter volume compared with healthy controls in brain regions underlying the affective component of pain (insula and cingulate cortex).[87]

Evidence suggests that the altered somatosensory representation in patients with CRPS can normalize with successful treatment.[88 89] In light of the similar normalization of specific brain changes (such as reduced gray matter volume) seen with successful treatment of other forms of chronic pain,[115 116] at least some of the brain changes in CRPS are likely to be an effect rather than a cause. Nonetheless, these changes seem to be related to symptom expression in some cases, as indicated by findings that clinical pain intensity in patients with CRPS is associated with the extent of some of the observed brain changes.[81-83]

Genetic factors

The role of genetic factors in CRPS is poorly understood. Studies that directly examined genetic associations with CRPS have identified several potential candidate polymorphisms, including those in genes encoding α1a adrenoceptors[90] and the HLA system (HLA-DQ8, HLA-B62).[91 92] The influences of the HLA system may be more prominent in patients with CRPS who have dystonia.[91 92] The identification of genetic influences in CRPS is made difficult by the heterogeneous phenotypic presentations related to different contributing mechanisms, as well as the need for large samples of a rare condition to produce conclusive findings.

Psychological factors

Psychological factors were assumed for many years to be involved in the development of CRPS partly because of clinical impressions that these patients were psychologically different from other patients with chronic pain. However, many studies suggest that patients with CRPS are not psychologically different from other patients with chronic pain and that psychological factors alone do not cause CRPS.[117] Comorbid axis I psychiatric disorders, mainly major depression, are common in patients with CRPS (24-49% of patients in various studies),[118-120] although their prevalence does not seem to be higher than in other chronic pain conditions.[119] Recent work suggests that patients with CRPS—particularly those with greater depression levels, higher pain intensity, and more functional impairments—have an increased risk of suicide.[118]

Evidence exists that psychological factors such as anxiety, depression, and anger expression may have a greater impact on pain in patients with CRPS than in those without.[93-95] This might be due to the effects of psychological distress on sympathetic nervous system arousal and catecholamine release and the potential impact of sympatho-afferent coupling on CRPS pain.[30]

In addition, prospective studies suggest that increased psychological distress in conjunction with physical injury might affect the later development of CRPS, or at least the condition's severity. In older patients undergoing total knee arthroplasty (n=77), greater increases in the extent of depressive symptoms from before surgery to one month after surgery predicted greater severity of CRPS symptoms at six month and 12 month follow-up.[96] Similar effects were seen for early increases in anxiety after surgery as a predictor of the severity of CRPS at six months.[96] In addition, preoperative anxiety significantly predicted the presence of a CRPS-like syndrome at one month after surgery, but not at three or six month follow-up.[97]

Similarly, in patients with an upper extremity fracture (n=50), higher anxiety (but not depression) two days after fracture predicted significantly higher risk of a diagnosis of CRPS at two to four month follow-up.[98] However, a larger prospective study of early post-fracture patients (n=596) found that none of the psychological variables assessed, including depression, predicted CRPS status at three month follow-up.[99] Nonetheless, the possible influence of anxiety on CRPS outcomes was not examined in this last study, leaving it unclear whether anxiety may contribute to the risk and severity of CRPS after injury.

Learnt disuse of the affected limb can also be considered a psychological factor, because it is typically the behavioral result of a desire to avoid pain, often driven by fear of future pain exacerbations.[100 101] Although expert opinion has long held that avoiding disuse and reactivating the affected limb are cornerstones of treatment,[121] only limited research supports this opinion. Results of one controlled human experimental study, however, do highlight the potential importance of disuse for CRPS. Among healthy people without CRPS (n=30), 28 days of upper limb casting in the absence of any injury resulted in pain with joint movement and several clinical features associated with CRPS, including hyperalgesia, hair growth changes (in a subset only), and skin temperature changes.[102]

The importance of disuse in the development of CRPS is also supported by recent animal work.[103] In a rat limb fracture model of CRPS type I, immobilization alone (casting) elicited the same increases in expression of inflammatory mediators (IL-1β, IL-6, TNF-α) and similar clinical changes (allodynia, temperature changes, and edema) as those elicited by limb fracture with casting.[103] Results such as these highlight the importance of early mobilization of the affected limb after injury to help prevent the development of chronic CRPS.

Natural course of CRPS

Clinical experience indicates that outcomes in patients with CRPS in tertiary pain care settings are often inadequate even with aggressive pain interventions. However, there are also reports suggesting high rates of resolution.[16] These discrepancies might be due to a substantial number of cases resolving with limited or no specific intervention early in the course of the condition, with a smaller subset of more persistent cases being seen in tertiary care pain clinics. A recent systematic review found some evidence to support this idea.[122]

Acute CRPS

The most convincing evidence would come from studies of untreated patients with CRPS because confounding with treatment effects would not influence the results. One study looked at the natural course of untreated CRPS.[123] Thirty patients with post-traumatic CRPS were followed without treatment for an average of 13 months after diagnosis; three patients were withdrawn from the study to be given treatment, and CRPS resolved over the

course of the study in 26 of the 30 patients.[123] Some may be skeptical of this extraordinarily high rate of CRPS resolution, yet other studies support relatively high, if not quite so dramatic, resolution rates for acute CRPS (operationally defined in this review as CRPS <1 year in duration). For example, in a prospective series of 60 consecutive patients with tibial fracture who underwent standard care, 14 of the 18 patients diagnosed with CRPS at bone union were free of CRPS at one year follow-up.[124] Neither of the studies above used the 1994 or current IASP diagnostic criteria, which may have influenced the results. However, the US population study of CRPS described previously, which applied the 1994 IASP criteria, similarly found that 74% of diagnosed CRPS cases resolved with relatively conservative care.[16]

Chronic CRPS

In contrast to these findings for acute CRPS, the limited data on the natural course of well established chronic CRPS (operationally defined as CRPS of >1 year in duration) suggest much lower resolution rates even with specialty pain care.[125] In one large (n=102) retrospective longitudinal study of patients over an average six year follow-up period, 30% of patients reported resolution of chronic CRPS (diagnosed using the 1994 IASP criteria), 16% reported progressive deterioration, and the remaining 54% reported stable symptoms.[126]

These findings underscore the importance of understanding how patterns of CRPS change over time. One question is how quickly CRPS emerges after injury. Although such data are sparse, the mechanisms involved in the emergence of CRPS (such as injury related sympathetic nervous system changes, peripheral and central sensitization, inflammatory and immune responses to injury) suggest that the initial onset of symptoms should occur within the first few weeks of the initiating event.

A prospective study in a large sample of post-fracture patients found that CRPS was more commonly diagnosed at three months after cast removal than at cast removal, and that diagnosis rates decreased after three months.[23] This suggests that CRPS develops during a three to four month window after the initiating injury. The onset of CRPS symptoms after this three to four month window seems to be increasingly unlikely and difficult to explain mechanistically.

Delayed healing versus emerging CRPS

It is clinically accepted that early intervention in CRPS will lead to better outcomes, although there are few high quality data to support this view. The potential importance of early diagnosis and intervention raises the question of how to distinguish between normal but delayed healing versus emerging CRPS. In both cases, an inflammatory presentation (a warm, red, and hypersensitive limb) is common.[97] One potential discriminating factor is suggested by studies indicating that more severe pain early after fracture predicts those who will develop CRPS.[24 127] This idea is supported by the finding that greater intensity of knee pain before surgery is a predictor of the development of CRPS after total knee arthroplasty.[97] Thus, a clinical rule of thumb might be that the greater the intensity of early pain and the longer a CRPS-like presentation persists, the more likely it is to be CRPS rather than delayed normal healing.

Warm and cold CRPS

Although not a formal diagnostic categorization, it is accepted that CRPS can be associated with two distinct presentations. "Warm CRPS" is associated with a warm, red, and edematous extremity, whereas "cold CRPS" presents with a cold, dusky, sweaty extremity. Acute CRPS is more often associated with a warm CRPS presentation, whereas chronic CRPS is more often characterized by a cold CRPS presentation,[128] although both subtypes can be seen in patients with CRPS of any duration.

Results of a retrospective longitudinal study reporting outcomes over an average eight year follow-up period suggest that CRPS is more likely to resolve in patients initially diagnosed with warm CRPS, the most common presentation in the acute CRPS phase, than in those initially diagnosed with cold CRPS.[129] Although there is no clear dividing line between acute and chronic CRPS, and these terms are inconsistently used in the literature, a recent prospective study of proinflammatory cytokines suggests that the inflammatory component that seems to underlie warm CRPS largely resolves within about 12 months of symptom onset, at least in patients on active treatment.[65]

This suggestion is supported by a recent report on patterns of cutaneous immune responses in patients with CRPS of different durations.[70] Local accumulation of mast cells was increased in CRPS of less than three months' duration but not in CRPS of longer than three months' duration.[70] Data regarding clinical features of CRPS also suggest that edema and warm or red skin, features caused by inflammatory processes, may become less prominent as the duration of CRPS increases.[2 128] These findings parallel observations of a transition from warm CRPS to cold CRPS as the condition becomes more chronic. One cross sectional study suggests that sympatho-afferent coupling, which may contribute to the sympathetically maintained component of CRPS pain, may also diminish over time.[130] The prospective cytokine data above suggest that the transition from inflammatory warm CRPS to cold CRPS may start during the first year after injury, providing a possible marker for the transition from acute to chronic CRPS.

Traditional CPRS stages

CRPS often changes in character over time, but the changes are highly variable—no definitive sequence of stages occurs in all patients. For many years, clinical lore has held that there are three sequential stages of CRPS during which symptom patterns change in a consistent way.[131] Contrary to this idea, two studies using statistical pattern recognition techniques found that when patients are categorized by symptom patterns into three groups, there is no difference in pain duration between groups.[126 132] Such findings argue more for CRPS subtypes rather than a uniform three stage sequential model.

CPRS spread

Data suggest that CRPS can spread outside of the originally affected limb,[133] although this is not a universal

phenomenon. A population based epidemiological approach is needed to define how common such spreading is. However, available studies in this area are based on samples from pain clinics that may be biased by referral patterns. For example, clinics that specialize in treating patients with CRPS probably receive more referrals of patients with extensive spreading, so data from such clinics would overestimate the frequency of spreading. Given this caveat, a retrospective study in 185 patients with CRPS (from a clinic specializing in treating CRPS associated with movement disorders) found that 48% reported spreading to another limb.[134]

Studies of patterns of CRPS spread suggest that proximal spread from the initial distal site of CRPS is common,[135] although in some cases this may reflect secondary myofascial pain related to altered use of the limb. The largest systematic study of CRPS spreading (n=185) suggests that contralateral spread is most common (mirror image spread), followed by ipsilateral spread (for example, hand to foot), or diagonal spread.[134] All four limbs were affected in more than 29% of cases in this study. The two most common spreading patterns (ipsilateral and contralateral) developed on average 19 months or more after the initial onset of symptoms,[134] although another study suggests that spreading may occur earlier.[135] Depending on the pattern of spread, Van Rijn and colleagues' results indicated that 37-91% of cases of spreading CRPS occurred in the context of a second trauma.[134] Mechanisms of spreading are not well understood. However, research in patients with unilateral CRPS found evidence of bilateral facilitated neurogenic inflammation,[136] bone demineralization,[137] impaired sympathetic nervous system function,[46] brain changes,[138 139] and systemically circulating autoantibodies against autonomic structures.[76 77] This suggests that bilateral systemic alterations in unilateral CRPS could contribute to later contralateral spread.

Diagnosis

Because the pathophysiological mechanisms of CRPS are not fully understood, mechanism based diagnosis is not yet feasible. Therefore, the diagnosis of CRPS is based solely on clinical signs and symptoms. The fact that objective tests are not needed for diagnosis is directly related to the lack of definitive pathophysiological mechanisms in CRPS that could serve as a gold standard against which such tests could be referenced.

Additional objective testing (thermography, triple phase bone scan, quantitative sudomotor axon reflex test, or a trial sympathetic ganglion block) is not necessary to make the diagnosis, but in some cases may be used to support a clinical diagnosis. Because bone changes are not currently part of the diagnostic criteria used to define CRPS,[1] the value of a triple phase bone scan to support a diagnosis of CRPS is questionable. During the diagnostic process, objective medical tests may be needed to rule out other conditions that could account for the signs and symptoms that would otherwise be used to support a diagnosis of CRPS, given that CRPS is explicitly a diagnosis of exclusion (see criterion 4 in box 1). For example, duplex ultrasound testing might be used to rule out a deep vein thrombosis as the cause of pain, hypersensitivity, edema, and skin temperature changes in one limb.

In the past, the diagnosis of CRPS (known by various names) was inconsistent and based on multiple competing diagnostic criteria, none of which was widely accepted.[140-143] In 1994 the IASP published consensus based diagnostic criteria for CRPS that it was hoped would become the internationally accepted standard for both research and clinical care.[18] Subsequent validation research found problems with lack of specificity and potential overdiagnosis using these criteria,[2 25 144 145] prompting an international effort to develop and validate CRPS diagnostic criteria with high sensitivity but better specificity.[25] The resulting criteria (often referred to as the Budapest criteria) became the official IASP diagnostic criteria for CRPS in 2012.[1] Although the new criteria retained the sensitivity of the 1994 criteria (0.99 *v* 1.00), the new criteria are notably more specific (0.68) than the 1994 criteria (0.41), thereby reducing false positive diagnoses.[25]

Unlike the 1994 IASP criteria, a clinical diagnosis of CRPS using the 2012 IASP criteria (box 1) requires the presence of both subjective symptom reports and objective signs on clinical examination. Because objective signs are now needed to make a diagnosis and CRPS related autonomic features (color and temperature changes) may be labile, evaluation of diagnostic criteria over several clinic visits may in some cases help ensure accurate diagnosis. The 2012 IASP criteria include an alternative, more stringent, decision rule for the diagnosis of CRPS in research settings that requires symptoms in all four symptom categories and at least two of four sign categories. These research criteria result in even greater diagnostic specificity (0.79) to enhance homogeneity of research samples (fewer false positive diagnoses).[25]

Treatment

Although data suggest that many acute cases of CRPS may resolve with conservative medical care, expert opinion is that chronic CRPS is a challenging and complex biopsychosocial condition. Chronic CRPS is most likely to respond to comprehensive, integrated multidisciplinary treatment that includes medical, psychological, and physical and occupational therapy components.[121] While this view is supported by clinical experience in patients with CRPS and numerous clinical trials of such programs in other types of chronic pain,[146] no randomized controlled trials (RCTs) of multidisciplinary care have been performed specifically in patients with CRPS.

Within an evidence based medicine approach, it would be preferable to use outcome data from RCTs to guide the management of CRPS as much as possible. It is beyond the scope of this article to provide a thorough review and evaluation of the CRPS treatment literature, and readers are referred to several systematic reviews and meta-analyses.[147-157] However, the results of two more recent reviews are described below.[150 153] Although the number of clinical trials in CRPS has been increasing in recent years,[154] each of the reviews published between 1997 and 2013 has drawn two general conclusions:

- There is little support from high quality RCTs for many of the most common treatment approaches to CRPS
- More and better quality clinical trials are needed in CRPS.

Summary of treatments for complex regional pain syndrome (CRPS)

Treatment	Category	Supporting RCT status
Multidisciplinary treatment	Standard	None
Physical and occupational therapy	Standard	Positive[150 153]
Oral corticosteroids (for acute CRPS)	Standard	Positive[150 162]
Anticonvulsants	Standard	Equivocal[164]
Analgesic antidepressants	Standard	None
Transdermal lidocaine	Standard	None
Opioids	Standard	None
Sympathetic nervous system blocks	Standard	Negative[150 153]
Spinal cord stimulation	Standard	Positive (<5 year efficacy)[167 168]
Pain focused psychological therapy	Standard	None
Graded motor imagery or mirror therapy	Uncommon	Positive[153 158]
Calcitonin	Uncommon	Positive[153]
Vitamin C (prevention after injury)	Uncommon	Positive[150 171-174 176]
Topical dimethylsulfoxide (DMSO)	Uncommon	Positive (warm CRPS)[150]
Oral N-acetylcysteine	Uncommon	Positive (cold CRPS)[150]
Bisphosphonates	Emerging	Positive[150 153 181-184]
Subanesthetic intravenous ketamine	Emerging	Positive[150 153 186 187]
Intravenous immunoglobulin	Emerging	Positive[189]
Oral tadalafil	Emerging	Positive[190]
Intrathecal baclofen (CRPS + dystonia)	Emerging	Positive[191]
Low dose oral naltrexone	Emerging	None

RCT=randomized controlled trial.

A 2013 Cochrane review of treatment for CRPS found at least low quality evidence for the efficacy of bisphosphonates, calcitonin, subanesthetic intravenous ketamine, graded motor imagery and mirror therapy (specific physical therapy interventions, with mirror therapy effective particularly in acute post-stroke CRPS), and CRPS focused physical and occupational therapy.[153] It also found low and medium quality evidence, respectively, that sympathetic ganglion blockade with local anesthetics and intravenous regional blocks with guanethidine are ineffective. Evidence was deemed insufficient to draw conclusions for other interventions.

There is moderate overlap between this Cochrane review and results of a systematic review published by a consortium of CRPS experts in the Netherlands.[150] This review found at least some evidence for the efficacy of subanesthetic intravenous ketamine, free radical scavengers (topical dimethylsulfoxide, oral N-acetylcysteine, or oral vitamin C for prevention), oral corticosteroids, bisphosphonates, calcium channel blockers, intravenous ketanserine, surgical sympathectomy, spinal cord stimulation, and physical and occupational therapy.

Both reviews found that physical and occupational therapy, bisphosphonates, and subanesthetic ketamine might be effective, and there was some agreement that sympathetic blocks are probably ineffective. Of those treatments likely to be effective, functional therapies are described by experts as the cornerstone of CRPS treatment,[121] for reasons that are not entirely clear bisphosphonates are not routinely used, and ketamine is generally considered to be an experimental therapy and can be associated with serious side effects.

There is clearly a disconnect between clinical practice and the evidence base. This is underscored by the second review, which concludes that many standard treatments in clinical practice have no supporting evidence (absence of RCTs or negative trials) for efficacy in CRPS, including opioid analgesics, antidepressants, anticonvulsants, sympathetic ganglion blockade, or epidural sympathetic blockade using local anesthetics.[150]

In the absence of sufficient high quality evidence from RCTs to support treatment decisions, the clinical care of patients with CRPS must be guided by the collective experience of other clinicians, as reflected in standard practice (acknowledging that there may be regional biases towards particular treatments). It should be emphasized that clinical acceptance as part of standard care does not necessarily imply efficacy, unless also supported by RCTs. The table summarizes the treatments used in CRPS.

CRPS experts, even those who use more invasive interventional techniques, broadly agree that effective treatment should be functionally focused, centering around physical and occupational therapy designed to normalize use of the affected limb and mitigate problems related to disuse.[121] Best evidence suggests that mirror therapy and graded motor imagery should be included in these functional therapy protocols,[153 158] although a more recent trial of graded motor imagery in routine clinical practice (n=35) did not replicate the pain reducing effects seen in more highly controlled trials.[159] Limited research suggests that inclusion of an exposure therapy component to target fear of pain and fear of using the affected limb may also help.[160 161] Despite some evidence for their utility, the specific approaches above are not yet routinely included in functional therapy for CRPS except at specialty treatment centers.

Drug treatment

An initial trial of oral corticosteroids is often used in patients with acute phase CRPS to dampen the large inflammatory component believed to be common in the acute phase. Dosages of 30-40 mg per day of oral prednisolone for two weeks followed by a tapering period have been reported to be effective in acute CRPS.[162 163]

Other drugs commonly used in standard CRPS care include anticonvulsants (for example, gabapentin) and analgesic antidepressants (for example, duloxetine). One RCT suggests that gabapentin may have a small effect on pain in CRPS, with a somewhat larger effect on sensory deficits.[164]

The search strategy described above found no RCTs of the effects of antidepressants specifically in CRPS. Transdermal lidocaine patches applied to the affected area are a common component of early treatment, although no RCTs have evaluated their efficacy in CRPS. Each of these treatments is palliative rather than curative. Opioid analgesics are sometimes used if additional pain control is needed to facilitate engagement in functional therapies and resumption of more normal daily activities. Only one small RCT of opioid analgesics has included patients with CRPS (seven of 43 patients in the sample), with overall results indicating no significant analgesic effects of sustained release morphine (90 mg/day) over eight days.[165]

Ganglion blocks

In addition to oral and transdermal agents, if sympathetic ganglion blocks (stellate ganglion, lumbar sympathetic) have not already been used, and an initial trial indicates

they provide sufficient relief to improve participation in functional therapies, a series of several blocks at weekly intervals is often used. Sympathetic blocks have not been shown to have significant efficacy in patients with CRPS overall.[153] However, clinical experience and one small randomized trial (n=7) suggest that in some patients they may provide additional pain relief beyond the duration of action of the local anesthetics used (≥3 days[166]). There is no evidence that sympathetic blocks are curative for any patients.

Spinal cord stimulation

If after an extended trial (longer if CRPS is more acute) the above approach has not improved the patient's condition, it is common to move on to a trial of spinal cord stimulation. If this trial is successful, which it was in two thirds of patients (n=24/36) in the only RCT in these patients,[167] permanent implantation will follow, with continued emphasis on achieving improved function and normalizing daily activities. The one RCT of spinal cord stimulation in patients with CRPS (n=36 spinal cord stimulation; n=18 physical therapy) suggests it may be effective for pain reduction (but not necessarily functional improvement) for several years, but that efficacy is no greater than physical therapy alone five years after implantation.[167-169]

Psychological interventions

Given the psychosocial complexity of CRPS, it is generally agreed that inclusion of pain focused cognitive behavioral therapy is beneficial as part of standard care for chronic CRPS.[121 170] However, no RCT evidence is available specifically in patients with CRPS to support this belief.

Can CRPS be prevented?

Vitamin C

In the absence of efficacious treatments for CRPS, it would be preferable to prevent CRPS from developing. Several RCTs have been published on the use of vitamin C for the prevention of CRPS after limb fracture or surgery.[171-175] This treatment is based on the known antioxidant effects of vitamin C that could theoretically reduce the inflammatory mechanisms (related to oxidative stress) that are thought to contribute to acute CRPS. A meta-analysis of the first four published studies on this topic suggested that vitamin C significantly reduced the likelihood of CRPS developing after limb fracture or surgery (risk ratio 0.22, 0.12 to 0.39; n=616 for the vitamin C; n=449 for control),[176] with 500 mg vitamin C recommended daily for at least 45 days after injury or surgery. However, a recent large RCT (n=336) that used this protocol for the prevention of post-fracture CRPS found that vitamin C was associated with an increased incidence of CRPS at six weeks after fracture relative to placebo, with no effect at subsequent time points.[175] The potential utility of vitamin C in the prevention of CRPS is therefore unclear.

Ischemic reperfusion injury

Another potential means of prevention also relates to the possible role of oxidative stress (particularly in relation to ischemic reperfusion injury) in the development of CRPS. During limb surgery procedures, such as total knee arthroplasty, a tourniquet is routinely applied to the surgical limb to reduce blood loss, sometimes for as long as two hours. Given that ischemic reperfusion injury can occur on removal of the tourniquet, with its severity related to the duration of ischemia, minimizing the duration of tourniquet use during such procedures could potentially reduce the incidence of CRPS.

CRPS in children

Although clinical lore suggests that CRPS presents differently in children than in adults, there is no empirical evidence on such differences and this assumption has been questioned.[177] CRPS is currently diagnosed in children using the same 2012 IASP criteria that are used in adults. Two detailed clinical evaluation studies (n=20; n=42) suggest that the same objective signs are seen in children and adolescents with CRPS as are seen in adults, including allodynia and hyperalgesia, edema, skin color and temperature changes, and motor changes.[178 179]

Data from more than 100 children and adolescents with CRPS meeting the 2012 IASP diagnostic criteria indicated that these children exhibited more functional impairments and disability than those with other forms of chronic pain, consistent with the high levels of impairment often noted in adult patients with CRPS.[180] A longitudinal study of patients (n=42) diagnosed as having CRPS in childhood found that on follow-up in adulthood an average of 12 years later, 52% still experienced pain, with 36% having documented recurrences of CRPS.[179] This suggests that in many cases of childhood CRPS there may be no sustained recovery. These longitudinal data contrast with the common clinical assumption, not yet supported by high quality trials, that children with CRPS respond more favorably to conservative functionally focused care than do adults, in many cases with complete resolution of the condition.[177]

Emerging treatments

Several treatments for CRPS are emerging that go beyond the current standard of clinical care. The best supported of these is treatment with bisphosphonates, which several small RCTs suggest may be effective for CRPS.[181-184] The mechanistic relevance of treatment with bisphosphonates, which inhibit osteoclast activity, is suggested by recent work supporting a role for impaired bone metabolism in CRPS.[104] A definitive RCT of bisphosphonates is currently under way (ClinicalTrials.gov identifier: NCT02402530).

Other placebo controlled studies suggest that topical ketamine or a series of daily subanesthetic ketamine infusions may be useful in otherwise treatment resistant patients,[185-187] although liver injury has been noted with repeated ketamine infusions in some patients.[188] Additional experimental CRPS treatments supported by small RCTs include intravenous immunoglobulin (n=13),[189] oral tadalafil (n=24),[190] and intrathecal baclofen for CRPS related dystonia (n=36),[191] although high complication rates were noted with this last intervention.

An RCT of low dose naltrexone (an opioid antagonist) for CRPS is also currently ongoing. This intervention is based on the hypothetical ability of naltrexone to reduce

RESEARCH QUESTIONS

How do the individual mechanisms shown to be associated with complex regional pain syndrome (CRPS) interact to produce the full syndrome?

Do different subtypes of CRPS exist that reflect different underlying mechanisms?

Can clinical signs and symptoms be clearly tied to underlying mechanisms?

Do different CRPS subtypes, signs, and symptom patterns and different mechanisms predict differential responsiveness to specific treatments?

glial inflammation by blocking Toll-like receptor 4, case reports suggesting efficacy in CRPS,[192] and positive results of a small RCT (n=31) in patients with fibromyalgia.[193]

Guidelines

Although several guidelines for the management of CRPS have been published over the past 20 years, evolving research and approaches to CRPS management make it particularly important to use the most recently developed guidelines. General treatment guidelines have been published by groups in the Netherlands,[150] UK,[194] Germany,[195] and the US.[148] Guidelines with a specific focus on interventional pain procedures, which cover interventional approaches in greater detail than in the general treatment guidelines, are also available.[157] Although the emphasis of the guidelines differs, a relatively high degree of overlap exists across the general treatment guidelines. Some regional differences are apparent, however, with US guidelines providing little information on the antioxidant agents (such as dimethylsulfoxide) that are recommended treatments in the Dutch and German guidelines.[148 150 195] In addition, specific criteria (if any) used for systematically evaluating efficacy data differ across guidelines, which can lead to different recommendations being made. For example, guidelines that focus on interventional procedures have more positive conclusions about the efficacy of sympathetic nervous system blocks and recommend these in routine treatment,[157] whereas other guidelines have more negative conclusions about these blocks.[150] Such differences highlight the need to consider clinical biases that may affect the interpretation of CRPS guidelines.

Conclusion

Although CRPS is uncommon in the general population, it occurs in 4-7% of patients who have a limb fracture or limb surgery. In many cases, acute CRPS that is typically associated with a warm, red, and edematous presentation resolves with limited intervention. In a subset of patients, CRPS becomes chronic, often accompanied by a transition to a cold, dusky, and sweaty presentation. Initial symptoms typically emerge within weeks of injury, and the transition from acute to chronic CRPS usually occurs within the first year. Multiple mechanisms underlie CRPS, both peripheral and central, and these may differ across patients and even within patients over time. CRPS should be diagnosed on clinical grounds using the 2012 IASP diagnostic criteria.

Inadequate data are available to guide CRPS treatment solely on the basis of RCTs, although trials suggest that the most commonly used intervention (sympathetic blocks) is probably ineffective for the average patient. Support for the efficacy of spinal cord stimulation in CRPS derives from a single RCT. There is some evidence for the efficacy of physical and occupational therapy, bisphosphonates, subanesthetic ketamine, free radical scavengers, and corticosteroids (for acute CRPS). Analgesic antidepressants, anticonvulsants, and transdermal lidocaine are thought to be effective clinically, although their efficacy in CRPS has not been evaluated adequately in RCTs. It is clinically accepted that standard care should emphasize functional therapies that target disuse. Pharmacological, interventional, and psychological techniques are also used because they facilitate participation in functional therapies and ideally enhance quality of life. The number of clinical trials of CRPS specific interventions is growing, raising hope that more effective treatments may eventually emerge.

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