

Complex regional pain syndrome: From diagnosis to rehabilitation

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of CRPS is not fully understood, it is recognised that inflammatory processes and autonomic dysfunction are involved. These processes are associated with peripheral and central sensitisation as well as changes in brain structure and function, and are reflected in the clinical presentation of CRPS. CRPS management requires an interdisciplinary team and requires the therapeutic approach to be individualised. With regard to pharmacological treatment, bisphosphonates, corticosteroids, ketamine and anticonvulsants have been demonstrated to be effective for CRPS management. Psychotherapy, including cognitive-behavioural therapy, has produced promising results but more studies are needed to confirm its efficacy. Among rehabilitation interventions, there is evidence of the efficacy of physiotherapy and occupational therapy in diminishing CRPS symptoms and achieving a higher level of functioning. In this regard, the rehabilitation modality that seems the most promising according to the actual literature is graded motor imagery, which can help to reverse the maladaptive neuroplasticity occurring in CRPS.

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Core tip: Complex regional pain syndrome (CRPS) involves a complex pathophysiology including sensory, motor and autonomic disturbances that causes functional disability and reduced quality of life. The management of CRPS remains challenging for health care professionals. This review provides a summary of the recent literature on CRPS pathophysiology and management. The potential mechanisms of effective interventions are also discussed.

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Abstract

Complex regional pain syndrome (CRPS) is a debilitating pathology characterised by intense chronic pain associated with vasomotor, sensory and motor dysfunction of the affected limb. Although the pathophysiology

INTRODUCTION

Initially known as causalgia, complex regional pain syndrome (CRPS) was reported for the first time in 1865 during the American Civil War in soldiers who were affected by neurologic injuries^[1]. In the early 20th century, CRPS was known as Sudeck's atrophy, after the German surgeon Sudeck^[2], who observed similar clinical features among patients who suffered from orthopaedic injuries without neurologic disorders. Later, CRPS was described as reflex sympathetic dystrophy because it was believed to be caused by an overactive sympathetic nervous system (SNS). The progressive advancement of the knowledge on CRPS pathophysiology led to several additional terminology changes over the years, during which CRPS was referred to as algodystrophy, algoneurodystrophy, neurodystrophy or shoulder-hand syndrome (because of distal symptoms expanding proximally)^[3]. The current term, CRPS, was adopted in 1994 by the International Association for the Study of Pain (IASP)^[4].

CRPS is a pathological condition characterised by chronic pain for which the duration and intensity are disproportional relative to the trigger event, which is frequently a trauma to the upper or lower limb^[5]. This painful disorder includes sensory, autonomic and motor disturbances^[6], which cause functional disability and a reduced quality of life^[7-9]. The literature reports two types of CRPS, depending on whether it is associated with nerve damage or not; CRPS-1: no nerve damage, formerly known as reflex sympathetic dystrophy, and CRPS-2: with nerve damage, formerly known as causalgia^[4,10]. However, it should be noted that there is no evidence supporting that the physiopathology, the therapeutic response, or the clinical presentation differ between both types of CRPS^[11]. Accordingly, a bone fracture or a surgery often causes damage to small nerve fibres, but most CRPS diagnosed after a fracture are classified as CRPS-1^[12,13]. Nevertheless, the distinction between CRPS-1 and CRPS-2 will be made in this review, when possible, in accordance with the IASP guidelines^[4]. Because our understanding of CRPS pathophysiology and the therapeutic approaches to treat CRPS have changed considerably over the past few years, this review will summarise the available literature on the pathophysiology, diagnostic criteria and the evidence-based approach to treat CRPS.

DIAGNOSIS AND PATHOPHYSIOLOGY

Diagnostic criteria

The diagnosis of CRPS is based on the clinical examination with the observation of physical signs and symptoms. To date, there is no biomarker or "gold standard" to confirm CRPS^[14-16]. The first diagnostic criteria for CRPS were established by the IASP in 1994. Table 1

Table 1 Orlando (International Association for the Study of Pain) criteria for complex regional pain syndrome

Criteria 1	The presence of an initiating noxious event or a cause of immobilisation
Criteria 2	Continuing pain, allodynia, or hyperalgesia with which the pain is disproportionate to any inciting event
Criteria 3	Evidence at some time of oedema, changes in skin blood flow, or abnormal sudomotor activity in the region of pain (can be sign or symptom)
Criteria 4	This diagnosis is excluded by the existence of other conditions that would otherwise account for the degree of pain and dysfunction

Table adapted from Merksey *et al*^[158].

Table 2 Budapest clinical diagnostic criteria for complex regional pain syndrome

Criteria 1	Continuing pain, which is disproportionate to any inciting event
Criteria 2	Must report at least one symptom in three of the four following categories: Sensory: reports of hyperesthesia and/or allodynia Vasomotor: reports of temperature asymmetry and/or skin colour changes and/or skin colour asymmetry Sudomotor/oedema: reports of oedema 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, nail, skin)
Criteria 3	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 and/or deep somatic pressure and/or joint movement) Vasomotor: evidence of temperature asymmetry and/or skin colour changes and/or asymmetry Sudomotor/oedema: evidence of oedema 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, nail, skin)
Criteria 4	There is no other diagnostic that better explains the signs and symptoms

Table adapted from Harden *et al*^[159].

describes these criteria, which are referred to as the Orlando criteria. Although their sensitivity was high (98%), their specificity was poor (36%), resulting in a fairly small number of correct diagnoses^[17].

More recently, a modified version of these criteria has been proposed to achieve a better specificity and to improve the efficacy of CRPS diagnosis, by adding more features of CRPS. Table 2 describes the Budapest Criteria, which have been validated^[18]. The use of different criteria across studies leads to variable results and makes the between-study comparisons difficult^[9]. The Budapest criteria are used for both CRPS-1 and CRPS-2. The method used to distinguish CRPS-1 from CRPS-2 is the absence (CRPS-1) or the presence (CRPS-2) of nerve damage. To date however, there is no standardised procedure to detect the presence or absence of nerve

damage^[4,19]. Thus, the distinction relies on clinical judgment that may be supported by diagnostic examinations such as electromyography with nerve conduction tests or surgical exploration.

EPIDEMIOLOGY

Although epidemiological studies on CRPS are scarce and limited, this is not surprising given that CRPS is reported to be a relatively rare disease. According to a population-based study conducted in the Olmsted County of Minnesota, the incidence of CRPS-1 has been estimated to be 5.46 cases/100000 per year in the United States^[20]. The results from another study conducted more recently in the Netherlands estimated the incidence of CRPS to be approximately 26.2 cases/100000 per year^[21]. This discrepancy has been attributed to differences in population characteristics, such as ethnicity and socio-economic factors, as well as methodological differences (inclusion criteria based on the retrospective use of the IASP criteria only^[20] vs the use of the IASP criteria or the opinion of a general practitioner^[21]). In addition, the authors of the study conducted on the Netherlands population did not clearly state if they included only CRPS-1 or both types of CRPS patients, which may also contribute to the higher incidence reported in that study. The prevalence of CRPS-1 has been estimated to be 20.57 cases/100000 in the United States^[20] and the number of new cases per year is expected to range between 20000 and 80000^[12]. To date, no other large population-based study is available. Nevertheless, it is generally accepted that CRPS-1 is more common than CRPS-2^[20].

Previous studies suggest the existence of risk factors for developing CRPS. In terms of demographic characteristics of the most commonly affected patients, women are two to three times more likely to develop CRPS than men and most CRPS cases among women occur after menopause^[21]. Accordingly, some authors have suggested that hormonal factors may be involved in the pathophysiology of the disease^[21,22]. Women with menstrual cycle-related problems and osteoporosis would be more likely to develop CRPS after a trauma^[23]. However, results of a population-based case-control study including 53 CRPS patients and 58 controls did not find any association between the development of CRPS and oestrogen exposure, but this finding may be related to the low statistical power of the study^[24]. Although it can affect people of all ages, CRPS is more likely to develop between 40 and 60 years old^[25] with a mean age of 53 years old at the time of the diagnosis^[26]. This finding is consistent with the prevalence of chronic pain in general, which peaks in middle age^[27,28]. Suffering from migraine is also considered a risk factor to developing CRPS, in accordance with the similar physiopathological processes between the conditions, such as neurogenic inflammation^[29].

The development of CRPS follows a minor injury to the upper limb twice as frequently compared with a lower limb injury^[20,21,30]. The most common triggering event is a distal radius fracture including Colles fracture^[20,21,31]. A

recent prospective multicentre cohort study conducted on 596 patients estimated the incidence of CRPS-1 after a distal radius fracture to be approximately 14%^[9]. Based on the Budapest CRPS criteria^[18], the general incidence rate for developing CRPS-1 after a fracture would be 7%^[9]. However, depending on the diagnostic criteria and the CRPS features (CRPS-1 vs CRPS-2, upper limb vs lower limb, surgical complications, association with another diagnosis, *etc.*), the incidence rate of CRPS after a fracture ranges from 0.9% to 51%, regardless of the location^[9,22,32-39]. Immobilisation of the hand or the upper extremity after any trauma is considered an important risk factor for the development of CRPS^[12,40]. To a lesser extent, other types of injury may also be a trigger event for developing CRPS. CRPS can occur after a central lesion such as stroke or can develop spontaneously in a small proportion of cases (less than 5%)^[10,20,21,30,41]. It has been suggested that psychological factors may constitute risk factors for the development of CRPS^[42-45], but this theory is no longer supported^[12,23,46,47]. For instance, a group of authors conducted a multicentre prospective study including 596 patients with an upper limb fracture, in which they examined the relationship between the development of CRPS-1 and several psychological factors, such as agoraphobia, depression, somatisation, interpersonal sensitivity and insomnia. The study revealed that none of these factors was significantly associated with the development of CRPS^[46]. The lack of association between psychological factors and CRPS is also corroborated by the results of a systematic review including 31 articles^[45] and also by previous prospective studies^[48-50] and a large retrospective case-control study including 186 CRPS patients and 697 controls matched for age, sex and trauma^[23]. Thus, the psychological symptoms reported by CRPS patients are thought to be a consequence of disability and chronic pain itself, rather than being a predisposing factor^[36,46,48,49]. Otherwise, some authors suggest a genetic predisposition to developing CRPS^[51], but larger studies are required to establish clearer patterns of inheritance. Finally, the severity of the triggering event is not considered as a risk factor in the development of CRPS^[10,12].

PATHOPHYSIOLOGY

Although the pathophysiology of CRPS is not completely understood at this time, it is generally accepted that it involves several mechanisms^[11], including an alteration of the central nervous system (CNS)^[25,31]. According to the authors of a recent review, physiological reactions to the initiating injury would lead to disturbances of inflammatory processes and autonomic function^[12]. These pathological processes would, in turn, lead to maladaptive neuroplasticity^[12], such as peripheral and central sensitisation. Each of these processes may appear concurrently or sequentially and is related to specific signs and symptoms observable during the evolution of the disease, which will be described below. There is also some evidence that the relative contribution of each mechanism to CRPS differs from one patient to another and also differs at different

time points in the course of the disease^[52].

Inflammatory component

Relatively recent theories suggest that the pathophysiology of CRPS is linked to disturbances of neurogenic inflammatory processes^[12,53], including higher plasma levels of bradykinin^[54], increased systemic levels of neuropeptides^[41,55], such as calcitonin gene-related peptides, and the release of pro-inflammatory cytokines such as tumour necrosis factor- α ^[56] or interleukin-6^[57]. It has also been found that patients with chronic pain may have lower endogenous anti-inflammatory activity^[58]. Accordingly, a recent meta-analysis conducted on 15 studies revealed that CRPS is associated with a predominantly pro-inflammatory state, with different inflammatory profiles in the acute vs the chronic stage of the disease^[53]. These findings are consistent with the vasodilation, oedema, increased sweating^[41,55] and the hyperalgesia observed in the acute stage of CRPS^[41,59]. These findings are also in agreement with a recent systematic review showing that corticosteroids improve the signs and symptoms of CRPS-1^[60]. Proinflammatory cytokines and neuropeptides may also be involved in peripheral sensitisation^[11,57]. Therefore, there is clear evidence that disturbances in neurogenic inflammatory processes are implicated in the pathophysiology of CRPS.

Involvement of the SNS

In addition to the inflammatory processes, alteration of the SNS has been proposed to contribute to the pathophysiology of CRPS. To explain the autonomic features, such as a cool and bluish limb, it was thought that CRPS was caused by a reflex vasoconstriction, reflecting post-traumatic SNS hyperactivity^[5,61]. However, this hypothesis is no longer supported, in spite of the involvement of the SNS in CRPS^[62,63]. It is now recognised that SNS activity is reduced in the first stages of the disease, which manifests as decreased reflex vasoconstriction in the affected area^[64,65]. This symptom is associated with the vasodilatation of the peripheral vessels and may explain the warming of the affected region^[11]. Changes in the pattern of clinical features as CRPS evolves from an acute to a chronic state may be related to circulating catecholamines^[11]. As an adaptive mechanism, the SNS hypoactivity seems to progressively increase the sensitivity of peripheral adrenergic receptors to circulating catecholamines that are released in response to psychological stress or pain itself^[11]. This phenomenon may contribute to the exaggerated vasoconstriction in later stages of the disease^[11,66]. Thus, the affected limb changes from a warm, swollen and reddish state to become cold and bluish^[64]. It is also known that a chronic dysregulation of the SNS may lead to sympathetically maintained pain in 10% of CRPS patients^[4].

Contribution of the oxidative stress in the pathophysiology of CRPS: Long-term sympathetic disturbances result in the redistribution of blood flow in micro-circulatory vessels. This process impairs their nourishment^[67], the

endothelial function, and reduces acetylcholine-induced vasodilatation^[68]. These alterations have been suggested to lead to hypoxemia and acidosis, which may produce free radicals and oxidative stress^[69]. A previous study proposed that free radicals are the result of mitochondrial dysfunction in the respiratory chain^[25]. Accordingly, free radicals have been detected in the saliva and the serum of the affected limb in CRPS-1 patients^[70], as well as in two animal models of CRPS^[71,72]. Furthermore, a multicentre randomised controlled trial (RCT) demonstrated the protective effect of vitamin C, a well-known antioxidant, on the development of CRPS after a wrist fracture treated with a plaster cast^[73] or by surgery^[74]. Therefore, oxidative stress may be involved in the pathophysiology of CRPS, but it is still not clear if it is a cause or a consequence of the disease^[25]. More prospective studies are needed to better understand the potential role of oxidative stress in the pathophysiology of CRPS, but it may constitute a biomarker of and a therapeutic target for CRPS.

Plasticity of the peripheral and CNS

Changes in the peripheral and CNS: Peripheral sensitisation is thought to play a role in CRPS pathophysiology^[75]. It is a form of neuroplasticity relying on the capacity of neurons to change their function, chemical profile or structure in response to a specific situation^[76]. Peripheral sensitisation results in a continuous release of catecholamines by the nociceptive fibres of the affected area^[77] and brings sustained nociceptive input to the spinal cord. This causes activity-dependant changes in the spinal cord and central sensitisation, resulting in enhanced central responsiveness to nociceptive inputs^[76]. This enhanced nociceptive transmission may induce a pain sensation that outlasts the initiating input or that requires lower level of peripheral drive to maintain it^[76].

Altered cortical representation of the affected limb:

In CRPS, motor and sensory deficits that are not limited to the area of injury have been suggested to be related to maladaptive neuroplasticity in the brain. For instance, the representation of the affected hand in the primary somatosensory cortex is significantly shrunk and shifted toward the lip compared with the unaffected hand^[78-81]. These changes in the hand primary somatosensory cortex representation are correlated with the amount of pain^[81] and mechanical hyperalgesia in CRPS^[79]. With rehabilitation, the cortical organisation is progressively re-established and correlates with the decrease in pain and the diminishing extent of mechanical hyperalgesia^[80]. The results of a follow-up study revealed a reversal of cortical reorganisation in agreement with clinical improvement at least 1 year after therapy^[80]. Thus, chronic CRPS pain seems to correlate well with the cortical representation of the affected limb, which may contribute to the persistence of pain^[80,81].

It has also been reported that the representation of the affected and unaffected hand muscles is asymmetrical in the motor cortex of patients with CRPS-1^[82]. In that study, the cortical representation (size, motor evoked po-

tentials, and calculated volumes) was significantly larger for the unaffected hand than for the affected hand and this asymmetry was not found in the control group of healthy subjects. An fMRI study also demonstrated sub-spatial adaptive changes in the CNS of CRPS patients by investigating cerebral activation during a finger tapping task^[83]. The authors found significantly larger brain activations compared with healthy controls and also compared with the unaffected side of the CRPS patients. This finding may be explained by defective inhibitory mechanisms in the motor cortex that were previously demonstrated^[84-86]. Besides, a transcranial magnetic stimulation study found a hyperactivity of the contralateral motor cortex in CRPS patients^[84]. The authors hypothesised that this hyperexcitability may be linked to an adaptive process related to the decreased mobility of the affected limb and not necessarily to the painful sensations^[84], but further studies are still required to fully understand this phenomenon^[6]. Alterations of the premotor cortex have also been observed in a study including eight chronic CRPS-1 patients with dystonia (mean duration of disease of 11 years)^[87]. Their results revealed that less cerebral activation was present in both the ipsi- and contralateral hemispheres when imagining movements, compared with the activation patterns of age-matched healthy controls^[87].

Results of a recent imaging study including voxel-based morphometry and DTI analyses revealed gray matter atrophy in the right hemisphere, especially in the right insula, right ventromedial prefrontal cortex (VMPFC), and right nucleus accumbens in 28 CRPS patients^[88]. Interestingly, gray matter atrophy in the VMPFC correlated with the interaction between pain intensity and duration in CRPS patients, while right anterior insula gray matter atrophy correlated with pain duration^[88]. In addition, the gray matter atrophy in the right anterior insula was associated with reduced autonomic responses^[89], consistent with the autonomic dysregulation in CRPS and the role of the insula in autonomic regulation^[88]. Furthermore, the gray matter atrophy observed in the VMPFC was associated with poor performance in an emotional decision-making task^[88,90], congruent with the clinical features of CRPS.

In summary, the literature exposes evidence about the pathophysiology of CRPS, but several questions on the mechanisms of the disease remain, especially in relation to the specific role of oxidative stress^[25] and the patterns of cortical reorganisation during the onset and the course of the disease^[6]. Further studies are also required to better understand the links between physiopathological processes and clinical features, to improve treatment modalities offered to CRPS patients.

CLINICAL PICTURE

Physical features

Nearly 100% of patients with CRPS report hyperalgesia, that is, an increased pain sensation to a normally painful stimulus^[91]. Allodynia, or a painful sensation elicited by a stimulus that usually does not elicit pain, is also com-

mon, affecting one third of patients with CRPS^[91]. These sensory disturbances are not limited to a single peripheral nerve territory but rather follow a glove distribution^[16], and may be linked with the sensitisation processes implied in the CRPS pathophysiology described above. It is recognised that CRPS patients may have impaired processing of proprioceptive or tactile input, but higher multisensory integration systems seem unaffected^[92]. Accordingly, the results of a recent study conducted on 24 CRPS patients and 24 controls revealed that CRPS patients had an intact perception of illusory ownership, which suggests unaffected functions of multisensory cortical areas^[92].

Autonomic disturbances resulting in distal oedema are present in 81% of patients^[91]. Skin changes in colour and temperature are also common symptoms of CRPS^[91]. Disorders of sweating can also be noted^[31] in 55% of patients, with hyperhidrosis being more frequent than hypohidrosis^[93]. Finally, trophic changes such as the increased growth of hair and nails of the affected limb are some of the physical symptoms related to CRPS^[91], in addition to bone demineralisation^[94]. All of these autonomic disturbances are related to the dysregulation of the SNS described above. Principal physical features induced by CRPS, such as oedema, skin colour changes and muscle atrophy, are illustrated in Figure 1.

In terms of motor function, 77% of patients present with weakness of the affected limb and 45% have exaggerated deep tendon reflexes^[91]. A recent kinematic study including 80 CRPS patients also suggests that voluntary motor control may be impaired, causing bradykinesia and akinesia in both the affected and the unaffected upper limb^[95].

Psychological features

The psychological factor most reportedly associated with CRPS is the fear of pain^[96]. In accordance with the fear-avoidance model of chronic pain^[97], the fear of pain may have a significant impact on global functioning. For instance, CRPS patients avoid certain activities fearing that they will trigger pain. This avoidance contributes to isolation and higher levels of anxiety^[98]. In addition, a large proportion of CRPS patients present symptoms of depression, such as mood or sleep disturbances, as the prevalence of depression in CRPS is estimated to range from 31% to 96%^[45]. Psychological factors, such as anxiety, stress or inconsistent emotional states may have an impact on catecholamines neurotransmission and may play a role in the pathophysiology of CRPS, including the dysregulation of the SNS and sensitisation^[11,98,99]. Psychological stress also seems to be related to the development or maintenance of CRPS-1^[45], which may results in repeated sympathetic activation and locally altered catecholamine responsiveness^[45,98,99].

In summary, stress or anxiety may have an impact in the maintenance of CRPS in relation with their influence on catecholamine activity^[99]. However, as mentioned previously, other psychological factors such as depression or somatisation seem to be consequences of the disability



Figure 1 Clinical signs of complex regional pain syndrome. A: Oedema and colouration changes around the metacarpophalangeal joints of a 42-year-old woman with bilateral upper limb complex regional pain syndrome (CRPS) in the acute phase (around six months); B: Thenar muscle atrophy and slick skin aspect of a 22-year-old woman with left upper limb CRPS for a duration of 3 yr; C: Significant knee oedema in a 46-year-old woman with right lower limb CRPS lasting 2 yr; D: Blue coloured left lower limb CRPS in the cold phase (3 yr) of a 23-year-old woman.

and chronic pain itself, rather than being predisposing factors^[36,46,48,49].

Cognitive and perceptual features

Recent studies revealed cognitive impairments in CRPS patients. In a neuropsychological study including 137 CRPS patients, significant neuropsychological deficits were present in 65% of patients, presenting with impairments in executive functions^[100]. Among the perceptual features, patients with CRPS may suffer from physical and spatial hemineglect^[16,101,102] as a result of a disturbed body schema induced by the changes in the cortical representation of the affected limb^[101,103-106]. Indeed, CRPS patients perceive their affected limb as bigger than it really is^[106] by more than 8%^[107] and have difficulty recognising their own limb^[108] and estimating its position^[104]. Moseley *et al.*^[102] found that when they receive concurrent vibrotactile stimulations at 140% of their tactile threshold to both limbs without the contribution of vision, CRPS patients tend to neglect stimulations of the affected limb. This finding suggests a complex alteration of the representation of the bodily space. A recent study including a group of 20 CRPS patients and two age- and gender-matched control groups (healthy volunteers and patients with chronic pain other than CRPS) revealed that CRPS patients show a slower reaction time in response to a visual stimulus presented in the visual field corresponding to the side of the affected limb^[101]. In that study, CRPS patients also had a significantly lower score in the clock-drawing test than the healthy controls, which is also consistent with spatial hemineglect.

In summary, CRPS can affect many aspects of daily life. It may have a devastating effect on the quality of life and productivity. A large proportion of patients (81%) have to quit their jobs at the peak of the disease and only 27% can return to a productive life after the crisis^[109].

This decrease in productivity generates significant costs for the society. Therefore, it is important to deal quickly and appropriately with CRPS. The next section will present the main treatment modalities currently used with this population.

CRPS MANAGEMENT

In this section, the most common treatments for CRPS will be presented. However, it should be emphasised that CRPS is a complex pathology, including both central and peripheral abnormalities, and it is sometimes associated with psychosocial components. Therefore, CRPS should be treated using an interdisciplinary approach^[19].

Pharmacology

Similar to other chronic pain syndromes, pharmacological treatments are widely used for the treatment of CRPS. However, drug therapy works best if prescribed in combination with other management modalities, such as rehabilitation^[19]. Various types of drugs such as opioids, calcitonin, bisphosphonates and antidepressants or anticonvulsants may be taken orally^[31,94,110]. Essentially, the strategies and drug combinations are the same as for neuropathic pain management. The goal in using pharmacological agents is to act on the pathophysiological processes generating pain, *i.e.*, inflammation or sympathetic dysfunction^[31]. However, scientific evidence supporting pharmacotherapy in CRPS remains limited^[94,110].

Opioids: According to the results of a study conducted on 102 CRPS patients, 21% of CRPS patients are treated with opioids^[111] and this type of drug is mostly used in the early stages of the disease^[111]. However, only one placebo-controlled RCT studied the use of oral sustained-release morphine in CRPS-1 patients who were previ-

ously treated with spinal cord stimulation ($n = 43$)^[112]. No significant effect on pain reduction has been found with the use of morphine compared with placebo^[112]. Additionally, the morphine group reported 20 side-effects a day compared with 2 a day for the placebo group^[112]. Accordingly, authors of the evidence-based guidelines in CRPS treatments stated that there is insufficient evidence regarding the efficacy of opioids in reducing CRPS pain^[110]. To our knowledge, no study has been conducted on opioids other than morphine for the treatment of CRPS. Even if opioids are well-known to inhibit nociceptive processes in the CNS, addiction may potentially develop in a small subset of patients^[113]. Because of their serious adverse effects, opioids should be prescribed with caution in the treatment of CRPS^[113].

Calcitonin: Calcitonin is of great interest in the treatment of CRPS for its analgesic properties, by producing the release of β -endorphins, and for its action in preventing bone resorption^[50]. In spite of these promising theoretical effects, however, results of recent systematic reviews demonstrated conflicting evidence of calcitonin's efficacy in the treatment of CRPS-1^[110] or in the treatment of both types of CRPS^[94], according to the outcomes of pain reduction, functional outcome, clinical features or bone mineralisation. The authors of a systematic review based on 41 articles related to CRPS treatment stated that to date, the beneficial effects of calcitonin on CRPS patients have not been demonstrated^[94]; further studies are required to establish a clear recommendation regarding the use of calcitonin in CRPS management.

Bisphosphonates: Bisphosphonates are effective in reducing the signs of inflammation associated with CRPS^[94,110]. In three placebo-controlled studies, bisphosphonates were significantly more effective than placebo for upper limb CRPS-1 patients ($n = 20$, $n = 39$ and $n = 32$) in decreasing inflammation signs, including pain and oedema, and improving mobility^[114-116]. These positive effects have been found among both early and long-standing CRPS patients^[117]. However, despite this significant beneficial effect on CRPS inflammation signs, evidence is lacking about the optimum dosage, frequency and duration of treatment^[110].

Antidepressants: There are published reports that support the use of tricyclic antidepressants for the management of neuropathic pain^[113,118-120]. Their analgesic effects are presumably due, in part, to their action on serotonergic and noradrenergic descending inhibitory pathways^[113,120]. Tricyclic antidepressants are reported to be part of pharmacotherapy for 19% of CRPS patients^[111]. There is also some evidence that serotonin and noradrenaline reuptake inhibitors, but not selective serotonin reuptake inhibitors, are efficient in the treatment of chronic pain^[113,120]. However, based on systematic reviews on CRPS management, no study has yet examined the efficacy of antidepressants for the treatment of CRPS spe-

cifically^[110,113]. Therefore, there is currently no evidence of the efficacy of antidepressants for the treatment of CRPS.

Corticosteroids: There are a few trials that studied the benefits of corticosteroids in CRPS management and the results of these studies are clinically positive with regard to pain, oedema and sweating^[94,110,121-123]. Most of these studies were conducted with patients presenting an acute CRPS with inflammation signs and it is actually unknown if corticosteroids offer similar benefits for chronic CRPS, when pro-inflammatory cytokines are at a lower level^[19,124]. However, because of their potentially severe adverse effects, corticosteroids should not be taken for a long period of time^[113] and appear to be rarely prescribed in clinical practice^[111]. Further studies should be conducted to establish guidelines on the duration and dosage before corticosteroids can safely be prescribed for CRPS^[110,113].

Anticonvulsants: Anticonvulsants, such as gabapentin, are one of the most effective and most commonly prescribed pain medication for neuropathic pain in general^[125,126], and are also prescribed for CRPS^[113]. It is reported that 12% of CRPS patients are treated with anticonvulsants^[111]. The benefits of gabapentin for CRPS has been studied in two RCTs^[127,128]. There is evidence that gabapentin has a small to moderate effect in reducing CRPS pain eight weeks after the beginning of the treatment^[127]. However, patients taking gabapentin feel more side effects, such as fatigue, sleepiness or dizziness, than patients taking a placebo^[128]. Another anticonvulsant, carbamazepine, has been studied in a RCT of CRPS patients and it has been found to significantly diminish pain compared to placebo^[112]. Even if other types of anticonvulsants, such as pregabalin, seem to have some effects on pain, no other type of anticonvulsants has been studied for the treatment of CRPS^[19]. Even if beneficial effects have been demonstrated for pain reduction in CRPS patients, the pros and cons should be weighed when adding anticonvulsants to the CRPS treatment plan because of the potential adverse side effects and the unknown long-term effects^[110].

Muscle relaxants: Muscle relaxants, such as baclofen, is used by 3% of CRPS patients^[111] and may be helpful for the treatment of CRPS^[129]. However, because of the small samples (less than 10 patients) included in studies conducted on the efficacy of muscle relaxants for CRPS, authors of recent evidence-based guidelines on CRPS management report that the evidence is insufficient to claim their efficacy^[110].

Ketamine: Even if large and well-designed RCTs need to be conducted, the intravenous administration of ketamine in sub-anaesthetic doses significantly reduces pain among CRPS patients, as revealed by both prospective and retrospective studies^[75,110]. As an NMDA receptor

antagonist, ketamine is of particular interest because of its potential ability to reverse central sensitisation^[75]. Although a promising effect has been demonstrated, larger studies are required to validate the routine use of ketamine in CRPS^[75,112,113].

Topical agents: Topical medications, such as lidocaine patches, are used by 79% of CRPS patients^[31,111]. In this drug category, dimethylsulphoxide cream seems to be more efficient in reducing CRPS symptoms in the early stages while inflammatory signs are present^[75,130]. When symptoms of cold temperature or bluish skin are present, N-acetylcysteine has been found to be the most effective, based on a randomised double-blind study including 146 CRPS patients^[131]. The efficacy of these two types of drugs that are free radical scavengers support the involvement of oxidative stress in the pathophysiology of CRPS.

Local and regional sympathetic blockade: Local sympathetic blockade (*e.g.*, with lidocaine or guanethidine) such as stellate ganglion blockade or lumbar sympathetic blockade are widely reported in the literature^[31,94] and aim to modify the activity of the SNS locally. The therapeutic response to sympathetic blockade is inconsistent and may only be more effective than placebo at reducing the duration but not the magnitude of pain^[94,132]. A Cochrane review also indicate that there is low quality evidence that local anaesthetic sympathetic blockade is not effective at reducing pain in CRPS^[133]. Intravenous regional blockade using a wide variety of pharmacological agents has also been described for the treatment of pain in CRPS^[133]. According to this Cochrane review, there is very low to moderate evidence that intravenous regional blockade with atropine, droperidol and guanethidine is not effective to reduce pain in CRPS, while there is very low evidence that ketanserin and bretylium plus lidocaine may be effective. Because sympathetic blockade is a relatively invasive modality, it is suggested that it should be used when other modalities do not bring positive changes in the patient's condition^[19]. In addition, it should be stressed that these interventions may have positive effects for a limited number of patients only, because it is known that pain in CRPS is sympathetically maintained for about 10% of patients^[4]. The other 90% patients, with sympathetically independent pain, should benefit from other types of treatment. Because there is no standardised method to determine if CRPS pain is sympathetically maintained or sympathetically independent^[113], sympathetic blockade remains a controversial modality.

In summary, among the pharmacological treatments for CRPS, strong evidence is available for bisphosphonates^[94,110,114,116], corticosteroids^[94,110,120,123], ketamine injections^[75,110] and anticonvulsants^[127], but further studies are required to establish the guidelines for well-validated routine administration. There is actually insufficient or conflicting evidence to recommend the use of opioids^[110,112,113], calcitonin^[94,110] or antidepressants^[110,113]. Because of the limited proportion of patients who may benefit from sympathetic blockade, this intervention also

remains controversial^[94,110].

Other medical treatments

Most surgical treatments reported in the literature refer to sympathectomy or more recently, intracranial neurostimulation^[31], and represent the most invasive treatment modalities to be used as a last resort because of the quite minimal evidence for their efficacy^[110,134]. Surgical treatments will not be discussed in more detail because they have been reviewed elsewhere^[135].

Recently, repetitive transcranial magnetic stimulation (rTMS) was shown as a potential therapeutic option for CRPS, when used in combination with pharmacotherapy and physiotherapy^[136]. The results of a double-blind, placebo-controlled randomised trial conducted with 23 patients with upper limb CRPS-1 revealed a significant reduction of pain and improvement of the emotional state with 10 daily sessions of rTMS applied on the primary motor cortex^[136]. However, these beneficial effects did not continue after the treatment period ended^[136]. Similar results had previously been found in a study conducted on 10 CRPS patients^[137].

Psychotherapy

The rationale of psychological interventions for CRPS management derives from the recognised benefits of these approaches in management of other chronic pain syndromes^[19]. In addition, psychological and behavioural factors are thought to interact with pathological processes involved in the physiopathology of CRPS, including changes in catecholamine levels, as discussed earlier^[11,19,99].

Randomised control trials on psychological interventions for CRPS are scarce. In most studies, the experimental design only allows limited conclusions^[11]. The available clinical studies show some benefits in the treatment of CRPS using cognitive-behavioural therapy^[98,138], operant conditioning, pain management techniques, relaxation training^[31] with biofeedback^[19] and family education^[98]. Regarding other chronic pain syndromes, one goal of psychotherapy is to develop abilities to control pain, to play an active role in pain management and rehabilitation^[98]. Psychotherapy can also have a beneficial effect on comorbidities related to CRPS, such as depression. Authors of recent clinical guidelines in CRPS management recommend that education about the condition should be a low cost psychological approach to be used for all acute and chronic CRPS^[19]. Specifically, information about negative effects of disuse, the importance of reactivation and the importance for the patient to take an active part in CRPS management should be provided to the patient and its family^[19]. Because some cases of CRPS may resolve spontaneously, individualised psychotherapy is mostly recommended for chronic CRPS and should begin 6-8 wk after the onset of the disease^[98]. These psychotherapy sessions should focus on empowerment, which is defined as the ability to gain control over the condition, diminish catastrophic thoughts and reactivate the affected limb^[19]. An *in vivo* graded exposure approach, which consists of gradually exposing patients to situations that they think

may trigger pain (associated with the fear avoidance theories^[97]) seems to have promising results in diminishing pain intensity and the fear of pain, as well as improving global functioning^[139]. However, results from this study need to be replicated with a larger sample (only eight female CRPS-1 patients were included) to determine the efficacy of this approach. Noteworthy, the implication of family members is found to be important in the rehabilitation process in order to maintain good patterns of thoughts and reactivation of the affected family member at home^[19].

In line with the interdisciplinary approach for CRPS management, psychotherapy should be considered among the possible treatment modalities, although the evidence remains mixed regarding the benefits of these approaches and further controlled studies are required to confirm their efficacy^[98]. However, because psychological approaches are effective for other chronic pain syndromes, it is plausible that they are also useful for CRPS management, according to authors of recent clinical guidelines in CRPS management^[11].

Rehabilitation

Functional restoration is found to be the key objective of rehabilitation for CRPS patients, according to authors of a recent systematic review^[19]. The principle of functional restoration is to obtain a gradual progression of the movement, beginning with an activation of pre-sensorimotor cortices, followed by very gentle active movements and eventually, gradual weight bearing^[19]. Although rehabilitation is typically part of the CRPS management, RCTs to assess rehabilitation strategies are lacking because of the various clinical presentations and evolution of CRPS, necessitating the development of personalised intervention.

Occupational therapy: Occupational therapists (OTs) are recognised to be ideal therapeutic leaders in functional restoration processes because they are trained with biopsychosocial principles and work primarily with functional assessments and treatments^[19,140,141]. Emerging research has made OT interventions to work towards earlier stages of movements, using graded motor imagery (GMI)^[19]. The use of GMI^[105,142-144] has attracted the attention of researchers in recent years (a video illustrating GMI is presented at the following web address: <http://www.youtube.com/watch?v=hMBA15Hu35M> and the steps are fully described in a 2011 article^[145]) because these modalities may have an effect on cortical reorganisation, which seems to be involved in CRPS. Only a few studies have been conducted on the use of GMI in the treatment of CRPS^[105,142,143,146,147] but strong evidence of effectiveness has been demonstrated^[117]. In general, the use of GMI would reduce pain, normalise autonomic signs, improve lateralisation and improve functioning in both the short- and long-term. GMI may also be helpful in normalising movements for CRPS patients^[19]. FMRI studies support the cortical activation sequence induced by GMI in healthy subjects, but no such studies have

been conducted with CRPS patients^[148]. Further studies with larger samples are required to generalise the effect of GMI to the entire population of CRPS patients^[145,148].

Following GMI, the objectives are to minimise oedema, normalise sensation, promote normal positioning/decrease muscle guarding and increase functional use of the affected limb in order to promote independence in all areas, such as work, leisure and personal cares^[149]. OT using various modalities, such as desensitisation^[150] or sensory discrimination training, splinting^[19] and adapting activities, is also effective in decreasing functional limitations and improving activity levels^[140,141]. Stress loading, including the two phases of scrubbing and carrying, is also a technique used by OTs in order to initiate active motion and compression of the affected joints^[151]. However, most of the studies that focused on OT interventions did not standardise the treatment modalities, which makes the replication of the results difficult.

Physical therapy: Physical therapy (PT) plays an important role in CRPS management by increasing the range of motion, flexibility and strength by gentle progressive exercise programs^[19]. The use of physiotherapy is documented in the literature^[110,140,152], but the efficacy of the interventions remains mixed. Used alone or in combination, treatment modalities such as heat/cold therapy, electrotherapy, manual therapy, exercises or simulation of occupations have been described^[31,138]. It is also common that some aspects of psychotherapy, such as pain management techniques or relaxation techniques, are included in rehabilitation^[153]. A recent meta-analysis suggests that physiotherapy has a beneficial effect on pain reduction, oedema, mobility and skin temperature and would be effective in acute and chronic CRPS^[110,154].

It is generally accepted that PT interventions must be executed within the limits of pain tolerance^[155]. A relatively new and controversial rehabilitation approach for CRPS treatment is the “pain exposure” treatment^[152,156,157]. Groups of researchers found that rehabilitation therapy focused on functional improvement based on rehabilitation time having regular PT interventions while avoiding pain (*i.e.*, following rehabilitation objectives while not considering pain severity as a guideline) could permit the safe improvement of the function of the affected arm, reduce pain, improve walking speed and improve muscle strength^[152,156,157]. Because of the ethical implication of this type of therapy and the rationale that is still not well described, there is actually no evidence supporting the efficacy of this rehabilitation modality in CRPS treatment.

In summary, most modalities (*e.g.*, manual therapy, electrotherapy, desensitisation, activity modification and adaptation, *etc.*) used in PT and OT, except for the “pain exposure treatment”, have been demonstrated to be effective in diminishing CRPS symptoms and improving the level of functioning and should play an important part in CRPS management. Although rigorous studies using standardised rehabilitation modalities are required to raise the level of evidence of rehabilitation strategies, GMI is a very promising avenue.

CONCLUSION

This review aimed at gathering evidence regarding the pathophysiology, clinical features and interventions in the management of CRPS. Even if future studies are necessary to achieve a better understanding of the disease, the literature supports the involvement of neurogenic inflammatory processes, autonomic dysfunction and maladaptive neuroplasticity, such as peripheral and central sensitisation, in CRPS pathophysiology. The potential involvement of oxidative stress in the pathophysiology of CRPS also opens the door to a secondary prevention treatment in prescribing vitamin C to people with a hand trauma. CRPS has a negative impact in physical, psychological, cognitive and perceptual aspects and that a multidisciplinary approach is required to treat these patients. Among the pharmacological approaches, little evidence supports the use of several drugs, except for bisphosphonates, corticosteroids, ketamine or anticonvulsants that have demonstrated positive effects on CRPS symptoms. With regard to rehabilitation, positive effects have been found in diminishing the patients' signs and symptoms and improving global functioning, but evidence remains mixed because of a lack of standardised procedures. However, GMI seems to be the most promising treatment for CRPS.

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