Complex regional pain syndrome: advances in epidemiology, pathophysiology, diagnosis, and treatment

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Lancet Neurol 2024; 23: 522–33

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Complex regional pain syndrome (CRPS) is a rare pain disorder that usually occurs in a limb after trauma. The features of this disorder include severe pain and sensory, autonomic, motor, and trophic abnormalities. Research from the past decade has offered new insights into CRPS epidemiology, pathophysiology, diagnosis, and treatment. Early identification of individuals at high risk of CRPS is improving, with several risk factors established and some others identified in prospective studies during the past 5 years. Better understanding of the pathophysiological mechanisms of CRPS has led to its classification as a chronic primary pain disorder, and subtypes of CRPS have been updated. Procedures for diagnosis have also been clarified. Although effective treatment of CRPS remains a challenge, evidence-based integrated management approaches provide new opportunities to improve patient care. Further advances in diagnosis and treatment of CRPS will require coordinated, international multicentre initiatives.

Introduction

Complex regional pain syndrome (CRPS) is a debilitating pain disorder that is most frequently triggered by trauma, such as surgery or fracture. The disorder is usually confined to a single limb and is characterised by severe pain that is disproportionate in magnitude or duration to the expected course after similar injury.[1] Pain is accompanied by sensory, autonomic, motor, and trophic signs and symptoms that fluctuate in severity and nature.[2]

CRPS presents diagnostic and therapeutic challenges for clinicians. For example, the clinical presentation is heterogeneous, and the response to treatment is often poor.[3] Validated diagnostic criteria have not provided guidance to assess fluctuating and spreading symptoms.[4] High-quality clinical guidance to manage the debilitating symptoms of CRPS and their effect on the lives of people with the condition has not been sufficient.[5,6] Moreover, the pathophysiological mechanisms of the disorder are incompletely understood because multiple interacting systems are involved.

During the past decade, advances have been made in the understanding of CRPS epidemiology, pathophysiology, diagnosis, and treatment, which have provided opportunities to improve patient care. In this Review, we assess the latest evidence about CRPS incidence and pathophysiological processes, discuss updates to diagnostic procedures, and describe advances in classification of CRPS and subtypes of the disorder. Furthermore, we outline a contemporary evidence-based approach for integrated CRPS management. We also discuss emerging treatments and highlight continuing uncertainties and priorities for future research. We mostly focus on evidence published in the past 5 years but have also included important studies published before this period.

Epidemiology

According to the European Medicines Agency and the US Food and Drug Administration (FDA), CRPS is a rare disease because no more than five in 10 000 people in Europe,[7] and fewer than 200 000 people in the USA,[8] have the disorder. Estimates of the incidence and prevalence of CRPS vary according to population, diagnostic criteria, and time since initiating trauma. Studies from the past decade show that the 5-year incidence of CRPS is 0·07% in the USA,[9] and the prevalence is 26 per 100 000 in South Korea,[10] although use of outdated International Classification of Diseases 9th revision (ICD-9) codes might have inflated these estimates. Women are disproportionately affected by CRPS, with up to four women affected for every one man.[9–12] The incidence of CRPS increases with age, with the highest incidence occurring between 50 years and 80 years.[9–12] CRPS also occurs in children, but this Review focuses on the disorder in adults.

In a Danish compensation database study,[12] CRPS was reported to affect hands and arms more frequently than feet and legs. CRPS is more common in patients with pre-existing chronic pain conditions, such as rheumatoid arthritis,[13] migraine,[14] and widespread body pain,[15] than those without. Retrospective case–control studies suggest that asthma (odds ratio [OR] 3·0, 95% CI 1·3–6·9),[16] and use of angiotensin-converting enzyme inhibitors (2·7, 1·1–6·8),[17] might increase the risk of CRPS. In a prospective cohort study,[18] people with diabetes were shown to have an increased risk of developing CRPS (3·2, 2·3–4·5).

Pathophysiology

The pathophysiology of CRPS could entail aberrant inflammatory and immune responses, vasomotor dysfunction, nervous system changes, genetic variations, and psychological processes (figure 1). Biological, psychological, and social factors might interact to trigger CRPS, although the precise mechanisms are unclear.[19]

Although rare occurrences of CRPS have been reported to arise spontaneously, most cases develop after trauma, such as surgery or fracture (table).[27] Common inciting events include wrist fracture (incidence 2–25%),[18,21,24,25] traumatic hand injury (incidence 26%),[26] and total knee arthroplasty (incidence up to 13%).[15,22] The reasons that

some injuries progress to CRPS and others do not are unknown. The nature of the trauma and the degree to which the injury evokes a post-traumatic proinflammatory response has been proposed to determine CRPS onset—eg, the risk of CRPS is higher with open fractures and crush injuries than with simple fractures.[26] A systematic review found that immobilisation of the injured limb (whether in a cast or splint) increases the risk of developing CRPS, possibly mediated through inflammatory pathways.[28,29] The most consistent predictor of CRPS onset, as shown by prospective cohort studies, is higher pain intensity after the initial trauma or surgery.[18,21,24,26] One large prospective study of 1549 patients with wrist fracture found that elevated pain intensity, measured within 1 week of fracture, accurately predicted a CRPS diagnosis 4 months later, with patients at greatest risk reporting pain scores of 7 or 8 on a 0–10 numerical rating scale, with 10 indicating the most severe pain.[30]

Inflammation and autoimmunity

An aberrant immune-mediated inflammatory response to the inciting event could be a key pathophysiological mechanism of CRPS. Cross-sectional studies have shown that individuals with acute CRPS (symptom duration <6 months) have upregulated cytokine production (eg, tumour necrosis factor-α [TNF-α] and interleukin [IL]-6) in the skin of the affected limb compared with the unaffected limb, which is associated with keratinocyte proliferation and mast cell accumulation.[31] People with acute CRPS also have increased IL-8 and soluble tumor necrosis factor receptors 1 and 2 in blood compared with healthy controls.[32] In individuals with chronic CRPS, a meta-analysis of cross-sectional studies showed increased cytokine concentrations in serum, blister fluid, and CSF.[32] Amounts of the neuropeptides bradykinin and substance P are also elevated in people with CRPS,[3,32] and cross-sectional studies from the past 5 years have shown that the metabolism of these neuropeptides is impaired,[33,34] although changes to substance P metabolism are probably an ongoing consequence of trauma and not specific to CRPS. The precise mechanisms by which these substances interact to induce pain and other key CRPS features (eg, redness, oedema, and temperature changes) are uncertain but might entail sensitisation of peripheral nociceptors. Angiotensin converting enzyme (ACE) is involved in the metabolism of substance P and bradykinin, and use of ACE inhibitors is proposed to increase CRPS risk by blocking this pathway.[17] Inflammatory processes can also be mediated partly by the adaptive immune system; a cross-sectional study showed that individuals with chronic CRPS have increased numbers of $CD4^+$ and $CD8^+$ T lymphocytes compared with a pain free control group.[35] Evidence for an autoimmune mechanism for CRPS has emerged in the past decade. Passive transfer of IgM and IgG in animal limb injury models of acute and persistent CRPS, respectively, induced CRPS-like signs,[36–38] suggesting that CRPS could be associated with an autoantibody-mediated autoimmune process.

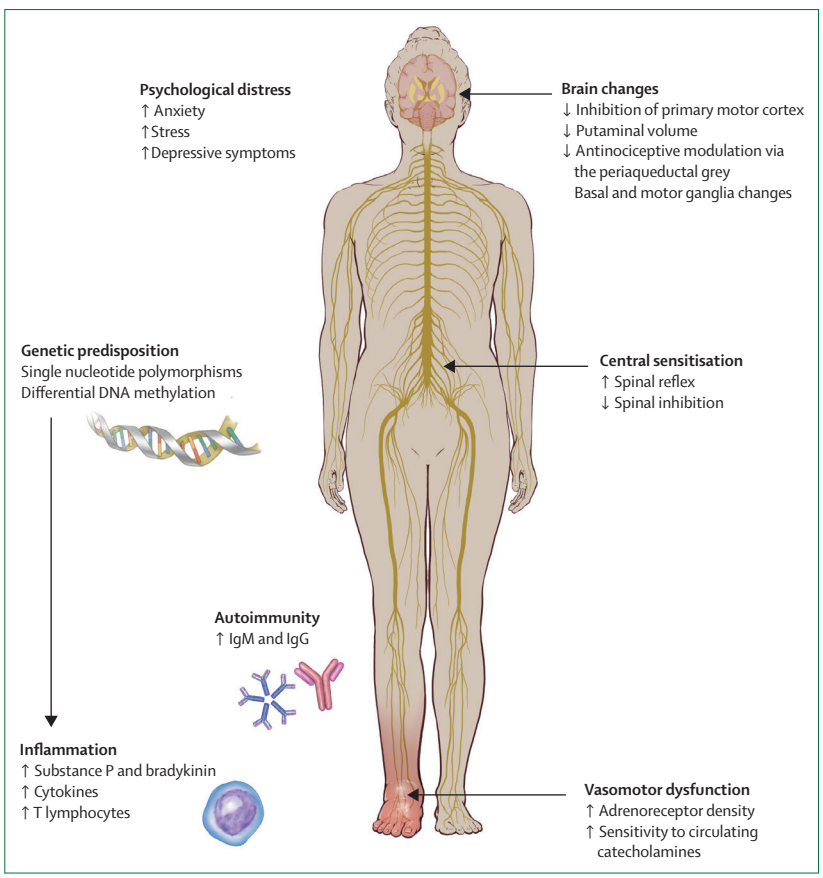

Figure 1: **Possible pathophysiological processes in complex regional pain syndrome**
Pathophysiological changes might arise because of symptoms and might not be causal. ↑ indicates increased and ↓ indicates decreased.

Vasomotor dysfunction

CRPS was previously thought to be a disorder of the autonomic nervous system because some affected individuals have excessive sympathetic nervous system output—such as increased sweating, temperature, and blood flow—that is apparently relieved by targeted sympathetic blockade. However, autonomic signs and symptoms can be accounted for by multiple mechanisms (eg, oedema via inflammation, and temperature changes via nervous system sensitisation),[3] and sympathetic blockade has not shown efficacy in randomised trials.[5] It is likely that the autonomic nervous system is involved in some people with CRPS. For example, in a cross-sectional study of individuals with CRPS, upregulation of adrenoreceptor density was noted in dermal nerve bundles that were evoked adrenergically,[39] suggesting that these receptors can be activated by circulating catecholamines. Additionally, in a retrospective study from South Korea of 199 people with CRPS who presented to a pain clinic, 26% of individuals showed

	Participants	Setting	Country	Baseline timepoint	Follow-up timepoint	Diagnostic criteria	Incidence (%)	Loss to follow-up (%)	Risk factors*
Bruehl et al (2022)[15]	113 patients undergoing unilateral total knee arthroplasty	Orthopaedic service of a university medical centre	USA	Median of 3 days before surgery	At 6 weeks and 6 months	2010 clinical criteria[20]	13% at 6 months	0·3%	Preoperative pain intensity, widespread pain
Farzad et al (2018)[21]	60 patients with distal radius fracture	Outpatient hand therapy clinic	Iran	2 weeks from fracture	Weekly for 8 weeks; 12 months	2010 research criteria[20] (CRPS I)	25% at 6 weeks; 17% at 12 months	1%	Age, pain
Gong et al (2022)[18]	553 patients with scaphoid fracture	Orthopaedic departments of four level one trauma centres	China	Before conservative treatment at hospital (median 3 days from injury to treatment)	Weekly during period of cast immobilisation and at 3, 6, 9, and 12 months	2010 criteria[20] (CRPS I)	20%	11%	Female sex, diabetes, pain intensity, anxiety, mental health, and patient-related wrist evaluation pain score
Kosy et al (2018)[22]	100 patients undergoing total knee arthroplasty	Hospital orthopaedic unit	UK	Not available	At 6 weeks	2007 research criteria[23]	0%	Not available	Not available
Parkitny et al (2022)[24]	702 patients with wrist fracture or wrist and hand fractures	Metropolitan hospital fracture clinic	Australia	Within 28 days of fracture	16 weeks after injury	2010 clinical criteria[20]	2% (95% CI 1–4)	3%	Fracture with articular involvement, pain intensity, stress, upper limb disability, depression, anxiety, and age
Román-Veas et al (2023)[25]	875 patients older than 60 years with distal radius fracture	Emergency care unit	Chile	Not reported	Approximately 8 weeks after treatment	2010 clinical criteria[20] (CRPS I)	14%	Not reported	Not available
Savaş et al (2018)[26]	291 patients undergoing surgery for traumatic hand injury	Hospital plastic and reconstructive surgery clinic	Türkiye	3 days after surgery	At 3 months	2010 research criteria[20]	26%	11%	Postoperative pain, crush injury, laceration injury, tendon injury, and tendon, nerve, and fracture injury

CRPS I=complex regional pain syndrome type I (ie, without peripheral nerve damage). The Budapest clinical criteria require reported symptoms in three categories and observed signs in two or more categories; the Budapest research criteria require reported symptoms in four categories and observed signs in two or more categories. *We defined risk factors as those that predict CRPS onset, without necessarily being causally associated. All risk factors were derived from unadjusted analyses, except for Bruehl et al (2022).[15]

Table: **Prospective studies (published 2018–23) in which the post-injury incidence of complex regional pain syndrome was assessed using International Association for the Study of Pain (Budapest) diagnostic criteria[20,23]**

features of systemic dysautonomia, as measured by deep breathing and orthostatic tests.[40]

Central sensitisation and brain changes

Changes in the CNS could have a role in the pathophysiology of CRPS. Amplification of neural signalling within spinal and trigeminal nociceptive neurons, known as central sensitisation, can facilitate pain hypersensitivity.[41] In cross-sectional studies, people with CRPS have shown features that suggest central sensitisation, including mechanical and thermal hyperalgesia in pain-free body regions and increased temporal summation of pain.[42,43] Signs of dysregulated sensory processing within the CNS—such as reduced tolerance of auditory, visual, and olfactory stimuli—have also been observed in cross-sectional studies in individuals with CRPS compared with controls without pain.[44–46] In the brain, changes in structure and function have been proposed to drive impairments in pain perception and sensorimotor function.[47] Emerging data from functional MRI studies raise the possibility that CRPS symptoms arise from impaired antinociceptive modulation via the periaqueductal grey (Hok P, Department of Neurology, University Medicine Greifswald, Greifswald, Germany, personal communication), altered thalamocortical and putaminal functional connectivity,[48,49] and changes in the basal and motor ganglia loops,[50] although these findings require validation in large cohorts.

Genetic factors

Data from a 2023 exome sequencing study suggest that CRPS might be heritable in about a third of individuals (57% of men and 24% of women) with associations reported for single nucleotide polymorphisms in *ANO10*, *P2RX7*, *PRKAG1*, and *SLC12A9*.[51] Epigenetic mechanisms involving differential DNA methylation might also have a determinative role in CRPS onset after trauma.[52] How genetic changes might affect CRPS onset is not understood, although inflammatory and immune mechanisms are possible.

Psychological distress

Individuals with CRPS commonly report psychological distress,[53] and researchers have postulated that symptoms, such as anxiety, stress, and depression might interact

with other pathophysiological mechanisms to predispose to CRPS and increase symptom severity. Unadjusted analyses from prospective studies published in the past decade have shown that people who had elevated anxiety, depression, stress, and catastrophising after wrist fracture had an increased risk of developing CRPS (table).[18,21,30] These psychological factors, as well as body perception disturbance and reduced perceived ownership of the affected limb, are also associated with severe and persisting CRPS symptoms.[54] Data from a cross-sectional study suggest that post-traumatic stress disorder associated with pre-injury events might be more common in individuals with CRPS than in those with non-CRPS-related chronic pain.[55]

Diagnosis

Clinical criteria

Diagnosis of CRPS is based on clinical assessment of signs and symptoms. Criteria from the International Association for the Study of Pain (IASP), known as the Budapest criteria, which have been in use since 2007, require several items for a diagnosis of CRPS.[20,23] These criteria comprise: ongoing pain that is disproportionate to the inciting trauma; reported symptoms in three categories and observed signs in two categories (ie, sensory [eg, allodynia], vasomotor [eg, temperature or skin colour changes], sudomotor or oedema [eg, changes in sweating], and motor or trophic [eg, motor dysfunction such as weakness, tremor, or dystonia]); and exclusion of other explanations after a thorough history and examination.

The Budapest criteria are widely used, but ambiguities in assessment instructions and difficulties applying the criteria prompted clarifications to be published by the IASP CRPS special interest group in 2021, which are known as the Valencia consensus adaptations.[4] Updates were made to clarify assessment of fluctuating symptoms (full diagnostic evaluation should be applied at every assessment) and spread of CRPS symptoms beyond a single limb (defined as meeting the full diagnostic criteria for CRPS in multiple limbs), and to better define the terms asymmetry and changes. Full assessment instructions are also provided in the ICD-11.[1]

Subtypes

CRPS is divided within the Budapest criteria into two main subtypes depending on the absence (type I) or presence (type II) of peripheral nerve damage.[23] Since the diagnostic signs and symptoms of these subtypes are identical, the clinical utility of this distinction is uncertain.[4] The Valencia consensus adaptations clarified that CRPS type II should not be classed as neuropathic pain. People with both disorders display features of a nerve lesion, but CRPS type II is distinguished from neuropathic pain by signs and symptoms that extend beyond an injured nerve territory.[4,56] A third subtype—CRPS in partial remission—has been introduced by IASP within the Valencia adaptations for individuals who previously had a diagnosis of CRPS on the Budapest criteria but who no longer meet these diagnostic criteria, despite still having some signs and symptoms.[4] These people often report continued debilitating pain. Individuals with some signs and symptoms of CRPS who have never been diagnosed according to the Budapest criteria are classed as having CRPS not otherwise specified in the absence of another diagnosis that explains the presentation. Although preliminary research has explored presentations of CRPS referred to as warm or cold and early or persistent, evidence is insufficient to establish formal subtypes.[4]

Classification

CRPS is classified by the IASP as a chronic primary pain disorder,[19] thereby recognising CRPS as a health condition in its own right. The term chronic primary pain is used by the IASP to group pain conditions that persist for more than 3 months, are associated with substantial emotional distress or functional disability, and cannot be accounted for by another condition.[19] These criteria are intended to be agnostic to the cause of pain and do not preclude the presence of an inciting event.[57] The biological, psychological, and social pathophysiological processes underlying CRPS are formally recognised by this classification.[57]

The classification of CRPS as a chronic primary pain condition is reflected in the ICD-11.[58] After a proposal from the IASP CRPS special interest group, the previous first parent classification of focal or segmental disorder (coded 8D8A.0) in ICD-10 was changed to chronic primary pain (MG30.04) in ICD-11. Chronic postsurgical or post-traumatic pain (MG30.2) is now linked to CRPS in ICD-11 as a secondary diagnostic parent classification, which reflects the most common inciting event for CRPS.[4]

The IASP proposed that CRPS might also meet criteria for the nociplastic mechanistic pain descriptor.[59] Nociplastic pain is defined by IASP as pain duration greater than 3 months, a regional rather than discrete distribution, pain not entirely explained by nociceptive or neuropathic mechanisms,[56] and clinical signs of pain hypersensitivity that can be evoked in the region of pain.[60] An evaluation of the nociplastic grading system showed that most people with CRPS meet these criteria.[61] Further field-testing studies in large cohorts of individuals with CRPS are required to confirm this proposal, as recommended by the IASP terminology task force.[60]

Management

Successful management of CRPS is a major challenge for clinicians because few interventions have been evaluated in randomised trials and, of those that have, most have not shown any benefit.[5] In the absence of moderate-certainty or high-certainty evidence of treatment efficacy, clinical management is best guided by risk of treatment-related harms, potential for drug–drug interactions, consideration of comorbidities, patient preferences, and out-of-pocket expenses. In line with methodological guidance for rare

diseases,[62] extrapolation of data from other chronic pain conditions—such as neuropathic pain—is sometimes considered appropriate because of similarity of symptoms.

The UK Royal College of Physicians (RCP) produced a guideline for the management of CRPS, which to date, is the only high-quality guidance available.[63,64] The evidence-based and consensus-based RCP guidelines recommend an integrated, individually tailored, multidisciplinary approach that incorporates education, pain relief (pharmacological and interventional), physical rehabilitation, and psychological intervention as four pillars of care—each with equal importance (figure 2). Evidence is insufficient to base treatment decisions on CRPS subtype.

Education

All clinicians involved in the diagnosis and management of CRPS should provide their patients with basic information and education about CRPS (figure 2). A Delphi study showed that people with CRPS want information on prognosis, self-management, social support, and factors that contribute to symptoms.[6] For patients presenting up to 18 months after symptom onset, the RCP guidelines recommend that clinicians should highlight the favourable recovery rate.[64] Reassurance that pain-related distress and bodily awareness disturbances (eg, the affected limb feeling foreign, or larger than normal) are common could help to reduce distress. For individuals with severe or persistent CRPS, for whom multidisciplinary management is required, education should emphasise active approaches to recovery, understanding how beliefs, behaviours, and social influences modulate the pain experience, why and how to pace activities, and how to manage flare ups.[6,65] The patient's partner or family should be involved in this educational process, wherever possible.

Pharmacological pain relief

Drug treatment should be offered to individuals with CRPS as early as possible to minimise pain and support physical rehabilitation. Simple analgesics (eg, oral paracetamol and non-steroidal anti-inflammatory drugs) are indicated as first-line therapy, according to the RCP guidelines.[64] These medicines are proposed to assist with ongoing trauma-related pain and mobilisation of the affected limb.[64] Patients should be screened for contraindications (eg, cardiovascular or gastrointestinal comorbidities) and advised on appropriate dosing and duration of therapy.

If pain is not relieved to at least mild intensity (<3 on 0–10 numerical rating scale) after 3–4 weeks of treatment with simple analgesics, a course of first-line neuropathic pain medicine—as determined by IASP and UK National

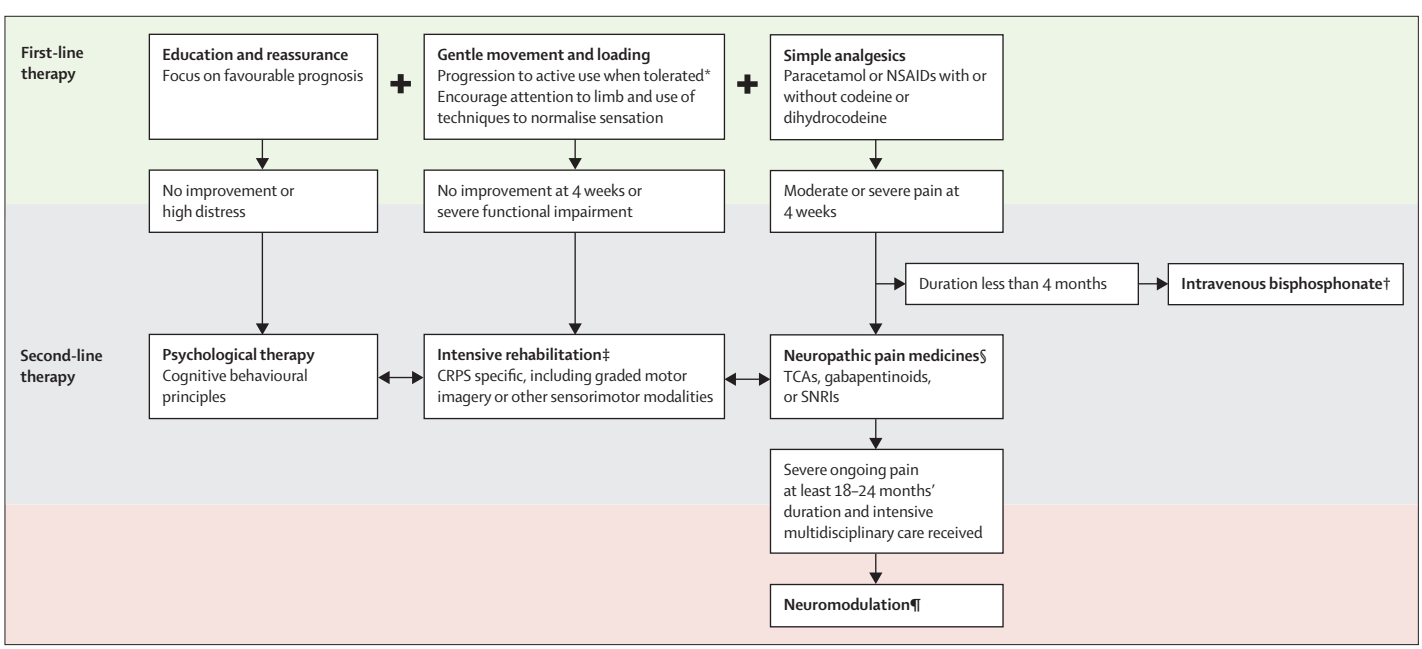

Figure 2: **Proposed algorithm for the management of complex regional pain syndrome**
Adapted from recommendations in the UK Royal College of Physicians guidelines.[64] First-line treatments are usually administered in non-specialist settings and, in most cases, irrespective of symptom duration. First-line treatments should be done together and have equal importance. Second-line treatments might be delivered individually or together within a multidisciplinary pain management programme. Referral to a multidisciplinary programme is usually appropriate after no response to 6 months of treatment but might be fast-tracked as determined by specialists with specific CRPS experience. The patient's partner or family should be involved in the treatment planning process when possible. CRPS=complex regional pain syndrome. NSAID=non-steroidal anti-inflammatory drug. TCA=tricyclic antidepressant. SNRI=serotonin–noradrenaline reuptake inhibitor. *For people with excessive fear that activity will cause pain, movement should be progressed using load or time contingencies within tolerance. †A single intravenous infusion of 60 mg pamidronate (or equivalent) could be given as a one-off treatment for CRPS of less than 4 months in duration, considering evidence available since publication of the RCP guideline. ‡Delivered by specialist physiotherapists or occupational therapists if possible. §Titrated to therapeutic levels. Where pain reduction is insufficient or tolerance develops, drug reduction or cessation is advised. ¶Only considered when symptoms are refractory and the patient has received intensive integrated multidisciplinary management. Preimplantation screening should entail a thorough psychosocial evaluation, and patients should be informed of risks and advised that benefit is likely to decline over time. Rarely appropriate for patients with symptom duration less than 18–24 months.

Institute for Health and Care Excellence guidelines—could be trialled.[64,66,67] Drugs that could be used include gabapentinoids, such as pregabalin and gabapentin, tricyclic antidepressants, such as amitriptyline and nortriptyline, and serotonin–noradrenaline reuptake inhibitors (SNRIs) such as duloxetine. Only gabapentin has been evaluated for CRPS, with a Cochrane overview finding very low-certainty evidence (due to risk of bias and small sample size) that the medication might not be effective (participants experiencing "much pain relief": gabapentin 17% *vs* placebo 4%; risk ratio 4·0 [95% CI 0·9 to 17·8]).[5] Meta-analyses of randomised trials provide moderate-certainty evidence of efficacy for pregabalin (number needed to treat 7·7 [95% CI 6·5 to 9·4]), gabapentin (7·2 [5·9 to 9·1]), and tricyclic antidepressants (3·6 [3·0 to 4·4]) for neuropathic pain, and for the SNRI duloxetine for chronic pain (standardised mean difference –0·3 [95% CI –0·2 to –0·4]), although these effect sizes are considered modest.[66,68] Adverse events such as dizziness and somnolence are common after administration of pregabalin (in 24% and 17% of patients, respectively), gabapentin (19% and 14%, respectively),[69] and amitriptyline (24% and 17%, respectively).[70,71] Tolerance to these drugs might develop, although data supporting this possibility are scarce. Careful evaluation of patients for a history of drug abuse is advised when prescribing gabapentinoids because of the potential for misuse and overdose, which often occurs with opioid analgesics.[72,73] Tricyclic antidepressants could be considered in individuals with comorbid depression or pain-related sleep interference. All neuropathic pain medicines should be used for the shortest period possible, and in people for whom pain reduction is insufficient or tolerance develops, the RCP guidelines recommend dose reduction or cessation.[64]

Use of bisphosphonates for treatment of CRPS could be considered in the early period after symptom onset because of the proposed anti-inflammatory properties of these drugs. A single intravenous administration of pamidronate 60 mg is recommended by RCP guidelines in patients with CRPS of less than 6 months in duration,[64] although other bisphosphonate formulations might be appropriate in equivalent doses. A Cochrane overview found low-certainty evidence (due to inconsistency and imprecision) that bisphosphonates might provide clinically important reductions in pain intensity for early CRPS type I.[5] By contrast, in the past 5 years, multinational trials in patients with CRPS of intravenous neridronate (NCT03530345 and NCT03560986; patients with CRPS of up to 2-year symptom duration) and oral zoledronate (NCT02504008; in patients with CRPS of up to 6 months symptom duration) were terminated for futility after independent interim analyses. Evidence suggests that bisphosphonates might only be efficacious very early after CRPS symptom onset (<4 months symptom duration). Clinicians should consider common adverse events, including gastrointestinal intolerance, polyarthralgia, and fever, particularly after intravenous administration. Additional caution is needed for individuals with reduced renal function and those undergoing dental procedures.[74,75]

Opioids have not been evaluated in randomised trials for CRPS despite their routine use. Weak opioids (eg, codeine and dihydrocodeine) could be added to first-line or second-line medicines to manage painful flares, according to the RCP guidelines.[64] Although a meta-analysis of randomised trials found modest effects of tramadol and strong opioids in neuropathic pain,[66] no data are available for their long-term efficacy, and only tramadol is recommended if used as acute rescue therapy.[67] Since high-certainty evidence for efficacy of opioids is scarce, and there is a risk of dependence, overdose, and death with use of these drugs,[76] commencement of strong opioid therapy should be avoided in patients with CRPS, according to RCP guidelines. In patients for whom strong opioids are considered, urgent referral to a consultant pain specialist is advised.[64]

Ketamine is commonly used as a third-line therapy for refractory CRPS,[77] but it is not recommended according to RCP guidelines.[64] A meta-analysis of randomised trials provided very low-certainty evidence (due to risk of bias and small sample size) that intravenous infusions of ketamine (administered 4·2 days continuously, or 4 h per day for 10 consecutive days) could be effective for persistent CRPS immediately after the intervention (mean difference on a 0–10 pain scale] –2·4 [95% CI –3·5 to –1·2]), but not at 12-week follow up (–0·5 [–1·5 to 0·4]).[5,78] The absence of benefit of intravenous ketamine beyond the immediate term, reduced efficacy with repeated administration, common psychotomimetic adverse events,[79] and high out-of-pocket costs limits the acceptability of this drug. High-quality placebo-controlled trials are needed to evaluate analgesic effects of ketamine for CRPS.

Interventional pain relief

Interventional procedures could be offered for people with CRPS who have severe pain intensity and functional impairments. The RCP guidelines recommend against the use of intravenous regional blocks with guanethidine, because no evidence of efficacy has been shown in randomised trials.[5,64] Local anaesthetic sympathetic blockade could be used with the aim of breaking a pain cycle or aiding physiotherapy,[64] although a Cochrane overview found moderate-certainty evidence that this approach is probably ineffective.[5]

Invasive neuromodulation interventions, such as spinal cord and dorsal root ganglion stimulation, are recommended by RCP guidelines for patients who have not responded to appropriate integrated management that includes education, physiotherapy, and psychological modalities (figure 2).[64] A Cochrane overview found very low-certainty evidence (due to risk of bias and small

sample size) that spinal cord stimulation might reduce pain intensity compared with physiotherapy, and has uncertain effects compared with sham stimulation.[5] Long-term follow-up data suggest that benefits of spinal cord stimulation might not be sustained over time.[80] Invasive neuromodulation interventions should only be delivered in the context of interdisciplinary care and after a thorough psychosocial evaluation.[81] The potential benefit must be considered against the risk of common procedure-related and device-related complications, including infection, lead failure, pain at the site of implantation, and surgical revisions to replace a failed device,[80,82] together with the costs required for device implantation and maintenance.

The role of surgical interventions in the treatment of refractory CRPS is unclear. Amputation of the CRPS-affected limb is reported to be increasingly sought by patients.[64] Data from uncontrolled studies suggest that, although patients might report initial satisfaction with the results of amputation, development of phantom limb pain, stump pain, or stump CRPS is likely, and prosthesis use is often problematic.[83]

Panel 1: The clinical course of a patient with complex regional pain syndrome

Risk factors and inciting event

A 54-year-old woman with a history of asthma sustains an undisplaced scaphoid fracture during work at a child-care facility. The fracture is managed with cast immobilisation, which she notes feels restrictive. 1 month after cast removal, she presents to her family doctor with severe wrist pain, swelling, redness, and sensitivity to touch. Her doctor suspects CRPS, advises use of simple analgesics, and refers the patient to a specialist, who could be a neurologist, pain specialist, or rheumatologist with adequate experience in CRPS management.

Diagnosis

The specialist visit takes place 4 months after the inciting injury. A full medical history is taken, followed by evaluation using the Budapest diagnostic criteria as instructed in the International Classification of Diseases 11th revision (ICD-11). The patient reports high ongoing pain (score of 8 on a 0–10 pain scale), symptoms in all four categories of the Budapest criteria (hyperalgesia and allodynia, increased temperature and redness, swelling, reduced range of motion, and weakness), and emotional distress relating to her workplace compensation claim. On assessment, the patient is judged by the specialist to be positive in all four categories of the Budapest criteria. The specialist confirms there is no other condition that accounts for the patient's signs and symptoms.

Classification

Using the ICD-11, the patient's presentation is coded as complex regional pain syndrome (MG30.04) of the radial border of the wrist (XA3LK1), with right laterality (XK9K), psychosocial factors present (XS7G), severe pain (XS2E), moderate distress (XS7C), and severe pain-related interference (XS2U).

Management

The specialist provides the patient with information on CRPS, reassuring her that she is likely to experience considerable improvement up to 18 months from symptom onset. She is offered neuropathic pain medicines to manage pain, comprising pregabalin (75 mg twice daily) and amitriptyline (up-titrated from 25 mg to 50 mg, taken at 1800 h to avoid next-day drowsiness), with paracetamol used to manage short-term flares. She is referred to a psychologist to manage stress relating to her injury and the ongoing workplace compensation case. Rehabilitation is commenced with a specialist pain physiotherapist who works within the pain department. This therapy comprises tactile and thermal desensitisation to reduce allodynic symptoms, and limb laterality recognition and mirror therapy exercises to gradually introduce pain-free movement.

Prognosis

At 18-months, the patient reports a marked improvement in symptoms. Average pain intensity has decreased to 2–3 on the 0–10 pain scale, with occasional spikes in pain and swelling after activity and cold temperatures. She has ceased pregabalin but continues to take amitriptyline 25 mg at night, which aids her sleep. There is reduced hand dexterity, and a 40% difference in grip strength of the affected hand compared with the non-affected hand. She is working at reduced hours, with work tasks modified to exclude manual activities. The workplace compensation case is closed, with the final report confirming a diagnosis of CRPS in partial remission.

CRPS=complex regional pain syndrome.

Rehabilitation

Active rehabilitation should be commenced as early as possible, according to the RCP guidelines (figure 2).[64] When managing acute CRPS, clinicians should encourage frequent attention to the affected limb, techniques to normalise skin sensation, gentle limb movement, and (when tolerated) progression to gentle weight bearing and stretching.[64] Referral to physical or occupational therapy is indicated for patients who require supervision to increase participation or who display early signs of severe functional impairment. When possible, therapists should have experience of CRPS management.

Several rehabilitation modalities are recommended by the RCP guidelines.[64] No head-to-head randomised trials have been done to determine the optimal rehabilitation approach, but different approaches might suit different patients. A 2022 Cochrane review found that, based on very low-certainty evidence (due to risk of bias and small sample size) from one randomised trial, multimodal rehabilitation (including pain management advice, relaxation exercises, connective tissue massage, trans-cutaneous electrical nerve stimulation, and exercise) could be more effective than minimal care comprising advice and education about CRPS from a therapist.[84] Sensorimotor approaches such as graded motor imagery and mirror therapy are routinely used, especially for individuals who display signs of disturbed body perception. A meta-analysis of randomised trials showed, with very low certainty (due to risk of bias and small sample size), that graded motor imagery (involving implicit motor imagery, imagined movements, and mirror therapy) might be more effective than treatment as usual for up to 6 months of follow-up (mean difference [on a 0–100 pain scale] –21·0 [95% CI –31·2 to –10·9]).[84] Sensorimotor approaches are time-intensive and require substantial commitment from the patient, which can limit clinical application. Exposure-based therapies might be appropriate for patients who avoid activities due to excessive fear that they will cause pain. Findings of one randomised trial provided very low-certainty evidence (due to risk of bias and small sample size) that

graded exposure to painful activities using a fear-based hierarchy might provide sustained reductions in pain compared with treatment as usual (mean difference [on a pain scale of 0–10] –2·8 [95% CI –4·2 to –1·5]).[84,85] This approach is promising but requires specially trained therapists and highly motivated patients.

Psychological interventions

Clinicians involved in the initial treatment of patients with CRPS should be aware of psychological factors that could predict persistence, such as elevated anxiety and depressive symptoms.[54] Identification of psychological factors, severe pain, or high distress could guide referral to specialised psychological management (figure 2). Psychological interventions are usually delivered in a group setting as part of a multidisciplinary pain management programme but, in some cases, one-to-one therapy is necessary. A meta-analysis of randomised trials showed moderate-certainty evidence that cognitive behavioural therapy (which involves modifying negative thoughts surrounding pain and reducing pain-contingent behaviours) probably improves patient-relevant outcomes in adults with chronic pain, although the beneficial effects are small.[86] Alternative approaches, such as acceptance and commitment therapy and behavioural therapy, could be used, but evidence of efficacy is uncertain.[86]

Prevention

Evidence is insufficient to provide recommendations for interventions or strategies to prevent CRPS.[64] Optimal post-fracture management entails non-restrictive casting and early functional rehabilitation, which are thought to prevent the onset of CRPS.[64,87] Vitamin C supplementation, which is proposed to reduce oxygen free radicals in the inflammatory period post-trauma, could be used prophylactically. A meta-analysis of three randomised trials (no certainty of evidence rating) showed a risk reduction of 46% with administration of 500 mg of vitamin C per day for 50 days after operative and non-operative fracture management.[88]

Panel 2: **Research priorities for complex regional pain syndrome**

Epidemiology

- To accurately estimate incidence and prevalence of CRPS by doing population-based studies using Budapest diagnostic criteria
- To establish the clinical course of CRPS and confirm the duration at which CRPS should be considered persistent
- To improve understanding of the factors that affect variability in CRPS outcomes, including those that are associated with the development of CRPS and, later, chronic widespread pain
- To externally validate risk prediction models

Pathophysiology

- To assess whether modulation of IgM and IgG serum autoantibodies has clinical relevance
- To improve understanding of binding targets of CRPS-associated autoreactive immunoglobulins
- To evaluate the effect of early post-trauma immune responses on the development of CRPS by doing prospective studies
- To explore whether individual variation in CRPS pathophysiology can inform mechanism-based treatments

Diagnosis

- To establish reliability of International Classification of Diseases 11th revision (ICD-11) diagnostic codes and specifiers for CRPS
- To investigate whether CRPS not otherwise specified belongs in the spectrum of CRPS and whether individuals with this presentation should be treated independently
- To establish whether CRPS types I and II are distinct subtypes or should be combined
- To explore other CRPS subtypes, including warm or cold and early or persistent

Treatment

- To develop CRPS-specific trial design parameters for evaluating treatment effectiveness by building on rare disease methodologies
- To define relevant endpoints by exploring patients' perspectives, and to provide thresholds for defining clinically meaningful effects across different classes of interventions
- To evaluate whether CRPS can be prevented through a very early rehabilitative pathway, and whether this strategy can address the return-to-work gap
- To do replication trials for routinely used treatments with uncertain evidence of efficacy or harm, such as intravenous ketamine and spinal cord stimulation

CRPS=complex regional pain syndrome.

Emerging treatments

Much of the development and evaluation of emerging pharmacotherapies for CRPS has entailed the targeting of EMA and FDA orphan drug designations. In the past 5 years, orphan status has been granted for low-dose oral naltrexone, a proprietary ketamine-based formulation, and delta-9-tetrahydrocannabinol and cannabidiol. The opioid antagonist naltrexone has been used off-label at low doses (4·5 mg per day) to treat CRPS and is proposed to modulate cytokine production via antagonistic effects on toll-like receptor 4.[89] A placebo-controlled trial of naltrexone is ongoing (NCT02502162). Cannabis-based compounds are increasingly used for chronic pain management, but their efficacy and safety remain uncertain,[90] and no studies in people with CRPS are available. Novel immunomodulatory approaches are also being explored. The immunosuppressant mycophenolate was effective in an exploratory randomised open-label trial and requires further evaluation.[91]

Emerging rehabilitation approaches combine multiple modalities into treatment packages that include education, novel methods to restore distorted bodily awareness and sensory processing, and promotion of movement and functional re-engagement. A large trial testing a combined rehabilitation approach for persistent CRPS is ongoing (ACTRN12621000175875). Virtual reality interventions might also be useful to improve altered body perception. One randomised trial of a brief visual illusion intervention that altered the image of the affected limb found a small reduction in pain intensity compared with the control.[92]

Search strategy and selection criteria

We searched PubMed for articles published from Jan 1, 2014, to Dec 31, 2023, using the MeSH terms and keywords: ([{"Complex Regional Pain Syndromes"[MeSH Terms]} OR {"complex regional pain syndrome"} OR {"CRPS"}] AND [{"Diagnosis"[MeSH Terms] OR "diagnosis"} OR {"Prognosis"[MeSH Terms] OR "prognosis" OR "predictors"} OR {"Epidemiology"[MeSH Terms] OR "epidemiology" OR "incidence" OR "prevalence"} OR {"Risk Factors"[MeSH Terms] OR "risk factors"} OR {"Therapeutics"[MeSH Terms] OR "therapeutics"} OR {"Pathologic Processes"[MeSH Terms] OR "pathophys*"}] AND ["Humans"[MeSH Terms] OR "humans"]). We also searched ClinicalTrials.gov using "complex regional pain syndrome". We applied no language restrictions. We also hand-searched the reference lists of included studies. We selected publications on the basis of originality and relevance to this Review. We prioritised publications from the past 5 years but included important studies published before this period.

Various non-invasive neuromodulation techniques have been proposed to treat CRPS[81] but evidence is conflicting regarding efficacy for chronic pain.[93]

Prognosis

Few high-quality, long-term prospective studies have characterised the course of CRPS. Data from available prospective studies show that acute CRPS improves rapidly within the first 6 months, but 14–27% of participants continue to fulfil the Budapest diagnostic criteria at 12 months, and complete remission of symptoms might be rare.[94,95] In a study of individuals with CRPS type I who had symptoms lasting up to 6 months, 48% met the Budapest criteria 1 year later.[96] A long-term prospective study found minimal change in CRPS severity between 1 year and 8 years.[97] Improvement of symptoms might be more likely than these data suggest, because the measures used to define recovery do not consider the intensity of ongoing pain. Despite continuing to satisfy diagnostic criteria, patients might report substantial improvement, with mild pain, hypersensitivity, and occasional swelling. Those who do not improve 18 months from onset might be at risk of developing CRPS spread or ongoing non-CRPS pain. Non-CRPS pain might have neuropathic features (such as burning) without autonomic signs and affect wider body areas, as with chronic widespread pain. Finally, a separate yet important measure of CRPS outcomes is work status. Up to 40% of people with CRPS are unable to return to work due to their symptoms, and about a third of those who do return require workplace adaptation (panel 1).[98]

Conclusions and future directions

The past decade has seen important advances in understanding CRPS. However, research progress is slowed by the rarity of CRPS. Uncertainty regarding CRPS epidemiology, pathophysiology, diagnosis, and treatment remains (panel 2).

The updates to CRPS classification in the ICD-11 are a major step towards harmonisation of population-based data. Rapid implementation of updated classification codes is needed to improve the validity and reliability of estimates in epidemiological studies. Combining diagnostic codes with other specifiers, such as pain severity and distress levels, will facilitate interpretation and comparison across studies and enable evaluation of changes in symptoms over time. Improved linkage of electronic health-care records will support the development and validation of clinically useful risk prediction models for patients in surgical and trauma settings, permitting stratification for evaluation of early preventive strategies.

Several areas of uncertainty can be addressed with improved collection and sharing of observational data. The development of an international registry with standardised data collection has been an important first step.[99] Sharing of individual participant data will improve data synthesis and maximise opportunities for discovery. These initiatives might allow identification of subtypes to reduce the well established clinical heterogeneity of CRPS. Furthermore, high-quality prospective data will provide key information regarding the progression of CRPS over time, inform trial endpoints, and serve as a cohort within which trial results can be extrapolated.

The need for high-quality evaluations of treatment effectiveness to guide management remains a great challenge. As a priority, infrastructure to do adequately powered randomised trials must be established. This process entails building on existing networks and developing new consortia of researchers to do international multicentre trials. Increased rigour in the treatment selection process is also required. An improved understanding of CRPS pathophysiology—including further exploration of genetic, metabolic, psychological, inflammatory, and autoimmune factors—is necessary to identify treatment targets. Treatments should have clear therapeutic rationales and undergo rigorous pilot testing to confirm feasibility and acceptability. Capture of supposed process variables and a priori planned mediation analyses,[100] embedded in randomised trials, will help adapt and refine interventions to increase their effectiveness. Finally, incorporating the preferences of people with CRPS is needed throughout every phase of the research cycle.

Contributors

MCF, NEO, GLM, and JHM had the idea for the Review. MCF did the literature search and wrote the original draft. All authors contributed to, reviewed, and approved the final version.

Declaration of interests

MCF is supported by an Australian Government Research Training Program scholarship and the Neuroscience Research Australia PhD Pearl supplementary scholarship; has received research grants from ERA-NET NEURON for research related to CRPS and neuropathic pain; and is a committee member of the IASP special interest group for CRPS. NEO has received funding from the National Health and Medical

Research Council of Australia and ERA-NET NEURON for research related to CRPS. CS is funded by the German Research Foundation for the Clinical Research Group KFO5001 ResolvePAIN and has received funding from Deutsche Forschungsgemeinschaft and Bundesministerium für Bildung und Forschung. AG has received funding from the UK Medical Research Council, Pain Relief Foundation Liverpool, and Versus Arthritis; has been a consultant for UCB and Novartis; is Chair of the Scientific Committee of the British Pain Society, past Chair of the IASP special interest group for CRPS, and Chair of the European Pain Federation CRPS task force; and is a member of the scientific committee for the Pain Relief Foundation. JHB is co-Chair of the IASP special interest group for CRPS; has received fees for speaking about CRPS paid by Theoria Congresos, at a conference organised by Hospital Intermutual de Levante; and has received research funding from the Reflex Sympathetic Dystrophy Syndrome Association, the Netherlands Organisation for Scientific Research, and the Experimental Psychological Society. AGC, GLM, and JHM receive salary support from investigator grants from the National Health and Medical Research Council of Australia. GLM receives royalties for a book about a specific rehabilitation approach to CRPS that is mentioned in this Review; is an unpaid board member of the consumer advocacy body Pain Australia, and is an unpaid Chief Executive Officer of the non-profit community outreach initiative Pain Revolution. GLM and JHM have received funding from the National Health and Medical Research Council of Australia for research on CRPS.

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