Current Pain and Headache Reports (2023) 27:269–298
https://doi.org/10.1007/s11916-023-01130-5

NEUROPATHIC PAIN (A ABD-ELSAYED, SECTION EDITOR)

Complex Regional Pain Syndrome: Evidence-Based Advances in Concepts and Treatments

Gerard Limerick[1,2] · Dana K. Christo[3] · Jennifer Tram[4] · Roya Moheimani[5] · John Manor[2] · Krishnan Chakravarthy[4] · Jay Karri[1,6,7] · Paul J. Christo[1]

Accepted: 29 May 2023 / Published online: 8 July 2023

Abstract

Purpose of Review This review presents the most current information about the epidemiology of complex regional pain syndrome (CRPS), classification and diagnostic criteria, childhood CRPS, subtypes, pathophysiology, conventional and less conventional treatments, and preventive strategies.

Recent Findings CRPS is a painful disorder with multifactorial pathophysiology. The data describe sensitization of the central and peripheral nervous systems, inflammation, possible genetic factors, sympatho-afferent coupling, autoimmunity, and mental health factors as contributors to the syndrome. In addition to conventional subtypes (type I and type II), cluster analyses have uncovered other proposed subtypes. Prevalence of CRPS is approximately 1.2%, female gender is consistently associated with a higher risk of development, and substantial physical, emotional, and financial costs can result from the syndrome. Children with CRPS seem to benefit from multifaceted physical therapy leading to a high percentage of symptom-free patients. The best available evidence along with standard clinical practice supports pharmacological agents, physical and occupational therapy, sympathetic blocks for engaging physical restoration, steroids for acute CRPS, neuromodulation, ketamine, and intrathecal baclofen as therapeutic approaches. There are many emerging treatments that can be considered as a part of individualized, patient-centered care. Vitamin C may be preventive.

Summary CRPS can lead to progressively painful sensory and vascular changes, edema, limb weakness, and trophic disturbances, all of which substantially erode healthy living. Despite some progress in research, more comprehensive basic science investigation is needed to clarify the molecular mechanisms of the disease so that targeted treatments can be developed for better outcomes. Incorporating a variety of standard therapies with different modes of action may offer the most effective analgesia. Introducing less conventional approaches may also be helpful when traditional treatments fail to provide sufficient improvement.

Keywords Complex regional pain syndrome · CRPS I · CRPS II · Neuropathic pain · Nociplastic pain · Reflex sympathetic dystrophy · Chronic pain · Acute pain · Neuromodulation · Ketamine · Spinal cord stimulation · DRG stimulation

Introduction

CRPS is a painful neurologic condition that is characterized by the presence of autonomic dysfunction, persistent regional inflammatory changes, immune and autoimmune dysfunction, and symptoms located in a non-dermatomal distribution [1, 2]. The pain is out of proportion to the inciting event (if present), both in intensity and temporality. The progression and severity of the disease are variable; while some patients experience mild, self-limited symptoms,

✉ Paul J. Christo
pchristo@jhmi.edu

1 Division of Pain Medicine, Department of Anesthesiology & Critical Care Medicine, Johns Hopkins University School of Medicine, Baltimore, USA

2 Department of Physical Medicine & Rehabilitation, Johns Hopkins University School of Medicine, Baltimore, USA

3 Division of General Internal Medicine, Johns Hopkins University School of Medicine, Baltimore, USA

4 Department of Anesthesiology, University of California, San Diego, CA, USA

5 Coast Spine and Sports Medicine, Covina, CA, USA

6 Department of Orthopedic Surgery, University of Maryland School of Medicine, Baltimore, MD, USA

7 Department of Anesthesiology, University of Maryland School of Medicine, Baltimore, MD, USA

other more severe cases can cause debilitating pain, and some patients even resort to amputation of the affected limb after exhausting all other treatment options. Much of the pathophysiology underlying CRPS has not yet been fully uncovered. A more thorough understanding of disease mechanisms along with insight into emerging and less conventional treatments will provide the basis for targeted therapies that will help combat this life-altering disorder.

Selection Criteria

The search strategy was run on March 15, 2021, in the electronic databases MEDLINE (Pubmed), Embase (Embase.com), and The Cochrane Library (Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials (CENTRAL), Cochrane Methodology Register). Controlled vocabulary words were identified and combined with keyword synonyms in all databases. Searches were limited to 2018 to present and English only. However, foundational CRPS articles predating 2018 were included in the writing of the review on as-needed basis. Additionally, 3 articles were identified by hand searching, and searching the citations of key studies.

Epidemiology

Incidence/Prevalence

High-quality studies quantifying the incidence and prevalence of CRPS are limited. Sufficient data collection for rare conditions such as CRPS requires large populations to be followed for extended periods of time. The task is further complicated by changes in diagnostic criteria over time which impact incidence and prevalence estimates due to variations in sensitivity and specificity.

In 2003, Sandroni et al. [3] reported the first population-based study to estimate the incidence and prevalence of CRPS in Olmsted County, Minnesota (representative of the US white population) based on medical records available for all residents. Cases were identified between 1989 and 1999 based on the IASP 1994 criteria. The incidence of CRPS I was 5.46 per 100,000 person years and the period prevalence (1999) was 20.57 per 100,000 person years. The incidence of CRPS II was 0.82 per 100,000 person years and the prevalence was 4.2 per 100,000 person years. Reclassification of CRPS I cases according to Harden's 1999 proposed revision of the diagnostic criteria resulted in only 43% of CRPS I cases fulfilling the criteria. In this population, 74% of CRPS cases are resolved [3].

Estimates from another large population-based retrospective cohort study in the Netherlands conducted from 1996 to 2005 suggest a higher incidence of CRPS (26.2 per 100,000 person years, 95% confidence interval: 23.0–29.7) compared to that reported by Sandroni et al. [3]. CRPS cases not limited to IASP diagnostic criteria were identified through electronic medical records that are available for the Dutch population and further verified by general practitioners' and specialists' records. When cases were restricted to only those that met the IASP diagnostic criteria, the incidence rate was 16.8 per 100,000 person years (95% confidence interval: 14.7–19.2) [4].

Studies based on claims data lack the detailed information found in medical records and do not specify the criteria used for diagnosis of CRPS; however, they are able to capture disease burden in a large segment of a population and may be more representative than study samples derived from tertiary referral centers.

The prevalence of CRPS was estimated to be 1.2% over a 13-year time period (2000–2012) in a retrospective cohort based on the Truven Reuters MarketScan Database. CRPS was identified by ICD9 codes and patient-level data were derived from inpatient, outpatient, prescription, and laboratory records from commercial insurers, Medicare Supplemental, and Medicaid populations in the USA. Murphy et al. [5] noted an increasing trend in prevalence across the 12 years with the most significant increase between 2009 and 2010 (approximately threefold) for CRPS.

In contrast, Bang et al. [6] reported declining estimates of CRPS (types I and II) prevalence in the Korean population from 2009 to 2013 (32.8 per 100,000 in 2009 to 26.2 per 100,000 in 2013). This retrospective cohort was constructed utilizing diagnostic codes from the National Health Insurance Service (NHIS), which covers the entire Korean population and included just under 50 million people [6].

Lee et al. [7] published updated incidence rates (2009–2016) in the Korean population using the same NHIS data as Bang et al. [6]. This retrospective cohort study considered changes in the incidence of CRPS that may be influenced by demographic trends, in particular, the aging population. Incidence rates for CRPS I rose steadily from 2010 to 2014 and by 2016 returned to levels observed in 2009. Conversely, CRPS II rates declined steadily from 2009 to 2016. A higher incidence of CRPS was noted with increasing age. The overall incidence of CRPS was 15.83 per 100,000 people; a higher incidence was reported for CRPS I (19.5 per 100,000 people) compared to CRPS II (12.1 per 100,000 people) [7].

Risk Factors (Demographics and Comorbidities)

Relatively few high-quality studies have evaluated the demographic and comorbid risk factors associated with CRPS. Female gender is consistently associated with up to a fourfold increased risk of developing CRPS [3–13], particularly during menopause [9]. A systematic review of potential

risk factors for CRPS concluded that age is not consistently associated with CRPS; however, most studies reviewed did suggest a higher risk for post-menopausal women [8]. Conversely, Lee et al. [7] reported higher incidence rates for CRPS I with increasing age and demonstrated the highest rates for those 60 years and older in the Korean population. Less frequently reported factors associated with increased risk include being Caucasian [3, 12] and having a higher income [12]. Comorbid conditions including headache/migraine [10, 12, 13], depression [12], asthma [13], and drug abuse [12] may increase the risk of CRPS. A population-based nested case–control study conducted in Taiwan identified 589 cases of incident CRPS between 2004 and 2009 and 5890 matched controls; the results suggested an association between CRPS and preexisting osteoporosis, myofascial pain, anxiety, and neuropathy [13]. Further research is warranted to clarify the relationship between potentially modifiable risk factors and CRPS.

Morbidity and Mortality/Burden

A diagnosis of CRPS potentially results in significant physical, emotional, and financial burden. Among a group of 65 patients in the Netherlands diagnosed with CRPS of the upper extremity with a mean interval of 5.5 years (SD 0.8; range 3–9) since diagnosis of CRPS, 62% reported limitations in activities of daily living (ADL) and instrumental activities of daily living (IADL) with pain as the most important contributing factor [14]. Galer et al. [15] described the impact of CRPS on quality of life (QOL) for a small group of patients ($n=31$), whose duration of symptoms ranged from 1 to 9 years. Sleep disturbance was reported by 80%. Significant interference with general activity, mood, normal work, and recreational activities was reported by 75%, and at least half of the participants had substantial interference with mobility, sleep, enjoyment, and social activities [15]. In 2014, Van Velzen et al. [16] administered the Dutch version of the MOS 36-Item Short-Form Health Survey to 975 Dutch patients with CRPS. It was determined that decreased physical function rather than changes in mental health was the prominent contributor to impaired QOL experienced by CRPS patients [16]. A large web-based survey, with 888 participants, conducted by Sharma et al. [17] reported that more than 90% of participants reported constant or nearly constant pain which interfered with sleep, mobility, and ADLs in more than 85% of people and self-care in more than 50%. Over 70% of patients experienced anxiety or depression; 49% had suicidal ideations and 15% acted upon their suicidal impulses. The majority of participants (61.8%) reported disability as their employment status while only 15% were fully employed [17].

Costs for healthcare services and pain medicine prescriptions have been estimated based on 35,316 incident cases of CRPS registered in a commercial insurance claims database. The highest median total (sum of outpatient and inpatient) costs ($8508; IQR $3943–$16,666), outpatient costs ($7251; IQR $3527–$13,568), and pain prescription costs ($2077; IQR $140–$8856) occurred in the year of CRPS diagnosis relative to a baseline of 2–3 years prior to CRPS diagnosis. The year prior to diagnosis saw a similar increase in costs and the 8 years following diagnosis carried higher costs compared to baseline. Elsamadicy et al. [18] estimated that a CRPS diagnosis increases annual total healthcare cost by 2.17-fold and pain prescription cost 2.56-fold compared to baseline expenditures. In Switzerland, an estimated 0.15% of auto accident victims receive a diagnosis of CRPS. Scholtz-Odermatt et al. [19] reported that over 5 years, a CRPS case costs an average of $86,900 USD in insurance costs (includes hospital care, medical procedures, medical specialist fees, ambulatory hospital care, general practice care, and paramedical care), a figure 19 times higher than non-CRPS cases. Over the same timeframe, an average of $23,300 USD was spent on treatment costs (13 times higher than non-CRPS cases). Additionally, the number of work days lost within the 2 years after an accident was 20 times higher for CRPS compared to non-CRPS cases and 68% of CRPS cases were absent from work more than 90 days [19].

The literature contains conflicting data regarding the proportion of CRPS patients who experience resolution of the condition within 3 months (74% reported by Sandroni et al. [3] and 21% according to Sharma et al. [17]) versus those who develop a chronic condition that persists [20]. Given the paucity of data on the incidence and prevalence of CRPS, it is difficult to estimate the total cost of treating patients with CRPS since those with long-term sequelae from CRPS will utilize more healthcare resources and suffer greater financial losses due to missed work or unemployment.

Definition and Diagnosis

CRPS I and II

CRPS may be separated into two primary subtypes: CRPS I and CRPS II. While both types can occur after an injury, CRPS I, previously known as reflex sympathetic dystrophy, reflects the absence of prior nerve injury. CRPS I accounts for the majority of CRPS cases. CRPS II, previously known as causalgia, is characterized by the presence of a prior nerve injury. A third, but less commonly diagnosed CRPS subtype, CRPS Not Otherwise Specified (CRPS-NOS) refers to patients that display some features of CRPS without fully satisfying diagnostic criteria and without another disease process that fully explains their symptoms. Patients may display a limb with allodynia and hyperalgesia, skin temperature or color changes, abnormal sweating, edema, range of motion or strength limitations, and alterations in hair, skin, or nail growth.

There is no single diagnostic test that establishes the diagnosis of CRPS. Rather, CRPS represents a constellation of symptoms characterized by sensory, motor, vascular, and autonomic dysfunction. In the acute or "warm" phase, patients report intense, burning pain, typically out of proportion to that expected for their injury (if associated with an inciting injury). The pain then gradually spreads beyond the site of injury in a non-dermatomal pattern. Early observable changes in the affected area can include increased hair or nail growth, increased skin temperature, and erythema. As the disease progresses to the chronic or '"cold" phase, hair and nail growth slows down, skin temperature decreases, and the limb becomes atrophied and mottled, often with a marked decrease in range-of-motion [21–24].

In 1994, the International Association for the Study of Pain (IASP) published the initial diagnostic criteria for CRPS [25]. While these criteria were easy to apply in clinical practice and offered high sensitivity, they were found to have low specificity [9]. This likely resulted in overdiagnosis. Subsequently, an international consensus meeting was held in Budapest in 2003 to propose revised diagnostic criteria, now commonly known as the Budapest criteria. Validation of the newer criteria demonstrated a specificity of 0.79, an improvement over the original IASP's criteria specificity of 0.41, and a reduction in the risk of false positive diagnoses [9, 24]. To date, the Budapest criteria remain the internationally agreed-upon standard for the diagnosis of CRPS, and the IASP officially incorporated them in 2012.

While the Budapest criteria are used for diagnosis of the disorder, metrics for tracking disease progression have historically been limited. To help address this problem, a continuous measure of CRPS severity, the CRPS Syndrome Severity Score (CSS), was developed to help track the progression of the syndrome [26]. An updated version of the CSS, published in 2017, is composed of 8 signs and 8 symptoms. While it has not yet been widely adopted in clinical settings, it has been validated as a tool to track syndrome severity [27].

Lastly, CRPS spread from the initial site(s) of pathology is a well-documented phenomenon. Some reports suggest that CRPS spread occurs in more than 50% of patients [28]. This may occur spontaneously, or as the result of a new trauma [29]. Additionally, CRPS spread may occur in the setting of ongoing treatment. While data detailing typical patterns of spread is limited, documented cases include spread from a single site to all four limbs and the face [29]. One case series details CRPS spreading to full-blown fibromyalgia [30]. The mechanisms behind the spread of CRPS are unclear. However, involved factors are thought to include genetic predisposition, aberrant regulation of neurogenic inflammation, activation of microglia along contiguous spinal segments, and maladaptive neuronal plasticity [30–32].

Inciting Events

Fractures are often an inciting event for the development of CRPS. Upper extremity fractures and distal fractures in particular are significant risk factors [33]. In one prospective study, 7% of patients with a single fracture of the wrist, scaphoid, ankle, or metatarsal developed CRPS I [34]. More severe fractures (requiring surgical repair), high energy mechanisms of injury, and prolonged time under anesthesia during surgical repair also increase the risk of developing CRPS [33, 35].

Independent of the presence of a fracture, the surgery itself also represents a risk factor [36, 37]. Estimates of the level of risk posed by surgery vary. In reviewing the literature, older studies that utilize the original CRPS diagnostic criteria find higher rates of CRPS in post-surgical patients, while more recent studies utilizing the Budapest criteria report lower rates. For example, a 2003 prospective study following 77 post-operative total knee arthroscopy patients and utilizing the original IASP diagnostic criteria found a prevalence rate as high as 21% [38]. However, a more recent prospective study following 100 post-operative total knee arthroscopy patients and utilizing the Budapest criteria for diagnosis of CRPS did not identify any new cases of CRPS [39]. Concordantly, a recent population-based study of South Korean patients undergoing surgery following distal radius fracture found the incidence to be fairly low at 0.64% [40].

Fracture and surgery lead as risk factors for CRPS; however, the complete list of risk factors, inciting events, and pre-existing conditions that have been linked to the development of CRPS is lengthy. These include (some rarer than others) transradial cardiac catheterization, angiotensin-converting-enzyme inhibitors, neurovegetative dystonia, hyperparathyroidism, post-traumatic stress disorder, metabolic syndrome, alcohol abuse, smoking, traumatic brain injury, rheumatoid arthritis, animal/insect bites, and basal cell carcinoma [34, 41–47]. Furthermore, female gender and high baseline levels of pain and disability have been associated with increased CRPS severity [48].

Budapest Criteria, Course, and Biomarkers

Clinicians diagnose CRPS by applying the Budapest criteria which require the presence of 3 of 4 symptoms, and 2 of 4 signs in the following categories: sensory, vasomotor, sudomotor/edema, motor/trophic [49] (Table 1). Importantly, the criteria emphasize that CRPS should not be diagnosed if another disease better explains the signs and symptoms. The available evidence suggests that CRPS develops within a period of 3–4 months after the onset of injury which helps differentiate CRPS from the clinical manifestations of normal healing [22]. To date, attempts at developing diagnostic tests for CRPS have been largely unsuccessful. For example, the quantitative

Table 1 New IASP diagnostic criteria for complex regional pain syndrome (Budapest criteria) (A–D must apply) https://doi.org/10.1097/j.pain.0000000000002245

A. The patient has continuing pain which is disproportionate to any inciting event			☐
B. The patient reports at least one symptom in 3 or more of the categories			☐
C. The patient reports at least one sign in 2 or more of the categories			☐
D. No other diagnosis can better explain the signs and symptoms			☐
Category	**Examples**	**Symptom (patient reported)**	**Sign (visible or tactile problem on examination)**
1. Sensory	*Allodynia* (to light touch/brush stroke and/or temperature sensation and/or deep somatic pressure and/or joint movement), and/or	☐	☐
	Hyperalgesia (to pinprick)	Reported hyperesthesia also qualifies as a symptom	
2. Vasomotor	Temperature asymmetry, and/or Skin color changes, and/or Skin color asymmetry	☐	☐
3. Sudomotor/Oedema	Oedema, and/or Sweating changes and/or Sweating asymmetry	☐	☐
4. Motor/Trophic	Decreased range of motion, and/or Motor dysfunction (weakness, tremor, dystonia), and/or Trophic changes (hair/nail/skin)	☐	☐

Goebel A, Birklein F, Brunner F, et al. The Valencia consensus-based adaptation of the IASP complex regional pain syndrome diagnostic criteria. Pain. 2021; 162(9):2346–2348

sensory axon reflex test was proposed as a potential diagnostic test for CRPS. However, a recent study of 196 patients with a diagnosis of CRPS found that the test produced low sensitivity and specificity, and was unlikely to be clinically useful as a screening or confirmatory test [50]. In chronic CRPS, plain radiographs may show bone demineralization, although these changes are nonspecific [51]. X-ray findings can be nonspecific, but it is prudent to obtain them to rule out limb fracture as the source of a patient's pain. Magnetic resonance imaging (MRI) of the affected area may demonstrate spotted bone marrow edema, cutaneous edema, joint effusion, or contrast uptake in the skin and synovium [51]. Collectively, these MRI findings have a high specificity (91%), but the sensitivity and predictive value are low [52]. Furthermore, these MRI abnormalities are inconsistent. For example, one study comparing MRI scans of an affected foot in CRPS patients to MRI scans in control patients was unable to identify any morphological differences [53]. Traditionally, three-phase bone scintigraphy (particularly phase 3, known as a triple-phase bone scan) has purportedly been the most sensitive test for detecting CRPS. However, current diagnostic criteria do not include bony abnormalities among signs or symptoms; therefore, there is an uncertain value of using three-phase bone scintigraphy to support a CRPS diagnosis. It may have additional value in predicting response to treatment and following the disease course, although more studies are needed to validate its utility in this capacity [54]. It is critical to note that more recent studies of three-phase bone scintigraphy have reported poor sensitivity in patients diagnosed with CRPS using the Budapest criteria (sensitivity is higher in older studies that utilized the original diagnostic criteria) [52, 55].

Validated biomarkers for CRPS do not yet exist. Given its dynamic and complex pathophysiology, it has been suggested that a single biomarker may never be discovered. However, efforts to identify a CRPS biomarker persist. Osteoprotegerin (OPG), also known as osteoclastogenesis inhibitory factor, is a cytokine receptor involved in the regulation of bone turnover [35]. It has been proposed as a possible biomarker for CRPS. OPG is found to be significantly elevated in CRPS patients when compared to control patients. In a small study evaluating osteoprotegerin as a diagnostic test, it was found to have a sensitivity of 0.74 and specificity of 0.80 [56].

Other work on identifying CRPS biomarkers has examined measurements of neurometabolites that are involved in inflammation [57]. A recent serum analysis of 15 CRPS patients found reduced levels of interleukin-37 (IL-37 has significant immunosuppressive and anti-inflammatory effects) and tryptophan (decreased levels are associated with low mood and depression) when compared to control patients. In the same study, a machine learning analysis found that evaluating a combination of GM-CSF levels (a cytokine that sensitizes peripheral nociceptors), IL-37 levels, Treg cell number (regulatory T lymphocyte), and CD8 + central memory T cells could help distinguish CRPS patients from controls [58]. Overall, the authors hypothesized that reduced IL-37 and Tryptophan and increased Tregs, CD8 + T cells, and GM-CSF may reflect

significant elements of the inflammatory response seen in CRPS. Many findings of immune system involvement have been documented in CRPS which support a greater immunoneurological component to the disorder [58].

Analyzing microRNA signatures is a newer area of research in the hunt for biomarkers for many different diseases, including CRPS. There is evidence that analyzing miRNA signatures may also help predict patient response to treatment with ketamine [59]. More specifically, the immunobarrier-protective hsa-miR-223-5p was found to be increased in plasma exosomes in patients experiencing normal healing following recent fracture, but was not elevated in CRPS patients or normal controls. Accordingly, measuring hsa-miR-223-5p levels may help distinguish normal fracture healing from patients developing CRPS [60]. Another study found that miR939 is downregulated 4.3 fold in patients with CRPS. In a follow-up analysis, miR939 was found to target mRNAs encoding multiple pro-inflammatory mediators, such as IL-6, vascular endothelial growth factor, nitric oxide synthase 2, and nuclear factorκB2. This suggests that downregulation of miR939 may lead to an increase of these factors which are involved in the perpetuation of inflammation and pain [35].

Other efforts to identify biomarkers have focused on analyzing skin biopsies of the affected area since patients with CRPS have been found to have decreased intraepidermal nerve fiber density when compared to age-matched controls [61]. A 2014 study analyzed skin biopsies from 55 patients with CRPS: a sample from the affected limb and a sample from a mirror site on the contralateral limb. In early CRPS, keratinocytes were found to be activated in the affected limb. There was also increased mast cell accumulation when compared to the unaffected limb. In chronic CRPS (defined as > 6 months in this study), the increased mast cell accumulation seen in acute CRPS was attenuated and keratinocyte proliferation reduced [62]. While the presence of these cells may not necessarily be used as a biomarker for illness, they do suggest differences that may eventually be used to differentiate acute CRPS from chronic CRPS.

One new and rarely used physical exam finding may help support a CRPS diagnosis: the tourniquet ischemia test. The test involves applying a blood pressure cuff to the affected extremity, inflating and deflating the cuff, positioning the affected extremity in a horizontal manner, and documenting changes in pain intensity and character. While the test is rarely performed in practice, a recent study of 78 patients with CRPS found that although the test had poor sensitivity (49%), it had a specificity of 88% and a positive predictive value of 85%, meaning that it could serve as a confirmatory test in patients with suspected CRPS [63].

Lastly, thermography is a tool that assesses skin temperature distribution. In a recent case series, thermographic analysis of CRPS patients revealed improvement in temperature distribution after therapeutic intervention. This suggests that thermography may be a useful tool in monitoring response to treatment [64].

Childhood

Abu-Arafeh and Abu-Arafeh [65] estimate an incidence of 1.2/100,000 cases of CRPS in school-aged children, per their experiences in a Scottish Pediatric Surveillance Unit. While discrete prevalence estimates of CRPS in the pediatric population are lacking, this phenomenon warrants careful consideration given its capacity to adversely affect psychological well-being and physical function, and even lead to disability in affected children [65–67]. Interestingly, CRPS often presents differently in children relative to the adult population. These differences in syndrome manifestation can impede appropriate diagnosis and goal-directed interventions, many of which also vary in utility and efficacy in children. Consequently, the timely recognition of CRPS in children is vital to optimize patient outcomes and prevent long-standing impairments.

The largest cohort study to date was published in 2015 where Bayle-Iniguez et al. [68] characterized the clinical presentation of 73 French children with CRPS. Briefly, they report a predominance of girls (87.7%), with an average age of 11.5 years at diagnosis, and primarily lower extremity involvement (89%) with a vast predilection for the foot and ankle. Interestingly, only 49% reported an antecedent physical injury, with a majority of these injuries being minor in nature without significant trauma, i.e., ankle sprains. Furthermore, Brooke and Janselewitz [69] in a cohort of 32 American children found that antecedent psychological stress was more prevalent, with an incidence of 57%. Bayle-Iniguez et al. [68] also note a history of atopy (52%) as more prevalent in the pediatric CRPS population. The prevailing clinical features reported at the time of CRPS diagnosis include sensory and vasomotor changes and include allodynia (95%), coolness (81%), and cyanosis (74%). In their pooled analysis of 9 separate clinical studies, Abu-Arafeh and Abu-Arafeh [70] describe significant variability in the reporting of motor and trophic changes and suggest that these symptoms are likely underdiagnosed and underreported in the literature [68, 70–77]. They estimate that approximately 33% of children with CRPS have motor dysfunction with dystonia being the most prevalent feature.

Unfortunately, objective measures for CRPS diagnosis including bone scintigraphy have not been well validated in the pediatric setting [65–67, 78]. Serological markers for bone-turnover (including bone-specific alkaline phosphatase) are unreliable given that they vary extensively with physiologic growth, especially given that most children with CRPS are affected by pubertal onset. Largely, the diagnosis remains clinical and exclusionary with the Budapest criteria serving as the only collective consensus diagnostic criteria [49]. However, the Budapest criteria

were primarily designed for the diagnosis of CRPS in the adult population. Given that most pediatric presentations are thought to be earlier in the disease course, the sensitivity of the Budapest criteria for pediatric populations has been questioned [65–69, 75, 78]. Given these diagnostic limitations, several studies note an approximate 3–4 month time frame from presentation to diagnosis with a suspected subsequent delay in optimal goal-directed interventions [65, 68, 70, 71]. This delay in diagnosis and timely intervention was reported as being a significant deterrent in achieving optimal outcomes.

As most children with CRPS are pre-adolescent and may lack the psychological coping mechanisms necessary for interventional strategies, a multidisciplinary pain treatment strategy with an emphasis on conservative measures must be extensively incorporated for favorable outcomes [65–68, 78, 79]. Tileston et al. [78] outlined a care map emphasizing the roles and needs for specialty services by various physicians and providers of clinical care (pain medicine and orthopedics), therapy (physical and occupation therapy), and mental health support (psychology and social work). Brooke and Janselewitz [69] report the successful use of inpatient rehabilitation and the physiatry team in coordinating and executing this multidisciplinary approach. Despite the specific approach, it is recognized that the use of multimodal strategies from these various interventions is necessary to treat pain, optimize physical function and conditioning, and provide necessary coping mechanisms along with self-efficacy. While precise treatment strategies are outlined in this article, it should be noted that many psychotropic agents and opioid medications produce sedative side effects that may be particularly pronounced and limiting in pediatric patients [65, 67, 79, 80]. Therefore, careful dose escalation and monitoring are necessary to ensure compliance and benefit. Physical therapy has been universally recognized as one of the most vital treatment strategies given its significant safety profile along with its capacity for pain modulation. Sherry et al. [71] report their success in a cohort of 103 children by using a multifaceted physical therapy program for an average of 14 days composed of aerobic rehabilitation, home exercises, hydrotherapy, and desensitization. Approximately 92% of children were symptom-free with the program and 88% remained symptom-free at 2 years. The data regarding the benefit of sympathetic blocks and epidural infusions with bupivacaine, fentanyl, ketamine, and clonidine are limited and vary extensively in reported efficacy [10, 80]. Moreover, the application of neuromodulation for treating CRPS in the pediatric setting has received little attention and lacks the clear supportive evidence necessary for these strategies to be recommended universally [79, 81, 82].

Pathophysiology

Current evidence supports a multifactorial etiology with input from the central nervous system, sympathetic nervous system, peripheral nervous system, and immune system, as well as an influence from underlying genetic factors. Furthermore, nociplastic pain, the latest addition to the IASP pain taxonomy, may include CRPS given evidence of changes in cerebral connectivity with altered nociception and no demonstrated damage to the tissue or somatosensory system [83]. Mental health factors probably exert an influence on the severity of CRPS symptoms.

Central and Peripheral Nervous System

The development of CRPS is most often spurred by a traumatic insult to the peripheral nervous system. The injury causes the release of inflammatory factors, such as prostaglandin E2 and tumor necrosis factor-alpha. These inflammatory factors drive the development of nociceptive sensitization, which contributes to the hyperalgesia experienced by these patients [84]. As the disease progresses, there are chronic morphologic changes that occur in the peripheral nervous system (PNS). For example, transmission electron microscopic analysis of peripheral neurons in a CRPS patient has demonstrated degeneration of large somatomotor Aα fibers with sparing of Aδ fibers. This imbalance in signaling may contribute to increased nociception [85].

PNS sensitization plays an important role in the pathophysiology of CRPS. The release of glutamate and substance P induces sensitization by lowering the threshold for response to mechanical stimuli. This increased sensitivity leads to a step-up in peripheral nerve activation, which in turn increases synaptic nociceptive signaling in the dorsal horn [84, 86].

Similar to the PNS, central nervous system (CNS) changes occur during the progression of CRPS. Prior work has demonstrated somatotopic reorganization in CRPS patients, with affected limbs exhibiting reduced representation in the somatosensory cortex [87]. In fact, in some CRPS patients, pain may be precipitated by simply thinking about moving the affected area [88]. Not only is there evidence suggesting sensory somatotopic reorganization, but imaging studies have found that patients with CRPS may have decreased gray matter volume in the dorsal insula, left orbitofrontal cortex, and cingulate cortex, and increased gray matter volume in the bilateral dorsal putamen and right hypothalamus. In the same study, pain duration appeared to be associated with decreased gray matter in the left dorsolateral prefrontal cortex, while pain

intensity was positively correlated with volume in the left posterior hippocampus and left amygdala and negatively correlated with the bilateral dorsolateral prefrontal cortex [89]. Additionally, CRPS has been found to impair the ability to observe the motor actions of others by affecting brain areas involved in pain processing and motor control, and leading to the perception by the CRPS patient of the action of the other as unpleasant or painful [90]. Collectively, these findings may help explain the pain and sensory changes that occur in CRPS. Other work has demonstrated that dystonia and decreased range of motion that can develop in advanced CRPS sometimes respond favorably to intrathecal baclofen, which points to CNS involvement in the development of these pathologic changes [91]. In particular, dysfunction in the primary motor cortex, supplemental motor cortices, posterior parietal cortices, and basal ganglia may account for some of these symptoms in CRPS patients [35, 92, 93].

Inflammation

Inflammation is an expected response to an insult and represents a normal step in the healing response. In the acute phase of CRPS, there is an increase in the aggregation of mast cells [46]. This increase is associated with the release of inflammatory neuropeptides such as substance P and calcitonin gene-related peptide (CGRP), which in turn stoke the production of pro-inflammatory cytokines such as TNF-α, IL-1, and IL-6. An activation loop is initiated in which these pro-inflammatory mediators help recruit other mast cells, which leads to the further release of pro-inflammatory mediators such as histamine, serotonin, and TNF-α. These pro-inflammatory mediators promote further inflammation and also potentiate peripheral sensitization by acting upon local Aδ fibers [46–48]. Elucidating the role of mast cells in chronic CRPS will require further investigation since tissue biopsy has demonstrated a reduction in the quantity of mast cells around the atrophied dermal nerve fibers in CRPS-affected limbs [50]. However, it is evident that mast cell-neural tissue interactions help drive pro-inflammatory changes in CRPS. Clinically, the effects of these pro-inflammatory changes manifest as the flushing, erythema, and edema seen in CRPS patients. CGRP in particular causes arteriolar vasodilation, while substance P and neurokinin A increase vascular permeability [94, 95]. In chronic CRPS, other pro-inflammatory mediators such as interferon-γ, IL-2, monocyte chemoattractant protein-1, and bradykinin have been found to be elevated [96].

Genetics

There is a growing although somewhat conflicting body of evidence to suggest that there is a genetic component to the development of CRPS. A study of 31 Dutch families with multiple affected family members found that familial linkage is associated with earlier onset of CRPS and a higher incidence of multiple limb involvement (no inheritance pattern could be delineated) [97]. More specifically, although no causative genetic mutations have been found, an upregulation of multiple genes with various roles in signal transduction, cell motility, and immunity has been discovered in CRPS patients. These include human leukocyte antigen (HLA) A29.1, matrix metalloproteinase 9, alanine aminopeptidase N, 1-histidine decarboxylase, granulocyte colony-stimulating factor 3 receptor, and signal transducer and activator of transcription 3 [1, 98]. Despite this evidence, it is worth mentioning that a separate study analyzed more than 200,000 single nucleotide polymorphisms and found no difference between CRPS patients and the control population [98].

Sympathetic Nervous System and Sympatho-afferent Coupling

CRPS can cause superficial vasomotor symptoms such as diaphoresis, warmth, or cooler skin [99, 100]. The etiology of these symptoms is multifactorial. Degenerative changes in nerve fibers likely contribute to these symptoms, as well as some of the autonomic instability (e.g., decreased heart rate variability) seen in CRPS patients [101–104]. However, these symptoms are also due, in part to a coupling between the peripheral and sympathetic nervous systems. There is evidence that peripheral nociceptive fibers may exhibit increased catecholamine sensitivity in CRPS [86, 103]. Other work has demonstrated that there is an increase in the expression of α1-adrenergic receptors in CRPS-affected limbs [104]. Moreover, intradermal injection of phenylephrine precipitates pain and allodynia in CRPS-affected limbs [105]. Although the mechanisms have not been completely elucidated, given the available evidence it may be deduced that Aδ and C afferent nerve fibers interact with the autonomic nervous system to cause some of the hyperpathia and allodynia seen in CRPS.

Autoimmune Component

There is evidence of a role for autoantibodies in CRPS pathophysiology. Research has shown that as many as 70% of CRPS patients display anti-autonomic immunoglobulin G antibodies in their serum [35]. Further analysis of these IgG antibodies has demonstrated that they may have β2-adrenergic and muscarinic-2 receptor activity [106]. Other work has demonstrated the presence of activating anti-alpha-1a adrenoceptor antibodies in CRPS [107]. In sum, these antibodies may help potentiate the inflammation that is a hallmark of CRPS. This theory is supported by work done

in mouse models. For instance, in a tibial fracture CRPS mouse model, mice that lacked B cells and IgM had attenuated nociceptive and inflammatory changes at 3 weeks post-fracture [108]. Follow-up work demonstrated that injecting mouse serum IgM antibodies from mice with acute tibial fractures into CRPS mouse models that lacked B cells and IgM produced pronociceptive effects. This lends support to the theory that autoimmunity is a likely contributor to the progression of CRPS [109].

Mental Health Component

Pre-existing mental health disorders may affect both the likelihood of developing CRPS, as well as the course of the disease. Patients with post-traumatic stress disorder (PTSD) have a significantly increased incidence of CRPS when compared to control populations [47]. Furthermore, CRPS patients with higher levels of anxiety, perception of disability, kinesiophobia, and pain-related fear have been found to have a worsened disease course [9, 110]. These findings may be due to increased catecholamine activity which worsens nociceptive sensitization [1]. Catastrophizing has likewise been linked to worsened pain severity in CRPS patients. This may occur through increased proinflammatory cytokine activity [24]. In contrast, a large, prospective multicenter did not find any association between the presence of psychological factors (e.g., agoraphobia) and CRPS [111].

Subtypes of CRPS

CRPS is typically subdivided into type I and type II. Type II (causalgia) demonstrates evidence of major peripheral nerve injury often manifesting as abnormalities in nerve conduction. Regardless of the type, the triggers can be similar and the diagnostic features are the same. In the past decade, some have scrutinized the existence of CRPS, and specifically CRPS type I as a disease entity [112–115]. Separate editorials by Bass [116] and del Piñal [117] express their concern that CRPS may be overdiagnosed given the increasing incidence in recent years. Consequently, they propose the abandonment of the term CRPS citing that this diagnosis leads to unwarranted "medicalization" and avoidable harm in these patients. However, others including Basler et al. [118] maintain that the CRPS type I taxonomy is vital and endorse careful use of the Budapest criteria with the recognition that the criteria were established by expert consensus and validation in small population studies. CRPS type II is rarely mentioned in these debates perhaps because there is objective evidence of nerve injury. There is a paucity of data on the subtype, CRPS-NOS (not otherwise specified) in the literature.

Given these limitations in appropriate diagnosis and challenges in stratifying CRPS subtypes, several studies have proposed new CRPS subtypes and taxonomies. However, it must be noted that CRPS subtypes should represent discrete disease states rather than varying stages in the expected disease course, i.e., acute, dystrophic, and atrophic manifestations represent different stages within the same CRPS disease state [119]. Furthermore, no clear sequence of these stages occurs in all patients. The distinction between CRPS subtypes as entities of various stages has not been clearly reported. Żyluk and Puchalski [120] propose the use of a "chronic refractory CRPS" subtype which follows trivial injuries including superficial wounds and minor contusions. They report that patients in this subtype (5.5% prevalence in their cohort of 220 CRPS patients) suffer from CRPS that is more severe and disabling and thus necessitates early diagnostic recognition. Interestingly, these patients were also thought to have varying treatment responses, which further encourages the need for increased CRPS subtype recognition and classification to assist in future research and clinical diagnostics.

Aside from etiology-specific subtypes, others have also proposed novel CRPS subtyping to differentiate phenotypic manifestations. In 2016, Bruehl et al. [121] utilized a cluster analysis of 152 baseline clinical CRPS presentations to dichotomize patients as having "warm CRPS" or "cold CRPS" subtypes. Patients with warm CRPS were found to have predominant warmth, erythema, and edema and were suggested to more likely have pro-inflammatory phenotypes. In contrast, cold CRPS patients manifested cool extremities, pallor, and an absence of edema, and were more likely to develop chronic complications. These subtypes were also suggested to have varying disease courses with cold CRPS often leading to chronic conditions while warm CRPS was rather self-limiting (< 6 months). The data suggest that patients presenting with warm CRPS more likely experience syndrome resolution compared to those who are diagnosed with cold CRPS [22]. Although not a definitive marker, a transition from warm to cold CRPS occurring in the first year after the insult may reflect the development of chronic CRPS [22]. In 2020, Dimova et al. [122] used a cluster analysis of 1037 patients from 3 independent sources to assess the validity of a "Central Phenotype" and "Peripheral Phenotype" of CRPS. Central phenotype patients were characterized as having minor antecedent injuries leading to allodynia, sensory deficits, and motor signs that suggested central nervous system pathophysiology. Peripheral phenotype patients exhibited sweating and edema, skin color and temperature changes, and trophic changes that were collectively thought to be concordant with peripheral inflammation. While they found evidence that these two CRPS subtypes represent varying pathogeneses, the clinical relevance was not explored. Subtyping proposed by both Bruehl et al.

[121] and Dimova et al. [122] has not yielded clinical recognition and is relatively novel. Moreover, the clinical relevance and treatment responses of these proposed subtypes require more in-depth study.

In 2019, the IASP CRPS Special Interest Group convened a group of experts in Spain to adapt the criteria. The newly published recommendations from the group incorporate changes to diagnostic parenting, diagnostic subtypes, and diagnostic procedure. Some of the primary recommendations include changing the ICD-11 parent classification of CRPS from "focal or segmental autonomic disorder" to "chronic primary pain," clarifying that the diagnostic signs of CRPS II must extend beyond any identified injured nerve territory, and creating a new CRPS subtype, "CRPS with Remission of Some Features" (patients previously documented as having met CRPS criteria, but now with features insufficient to meet the diagnostic criteria) [123].

Treatment

There is an array of treatment options for CRPS including physical therapy, pharmacologic agents, interventional strategies, and amputation (see Table 2 for treatment summary). Considering the complex pathophysiology and heterogenous presentation of this condition, a multimodal approach is generally recommended.

Pharmacological Therapies

Gabapentin

Gabapentin inhibits the function of voltage-gated calcium channels and is frequently used to relieve pain in CRPS patients. One case report of a patient with CRPS associated with basal cell carcinoma suggested that gabapentin 900 mg/day could be useful in treating paroxysmal crises [44]. However, there are few studies demonstrating the consistent efficacy of gabapentinoids in improving the long-term outcomes of CRPS. Within the last 30 years, only three randomized controlled trials (RCTs) have reported significant pain relief with gabapentin therapy [124–126]. Furthermore, gabapentin may not necessarily be more efficacious than other pharmacologic agents. A 2016 study found no significant difference in pain reduction or restoration of function between amitriptyline and gabapentin in pediatric patients with CRPS or neuropathic pain [126, 127]. Neuropathic pain medications like gabapentin may be effective in controlling short-term or even long-term pain, but these agents have not been demonstrated to significantly change the disease course [128]. Adverse effects such as sedation, cognitive impairment, and depression should be monitored in patients on long-term gabapentin, especially in the pediatric population [78].

Antidepressants

Tricyclic antidepressants (TCAs) and selective serotonin-norepinephrine reuptake inhibitors (SNRIs) are successfully used to treat neuropathic pain, but few specific antidepressants have been studied or used for the treatment of CRPS [126, 127, 129]. One RCT in 2016 investigated the efficacy of amitriptyline versus gabapentin in pediatric patients and concluded that both drugs reduced pain and improved sleep without significant differences in outcomes between the two medications [1]. Selective serotonin reuptake inhibitors (SSRIs) have demonstrated poor analgesia in the treatment of CRPS in particular [130]. The side effect profile of antidepressants such as amitriptyline must also be considered when selecting medications from this category [131].

Transdermal/Topical Agents

Some medications for the treatment of CRPS that can be administered transdermally include patch formulations of capsaicin, clonidine, and buprenorphine. One study demonstrated that the application of an 8% capsaicin patch led to decreased pain regionally and a reduced need for chronic analgesics within 3 months [132]. There is no strong evidence regarding the long-term benefits of capsaicin patches, but they are generally well tolerated by most patients and may be useful in providing short-term analgesia. Transdermal clonidine has also been proven to have some benefits in improving local pain symptoms [133]. Several case reports have demonstrated a decrease in pain intensity scores with transdermal buprenorphine patches for systemic analgesia [134], but one literature review by Wiffen et al. [135] reported that there was not sufficient evidence to conclusively recommend transdermal buprenorphine. In clinical practice, topical lidocaine can relieve cutaneous pain such as allodynia associated with CRPS, but no RCTs have studied the efficacy of topical formulations.

Opioids

While opioids are frequently prescribed for pain control, there is little evidence in the literature regarding their efficacy for CRPS [127]. One study suggests that weak opioids may be useful in providing simple analgesia with the addition of neuropathic pain medications later as needed [136]. Investigators in another study successfully treated ten chronic CRPS patients with progressively increasing morphine dosages up to 30 mg/day, along with daily memantine, physical therapy, and graded motor imagery exercises. The

Table 2 Evidence-based treatment of complex regional pain syndrome

Treatment	Dosing Regimen	Range of Levels of Evidence*	Selected Studies
PHARMACOLOGICAL THERAPIES			
Gabapentin	Gabapentin 900mg total per day	I-V (systematic review down to case study)	Gofiţă CE, et al. 2019; van de Vusse AC, et al. 2004
	Gabapentin 600 daily up to TID		
Antidepressants	Amitriptyline 10mg nightly	II-III (small RCT down to retrospective cohort)	Brown S, et al. 2016
Transdermal/Topical Agents	8% Capsaicin Patch for 30-60 minutes	III-V (retrospective analysis down to case series)	Goncalves D, et al. 2020; Onofrio S, et al. 2016
	Buprenorphine 5-20mcg/hr/wk		
Opioids	Morphine 10-30mg daily with Memantine 5-40mg daily and physiotherapy	II (prospective cohort with no control)	Elomaa M, et al. 2019
Corticosteroids	Prednisolone 180-360mg over 3-6 days	I-V (open RCT and systematic review down to case reports)	Kumowski N, et al. 2019; Jamroz A, et al. 2020; Park S, et al. 2020; Pai RS, et al. 2018; Zych-Litwin C, et al. 2019
	Prednisone taper: 40-60mg, decreased by 5mg daily to 20mg; then 15mg/10mg/5mg for one week each		
	10mg/mL Triamcinolone with 2mL 1.5% lidocaine		
	Dexamethasone spray, 0.28mg/g for 10 days		
	Prednisolone 200-450mg total over 14 days with taper		
Physical and Occupational Therapy		I-V (systematic reviews down to case reports)	
NEUROMODULATION			
Spinal Cord Stimulation		II-V (small RCTs down to case series)	
Dorsal Root Ganglion Stimulation		I-V (medium/large RCTs down to case studies)	
Peripheral Nerve Stimulation		III-V (prospective cohorts down to case reports)	
Transcutaneous Electrical Nerve Stimulation		II-V (small RCTs down to case reports)	
Neural and Sympathetic Blockage	0.25% Bupivacaine 5mL with Triamcinolone 1mL	I-V (systematic review and small RCTs down to case report)	Gungor S, et al. 2018; Herman J, et al. 2020; Imani F, et al. 2016; Kang SH, et al. 2020; Kim YH, et al. 2019; Nascimento MSA, et al. 2010; de Oliveira Rocha R, et al. 2014
	0.75% Ropivacaine 5mL with 2% Triamcinolone 5mL		
	1% Lidocaine 70mg with Clonidine 30mcg		
	0.2% Ropivacain 20mL, with Dexamethasone 5mg and Dexmedetomidine 25mcg		
	0.125% Ropivacaine 10mL with Dexmdetomidine 40mcg		
	1% Lidocaine 5-10mL		
	0.5% Bupivacaine 10mL		
EMERGING THERAPIES			
Ketamine	Ketamine 0.7-1mg/kg/day for 5 days	I-V (systematic review and small RCT down to case reports)	Hewitt NA, et al. 2018; Kirkpatrick A, et al. 2020; Sigtermans MJ, et al. 2009; Sorel M, et al. 2018; Sorel M, et al. 2018
	Ketamine 60-200mg/hr for 4 hours for 4 consecutive days		
	Ketamine 22.2+/-2.0mg/hr/70kg for 5 consecutive days		
	Ketamine 8-24mg/hr over 3 days		
	Ketamine 0.7-1mg/kg/day for 5 days		
Intrathecal Strategies	Baclofen 25-75μg	II (small RCT)	van Hilten BJ, et al. 2000
Calcitonin		I-V (systematic review down to case reports)	
Bisphosphonates	Clodronate 200mg IM daily for 15 days or Alendronate 20mg/wk	I-V (systematic review and meta-analysis down to case series)	Galluccio F, et al. 2020
N-acetylcysteine		I-III (systemiatic review down to retrospective analysis)	
Low-dose Naltrexone	Naltrexone 3-4.5mg daily	V (case reports)	Chopra P, et al. 2013
Scrambler Therapy		III-V (prospective cohort down to case series)	
Mirror Box Therapy		I-V (systematic review down to case reports)	
Cannabinoids	Δ9-THC 0.5mg or 1mg	III (randomized cross-over study)	Almog S, et al. 2020
Photobiomodulation		V (mouse model)	
Plasma Exchange		IV-V (prospective and retrospective case series down to case report)	
Transcranial Magnetic Stimulation/Transcranial Direct Current Stimulation		I-V (systematic review down to case report)	
Botulinum Toxin	IncobotulinumtoxinA 100 units in 2mL	III-V (prospective case-control down to case report)	Bellon G, et al. 2019; Kwak H, et al. 2020; Safarpour D, et al. 2010
	BoNT-A 220 units total		
	Unspecified Botulinum toxin 50 units total		
Immunoglobulin Therapy	IVIG 90g every 3 weeks	I-V (systematic review down to case report)	Aradillas E, et al. 2015; Goebel A, et al. 2010; Goebel A, et al. 2017
	IVIG 0.5mg/kg for one treatment		
	IVIG 0.5g/kg infused 2 times over 23 days		
Surgical Sympathectomy		V (uncritical review articles)	
Amputation		I-V (systematic review down to case study)	

Table 2 (continued)

*Levels of evidence: level I, large randomized control trials (RCTs) with clear results and systematic reviews; level II, small RCTs with unclear results; level III, prospective cohort and case-control studies; level IV, historical cohort or case-control studies; level V, case series, case studies, and studies with no controls. Adapted from Burns PB, Rohrich RJ, Chung KC. The Levels of Evidence and their role in Evidence-Based Medicine. Plast Reconstr Surg. 2011; 128(1):305–310

researchers reported the most benefit in the improvement of motor and sensory dysfunction with variable improvement in pain and psychological distress [137]. Generally, the goal of opioid therapy in CPRS should be to sufficiently reduce nociception so that patients can actively participate in physical therapy. The side effect profile of opioids including respiratory depression, abuse, constipation, and the development of tolerance should be carefully examined before initiating therapy, especially in pediatric patients. The possible development of hyperalgesia may deter physicians from prescribing chronic opioids for CRPS, although if other treatments insufficiently control pain, opioids may be an important therapy.

Serotonin and Norepinephrine Reuptake Inhibitors

SNRIs, particularly venlafaxine and duloxetine, are efficacious in reducing neuropathic pain, but have limited evidence for treatment of neuropathic pain specific to CRPS [130, 138]. However, in cases of concomitant CRPS and depression, SNRIs are preferred over SSRIs due to their analgesic properties and their FDA approval for treating neuropathic pain [139].

Corticosteroids

Glucocorticoids reduce inflammation by modulating immune cells, inhibiting inflammatory genes, and interfering with the transcription of several cytokines. There is strong evidence that chronic inflammation may play a role in early disease development and progression. Mouse models have demonstrated that the transfer of IgG autoantibodies from human CRPS patients to mice will cause similar CRPS symptomology, and blocking the IL-1 inflammatory pathway in these mice successfully prevents the development of pain [140]. In an immunophenotyping study of 14 CRPS patients, Russo et al. [141] demonstrated that CRPS patients had increased levels of memory CD8 + T cells, TH1 cells, regulatory T cells, phosphorylated NFkB, and STAT1. Another study by Russo et al. [58] demonstrated a positive correlation between high levels of inflammatory cytokines such as TNF-a and positive stress, anxiety, and depression scores in CRPS patients. These immunological changes demonstrate the probable importance of steroids in decreasing systemic inflammation and downregulating these active inflammatory processes [58, 141, 142]. For example, one study suggested that an oral steroid pulse (between 3 and 6 days with a total dose between 180 and 360 mg of oral prednisolone) may decrease pain by improving perfusion and oxygen extraction in affected limbs, and may be especially useful in the treatment of early CRPS (< 1 year) [143].

Prednisone, methylprednisolone, and prednisolone have been used for the treatment of CRPS with significant pain reduction and improvement in other associated symptoms [144]. Jamroz et al. [145] reported that prednisone treatment was associated with improved range of motion, pain control, and overall functionality. It is unclear when the maximum benefit of steroid therapy may be expected, however. One recent study demonstrated that daily oral prednisone over the course of several weeks significantly improved CRPS symptoms but that these benefits were limited to patients with refractory chronic CRPS [144]. However, Bean et al. [110] suggested that the maximum benefits of steroid therapy occur within 6 months of disease onset.

In multiple case reports, intra-articular corticosteroid injections (CSIs) have been demonstrated to reduce pain in the affected limb [146]. One case report by Pai and Vas [146] showed that CSIs into the radio-ulnar and radiohumeral joints improved pain and range of movement in the forearm. The authors hypothesized that CSIs reduce local nociceptive sensitization and may be especially useful in improving motor functionality in conjunction with physical therapy [146].

Another case report by Zych-Litwin and Litwin [147] showed that prompt treatment with local dexamethasone spray and oral meloxicam could result in the complete resolution of early CRPS. Therefore, early initiation of anti-inflammatory medications may induce full recovery in selected patients. The benefits of steroid therapy must be carefully weighed with the risk of adverse effects including worsening diabetes mellitus or gastrointestinal bleeding. A low-dose steroid taper is recommended in patients with underlying comorbidities that may predispose them to complications from steroid therapy. In some patients with post-stroke CRPS, low-dose steroids have also been shown to be as effective as high-dose steroids [148].

Other immunomodulatory pharmacologic agents that have been used to treat CRPS include mycophenolate and hydroxychloroquine [149, 150]. Hydroxychloroquine is thought to improve pain by reducing microglial activation in the dorsal horn and normalizing levels of inflammatory cytokines [149].

Physical and Occupational Therapy

Current guidelines recommend a multimodal treatment approach involving physical and occupational therapy [1, 43, 151, 152]. Experts in CRPS feel that these modalities are helpful in restoring the use of the affected limb and reducing the sequelae related to disuse. CRPS is often associated with emotional and psychological distress that deters patients from voluntarily using the affected limb. Physical therapy is thought to help recover mobility in affected limbs, reduce edema, improve strength, and prevent long-term functional complications [9, 45]. Some theories suggest that physical therapy may also induce endorphin release in the central nervous system and enhance analgesia in the spinal cord [144]. Therefore, early mobilization of the affected limb is crucial to slowing disease progression and preventing long-term functional sequalae [128, 136, 153]. Physical therapy should be initiated as soon as is medically safe [153].

Physical therapy should involve a comprehensive assessment of functionality and be individualized for each patient [154]. Analgesics such as low-dose opioids or neuropathic pain medications may be needed for patients who are unable to tolerate therapy due to pain. In one case report, passive range of motion exercises was successfully performed under sedation for a pediatric patient with severe CRPS who was unable to tolerate physical therapy [155].

A 2022 Cochrane review reports uncertain evidence regarding the role and efficacy of physical therapy in CRPS and the necessity of further RCTs in evaluating this treatment modality [156]. Some physical therapy techniques that have been reported in the literature include acupuncture, manual lymphatic drainage massage, whirlpool bath, laser therapy, and electromagnetic therapy [156]. Similar to the 2016 Cochrane review, this most recent Cochrane review suggests that graded motor imagery and mirror therapy may provide some long-term and short-term improvement, respectively, in pain and functionality for CRPS I, but these trials were considered low-certainty studies [156]. In graded motor imagery, the patient first imagines moving the affected limb into the desired position and then progresses to mirror therapy, in which a strategically placed mirror over the affected limb lends the illusion of both limbs moving in tandem [78, 92, 133]. Graded motor imagery has been associated with reduced pain and improved functionality after 6 months of treatment [1]. Overall, the 2022 Cochrane review did not identify sufficient high-level evidence to strongly or definitively recommend any physical therapy intervention for the treatment of CRPS [156].

Despite the paucity of high-quality evidence in the literature, physical therapy continues to be widely recommended for the treatment of CRPS. Physical therapy is especially important in the treatment of childhood CRPS [157–163]. It has also been shown to decrease pain scores and improve function in CRPS patients older than 60 years [164]. In addition to its role in improving limb function, physical therapy may also be useful in providing patients with assistive or functional devices including splints or braces, especially during the initial stages of CRPS [165]. New physical therapy modalities for CRPS include exergames, which combine physical therapy with interactive video games and pain exposure physical therapy [166–169]. However, one RCT investigating pain exposure physical therapy reported no significant differences in the range of motion or pain scores after pain exposure physical therapy versus conventional treatment [168, 170].

Neuromodulation

When more conservative therapeutic options have been ineffective or inadequate, it is common to consider neuromodulation interventions including transcutaneous electrical neurostimulation (TENS), spinal cord stimulation (SCS), dorsal root ganglion stimulation (DRGS), or peripheral nerve stimulation (PNS).

Spinal Cord Stimulation

SCS involves electrical stimulation of the dorsal columns via percutaneous or surgical placement of electrodes in the epidural space. While the precise mechanisms of action have yet to be clearly delineated, prevailing theories suggest the SCS operates by way of the gate control theory wherein preferential neurostimulation of faster A-beta fibers leads to diminished propagation of painful stimuli from slower C-fibers [127]. While unsubstantiated, newer theories suggest that SCS may reverse maladaptive cortical neuroplastic changes or even have some immunomodulatory properties via the mediation of T cell activation as well; however, such theories have yet to be more clearly elucidated [171]. The maximum benefit of SCS may be seen when therapy is initiated earlier in the disease process, especially within 1 year of diagnosis or in patients younger than 40 years old [9]. Conversely, pain relief from SCS appears to be more short-lived in patients who smoke [172]. While SCS may not change the overall CRPS disease course, it has been associated with decreased oral medication consumption, enhanced quality of life, and improved physical function [9, 144, 173].

Similar benefits including improved function and pain control have been seen with SCS in pediatric patients as well [79, 82]. There is also preliminary evidence suggesting that younger patients continue to experience significant pain relief even after the removal of the SCS device within 5 years of implantation [174]. A Cochrane review in 2017 concluded that there was strong evidence for the role of SCS in improving pain intensity scores and quality of life [175].

Newer paresthesia-free SCS stimulation as well as high-frequency SCS may prove even more useful in treating CRPS [176–178]. However, enhanced benefit with novel waveforms has not been established or explored in the literature.

Dorsal Root Ganglion Stimulation

DRGS is a relatively newer neuromodulation intervention that appears promising in the treatment of CRPS. Relative to SCS, DRGS allows for more precise targeting of painful regions and thus is thought to be more effective for focal pain presentations. In addition to improved pain and mood, DRGS attenuates the chronic inflammatory state associated with CRPS, as demonstrated through decreased levels of pro-inflammatory markers such as IL-1B post-treatment [179]. DRGS has also been proven effective in reducing CRPS symptomatology in pediatric patients [79, 81].

One study by Bussel et al. [180] reported that patients prefer DRGS over dorsal column SCS in treating CRPS that is limited to the knee. The ACCURATE trial in 2017 also concluded that DRGS was superior to SCS in providing pain relief and improving quality of life and functional status in CRPS patients with no differences in adverse effects [127, 181]. Additionally, DRGS causes chronic stable pain relief up to 1 year after implant, whereas SCS has been associated with progressively declining pain relief at approximately 10 months after implantation [182]. More notably, there have been several case reports describing the use of DRGS as a salvage therapy by successfully treating patients after they failed conventional SCS [183, 184]. DRGS can be more expensive than SCS due to a shorter battery life and thus more pulse generator replacements are needed. However, both SCS and DRGS have been shown to be clearly cost-effective relative to long-term medical management [185]. While DRGS appears to be superior to SCS, one retrospective study demonstrated that DRGS in conjunction with simultaneous SCS decreased pain scores and improved function more than DRGS or SCS alone [186].

Peripheral Nerve Stimulation

PNS for the treatment of CRPS is less frequently reported in the literature than SCS or DRGS. Benefits of PNS are thought to arise from preferential neurostimulation of non-nociceptive A and B fibers along peripheral nerves, which in turn disrupts nociceptive transmission from C fibers [187]. One case report demonstrated successful alleviation of pain and restoration of movement following percutaneous PNS of the ulnar nerve in the treatment of upper extremity CRPS [187]. However, PNS utilization is not limited to CRPS confined to a single peripheral nerve; PNS utilization along multiple peripheral nerves and even neural plexi has been reported. A 2020 case series by Frederico, and da Silva Freitas [188] demonstrated significantly reduced pain scores after PNS of the brachial plexus for upper extremity CRPS. A larger retrospective chart review proved that PNS was associated with decreased pain scores, improved functional status, and decreased opioid consumption overall [189]. One case report has also demonstrated success with wireless PNS of the radial and median nerves with minimal side effects or complications [190]. Studies comparing PNS to neuraxial modalities like SCS and DRGS are non-existent, but PNS has a more favorable safety profile and involves less invasive instrumentation. However, only SCS and DRGS are approved by the Food and Drug Administration (FDA) for the treatment of CRPS.

Transcutaneous Electrical Nerve Stimulation

TENS can be an effective, minimally invasive treatment for CRPS, especially for pediatric patients [191, 192]. There is a paucity of literature on this topic, but one study has demonstrated a significant reduction in pain intensity scores and edema after TENS therapy in upper extremity CRPS [193]. Despite this dearth of data, given that TENS is a highly safe intervention it should be readily utilized if tolerated, especially as an adjunct to physical therapy and other treatment modalities.

Neural and Sympathetic Blockade

Sympathetic blocks represent another minimally invasive treatment modality that can attenuate the sympathetic hyperactivity seen in CRPS. Upper extremity CRPS can be targeted with a stellate ganglion block, while a lumbar sympathetic block can be used for reducing the symptoms of lower extremity CRPS [127, 133, 176, 194]. Sympathetic blocks are usually performed with fluoroscopy, but ultrasonography has also been used in certain cases [176]. In fact, there is increasing evidence for performing stellate ganglion blocks under ultrasound versus fluoroscopy [195]. Successful reduction of pain after sympathetic blockade can increase tolerance for physical therapy and decrease dependence on oral pain medications [194]. In clinical practice, these blocks are performed in series if they allow patients to engage in physical restoration therapies by reducing pain sufficiently. Many patients continue to experience pain relief for at least several weeks after sympathetic block according to a retrospective review of 155 patients [196]. Measuring an elevation in temperature of the affected limb after the procedure assists in confirming the accuracy of sympathetic blocks [1].

One RCT reported significantly lower pain scores at a 12-month follow-up after thoracic sympathetic block in patients with upper extremity CRPS [194, 197]. Another study by Lee et al. [198] investigated differences in pain reduction between lumbar sympathetic block with botulinum

toxin type A versus botulinum toxin type B and concluded that both types of botulinum toxins successfully reduced pain scores, but botulinum toxin B was more effective in terms of duration of pain reduction. One RCT investigating upper extremity CRPS concluded that there was no difference in pain relief at 1-month follow-up between stellate ganglion block with lidocaine, stellate ganglion block with lidocaine and clonidine, and regional anesthetic block with lidocaine and clonidine [144, 199].

Other nerve blocks for the treatment of CRPS have been reported in the literature. For example, several case reports have documented success with the reduction of refractory CRPS pain with supraclavicular brachial plexus blocks [200, 201]. There is also some evidence to suggest that T2 paravertebral block may be even more efficacious in prolonging block duration than standard stellate ganglion block [202].

Although a Cochrane review in 2003 concluded that sympathetic blocks were not useful in reducing CRPS pain, an updated Cochrane review in 2013 reported that no conclusions could be drawn due to a lack of high-quality evidence [175]. Similarly, a systematic review by Żyluk and Puchalski [144] suggested that there was only weak evidence to support the use of stellate ganglion blocks in CRPS. Nerve blocks are generally well tolerated, but a case report demonstrated the development of extrapyramidal motor symptoms following lumbar sympathetic block; these extrapyramidal effects resolved with intravenous administration of diphenhydramine [203].

Emerging Therapies

Ketamine

Ketamine acts by inhibiting the N-methyl-D-aspartate (NMDA) receptor and is often delivered in a topical, subanesthetic, or anesthetic form [204]. It is believed to reverse the maladaptive cortical neuroplastic changes and central hypersensitization that are characteristic of CRPS [144, 175, 205]. More specifically, some studies suggest that ketamine may reduce cortical hyperexcitability by promoting GABAergic transmission [206]. The heterogeneity of ketamine administration, dose, duration, and outcome measures in previously published trials make it difficult to provide clinical recommendations, but several researchers have proposed guidelines on ketamine infusion including rate, titration, duration, tapering, and maintenance therapy [207].

There is some evidence that ketamine may be effective in inducing short-term pain reduction in CRPS patients for several months [127, 175, 208, 209]. Application of topical 10% ketamine has been associated with reduced allodynia without significant improvement of function [144, 205, 210]. Kirkpatrick et al. [211] demonstrated that escalating subanesthetic ketamine infusions, starting at 60 mg/h and ultimately increasing to 200 mg/h, led to diminished hyperalgesia within 4 days of treatment of lower extremity CRPS. The study also suggested that ketamine therapy for upper extremity CRPS may require more than 4 days to achieve maximal benefit [211]. Another study by Sigtermans et al. [212] reported lower pain scores in patients treated with subanesthetic-dose ketamine therapy with a mean infusion rate of 22.2 ± 2.0 mg/h compared to the placebo group, although these differences diminished by the end of the 12 weeks of therapy.

Anesthetic doses of ketamine (ketamine comas) have been used in patients with severe CRPS refractory to more conventional therapies including subanesthetic ketamine infusion. One study induced a "ketamine coma" via high-dose ketamine and midazolam infusion in intubated patients and reported improved quality of life in 85% of patients within 6 months of therapy, and complete resolution of pain in 50% of patients after 10 years [210, 213]. Another study reported inducing coma with high-dose ketamine, midazolam, and clonidine with 50% of patients remaining pain-free for up to 11 years after therapy [210, 213].

A systematic review by Connolly et al. [204] in 2015 concluded that there is not sufficient high-quality evidence to recommend ketamine for the treatment of CRPS. Yet, a meta-analysis by Zhao et al. [214] in 2018 concluded that ketamine infusion can provide effective pain relief in the short term (< 3 months), but more RCTs are necessary to confirm these results for long-term pain relief.

Adverse side effects of ketamine including hypertension, hallucinations, dissociation, agitation, salivation, mania, anxiety, and nausea should be carefully monitored [9, 207, 211]. Hepatotoxicity and cholangitis are known complications of chronic ketamine use, and one case report noted the development of biliary dilation and cholangitis with recurrent ketamine infusion at subanesthetic doses [215]. The risk of hepatoxicity is approximately 1.9%; therefore, it is reasonable to monitor liver enzymes before and after a series of outpatient systemic treatments [214]. Considering this risk profile, it may be useful to predict patient response to ketamine before initiation of therapy. Patients with positive responses to ketamine therapy express different miRNAs before treatment than do patients with poor responses, suggesting that these biomarkers can be used to predict response to ketamine therapy [35]. Similarly, the ratio of phases (vascular, tissular (tissue), and bone phases) during three-phase bone scintigraphy before ketamine therapy can help predict patient response; increased ratios of bone phase to tissular phase, bone phase to vascular phase, and tissular phase to vascular phase has been significantly associated with more positive outcomes after ketamine therapy [216].

Intrathecal Strategies

CRPS-induced dystonia may be treated with intrathecal baclofen if oral administration of baclofen is not feasible or effective [91]. Baclofen is a GABA receptor agonist that reduces nociceptive transmission at the dorsal horn [9]. A randomized controlled trial demonstrated that intrathecal baclofen was associated with decreased dystonia compared to intrathecal saline administration [217]. Side effects of intrathecal baclofen administration including headache, nausea, and hallucinations are not uncommon and should be monitored appropriately [91, 217].

In the literature, other medications including steroids, clonidine, adenosine, glycine, opioids, and various interleukins have been administered intrathecally with differing levels of success. A randomized controlled trial reported no significant improvement in pain as well as worsening myoclonus in patients treated with intrathecal methylprednisolone [1, 127, 170]. Another randomized controlled trial by Rauck et al. [218] showed no significant difference in pain reduction between intrathecal clonidine and intrathecal adenosine therapy. Similarly, intrathecal glycine was not associated with improved pain or functionality [170]. A study by Herring et al. [219] concluded that intrathecal opioid therapy did not reduce chronic oral opioid intake in CRPS patients. Several mouse models have demonstrated the efficacy of intrathecal IL-10 or intrathecal recombinant FTY720, which downregulates the sphingosine-1 phosphate receptor and inhibits lymphocyte migration, in reducing allodynia [220, 221].

Calcitonin

Calcitonin is thought to be efficacious in the treatment of CRPS due to its analgesic and vasoactive properties [45, 144]. It reduces bone resorption and may also promote analgesia via stimulation of b-endorphin release [133, 222]. Nasal calcitonin spray is typically administered as 200–400 units/day over 1 month, whereas subcutaneous calcitonin injection can be delivered as 100U/day over 2 months [144]. The literature regarding the benefits of calcitonin is mixed. One study demonstrated that intranasal calcitonin therapy in conjunction with physical therapy was associated with a greater reduction in pain and improved range of motion when compared to physical therapy and placebo [92]. However, other RCTs have denied any significant clinical improvements with intranasal calcitonin [222]. Calcitonin appears to be most efficacious in improving pain and range of motion and reducing edema and vasomotor dysfunction when administered in patients with early CRPS [144]. There is no compelling evidence for preference of calcitonin over other therapeutics, but considering its relatively safe pharmaceutical profile, it may be considered as part of a multimodal approach.

Bisphosphonates

Patients with CRPS of the lower limb can exhibit decreased bone mineral density and decreased bone volume, suggesting a state of increased bone resorption that may be amenable to bisphosphonate therapy [223]. Bisphosphonates, including alendronate, pamidronate, zoledronic acid, and clodronate, decrease osteoclast-mediated bone resorption and pain caused by osteopenia [45, 222, 224]. The improved blood flow and bone strength may also result in better tolerance to physical therapy and overall improved mobility and functionality in the affected limb [225].

Bisphosphonates have established therapeutic value for treating bone disorders including Paget's disease and osteoporosis, but the literature regarding their efficacy in CRPS is not as compelling [1]. Several RCTs have suggested that bisphosphonates can improve classic CRPS symptoms, have low misuse potential, and result in minimal adverse effects that are usually limited to upper gastrointestinal symptoms [92, 127, 131, 222, 226]. Another randomized study demonstrated that IV pamidronate was as effective in controlling pain as oral prednisolone in post-stroke CRPS patients [92, 208]. However, a Cochrane review of these trials cautions that the evidence supporting bisphosphonate therapy is of low quality [9, 175].

The benefits of bisphosphonate therapy may also be limited to short-term outcomes. Several studies have demonstrated that bisphosphonate administration in conjunction with physical therapy may convey favorable short-term outcomes including reduced pain and improved functionality [144, 209, 224]. In some situations, pain reduction may be apparent even after the first dose of IV pamidronate [222, 224]. Similarly, Scholz-Odermatt et al. [227] reported that patients in the early stages of CRPS responded more favorably to bisphosphonate treatment than did patients with more advanced disease. There is also evidence that patients who respond favorably to bisphosphonate therapy experience a quicker resolution of CRPS symptoms [228].

Other pharmacologic agents including teriparatide, a parathyroid hormone analog, may be efficacious in reducing bone edema and improving range of motion due to CRPS. Teriparatide has already been shown to improve fracture healing and decrease degeneration of articular cartilage [229].

N-acetylcysteine

N-acetylcysteine and other free radical scavengers may help treat CRPS by reducing inflammation and improving edema, skin color, and limb functionality. Their therapeutic effect is

based on the belief that excessive production of toxic oxygen radicals mediates the CRPS disease process. Other free radical scavengers that have been used in the treatment of CRPS include topical dimethyl sulfoxide and IV mannitol [92, 170]. Dimethyl sulfoxide cream is particularly useful in treating early CRPS while oral N-acetylcysteine may be more useful for pain reduction of chronic CRPS [144]. However, a 2021 meta-analysis on N-acetylcysteine for treating chronic pain, including CRPS concluded that insufficient evidence exists for its efficacy and safety [230]. Evidence for mannitol is mixed, as one randomized trial demonstrated only minimal benefit of mannitol infusion when compared to placebo [92].

Low-Dose Naltrexone

Naltrexone, a μ and κ opioid antagonist has been a possible therapy for chronic pain conditions and autoimmune disorders such as multiple sclerosis, diabetic neuropathy, and fibromyalgia [130, 231]. There have been two case reports of attenuation of dystonia in CRPS patients after administration of low-dose naltrexone [232]. The benefits of naltrexone in CRPS are thought to arise from the antagonism of specific TLR4 receptors on hyperactive glial cells [232]. Otherwise, there is little guidance from the literature regarding the use of naltrexone in CRPS.

Scrambler Therapy

Scrambler therapy is a relatively new, non-invasive technique that involves electrocutaneous stimulation of C fibers and has demonstrated some efficacy in the treatment of several chronic pain disorders [233–235]. Traditionally, electric stimulation of cutaneous A-beta fibers has been used to block nociceptive transmission from C fibers and induce analgesia. While scrambler therapy does stimulate C fibers, it instead enhances the transmission of non-painful sensations from C fibers [234]. Therefore, the utility of scrambler therapy lies in changing the transmission of pain along traditional C fiber pathways rather than blocking their transmission. Several scrambler therapy studies have included CRPS patients, but there are few studies exclusively examining these patients [234]. Several small case reports have demonstrated persistent pain relief and improved quality of life in CRPS patients after scrambler therapy with few adverse side effects [236].

Mirror Box Therapy

Some CRPS patients experience altered sensation and perception of the affected limb and frequently describe physical changes of the affected limb that are out of proportion with physical exam findings [237]. These sensations were previously thought to lead to a visuospatial attention bias, although this theory has largely fallen out of favor [238]. Mirror box therapy may help to correct these abnormal sensations. In mirror therapy, the affected limb is concealed with a mirror, and the patient is asked to move the unaffected limb. The mirror creates the illusion that the affected limb is moving in tandem with the unaffected limb and may assist with neural perception retraining in CRPS patients [78, 92, 127, 239, 240]. MRI brain comparison before and after treatment supports the theory that mirror box therapy is associated with some reversal of maladaptive cortical neuroplastic changes and attenuation of pain [240, 241].

Multiple studies have demonstrated that mirror therapy can mitigate phantom limb pain and lead to better functionality in the affected limb [240]. In CRPS, Kotiuk et al. [237] reported that over 80% of CRPS patients experienced an improvement in body perception disturbances as measured by the Bath scale as well as improved pain relief, functional status, positional awareness, and attention deficits. Recent RCTs suggest that the benefits of mirror therapy become apparent with a 4-week program, and may be present for up to 6 months afterwards [144]. The 2022 Cochrane review similarly suggests that mirror therapy may be useful in reducing pain symptoms and improving limb functionality, but warns that the current quality of evidence in the literature regarding mirror therapy is uncertain and low level [156]. Although evidence supporting mirror box therapy is moderate at best, it continues to be used in the treatment of CRPS [144].

In the event that mirror box therapy is not tolerated by the patient, alternative strategies such as body shadow, in which images of the affected limb are projected onto a wall may be considered [242]. Virtual reality provides another alternative for mirror therapy in patients without an intact limb and may even more closely simulate the movement of the affected limb. Initial data on immersive virtual reality and home virtual reality systems appear promising [240].

Cannabinoids

There is some evidence that cannabinoids can ease cancer pain and neuropathic pain, but there is little evidence supporting the use of cannabinoids for the treatment of CRPS. There have been some clinical trials exploring the use of an inhaled cannabinoid-based drug (delta-9-tetrahydrocannabinol (9.5%) and cannabidiol (2.5%)) which was previously used to treat cancer pain for the treatment of CRPS patients [243]. A recent RCT by Almog et al. [244] in 2020 reported significant pain reduction in patients given inhaled doses of tetrahydrocannabinol (THC) at both 0.5 mg and 1 mg concentrations. However, less than half of the patients in this study were diagnosed with CRPS; the majority were diagnosed with diabetic neuropathic pain [244]. Dedicated

RCTs evaluating the effectiveness of cannabinoids in treating CRPS patients are warranted. Currently, recommendations for cannabinoid therapy should be carefully considered since the potential for misuse is high [131].

Photobiomodulation

Photobiomodulation is a relatively new technique that is hypothesized to decrease peripheral sensitization, lower inflammatory cytokine levels, and promote endorphin release [245]. Rodrigues et al. [245] investigated the efficacy of photobiomodulation at 660 nm and 830 nm wavelengths in a preclinical model of CRPS and concluded that 660 nm therapy in particular was effective in decreasing hyperalgesia to thermal and mechanical stimuli. Both wavelength therapies were also associated with reduced limb edema. Although limited, the evidence for photobiomodulation appears promising and may find value as a complementary treatment for CRPS.

Plasma Exchange

Plasma exchange involves the removal of autoantibodies and immune complexes that contribute to systemic inflammation, and is used to treat various immunological disorders [246]. One study by Ramanathan et al. [246] suggested that dysregulation of exosomal miRNAs could contribute to the inflammatory state seen in CRPS; therefore plasma exchange may be effective in removing these inflammatory large molecules from the circulation. A large retrospective case series by Aradillas et al. [247] in 2015 reported that approximately 90% of CRPS patients reported a significant reduction in pain after plasma exchange therapy. Continued benefits appear to be contingent on repeated therapy because patients who did not undergo maintenance therapy experienced a recurrence of their pain [247]. Preliminary findings support the possible benefits of therapeutic plasma exchange, but RCTs are necessary before this therapy can be confidently recommended. Additionally, plasma exchange is time intensive and costly in nature.

Transcranial Magnetic Stimulation/Transcranial Direct Current Stimulation

Transcranial magnetic stimulation (TMS) has been effective for certain chronic pain disorders including neuropathic pain and fibromyalgia, but the literature on TMS for treating CRPS is scarce [248, 249]. This therapy involves the placement of an electromagnetic coil on the patient's head to generate a magnetic field and provide magnetic stimulation that modulates cortical excitability [248, 249]. A literature review in 2017 by Nardone et al. [249] provided evidence of hyperexcitability within specific cortical regions including the bilateral motor cortex which may contribute to the development of CRPS. More recent studies have demonstrated positive pain reduction benefits in patients with CRPS after TMS therapy, although the current evidence is limited by small sample sizes [250]. One randomized controlled trial by Picarelli et al. [251] demonstrated that adjuvant therapy consisting of repetitive TMS targeting the motor cortex is efficacious in the reduction of sensory-discriminative and emotional-affective pain in CRPS 1 confined to a single upper limb. Transcranial magnetic stimulation is generally safe and non-invasive, but patients with a low seizure threshold such as those with pre-existing seizure disorders or chronic alcohol use should be carefully monitored given that one study reported the occurrence of a generalized seizure during treatment [251, 252]. Overall, transcranial magnetic stimulation may be a viable option for CRPS patients with pain refractory to other treatment modalities, but RCTs are needed to further elucidate its therapeutic benefits [251, 252].

There has been some promising evidence about transcranial direct current stimulation (tDCS) in the treatment of CRPS. Unlike TMS, tDCS involves stimulation by low-intensity electrical currents. One case report has demonstrated mild but positive pain reduction when combining tDCS therapy with transcutaneous electrical nerve stimulation (TENS) [252]. The combination of tDCS and TENS has proven more effective than either therapy alone in the treatment of low back pain and may be useful in CRPS patients with refractory pain [252, 253].

Botulinum Toxin

Botulinum toxin acts by inhibiting the release of acetylcholine at the motor end plate and treats a wide range of muscular and painful disorders such as dystonia and chronic migraine. Some studies suggest that botulinum toxin may have anti-nociceptive properties by suppressing TRPV1 nociceptive channels [254]. It has been infrequently used to interrupt the sympathetic flow in the form of an injection therapy along the sympathetic chain, intraarticular injection, or subcutaneous injection. For example, work by Lee et al. [198] in 2018 investigated the differences between botulinum toxin type A and botulinum toxin type B in lumbar sympathetic ganglion blocks of patients with CRPS. The researchers concluded that pain scores decreased with both groups although significantly prolonged pain relief was seen with botulinum toxin B [198]. A case report by Bellon et al. [254] presented a patient with significant pain reduction and improved range of motion after intraarticular injection of botulinum toxin A into the glenohumeral joint.

Several case reports have documented success in pain reduction with injection of botulinum toxin type A into myofascial trigger points of the upper limb, and specifically the trapezius, scalenes, and paraspinal muscles of CRPS patients with distal symptoms [255, 256]. Similarly, a more recent

case report in 2020 showed a significant reduction in allodynia with subcutaneous injection of botulinum toxin A to the palm [2]. Interestingly, the researchers also noted a progressively lengthening duration of pain reduction after each subsequent botulinum toxin A injection [2]. Overall, more data is needed to determine the efficacy of botulinum toxin as well as clinical guidelines for its administration.

Immunoglobulin Therapy

There is increasing evidence from preclinical studies that autoimmunity contributes to the pathophysiology of CRPS [257]. Some evidence suggests that an overactive immune response, perhaps involving autoantibodies targeted at the beta2-adrenergic receptor and the muscarinic-2 receptor, may play a role in the development of this disease [258]. Consequently, some case reports have examined immunoglobulin infusion therapy, though immunoglobulin therapy has been met with mixed results [246, 247, 258]. A narrative review by Chang et al. [258] in 2020 did report that IVIG appeared to significantly reduce neuropathic pain with a low risk for any adverse effects. Similarly, Goebel et al. [259] performed a small RCT in 2010 that demonstrated decreased pain scores during IVIG infusion with no adverse effects. However, a large RCT in CRPS patients performed by Goebel et al. [260] did not show benefit. The literature suggests that benefits in pain reduction from IVIG infusion may arise within 1–2 days of therapy [259, 260]. The peak or duration of pain reduction is unknown, and the data lack consistency which makes it challenging to recommend IVIG as a standard treatment, or to establish a therapeutic protocol for administration.

Surgical Sympathectomy

Surgical sympathectomy is rarely performed in CRPS and has variable levels of success [133]. Sympathectomy was previously performed via an open surgical approach, but is now accomplished via minimally invasive endoscopy. A literature review by Kim et al. [261] reported surgical sympathectomy failure rates as high as 35%. The authors attributed this high failure rate to the poor predictive value of sympathetic blockade in assessing the success of surgical sympathectomy. Moreover, nearly half of the patients may experience a recurrence of CRPS or neuralgia after surgical sympathectomy [261]. Sympathectomy may also be accomplished through less invasive approaches such as radiofrequency ablation, but the recurrence of CRPS remains a concern.

Amputation

Amputation is viewed as an intervention of last resort for CRPS after many previous therapies have failed [49]. Approximately 15% of patients diagnosed with CRPS experience symptoms after 18 months even with appropriate treatment [262]. Regardless, some professional guidelines such as those set by the Royal College of Physicians in England discourage amputation for CRPS within 24 months of the diagnosis [83]. Patients with chronic CRPS have usually tried multiple therapies without adequate relief of symptoms and may request amputation. Pain and limb dysfunction rank as the two most common reasons that patients request amputation [49, 263].

A systematic review by Ayyaswamy et al. [263] found that 66% of patients experienced improved quality of life while 16% of patients reported decreased quality of life after amputation. Patients who continued multidisciplinary treatment including physical therapy, psychology, and pain management after amputation reported the greatest benefits in quality of life. Conversely, psychological factors including lower baseline resilience and poor social support have been associated with poorer outcomes after amputation including decreased improvement in mobility [264]. The most common complications associated with amputation included phantom pain, stump pain, and recurrence of CRPS, which can occur in nearly 50% of patients [146, 263]. Recurrence of pain or other post-operative complications may also impede prosthetic fitting and use [83, 264].

One case report in the UK highlighted a trans-tibial amputation in a patient who had failed conservative treatment including spinal cord stimulation [183]. Unfortunately, the patient subsequently developed a stump neuroma. Excision of the neuroma led to a recurrence of CRPS that was refractory to steroid, opioid, bisphosphonate, intravenous immunoglobulin, and physical therapy but did respond positively to dorsal root ganglion stimulation [183]. This case report demonstrates that amputation does not guarantee complete resolution of symptoms, and may lead to further distressing complications.

Another case report found that amputation coupled with ketamine infusions was successful in controlling pain for a patient with extremely debilitating CRPS of the lower extremity [265]. The authors attribute the beneficial outcome to the utilization of multiple modalities for preventing phantom limb pain, including aggressive PT and regional anesthesia.

There is not sufficient evidence in the literature to confidently recommend amputation, but amputation may be justifiable in patients with intractable end-stage CRPS and poor quality of life who specifically request surgical intervention. Ketamine infusions may serve as an adjuvant to assist in pain control.

Prevention

The management of CRPS can be challenging, especially in patients with later stages of the disease and/or longstanding pain [266]. Recently, emerging evidence has suggested a

role for CRPS prevention in patients following extremity fractures. While such measures may serve to be beneficial, robust clinical evidence is largely lacking at this time for CRPS prevention to be included in standard clinical practice.

Multiple RCTs have demonstrated that daily administration of 500 mg of vitamin C decreases 1-year incidence of CRPS following wrist fracture when compared to placebo alone [1, 92, 267, 268]. Vitamin C is thought to be preventative by reducing local oxidative stress and thereby decreasing the risk of CRPS development after a recent fracture or orthopedic surgery. However, Keef and Keef [269] reported that the prophylactic value of vitamin C after wrist fracture has decreased over the past decade, with more recent studies demonstrating no significant difference between the experimental group that was treated with vitamin C and the control group. Other authors recommend the administration of vitamin C after foot and ankle surgery, although at significantly higher dosages of 1000 mg [267, 268, 270]. While the efficacy of vitamin C in preventing the onset of CRPS is unclear, it is generally well tolerated with minimal side effects and thus warrants more extensive study as a prophylactic measure after extremity fractures.

With respect to preventative procedural interventions, there is no clear evidence for the use of sympathetic blocks or epidural procedures. Alimian et al. [270], however, recently published successful use of vitamin C adjuvant Bier blocks performed for a cohort of patients with distal radial fractures. In a total cohort of 74 patients, they found that patients who received a Bier block with vitamin C injectate were far less likely to develop CRPS across a 12-week time frame. Studies exploring other regional anesthesia injectates and strategies for CRPS prevention are lacking.

Conclusion

CRPS leads to a constellation of progressive painful sensory changes, vascular abnormalities, edema, extremity weakness or immobility, and trophic disturbances. The diagnosis is clinical and requires the application of the Budapest criteria (2012 IASP diagnostic criteria). Although an uncommon phenomenon, those patients who develop chronic CRPS suffer from a considerable health burden. There is mounting evidence that the pathophysiology involves inflammation and neuroinflammation, autoimmunity, aberrations in autonomic processing, and both peripheral and central sensitization. The best available evidence coupled with standard clinical practice supports modalities of physical restoration, steroids for acute CRPS, analgesic anticonvulsants and antidepressants, sympathetic blocks or short-duration opioids for engaging physical/occupational therapy, topical analgesics, spinal cord or dorsal root ganglion stimulation, topical or subanesthetic ketamine, and intrathecal baclofen for dystonia. Emerging treatments discussed in this article such as scrambler therapy, transcranial magnetic stimulation, botulinum toxin, peripheral nerve stimulation, and immunoglobulin therapy can be considered for patients whose care requires less conventional treatment, and amputation only in end-stage patients. Vitamin C as a preventive strategy may be of value after a limb fracture.

Compliance with Ethical Standards

Conflict of Interest Gerard Limerick: No disclosures. Dana Christo: No disclosures. Jennifer Tram: No disclosures. Roya Moheimani: No disclosures. John Manor: No disclosures. Krishnan Chakravarthy: Consultant for Medtronic, Biotronik, Mainstay Medical, PAINTEQ, Vertos Medical. He has stock options in Aya Bioscience, Higgs Boson Health, Nalu Medical, Rune Labs, UMEHEAL, Yantra Biomedical, Oska Wellness, Mainstay Medical, Neuronoff. He is founder of NXTSTIM, Coastal Research Institute, Accufix Medical, Douleur Therapeutics. Jay Karri: No disclosures. Paul Christo: Consultant for Y-mAbs, Eli Lilly, GlaxoSmithKline Consumer Healthcare, Exicure, Neurana, Neumentum.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

1. Shim H, Rose J, Halle S, Shekane P. Complex regional pain syndrome: a narrative review for the practising clinician. Br J Anaesth: BJA. 2019;123(2):e424–33. https://doi.org/10.1016/j.bja.2019.03.030.
2. Kwak H, Koh J, Min K. Botulinum toxin treatment for intractable allodynia in a patient with complex regional pain syndrome: a case report. Neurol Asia. 2020;25(2):215–9. https://www.neurologyasia.org/articles/neuroasia-2020-25(2)-215.pdf.
3. Sandroni P, Benrud-Larson LM, McClelland RL, Low PA. Complex regional pain syndrome type I: incidence and prevalence in olmsted county, a population-based study. Pain (Amsterdam). 2003;103(1–2):199–207. https://www.ncbi.nlm.nih.gov/pubmed/12749974. https://doi.org/10.1016/S0304-3959(03)00065-4.
4. de Mos M, de Bruijn AGJ, Huygen FJPM, Dieleman JP, Stricker BHC, Sturkenboom MCJM. The incidence of complex regional pain syndrome: a population-based study. Pain (Amsterdam). 2007;129(1):12–20. https://doi.org/10.1016/j.pain.2006.09.008.
5. Murphy KR, Han JL, Yang S, et al. Prevalence of specific types of pain diagnoses in a sample of United States adults. Pain Physician. 2017;20(2):E257-E268. https://www.ncbi.nlm.nih.gov/pubmed/28158163.
6. Bang S, Kim YS, Lee S, Park U, Kim T, Choi Y. Prevalence of common causes of neuropathic pain in korea: population-based observational study. J Int Med Res. 2020;48(7):300060519888102. https://journals.sagepub.com/doi/full/10.1177/0300060519888102. https://doi.org/10.1177/0300060519888102.
7. Lee J, Park S, Kim JH. A korean nationwide investigation of the national trend of complex regional pain syndrome vis-à-vis age-structural transformations. Korean J Pain. 2021;34(3):322–331. https://kiss.kstudy.com/thesis/thesis-view.asp?key=3894978.

8. Pons T, Shipton EA, Williman J, Mulder RT. Potential risk factors for the onset of complex regional pain syndrome type 1: a systematic literature review. Anesthesiol Res Practice. 2015;2015:956539–15. https://www.airitilibrary.com/Publication/alDetailedMesh?DocID=P20151124003-201512-201708110018-201708110018-81-95. https://doi.org/10.1155/2015/956539.
9. Urits I, Shen A, Jones M, Viswanath O, Kaye A. Complex regional pain syndrome, current concepts and treatment options. Curr Pain Headache Rep. 2018;22(2):1–9. https://www.ncbi.nlm.nih.gov/pubmed/29404787. https://doi.org/10.1007/s11916-018-0667-7.
10. Stanton-Hicks M. Plasticity of complex regional pain syndrome (CRPS) in children. Pain Med (Malden, Mass.). 2010;11(8):1216–1223. https://api.istex.fr/ark:/67375/WNG-Q7KZPTJS-V/fulltext.pdf. https://doi.org/10.1111/j.1526-4637.2010.00910.x.
11. Kessler A, Yoo M, Calisoff R. Complex regional pain syndrome: an updated comprehensive review. NeuroRehabilitation (Reading, Mass.). 2020;47(3):253–64. https://www.ncbi.nlm.nih.gov/pubmed/32986618. https://doi.org/10.3233/NRE-208001.
12. Elsharydah A, et al. Complex regional pain syndrome type 1 predictors – Epidemiological perspective from a national database analysis. J Clin Anesth. 2017;39:548–53.
13. Wang YC, et al. Injury location and mechanism for complex regional pain syndrome: a nationwide population-based case-control study in Taiwan. Pain Pract. 2015;15(6):548–53.
14. Geertzen JH, et al. Relationship between impairments, disability and handicap in reflex sympathetic dystrophy patients: a long-term follow-up study. Clin Rehabil. 1998;12(5):402–12.
15. Galer BS, et al. Course of symptoms and quality of life measurement in complex regional pain syndrome: a pilot survey. J Pain Symptom Manage. 2000;20(4):286–92.
16. Van Velzen GAJ, et al. Health-related quality of life in 975 patients with complex regional pain syndrome type 1. Pain. 2014;155(3):629–34.
17. Sharma A, et al. A web-based cross-sectional epidemiological survey of complex regional pain syndrome. Reg Anesth Pain Med. 2009;34(2):110–5.
18. Elsamadicy AA, et al. Prevalence and cost analysis of complex regional pain syndrome (CRPS): a role for neuromodulation. Neuromodulation. 2018;21(5):423–30.
19. Scholz-Odermatt SM, et al. Direct health care cost and work incapacity related to complex regional pain syndrome in Switzerland: a retrospective analysis from 2008 to 2015. Pain Med. 2019;20(8):1559–69.
20. Bruehl S, Chung OY. How common is complex regional pain syndrome-Type I? Pain. 2007;129(1–2):1–2.
21. Avdic D, Jaganjac A, Katana B, Bojicic S, Hadziomerovic AM, Svraka E. Complex regional pain syndrome (CRPS). J Health Sci. 2015;5:1–4.
22. Bruehl S. Complex regional pain syndrome. BMJ. 2015;351:h2730.
23. Ghai B, Dureja GP. Review article - complex regional pain syndrome: a review. Review Article - Complex regional pain syndrome: A review. 2004. http://bioline.utsc.utoronto.ca/archive/00002847/.
24. Harden R, Oaklander AL, Burton AW, et al. Complex regional pain syndrome: practical diagnostic and treatment guidelines, 4th edition. Pain Med (Malden, Mass.). 2013;14(2):180–229. https://www.narcis.nl/publication/RecordID/oai:pure.atira.dk:publications%2F48ad889e-4bf5-408f-ac31-c6cd161862d3. https://doi.org/10.1111/pme.12033.
25. Merskey H. Classification of chronic pain. 2nd ed. Seattle: IASP Press; 1994.
26. Harden RN, Bruehl S, Perez RSGM, et al. Development of a severity score for CRPS. Pain (Amsterdam). 2010;151(3):870–6. https://doi.org/10.1016/j.pain.2010.09.031.
27. Harden RN, Maihofner C, Abousaad E, et al. A prospective, multisite, international validation of the complex regional pain syndrome severity score. Pain (Amsterdam). 2017;158(8):1430–6. https://www.ncbi.nlm.nih.gov/pubmed/28715350. https://doi.org/10.1097/j.pain.0000000000000927.
28. Sharma A, Agarwal S, Broatch J, et al. A web-based cross-sectional epidemiological survey of complex regional pain syndrome. Reg Anesth Pain Med. 2009;34:110–5.
29. Alkali NH, Al-Tahan AM, Al-Majed M, Al-Tahan H. Complex regional pain syndrome: a case report and review of the literature. Ann Afr Med. 2020;19(1):68–70. https://doi.org/10.4103/aam.aam_23_19. PMID: 32174618; PMCID: PMC7189882.
30. Martínez-Lavín M, Vargas A, Silveira LH, Amezcua-Guerra LM, Martínez-Martínez L-A, Pineda C. Complex regional pain syndrome evolving to full-blown fibromyalgia: a proposal of common mechanisms. JCR: J Clin Rheumatol. 2021;27(6S):S274–7. https://doi.org/10.1097/RHU.0000000000001304.
31. van Rijn MA, Marinus J, Putter H, et al. Spreading of complex regional pain syndrome: not a random process. J Neural Transm. 2011;118:1301–9. https://doi.org/10.1007/s00702-011-0601-1.
32. Edinger L, Schwartzman RJ, Ahmad A, Erwin K, Alexander GM. Objective sensory evaluation of the spread of complex regional pain syndrome. Pain Physician. 2013;16(6):581–91. PMID: 24284843.
33. Petersen PB, Mikkelsen KL, Lauritzen JB, Krogsgaard MR. Risk factors for post-treatment complex regional pain syndrome (CRPS): an analysis of 647 cases of CRPS from the danish patient compensation association. Pain Practice. 2018;18(3):341–349. https://onlinelibrary.wiley.com/doi/abs/10.1111/papr.12610. https://doi.org/10.1111/papr.12610.
34. Beerthuizen A, Stronks DL, van't Spijker A, et al. Demographic and medical parameters in the development of complex regional pain syndrome type 1 (CRPS1): prospective study on 596 patients with a fracture. Pain (Amsterdam). 2012;153(6):1187–92. https://doi.org/10.1016/j.pain.2012.01.026.
35. Birklein F, Ajit SK, Goebel A, Perez RS, Sommer C. Complex regional pain syndrome-phenotypic characteristics and potential biomarkers. Nat Rev Neurol. 2018;14(5):272–84. https://www.narcis.nl/publication/RecordID/oai:pure.atira.dk:publications%2Fd4c0ef22-a630-4953-a9d8-a7668e85df73. https://doi.org/10.1038/nrneurol.2018.20.
36. Rewhorn MJ, Leung AH, Gillespie A, Moir JS, Miller R. Incidence of complex regional pain syndrome after foot and ankle surgery. J Foot Ankle Surg. 2014;53(3):256–58. https://www.clinicalkey.es/playcontent/1-s2.0-S1067251614000076. https://doi.org/10.1053/j.jfas.2014.01.006.
37. da Costa VV, de Oliveira SB, Fernandes MDCB, Saraiva RÂ. Incidence of regional pain syndrome after carpal tunnel release. Is there a correlation with the anesthetic technique? Rev Bras Anestesiol. 2011;61(4):425–33. https://doi.org/10.1016/S0034-7094(11)70050-2.
38. Harden RN, Bruehl S, Stanos S, et al. Prospective examination of pain-related and psychological predictors of CRPS-like phenomena following total knee arthroplasty: a preliminary study. Pain (Amsterdam). 2003;106(3):393–400. https://doi.org/10.1016/j.pain.2003.08.009.
39. Kosy JD, Middleton SWF, Bradley BM, Stroud RM, Phillips JRA, Toms AD. Complex regional pain syndrome after total knee arthroplasty is rare and misdiagnosis potentially hazardous—prospective study of the new diagnostic criteria in 100 patients with no cases identified. J Knee Surg. 2018;31(8):797–803. https://doi.org/10.1055/s-0037-1615746.

40. Jo Y, Kim K, Lee B, Kim J, Lee C, Lee K. Incidence of and risk factors for complex regional pain syndrome type 1 after surgery for distal radius fractures: a population-based study. Sci Rep. 2019;9(1):4871. https://www.ncbi.nlm.nih.gov/pubmed/30890732. https://doi.org/10.1038/s41598-019-41152-x.
41. Wiper A, Amoroso G, Rao S, Nolan J. Complex regional pain syndrome: a rare but potentially disabling complication of transradial cardiac catheterization. Catheter Cardiovasc Interv. 2020;95(5):E140-E143. https://onlinelibrary.wiley.com/doi/abs/10.1002/ccd.28357. https://doi.org/10.1002/ccd.28357.
42. Jang SH, Seo YS. Diagnosis of complex regional pain syndrome I following traumatic axonal injury of the corticospinal tract in a patient with mild traumatic brain injury. Diagnostics (Basel). 2020;10(2):95. https://www.ncbi.nlm.nih.gov/pubmed/32050691. https://doi.org/10.3390/diagnostics10020095.
43. Cruz Salcedo EM, Blanco A, Reed J. Complex regional pain syndrome developing after a coral snake bite: a case report. Curēus (Palo Alto, CA). 2020;12(8). http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=7491678&tool=pmcentrez&rendertype=abstract. https://doi.org/10.7759/cureus.9787.
44. Gofiţă CE, Ciurea ME, Dinescu ŞC, et al. Complex regional pain syndrome as a paraneoplastic disorder associated with metatypical basal cell carcinoma. Romanian J Morphol Embryol. 2019;60(2):685–689. https://www.ncbi.nlm.nih.gov/pubmed/31658345.
45. Gofiţă CE, Mușetescu AE, Ciurea PL, et al. Posttraumatic complex regional pain syndrome and related comorbidities. Curr Health Sci J. 2019;45(3):321–28. https://www.ncbi.nlm.nih.gov/pubmed/32042462. https://doi.org/10.12865/CHSJ.45.03.12.
46. Thumtecho S, Schimmel J, Trakulsrichai S. Complex regional pain syndrome following a centipede bite: a case report. Clin Toxicol (Philadelphia, Pa.). 2020;58(7):777–779. http://www.tandfonline.com/doi/abs/10.1080/15563650.2019.1686515. https://doi.org/10.1080/15563650.2019.1686515.
47. Speck V, Schlereth T, Birklein F, Maihöfner C. Increased prevalence of posttraumatic stress disorder in CRPS. Eur J Pain. 2017;21(3):466–73. https://onlinelibrary.wiley.com/doi/abs/10.1002/ejp.940. https://doi.org/10.1002/ejp.940.
48. van Eijs F, Geurts J, van Kleef M, et al. Predictors of pain relieving response to sympathetic blockade in complex regional pain syndrome type 1. Anesthesiology (Philadelphia). 2012;116(1):113–121. https://www.narcis.nl/publication/RecordID/oai:cris.maastrichtuniversity.nl:publications%2F5cb295e0-61ed-40b6-afad-09bd7b5ef7b0. https://doi.org/10.1097/ALN.0b013e31823da45f.
49. Geertzen JHB, Scheper J, Schrier E, Dijkstra PU. Outcomes of amputation due to long-standing therapy-resistant complex regional pain syndrome type I. J Rehabil Med. 2020;52(8):jrm00087. https://www.narcis.nl/publication/RecordID/oai:pure.rug.nl:publications%2F4feb3992-d887-458d-ba98-de6c0ab9f1c9. https://doi.org/10.2340/16501977-2718.
50. Lee H, Kim SE, Moon JY, Shin J, Kim Y. Analysis of quantitative sudomotor axon reflex test patterns in patients with complex regional pain syndrome diagnosed using the Budapest criteria. Reg Anesth Pain Med. 2019;44(11):1026–32. https://doi.org/10.1136/rapm-2019-100415.
51. Wasner G, Schattschneider J, Binder A, Barony R. Complex regional pain syndrome - diagnostic, mechanisms, CNS involvement and therapy. Spinal Cord. 2003;41(2):61–75. https://doi.org/10.1038/sj.sc.3101404.
52. Cappello ZJ, Kasdan ML, Louis DS. Meta-analysis of imaging techniques for the diagnosis of complex regional pain syndrome type I. J Hand Surg (American ed.). 2012;37(2):288–296. https://www.clinicalkey.es/playcontent/1-s2.0-S0363502311013530. https://doi.org/10.1016/j.jhsa.2011.10.035.
53. Agten CA, Kobe A, Barnaure I, Galley J, Pfirrmann CW, Brunner F. MRI of complex regional pain syndrome in the foot. Eur J Radiol. 2020;129:109044. https://doi.org/10.1016/j.ejrad.2020.109044.
54. Howard B, Roy L, Kaye A, Pyati S. Utility of radionuclide bone scintigraphy in complex regional pain syndrome. Curr Pain Headache Rep. 2018;22(1):1–8. https://www.ncbi.nlm.nih.gov/pubmed/29388057. https://doi.org/10.1007/s11916-018-0659-7.
55. Wüppenhorst N, Maier C, Frettlöh J, Pennekamp W, Nicolas V. Sensitivity and specificity of 3-phase bone scintigraphy in the diagnosis of complex regional pain syndrome of the upper extremity. Clin J Pain. 2010;26(3):182–89. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&NEWS=n&CSC=Y&PAGE=fulltext&D=ovft&AN=00002508-201003000-00003. https://doi.org/10.1097/AJP.0b013e3181c20207.
56. Krämer HH, Hofbauer LC, Szalay G, et al. Osteoprotegerin: a new biomarker for impaired bone metabolism in complex regional pain syndrome? Pain (Amsterdam). 2014;155(5):889–95. https://doi.org/10.1016/j.pain.2014.01.014.
57. Jung Y, Kim H, Yeon Jeon S, et al. Brain metabolites and peripheral biomarkers associated with neuroinflammation in complex regional pain syndrome using [11C]-(R)-PK11195 positron emission tomography and magnetic resonance spectroscopy: a pilot study. Pain Med (Malden, Mass.). 2019;20(3):504–514. https://www.ncbi.nlm.nih.gov/pubmed/29986072. https://doi.org/10.1093/pm/pny111.
58. Russo MA, Georgius P, Pires AS, et al. Novel immune biomarkers in complex regional pain syndrome. J Neuroimmunol. 2020;347:577330. https://doi.org/10.1016/j.jneuroim.2020.577330.
59. Douglas SR, Shenoda BB, Qureshi RA, et al. Analgesic response to intravenous ketamine is linked to a circulating microRNA signature in female patients with complex regional pain syndrome. J Pain. 2015;16(9):814–824. https://www.clinicalkey.es/playcontent/1-s2.0-S1526590015007002. https://doi.org/10.1016/j.jpain.2015.05.008.
60. Dietz C, Müller M, Reinhold A, et al. What is normal trauma healing and what is complex regional pain syndrome I? an analysis of clinical and experimental biomarkers. Pain (Amsterdam). 2019;160(10):2278–89. https://www.ncbi.nlm.nih.gov/pubmed/31095096. https://doi.org/10.1097/j.pain.0000000000001617.
61. Rasmussen VF, Karlsson P, Drummond PD, et al. Bilaterally reduced intraepidermal nerve fiber density in unilateral CRPS-I. Pain Med (Malden, Mass.). 2018;19(10):2021–30. https://www.ncbi.nlm.nih.gov/pubmed/30299507. https://doi.org/10.1093/pm/pnx240.
62. Birklein F, Drummond PD, Li W, et al. Activation of cutaneous immune responses in complex regional pain syndrome. J Pain. 2014;15(5):485–95. https://www.clinicalkey.es/playcontent/1-s2.0-S1526590014005185. https://doi.org/10.1016/j.jpain.2014.01.490.
63. Lambeck J, Kesenheimer EM, Kleinmann B, Reinhard M. The tourniquet ischemia test in the diagnosis of complex regional pain syndrome. Pain Pract. 2021;21(3):308–15. https://onlinelibrary.wiley.com/doi/abs/10.1111/papr.12960. https://doi.org/10.1111/papr.12960.
64. Dhatt S, Winston P. The role of FLIR ONE ® thermography in complex regional pain syndrome: a case series. Am J Phys Med Rehabil. 2020;100(4):e48-e51. https://www.ncbi.nlm.nih.gov/pubmed/32618755. https://doi.org/10.1097/PHM.0000000000001522.
65. Abu-Arafeh H, Abu-Arafeh I. Complex regional pain syndrome in children: incidence and clinical characteristics. Arch Dis Child. 2016;101(8):719–23. https://doi.org/10.1136/archdischild-2015-310233.

66. Borucki AN, Greco CD. An update on complex regional pain syndromes in children and adolescents. Curr Opin Pediatr. 2015;27(4):448–52. https://www.ncbi.nlm.nih.gov/pubmed/26087424. https://doi.org/10.1097/MOP.0000000000000250.
67. Lascombes P, Mamie C. Complex regional pain syndrome type I in children: what is new? Orthop Traumatol Surg Res. 2016;103(1):S135-S142. https://www.clinicalkey.es/playcontent/1-s2.0-S1877056816301906. https://doi.org/10.1016/j.otsr.2016.04.017.
68. Bayle-Iniguez X, Audouin-Pajot C, Sales de Gauzy J, Munzer C, Murgier J, Accadbled F. Complex regional pain syndrome type I in children. clinical description and quality of life. Orthop Traumatol Surg Res. 2015;101(6):745–8. https://www.clinicalkey.es/playcontent/1-s2.0-S187705681500167X. https://doi.org/10.1016/j.otsr.2015.06.013.
69. Brooke V, Janselewitz S. Outcomes of children with complex regional pain syndrome after intensive inpatient rehabilitation. PM & R. 2012;4(5):349–54. https://www.clinicalkey.es/playcontent/1-s2.0-S1934148212000378. https://doi.org/10.1016/j.pmrj.2012.01.014.
70. Abu-Arafeh H, Abu-Arafeh I. Complex regional pain syndrome in children: a systematic review of clinical features and movement disorders. Pain Manag (London). 2017;7(2):133–40. https://doi.org/10.2217/pmt-2016-0036.
71. Sherry D, Wallace C, Kelley C, Kidder M, Sapp L. Short- and long-term outcomes of children with complex regional pain syndrome type I treated with exercise therapy. Clin J Pain. 1999;15(3):218–223. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&NEWS=n&CSC=Y&PAGE=fulltext&D=ovft&AN=00002508-199909000-00009. https://doi.org/10.1097/00002508-199909000-00009.
72. Murray CS, Cohen A, Perkins T, Davidson JE, Sills JA. Morbidity in reflex sympathetic dystrophy. Arch Dis Child. 2000;82(3):231–3. https://doi.org/10.1136/adc.82.3.231.
73. Sethna NF, Meier PM, Zurakowski D, Berde CB. Cutaneous sensory abnormalities in children and adolescents with complex regional pain syndromes. Pain (Amsterdam). 2007;131(1):153–61. https://doi.org/10.1016/j.pain.2006.12.028.
74. Low A, Ward K, Wines A. Pediatric complex regional pain syndrome. J Pediatr Orthop. 2007;27(5):567–72. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&NEWS=n&CSC=Y&PAGE=fulltext&D=ovft&AN=01241398-200707000-00016. https://doi.org/10.1097/BPO.0b013e318070cc4d.
75. Tan EC, Zijlstra B, Essink ML, Goris RJA, Severijnen RS. Complex regional pain syndrome type I in children. Acta Pædiatr (Oslo). 2008;97(7):875–9. http://www.ingentaconnect.com/content/bpl/apa/2008/00000097/00000007/art00014. https://doi.org/10.1111/j.1651-2227.2008.00744.x.
76. Kachko L, Efrat R, Ben Ami S, Mukamel M, Katz J. Complex regional pain syndromes in children and adolescents. Pediatr Int. 2008;50(4):523–7. https://api.istex.fr/ark:/67375/WNG-R92S0DVK-F/fulltext.pdf. https://doi.org/10.1111/j.1442-200X.2008.02625.x.
77. Wager J, Brehmer H, Hirschfeld G, Zernikow B. Psychological distress and stressful life events in pediatric complex regional pain syndrome. Pain Res Manag. 2015;20(4):189–194. https://www.ncbi.nlm.nih.gov/pubmed/26035287. https://doi.org/10.1155/2015/139329.
78. Tileston KR, Griffin A, Wagner JFM, O'Day MN, Krane EJ. Team approach: complex regional pain syndrome in children and adolescents. JBJS Rev. 2020;8(4):e0174. https://www.ncbi.nlm.nih.gov/pubmed/32304498. https://doi.org/10.2106/JBJS.RVW.19.00174.
79. Karri J, Palmer JS, Charnay A, et al. Utility of electrical neuromodulation for treating chronic pain syndromes in the pediatric setting: a systematic review. Neuromodulation (Malden, Mass.). 2021. https://www.ncbi.nlm.nih.gov/pubmed/33556220. https://doi.org/10.1111/ner.13365.
80. Guite JW, Sherry DD, Jarvis EW, Lewen MO, Khan S, Kraemer FW. Medication use among pediatric patients with chronic musculoskeletal pain syndromes at initial pain clinic evaluation. Pain Manag (London). 2018;8(1):15–25. https://doi.org/10.2217/pmt-2017-0034.
81. Pinckard-Dover H, Palmer A, Petersen EA. A review of neuromodulation for treatment of complex regional pain syndrome in pediatric patients and novel use of dorsal root ganglion stimulation in an adolescent patient with 30-Month Follow-Up. Neuromodulation (Malden, Mass.). 2021;24(4):634–8. https://onlinelibrary.wiley.com/doi/abs/10.1111/ner.13257. https://doi.org/10.1111/ner.13257.
82. Bakr SM, Knight J, Johnson SK, Williams AE, Tolley JA, Raskin JS. Spinal cord stimulation improves functional outcomes in children with complex regional pain syndrome: case presentation and review of the literature. Pain Practice. 2020;20(6):647–55. https://onlinelibrary.wiley.com/doi/abs/10.1111/papr.12882. https://doi.org/10.1111/papr.12882.
83. Henderson J. Updated guidelines on complex regional pain syndrome in adults. J Plast Reconstr Aesthet Surg. 2019;72(1):1–3. https://doi.org/10.1016/j.bjps.2018.08.017.
84. Schwartzman RJ, Alexander GM, Grothusen J. Pathophysiology of complex regional pain syndrome. Expert Rev Neurother. 2006;6(5):669–81. http://www.tandfonline.com/doi/abs/10.1586/14737175.6.5.669. https://doi.org/10.1586/14737175.6.5.669.
85. Yvon A, Faroni A, Reid AJ, Lees VC. Selective fiber degeneration in the peripheral nerve of a patient with severe complex regional pain syndrome. Front Neurosci. 2018;12:207. https://www.ncbi.nlm.nih.gov/pubmed/29670505. https://doi.org/10.3389/fnins.2018.00207.
86. Woolf CJ. Central sensitization: implications for the diagnosis and treatment of pain. Pain (Amsterdam). 2011;152(3):S2–15. https://doi.org/10.1016/j.pain.2010.09.030.
87. Di Pietro F, McAuley JH, Parkitny L, et al. Primary somatosensory cortex function in complex regional pain syndrome: a systematic review and meta-analysis. J Pain. 2013;14(10):1001–18. https://www.clinicalkey.es/playcontent/1-s2.0-S1526590013009371. https://doi.org/10.1016/j.jpain.2013.04.001.
88. Maihöfner C, Forster C, Birklein F, Neundörfer B, Handwerker HO. Brain processing during mechanical hyperalgesia in complex regional pain syndrome: a functional MRI study. Pain (Amsterdam). 2005;114(1):93–103. https://doi.org/10.1016/j.pain.2004.12.001.
89. Barad MJ, Ueno T, Younger J, Chatterjee N, Mackey S. Complex regional pain syndrome is associated with structural abnormalities in pain-related regions of the human brain. J Pain. 2014;15(2):197–203. https://www.clinicalkey.es/playcontent/1-s2.0-S1526590013013527. https://doi.org/10.1016/j.jpain.2013.10.011.
90. Hotta J, Saari J, Koskinen M, Hlushchuk Y, Forss N, Hari R. Abnormal brain responses to action observation in complex regional pain syndrome. J Pain. 2016;18(3):255–65. https://www.clinicalkey.es/playcontent/1-s2.0-S1526590016303091. https://doi.org/10.1016/j.jpain.2016.10.017.
91. van Rijn MA, Marinus J, Putter H, van Hilten JJ. Onset and progression of dystonia in complex regional pain syndrome. Pain (Amsterdam). 2007;130(3):287–93. https://doi.org/10.1016/j.pain.2007.03.027.
92. Misidou C, Papagoras C. Complex regional pain syndrome: an update. Mediterr J Rheumatol. 2019;30(1):16–25. https://www.ncbi.nlm.nih.gov/pubmed/32185338. https://doi.org/10.31138/mjr.30.1.16.
93. Azqueta-Gavaldon M, Schulte-Göcking H, Storz C, et al. Basal ganglia dysfunction in complex regional pain syndrome – a valid hypothesis? Eur J Pain. 2017;21(3):415–24. https://onlinelibrary.

wiley.com/doi/abs/10.1002/ejp.975. https://doi.org/10.1002/ejp.975.
94. Bussa M, Mascaro A, Cuffaro L, Rinaldi S. Adult complex regional pain syndrome type I: a narrative review. PM & R. 2016;9(7):707–19. https://www.clinicalkey.es/playcontent/1-s2.0-S1934148216311777. https://doi.org/10.1016/j.pmrj.2016.11.006.
95. Littlejohn G. Neurogenic neuroinflammation in fibromyalgia and complex regional pain syndrome. Nat Rev Rheumatol. 2015;11(11):639–48. https://www.ncbi.nlm.nih.gov/pubmed/26241184. https://doi.org/10.1038/nrrheum.2015.100.
96. Parkitny L, Mcauley JH, Di Pietro F, et al. Inflammation in complex regional pain syndrome: a systematic review and meta-analysis. Neurology. 2013;80(1):106–17. https://www.ncbi.nlm.nih.gov/pubmed/23267031. https://doi.org/10.1212/WNL.0b013e31827b1aa1.
97. de Rooij AM, de Mos M, Sturkenboom MCJM, Marinus J, van den Maagdenberg AMJM, van Hilten JJ. Familial occurrence of complex regional pain syndrome. Eur J Pain. 2008;13(2):171–7. https://www.clinicalkey.es/playcontent/1-s2.0-S1090380108000815. https://doi.org/10.1016/j.ejpain.2008.04.004.
98. Janicki PK, Alexander GM, Eckert J, Postula M, Schwartzman RJ. Analysis of common single nucleotide polymorphisms in complex regional pain syndrome: genome wide association study approach and pooled DNA strategy. Pain Med (Malden, Mass.). 2016;17(12):2344–52. https://www.ncbi.nlm.nih.gov/pubmed/28025368. https://doi.org/10.1093/pm/pnw133.
99. Albrecht PJ, Hines S, Eisenberg E, et al. Pathologic alterations of cutaneous innervation and vasculature in affected limbs from patients with complex regional pain syndrome. Pain (Amsterdam). 2006;120(3):244–66. https://doi.org/10.1016/j.pain.2005.10.035.
100. Oaklander AL, Fields HL. Is reflex sympathetic dystrophy/complex regional pain syndrome type I a small-fiber neuropathy? Ann Neurol. 2009;65(6):629–38. https://api.istex.fr/ark:/67375/WNG-CLLNTRRW-W/fulltext.pdf. https://doi.org/10.1002/ana.21692.
101. Van Der Laan L, Ter Laak HJ, Gabreëls-Festen A, Gabreëls F, Goris RJA. Complex regional pain syndrome type I (RSD): pathology of skeletal muscle and peripheral nerve. Neurology. 1998;51(1):20–5. https://www.ncbi.nlm.nih.gov/pubmed/9674773. https://doi.org/10.1212/WNL.51.1.20.
102. Terkelsen AJ, Mølgaard H, Hansen J, Finnerup NB, Kroner K, Jensen TS. Heart rate variability in complex regional pain syndrome during rest and mental and orthostatic stress. Anesthesiology (Philadelphia). 2012;116(1):133–46. https://www.ncbi.nlm.nih.gov/pubmed/22089824. https://doi.org/10.1097/ALN.0b013e31823bbfb0.
103. Jänig W, Baron R. Complex regional pain syndrome: mystery explained? Lancet Neurol. 2003;2(11):687–97. https://doi.org/10.1016/S1474-4422(03)00557-X.
104. Finch PM, Drummond ES, Dawson LF, Phillips JK, Drummond PD. Up-regulation of cutaneous α1-adrenoceptors in complex regional pain syndrome type I. Pain Med (Malden, Mass.). 2014;15(11):1945–1956. https://onlinelibrary.wiley.com/doi/abs/10.1111/pme.12548. https://doi.org/10.1111/pme.12548.
105. Mailis-Gagnon A, Bennett GJ. Abnormal contralateral pain responses from an intradermal injection of phenylephrine in a subset of patients with complex regional pain syndrome (CRPS). Pain (Amsterdam). 2004;111(3):378–84. https://doi.org/10.1016/j.pain.2004.07.019.
106. Kohr D, Singh P, Tschernatsch M, et al. Autoimmunity against the β 2 adrenergic receptor and muscarinic-2 receptor in complex regional pain syndrome. Pain (Amsterdam). 2011;152(12):2690–700. https://doi.org/10.1016/j.pain.2011.06.012.
107. Dubuis E, Thompson V, Leite MI, et al. Longstanding complex regional pain syndrome is associated with activating autoantibodies against alpha-1a adrenoceptors. Pain (Amsterdam). 2014;155(11):2408–17. https://doi.org/10.1016/j.pain.2014.09.022.
108. Li W, Guo T, Shi X, et al. Autoimmunity contributes to nociceptive sensitization in a mouse model of complex regional pain syndrome. Pain (Amsterdam). 2014;155(11):2377–89. https://doi.org/10.1016/j.pain.2014.09.007.
109. Guo T, Shi X, Li W, Wei T, Clark JD, Kingery WS. Passive transfer autoimmunity in a mouse model of complex regional pain syndrome. Pain (Amsterdam). 2017;158(12):2410–21. https://www.ncbi.nlm.nih.gov/pubmed/28891866. https://doi.org/10.1097/j.pain.0000000000001046.
110. Bean D, Johnson M, Kydd R. Relationships between psychological factors, pain, and disability in complex regional pain syndrome and low back pain. Clin J Pain. 2014;30(8):647–653. https://www.ncbi.nlm.nih.gov/pubmed/24135903. https://doi.org/10.1097/AJP.0000000000000007.
111. Beerthuizen A, Stronks DL, Huygen FJPM, Passchier J, Klein J, Spijker AV. The association between psychological factors and the development of complex regional pain syndrome type 1 (CRPS1) – a prospective multicenter study. Eur J Pain. 2011;15(9):971–75. https://www.clinicalkey.es/playcontent/1-s2.0-S1090380111000632. https://doi.org/10.1016/j.ejpain.2011.02.008.
112. Bullen M, Lang C, Tran P. Incidence of complex regional pain syndrome I following foot and ankle fractures using the Budapest criteria. Pain Med (Malden, Mass.). 2016;17(12):2353. https://www.ncbi.nlm.nih.gov/pubmed/28025369.
113. Oh S, Choi S, Park M, Shin J. Validity of the budapest criteria for poststroke complex regional pain syndrome. Clin J Pain. 2019;35(10):831–35. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&NEWS=n&CSC=Y&PAGE=fulltext&D=ovft&AN=00002508-201910000-00004. https://doi.org/10.1097/AJP.0000000000000741.
114. V Pergolizzi J, LeQuang JA, Nalamachu S, Taylor R, Bigelsen RW. The Budapest criteria for complex regional pain syndrome: the diagnostic challenge. Anesthesiol Clin Sci Res. 2018;2(1). https://doi.org/10.35841/anesthesiology.2.1.1-10.
115. Jänsch P, Asmus A, Pappa-Eisenschenk S, Eisenschenk A, Miillrose M, Diehl J, Kim S. Diagnostic accuracy of hand surgeons and pain specialists in diagnosing CRPS based on the Budapest criteria. 2020.
116. Bass C. Complex regional pain syndrome medicalises limb pain. BMJ Br Med J. 2014;348:g2631. https://doi.org/10.1136/bmj.g2631.
117. del Piñal F. Editorial: I have a dream … reflex sympathetic dystrophy (RSD or complex regional pain syndrome - CRPS I) does not exist. J Hand Surg Eur Vol. 2013;38(6):595–97. https://journals.sagepub.com/doi/full/10.1177/1753193413477058. https://doi.org/10.1177/1753193413477058.
118. Basler MH, Rae CP, Stewart G. Diagnosis of complex regional pain syndrome needs to be tightened. BMJ Br Med J. 2014;348:4029. https://doi.org/10.1136/bmj.g4029.
119. Bruehl S, Harden RN, Galer BS, Saltz S, Backonja M, Stanton-Hicks M. Complex regional pain syndrome: are there distinct subtypes and sequential stages of the syndrome? Pain (Amsterdam). 2002;95(1):119–24. https://doi.org/10.1016/S0304-3959(01)00387-6.
120. Żyluk A, Puchalski P. Complex regional pain syndrome: observations on diagnosis, treatment and definition of a new subgroup. J H Surg Eur Vol. 2013;38(6):599–606. https://journals.sagepub.com/doi/full/10.1177/1753193412469143. https://doi.org/10.1177/1753193412469143.
121. Bruehl S, Maihoefner C, Stanton-Hicks M, et al. Complex regional pain syndrome: evidence for warm and cold subtypes in a large prospective clinical sample. Pain (Amsterdam). 2016;157(8):1674–81. https://www.narcis.nl/publication/RecordID/oai:pure.atira.dk:publications%2Fb95c60f5-3920-44fc-af72-1a33c570bb97. https://doi.org/10.1097/j.pain.0000000000000569.

122. Dimova V, Herrnberger M, Escolano-Lozano F, et al. Clinical phenotypes and classification algorithm for complex regional pain syndrome. Neurology. 2020;94(4):e357-67. https://www.ncbi.nlm.nih.gov/pubmed/31874923. https://doi.org/10.1212/WNL.0000000000008736.
123. Goebel A, Birklein F, Brunner F, et al. The Valencia consensus-based adaptation of the IASP complex regional pain syndrome diagnostic criteria. Pain (Amsterdam). 2021;Publish Ahead of Print(9):2346–48. https://search.proquest.com/docview/2502212445. https://doi.org/10.1097/j.pain.0000000000002245.
124. van de Vusse AC, Stomp-van den Berg SG, Kessels AH, Weber WE. Randomised controlled trial of gabapentin in complex regional pain syndrome type 1. [ISRCTN84121379]. BMC Neurol. 2004;4:13. https://doi.org/10.1186/1471-2377-4-13. PMID: 15453912; PMCID: PMC523854.
125. Brown S, Johnston B, Amaria K, et al. A randomized controlled trial of amitriptyline versus gabapentin for complex regional pain syndrome type I and neuropathic pain in children. Scand J Pain. 2016;13:156e63 –.
126. Javed S, Abdi S. Use of anticonvulsants and antidepressants for treatment of complex regional pain syndrome: a literature review. Pain Manag (London). 2021;11(2):189–99. https://doi.org/10.2217/pmt-2020-0060.
127. Dey S, Guthmiller K, Varacallo M. Complex regional pain syndrome. Treasure Island, FL: StatPearls Publishing; 2021.
128. Pina M, Messina J, Geaney L. Persistent nerve injury and CRPS after ankle sprains. Techniques in Foot & Ankle Surgery. 2021;Publish Ahead of Print. https://doi.org/10.1097/BTF.0000000000000314.
129. Rowbotham M. Pharmacologic management of complex regional pain syndrome. Clin J Pain. 2006;22(5):425–9. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&NEWS=n&CSC=Y&PAGE=fulltext&D=ovft&AN=00002508-200606000-00004. https://doi.org/10.1097/01.ajp.0000194281.74379.01.
130. Mackey S, Feinberg S. Pharmacologic therapies for complex regional pain syndrome. Curr Pain Headache Rep. 2007;11(1):38–43. https://www.ncbi.nlm.nih.gov/pubmed/17214920. https://doi.org/10.1007/s11916-007-0020-z.
131. Chang C, McDonnell P, Gershwin ME. Complex regional pain syndrome – false hopes and miscommunications. Autoimmun Rev. 2019;18(3):270–8. https://doi.org/10.1016/j.autrev.2018.10.003.
132. Goncalves D, Rebelo V, Barbosa P, Gomes A. 8% capsaicin patch in treatment of peripheral neuropathic pain. Pain Physician. 2020;23(5):E541–8. https://www.ncbi.nlm.nih.gov/pubmed/32967405. https://doi.org/10.36076/ppj.2020/23/E541.
133. Rand SE, Basu S, Khalid S. Complex regional pain syndrome: current diagnostic and treatment considerations. Curr Sports Med Rep. 2019;18(9):325–9. https://www.ncbi.nlm.nih.gov/pubmed/31503044. https://doi.org/10.1249/JSR.0000000000000633.
134. Onofrio S, Vartan CM, Nazario M, DiScala S, Cuevas-Trisan R, Melendez-Benabe J. The use of transdermal buprenorphine in complex regional pain syndrome: a report of two cases. J Pain Palliat Care Pharmacother. 2016;30(2):124–7. http://www.tandfonline.com/doi/abs/10.3109/15360288.2016.1173756. https://doi.org/10.3109/15360288.2016.1173756.
135. Wiffen PJ, Derry S, Moore RA, et al. Buprenorphine for neuropathic pain in adults. Cochrane Libr. 2015;2019(5):CD011603. https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD011603.pub2. https://doi.org/10.1002/14651858.CD011603.pub2.
136. Cowell F, Gillespie S, Narayan B, Goebel A. Complex regional pain syndrome (CRPS) in orthopaedics: an overview. Orthop Trauma. 2019;33(4):217–23. https://doi.org/10.1016/j.mporth.2019.05.003.
137. Elomaa M, Hotta J, de C Williams, AC, et al. Symptom reduction and improved function in chronic CRPS type 1 after 12-week integrated, interdisciplinary therapy. Scand J Pain. 2019;19(2):257–70. http://www.degruyter.com/doi/10.1515/sjpain-2018-0098. https://doi.org/10.1515/sjpain-2018-0098.
138. Resmini G, Ratti C, Canton G, Murena L, Moretti A, Iolascon G. Treatment of complex regional pain syndrome. Clin Cases Miner Bone Metab. 2015;12(1):26–30.
139. Brinkers M, Rumpelt P, Lux A, Kretzschmar M, Pfau G. Psychiatric disorders in complex regional pain syndrome (CRPS): the role of the consultation-liaison psychiatrist. Pain Res Manage. 2018;2018:2894360–8. https://doi.org/10.1155/2018/2894360.
140. Helyes Z, Tékus V, Szentes N, et al. Transfer of complex regional pain syndrome to mice via human autoantibodies is mediated by interleukin-1-induced mechanisms. Proc Natl Acad Sci - PNAS. 2019;116(26):13067–76. https://www.ncbi.nlm.nih.gov/pubmed/31182576. https://doi.org/10.1073/pnas.1820168116.
141. Russo MA, Fiore NT, van Vreden C, et al. Expansion and activation of distinct central memory T lymphocyte subsets in complex regional pain syndrome. J Neuroinflammation. 2019;16(1):63. https://www.ncbi.nlm.nih.gov/pubmed/30885223. https://doi.org/10.1186/s12974-019-1449-9.
142. Heyn J, Azad SC, Luchting B. Altered regulation of the T-cell system in patients with CRPS. Inflamm Res. 2018;68(1):1–6. https://link.springer.com/article/10.1007/s00011-018-1182-3. https://doi.org/10.1007/s00011-018-1182-3.
143. Kumowski N, Hegelmaier T, Kolbenschlag J, Mainka T, Michel-Lauter B, Maier C. Short-term glucocorticoid treatment normalizes the microcirculatory response to remote ischemic conditioning in early complex regional pain syndrome. Pain Practice. 2019;19(2):168–75. https://onlinelibrary.wiley.com/doi/abs/10.1111/papr.12730. https://doi.org/10.1111/papr.12730.
144. Żyluk A, Puchalski P. Effectiveness of complex regional pain syndrome treatment: a systematic review. Neurol Neurochir Pol. 2018;52(3):326–33. https://doi.org/10.1016/j.pjnns.2018.03.001.
145. Jamroz A, Berger M, Winston P. Prednisone for acute complex regional pain syndrome: a retrospective cohort study. Pain Res Manage. 2020;2020:8182569–610. https://doi.org/10.1155/2020/8182569.
146. Pai RS, Vas L. Ultrasound-guided intra-articular injection of the radio-ulnar and radio-humeral joints and ultrasound-guided dry needling of the affected limb muscles to relieve fixed pronation deformity and myofascial issues around the shoulder, in a case of complex regional pain syndrome type 1. Pain Practice. 2018;18(2):273–82. https://onlinelibrary.wiley.com/doi/abs/10.1111/papr.12596. https://doi.org/10.1111/papr.12596.
147. Zych-Litwin C, Litwin JA. Complex regional pain syndrome: diagnosis and treatment at the very onset as the key to success? A case report with implications for first contact doctors. Reumatologia. 2019;57(2):117–9. https://www.ncbi.nlm.nih.gov/pubmed/31130751. https://doi.org/10.5114/reum.2019.84818.
148. Park S, Kim H, Kim DK, Kim TH. Use of oral prednisolone and a 3-phase bone scintigraphy in patients with complex regional pain syndrome type I. Healthcare (Basel). 2020;8(1):16. https://www.ncbi.nlm.nih.gov/pubmed/31936474. https://doi.org/10.3390/healthcare8010016.
149. Haight ES, Johnson EM, Carroll IR, Tawfik VL. Of mice, microglia, and (wo)men: a case series and mechanistic investigation of hydroxychloroquine for complex regional pain syndrome. Pain Rep. 2020;5(5):e841. https://doi.org/10.1097/PR9.0000000000000841. PMID: 33490839; PMCID: PMC7808678.
150. Goebel A, Jacob A, Frank B, et al. Mycophenolate for persistent complex regional pain syndrome, a parallel, open, randomised, proof of concept trial. Scand J Pain. 2018;18(1):29–37. http://www.degruyter.com/doi/10.1515/sjpain-2017-0154. https://doi.org/10.1515/sjpain-2017-0154.
151. Dunbar J, Wilson H. Emerging models for successful treatment of complex regional pain syndrome in children and young

adults. J Prim Health Care. 2019;11(3):283–7. https://natlib-primo.hosted.exlibrisgroup.com/primo-explore/search?query=any,contains,9990184061028 37&tab=innz&search_scope=INNZ&vid=NLNZ&offset=0. https://doi.org/10.1071/HC19025.
152. Goebel A, Barker C, Birklein F, et al. Standards for the diagnosis and management of complex regional pain syndrome: results of a European pain federation task force. Eur J Pain. 2019;23(4):641–51. https://www.narcis.nl/publication/RecordID/oai:pure.atira.dk:publications%2F51dc354d-759f-40e8-8590-361a8635bc3a. https://doi.org/10.1002/ejp.1362.
153. Baygutalp F, Kul A. Effect of early orthopedic rehabilitation on development of complex regional pain syndrome type 1. Eurasian J Med. 2020;52(2):110–4. https://search.proquest.com/docview/2419713209. https://doi.org/10.5152/eurasianjmed.2020.19231.
154. Packham T, Holly J. Mechanism-specific rehabilitation management of complex regional pain syndrome: proposed recommendations from evidence synthesis. J Hand Ther. 2018;31(2):238–49. https://doi.org/10.1016/j.jht.2018.01.007.
155. Oh H, Kim C, Kim A. Dramatic effect in passive ROM exercise under sedation in a patient with intractable complex regional pain syndrome (type I): a case report. Medicine (Baltimore). 2019;98(13):e14990. https://www.ncbi.nlm.nih.gov/pubmed/30921212. https://doi.org/10.1097/MD.0000000000014990.
156. Smart KM, Ferraro MC, Wand BM, O'Connell NE. Physiotherapy for pain and disability in adults with complex regional pain syndrome (CRPS) types I and II. Cochrane Database Syst Rev. 2022;5(5):CD010853. https://doi.org/10.1002/14651858.CD010853.pub3. PMID: 35579382; PMCID: PMC9112661.
157. Tubic G. Epidural anesthesia to effectively manage pain and facilitate rehabilitation in a pediatric case of complex regional pain syndrome. Pain Medicine Case Reports. 2018:209–12. https://doi.org/10.36076/pmcr.2018/2/209.
158. Boichat C, Llewellyn A, Grieve S, McCabe C. The role of nonmedical therapeutic approaches in the rehabilitation of complex regional pain syndrome. Curr Treat Options in Rheum. 2020;6(3):299–311. https://link.springer.com/article/10.1007/s40674-020-00156-9. https://doi.org/10.1007/s40674-020-00156-9.
159. Altas EU, Onat ŞŞ, Konak HE, Polat CS. Post-stroke complex regional pain syndrome and related factors: experiences from a tertiary rehabilitation center. J Stroke Cerebrovasc Dis. 2020;29(9):104995. https://doi.org/10.1016/j.jstrokecerebrovasdis.2020.104995.
160. Smart KM, Wand BM, O'Connell NE, Smart KM. Physiotherapy for pain and disability in adults with complex regional pain syndrome (CRPS) types I and II. Cochrane Libr. 2016;2016(3):CD010853. https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD010853.pub2. https://doi.org/10.1002/14651858.CD010853.pub2.
161. Wong BJ, Yoon IA, Krane EJ. Outcome in young adults who were diagnosed with complex regional pain syndrome in childhood and adolescence. Pain Rep. 2020;5(6):e860. https://search.proquest.com/docview/2456855564. https://doi.org/10.1097/PR9.0000000000000860.
162. González-Cantero Á, Sánchez-Moya AI, Pérez-Hortet C, et al. Complex regional pain syndrome of the face in a child. Int J Dermatol. 2018;57(12):1502–3. https://onlinelibrary.wiley.com/doi/abs/10.1111/ijd.14045. https://doi.org/10.1111/ijd.14045.
163. Burian A, Schuhfried O, Crevenna R. A mysterious case of complex regional pain syndrome in a 9-year-old girl. Disabil Rehab. 2019;41(8):9913. http://www.tandfonline.com/doi/abs/10.1080/09638288.2017.1413430. https://doi.org/10.1080/09638288.2017.1413430.
164. Martini G, Viale S, Sequi G, Ambrosio F. Infrared thermography in paediatric complex regional pain syndrome. Arch Dis Child. 2021;106(9):841. https://doi.org/10.1136/archdischild-2020-319949.
165. Gutiérrez-Espinoza H, Tabach-Apraiz A, Oyanadel-Maldonado M. Physical therapy in patients with complex regional pain syndrome type I after distal radius fracture: a case series. J Phys Ther Sci. 2019;31(4):403–7. https://www.jstage.jst.go.jp/article/jpts/31/4/31_jpts-2018-426/_article/-char/en. https://doi.org/10.1589/jpts.31.403.
166. Storz C, Schulte-Göcking H, Woiczinski M, Azqueta-Gavaldon M, Azad SC, Kraft E. Exergames for patients with complex regional pain syndrome : a feasibility study. Schmerz (Berlin, Germany). 2020;34(2):166–171. https://www.ncbi.nlm.nih.gov/pubmed/32095887. https://doi.org/10.1007/s00482-019-00436-x.
167. Tobaigy A, Alshehri MA, Timmons S, Helal OF. The feasibility of using exergames as a rehabilitation tool: the attitudes, awareness, opinions and experiences of physiotherapists, and older people towards exergames. J Phys Ther Sci. 2018;30(4):555–62. https://www.jstage.jst.go.jp/article/jpts/30/4/30_jpts-2017-614/_article/-char/en. https://doi.org/10.1589/jpts.30.555.
168. Barnhoorn K, Staal JB, van Dongen RTM, et al. Pain exposure physical therapy versus conventional treatment in complex regional pain syndrome type 1-a cost-effectiveness analysis alongside a RCT. Clin Rehabil. 2018;32(6):790–8. https://www.narcis.nl/publication/RecordID/oai:hbokennisbank.nl:repository_han:oai:repository.han.nl:20.500.12470%2F1123. https://doi.org/10.1177/0269215518757050.
169. Staal JB, Klomp FP, Nijhuis-van der Sanden MWG. Pain exposure physical therapy in complex regional pain syndrome: promising enough to warrant further investigation. Can J Anesth/J Can Anesth. 2018;66(1):115–6. https://www.narcis.nl/publication/RecordID/oai:hbokennisbank.nl:repository_han:oai:repository.han.nl:20.500.12470%2F1122. https://doi.org/10.1007/s12630-018-1173-4.
170. Duong S, Bravo D, Todd KJ, Finlayson RJ, Tran Q. Treatment of complex regional pain syndrome: an updated systematic review and narrative synthesis. Can J Anaesth. 2018;65(6):658–84. English. https://doi.org/10.1007/s12630-018-1091-5. Epub 2018 Feb 28. PMID: 29492826.
171. Kriek N, Schreurs MWJ, Groeneweg JG, et al. Spinal cord stimulation in patients with complex regional pain syndrome: a possible target for immunomodulation? Neuromodulation (Malden, Mass.). 2018;21(1):77–86. https://onlinelibrary.wiley.com/doi/abs/10.1111/ner.12704. https://doi.org/10.1111/ner.12704.
172. Mekhail N, Costandi S, Mehanny DS, et al. The impact of tobacco smoking on spinal cord stimulation effectiveness in complex regional pain syndrome patients. Neuromodulation (Malden, Mass.). 2020;23(1):133–9. https://onlinelibrary.wiley.com/doi/abs/10.1111/ner.13058. https://doi.org/10.1111/ner.13058.
173. Kumar K, Rizvi S, Bnurs SB. Spinal cord stimulation is effective in management of complex regional pain syndrome I: fact or fiction. Neurosurgery. 2011;69(3):566–80. https://www.ncbi.nlm.nih.gov/pubmed/21441839. https://doi.org/10.1227/NEU.0b013e3182181e60.
174. Lee SJ, Yoo YM, You JA, et al. Successful removal of permanent spinal cord stimulators in patients with complex regional pain syndrome after complete relief of pain. Korean J Pain. 2019;32(1):47–50. http://kiss.kstudy.com/thesis/thesis-view.asp?key=3658307.
175. O'Connell NE, Wand BM, McAuley J, Marston L, Moseley GL. Interventions for treating pain and disability in adults with complex regional pain syndrome. Cochrane Database Syst Rev. 2013(4):CD009416. https://www.ncbi.nlm.nih.gov/pubmed/23633371. https://doi.org/10.1002/14651858.CD009416.pub2.
176. Wie C, Gupta R, Maloney J, Pew S, Freeman J, Strand N. Interventional modalities to treat complex regional pain syndrome. Curr Pain Headache Rep. 2021;25(2):10. https://link.springer.

com/article/10.1007/s11916-020-00904-5. https://doi.org/10.1007/s11916-020-00904-5.
177. Gill JS, Asgerally A, Simopoulos TT. High-Frequency spinal cord stimulation at 10 kHz for the treatment of complex regional pain syndrome: a case series of patients with or without previous spinal cord stimulator implantation. Pain Pract. 2019;19(3):289–94. https://onlinelibrary.wiley.com/doi/abs/10.1111/papr.12739. https://doi.org/10.1111/papr.12739.
178. Canós-Verdecho A, Abejón D, Robledo R, et al. Randomized prospective study in patients with complex regional pain syndrome of the upper limb with high-frequency spinal cord stimulation (10-kHz) and low-frequency spinal cord stimulation. Neuromodulation (Malden, Mass.). 2021;24(3):448–58. https://onlinelibrary.wiley.com/doi/abs/10.1111/ner.13358. https://doi.org/10.1111/ner.13358.
179. Gravius N, Chaudhry SR, Muhammad S, et al. Selective L4 dorsal root ganglion stimulation evokes pain relief and changes of inflammatory markers: part I profiling of saliva and serum molecular patterns. Neuromodulation (Malden, Mass.). 2019;22(1):44–52. https://onlinelibrary.wiley.com/doi/abs/10.1111/ner.12866. https://doi.org/10.1111/ner.12866.
180. Bussel CM, Stronks DL, Huygen FJPM. Dorsal column stimulation vs. dorsal root ganglion stimulation for complex regional pain syndrome confined to the knee: patients' preference following the trial period. Pain Pract. 2018;18(1):87–93. https://onlinelibrary.wiley.com/doi/abs/10.1111/papr.12573. https://doi.org/10.1111/papr.12573.
181. Deer TR, Levy RM, Kramer J, et al. Dorsal root ganglion stimulation yielded higher treatment success rate for complex regional pain syndrome and causalgia at 3 and 12 months: a randomized comparative trial. Pain (Amsterdam). 2017;158(4):669–81. https://www.ncbi.nlm.nih.gov/pubmed/28030470. https://doi.org/10.1097/j.pain.0000000000000814.
182. Levy RM, Mekhail N, Kramer J, et al. Therapy habituation at 12 months: spinal cord stimulation versus dorsal root ganglion stimulation for complex regional pain syndrome type I and II. J Pain. 2020;21(3–4):399–408. https://doi.org/10.1016/j.jpain.2019.08.005.
183. Goebel A, Lewis S, Phillip R, Sharma M. Dorsal root ganglion stimulation for complex regional pain syndrome (CRPS) recurrence after amputation for CRPS, and failure of conventional spinal cord stimulation. Pain Pract. 2018;18(1):104–8. https://onlinelibrary.wiley.com/doi/abs/10.1111/papr.12582. https://doi.org/10.1111/papr.12582
184. Pendem K, Jassal N. Dorsal root ganglion stimulation as treatment for complex regional pain syndrome of the foot refractory to spinal cord stimulation: a case report. Curēus (Palo Alto, CA). 2021;13(1):e12753. https://www.ncbi.nlm.nih.gov/pubmed/33614347.
185. Mekhail N, Deer TR, Poree L, et al. Cost-Effectiveness of dorsal root ganglion stimulation or spinal cord stimulation for complex regional pain syndrome. Neuromodulation (Malden, Mass.). 2021;24(4):708–718. https://onlinelibrary.wiley.com/doi/abs/10.1111/ner.13134. https://doi.org/10.1111/ner.13134.
186. Ghosh P, Gungor S. Utilization of concurrent dorsal root ganglion stimulation and dorsal column spinal cord stimulation in complex regional pain syndrome. Neuromodulation (Malden, Mass.). 2021;24(4):769–73. https://onlinelibrary.wiley.com/doi/abs/10.1111/ner.13144. https://doi.org/10.1111/ner.13144.
187. Fritz AV, Ferreira-Dos-Santos G, Hurdle MF, Clendenen S. Ultrasound-guided percutaneous peripheral nerve stimulation for the treatment of complex regional pain syndrome type 1 following a crush injury to the fifth digit: a rare case report. Curēus (Palo Alto, CA). 2019;11(12):e6506. https://www.ncbi.nlm.nih.gov/pubmed/32025427. https://doi.org/10.7759/cureus.6506.
188. Frederico TN, da Silva Freitas T. Peripheral nerve stimulation of the brachial plexus for chronic refractory CRPS pain of the upper limb: description of a new technique and case series. Pain Med (Malden, Mass.). 2020;21(Supplement_1):S18–26. https://www.ncbi.nlm.nih.gov/pubmed/32804227. https://doi.org/10.1093/pm/pnaa201.
189. Chmiela MA, Hendrickson M, Hale J, et al. Direct peripheral nerve stimulation for the treatment of complex regional pain syndrome: a 30-year review. Neuromodulation (Malden, Mass.). 2021;24(6):971–82. https://onlinelibrary.wiley.com/doi/abs/10.1111/ner.13295. https://doi.org/10.1111/ner.13295.
190. Herschkowitz D, Kubias J. A case report of wireless peripheral nerve stimulation for complex regional pain syndrome type-I of the upper extremity: 1 year follow up. Scand J Pain. 2019;19(4):829–35. http://www.degruyter.com/doi/10.1515/sjpain-2019-0071. https://doi.org/10.1515/sjpain-2019-0071.
191. Beytemür O, Tetikkurt ÜS, Yüksel S, Öncü M. A rare cause of type 1 complex regional pain syndrome: osteoblastoma of the talus. Acta Orthop Traumatol Turc. 2019;53(1):77–80. https://doi.org/10.1016/j.aott.2018.06.011.
192. Somers DL, Clemente FR. Transcutaneous electrical nerve stimulation for the management of neuropathic pain: the effects of frequency and electrode position on prevention of allodynia in a rat model of complex regional pain syndrome type II. Phys Ther. 2006;86(5):698–709. http://ptjournal.apta.org/content/86/5/698.abstract. https://doi.org/10.1093/ptj/86.5.698.
193. Bilgili A, Çakır T, Doğan ŞK, Erçalık T, Filiz MB, Toraman F. The effectiveness of transcutaneous electrical nerve stimulation in the management of patients with complex regional pain syndrome: a randomized, double-blinded, placebo-controlled prospective study. J Back Musculoskelet Rehabil. 2016;29(4):661–71. https://www.ncbi.nlm.nih.gov/pubmed/26922847. https://doi.org/10.3233/BMR-160667.
194. Gungor S, Aiyer R, Baykoca B. Sympathetic blocks for the treatment of complex regional pain syndrome: a case series. Medicine (Baltimore). 2018;97(19):e0705. https://www.ncbi.nlm.nih.gov/pubmed/29742728. https://doi.org/10.1097/MD.0000000000010705.
195. Imani F, Hemati K, Rahimzadeh P, Kazemi MR, Hejazian K. Effectiveness of stellate ganglion block under fuoroscopy or ultrasound guidance in upper extremity CRPS. J Clin Diagn Res. 2016;10(1):UC09–12. https://www.ncbi.nlm.nih.gov/pubmed/26894152. https://doi.org/10.7860/JCDR/2016/14476.7035.
196. Cheng J, Salmasi V, You J, et al. Outcomes of sympathetic blocks in the management of complex regional pain syndrome: a retrospective cohort study. Anesthesiology (Philadelphia). 2019;131(4):883–93. https://www.ncbi.nlm.nih.gov/pubmed/31365367. https://doi.org/10.1097/ALN.0000000000002899.
197. de Oliveira RR, Teixeira MJ, Yeng LT, et al. Thoracic sympathetic block for the treatment of complex regional pain syndrome type I: a double-blind randomized controlled study. Pain (Amsterdam). 2014;155(11):2274–81. https://doi.org/10.1016/j.pain.2014.08.015.
198. Lee Y, Lee CJ, Choi E, Lee PB, Lee H, Nahm FS. Lumbar sympathetic block with botulinum toxin type A and type B for the complex regional pain syndrome. Toxins. 2018;10(4):164. https://www.ncbi.nlm.nih.gov/pubmed/29671801. https://doi.org/10.3390/toxins10040164.
199. Nascimento MSA, Klamt JG, Prado WA. Intravenous regional block is similar to sympathetic ganglion block for pain management in patients with complex regional pain syndrome type I. Braz J Med Biol Res. 2010;43(12):1239–44. https://www.ncbi.nlm.nih.gov/pubmed/21085893. https://doi.org/10.1590/S0100-879X2010007500123.

200. Herman J, Urits I, Urman RD, Kaye AD, Viswanath O, Eskander JP. Combination of perineural dexamethasone and dexmedetomidine prolong analgesic duration of a supraclavicular block in a patient with complex regional pain syndrome. J Clin Anesth. 2020;65:109873. https://doi.org/10.1016/j.jclinane.2020.109873.
201. Kang SH, Sim WS, Park HJ, Moon JY, Seon HJ, Lee JY. Efficacy of adjuvant dexmedetomidine in supraclavicular brachial plexus block for intractable complex regional pain syndrome: a case report with a 3-year follow-up. J Clin Pharm Ther. 2020;45(2):365–7. https://onlinelibrary.wiley.com/doi/abs/10.1111/jcpt.13063. https://doi.org/10.1111/jcpt.13063.
202. Kim YH, Kim SY, Lee YJ, Kim ED. A prospective, randomized cross-over trial of T2 paravertebral block as a sympathetic block in complex regional pain syndrome. Pain Physician. 2019;22(5):E417–24. https://www.ncbi.nlm.nih.gov/pubmed/31561653.
203. Gungor S, Aiyer R. Extrapyramidal signs occurring after sympathetic block for complex regional pain syndrome responding to diphenhydramine. Medicine (Baltimore). 2018;97(26):e11301. https://search.proquest.com/docview/2061404049. https://doi.org/10.1097/MD.0000000000011301.
204. Connolly SB, Prager JP, Harden RN. A systematic review of ketamine for complex regional pain syndrome. Pain Med (Malden, Mass.). 2015;16(5):943–69. https://onlinelibrary.wiley.com/doi/abs/10.1111/pme.12675. https://doi.org/10.1111/pme.12675.
205. Azari P, Lindsay DR, Briones D, Clarke C, Buchheit T, Pyati S. Efficacy and safety of ketamine in patients with complex regional pain syndrome. CNS Drugs. 2012;26(3):215–28. https://link.springer.com/article/10.2165/11595200-000000000-00000. https://doi.org/10.2165/11595200-000000000-00000.
206. Sorel M, Zrek N, Locko B, Armessen C, Ayache SS, Lefaucheur J. A reappraisal of the mechanisms of action of ketamine to treat complex regional pain syndrome in the light of cortical excitability changes. Clin Neurophysiol. 2018;129(5):990–1000. https://doi.org/10.1016/j.clinph.2018.02.124.
207. Xu J, Herndon C, Anderson S, et al. Intravenous ketamine infusion for complex regional pain syndrome: survey, consensus, and a reference protocol. Pain Med (Malden, Mass.). 2019;20(2):323–34. https://www.ncbi.nlm.nih.gov/pubmed/29534218. https://doi.org/10.1093/pm/pny024.
208. Taylor S, Noor N, Urits I, et al. Complex regional pain syndrome: a comprehensive review. Pain Ther. 2021;10(2):875–92. https://link.springer.com/article/10.1007/s40122-021-00279-4. https://doi.org/10.1007/s40122-021-00279-4.
209. Birklein F, Ibrahim A, Schlereth T, Kingery WS. The rodent tibia fracture model: a critical review and comparison with the complex regional pain syndrome literature. J Pain. 2018;19(10):1102.e1-1102.e19. https://doi.org/10.1016/j.jpain.2018.03.018.
210. Mundluru T, Saraghi M. Anesthetic management of a complex regional pain syndrome (CRPS) patient with ketamine. Anesthesia Prog. 2020;67(4):219–25. https://www.ncbi.nlm.nih.gov/pubmed/33393601. https://doi.org/10.2344/anpr-67-02-07.
211. Kirkpatrick A, Saghafi A, Yang K, et al. Optimizing the treatment of CRPS with ketamine. Clin J Pain. 2020;36(7):516–23. https://www.ncbi.nlm.nih.gov/pubmed/32243301. https://doi.org/10.1097/AJP.0000000000000831.
212. Sigtermans MJ, van Hilten JJ, Bauer MCR, et al. Ketamine produces effective and long-term pain relief in patients with complex regional pain syndrome type 1. Pain (Amsterdam). 2009;145(3):304–11. https://doi.org/10.1016/j.pain.2009.06.023.
213. Schwartzman RJ, Alexander GM, Grothusen JR. The use of ketamine in complex regional pain syndrome: possible mechanisms. Expert Rev Neurother. 2011;11(5):719–34. http://www.tandfonline.com/doi/abs/10.1586/ern.11.31. https://doi.org/10.1586/ern.11.31.
214. Zhao J, Wang Y, Wang D. The effect of ketamine infusion in the treatment of complex regional pain syndrome: a systemic review and meta-analysis. Curr Pain Headache Rep. 2018;22(2):1–8. https://link.springer.com/article/10.1007/s11916-018-0664-x. https://doi.org/10.1007/s11916-018-0664-x.
215. Hewitt NA, Cox P. Recurrent subanesthetic ketamine infusions for complex regional pain syndrome leading to biliary dilation, jaundice, and cholangitis: a case report. A A Pract. 2018;10(7):168–70. https://www.ncbi.nlm.nih.gov/pubmed/29135531. https://doi.org/10.1213/XAA.0000000000000650.
216. Sorel M, Beatrix J, Locko B, et al. Three-phase bone scintigraphy can predict the analgesic efficacy of ketamine therapy in CRPS. Clin J Pain. 2018;34(9):831–37. https://www.ncbi.nlm.nih.gov/pubmed/29538095. https://doi.org/10.1097/AJP.0000000000000607.
217. van Hilten BJ, van de Beek WJ, Hoff JI, Voormolen JH, Delhaas EM. Intrathecal baclofen for the treatment of dystonia in patients with reflex sympathetic dystrophy. N Engl J Med. 2000;343(9):625–30. https://doi.org/10.1056/NEJM200008313430905. PMID: 10965009.
218. Rauck RL, Eisenach JC, Jackson K, Young LD, Southern J. Epidural clonidine treatment for refractory reflex sym-pathetic dystrophy [see comments]. Anesthesiology. 1993;79:1163–9.
219. Herring EZ, Frizon LA, Hogue O, et al. Long-term outcomes using intrathecal drug delivery systems in complex regional pain syndrome. Pain Med (Malden, Mass.). 2019;20(3):515–20. https://www.ncbi.nlm.nih.gov/pubmed/29889241. https://doi.org/10.1093/pm/pny104.
220. Lee BJ, Kim JY, Cho H, Park D. Sphingosine 1-phosphate receptor modulation attenuate mechanical allodynia in mouse model of chronic complex regional pain syndrome by suppressing pathogenic astrocyte activation. Reg Anesth Pain Med. 2020;45(3):230–8. https://doi.org/10.1136/rapm-2019-100801.
221. Kim J, Park J, Park D. Anti-allodynic effect of interleukin 10 in a mouse model of complex regional pain syndrome through reduction of NK1 receptor expression of microglia in the spinal cord. J Pain Res. 2018;11:1729–41. https://www.ncbi.nlm.nih.gov/pubmed/30233230. https://doi.org/10.2147/JPR.S166624.
222. Chevreau M, Romand X, Gaudin P, Juvin R, Baillet A. Bisphosphonates for treatment of complex regional pain syndrome type 1: a systematic literature review and meta-analysis of RCTs versus placebo. Joint Bone Spine. 2017;84(4):393–9. https://www.clinicalkey.es/playcontent/1-s2.0-S1297319X17300726. https://doi.org/10.1016/j.jbspin.2017.03.009.
223. Oehler N, Rolvien T, Schmidt T, et al. Bone microstructure is significantly altered in CRPS-affected distal tibiae as detected by HR-pQCT: a retrospective cross-sectional study. J Bone Miner Metab. 2018;37(4):741–48. https://link.springer.com/article/10.1007/s00774-018-0976-2. https://doi.org/10.1007/s00774-018-0976-2.
224. Varenna M, Crotti C. Bisphosphonates in the treatment of complex regional pain syndrome: is bone the main player at early stage of the disease? Rheumatol Int. 2018;38(11):1959–62. https://link.springer.com/article/10.1007/s00296-018-4101-6. https://doi.org/10.1007/s00296-018-4101-6.
225. Jogani A, Rathod T, Mohanty SS, Kamble P. Bimalleolar fracture: a unique case of complication of complex regional pain syndrome of lower extremity after prolonged undue immobilisation. J Orthop Case Rep. 2019;9(5):20–22. http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=7276611&tool=pmcentrez&rendertype=abstract. https://doi.org/10.13107/jocr.2019.v09.i05.1514.
226. Pruthi P, Arora P, Bahrani K, Mittal M. Complex regional pain syndrome with an unusual aetiology. Indian J Rheumatol. 2018;13(4):277–9. http://www.indianjrheumatol.com/article.asp?issn=0973-3698;year=2018;volume=13;issue=4;spage=277;epage=279;aulast=Pruthi;type=0. https://doi.org/10.4103/injr.injr_104_18.

227. Scholz-Odermatt SM, Luthi F, Wertli MM, Brunner F. Direct health care cost and work incapacity related to complex regional pain syndrome in Switzerland: a retrospective analysis from 2008 to 2015. Pain Med (Malden, Mass.). 2019;20(8):1559–69. https://www.ncbi.nlm.nih.gov/pubmed/30848817. https://doi.org/10.1093/pm/pnz030.
228. Benchouk S, Buchard P, Luthi F. Complex regional pain syndrome and bone marrow oedema syndrome: family ties potentially closer than expected. BMJ Case Rep. 2020;13(8):e234600. https://doi.org/10.1136/bcr-2020-234600.
229. Galluccio F, Allam AES, Perdisa F, Chang K. Short-term teriparatide for bone marrow edema secondary to complex regional pain syndrome: case reports on efficacy after two years of follow-up. Curēus (Palo Alto, CA). 2020;12(5):e8119. https://www.ncbi.nlm.nih.gov/pubmed/32426199. https://doi.org/10.7759/cureus.8119.
230. Mohiuddin M, Pivetta B, Gilron I, Khan JS. Efficacy and safety of N-acetylcysteine for the management of chronic pain in adults: a systematic review and meta-analysis. Pain Med. 2021;22(12):2896–907. https://doi.org/10.1093/pm/pnab042. PMID: 33560443.
231. Trofimovitch D, Baumrucker SJ. Pharmacology update: low-dose naltrexone as a possible nonopioid modality for some chronic, nonmalignant pain syndromes. Am J Hosp Palliat Med. 2019;36(10):907–12. https://journals.sagepub.com/doi/full/10.1177/1049909119838974. https://doi.org/10.1177/1049909119838974.
232. Chopra P, Cooper MS. Treatment of complex regional pain syndrome (CRPS) using low dose naltrexone (LDN). J Neuroimmune Pharmacol. 2013;8(3):470–6. https://link.springer.com/article/10.1007/s11481-013-9451-y. https://doi.org/10.1007/s11481-013-9451-y.
233. Ricci M, Fabbri L, Pirotti S, Ruffilli N, Foca F, Maltoni M. Scrambler therapy: what's new after 15 years? The results from 219 patients treated for chronic pain. Medicine (Baltimore). 2019;98(2):e13895. https://www.ncbi.nlm.nih.gov/pubmed/30633163. https://doi.org/10.1097/MD.0000000000013895.
234. Marineo G. Inside the scrambler therapy, a noninvasive treatment of chronic neuropathic and cancer pain: from the gate control theory to the active principle of information. Integr Cancer Ther. 2019;18:1534735419845143. https://journals.sagepub.com/doi/full/10.1177/1534735419845143. https://doi.org/10.1177/1534735419845143.
235. Raucci U, Tomasello C, Marri M, Salzano M, Gasparini A, Conicella E. Scrambler therapy® MC-5A for complex regional pain syndrome: case reports. Pain Pract. 2016;16(7):E103–9. https://api.istex.fr/ark:/67375/WNG-PLRHCDG4-R/fulltext.pdf. https://doi.org/10.1111/papr.12474.
236. Karri J, Marathe A, Smith TJ, Wang EJ. The use of scrambler therapy in treating chronic pain syndromes: a systematic review. Neuromodulation. 2022.
237. Kotiuk V, Burianov O, Kostrub O, Khimion L, Zasadnyuk I. The impact of mirror therapy on body schema perception in patients with complex regional pain syndrome after distal radius fractures. Br J Pain. 2019;13(1):35–42. https://journals.sagepub.com/doi/full/10.1177/2049463718782544. https://doi.org/10.1177/2049463718782544.
238. Ten Brink AF, Halicka M, Vittersø AD, Keogh E, Bultitude JH. Ignoring space around a painful limb? no evidence for a body-related visuospatial attention bias in complex regional pain syndrome. Cortex. 2021;136:89–108. https://doi.org/10.1016/j.cortex.2020.12.007.
239. Verfaille C, Filbrich L, Cordova Bulens D, et al. Robot-assisted line bisection in patients with complex regional pain syndrome. PLoS ONE. 2019;14(5):e0213732. https://www.ncbi.nlm.nih.gov/pubmed/31048861. https://doi.org/10.1371/journal.pone.0213732.
240. Diers M. Neuroimaging the pain network – implications for treatment. Best Pract Res Clin Rheumatol. 2019;33(3):101418. https://doi.org/10.1016/j.berh.2019.05.003.
241. Strauss S, Barby S, Härtner J, Neumann N, Moseley GL, Lotze M. Modifications in fMRI representation of mental rotation following a 6 week graded motor imagery training in chronic CRPS patients. J Pain. 2021;22(6):680–91. https://doi.org/10.1016/j.jpain.2020.12.003.
242. Hirakawa Y, Imai R, Shigetoh H, Morioka S. Intervention using body shadow to evoke loading imagery in a patient with complex regional pain syndrome in the foot: a case report. Brain Sci. 2020;10(10):1. http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=7600743&tool=pmcentrez&rendertype=abstract. https://doi.org/10.3390/brainsci10100718.
243. Sivanesan E, Goebel A. Complex regional pain syndrome: developing diagnostic tools and treatments from sympathetic nervous system, neuroimmune and neuromodulation discoveries in neuropathic pain. Reg Anesth Pain Med. 2021;46(3):193–5. https://doi.org/10.1136/rapm-2020-102327.
244. Almog S, Aharon-Peretz J, Vulfsons S, et al. The pharmacokinetics, efficacy, and safety of a novel selective-dose cannabis inhaler in patients with chronic pain: a randomized, double-blinded, placebo-controlled trial. Eur J Pain. 2020;24(8):1505–16. https://onlinelibrary.wiley.com/doi/abs/10.1002/ejp.1605. https://doi.org/10.1002/ejp.1605.
245. Rodrigues M, Cardoso RB, Kuriki HU, Marcolino AM, de Oliveira Guirro EC, Barbosa RI. Photobiomodulation decreases hyperalgesia in complex regional pain syndrome: an experimental mouse model subjected to nicotine. Lasers Surg Med. 2020. https://doi.org/10.1002/lsm.23240.
246. Ramanathan S, Douglas SR, Alexander GM, et al. Exosome microRNA signatures in patients with complex regional pain syndrome undergoing plasma exchange. J Transl Med. 2019;17(1):81. https://www.ncbi.nlm.nih.gov/pubmed/30871575. https://doi.org/10.1186/s12967-019-1833-3.
247. Aradillas E, Schwartzman RJ, Grothusen JR, Goebel A, Alexander GM. Plasma exchange therapy in patients with complex regional pain syndrome. Pain Physician. 2015;18(4):383–94. https://www.ncbi.nlm.nih.gov/pubmed/26218942. https://doi.org/10.36076/ppj.2015/18/383.
248. Chang MC, Kwak SG, Park D. The effect of rTMS in the management of pain associated with CRPS. Transl Neurosci. 2020;11(1):363–70. https://doi.org/10.1515/tnsci-2020-0120. PMID: 33335776; PMCID: PMC7711855.
249. Nardone R, Brigo F, Höller Y, et al. Transcranial magnetic stimulation studies in complex regional pain syndrome type I: a review. Acta Neurol Scand. 2018;137(2):158–64. https://onlinelibrary.wiley.com/doi/abs/10.1111/ane.12852. https://doi.org/10.1111/ane.12852.
250. Gaertner M, Kong J, Scherrer KH, Foote A, Mackey S, Johnson KA. Advancing transcranial magnetic stimulation methods for complex regional pain syndrome: an open-label study of paired theta burst and high-frequency stimulation. Neuromodulation (Malden, Mass.). 2018;21(4):409–16. https://onlinelibrary.wiley.com/doi/abs/10.1111/ner.12760. https://doi.org/10.1111/ner.12760.
251. Picarelli H, Teixeira MJ, de Andrade DC, et al. Repetitive transcranial magnetic stimulation is efficacious as an add-on to pharmacological therapy in complex regional pain syndrome (CRPS) type I. J Pain. 2010;11(11):1203–10. https://www.clinicalkey.es/playcontent/1-s2.0-S1526590010003275. https://doi.org/10.1016/j.jpain.2010.02.006.
252. Houde F, Harvey M, Tremblay Labrecque P, Lamarche F, Lefebvre A, Leonard G. Combining transcranial direct current

stimulation and transcutaneous electrical nerve stimulation to relieve persistent pain in a patient suffering from complex regional pain syndrome: a case report. J Pain Res. 2020;13:467–73. https://www.ncbi.nlm.nih.gov/pubmed/32184651. https://doi.org/10.2147/JPR.S226616.
253. Schabrun SM, Jones E, Elgueta Cancino EL, Hodges PW. Targeting chronic recurrent low back pain from the top-down and the bottom-up: a combined transcranial direct current stimulation and peripheral electrical stimulation intervention. Brain Stimul. 2014;7(3):451–9. https://www.clinicalkey.es/playcontent/1-s2.0-S1935861X14000618. https://doi.org/10.1016/j.brs.2014.01.058.
254. Bellon G, Venturin A, Masiero S, Del Felice A. Intra-articular botulinum toxin injection in complex regional pain syndrome: case report and review of the literature. Toxicon (Oxford). 2019;159:41–4. https://doi.org/10.1016/j.toxicon.2019.01.002.
255. Dor A, Vatine J, Kalichman L. Proximal myofascial pain in patients with distal complex regional pain syndrome of the upper limb. J Bodyw Mov Ther. 2019;23(3):547–54. https://doi.org/10.1016/j.jbmt.2019.02.015.
256. Safarpour D, Jabbari B. Botulinum toxin A (botox) for treatment of proximal myofascial pain in complex regional pain syndrome: two cases. Pain Med (Malden, Mass.). 2010;11(9):1415–1418. https://onlinelibrary.wiley.com/doi/abs/10.1111/j.1526-4637.2010.00929.x. https://doi.org/10.1111/j.1526-4637.2010.00929.x.
257. Prasad A, Chakravarthy K. Review of complex regional pain syndrome and the role of the neuroimmune axis. Mol Pain. 2021;17:1–10. https://doi.org/10.1177/17448069211006617.
258. Chang C, McDonnell P, Gershwin ME. Complex regional pain syndrome – autoimmune or functional neurologic syndrome. J Transl Autoimmun (Online). 2021;4:100080. https://doi.org/10.1016/j.jtauto.2020.100080.
259. Goebel A, Baranowski A, Maurer K, Ghiai A, Mccabe C, Ambler G. Intravenous immunoglobulin treatment of the complex regional pain syndrome: a randomized trial. Ann Inter Med. 2010;152(3):152–8. https://www.ncbi.nlm.nih.gov/pubmed/20124231. https://doi.org/10.7326/0003-4819-152-3-201002020-00006.
260. Goebel A, Bisla J, Carganillo R, Cole C, Frank B, Gupta R, et al. A randomised placebo-controlled phase III multicentre trial: low-dose intravenous immunoglobulin treatment for long-standing complex regional pain syndrome (LIPS trial). Southampton (UK): NIHR Journals Library. 2017. PMID: 29144634.
261. Kim K, DeSalles A, Johnson J, Ahn S. Sympathectomy: open and thorascopic. In: Burchiel K, editor. Surgical Management of Pain. New York: Thieme Publishers; 2002. p. 688–700.
262. de Mos M, Huygen FJPM, van der Hoeven-Borgman M, Dieleman JP, Stricker BHC, Sturkenboom MCJM. Outcome of the complex regional pain syndrome. Clin J Pain. 2009;25:590–7.
263. Ayyaswamy B, Saeed B, Anand A, Chan L, Shetty V. Quality of life after amputation in patients with advanced complex regional pain syndrome: a systematic review. EFORT Open Rev. 2019;4(9):533–40. https://search.proquest.com/docview/2303746124. https://doi.org/10.1302/2058-5241.4.190008.
264. Schrier E, Geertzen JHB, Scheper J, Dijkstra PU. Psychosocial factors associated with poor outcomes after amputation for complex regional pain syndrome type-I. PLoS ONE. 2019;14(3):e0213589. https://www.narcis.nl/publication/RecordID/oai:pure.rug.nl:publications%2F20df0052-97f0-44fb-bf2a-24c1b9e5dc0e. https://doi.org/10.1371/journal.pone.0213589.
265. Dworkin ID, Moheimani R, Pang E, Zirovich M, Pangarkar S. Improving outcomes of therapy-resistant complex regional pain syndrome utilizing ketamine infusions and comprehensive rehabilitations following amputation: a case report. Pain Medicine Case Reports. 2021;5(5):255–8.
266. Zollinger PE. Upper and lower limb orthopaedics: prevention of CRPS & other traumatology. Open Orthop J. 2010;4:61.
267. Aïm F, Klouche S, Frison A, Bauer T, Hardy P. Efficacy of vitamin C in preventing complex regional pain syndrome after wrist fracture: a systematic review and meta-analysis. Orthop Traumatol Surg Res. 2017;103(3):465–70.
268. Hernigou J, Labadens A, Ghistelinck B, Bui Quoc E, Maes R, Bhogal H, et al. Vitamin C prevention of complex regional pain syndrome after foot and ankle surgery: a prospective randomized study of three hundred and twenty nine patients. Int Orthop. 2021;45(9):2453–9.
269. Keef T, Keef S. The efficacy of vitamin C in the prevention of complex regional pain syndrome after distal radius fractures: a synthesis. J Pain Palliat Care Pharmacother. 2018;32(4):208–211. http://www.tandfonline.com/doi/abs/10.1080/15360288.2019.1598530. https://doi.org/10.1080/15360288.2019.1598530.
270. Alimian M, Sobhani Eraghi A, Chavoshizadeh SA, Mohseni M, Mousavi E, Movassaghi S. Regional vitamin C in Bier block reduces the incidence of CRPS-1 following distal radius fracture surgery. Eur J Orthop Surg Traumatol. 2021;31(4):689–93.