Complex Regional Pain Syndrome

A Clinical Guide

Erin F. Lawson
Joel P. Castellanos
Editors

Springer

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We would like to dedicate this text to the scientists and providers who have worked determinedly for decades in order to develop an understanding of CRPS. The advances in knowledge of the origins and pathophysiology of CRPS have led to tangible gains in patients' lives through ever-improving treatment programs and options.

Preface

Complex regional pain syndrome (CRPS) is a devastating chronic disease of severe pain and dysfunction. While much has changed in our understanding of the disease since the suffering first widely seen on the American Civil War battlefield, treatment remains a vexing challenge. Recent decades have brought several meaningful changes in the approach to diagnostics and new treatments. However, managing CRPS often remains a disheartening venture for healthcare providers who struggle to alleviate pain and disability and for patients who often struggle mightily with everyday activities. This text brings together experts in CRPS to elucidate the current understanding of the disease, approach to diagnosis, and the scope of treatments available. We are happy to share the treatment approaches of these leaders in the field in order to help patients and providers address this unfortunate syndrome.

Lexington, SC, USA — Erin F. Lawson
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Part I

CRPS Basics

Complex Regional Pain Syndrome: An Introduction

1

Elena S. Haight, Nolan A. Huck, Claire E. Jordan, and Vivianne L. Tawfik

Introduction

Complex regional pain syndrome (CRPS) is a debilitating chronic pain disorder that typically results after minor trauma such as surgery or fracture. The first reports of CRPS-like syndromes date back to the sixteenth century, when Ambroise Pare recorded King Charles's unremitting pain and contractures following blood-letting [81]. Centuries later during the American Civil War, Silas Weir Mitchell described a cohort of patients with gunshot wounds who developed persistent pain distal to their wound and disproportionate to the inciting injury, accompanied by motor and trophic changes [47]. Research and effective clinical therapies evaded clinicians due to profound clinical heterogeneity among patients, with numerous taxonomic changes over time as the medical community explored mechanisms underlying the condition and sought names to fit the pathophysiology. The term *causalgia* applied to the observed persistent pain in response to a peripheral nerve injury [81], while *Sudeck's atrophy* addressed the pain and trophic changes that resulted from neurovascular and osseous changes [46]. The late 1940s sparked yet another evolution in understanding this syndrome, when the American physician James Evans coined the term *reflex sympathetic dystrophy (RSD)* [46]. With this taxonomy, Dr. Evans proposed a contribution of persistent sympathetic nervous stimulation to the mottling, temperature change, and pain that characterized the syndrome, a theory he suggested was confirmed by analgesic efficacy of sympathetic ganglion blockade. Importantly, despite evolving terminology to describe the same clinical syndrome, none ever encompassed the entirety of patients who presented after a trauma with

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unremitting pain, vasomotor, sudomotor, and motor changes. As such, the term *CRPS* was adopted in 1994 [85], moving the medical community away from etiological descriptors to a diagnosis that began to accommodate heterogeneity in clinical presentation, and reflected the lack of concrete pathophysiologic understanding. Two CRPS subtypes were established based on the absence (CRPS type I, previously RSD) or presence (CRPS type II, previously causalgia) of an identifiable nerve injury.

Diagnosis

In its early stages, CRPS can bear close resemblance to acute inflammation, characterized by pain, temperature changes, and erythema of the injured limb. As a result, it is important for physicians to consider the expected trajectory of a patient's injury. For example, in a patient with an uncomplicated distal radius or carpal fracture—a common inciting injury for CRPS [70]—the expected time to complete healing is approximately 6–8 weeks [74]. It would therefore be prudent to consider CRPS in a patient presenting 3 months after injury with persistent pain and signs of inflammation. To distinguish CRPS from acute inflammation, the International Association for the Study of Pain (IASP) established a cluster of hallmarks of CRPS, including sensory, sudomotor, and vasomotor symptoms [85]. Clinically, these criteria were based only on patient-reported symptoms, and they did not include motor criteria, which resulted in reduced diagnostic accuracy and low specificity. This rendered CRPS somewhat of a "garbage bag diagnosis" offered to patients who lacked a clear explanation for persistent pain. This resulted in such heterogeneity among patients with a CRPS diagnosis that clinical research was frequently hindered by confounds [8, 38]. In 2003, a group of scholars convened in Budapest to establish updated diagnostics criteria for CRPS which included signs and symptoms in four categories: sensory, vasomotor, sudomotor, and motor/trophic. Diagnosis with CRPS required one or more patient-reported symptoms in at least three of the four categories, and one or more objective signs on evaluation in at least two of the four categories [41]. These criteria—the "Budapest Criteria" (Table 1.1)—comprise the modern standards for CRPS diagnosis and have been validated as a specific and accurate means of diagnosis [39].

Since the development of the Budapest Criteria, numerous efforts have been made to understand whether subgroups of patients with CRPS exist based on condition severity and/or presentation. One such effort was the development of the CRPS Severity Score (CSS) [40], a tool for quantifying CRPS severity based on the presence of both patient-reported symptoms and physician-observed signs (Table 1.2). Although its use has not been widespread among clinicians treating patients with CRPS, the CSS represents a useful tool for assessing the severity of a patient's condition at a given point in time and for tracking the evolution of a case over time. As would be expected, in initial studies of the CSS, a higher CSS was associated with increased disease burden, higher pain intensity, comorbid mood disorders, and poor physical and social functioning [40]. Incorporating the CSS into

Table 1.1 Budapest criteria for CRPS

Category	Symptom/sign
Sensory	Allodynia Hyperalgesia
Sudomotor	Asymmetric edema Sweating changes Sweating asymmetry
Vasomotor	Temperature asymmetry (>1 °C) Skin color changes Skin color asymmetry
Motor	Decreased range of motion Motor dysfunction (weakness, tremors, dystonia) Trophic changes (hair, nails, skin)
Continuing pain, disproportionate to the inciting event Must have 1 symptom in 3 of 4 categories Must have 1 sign in at least 2 categories at time of evaluation No other diagnosis better explains symptoms and signs	

Adapted from: Harden et al. [39]

Table 1.2 CRPS severity score (CSS)

Self-reported symptoms	
Continuing disproportionate pain	
Sensory	Allodynia or hyperalgesia
Sudomotor	Asymmetric edema Sweating asymmetry or changes
Vasomotor	Temperature asymmetry Skin color asymmetry or changes
Motor	Motor dysfunction (weakness, tremors, dystonia) Trophic changes
Signs observed during evaluation	
Sensory	Allodynia Hyperalgesia to pinprick
Sudomotor	Asymmetrical edema Sweating asymmetry or changes
Vasomotor	Temperature asymmetry Skin color asymmetry or changes
Motor	Motor dysfunction (weakness, tremors, dystonia) Trophic changes

Adapted from: Harden et al. [40]

practice may serve as a way to streamline patients into certain treatment regimens, such as physical therapy and pain psychology, and to evaluate the impact of these interventions with a more objective measure than is typically used (e.g., visual analog scale).

As mentioned, traditional nomenclature distinguishes two subtypes of CRPS: CRPS-I, in the absence of a *known* nerve injury, and CRPS-II, which involves an identified nerve injury. Historically, however, there has been limited effort both to identify nerve injuries in patients presenting with CRPS after physical trauma and to offer targeted treatment based on a known nerve injury [71]. That said, identifying a

nerve injury may offer patients considerable benefit, creating alternative focused therapeutic and interventional options. Electrodiagnostic studies (nerve conduction and electromyography) in patients who tolerate it represents one avenue for identifying patients with CRPS-II. Advanced imaging, such as magnetic resonance neurography (MRN) of peripheral nerves [12], may provide an additional diagnostic modality for patients with CRPS and is an area of current active study [52].

Epidemiology

There have been multiple retrospective population-based studies investigating the incidence of CRPS. One study, completed in Olmsted County, Minnesota, USA, by Sandroni et al. [78] found an incidence of 5.5 cases per 100,000 person-years. A retrospective cohort study performed in the Netherlands by de Mos et al. [18] found an incidence of 26.2 cases per 100,000 person-years using a sensitive search algorithm to look for the diagnosis of CRPS in 600,000 electronic health records. Recently, two major epidemiologic studies were completed to estimate an updated incidence of CRPS. One study took advantage of the fact that there is one primary CRPS outpatient clinic serving the city of Erlangen, Germany [72]. Based on the local population size, they calculated an incidence of 13.6 cases per 100,000 person-years. This was suggested to be an underestimate, as CRPS is relatively underdiagnosed due to factors such as limited clinician awareness and the similarity of CRPS to post-injury inflammation. An additional study from the Republic of Korea by Kim et al. [55] found an overall CRPS incidence rate of 29.0 per 100,000 person-years. It is worth noting that this study identified a significantly higher population incidence of CRPS than previous studies, in addition to a more balanced incidence between sexes (1:1.3 male-to-female); however, an advantage of the study is that South Korea has a national health insurance program, so the total number of CRPS diagnoses could be extracted for the entire country between 2011 and 2015. The variable incidence reported in these studies highlights regional variations in the presentation or diagnosis of CRPS. For example, in the latter study [55], in legal disability claims, many clinicians utilized the Persistent Disability and Assessment Guidelines by the American Medical Association rather than the IASP or Budapest criteria. The four epidemiological studies pertaining to CRPS are summarized in Table 1.3.

The incidence of CRPS in adults increases with age until 70 years old [18, 72, 78]; however, in the above-mentioned study [55], the peak incidence of CRPS was found at ages 70–79. Although limited in sample size, a recent study investigating the pediatric incidence of CRPS in Scotland by Abu-Arafeh et al. (2016) found that the age at diagnosis ranged from 5.5 to15.4 years with a mean of 11.9 years. As is true for numerous chronic pain conditions, females are more likely to develop CRPS than males, at a ratio of 2–4:1 [1, 18, 72, 78]. Additionally, female patients are at higher risk of developing severe complications of CRPS including infections, ulcers, chronic edema, or marked movement disorders [91, 94].

Table 1.3 Summary of epidemiological studies on CRPS

Comparison of complex regional pain syndrome epidemiological studies							
Reference	Country, years surveyed	Incidence (per 10^5/yr)	Incidence female:male (per 10^5 person yrs)	Prevalence (per 10^5)	Number of cases	Average age of onset (yr)	Most common extremity affected
Sandroni et al. [78]	MN, USA 1989–1999	Type I: 5.46 Type II: 0.82	8.57:2.16[a]	Type I: 20.57 Type II: 4.2	85[c]	46	Upper extremity
De Mos M et al. [18]	The Netherlands, 1996–2005	26.2	40.4:11.9	–	238	52.7	Upper extremity
Kim et al. [55]	Korea, 2011–2015	Type I: 18.2 Type II: 10.8	10.2:8.0	–	74,349	70–79[d]	Lower extremity/ pelvis
Ott and Mihöfner [72]	Nuremberg, Germany, 1993–2014	13.6	71:29[b]	–	1043	50.9	Upper extremity

[a]Incidence only for CRPS I. CRPS = Complex regional pain syndrome
[b]Incidence reported as percentage
[c]Extrapolated data from study
[d]Data reported as highest incidence per decade

With respect to the distribution of affected limbs, three of the four epidemiological studies of CRPS reported that 60% or more of CRPS cases occur in the upper extremity, with the remaining 40% in the lower extremity [18, 72, 78]. In the South Korean study of insurance claims [55], however, they found that the pelvis, thigh, and lower limb were more likely to be affected than the upper limb. One explanation for this discrepancy could be varying diagnostic criteria between studies, as previously mentioned. Finally, resolution rates for CRPS vary depending on length of disease, ranging from 74% in the first year after onset [78] to 36% by 6 years after onset [21]. Understanding the true rate of resolution is limited by heterogeneity of patient presentation, inconsistencies in diagnostic criteria between practices and adherence to a uniform set of criteria even within a single practice, and a lack of consensus on the definition of recovery.

Risk Factors

Certain injuries, such as fracture, sprain, and elective surgery, are associated with a higher risk of developing CRPS, while spontaneous onset is uncommon [18, 25, 95]. Several investigators have studied distal radius fracture as an inciting injury for CRPS. Most recently, Moseley et al. [70] performed a prospective cohort study in 1549 consecutive patients who presented with wrist fracture. Patients were managed nonsurgically, and the initial assessment was completed within 1 week of injury and followed up at 4 months. The incidence of CRPS in this cohort was 3.8% at 4 months,

and a pain score in the first week of 5 or greater was a predictor for the development of CRPS and a suggested "red flag" during patient evaluation.

The management of bone fractures often requires immobilization of the injured limb, and an early report by Schwartzman and McLellan [80] indicated that such immobilization may be a risk factor for CRPS. Interestingly, healthy human volunteers subjected to immobilization displayed mild signs of CRPS, including cold and mechanical hypersensitivity [73, 88]. In addition, perceived cast "tightness" has also been suggested as a risk factor for the development of CRPS [100]. In rodent models of CRPS, immobilization (casting) alone elicits expression of inflammatory mediators and CRPS-like changes, such as allodynia, warmth, and edema of the injured limb [34]. Taken together, these findings all suggest that careful consideration of the need for post-injury immobilization is necessary, particularly for high-risk patients.

Some studies have also assessed the interaction between certain medications and medical conditions and the development of CRPS. In a series of large population-based studies, de Mos et al. [19, 20] found that the use of angiotensin-converting-enzyme (ACE) inhibitors at the time of trauma or a history of migraine or asthma was associated with an increased risk of CRPS. In an additional study, migraine was also a noted risk factor for CRPS [75]. At this time, the pathophysiologic connection between ACE inhibitors, migraine, or asthma and CRPS remains elusive.

It is unclear if psychological factors confer risk for the development of CRPS or whether some patients, once diagnosed with CRPS, develop mood disorders. A large population-based case-control study found that psychological factors were not associated with CRPS onset [19]. Another prospective multicenter study of 600 consecutive patients with a single fracture showed that psychological factors did not predict the development of CRPS [3]. In contrast, there is evidence that patients with CRPS have higher rates of anxiety and depression compared to healthy controls [59]. However, it is unclear whether patients with CRPS are more severely anxious or depressed than patients suffering from other forms of chronic pain [2, 69]. As a result, cause and effect remains to be investigated.

There have been several case reports describing familial clusters of early onset CRPS, suggesting a potential genetic predisposition [22, 23, 44]. Certain alleles of the human leukocyte antigen (HLA) system have been described as a susceptibility factor for CRPS, first in 1994 by Mailis and Wade [66]. Further studies supported an association between different CRPS phenotypes, such as dystonia-predominant, and specific HLA loci, such as HLA-B62 and HLA-DQ8 [24, 54, 89, 92]; however, consensus has not been reached on the predictive value of these genetic factors. A study published in 2016 by Janicki et al. [48] investigating 83% of all of the common single nucleotide polymorphisms between CRPS patients and controls did not identify a significant difference between the two groups. While whole genome-wide expression profiles can develop a picture of genetic predisposition to CRPS, more studies are needed to determine if specific genetic alterations are causative in the development of CRPS.

One further highly controversial area is post-vaccination CRPS. Following media reports in Japan alleging an association between HPV vaccination and CRPS,

the country temporarily suspended the national HPV vaccination recommendation (R. Wilson, P. Paterson and H. Larson A Report of the CSIS Global Health Policy Centre, Cent Strateg Int Stud (2014) http://csis.org/publication/hpv-vaccination-japan). Given the gravity of such a sweeping move to the health of young women, the risk of CRPS after receiving the HPV 16/18 vaccine was further explored in a study by Huygen et al. [45]. After independent analysis of all possible HPV vaccine-associated cases of CRPS and comparison to the expected background rate of girls in this age group developing CRPS, they concluded that there was insufficient evidence to suggest an association between CRPS and HPV 16/18 vaccination. A follow-up study conducted by Weinbaum and Cano [97] used the US primary reports in the Vaccine Adverse Event Reporting System to explore how US-reported data compared to the study by Huygen et al. For a 10-year period from 2006 to 2015, they found that 0.07% of "vaccine-associated CRPS" reports satisfied diagnostic criteria for CRPS; however, these were correlative data. It has been suggested that cases of CRPS-like conditions may have been due to minor tissue trauma from the vaccine injection, as seen in other rare cases [31, 77]. A review from the European Medicines Agency (EMA) concluded, however, that the evidence is insufficient to establish a causal link of HPV vaccination to CRPS [49].

Pathophysiology

Much of the complexity inherent in CRPS is the result of heterogeneous pathophysiology, with multiple mechanisms underlying a single patient's condition and underlying mechanisms likely varying between patients. In recent years, considerable advances have been made in understanding the myriad pathophysiologic drivers of CRPS, although clinical efforts to establish targeted interventions have lagged behind (Fig. 1.1).

Sympathetically Maintained Pain

Much of the early literature surrounding CRPS was based on the premise of sympathetically maintained pain (SMP), and it was this theory of sympathetic hyperactivity that generated the term RSD. By definition, patients with CRPS have physical changes on the affected limb that appear autonomically mediated (temperature change, erythema, trophic disturbances). As a result, early interventions for patients with CRPS included sympathetic ganglion blockade, which provided analgesia for a significant proportion of patients with CRPS-I [10] and was long considered of diagnostic value in patients suspected of having CRPS. In conflict with this theory of sympathetic hyperactivation, studies demonstrated decreased concentrations of neuropeptide Y [27] and norepinephrine [28] in plasma of the ipsilateral (injured) limb. Instead of tonic sympathetic activation, researchers posited that patients' pain resulted from abnormal responses to sympathetic stimuli or alterations in adrenergic receptor expression [42]. With continued study, however, patients were identified

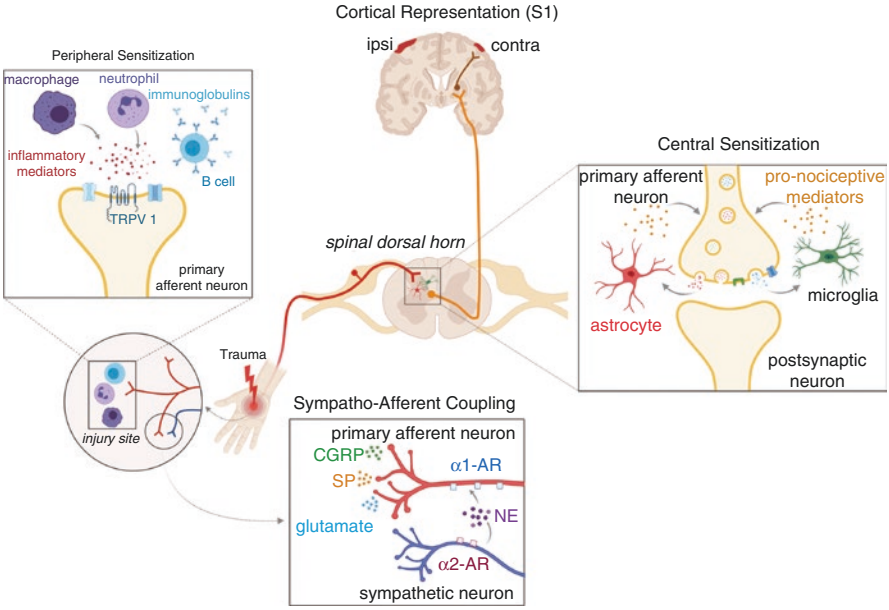

Fig. 1.1 Proposed pathophysiological mechanisms of complex regional pain syndrome (CRPS). Injury to a limb results in peripheral sensitization. Immune cells, such as macrophages and neutrophils, home to the site of injury and release inflammatory mediators that lead to the sensitization of pro-nociceptive channels (TRPV1 channel) on primary afferent neurons. B cells at the injury site release immunoglobulins that may target autoantigens and contribute to CRPS-related autoimmunity. Sympatho-afferent coupling may occur due to the expression of α1-AR on primary afferent neurons. Norepinephrine (NE) released by neighboring sympathetic neurons binds to the α1-AR, causing increased release of calcitonin gene-related peptide (CGRP), substance P (SP), and glutamate from primary afferent neurons. In the spinal cord dorsal horn, local neuroimmune cells such as astrocytes and microglia are activated by pro-nociceptive substances released from central terminals of sensitized primary afferent neurons and contribute to central sensitization by releasing pro-nociceptive mediators themselves. In the somatosensory cortex (S1), cortical representation of the affected limb decreases on the contralateral side contributing to hemi-neglect phenomena in these patients. S1: somatosensory cortex 1, ipsi: ipsilateral, contra: contralateral, NE: norepinephrine, CGRP: calcitonin gene-related peptide, SP: substance P, α1-AR: alpha-1 adrenergic receptor, α2-AR: alpha-2 adrenergic receptor, TRPV1: transient receptor potential cation channel subfamily V member 1

who did not respond to sympathetic blockade, or whose response declined with increasing disease chronicity [37, 84]. Thus, sympathetic aberrancy explained only one component of CRPS in a subset of patients.

Peripheral Sensitization

The onset of inflammation and pain following injury results from the release of inflammatory mediators including cytokines such as interleukins and tumor necrosis

factor-α (TNF-α), nerve growth factor (NGF), bradykinin, ATP, and prostaglandin E_2 (PGE_2) from immune cells [11]. With increased circulating levels of these mediators, mitogen-activated protein kinase (MAPK) pathways become activated, resulting in increased sensitivity of pro-nociceptive channels on primary afferent neurons [53], such as the TRP channels TRPV1-TRPV4, which are believed to mediate the burning sensation in persistent neuropathic pain [13, 17, 51].

Central Sensitization

Central sensitization has been offered as one explanation underlying the persistent pain observed in patients with CRPS and has been confirmed through functional magnetic resonance imaging (fMRI) studies in patients with chronic CRPS [64]. Past literature has emphasized the importance of early diagnosis of CRPS due to the increased challenge of achieving symptom remission in patients with chronic CRPS. The refractory nature of chronic CRPS may be partly explained by preclinical studies demonstrating a transition from peripheral inflammation in the acute stages of CRPS to central inflammation in chronic CRPS mediated in part by microglia [16] and astrocytes [86], which release pro-nociceptive mediators to create a state of persistent inflammation. The development of central sensitization likely results in part from peripheral sensitization, with increased neurotransmitter release (substance P, CGRP, BDNF, glutamate) from primary afferents at their central terminals, leading to chronic neuronal hyperactivity in the CNS [50, 98, 99].

Acute-Warm-Peripheral CRPS Versus Chronic-Cold-Central CRPS

The pathophysiologic mechanisms underlying disease duration-associated subtypes of CRPS have largely been studied in preclinical models, with efforts to translate findings achieving limited success. The warm, edematous, erythematous phenotype that characterizes CRPS is more associated with a shorter duration of disease (<1 year), whereas with increasing chronicity, patients are more likely to have a cold, atrophic, blue limb [9]. These findings have been replicated in a clinically relevant, validated rodent model of CRPS, which involves distal tibial fracture followed by 3 weeks of cast immobilization [5]. At the time of cast removal, the rodent's injured limb is warm, edematous, and erythematous [96]. Around 5 weeks post-fracture, peripheral signs of inflammation dissipate, but pain-like behaviors persist. Inflammatory mediators track this transition, with increased peripheral inflammatory cytokines observed during the acute phase returning to normal as central inflammatory cytokines become elevated in the chronic phase [30]. These findings suggest that peripheral inflammation mediates the signs observed in acute CRPS while central inflammation mediates the continued pain associated with chronic CRPS. Efforts to attenuate central inflammation, mediated by microglia and astrocytes, have thus far been mainly conducted in preclinical models [62]. Several currently approved drugs may work in part through glial modulation including

ketamine, which acts on many CNS cell types; low-dose naltrexone, which may antagonize the microglial receptor toll-like receptor 4 (TLR4) [83]; and hydroxychloroquine, which reduces pain in a subset of patients with chronic CRPS and attenuates microglial activation in a mouse model of CRPS [36]. There are likely superior pharmacologic ways to optimize glial modulation for patients with CRPS, and the development of glial-specific pharmacotherapies is an important area for future investigation [35]. That said, preclinical studies showing analgesic efficacy of the centrally acting anesthetic agent ketamine only in the chronic phase of CRPS support the notion that chronic CRPS is centrally mediated [86]. To this point, the mechanisms mediating the transition from acute to chronic CRPS have not been well elucidated, although studies suggest intricate interactions between the nervous and immune systems are a factor [16].

Oxidative Stress

There is a body of evidence suggesting CRPS-I may reflect an ischemic process in the setting of physical injury. Clinically, patients with CRPS have decreased hemoglobin oxygenation in the skin of their affected limb [56], in addition to increased lactate [6]. These findings combined with histologic examination of muscle tissue in CRPS-affected limbs demonstrating lipofuscin accumulation, fiber atrophy, and thickened basement membrane [90] suggest oxidative stress to the affected limb. Moreover, preclinical studies have demonstrated that a model of ischemia and reperfusion wherein a tourniquet is applied to the hindlimb of an anesthetized rodent for 3 hours, then removed to allow reperfusion, is sufficient to induce a chronic neuropathic-like pain state with spreading to other limbs [15], a phenomenon commonly seen in patients with CRPS.

Autoimmunity

Perhaps the most rapidly growing area of CRPS research seeks to understand autoimmune mechanisms in CRPS [14]. Autoimmunity is a maladaptive response of the adaptive immune system, characterized by autoantibody-mediated disease. In preclinical studies, researchers found that depleting CD20+ B cells prior to injury attenuated the signs of CRPS [61], suggesting a contribution of autoimmunity. Interestingly, recent research also shows that the transfer of IgG from patients with CRPS to uninjured mice is sufficient for the establishment of hyperalgesia, edema, and motor impairment in mice [33, 87] and that this may occur in an IL-1B-mediated fashion [43]. Finally, autoimmunity is supported by studies showing autoantibodies against β_2 adrenergic and muscarinic type 2 receptors in some patients with CRPS [7, 57, 58]. Despite these promising data elucidating autoimmune contributions to CRPS, interventions such as intravenous immunoglobulin (IVIg) infusions have not been more effective than placebo at controlling pain for patients with moderate-to-severe CRPS of 1–5 years duration [32].

Central Nervous System Alterations

Brain imaging has long contributed to CRPS research, showing cortical changes that are the target of common physical therapy interventions such as graded motor imagery and mirror box therapy. Patients with CRPS commonly have disruption in the cortical map of their CRPS limb, the extent of which is directly proportional to the severity of pain they report [29, 65, 76]. Patients describe altered perception of the size of their limb and its location in space, feel extreme hostility or disgust toward their affected limb, or lack the ability to create a mental image of their limb [60]. Still others may report pain in their affected limb upon being stimulated with light touch or pinprick at another unaffected site [68]. These changes resemble neglect syndromes seen in other neurologic disorders, and they commonly persist into the chronic stage of CRPS, resolving only if the patient's pain is resolved [65]. Additionally, fMRI studies of patients with CRPS demonstrated enlargement of the contralateral compared to the ipsilateral motor cortex and reduction in size of the contralateral compared to ipsilateral somatosensory cortex [63]. Such findings underscore the need for patients to engage their affected limb to prevent fear-avoidance cycles of limb disuse and subsequent pain exacerbation.

Psychological Mechanisms

As described above, patients with CRPS are more likely to have psychiatric comorbidities, namely depression and anxiety [59]. It is possible that psychiatric conditions such as depression and anxiety contribute to the pathophysiology of CRPS by enhancing CNS catecholamine release and activating sympathetic nerves. Providing adequate psychological services to patients with CRPS, then, is critically important in light of the contribution of sympathetic activation to CRPS, particularly in the acute stage.

Natural History

Acute Versus Chronic

It is generally accepted among clinicians that CRPS treated early is significantly more likely to resolve, or be managed well, than CRPS that is first treated in its chronic stage. For this reason, early evaluation is critical for patients suspected of having CRPS. Studies have shown that CRPS is most commonly diagnosed within approximately 3 months of the expected time to resolution of the inciting injury [4]. Interestingly, the patients in this study ($n = 596$) had developed CRPS after a fracture and were more likely to be diagnosed at 3 months after cast removal instead of at the time of cast removal. This, in conjunction with cast immobilization being an independent risk factor for CRPS [73], suggests that the most likely time to develop CRPS is within 3 months of an inciting trauma.

While monitoring the natural history of CRPS following diagnosis has proven challenging, some research has been conducted on this matter, including a 1998 study wherein patients with a CRPS diagnosis were monitored for a year after their diagnosis without treatment [101]. In this study, 26 of the 30 patients experienced resolution of their symptoms by the end of the study period. Just 3 of the 30 patients withdrew from the study to receive treatment. It is important to note that this study was conducted prior to implementation of the Budapest criteria, so the findings of this study may not reflect the natural course of CRPS we would observe with stricter diagnostic criteria. One additional study conducted with the IASP diagnostic criteria (pain, vasomotor, and sudomotor changes; excludes the motor changes of the Budapest criteria) suggests a similarly high rate of resolution (74%) of acute CRPS-I. This is in contrast to chronic CRPS-I, which had a 30% resolution rate in a study of 102 patients. Sixteen percent of these patients had progressive deterioration, while 54% continued to experience stable pain and CRPS-like vasomotor, sudomotor, and motor changes [79]. Understanding the natural history of CRPS in coming years will likely depend on widespread adoption of registries to track patients with CRPS, such as the CRPS-UK Registry, which was established in the United Kingdom in 2008 and has more than 600 patients enrolled as of March 2020 [82].

CRPS Spread

Non-dermatomal spreading of CRPS is a feared complication of CRPS, most common in patients with a young age of CRPS onset and those reporting a more significant impact of their CRPS [93]. CRPS spread was evaluated among 185 patients with a CRPS diagnosis; 89 patients had CRPS in multiple limbs, with 49% spreading to the contralateral limb, 30% spreading ipsilaterally, and 14% spreading diagonally [93]. Trauma to the region of spread was reported in 37% of patients with contralateral spread, 44% of patients with ipsilateral spread, and 91% of patients with diagonal spread. The risk of spread following trauma was higher in patients with more limbs affected. Proposed pathophysiologic mechanisms for spread include peripheral hyperexcitability causing hyperexcitability in the brainstem and higher brain regions, in addition to impaired pain modulation [26], and compromised response by the CNS to neurogenic inflammation [67].

Conclusions

CRPS is an enigmatic condition that typically develops after minor injury such as surgery or fracture, with a 3–4:1 female-to-male predominance. Our understanding of CRPS has evolved significantly since it was first described in the sixteenth century, creating more specific diagnostic criteria and targeted research. Distinct stages characterize CRPS—an acute stage mediated by peripheral factors such as sympathetic dysregulation and circulating pro-inflammatory mediators, and a

chronic stage mediated by central mechanisms such as CNS glial activation and central sensitization. Clinical experience suggests that the acute stage of the disorder is more likely to achieve remission or successful management, which creates a challenge for clinicians given that CRPS has myriad presentations and underlying pathophysiologic mechanisms, both of which contribute to the delayed diagnosis and treatment that is common for patients with CRPS. Moving forward, we expect that our growing understanding of the mechanisms underlying CRPS will enable more targeted, successful management of the disorder.

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Peripheral Injury and CRPS

2

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For the vast majority of cases, CRPS comes as a result of injury and is frequently associated with immobilization, both of which are implicated in the mechanisms that lead to manifestations of CRPS [7–9]. Injury leads to disruption of tissue integrity and sets off reparatory mechanisms, and when these mechanisms fail, the clinical picture evolves into CRPS. Inflammatory processes predominate at the level of the periphery especially early, which would account for many of the clinical manifestations of CRPS at that stage. Clinical evidence that would support a role for inflammatory mechanisms is the response of CRPS to corticosteroids [3, 33], implicating general nonspecific role of inflammatory mechanism, and in case of specific dysregulation of osteoclast and osteoblast balance by a positive response to bisphosphonates [13, 27, 68]. Of note, such clinical results report the mean group response supporting this type of conclusion, but these results cannot necessarily be extended to individual patients, since there is a significant proportion of patients who do not respond to such therapies.

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Peripheral Sensitization

Sensitization in the peripheral nervous system, peripheral sensitization plays a significant role in CRPS. Inflammatory mediators such as proinflammatory cytokines (TNF-a, IL-1b), PGE2, bradykinin, and NGF increase the sensitivity and excitability of nociceptors by enhancing the activity of pronociceptive receptors and ion channels (e.g., TRPV1 and Nav1.8). Activation of multiple intracellular signal pathways such as MAPK pathways in primary sensory neurons results in the induction and maintenance of peripheral sensitization and produces persistent pain.

It is possible to distinguish molecular mechanisms between induction and maintenance of neuropathic pain, including CRPS. Induction of peripheral sensitization starts with peripheral tissue injury or nerve damage, which than leads to the production of various inflammatory mediators, such as TNF-α, PGE2, bradykinin, and NGF. These mediators are released and stimulate the corresponding receptors on terminals, axons, or cell bodies of nociceptive primary sensory neurons. When activated, these receptors result in the activation of multiple protein kinase pathways, leading to rapid posttranslational regulation of TRPV1 and TTX-R Na+ channels. In turn, hyperactivity of TRPV1 and TTX-R Na+ channels results in peripheral sensitization, manifesting with hyperalgesia [28]. Peripheral sensitization is maintained under the influence of transcriptional or translational mechanisms. Inflammatory mediators produced after peripheral tissue injury, in particular due to nerve damage, as well as spontaneous electrical activity, continue to activate MAPK pathways (p38, ERK, JNK) in different subsets of nociceptive primary sensory neurons. Activation of these pathways results in transcriptional regulation via transcription factors CREB, ELK-1, Jun, and ATF and translational regulation via translation initiation factors. Consequently, there is increased synthesis of ion channels such as TRPV1, TRPA1, TTX-R Na+ channels, P2X3, and Ca2+ channel a2d subunit and neuromodulators such as BDNF, substance P, CGRP, TNF-α, and IL-1b. Increase in the synthesis of these pronociceptive proteins in primary sensory neurons maintains hypersensitivity of these neurons and as a result persistent pain [12, 28]. Another mechanism implicated in maintenance of persistent neuropathic pain, including and not exclusive to CRPS, is abnormal functional status of primary afferents, manifesting with spontaneous electrical activity and increase in its responsiveness to heat, in particular on small C-fiber afferents, leading to heat hyperalgesia [30, 48].

Inflammatory Processes in CRPS

It is generally accepted that an inflammatory cascade occurs after initial injury, both from CRPS research and from inflammation and trauma research [11, 40], and initiates the subsequent development of CRPS. What makes the research difficult is that trauma and inflammation do not consistently progress to CRPS in every patient and only a small percentage (~7%) of patients go on to develop typical CRPS symptoms [8].

The Budapest criteria include sensory, vasomotor, sudomotor, and motor/trophic changes for diagnosis. The majority of CRPS cases are type I [19], and these cases more often than not start off in a "warm" phase where the affected limb becomes warm, edematous, painful, and erythematous—signs consistent with Celsus' cardinal signs of inflammation: calor, tumor, dolor, and tumor, respectively [19]. Warm CRPS cases usually will progress over several months to a "cold" phenotype. Cold CRPS is mostly differentiated with warm CRPS by temperature differences between the affected and unaffected limbs [8]. In most clinical practices, a difference of 2ºC in either direction is considered clinically significant. Other signs of cold CRPS, besides reduced temperature in the affected limb, would include atrophy and vasoconstriction with subsequent reduced regional blood flow [69].

CRPS cases often start with warm CRPS, which would support the theory that inflammation is the initial factor that transitions to a more centralized phenomenon with signs of cold CRPS [67]. It is important to note that not all CRPS patients will have this progression from warm to cold and some will start with the cold symptoms. Patients who present initially with cold CRPS are often considered more difficult to treat.

Much of the research includes bloodstream sampling systematically as well as sampling from tissue in the affected limb. There are known local inflammatory responses which occur after trauma that include the release of specific inflammatory mediators such as cytokines such as interleukins (IL) and tumor necrosis factor (TNF) from neutrophils, lymphocytes, and endothelial cells [26]. There are proinflammatory and anti-inflammatory cytokines released after trauma. Specific cytokines are known to be released after trauma which include significant increases in IL-6, IL-8, IL-16, IL-1Ra and decreases in IL-1 and IL-12 systemically when measured acutely after trauma [4, 53]. TNF-α is also released after trauma [14], inducing a cascade of other cytokines and increasing endothelial cell permeability and adhesion of leukocytes, furthering the inflammatory response at the site of trauma. The question of which factors may be involved in the future development of CRPS has been examined, and proinflammatory mediators TNF-c, IL-1β, IL-8, and IL-12 have been detected at higher levels in the affected limb in the early stages of CRPS patients. Interestingly, other inflammatory mediators such as IL-4, IL6, IL-10, interferon-γ, TNF-α, CGRP, substance P, and endothelin-1 were not significantly different in CRPS patients compared to controls [56, 63]. The sampling for characterization of CRPS is challenging as these factors change chronologically from an inflammatory picture of warm CRPS to cold CRPS when measurement of inflammatory mediators no longer plays a role [64].

HLA is another marker of inflammation that has been studied with respect to CRPS, though the expression of these genes is usually found in nonspecific responses to inflammation and not with CRPS specifically. However, study of specific HLA haplotypes may be valuable in finding whether specific genes may predispose the progression to CRPS. Data from these studies have found a correlation with some specific HLA haplotypes HLA-A3, -B7, -B62, -DR13, -DQ1, and -DR2 with CRPS patients [8, 35, 65, 66]. Some of these haplotypes are associated with different CRPS phenotypes, such as HLA-DQ8 being associated with CRPS both

with and without dystonia but that HLA-B62 is associated only in CRPS patients with dystonia [66]. As our understanding of CRPS continues to build, these differences across specific inflammatory markers and genetic traits may provide clues to predict the susceptibility of a patient who develops CRPS as well as the symptom phenotype.

Besides the peripheral inflammatory response, central changes occur after trauma as well. These changes would include the release of adrenaline with direct effects on hormonal balance, affecting gluconeogenesis and glycolysis. Other inflammatory mediators including substance P, CGRP, and neuropeptide Y are known to occur with inflammation and hypothesized to play a role in the development of both the pain and vascular components of CRPS. These may suggest a genetic predisposition for CRPS, possibly from susceptibility or upregulation of pro- and anti-inflammatory mediators.

The chronic cold phase of CRPS is characterized by changes in circulation and endothelial vascular changes [29]. These changes can lead to possible tissue hypoxia and acidosis [6, 37], which play a role in the manifestation of cold CRPS. Again, as with warm CRPS, at this point in time, there does not seem to be a consistent phenotype of a population or gender or age for which CRPS is more likely to develop after initial injury.

Recent research has identified microRNAs to be involved in the pain process and in CRPS. MicroRNAs (miRNAs) are noncoding RNAs transcribed from DNA sequences and the expression of these miRNAs been shown to be correlated in the inflammatory process [2, 16, 59]. MicroRNAs have been called "master switches" of inflammation [59] via cell signaling and release of inflammatory mediators. Sequencing studies have found increased expression of miRNAs in nerve injury models [55, 60, 71], and specific miRNA signatures appear to be associated with specific diseases such as peripheral neuropathies, migraine, arthritis, as well as CRPS [47, 49, 61, 70]. Because of this, miRNA expression is being explored as a biomarker for pain [21, 39, 72] and may be involved in the variable expression of inflammatory mediators [49]. The previously mentioned increases of proinflammatory cytokines and decreases of anti-inflammatory cytokines in CRPS may be related to the expression of these genetic determinants. CRPS patients were found in one study to have higher gene expression of the proinflammatory markers TNF and IL-2 and reduced gene expression of anti-inflammatory cytokines IL-4 and IL-10 [59]. These data may play a significant part in delineating the susceptibility of patients who develop CRPS after nerve injury.

CRPS and Brain Plasticity

Brain morphological changes are known to occur in chronic pain [62] and phantom limb syndrome [31]. Because of similarities of these conditions to CRPS, investigators have examined brain changes using several techniques including EEG, MEG, and fMRI in mapping out these changes [17, 18]. Studies have mostly focused on changes in the frontal and parietal lobes, specifically in the somatosensory and

motor cortices. Nerve inputs from the different parts of the body terminate onto the cortex as a body representation map called the homunculus [10, 45], which is Latin for "little man" being that the body is mapped onto the cortex anatomically. This nonrandom representation is true for both the motor and sensory cortex in that neighboring body parts are characterized in neighboring cortical areas. For example, the face comprising the eyes, nose, and lips are mapped as adjoining regions on the cortex while the legs, foot, and toes are mapped together but on the opposite side of the sensory and motor cortices.

The typical symptoms of CRPS include pain, sensitivity, and changes in color, texture, stiffness, and weakness. Brain imaging studies have focused on the mapping of affected limbs on the cortex using the above imaging modalities in combination with clinical findings known to be associated with the cortical areas in question. For example, it is known that neurological signs such as digit misidentification and neglect are attributed to parietal lobe dysfunction and have been described in patients with CRPS [15, 24]. Other signs of cortical dysfunction include astereognosis, body scheme misrepresentation, mislocalization of tactile sensation, and impaired hand laterality recognition [38, 44]. These impaired clinical signs are associated with dysfunction of the parietal and somatosensory cortices and have been described in the affected limb of CRPS patients. Again, these have also been described in patients with CRPS. Because the primary form of CRPS treatment comprise of physical therapy and cognitive behavioral therapy, investigators have and continue to describe changes in motor cortex and frontal cortex with CRPS. Combined, all of these factors together allude to morphological brain changes occurring with CRPS.

Phantom limb syndrome occurs after limb amputation where the patient continues to experience limb pain and sensations despite the lost limb. Cortical remapping is known to occur after limb amputation, where neighboring body representations in the brain expand into the area previously represented by the amputated limb. Similar to phantom limb pain, brain plasticity has been presumed to play a role in CRPS given that CRPS arises after limb and nerve trauma. For example, imaging studies have found that primary somatosensory cortical representation of the face (especially the lips) to expand into the somatosensory cortical map previously representing the now-amputated limb [23, 36, 45, 46]. This has been presumed to be due to decreased input to the somatosensory cortex leading what is called "maladaptive plasticity" in the brain [36].

Currently available imaging studies have been somewhat difficult due to several factors. These include the continued development of technologies like fMRI. Outcomes are not specifically assessed in many studies. Appropriate diagnosis of CRPS relies on signs and symptoms, instead of a gold standard diagnostic test. This can cause a misrepresentation of CRPS diagnosis and thus studies are limited to small sample sizes. Many imaging studies lack blinding leading to a high risk of bias. These factors all contribute to mixed and inconclusive results of studies to date.

Results of early EEG and MEG studies in CRPS patients lead researchers to postulate that there is diminished representation of the affected limb in the primary

somatosensory cortex [34, 51, 52, 58]. This is similar to what was found with brain changes in phantom limb studies described above. The conclusions from studies of phantom limb pain indicate a possible maladaptive plasticity occurring within the brain where cortical mapping of the phantom limb shrinks. This was thought to occur in early studies of CRPS with decreased representation of the affected limb. However, later studies using fMRI revealed that this change in representation was more consistent with enlarged representation of the nonaffected limb in the primary somatosensory cortex rather than a decreased representation of the affected limb. A recent review of the imaging studies found that the reduced representation is consistent across studies [17]. However, the implication of this phenomenon is yet to be determined.

Motor disturbances such as weakness and altered motor control are observed in CRPS. Investigators have examined changes in the primary motor cortex using fMRI, TMS, MEG, and PET. A systematic review of the literature [18] found that the few studies show no differences in motor-evoked potentials, motor thresholds, or cortical silent periods between hemispheres in CPRS. There were also no observed hemispheric differences. However, in an interesting study using MRI to look at pediatric CRPS patients who had undergone interdisciplinary psychophysical pain treatment, increases in gray matter were found in the dorsolateral prefrontal cortex, thalamus, basal ganglia, amygdala, and hippocampus [22]. These are areas of the brain involved in many of the symptomatic components of CRPS including motor and sensory disturbances. These areas are also responsible for emotion and cognition, both of which are also critical components of CRPS. Changes in connectivity between the dorsolateral prefrontal cortex and the periaqueductal gray (PAG) were also found. These areas are known centers of descending pain modulation [41, 54, 57]. Another study using MRI data found increased gray matter density in the contralateral primary motor cortex in CRPS patients, possibly explaining compensatory mechanisms caused by motor dysfunction [50]. The same study also found increased gray matter structure in the dorsomedial prefrontal cortex, a region implicated in emotional processing.

Some studies have delved into specific brain changes such as altered white matter connectivity throughout the brain and gray matter changes. Diffuse white matter tract changes are seen in CRPS patients with branching pattern alterations and changes in connectivity between specific brain areas such as the prefrontal cortex to insula and basal ganglia [32]. Gray matter atrophy has been observed in the prefrontal cortex, insula, and nucleus accumbens in CRPS [25].

Brain reorganization appears to occur with CRPS and studies continue to elucidate these changes using the more advanced imaging modalities such as fMRI in addition to EEG/MEG, PET, and MRI. The morphological changes in the brain that occur with CRPS appear to be similar to changes seen in chronic pain to specific brain regions such as the prefrontal cortex and thalamus [1, 42, 43]. These changes can perhaps help to explain some of the phenomena associated with CRPS as further studies continue to expand the field. These studies would also help the development of more specific and targeted treatment for bottom-up as well as top-down treatment such as cognitive behavioral therapy and targeted motor and sensory training [20].

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Differential Diagnosis of Complex Regional Pain Syndrome

3

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Introduction

Complex regional pain syndrome (CRPS) is often difficult to diagnose for a variety of reasons. CRPS remains a clinical diagnosis with the gold standard criteria being the Budapest Criteria [1]. Laboratory studies, imaging, and injections can be used to support the diagnosis; however, there are many mimicking diagnoses that can be confused for CRPS. There remains an average delay of 6 months prior to clinicians making a diagnosis of CRPS due to these difficulties in differentiating the syndrome from others [1]. Delays like this are not unexpected given that patients with CRPS exhibit signs and symptoms that appear like a variety of neurologic, inflammatory, vascular, infectious, traumatic, and psychological diseases making it sometimes daunting for many providers to confidently make the diagnosis. Understanding of the diagnostic criteria for CRPS, clinical presentations, and diagnostic criteria of diseases with similar symptomatic presentations is essential for proper diagnosis and treatment. We aim to review common pathologies that can most commonly be confused with CRPS and highlight important differentiating factors that can be used to distinguish them. The diagnosis of CRPS is covered elsewhere in this text but going forth, the differences among these diseases will be discussed with relationship to CRPS as diagnosed via the Budapest criteria seen in Table 3.1 [1, 2].

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Table 3.1 The Budapest Criteria for diagnosis of CRPS [1, 2]

Budapest Criteria for diagnosis of complex regional pain syndrome (CRPS)		
Diagnosis for CRPS requires presence of **all** of the following criteria:		
Continuous pain that is not proportionate to the event responsible for the pain		
Patient must have at least 1 objective sign (**column 3**) in 2 or more different categories (**column 2**)		
Patient must report at least 1 symptom (**column 3**) in 3 or more different categories (**column 2**)		
The previous must be fulfilled and no other diagnosis can account for the disease's signs and symptoms		
	Category (column 2)	**Signs and symptoms (column 3)**
1	Sensory	Allodynia (pain from typically non-painful stimuli) Hyperalgesia (disproportionate pain intensity to mildly painful stimuli)
2	Vasomotor	Differences in skin temperature/asymmetry Changes in skin coloration
3	Sudomotor/edema	Edema (changes and/or asymmetry in swelling) Sudomotor changes (changes and/or asymmetry in sweating)
4	Motor/trophic	Decreased range of motion Motor symptoms (tremor, weakness, dystonia, etc.) Changes in hair, skin, nails (trophic)

Neurologic

The pathophysiology of CRPS is complex and multifaceted [3]. There is evidence of somatosensory dysfunction at peripheral, spinal, and supraspinal levels, including peripheral and central sensitization, which can lead to misinterpretation of CRPS for other neuropathic pain syndromes (e.g., neuralgias, neuropathies, nerve entrapment syndromes, radiculopathies, and central pain syndromes) [3, 4]. Additionally, the presence of neuropathic pain syndromes does not preclude concomitant CRPS, and vice versa, as the two groups are not mutually exclusive potentially making proper diagnosis difficult.

Nerve Entrapment Syndromes

Nerve entrapment syndromes involve peripheral nerve compression or entrapment at specific anatomic locations, which acts to create a wide constellation of symptoms including pain, loss of sensation, and potentially reduction of motor function. Typically, nerve entrapment syndromes are diagnosed clinically via history and physical but can be confirmed with diagnostic tests such as nerve conduction studies/electromyography (NCS/EMG). Magnetic resonance imaging (MRI) also can be utilized to show areas of nerve entrapment or injury though this is not always necessary for diagnosis [5]. The symptoms of these diseases go beyond just pain, however. Patients can show evidence of vasomotor dysfunction, motor dysfunction, and sensory abnormalities with advanced disease.

Carpal Tunnel Syndrome

Carpal tunnel syndrome (CTS) is a disease that originates from compression or increased pressure on the median nerve in the wrist at the carpal tunnel and is the most common nerve entrapment syndrome [5]. This increased pressure leads to impaired microcirculation and can ultimately result in spontaneous action potential generation, demyelination of the median nerve, and axonal loss. Patients can develop paresthesias of the affected hand, chronic neuropathic pain, and motor dysfunction if left untreated. The severity of this condition ranges from transient symptoms to irreversible wasting of the thenar process and sensory loss. In addition to dull aching pain, and paresthesias in the distribution of the median nerve, patients can sometimes report dry skin, swelling, or color changes in the affected hand. Treatment is often conservative with anti-inflammatory medications, but in severe cases or in cases refractory to medical management, surgical decompression may be warranted [5–7]. Vasomotor and sudomotor symptoms, though less common, have been reported in CTS patients. One study showed evidence that 80% of test subjects (n = 23) had impaired sympathetic sweat responses, calculated by determining sweat output via a sudorometer, or skin vasomotor reflexes determined by cutaneous blood flow via Doppler flowmeter during various trials designed to cause to sympathetic activation [8].

CTS and similarly other nerve entrapment syndromes can easily be misdiagnosed as CRPS as they have the potential to share many signs and symptoms as described by the Budapest Criteria. In addition to sharing many characteristics with CRPS, nerve entrapment syndromes such as CTS can occur following traumatic injury similarly to CRPS, although this is uncommon [6]. Nerve entrapment syndromes differ from CRPS, however, as patients will demonstrate symptoms in a specific nerve distribution usually in the absence of an injury or nerve injury. Physical exam in CTS may have positive Tinel sign (sensitivity: 36–50%, specificity; 77%) or Phalen's test (sensitivity: 57–68%, specificity; 58–73%) [7]. Diagnostic corticosteroid injections can be performed and have been shown to be effective in CTS at symptomatic relief and delaying surgery. Imaging modalities such as ultrasonography can be used to measure the cross-sectional area of the median nerve, which is closely correlated with CTS symptoms and severity. Additional electrodiagnostic testing such as NCS/EMG can also be done as mentioned above for patients for whom the diagnosis is not clear. Electrodiagnostic studies have a sensitivity of 56–85% and specificity of 94–99% for CTS, though results may be normal in one third of patients with mild CTS [7].

Distal Symmetric Polyneuropathies

Distal symmetric polyneuropathies is a category of conditions that lead to damage of the peripheral nervous system. The causes of these disorders range from vitamin deficiencies, metabolic disorders, medication side effects, autoimmune disorders, neoplasms, and infectious etiologies [9]. These patients can present with numbness,

tingling, and/or pain usually in the extremities. There are a multitude of these peripheral neuropathies that can produce signs and symptoms similar to CRPS; however, we will focus on two of the most common: diabetic polyneuropathy (DPN) and HIV polyneuropathy.

Diabetic Polyneuropathy

Diabetic patients with longstanding disease and poor glycemic control are at increased risk of developing DPN. DPN is the most common complication of diabetes and can be found in up to 50% of patients who have suffered from diabetes for greater than 25 years [10]. Patients who suffer from this symmetric sensorimotor polyneuropathy are most likely to have the symptoms from both large and small nerve fiber loss. Symptoms from large nerve fiber damage include impairments in vibratory sensation, proprioception, and diminished reflexes. Symptoms from small nerve fiber damage include pain, often displaying evidence of hyperalgesia or allodynia, paresthesias, and impaired temperature sensation. Most commonly, the symptoms present with progressive distal sensory polyneuropathy that is symmetric in both extremities, often described as a "glove and stocking" distribution. Typically, sensory function, including ability to detect vibrations and temperature, is affected more so than motor function with muscle wasting being very rare [11]. Patients with longstanding diabetes are often afflicted with dysautonomia similar to CRPS. As such, patients may experience sudomotor dysfunction with impaired sweat production [12].

Similar to CRPS, diagnosis is largely a clinical diagnosis. A monofilament test in the office may reveal decreased sensitivity in affected limbs. There may also be open skin ulcers in patients with DPN due to the decreased sensitivity and impaired wound healing, while CRPS patients do not usually have ulcerations, though they can have skin discoloration associated with the sensory symptoms. Electrodiagnostic testing such as EMG/NCS is a diagnostic tool that can help differentiate among many of the differentials that we will discuss when they have atypical presentations. Typically, in long-standing DPN, one may see lower amplitudes of the compound muscle action potential, slowing of sensory and motor nerve conduction velocities, prolonged F-wave latency, and an absent Hoffman reflex. NCS can provide information for peripheral large nerve fiber dysfunction but cannot assess small sensory fibers as thoroughly, which happens to be the earliest findings in DPN [11, 13].

While DPN shares many symptoms of CRPS such as pain and skin changes, clinical context and the slow progression of symptoms in DPN will help the clinician to differentiate. CRPS is generally a unilateral disease process affecting only one limb usually as opposed to DPN, which involves multiple limbs. CRPS also is a consequence of some form of injury, be it major or minor, while diabetic polyneuropathy is a progressive disease that can be seen as a sequela of poor glycemic control without evidence of any inciting injury. Trophic changes can be seen in both diseases.

HIV Polyneuropathy

As many as 50% of patients with HIV have been found to have evidence of distal symmetric polyneuropathy [14]. The hypothesized mechanism of HIV polyneuropathy is direct neurotoxicity from the virus, as well as potentially resulting from antiretroviral treatments. Patients with HIV polyneuropathy show decreased deep tendon reflexes, pain in a "glove and stocking" distribution, paresthesias, and decreased sensation most often in the lower extremities. Motor dysfunction and muscle atrophy are rare presentations. Older patients and those with more advanced disease are at higher risk of developing HIV polyneuropathy. In more advanced disease, temperature regulation dysfunction may also occur as it does in CRPS. Diagnosis is often clinical, but electrodiagnostic studies can be performed to support the diagnosis in more complicated cases [14, 15]. While NCS is not the gold standard of diagnosis, it may reveal slowed conduction velocities and reduced sensory nerve action potentials, which can help differentiate it from CRPS [14].

Other rarer variations of HIV neuropathies have been described including inflammatory demyelinating polyneuropathy, progressive polyradiculopathy, mononeuritis multiplex, and autonomic neuropathy. Inflammatory demyelinating polyneuropathy is associated with weakness and mild sensory loss, and treatment is immunomodulatory therapy. Diagnosis can be suggested by evidence of CSF pleocytosis [15]. Progressive polyradiculopathy can result in progressive flaccid paraparesis and is associated with cytomegalovirus (CMV) with treatment focused on anti-CMV therapy. Mononeuropathy multiplex is self-limited sensory and motor dysfunction affecting multiple peripheral or cranial nerves and is present early after HIV infection. Autonomic neuropathy is thought to be caused secondary to central or peripheral nervous system abnormalities that could be due to drug treatment or metabolic derangements, and treatment is supportive and aimed at correcting metabolic derangement or discontinuing the drug responsible [15].

Similarly to DPN as discussed above, HIV polyneuropathy shares many symptoms with CRPS, though key differences will aid in separating the diagnoses. CRPS is typically a disease precipitated by an inciting injury that is most often unilateral at the site of injury, while HIV polyneuropathy occurs without a specific sentinel event and is symmetric in a "glove and stocking distribution" in a patient diagnosed with HIV. Alternate forms of HIV neuropathies described above could also be distinguished from CRPS as inflammatory demyelinating polyneuropathy would have evidence of lymphocytic pleocytosis, progressive polyradiculopathy would have evidence of CMV infection, mononeuritis multiplex is typically self-limiting or can be associated with CMV infection, and autonomic neuropathy does not involve motor or sensory dysfunction [14, 15].

Postherpetic Neuralgia

Postherpetic neuralgia (PHN) is a pain syndrome associated with the reactivation of the varicella zoster virus which can lie dormant in the dorsal root ganglion for

extended periods of time. Upon reactivation, patients are stated to have herpes zoster, classically with an extremely painful rash in the dermatomal distribution in which the virus has previously laid dormant, though the pain can precede the rash and can be associated with severe allodynia [16–19]. Of those affected by herpes zoster, approximately 10% of patients may subsequently experience a chronic pain syndrome called PHN. This percentage affected increases with increasing age, with potentially greater than 30% of patients greater than 80 years of age being affected [16–19]. The exact cutoff point at which point an acute herpes zoster infection progresses to being deemed PHN has not been specifically delineated but is often discussed as cases that continue to have persisting pain and allodynia greater than 90 days after the onset of the rash [20, 21].

PHN and CRPS can both be debilitating pain syndromes but when considered clinically have very apparent differences. PHN, while associated with allodynia and severe neuropathic pain, is not classically associated with edema, temperature changes, or trophic changes. Furthermore, motor dysfunction can be present but is very rare [16]. In patients with a history of recent painful rash isolated in a dermatomal distribution, the diagnosis of PHN is far more likely than CRPS and should be the initial working diagnosis. It should be noted, however, that patients can subsequently develop CRPS following an episode of PHN, so in patients with prolonged symptoms or in cases where patients begin to develop other symptoms such as temperature differences between affected limbs, edema, or other trophic changes, the possibility of CRPS should be reevaluated [22].

Neurogenic Claudication

Neurogenic claudication is the classic presentation of lumbar spinal stenosis and is associated with pain, paresthesia, cramping, or weakness. Symptoms can be either unilateral or bilateral and are classically exacerbated with walking or any maneuver associated with extension of the spine and relieved with sitting or positions that flex the spine, as extension is thought to exacerbate cauda equina and lumbosacral nerve root compression. Many patients who have lumbar spinal stenosis are asymptomatic without evidence of neurogenic claudication, and furthermore, the correlation between severity of stenosis on imaging studies and severity of disease is poor. As such, the diagnosis of neurogenic claudication is generally a clinical diagnosis made based on characteristic position induced pain exacerbation [23, 24]. CRPS can be easily differentiated based upon history and physical exam and potentially imaging studies such as lumbar MRI to evaluate if any evidence of spinal stenosis is present. In addition, sudomotor or vasomotor dysfunction is not a presentation of neurogenic claudication. There may be motor dysfunction though there should not be allodynia/hyperalgesia, skin color/temperature, or trophic changes with neurogenic claudication. Radiation of pain in neurogenic claudication is often proximal to distal as opposed to distal to proximal in CRPS. Patients with CRPS also may have their symptoms at rest where symptoms of neurogenic claudication are often relieved with rest.

Central Post-stroke Pain

Central neuropathic pain is the result of insult or injury to the central nervous system. Of the many conditions leading to central neuropathic pain, cerebrovascular accidents (CVA) are the most common and share the most similarities with CRPS. Cerebrovascular accidents can be the source for both post-stroke central pain and CRPS in some patients.

Central post-stroke pain (CPSP) occurs in about 8% of patients surviving a cerebrovascular accident; however, the high incidence of cerebrovascular accidents makes CPSP more prevalent than central pain secondary to spinal cord injury, multiple sclerosis, or limb amputation [25, 26]. As most cerebrovascular accidents are ischemic and right-sided, these patients constitute the bulk of CPSP sufferers [25]. However, the risk of developing CPSP is similar between ischemic and hemorrhagic cerebrovascular accidents [26]. As central disinhibition secondary to disrupted communication between the sensory thalamus and somatosensory cortex is a prerequisite for central neuropathic pain, patients with strokes along with spinothalamocortical or lateral medullary pathways are at higher risk of developing CPSP [25]. Several studies cite a history of depression and younger age at the time of cerebrovascular accident as independent risk factors for CPSP [25–28].

CPSP is almost always unilateral and contralateral to the lesioned brain. Unlike other central neuropathic pain syndromes where pain begins shortly after CNS injury, CPSP can take 3–6 months to manifest [25]. Spontaneous pain is near constant with concurrent intervals of burning, squeezing, throbbing, lancinating pain [28]. Evoked pain can occur with pinprick testing and can follow limb movement, temperature changes, and even alterations in emotional states [29].

Diagnosis of CPSP is wholly clinical, and no single ancillary test yields sufficient sensitivity or specificity for CPSP. However, a definitive criterion for CPSP including an image-proven lesion and neuropathic pain along plausible somatosensory distributions has been previously recommended [30].

It is plausible to confuse CPSP and CRPS as both syndromes are diagnoses of exclusion and encompass stereotypical neuropathic pain. Additionally, CPSP is also more associated with nociceptive (musculoskeletal) limb pain than CRPS, hemiplegic shoulder pain being one of the most common pain complaints in stroke survivors [31, 32]. In contrast, isolated CPSP does not typically present with autonomic and vasomotor dysfunction, or trophic changes and therefore would not satisfy Budapest Criteria. Bone scintigraphy and autonomic function tests would likely prove ineffective. As mentioned before, and possibly obscuring the diagnosis, CRPS can be a consequence of stroke with an incidence as high as 48.8% [33]. However, recent studies investigating the validity of Budapest Criteria for diagnosing post-stroke CRPS is low and likely inappropriate [34].

Thoracic Outlet Syndrome

Thoracic outlet syndrome (TOS) is an umbrella term for the signs and symptoms associated with three related compression or impingement disorders involving

thoracic outlet structures: the subclavian vein (causing venous TOS or vTOS), subclavian artery (causing arterial TOS or aTOS), and brachial plexus (causing neurogenic TOS or nTOS, the most common presentation). These structures are most often compromised within the scalene triangle, or the space between the anterior scalene muscle, middle scalene muscle, and the superior border of the first rib. The costoclavicular space between the clavicle and first rib tends to be the site for subclavian vein compression. The pectoralis minor space between the pectoralis minor muscle and chest wall, and its tendinous insertion onto the coracoid process, may be the site for recurrent or refractory TOS [35].

Risk factors for TOS include younger age, female gender, the presence of cervical or anomalous first ribs, supernumerary scalene muscles, variations in bony structures and scalene muscle insertions, and changes in the brachial plexus anatomy or muscle fiber type, trauma, first rib and clavicular fractures, neck flexion/hyperextension injuries, and repetitive strain or overuse injuries [36]. TOS can be secondary to soft tissue or bony abnormalities [35].

NTOS should be suspected in patients with neck trauma and repetitive or overuse injuries with resulting upper extremity dysesthesia, paresthesia, numbness, and weakness several weeks to a month following the insult. Pain may extend beyond discrete peripheral nerve distributions. Additionally, NTOS can mimic cervical radiculopathy with pain extending to the occiput, neck, jaw, shoulders, and arms to the digits. Pain associated with TOS is typically aggravated with arm elevation, and patients will describe an inability to self-groom, retrieve objects from overhead, use the telephone or computer, play instruments, or drive. Affected limbs are normal in appearance and devoid of swelling or cyanosis with nTOS [35].

Venous congestion with marked pain, edema, and cyanosis of the affected upper extremity, and a propensity for deep vein thrombosis is consistent with vTOS. Paresthesias in vTOS appear to be secondary to profound swelling than neurogenic impingement [35]. VTOS is also common following neck trauma and injury and makes up 3% of TOS [37].

True ischemic claudication is characteristic of aTOS following compression of the subclavian artery. The propagation of mural thrombi at the subclavian artery is responsible for aTOS symptomatology. Upper extremity pain, pallor, paresthesia, coldness, or frank cyanosis may be observed. ATOS is rare and about 1% of all TOS cases [37]. With aTOS, cervical ribs and anomalous first ribs are nearly pathognomonic.

Ancillary testing for TOS diagnosis can be equivocal, especially with nTOS. EMG evaluations are frequently negative in cases of nTOS, and positive results tend to lack specificity for nTOS [38]. The utility of nerve conduction studies for TOS is controversial [39]. Somatosensory evoked potentials have been previously described as more sensitive for the diagnosis of TOS. Scalene muscle blockade with local anesthetic may help diagnose TOS and prognosticate recovery following surgical decompression [37]. Chest X-rays can help identify cervical and anomalous ribs. MRI can highlight finer soft tissue and bony abnormalities, but is more effective in ruling out other pathologies than it is for diagnosing TOS. Duplex upper extremity ultrasound is noninvasive, inexpensive, highly specific, and

sensitive for thromboembolization with vTOS and aTOS. The provocative maneuver detailed by Roos, consisting of bilateral 90-degree abduction-external rotation of the upper extremities with a three-minute period of hand opening and closing, has been cited as one of the more reliable tests for TOS. Also the Adson test can be performed, looking for decreased or disappearance of the radial pulse when the patient abducts and extends their shoulder while rotating their neck toward the symptomatic side [35].

As TOS can present with localized upper extremity limb pain, atrophy, color, and temperature changes, it can be difficult to distinguish TOS from CRPS. The paucity of allodynia, hyperesthesia, hyperpathia, and trophic changes associated with cases of TOS precludes agreement with the Budapest Criteria. Furthermore, radiographic evidence of bony and soft tissue abnormalities or external compression of the thoracic outlet can help further delineate TOS from CRPS. Finally, patients with TOS may display positive responses to provocative physical exam maneuvers as described above.

Vascular Disease

Vascular diseases such as peripheral arterial disease (PAD), ischemic claudication and deep vein thrombosis, or other sources of thrombophlebitis can be associated with burning, aching pain that also can have associated changes in temperature or edema, similarly to CRPS. With appropriate history, physical exam, and diagnostic studies, however, these syndromes can be differentiated from CRPS.

Peripheral Artery Disease and Ischemic Claudication

Ischemic claudication is a painful symptom of peripheral arterial disease where pain can occur distal to an area of chronic arterial occlusion. This most commonly affects the calf as the superficial femoral and popliteal arteries are the most common sites affected by atherosclerosis [40]. In addition to ischemic pain, patients may also suffer from cold, dry skin, and/or ulcerations in the area of impaired perfusion. Peripheral arterial disease can progress to a point where there is critical limb ischemia at rest that may necessitate surgical intervention or amputation to remove necrotic tissue [40, 41].

While PAD could be definitively diagnosed with use of contrast angiography, ankle brachial index (ABI) is far more frequently utilized as it is inexpensive, noninvasive, and can be conducted quickly. Diagnosis of PAD of the lower extremity can be made using ABI with very high sensitivity and specificity, 95% and 99%, respectively. A lower ABI correlates with worse disease and more profound ischemia [40]. As such, in patients who are at risk of PAD, this diagnosis could easily be made over CRPS with utilization of this quick and noninvasive study. It should be noted, however, that one of the major risk factors for the development of PAD is diabetes, and as such these patients may also be at risk for diabetic polyneuropathy

as described above [40]. Due to this confounder, even in the absence of an abnormal ABI in a patient with high clinical suspicion for PAD, further history and physical exam should be conducted prior to making the diagnosis of CRPS. Pain related to PAD should improve with interventions aimed at improving perfusion to ischemic tissues such as with phosphodiesterase III inhibitors, angioplasty, and bypass [40, 41]. Also, pain related to PAD typically worsens with exertion and is relieved with rest as opposed to pain related to CRPS, which occurs at rest as well as with exertion. Patients with PAD may respond favorably to sympathetic blocks due to improved perfusion just as a patient afflicted with CRPS may, so this should be kept in mind when differentiating between diagnoses. Again, a preceding injury, either major or minor, is required in CRPS, which is not seen in the clinical presentation of PAD.

Lymphedema

Lymphedema is the result of defects within the lymphatic circulation resulting in protein-rich fluid accumulating within tissues. The characteristic findings of lymphedema typically include localized pain, edema, atrophic skin changes, and superimposed infections. Lymphedema can either be primary or secondary with a primary being a developmental defect in lymphatic drainage while secondary is the result of some form of insult to the lymphatic system including surgery, trauma, infections, etc. In the developed world, the most common form of lymphedema is secondary to axillary lymph node dissection in breast cancer patients, occurring in 41–94% of breast cancer survivors [42, 43].

No diagnostic criteria for lymphedema is available, diagnosis typically being made by history and physical. Similarly to CRPS, lymphedema is a chronic pain syndrome with edema and atrophic skin changes that often occurs following trauma or surgery. A variety of tests are often utilized in the assessment of lymphedema, predominantly focused around measuring volume overload, but these tests are not specific as they would be positive in any syndrome with edema. Imaging studies would show evidence of fluid extravasation. Lymphoscintigraphy and magnetic resonance lymphangiography directly assess the lymphatic drainage and can be used more specifically to determine if lymphedema is responsible for swelling, though this is rarely conducted as these tests are expensive and can cause damage to lymph vessels [42, 43]. While lymphedema does share many similarities to CRPS and can occur in similar clinical contexts, the characterization of lymphedema pain is very different. While allodynia and hyperalgesia are extremely common in CRPS, it is not described in lymphedema, which is characterized by chronic aching pain [44]. One of the difficulties in differentiating lymphedema from CRPS is the predisposing surgery that can lead to both diagnoses, so very careful attention to pain characteristics must be noted.

Deep Vein Thrombosis and Thrombophlebitis

Deep vein thrombosis (DVT) and thrombophlebitis involve the formation of a blood clot in a vein. These patients typically display components of Virchow's triad of hypercoagulable state, endothelial injury, or prolonged stasis prior to being found to have a DVT [45]. This diagnosis can present very similarly to CRPS with findings of leg pain, warmth, swelling, and color changes, with the affected limb typically red or blue [46]. While the presentation may be very similar to CRPS, the differentiation between these two conditions can be achieved quickly with additional testing.

Patients for whom there is clinical suspicion of DVT are risk stratified using clinical models to place a patient as either high risk or low risk. Low-risk patients have their D-dimer levels evaluated, which would be elevated in the setting of DVT with high sensitivity and low specificity. In the setting of elevated D-dimer, further evaluation could be taken, but in the setting of low D-dimer, the diagnosis of DVT can almost certainly be ruled out. In higher risk patients based upon previously mentioned clinical models, more definite testing can be conducted such as ultrasound imaging to evaluate the presence of blood clots in the affected limb, or less commonly, CT angiography [46].

Erythromelalgia

Erythromelalgia (previously coined Mitchell's disease) is a rare disorder of the upper and lower extremities, originally described by Dr. Silas Weir Mitchell, who also first detailed residual limb pain and CRPS. With erythromelalgia, affected limbs appear edematous, erythematous, exhibit local heat, and bare the stigmata of a commonly intermittent neuropathic pain [47, 48]. Attacks are exacerbated by strenuous activity and alleviated by rest, cold compresses, judicious use of cool water, and fans [49]. More importantly, administration of aspirin effectively terminates erythromelalgia attacks. Erythromelalgia is so often concomitant with polycythemia vera and essential thrombocythemia, that it is considered pathognomonic for myeloproliferative disorders [48]. While the pathophysiology of erythromelalgia remains unclear, the responsivity to aspirin suggests an abnormal arachidonic acid metabolism [50]. Inherited or primary erythromelalgia may be due to genetic mutations of voltage-gated sodium channels of somatosensory nerves. Management of this disorder typically involves avoidance of triggering factors. Of note, certain interventions including sympathetic blocks and steroid administration may aggravate symptoms of erythromelalgia [49]. Objective measures to diagnose erythromelalgia are limited; however, recent studies have demonstrated significant distal small fiber neuropathy and postganglionic sudomotor dysfunction with autonomic and neurophysiologic studies [51]. In comparison to CRPS, three points can help

delineate diagnosis: erythromelalgia demonstrates predominance in the lower extremities with a bilateral and symmetric distribution, pain from erythromelalgia is relieved by cold as opposed to CRPS patients who often demonstrate allodynia to cold exposure, and erythromelalgia usually lacks prior peripheral injury or nerve damage [51].

Inflammatory Disease

Despite CRPS having mainly neuropathic components, a variety of inflammatory diseases share many symptomatic similarities. Inflammatory processes are often associated with pain and temperature changes of affected regions. Laboratory findings in conjunction with history and physical can help differentiate many of these disease processes from CRPS, which is paramount as these diseases can be provided therapies, which can help with reducing morbidity.

Rheumatoid Arthritis

Rheumatoid arthritis (RA) is a common systemic inflammatory arthritis most commonly appearing between the ages of 30–50, and most commonly affects females, smokers, and those with family histories of RA [52, 53]. Rheumatoid arthritis typically presents with stiffness and pain seen in multiple joints, most commonly the proximal interphalangeal and metacarpophalangeal joints and is classically symmetrical, though not always. Muscle atrophy and weakness are common in long-standing disease [52, 53]. Autonomic neuropathies and sudomotor dysfunction can be seen in RA though the etiology of these pathologies is not entirely understood [54]. Patients may also suffer from edema secondary to synovitis and may have nonspecific systemic symptoms such as fever and fatigue. Two main diagnostic criteria have been used, the 1987 American College of Rheumatology classification criteria and the 2010 American College of Rheumatology/European League Against Rheumatism Classification Criteria with the 2010 criteria being utilized more recently to attempt to diagnose patients with earlier disease as the 1987 criteria have many symptoms and presentations that do not reveal themselves until further along the disease process. The 2010 guidelines focus diagnosis on the amount of joints involved, serologic markers (rheumatoid factor or anti-citrullinated protein antibody), evidence of acute phase reactants (CRP or ESR), and duration of symptoms greater than 6 weeks. Treatment is centered on disease-modifying antirheumatic drugs (DMARDS) such as methotrexate. Treatments can also include corticosteroid injections, NSAIDs, and physical therapy [52, 53].

Certain presentations of rheumatoid arthritis can easily be misdiagnosed as CRPS, but with careful clinical history and diagnostic tools such as the 2010 diagnostic guidelines, the proper diagnosis can be made. RA is generally a symmetric disease not associated with an inciting insult and is associated with elevated seromarkers and acute phase reactants while CRPS is not [55].

Infection and Cellulitis

Cellulitis is an infection of the skin and subcutaneous tissue most commonly secondary to Gram-positive cocci. Patients classically present with redness, swelling, warmth and pain in the affected area. The severity of cellulitis varies anywhere from small localized infections to life threatening necrotizing fasciitis. Blood cultures have been shown to have poor sensitivity for cellulitis. Wound cultures, while more sensitive than blood cultures, are negative in up to 70% of cases [56]. Diagnosis is often clinical but can be made with a variety of laboratory and imaging studies. CT and MRI imaging are highly sensitive and specific for soft tissue infections though ultrasound is becoming increasingly utilized [57].

Cellulitis and CRPS can be easily differentiated from one another given clinical history, laboratory values, response to antibiotics, and imaging studies. While both can present with color changes, temperature changes, and pain, cellulitis should not cause any muscle weakness, should be responsive to antibiotics, likely is associated with a leukocytosis and would show characteristic findings under imaging studies [56, 57]. Cellulitis can occur after a minor injury with a skin breakdown, which can cloud the diagnostic picture. Patients with advanced infection can have constitutional symptoms such as fever and chills, which should not be seen in CRPS.

Chronic Inflammatory Demyelinating Polyneuropathy

Chronic inflammatory demyelinating polyneuropathy (CIDP) is an often underdiagnosed, acquired, chronic neuropathy characterized by a symmetric, predominantly motor impairment of both proximal and distal limbs [58]. Sensory loss and diminished or absent reflexes are often seen. Risk factors include male gender and advanced age. Akin to other demyelinating disorders, the disease course can be relapsing or progressive, with the latter observed more frequently in older populations [58].

The cause of CIDP is unknown. The similarities between CIDP and Guillain–Barre disease, which is an acute and self-limiting disease, and responsivity to steroids and immunosuppressant therapies suggest an immune-mediated pathogenesis [58]. CIDP can be associated with a variety of presentations, regional, asymmetric, sensory predominant, temporospatial, and disease-associated variants have all been described [59].

The diagnosis of CIDP is based primarily on clinical examination and nerve conduction studies [60]. Partial motor nerve conduction blockade, as well as reduced velocity, increased latency and prolonged F wave latency must be apparent. The presence of elevated protein in cerebrospinal fluid and biopsy-proven demyelination are supportive but not required [61]. There are many accepted diagnostic criteria that exist for CIDP: the American Academy of Neurology, Saperstein, European Federation of Neurological Societies and the Peripheral Nerve Society (EFNS/PNS), Koski, and the Inflammatory Neuropathy Cause and

Treatment criteria [61]. There is no consensus, however, regarding which one is superior. Proper diagnosis of CIDP is paramount as it can be treated. Randomized controlled trials have been conducted and show supporting management with intravenous immunoglobulin, plasma exchange, and corticosteroids to be beneficial [58].

CIDP and CRPS share the potential for motor impairments. Only polyneuropathy variants of CIDP may share neuropathic pain components with CRPS. The slowed initiation of limb movement, tremor, dystonia, weakened grip, or stance with CRPS can be confused with CIDP. Still the functional abnormalities of CRPS are more pain-focused, either avoidant or resultant, in contrast to CIDP. The lack of symmetrical areflexia more supports CRPS diagnosis rather than CIDP.

Gout

Gout is the most common inflammatory arthritis that is the result of chronic deposition of monosodium urate crystals in patients with elevated urate concentrations [62]. Patients often describe gout flares, most commonly in the first metatarsophalangeal joint, where intra-articular depositions of the monosodium urate crystals develop an acute inflammatory reaction [62, 63]. Patients can also present with nonspecific symptoms associated with inflammation such as swelling, warmth, and redness of the affected joints. Chronically, these patients can develop skin changes known as tophi as the consequence of chronic inflammation in the area. These tophi are characterized by swelling and impaired mobility of the joint and can infiltrate the bone causing erosion and damage to the associated joints, often resulting in chronic pain [62, 63].

While patients suffering from chronic gout often have evidence of a variety of similar symptoms to those experiencing CRPS, clinically these syndromes are generally very easily distinguished from one another. The gold standard for diagnosis of gout is visualization of monosodium urate crystals upon aspiration of synovial fluid or within a tophus. Patients suffering from gout often also have elevated inflammatory markers during acute exacerbations, which would not be appreciated in CRPS [55, 62, 63].

Myofascial Pain Syndromes

Myofascial pain syndromes are a broad category of diseases that sometimes present with chronic pain in a specific limb following injury. Patients who suffer from myofascial pain syndromes, as described below, could potentially progress to development of CRPS. However, in the acute setting, these syndromes can be easily differentiated from CRPS.

Sprains/Strains/Tendinopathies

Tendinopathies are painful syndromes of degenerated tendons. Despite the absence of inflammatory infiltrates and minimal response to anti-inflammatory medications, recent studies suggest that chronic inflammation may play a large role [64, 65]. Sprains are ligament injuries that result from excessive force exceeding the tensile strength of the ligament. While often described in the ankle following falls during sports, any ligament could be affected [66]. Strains differ from sprains as they result in damage to muscles as opposed to ligaments and are the result of excessive stress on a muscle [67].

While tendinopathies, sprains, and strains can all progress to CRPS, as they often occur after injury, they classically do not have any trophic changes, vasomotor dysfunction, or muscle wasting/weakness beyond difficulty moving affected joint secondary to pain. Patients may experience warmth or edema to an affected joint, but it is generally self-limited with conservative treatment. Imaging modalities can be used such as MRI to further confirm suspicions in less obvious cases, though most cases are diagnosed clinically [67, 68]. Furthermore, the acuity of symptoms in sprains and strains following a trauma would far more likely lead to the diagnosis of sprains or strains with the diagnosis of CRPS being considered if symptoms do not regress or evolution of other classic CRPS symptoms follow. Triple-phase bone scan and sympathetic blocks may be helpful tools to help differentiate the diagnoses if the patient's symptoms are lasting longer than should be expected based on the initial injury.

Fibromyalgia

Fibromyalgia, in a similar fashion to CRPS, is often a difficult diagnosis for physicians to make due to vague and widespread symptomatology. The diagnostic criteria of fibromyalgia has been an ongoing debate; however, most acknowledge certain symptoms to appear in most individuals. Most patients report hyperalgesia or allodynia, bilateral axial pain, and chronic distress or fatigue [69, 70]. The 2010 American College of Rheumatology (ACR) diagnostic criteria and 2016 revisions are often utilized to make a diagnosis of fibromyalgia. They include four main components: widespread pain index and symptom severity scale, symptoms lasting for at least 3 months, generalized pain in at least four regions, and a diagnosis of fibromyalgia is valid even in the presence of other diagnoses [71]. Widespread pain index is determined by a questionnaire asking how many locations the patient has been experiencing pain and symptom severity score is a questionnaire evaluating quality of life impairment as a result of the disease [71]. While patients may report evidence of hyperalgesia or allodynia, fibromyalgia can be differentiated from CRPS due to its typically bilateral nature and lack of vasomotor, trophic, sudomotor, or motor dysfunction, as well as a lack of preceding injury.

Psychological Syndromes

Finally, certain psychiatric conditions can be mistaken for CRPS though further work up often results in the ability to easily differentiate the conditions with thorough history, physical exam, and additional studies such as imaging and lab results. These diagnoses are always a diagnosis of exclusion.

Somatoform Syndrome

Somatoform syndrome is a psychiatric disease where patients often can express pain in multiple locations throughout the body, fatigue, and a wide array of nonspecific complaints that all are found to have no clear pathology, usually after extensive testing. The reported symptoms may change over the course of the disease but must persist for at least 6 months in order to reach the diagnostic criteria set forth by DSM-V [72, 73]. Physical exam can distinguish this disease from CRPS as no evidence of edema, vasomotor, sudomotor, motor, or sensory deficits would be seen in somatoform syndrome. Somatoform symptoms will likely be widespread with an absence of an inciting injury.

Factitious Disorder/Munchausen's Syndrome

Unlike Somatoform syndrome in which patients report symptoms that they perceive despite no clear pathology, factitious disorder, also often referred to as Munchausen's syndrome is a condition where patients fabricate symptoms, physical exam findings, or laboratory results in order to play the "sick role" [74, 75]. Patients can have a variety of presentations with nonspecific abdominal pain or in multiple limbs being common complaints [74]. Factitious disorder should be distinguishable from CRPS thorough history, physical exam, and psychological evaluation. Patients demonstrating factitious disorder will not display any physical evidence of edema, vasomotor, sudomotor, or sensory deficits.

Conclusion

As we have discussed, many diseases sharing similar characteristics to CRPS can complicate diagnosis and delay appropriate treatment. Many of these diagnoses are made clinically, further complicating differentiating between etiologies. Despite the similarities, the majority of these diseases can be properly differentiated with very careful attention to specific components of physical, history, and lab testing. Table 3.2 summarizes the means by which to help differentiate the aforementioned diseases from CRPS.

Table 3.2 Overview of common mimickers of CRPS with key differentiating factors

Category	Disease	Differentiation from CRPS
Neurologic	Nerve entrapment syndromes (i.e., Carpal Tunnel syndrome)	Typically in a specific nerve distribution without an inciting nerve injury Usually abnormal NCS/EMG findings Ultrasonography may show smaller than average nerve cross-sectional area
	Diabetic polyneuropathy	History of DM, typically with longer disease process and poor glycemic control Pain in a "glove and stocking" distribution with symmetric symptoms Not associated with a traumatic event
	HIV polyneuropathy	Patients have a diagnosis of HIV Pain in a "glove and stocking" distribution with symmetric symptoms Inflammatory demyelinating polyneuropathy variant would have lymphocytic pleocytosis Progressive polyradiculopathy and mononeuritis variant would have evidence of CMV infection Autonomic neuropathy variant would not involve any motor or sensory dysfunction and would be associated with a metabolic derangement or new medication being started Not associated with a traumatic event
	Postherpetic neuralgia	Associated with preceding painful rash isolated in a specific dermatomal distribution Rarely associated with edema, trophic changes, vasomotor, or motor dysfunction Viral PCR positive in active zoster infection Not associated with a traumatic event
	Neurogenic claudication/lumbar stenosis	Pain worse with extension of back Imaging studies would show spinal stenosis No sudomotor and vasomotor dysfunction
	Central post-stroke pain	Typically no autonomic or vasomotor dysfunction No trophic changes
	Thoracic outlet syndrome	Typically minimal allodynia, hyperesthesia, hyperpathia or trophic changes Radiologic imaging can show evidence of thoracic outlet obstruction or compression Provocative physical exam findings can exacerbate pain (Roos, Adson tests)
Vascular	Ischemic claudication	Abnormal ankle/brachial index Brought on with repeated movements, typically pain free at rest until achieving critical limb ischemia
	Lymphedema	Allodynia typically not a component of diagnosis, predominate symptom being edema Lymphoscintigraphy findings
	Deep vein thrombosis	Positive D-dimer Positive radiologic imaging studies consistent with DVT Unlikely to have motor or trophic changes
	Erythromelalgia	Usually bilateral, distal, and symmetric Relieved by cold Aspirin can alleviate symptoms Not associated with a traumatic event

(continued)

Table 3.2 (continued)

Category	Disease	Differentiation from CRPS
Inflammatory/ infectious	rheumatoid arthritis	Typically bilateral, predominantly located in joints Elevated CRP/ESR, elevated RF, and anti-citrullinated protein Not associated with a traumatic event
	Cellulitis	No motor changes Characteristic findings on radiological studies Associated with characteristic findings of infection, i.e., bandemia, tachycardia, tachypnea, etc.
	Chronic inflammatory Demyelinating Polyneuropathy	Burning pain with profound weakness Associated with symmetrical areflexia Can be seen in multiple extremities simultaneously EMG/NCS and lumbar puncture can be performed to help differentiate
	Gout	Visualization of monosodium urate crystals in synovial fluid May have elevated ESR/CRP, serum uric acid, and/or leukocytosis Not associated with a traumatic event
Myofascial pain syndromes	Sprains/strains/ tendinopathies	No trophic, sudomotor, vasomotor, or motor deficits Characteristic findings on imaging
	Fibromyalgia	No trophic, sudomotor, vasomotor, or motor deficits Typically bilateral symmetric symptoms Not associated with a traumatic event
Psychological syndromes	Somatoform disorder	No edema, trophic, sudomotor, vasomotor, or motor deficits Not associated with a traumatic event
	Factitious disorder/ Munchausen syndrome	No edema, trophic, sudomotor, vasomotor, or motor deficits Not associated with a traumatic event

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Diagnostic Tests and Physical Exam for CRPS

4

Chris Woolley and Joel P. Castellanos

Key Points

- The diagnosis of CRPS can be challenging
- There are common physical exam findings in CRPS
- There are validated diagnostic criteria and severity scales for CRPS
- There are minor diagnostic tests which have shown some clinical relevance in the diagnosis and guiding of treatments for CRPS

Definition

Chronic regional pain syndrome (CRPS) is a disorder affecting upper and lower extremities, which typically presents with pain elicited by normally non-painful stimuli (allodynia), non-dermatomal burning pain, erythema, and edema. CRPS is often divided into two classes: CRPS-1 and CRPS 2.

- *CRPS-1:*

CRPS-1 is previously referred to as reflex sympathetic dystrophy (RDS.) It is defined as nociceptive pain in the absence of peripheral nerve damage, as demonstrated by electrodiagnostic testing or physical exam [1].

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- *CRPS-2:*

CRPS-2, previously known as causalgia, is characterized by neuropathic pain in the presence of damage to a known peripheral nerve [1].

- *CRPS-NOS:*

CRPS not otherwise specified (NOS) is defined as CRPS that partially meets diagnostic criteria and is not better explained by any other condition [1, 2].

Presentation and Physical Exam

The diagnosis of complex regional pain syndrome (CRPS) is often challenging for physicians due to nonspecific presentation of the disease. Patients with CRPS can present with a myriad of symptoms, including sensory abnormalities, autonomic signs, and motor dysfunction [3].

Although patients with CRPS can present with many nonspecific physical exam findings, the most common finding is intense, burning pain in a location where the patient experienced a previous injury (often a distal limb injury). Symptoms typically present 4–6 weeks after an inciting event. CRPS more commonly affects upper limbs and has a higher incidence in females. Pain can be triggered by acute mechanical or thermal stimuli to the area. Pain out of proportion to the nature of the inciting event is often observed. The severity of the disease may wax and wane. Patients experiencing an acute CRPS exacerbation often describe burning pain spreading from the area of insult in a non-dermatomal pattern and may experience skin temperature changes and erythema. With chronicity of the disease, decreased hair growth and dystrophic nail changes may occur. Muscle weakness and/or decreased muscle mass can be observed. Classically, CRPS has been described to impact a patient in three "stages" [1]:

1. An early stage that is classified by hyperalgesia, allodynia, vasomotor and pseudomotor changes, and edema.
2. A middle stage (3–6 months after onset of symptoms) consisting of dystrophic changes, including progressive pain and sensory dysfunction with increased motor and trophic changes.
3. A late phase characterized by atrophic changes including decreased pain and sensory disturbances, and markedly increased motor and trophic changes. While there can be significant overlap of symptoms between the three groups, and the disease may develop in a nonsequential manner, this "three-stage" theory is often used clinically as a guide to the chronicity of the disease [4]. A complete list of physical exam findings in these three stages can be found in Table 4.1.

Table 4.1 Common physical exam findings in CRPS [1]

1. Acute stage	2. Dystrophic stage	3. Atrophic stage
Allodynia	Increased hyperalgesia/ allodynia	Decreased pain/sensory disturbances
Hyperalgesia	Increased sensory dysfunction	Dystrophic nail changes
Burning pain spreading in a nondermatomal pattern	Continued skin temperature changes	Irreversible muscle weakness, decreased muscle mass
Skin temperature changes (increased or decreased)	Muscle weakness	Decreased hair growth
Skin erythema	Skin, hair, and nail changes	Myoclonus
		Movement disorders (tremors, dystonia)

Table 4.2 1994 IASP criteria [3, 5]

Presence of pain after an initial inciting event
Allodynia or hyperalgesia out of proportion for the inciting event
Evidence of skin changes, pseudomotor dysfunction, or edema
The absence of any other syndrome that would otherwise explain the presenting syndromes

Diagnosis Criteria

Diagnostic criteria for CRPS was initially established in 1994 by the International Association for the Study of Pain (IASP) and included allodynia after an initial inciting event, physical skin changes, and edema. The full 1994 IASP criteria can be found in Table 4.2. These original criteria were criticized for being ambiguous, having a low specificity, and ultimately lead to overdiagnosis [2]. In 2003, a new diagnostic criterion known as the Budapest Criteria was established. These criteria have been found to be much more specific than the original IASP criteria for the diagnosis of CRPS [5, 6]. The Budapest Criteria can be found in Table 4.3.

Severity of Disease

The clinical features of CRPS can differ from one patient to another. Furthermore, significant changes in clinical features can be seen within the same patient over time. It has been theorized that diagnosing CRPS as a dichotomous "yes/no" diagnosis may not entirely convey the subtle gradations in severity of the condition, or progress made in treatment. The CRPS Severity Score (CSS) was created in order to provide information about individual differences in severity or lability of CRPS signs and symptoms [7]. The CSS includes 17 signs and symptoms derived from the Budapest Criteria. Each response is graded as present (1 point) or absent (0 points). Using the CSS, higher

Table 4.3 Budapest Criteria [3, 5, 6]

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

Table 4.4 CRPS Severity Score (CSS): Diagnostic signs and symptoms [7]

Self-reported symptoms:
Allodynia, hyperpathia
Temperature asymmetry
Skin color asymmetry
Sweating asymmetry
Asymmetric edema
Trophic changes
Motor changes
Decreased active range of motion
Signs observed on examination:
Hyperpathia to pinprick
Allodynia
Temperature asymmetry by palpation
Skin color asymmetry
Sweating asymmetry
Asymmetric edema
Trophic changes
Motor changes
Decreased active range of motion

scores correlated with increased pain intensity, functional limitations, and emotional distress [7]. While there is no threshold for a "severe" score, an internal validation study of the CSS demonstrated that a baseline score of a patient newly diagnosed with CRPS and one with stable CRPS were both roughly 11 out of 17. Any therapy that resulted in a decrease in a patient's CSS value of 4.9 points indicated a real change in CRPS severity [8, 9]. There has been found to be more variation in CSS values over time among patients with new diagnoses of CRPS than in established patients with CRPS who are on stable treatment regimens [8]. The CSS has validity when used as a measurement to track the response to treatment and to communicate CRPS severity between clinicians [7]. The CRPS Severity Score can be found in Table 4.4.

Diagnostic Tests

Tests such as thermography and bone scintigraphy have been utilized as diagnostic tests for CRPS and have some validation in current literature. However, while diagnostic criteria are well established, there is no definitive diagnostic test for CRPS, with the diagnosis being predominately clinical through the Budapest Criteria.

Thermography

Thermography is an optional diagnostic tool for CRPS, which can be performed in a clinical setting using infrared or adhesive contact thermometers. Patients may present with temperature changes in the effected limb, and it has been shown that acute disease is associated with higher maximal temperatures than patients with chronic CRPS [7]. Maximal skin temperature differences (either an increase or decrease) of 2.2 °C between affected and non-affected limb has been found to be highly sensitive for diagnosis of CRPS [7]. Unfortunately, temperature differences, and even color changes, can be present in several other disease states such as neuropathic pain after nerve injury, soft tissue injury, posttraumatic arthrosis, psychosomatic pain disorder, short-term immobility, and dependency of the limb [10]. Therefore, it has been proposed that long-term period skin temperature measurement on a daily basis may be a superior diagnostic test than a singular skin temperature side difference measurement. Patients with CRPS have been found to exhibit profound differences in long-term averaged side temperatures when compared to healthy controls and patients with chronic limb pain not due to CRPS. One study found long-term thermography to be diagnostic for CRPS with a specificity between 67 and 79% [10].

Radionuclide Bone Scintigraphy

Radionuclide bone scintigraphy (RNBI) is an imaging technique that utilizes radiotracer technetium 99m-labeled methyldiphosphonate (MDP) affinity for binding to hydroxyapatite crystal surface at the mineralization front of bone [11]. The localization of the tracer at mineralization front is dependent on the vascular perfusion and extraction to/from the bone [11]. RNBI is an established technique used in the diagnosis of benign bone lesions, malignancy staging and follow-up, trauma, and degenerative joint diseases as it provides information about perfusion status, soft tissue edema, and inflammation [11]. Three-phase bone scanning (TPBS) is a multistep imaging procedure that utilizes RNBI measured at different time intervals. TPBS is most commonly used during differentiation of osteomyelitis vs. cellulitis, assessment of joint hardware, bone viability in avascular necrosis, and CRPS. The three phases are (1) the “flow” phase, which captures the injection of tracer; the (2) immediate blood pool phase, which is acquired as the tracer leaves the intravascular compartment and is distributed into the extracellular space and soft tissues; and the

Table 4.5 Three-phase bone scanning (TPBS) [11]

Phase	Description/details	Clinical evaluation
1. Flow phase	Immediately following intravenous injection of Tc99m-MDP. Image acquisition is commonly obtained over 60 seconds	Presence of preferential Hyperemia
2. Blood pool/ soft tissue phase	Continuous acquisition over 3 minutes following initial injection	Presence of preferential Hyperemia
3. Delayed phase	Obtained 2–3 hours after initial injection (4–6 hours for patients with peripheral vascular disease, or poor renal function.)	

(3) delayed phase, which is captured hours after initial injection to evaluate level of radiotracer bound to osseous structures. Table 4.5 summarizes the three phases of TPBS [11].

Adults with CRPS have characteristic scintigraphic findings on TPBS. Typically, the affected limb will demonstrate asymmetrically increased uptake on flow, blood pool, and delayed phases, and the delayed phase will demonstrate increased periarticular activity [11]. Various studies have found that the increased tracer uptake in the delayed phase is particularly diagnostic for CRPS in adults with sensitivity of roughly 80% and specificity of ~70%. The prominence of these findings appears to be the greatest within the first 6 months after inciting injury. The early phases (flow and blood pooling phases) have been found to have more variability in appearance and are less reliable for diagnosis [11, 12]. Recently, it has been hypothesized that the early phases of TPBS may be useful in detection of CRPS early in the disease process and may show asymmetry when there are no differences recognized on delayed phase scans [11, 13]. Additionally, sequential changes on TPBS between early acute, acute, and chronic stages of CRPS have been found to correlate with CRPS diagnosis [13]. However, these findings are controversial, as there have been contradictions with the correlation of imagining with clinical stage of the disease.

Children with CRPS have been found to exhibit a reduced tracer uptake in the affected limb when imaged using TPBS, exhibited by reduced flow, blood pool, and uptake. This has been deemed a "cold variant." While most commonly seen in children, it can also occur in adults [11].

Diagnostic Imaging Techniques

Electromyography (EMG)

Dystonia and myoclonus are symptoms found in ~10–35% of patients presenting with CRPS. Although the origin of these symptoms is unknown, they may stem from disinhibition on the spinal and cortical level [14]. Recently, small studies

have demonstrated the utility of electromyography (EMG) to evaluate the myoclonus observed in patients with CRPS. These studies concluded that movement disorders in CRPS have a distinct clinical presentation and may differ from myoclonus found in patients with other movement disorders [14]. The use of EMG for the evaluation of movement disorders in CRPS may increase as future studies take place.

Musculoskeletal Ultrasound

Musculoskeletal ultrasound (MSK USG) can be used to identify myofascial structural lesions such as tendon and ligament trauma. In limited studies, MSK USG has been shown to characterize structural differences in effected muscle tissue in CRPS patients when compared to patients with postsurgical neuropathic pain [15]. CRPS-affected musculature may demonstrate loss of normal architecture, increased homogeneity, and hyperechoic appearance on ultrasound visualization. A decrease in muscle fibers inside fibrous septa leaves an increased fibrotic appearance, which can be found in other diseases of muscle atrophy. CRPS-affected musculature may exhibit a fibrous appearance within 1 week of disease onset [14].

Skin Biopsy

A 2012 case series by Kharker et al. investigated skin biopsy findings in patients with CRPS-I and attempted to correlated them with quantitative sensory testing (QST) [4]. They evaluated changes included epidermal nerve fiber density, sweat gland nerve fiber density, and morphological abnormalities. They noted changes in skin innervation in approximately 20% of patients but were unable to correlate this with any consistent patient characteristics including QST, severity of hypoesthesia, or severity of allodynia.

Conclusion

CRPS is a complex condition, which entails pathophysiology that is still not entirely understood [16]. It is a disorder that can have debilitating effects on a patient's life, and these patients can often present to a chronic pain management physician. The diagnosis of CRPS can be made using a combination of thorough history, physical exam, diagnostic measures, and clinical judgment. Although diagnosis may be difficult, measures such as the Budapest Criteria, and tests such as EMG, or thermography have aided physicians in this process. Early diagnosis is often beneficial in order to guide patients to appropriate therapies and can ultimately make the chronic management of CRPS more successful.

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Part II

Treatment of CRPS

Pharmacologic Treatments for CRPS

5

Trusharth Patel

Nonsteroidal Anti-inflammatory Drugs

A cascade of inflammatory mediators are released in the early stages of complex regional pains syndrome and are believed to cause sensitization seen in CRPS. Prostaglandins are part of this inflammatory cascade, and inhibition of synthesis by NSAIDs via inhibition of cyclooxygenase 1 and 2 enzymes is the mechanism of analgesia. Theoretically, reduction of inflammatory mediators in CRPS with the use of NSAIDs should help alleviate hyperalgesia. Only a few studies have examined the use of NSAIDs for treatment of CRPS. Unfortunately, results have only shown short-term analgesia and no clear benefit with other measurable CRPS findings such as edema. A small study of 20 patients with CRPS published in 2014 examined the use of selective Cox 2 inhibitor using 80 mg of intravenous parecoxib over 2 days. The researchers did not find any reduction in spontaneous pain, pressure hyperalgesia, heat hyperalgesia, edema, or maximal pain intensity with the treatment of intravenous parecoxib [1]. An earlier smaller pilot study of 12 patients performed in 2011 used ketorolac 30–120 mg combined with lidocaine for an intravenous regional block of lower extremity CRPS. This was done with four treatments, each approximately 1 week apart. The researchers only found a reduction of pain from 6 to 4 (NRS 0–10) 1 day post-treatment but failed to see benefit beyond this. There was no benefit seen in pain with movement at 1 week or difference in lower extremity volume [2]. Earlier studies did show some favorable findings in pain reduction with intravenous regional block with ketorolac and lidocaine in the adult and pediatric population [3–5], though these were small case series. One larger three-arm study with $n = 10$ in each group did show that the addition of parecoxib to intravenous regional containing lidocaine/clonidine resulted in reduced visual analog scale at 2 and 3 weeks of treatment compared to controls of systemic

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parecoxib and control intravenous regional lidocaine/clonidine [6]. Results overall are mixed, and limitations of all studies conducted thus far being underpowered as well as heterogeneous in duration of CRPS of study patients make it difficult to define the role of NSAIDs in the treatment of CRPS. However, a fairly low incidence of adverse events and high tolerability for a short course make this class of drug a reasonable early treatment option in the management of hyperalgesia of CRPS.

Bisphosphonates

One of the characteristic findings and defining diagnostic criteria of CRPS is atrophy of tissue. This may involve bone deterioration resulting in positive early findings seen on triple phase bone scan, or a pattern of visible changes on MRI. Plain radiographic imaging may show skeletal changes later in the course of CRPS [7]. One study has demonstrated dysregulation of bone metabolism via overexpression of osteoprotegerin, a bone metabolism regulating molecule in CRPS [8]. It seems logical to conclude that medications with antiresorptive properties such as bisphosphonates can block the trophic changes of CRPS, thus reducing associated pain. The mechanism of bisphosphonates in CRPS, however, is believed to be more complex than this. Bisphosphonates can reduce the acidic environment created by osteoclastic activity seen in CRPS, though the mechanism of enhanced osteoclastic activity in CRPS remains controversial and not clearly demonstrated [9–11]. Bisphosphonates also inhibit macrophage activity, inhibit pro-inflammatory cytokines, and regulate expression of nerve growth factors. Thus, they can modulate the microenvironment pH, inflammatory cascade, immune pathways, and nociceptive pain signaling [9, 12, 13]. Bone changes are seen typically in the earlier phases of CRPS, and maximal therapeutic benefit from bisphosphonates is likely seen with early administration [7].

Few high-quality studies exist examining the efficacy and safety profile of bisphosphonates. A recent meta-analysis evaluating pooled analysis from four randomized clinical trials suggests that bisphosphonates have a favorable effect on pain reduction and a positive trend toward improved function [14]. All four studies showed reduced short-term pain VAS of 2.6 ranging from 30 to 40 days. Two studies demonstrated statistically significant improvement in medium-term pain VAS of 2.5 ranging in the 2nd and 3rd months. All four studies showed improvement in functionality measures in which one study showed improvement in mobility tolerance and the others showed improvement on multiple measures of the Short Form-36 [11, 15–17]. Of the 181 patients in the meta-analysis with 90 in the bisphosphonate group and 91 in the placebo group, 35.5% of the treatment group experienced nonserious adverse events of fevers, gastrointestinal intolerance, erythema, injection site discomfort, nonclinically significant hypocalcemia, and polyarthralgia compared to 16.4% in the placebo group. No serious adverse events were observed suggesting that bisphosphonates are a relatively safe therapy in a short course for

CRPS. There is some heterogeneity in the data in that all four studies used different bisphosphonates which, in the studied doses, may not have been equivalent in bioavailability. The formulations used include alendronate PO daily for 8 weeks, pamidronate IV 60 mg once, clodronate IV 300 mg daily for 10 days, and neridronate IV 100 mg four times in 10 days. This raises uncertainty in optimal dose, frequency, route of administration, and duration of treatment. Long-term data beyond 4 months are lacking [14].

Calcitonin

Calcitonin, like bisphosphonates, imparts its effect on bone metabolism, tilting the scale toward possible bone osteoblastic activity rather than osteoclastic activity with the theory that this counters the atrophy of bone tissue and ensuing pain seen in CRPS. Calcitonin may also provide analgesia through β-endorphin release and through central pain processing in the thalamus, periaqueductal gray, nucleus gigantocellularis, and raphe nucleus [18, 19]. Another theory is that calcitonin modulates vascular flow in CRPS which can have an anti-inflammatory effect [20]. One of the early randomized controlled trials examined intranasal calcitonin 100 units 3×/day for 3 weeks in conjunction with physical therapy versus physical therapy and intranasal saline placebo. Pain at rest, pain with movement, and range of motion were slightly improved at 8 weeks in the treatment group versus placebo. Ability to work was slightly improved in the treatment group but only if the CRPS was in the upper extremity and not in the lower extremity. There was no difference in edema changes between groups and no observed serious adverse events. Some of the reported mild to moderate adverse event in the calcitonin group included epigastric pain, pruritus, headache, and vertigo [21]. Another smaller RCT of similar methodology was performed examining intranasal calcitonin 200 units per day plus calcium 500 mg/day versus a control group of acetaminophen 1500 mg/day. Calcium was added likely due to calcitonin's transient effect of lowering serum calcium level. Both groups underwent physical therapy and did include other modalities of analgesia such as stellate ganglion blocks and TENS unit. The researchers did not find much change in allodynia, hyperalgesia, or trophic disturbances at 8 weeks in either group. Both the control and calcitonin group showed similar improvement in pain reduction at the end of 8 weeks, concluding that calcitonin did not produce additional benefit. Studies looking at higher doses of intranasal calcitonin at 400 units for CRPS have not shown benefit [22]. Other earlier studies have shown some favorable findings of pain reduction with calcitonin for CRPS, though they are fraught with limitations of small study size and lack of standard Budapest criteria used for diagnosis of CRPS [23]. Routine use of calcitonin for CRPS remains controversial. Caution should be advised for use beyond 6 weeks given its potential to cause neoplasm in women treated for postmenopausal osteoporosis [24]. Caution should also be advised in concomitant use of bisphosphonates.

Corticosteroids

An inflammatory response is believed to be a well-accepted mechanism in the pathophysiology of CRPS, likely through modulation of cytokines, chemokines, and neuropeptides. Studies have described a neurogenic inflammatory reaction, mast cell activation, elevation in markers of oxidative stress, and a rise in cytokines such as IL-6 and TNF-α in fluid of blisters CRPS [25–27]. Similar to NSAIDs, corticosteroids with an anti-inflammatory action have sound reasoning as a therapeutic strategy. One early smaller RCT did examine the analgesic effect of oral prednisolone 10 mg three times per day in 13 patients with early-stage CRPS compared to 10 placebo patients until clinical remission was observed. The researchers were able to show a 75% improvement in clinical condition in a 12-week period and concluded this to be superior to placebo [28]. Other case series have also shown significant pain reduction with prednisolone ranging from 40 to 80 mg per day for 2–4 days in patients with CRPS with disease duration ranging from 2 to 3 months [29, 30]. One study looked at the effects of corticosteroids in 31 patients diagnosed with CRPS of chronic duration of greater than 3 months using the Budapest criteria. One arm of the study was treated with 100 mg of daily oral prednisolone followed by 25 mg taper every 4 days, and the second arm was treated with 60 mg of daily oral prednisolone for 14 days followed by a 20-mg taper every 4 days. There was no control group. The researchers concluded low efficacy of oral steroid treatment for CRPS of chronic duration. Six patients in the study had serious side effects of malaise, depression, severe sickness, stomach ache, and fatigue [27]. Another RCT study looked at analgesic efficacy of 60 mg of intrathecal methylprednisolone in patients with chronic CRPS of greater than 6 months. The study did not find any clinical improvement in pain in the treatment group and was terminated early [31]. Based on the available data, corticosteroids seem to have efficacy in early stages of CRPS of less than 3-month duration, though this is only supported by small studies and case series. In chronic stages of greater than 3-month duration of CRPS, data supporting benefit is lacking. A couple of studies have shown benefit of corticosteroids in chronic stages of CRPS, but the study population was not the classic traumatic or postsurgical involving an extremity but was a poststroke population which arguably may not be homogenous to the classic population [32, 33].

Anticonvulsants and Antidepressants

The sensitization of the peripheral nervous system is believed to be one of the leading theories behind hyperalgesia reported in CRPS and a defining characteristic in its pathogenesis. Pro-inflammatory agents sensitize nociceptive pathways resulting in continuous neural activation through Aδ and c fibers to the point where there is aberrant coupling to the autonomic nervous system [34]. Chronic changes to neural tissue morphology have been demonstrated in CRPS patients using electron

microscopy in which there is observed degenerative changes to Aα somatomotor neural fibers and increased expression of α1 adrenergic receptors. It is theorized that this creates an imbalance in normal signaling resulting in hyperalgesia [35, 36]. Peripheral and autonomic nervous system sensitization leads to central nervous system activation seen as increased firing at the dorsal horn mediated by the neurotransmitters glutamate and substance P. Further upstream sensitization has also been reported to occur in the somatosensory cortex [34, 37]. Though a neuropathic mechanism has been at the forefront of CRPS pathophysiology, few studies of neuropathic agents exist. A demonstrable benefit in other neuropathic conditions serves as the basis for use of anticonvulsants and antidepressants in CRPS.

Gabapentin is one of the widely used neuropathic pain medications in the world. It blocks voltage-dependent calcium channels by binding the α2-δ subunit to reduce neural transmission. One study examined the analgesic effect of 2400 mg/day of gabapentin for various neuropathic conditions in which 85 of the 305 patients in the study were diagnosed with having CRPS. There was a 1.5 reduction (NRS 0–10) in pain score in the gabapentin treatment group compared to 1.0 reduction in the placebo group by the 8th week of treatment [38]. Another RCT study done in 2004 enrolled 58 CRPS subjects in a cross-over study design in which the treatment group was titrated to 1800 mg/day of gabapentin over a 3-week period. Improvement in sensory deficit was seen in the gabapentin group. No improvement was observed in mechanical allodynia, edema, skin discoloration, or range of motion. Analgesic benefit was seen in the first half of the study, but overall the researchers concluded gabapentin did not relieve pain compared to placebo [39]. A smaller study with 22 CRPS patients enrolled treated with gabapentin in the range of 900–1800 mg/day was able to find a reduction in spontaneous pain score by 1.7 and provoked pain score by 3.7. The researchers did not find improvement in physical findings or functional measures [40]. Pregabalin is also an anticonvulsant with similar mechanism of action as gabapentin but has improved gastric absorption. There are no studies on its efficacy in CRPS, but there is one case report of a pediatric patient experiencing improvement in extremity edema and range of motion with 75 mg 2×/day of pregabalin with sustained benefit reported at 8 months [41]. Scant data for use of other anticonvulsants in CRPS exist. A case series of eight patients diagnosed with CRPS were treated with lamotrigine, a voltage-dependent sodium channel inhibitor. Patients were treated with 200–600 mg until effect was achieved. All eight patients reported a reduction in pain and swelling. Most patients reported a reduction in discoloration. Lamotrigine also decreases presynaptic release of glutamate and aspartate which may be involved in reducing hyperalgesia [42]. Only one study on the use and efficacy of antidepressants for CRPS exits. Thirty-four pediatric patients diagnosed with CRPS or other neuropathic pain conditions were randomized to receive either gabapentin 300 mg 3×/day or amitriptyline 10 mg at bedtime for 6 weeks. Study findings indicated that amitriptyline did provide clinically significant pain relief and improved sleep scores to the same degree as gabapentin [43].

Local Anesthetics

Local anesthetics have been used for the treatment of neuropathic pain for many years. The analgesic effect of local anesthetics given intravenously as an infusion for postoperative pain was first reported in 1962 and has been used to treat many neuropathic conditions with analgesic effect comparable to medications such as opioids, gabapentinoids, and TCAs [44, 45]. Local anesthetics have been used to treat CRPS in multiple ways including perineural injection around the sympathetic chain, as well as suspended intravenous injection in the afflicted extremity with the use of a tourniquet; a technique termed Bier block or intravenous regional block IVRB. A Cochrane review in 2016 concluded there is a lack of high quality evidence to support or refute local anesthetic sympathetic blockade [46]. A RCT with cross-over design comparing lidocaine IVRB with increasing doses of ketorolac failed to show analgesic benefit beyond 1 day with weekly treatments for 4 weeks [2]. There is more recent evidence to support intravenous infusion of local anesthetic for treatment of pain related to CRPS. An RCT was performed examining the efficacy of lidocaine infusion at 3 mg/kg compared to saline placebo once per week for a 4 week treatment period. Though a relatively small group of patients with CRPS in which six were in the treatment group and six in the control, the researchers did find a statistically significant reduction in % pain score from baseline in the lidocaine infusion groups compared to control, but prolonged effect was not demonstrated [47].

N-methyl D-aspartate (NMDA) Receptor Antagonists

Neural sensitization at the peripheral and central level has been a long-standing proposed mechanism for CRPS. This development and maintenance occur through activation of neuroinflammatory pathways involving cytokines, substance P, and calcitonin gene-related peptide, all of which result in downstream release of glutamate. Glutamate then acts on NMDA receptors to promote afferent pain signaling [48]. Thus, antagonists of NMDA receptor activation theoretically can attenuate the sensitization process in CRPS. Magnesium is such a molecule with ability to block NMDA receptor activation. Unfortunately, two RCTs comparing infusion of magnesium and intramuscular injection of magnesium in CRPS patients compared to control saline groups did not find any intergroup differences [49, 50]. Memantine has shown promising findings in some small studies. In one retrospective study, a daily dose of 40–60 mg of memantine for 2 months or greater in 56 CRPS patients showed complete resolution of CRPS symptoms in 13 subjects and partial improvement of pain scores as well as allodynia in 18 [51]. Another RCT study examined functional MRI changes in 20 CRPS treated with either combination morphine with memantine titrated to 40 mg daily for 49 days versus morphine alone. The

researchers did show reduced pain with rest and movement in the combination group and concluded memantine affects cerebral processing of nociceptive information in CRPS [52]. Ketamine is also a well-known NMDA antagonist which has had long-standing use for the treatment of pain. Numerous studies have been performed examining the efficacy of ketamine for CRPS. A recent meta-analysis reviewed the available data to show that ketamine does produce a significant reduction in pain related to CRPS. The authors reported great heterogeneity among the various studies and relied on a 30% reduction in pain as a standard measure of clinical meaningfulness. Once this was applied in analysis, there was a 69% response rate of ketamine to produce a 30% reduction in pain immediately after treatment and an ongoing 58% response rate at 1–3 months posttreatment [53]. Data on the chronic effect of ketamine for CRPS is limited to two studies. One study showed a 31% rate of being in remission of pain symptoms at 6 months after inpatient ketamine infusion starting at subanesthetic dose of 10 mg/hr. titrated to analgesic effect and dose tolerated. Infusions typically lasted for several days. After a second treatment, 58% experienced remission at 1 year and 33% experienced remission at 3 years [54]. Another study showed an 80% rate of remission at 6 months after ketamine infusion titrated to anesthetic doses of up to 7 mg/kg/hr over 5 day therapy [55]. Patients in this study had long-standing CRPS or rapidly progressing CRPS, which contradicts the notion that treatment with ketamine has to be initiated early in the disease course to be efficacious. There is one small RCT of 19 patients with CRPS comparing outpatient infusion of ketamine up to 100 mg over 4 hours for 10 days versus saline infusion. The researchers did show significant reduction in pain on several pain parameters with an overall average pain reduction at 4 weeks of 26.7 on a 0–100 scale [56]. Psychotropic side effects are observed with prolonged ketamine infusion as are elevated liver enzymes, requiring close monitoring of this anesthetic. Side effects are ultimately related to dose of ketamine administered [55].

Vitamin C

Vitamin C, also known as ascorbic acid, is a component of collagen formation needed in human growth and development. It also functions as an antioxidant needed in neuroprotection. The role of vitamin C as an analgesic has been described in several studies, though its mechanism of action remains largely unclear. Effect of vitamin C on preventing CPRS after orthopedic trauma or surgery has been somewhat controversial. A recent meta-analysis in 2017 concluded that there is high level evidence for 1000 mg of vitamin C daily for 50 days perioperatively in reducing the incidence of CRPS. The authors concluded a relative risk of 2.25 of developing CRPS in the non-vitamin C groups based on 2 RCT and 1 nonrandomized control trial [57]. A more recent large retrospective study of 533 patients undergoing orthopedic shoulder surgery evaluated the incidence of CRPS (diagnosed using the

Budapest Criteria) 6 months postoperatively. One group was treated with 500 mg of vitamin C for 50 days postoperatively and the other was a control. The vitamin C group had a significantly lower incidence of CRPS at 7% compared to the control of 13% [58]. Another RCT conducted in 2014 evaluated 336 subjects with acute distal radial fractures who were randomized to vitamin C 500 mg daily for 50 days versus placebo. Participants were followed for 1 year, but the authors did not observe an intergroup difference in the incidence of CRPS [59]. The dose and duration most commonly studied seems to be between 500 and 1000 mg daily for 50 days initiated shortly after trauma or surgery. The available evidence for vitamin C to prevent CRPS after orthopedic trauma is somewhat mixed. The benign nature of the supplement lead many to believe it should be routinely used as a preventive measure for CRPS after onset of trauma. Use of vitamin C as a preventive measure for flare up of CRPS or as an analgesic treatment in a population with chronic CRPS has not been studied.

Opioids

There is a scarcity of studies examining the analgesic efficacy of opioids for the treatment of CRPS, likely due to the accepted neuropathic and inflammatory mechanistic dominance of the disorder and safety concerns over chronic and high dose opioid use. An alteration in central opioid receptor-binding potential, hence, opioid receptor availability, has been demonstrated in a study of 10 CRPS subjects [60]. The clinical correlation of altered response to opioids based on this study findings is yet to be determined. One study of 43 patients with varying types of neuropathic pain in which 7 of 43 had CRPS looked at the efficacy of morphine in controlling neuropathic pain. All patients had well-controlled pain with a spinal cord stimulator that did not require additional pharmacologic analgesics. The researchers concluded that when stimulators were turned off and pain had returned, morphine doses between 60 and 90 mg was inadequate to provide pain relief [61]. A subgroup analysis specific to individual diagnosis was not performed. Another study compared the combination of memantine with morphine in CRPS patients and found a significant reduction in pain with rest and movement compared to morphine with placebo. Unfortunately, a control arm without morphine was not performed making the efficacy of morphine alone difficult to assess [52]. One publication of two case reports showed a 50% reduction in baseline pain in two CRPS patient treated with buprenorphine. One patient was titrated to 20 μg/hour of buprenorphine with oxycodone 7.5 mg twice daily, and the other patient was titrated to 10 μg/hour of buprenorphine without need for additional breakthrough opioids. Both patients failed multiple other opioids. Buprenorphine has a unique mechanism of binding of mu-opioid receptors and antagonizing NMDA receptors. This combined receptor activity may produce analgesia and reduce hyperalgesia [62]. Opioids are a reasonable analgesic option in the acute phase of trauma or for a short course during a flare up while more evidence-based multimodal therapies are optimized for most effective and safest outcome.

Topical Agents

Given the predominance of visible extremity involvement and the neuroinflammatory quality of CRPS with microvascular vasoactive dysfunction, several studies have examined the efficacy of topical pharmacological agents for the treatment of CRPS. Results on efficacy of topical agents has been somewhat mixed. One retrospective study looked at combined ketamine 10%, pentoxifylline 6%, clonidine 0.2%, and dimethyl sulfoxide 6–10% compound cream in CRPS patients. Topical application was done three times per day. The authors found that 9/13 patients had significant pain reduction with an overall reduction of 2.1 on a 0–10 pain scale. The idea behind use of clonidine and pentoxifylline is to help restore microvascular dysfunction. DMSO was used for its tissue-penetrating ability, as a free radical scavenger, and as a nitric oxide donor molecule [63]. Ketamine as a single agent was studied in a small prospective study of 20 patients with CRPS treated with 10% ketamine topical. The researchers did not find a reduction in pain scores but did find a reduction in allodynia [64]. Another group also studied the efficacy of topical ketamine as a sole agent in 16 CRPS patients and found that 50% reported improved pain but 44% reported increased pain [65]. DMSO has been previously studied as a sole agent to be effective in reducing pain related to CRPS by 3 on a 0–10 scale and also improved scores on quality of life questionnaire [66]. Another study found DMSO to be more effective for CRPS during its warm phase [67]. A more recent case series looked at the potential effects of 20% compound cream consisting primarily of ambroxol in 8 CRPS patients. DMSO and linola cream were also mixed in as minor components. Though the outcome measures were not standardized across patients and the reporting period was very short, the authors found a reduction in spontaneous pain in six patients and also a reduction in pain on movement in six patients. They also reported improvement in skin discoloration, temperature, and edema, findings not readily seen with other pharmacotherapies. Favorable properties of ambroxol for CRPS include blocking sodium channels, attenuating oxidative stress and inflammation, and modulating dysfunctional vasomotor changes [68]. Microvascular dysfunction can, in part, be attributed to localized autonomic disruption. One theory to attenuate microvascular dysfunction is to block localized sympathetic activation. Prazosin is an α1-adrenergic receptor blocker. One case–control study examined the effect of prazosin to reduce sensitivity to mechanical and thermal stimulation in 19 CRPS patients. The researchers were able to show reduced hyperalgesia to sharp stimulation and dynamic allodynia [69].

Botulinum Toxin

Botulinum toxin has been used more classically for disorders such as dystonia and blepharospams as well as a preventive therapy for intractable migraines. There is growing investigation on its potential as a neuropathic analgesic. Botulinum toxin is a neurotoxic protein produced by *Clostridium botulinum*, a bacterium that imparts its primary mechanism of action on the neuropeptide acetylcholine. Botulinum

toxin inhibits exocytosis of acetylcholine at neuromuscular junctions, thus inhibiting initiation and propagation of action potentials. This can explain the benefit seen in spasticity conditions but can also explain the potential analgesic benefit seen in neuropathic hyperalgesia conditions such as postherpetic neuralgia. A randomized, double-blind, placebo-controlled study looking at the efficacy of botulinum toxin A on 56 patients with postherpetic neuralgia was conducted in which the botulinum toxin A group had the lowest pain scores post injection at 7 days and 3 months. There was also an observed improvement in sleep as well as a reduction in opioid use that was significant over the comparison of lidocaine and saline groups [70]. Unfortunately, an RCT study examining the efficacy in 14 CRPS patients injected with subcutaneous and intradermal botulinum toxin A at 5 units/site followed out to 2 months did not show benefit with pain intensity. The study did have to stop enrollment due to lack of tolerance of the intervention [71]. Another study performed local nerve blocks with lidocaine prior to injecting 10 units/site of intradermal botulinum toxin A in 16 patients with CRPS of the hand. Four to twelve monthly treatment sessions were conducted in which an average of 8.85 sessions were needed to reach an average maximal benefit of 2.05 on a numerical pain scale of 0–10. This was calculated to be an approximately 23% reduction from preinjection baseline pain scores [72]. The mechanism of analgesia, if any, of botulinum toxin A for CRPS remains unclear. The inhibition of release of other neuropeptides such as substance P, calcitonin gene-related peptide, and glutamate by the botulinum toxin has been described which supports its theoretical potential as an analgesic medication for neuroinflammatory conditions such as CRPS [73].

Immunoglobulins

Pathogenic antibodies mediating pain in CRPS has been described, yet immunoglobulin therapy for CRPS has been somewhat controversial. Early studies have shown that IVIG therapy may attenuate the pathogenic effects of antibodies. One of the first randomized controlled, cross-over trial looking at low dose IVIG of 0.5 gram/kg reduced pain scores by 30% compared to a saline group in 13 subjects with CRPS of greater than 6 months [74]. However, a more recent larger RCT with 103 subjects with chronic CRPS of greater than 1 year receiving low dose IVIG of 0.5 gram/kg was not able to reproduce positive findings of early cases series and reports. At 6 weeks posttreatment, none of the outcome measures, inclusive of pain measurements, differed from placebo saline [75]. It remains unclear what benefit immunoglobulins may have for the treatment of CRPS.

Conclusion

The continuously expanding knowledge of the pathophysiology of CRPS will likely shape the pharmacologic therapies used for CRPS. Early therapies have been somewhat anecdotal based on small case reports and case series; however, more recent

rigorous study trials with consistent criteria used to diagnosis CRPS have provided some clearer clinical guidance. Still much remains to learn about CRPS which will continue to evolve the pharmacological therapies to better serve this ongoing complex medical problem.

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Behavioral Health Interventions for CRPS

6

Patricia A. Richardson, Heather Poupore-King, Anya Griffin, Corinne Cooley, and Rashmi P. Bhandari

Diagnostic Considerations and Theoretical Foundations

Complex regional pain syndrome is a pain condition that presents as intense regional pain most often manifesting in patients' upper and/or lower extremities. Pain may develop after an injury or illness without confirmed nerve damage (CRPS Type I) or when nerve damage has been confirmed (CRPS Type II). Pain is considered to be out of proportion to the original injury (which can sometimes be minor) and extends beyond the area involved by the initial trauma, across both subtypes. Associated autonomic and inflammatory symptoms and signs include swelling of the affected limb and joints, sensitivity to touch, changes in temperature and skin texture, and motor impairments, among others [1]. Symptoms and signs can vary across time and person. Per the International Classification of Diseases (ICD-11), CRPS lasting >3 months is considered to be a *primary chronic pain diagnosis* [2, 3], which means that for patients with CRPS, pain itself is the disease. Primary chronic pain conditions include chronic headache, functional abdominal pain, and fibromyalgia, among others. Primary chronic pain conditions can be contrasted with *secondary chronic pain conditions*, where chronic pain develops as a symptom of a different disease (e.g., cancer-related pain; post-concussive headache) [2].

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Evidence-based behavioral health assessment and intervention for primary chronic pain conditions is rooted in biopsychosocial theory-driven frameworks. Biopsychosocial theory, as applied to chronic pain, is an integrative approach describing how the complex nature of pain and associated functional disability is related to interacting biological, cognitive, behavioral (e.g., health habits), and sociocultural influences [4, 5] (see Fig. 6.1). As guided by biopsychosocial theory, optimal interventional paradigms for CRPS and other primary chronic pain conditions hinge on the multidisciplinary integration of pain management, rehabilitation, and behavioral health treatments [6]. There is a nascent literature reporting on the clinical utility of behavioral health treatments for CRPS and a much larger literature on effective and efficient treatments for primary chronic pain conditions. Given that CRPS is classified as a *primary chronic pain condition* by the ICD-11, this chapter reviews behavioral health interventions for CRPS by incorporating the CRPS-specific literature and broader extant evidence base for primary chronic pain conditions.

Assessment

Comprehensive biopsychosocial assessment is essential to inform patient diagnostic presentation and develop targeted treatment plans [5]. Behavioral chronic pain assessments generally include the following key domains: (1) functional impact of pain on quality of life; (2) cognitive, behavioral, and emotional coping; (3)

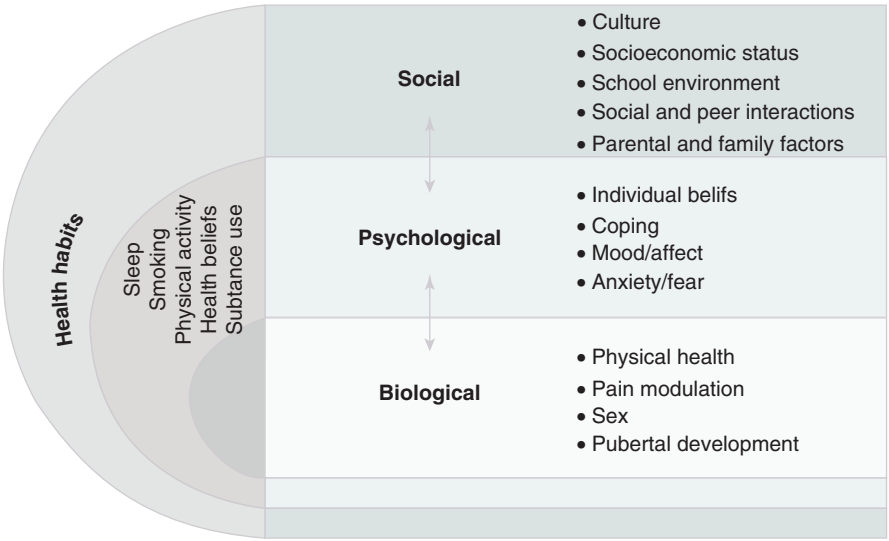

Fig. 6.1 Guiding conceptual model for understanding pediatric chronic pain and disability [20]. (Note: permission granted by Oxford University Press)

comorbid psychiatric vulnerabilities; and (4) administering validated and normed self-reported symptom measures. Research has shown that each of these domains impact patient pain experience and response to treatment [7].

Functional Impact

Consistent across chronic pain conditions, CRPS can negatively impact the patient's ability to engage in most functional domains, including: sleep, self-care, work, school, physical activity, social relationships, and mood. Behavioral health assessment inventories patient pain from a differing perspective than the medical evaluation, by focusing on how the experience of pain impacts physical functioning and cognitive and emotional adjustment. For example, assessment seeks to characterize pain persistence, intensity, and patterns, as well as the impact of pain on stress, emotional state, cognitive style, and coping. Understanding how CRPS is impacting the biopsychosocial aspects of the patient's life becomes the underpinning of enacting efficient and effective rehabilitation treatment efforts.

Pain Coping

Strategies employed to manage pain encompass a range of behavioral and/or cognitive techniques that can be maladaptive, adaptive, or both, depending on the strategy employed and/or the context of deployment. Patients' approach to coping predicts their pain-related adaption, emotional distress, and functional disability [8]. Assessment of maladaptive coping often focuses on evaluating the presence of pain catastrophizing and avoidance. Pain catastrophizing refers to the maladaptive cognitive-affective experience of pain including rumination, feelings of helplessness, and magnification of pain. Among patients with chronic pain, pain catastrophizing is a robust predictor of deleterious outcomes, including higher pain intensity and greater functional disability [9]. Given the intensity and unusual nature of allodynic pain (i.e., pain from nonpainful stimuli) experienced by many patients with CRPS, catastrophic thinking may include incorrect beliefs about the meaning of CRPS pain (e.g., pain means tissue damage). Such beliefs may be a primary contributor to limb guarding, limb disuse, and activity avoidance. Activity avoidance frequently has the unintended side effect of maintaining chronic pain through processes such as physical deconditioning.

Adaptive approaches to coping may include setting positive expectations for recovery, relaxation exercises, distraction, positive self-statements, and acceptance (i.e., willingness to engage in personally meaningful activities even when in pain, without avoidance or attempting to control pain). Positive pain recovery expectations [10] and pain acceptance are negatively correlated with physical disability, depression, and pain-related anxiety among other variables [11]. Finally, pain-related self-efficacy assesses patients' perceived ability to manage pain symptoms and function in spite of pain and serves as a protective factor for patients with persistent pain and a resiliency factor for children, adolescents, and adults with chronic pain [12].

Psychiatric Comorbidities

Depression Depression is the most common mental health disorder to co-occur with chronic pain [13]. Depression can contribute to the development of chronic pain, decreased pain tolerance, and impede adherence to rehabilitation efforts [14]. Conversely, factors such as the reduced engagement in pleasurable activities, decreased mood, and increased feelings of distress and helplessness that accompany chronic pain can further contribute to the development of depression [3, 13]. While the bidirectional relationship between the two disorders can make diagnosis difficult at times and can complicate treatment, the best treatment outcomes have been demonstrated by treating both disorders concurrently utilizing a multidisciplinary approach [3].

Anxiety The prevalence rate for anxiety among chronic pain patients is almost double that of the anxiety found in community samples (35% vs. 18%) [15]. Pain-related anxiety leads to worse treatment outcomes and higher health costs [16]. Pain-related anxiety can lead to avoidance of activities which can exacerbate pain, in addition to creating problematic cognitive and affective experiences. Patients with CRPS often display extreme social avoidance and explain that they are trying to avoid being accidentally bumped in their region of pain (severe allodynia) by those around them. Although patients may admit that this is unlikely to occur, the social avoidance behavior persists. This pattern highlights that activity avoidance and limb disuse in CRPS can be operantly reinforced by the decreased fear that accompanies avoidance of expected pain exacerbations [17]. Accurate assessment of fear of pain and anxiety informs treatment, which usually includes graded exposures to avoided activities, and desensitization of the effected limb.

Validated Measures

It is challenging to globally assess the psychological underpinnings of CRPS during time-limited clinical interviews and physical exams. Assessment is enhanced by capturing patient symptoms via validated and normed self-report measures. Frequently employed self-report measures seek to assess the above-described domains and are rooted in classical test theory (e.g., Pain Catastrophizing Scale, Functional Disability Inventory, Fear of Pain Questionnaire, and Beck Depression Inventory) and item response theory (IRT), such as the freely available National Institute of Health Patient-Reported Outcomes Measurement System (PROMIS) [18]. The incorporation of validated tools in the assessment and treatment of chronic pain allows the clinician to have a more accurate picture of what are most often non-observable factors critical to the accurate assessment and treatment of chronic pain conditions and track response to treatment across key clinical outcomes. A list of commonly utilized, yet not exhaustive, measures are suggested in Table 6.1.

Table 6.1 Sample assessment measures

	Adult	Child
PROMIS (Pain)	http://www.healthmeasures.net/search-view-measures	http://www.healthmeasures.net/search-view-measures
Pain Catastrophizing	Pain Catastrophizing Scale (PSC) Sullivan MJL, Bishop SR, Pivik J. The Pain Catastrophizing Scale: Development and validation. Psychol Assess. 1995;7:524–32. PubMed PMID: 1996007788.	PCS-Child Crombez G, Bijttbier P, Eccleston C, Mascagni T, Mertens G, Goubert L, Verstraeten K. The child version of the pain catastrophizing scale (PCS-C): A preliminary validation. Pain. 2003;104(3): 639–46 PCS-ParentEccleston C, Vervoort T, Jordan A, Crombez G. Parental catastrophizing about their child's pain. The parent version of the Pain Catastrophizing Scale (PCS-P): A preliminary validation. Pain. 2006;123: 254–263
Fear of Pain	Fear of Pain Questionnaire (FOPQ) McNeil DW, Rainwater AJ. Development of the fear of pain questionnaire—III. J Behav Med. 1998; 21(4):389–410	FOPQ Simons LE, Sieberg CB, Carpino E, Logan D, Berde C. The fear of pain questionnaire (FOPQ): Assessment of pain-related fear among adolescents with chronic pain. J Pain. 2011;12(6):677–86
Functional Disability	Short Form Health Survey (SF-36) Ware JE Jr., Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. Med Care. 1992;30:473–483	Functional Disability Index (FDI) Walker LS, Greene JW. The functional disability inventory: Measuring a neglected dimension of child health status. 1991;16(1): 39–58
Anxiety	State Trait Anxiety Inventory (STAI): Spielberger CD. Manual for the State-Trait Anxiety Inventory STAI (Form Y)("Self-Evaluation Questionnaire") Mountain View (CA): Consulting Psychologists Press; 1983	The Screen for Child Anxiety Related Emotional Disorders (SCARED): Birmaher B, Khetarpal S, Brent D, Cully M, Balach L, Kaufman J, Neer SM J Am Acad Child Adolesc Psychiatry. 1997 Apr; 36(4):545–53
Depression	Beck Depression Inventory Beck AT, Steer RA, & Brown GK (1996). BDI-II Manual San Antonio, Texas: The Psychological Corporation	Children's Depression Inventory Kovacs, M. (2003). *Children's Depression Inventory (CDI): Technical manual update*. North Tonawanda, NY: Multi-Health Systems

Behavioral Health Interventions

Cognitive Therapy

Behavioral health interventions primarily described as cognitive behavior therapy (CBT) are well established in the treatment of chronic pain [19, 20]. CBT

harnesses cognitive and behavioral techniques to help patients recognize the relationships between thoughts, feelings, behaviors, and pain. Cognitive therapy specifically teaches patients to notice maladaptive thoughts and their influence on pain and targets these thoughts for change. Common cognitive therapy strategies applied to the treatment of CRPS include psychoeducation, reframing, and cognitive restructuring.

Psychoeducation

Patients with chronic pain who believe that their condition is harmful, permanent, and or unexplained are less likely to use active pain coping strategies known to be important in treatment and regaining function [21]. Patients often possess inaccurate beliefs regarding the meaning of CRPS pain. Not surprisingly, given the intensity and unusual nature of allodynic pain, patients may assume that pain signals damage and conclude "if it hurts, don't do it." Thus, offering education about what CRPS is and is not becomes an important first step. Educational treatment is known as pain neuroscience education (PNE), Explain Pain (EP), or pain biology [22]. The goal of the intervention is to emphasize the difference of nociception and pain experience with a biopsychosocial approach in order to decrease the threat value of pain. Systematic reviews have found that PNE/EP are effective for improving function, reducing fear of movement, pain catastrophizing, and health care utilization [23–26]. PNE/EP can promote positive expectations for the efficacy of interdisciplinary treatment of CRPS [27] and, thus, set the stage for progress.

Reframing

Effective CRPS treatment and management necessitates an active rehabilitation approach [28] by reframing the role of the patient as an active participant in the treatment process. Clinical experience indicates that patients who adopt a passive role in treatment (overly depend on medications and interventional procedures, e.g., nerve blocks to be curative) tend to be refractory to treatment [29]. Instead, reframing interventional procedures as a bridge to facilitate active participation in rehabilitation allows the patient to set appropriate expectations of their role in the treatment process. Although integrated medical, psychological, and physical therapy procedures are critical to resolution of CRPS, the patient should be encouraged to focus on making functional gains before anticipating pain relief [30]. As part of this active treatment focus, exacerbated pain should be reframed as a cue to practice self-management interventions that may help the patient gain some control over their symptoms. Increased perceived control is known to be an important factor in determining positive outcomes in chronic pain treatment [29].

Cognitive Restructuring

As in all chronic pain conditions, anxiety and catastrophic thinking are common in CRPS patients [31]. *Cognitive restructuring* refers to the process of identifying dysfunctional thinking patterns and replacing them with more adaptive cognitions.

Given the importance of addressing limb disuse and reactivating the affected extremity in CRPS, thoughts such as "using my leg will worsen my pain" hinders behavioral activation. Using positive coping self-statements (e.g., "I won't know until I try it," "I can handle it") may facilitate increased confidence, management of fear of pain, and improved self-efficacy. Patients also benefit from reminding themselves that they now have pain management tools to manage pain exacerbation. *Thought challenging* is another cognitive restructuring strategy to counter avoidance and disuse. For example, a patient may experience the cognition: "If I go to outside, someone will bump into me." This cognition could be addressed through questioning the facts (i.e., "How many times has that actually happened?") and use of positive coping self-statements ("I can practice my skills if it happens" "when pain increases, it generally goes back down"). Finally, restructuring can be utilized to counter hopelessness by adopting realistic self-affirmations (e.g., "everyone's journey is different, I am making progress everyday") and presenting data that demonstrate the success of multidisciplinary approaches in the treatment of CRPS.

Behavioral Therapy

Behavioral therapy (BT) for chronic pain originated from classical learning theory, most notably operant conditioning. In brief, operant learning notes that behaviors that are reinforced are likely to increase in frequency. Conversely, when behaviors are not reinforced or are punished, they decrease in frequency. Operant learning as applied to chronic pain conditions often focuses on the role of pain behaviors (i.e., actions, verbalizations, facial expressions that occur in response to pain). Protective pain behaviors (e.g., activity reduction, limb guarding) may be adaptive within the context of *acute* pain as they serve to reduce the extent of damage from the source of pain and garner helpful social support. However, for individuals with *chronic* pain, protective pain behaviors can become maladaptive over time, as they maintain pain intensity, decrease physical activity, and increase likelihood of functional disability [32, 33]. Thus, BT for chronic pain seeks to improve pain and disability by shifting the contingencies of pain behaviors. BT for CRPS is accomplished using a number of techniques; this chapter reviews activity pacing and graded exposure.

Activity Pacing (AP)

Among patients with chronic pain, approach to activity engagement can have an impact on pain and disability. As noted in Fordyce's seminal work, it is problematic when patients base activity on pain levels as opposed to the goal of the activity itself (e.g., gardening until back pain becomes unbearable versus working on the garden) [34]. When activity becomes pain-contingent, patients use their pain intensity to make decisions about when to initiate, continue, and stop activity (e.g., pain behaviors are reinforced) [35]. Based on patterns of activity engagement, patients with chronic pain have been characterized as "persisters" or "rest/avoiders." A persister may continue to do a relatively high-impact activity, such as gardening, on a "good day" (i.e., low pain day) for an extended period. This overactivity may result in

increased pain that could last for several days or weeks. Conversely, rest-avoiders have opted to limit activity, for example, no longer gardening to prevent previous pain experiences associated with gardening [33]. Underactivity results in physical deconditioning that serves to increase pain and disability.

To address these maladaptive activity patterns, activity pacing (AP) was developed to restructure activity to achieve one or more adaptive goals [35]. In *time-contingent* AP, the intervention seeks to shift activity engagement to being time-contingent as opposed pain-contingent. AP often proceeds as follows: (1) select a target behavior (e.g., gardening); (2) establish a baseline level of time the patient can do an activity without increased symptoms (e.g., 15 minutes); (3) create a schedule of activity pacing that allows the entire task (tending to the garden) to be completed within the predefined time-contingent breaks, with activity-rest cycling; and (4) provide positive reinforcement when the time-contingent quota is reached, and then (5) increase the time-contingent goal after the patient is successful until patient has reached desired activity tolerance [35]. Of note, guidelines for the rate of time increase vary, though time goals should be tailored to the individual and mindful of injury prevention.

Operant AP strategies are commonly delivered with other treatment approaches within a multidisciplinary treatment program, intensive interdisciplinary pain treatment (IIPT) programs, which have shown to be effective for patients with chronic pain [36, 37]. The clinician should emphasize the intention and goal of the intervention, as researchers note this may influence whether AP programs are adaptive and assist in improving the patient's function, activity tolerance, and reducing disability, as opposed to using them as a pain-avoidant strategy [38]. Several variations of AP have been developed that focus on energy conservation and pain reduction, where the goal is to avoid energy depletion, rather than shifting from pain-contingent to goal/time-contingent activities [39]. Currently, there is little data on whether energy-conservation activity pacing approach is efficacious for chronic pain [35].

Graded Exposure

As outlined by the fear-avoidance model of chronic pain, which integrates behavioral and cognitive affective components of pain, negative appraisals of pain and consequences of pain may lead to pain-related fear of functional activities (e.g., school, work, social experiences, physical activity). Over time, functional activity is avoided which results in the overestimation of future pain from activity, physical deconditioning, and functional disability (see Fig. 6.2) [40]. Extinction of pain-related fear is achieved when the patient is exposed to previously avoided activities.

Inspired by the fear-avoidance model, graded exposure (GEXP) uses a graded hierarchy of fear-eliciting situations to expose patients to avoided functional activities. In GEXP, the clinician works collaboratively with the patient to identify situations and activities that are feared and avoided. The patient then rank-orders the above-described situations and activities into an exposure hierarchy, where least feared and avoided situations are on the bottom (and addressed first) and most

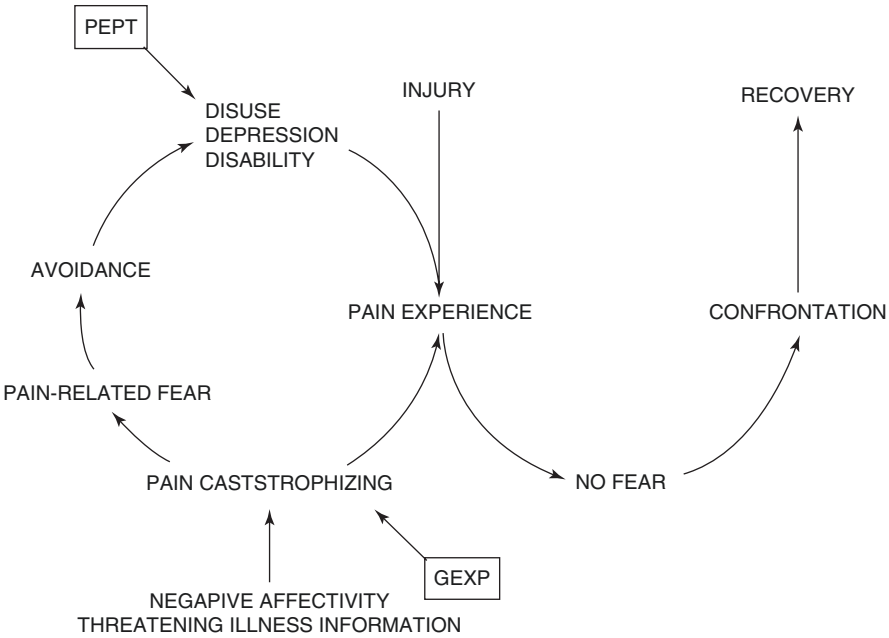

Fig. 6.2 Fear-avoidance model of chronic pain. (Note: The fear-avoidance model showing the targets of graded exposure treatment [40]. PEPT Pain Exposure Physical Therapy, GEXP Graded Exposure treatment. (Permission to reprint granted from Vlaeyen and Linton [40])

feared and avoided situations are at the top. Associated negative appraisals and dysfunctional beliefs (e.g., fear of pain and injury) are also inventoried. Psychoeducation and cognitive techniques address patient misconceptions about fear of pain and injury and help patients learn that engaging in feared and avoided situations without protective behavior (e.g., limb guarding) does not lead to catastrophic results [41]. Patients then engage in gradual in vivo exposure based on their exposure hierarchy until they are able to confidently engage in all situations and activities on their hierarchy with minimal support [18].

For example, a patient may be fearful to walk given CRPS of the left lower extremity. This fear may be particularly elevated in crowded environments, such as the mall, grocery store, and concerts. This information would be used to generate an exposure hierarchy. Exposing the patient to using the limb and walking would first occur in a very controlled environment and then move to more populated environments over time, as the patient successfully moves through steps on their exposure hierarchy. Concurrent cognitive techniques would be implemented to shift the patient's beliefs of the relative importance of "protection" of the affected limb to "exposure" or "use" of the painful limb.

GEXP has been used with individuals with chronic musculoskeletal pain [42] and anxiety-related disorders [43, 44]. More recent clinical trials have supported the

use of GEXP as a treatment for patients with CRPS, demonstrating that patients randomized to GEXP had improved function and reduced pain catastrophizing and perceived harmfulness of activities and pain as compared to patients randomized to a conventional therapy control [21, 45, 46]. One potential limitation of GEXP is that it has higher treatment dropout rates as compared to other psychological or behavioral treatments [42]. Thus, there may be a benefit to utilizing strategies to enhance motivation for engagement in GEXP (e.g., motivational interviewing).

During behavioral assessment, it is important to distinguish the type of coping mechanisms the patient uses in order to optimally select the BT approach (e.g., AP vs. GEXP). For example, it is recommended that patients who are high "avoiders" of an activity commence treatment with GEXP with the goal of reducing the fear associated with pain activity. However, those who are continuing to "persist" in their activities but with difficulty managing their pain levels subsequent to overactivity would be more likely to benefit from an AP approach [47].

Physiological Self-regulation Strategies

The pain of CRPS may cause muscle tension, restricted movements, shallow breathing, emotional distress, and anxious reactions. Anxiety may also increase as individuals with CRPS begin to engage in physical activity to improve their daily function [48–50]. In order to reduce the impact of aversive physiological arousal and anxiety secondary to pain, techniques to support self-regulation are indicated [51]. Rooted in biopsychosocial theory, physiological self-regulation strategies teach patients how to regulate pain-related autonomic responses (e.g., respiration rate, heart rate, and muscle tension) and emotional states (e.g., stress and anxiety) and to achieve a relaxation response. These strategies are considered to be a core component of pain management interventions and empower patients to be active participants in their own care. Physiological self-regulation interventions reviewed in this chapter include (1) relaxation training; (2) mindfulness-bases stress reduction; (3) self-hypnosis; and (4) biofeedback.

Relaxation Training (RT)

Relaxation training (RT) seeks to increase mind-body awareness and has been found to optimize pain management and improve daily functioning [51–53]. The primary goal of RT is to elicit the relaxation response to counter the sympathetic nervous system "fight or flight" reactions, common in CRPS. In addition to supporting the relaxation response, RT also provides patients with active coping that they can utilize during physically uncomfortable components of multidisciplinary care, including physical therapy and occupational therapy [50]. Utilization of these relaxation interventions during more physically challenging interventions may foster increased engagement and participation in treatments [50, 51].

RT incorporates a number of techniques including diaphragmatic breathing, guided imagery, progressive muscle relaxation, meditation techniques, and autogenic training. *Diaphragmatic breathing*, also referred to as belly breathing or

abdominal breathing, is a type of breathing technique designed to strengthen the diaphragm and downregulate autonomic nervous system reactivity. Box breathing is a simple diaphragmatic breathing strategy that involves inhaling through the nose to a count of 4 seconds, holding breath for 4 seconds, exhaling through mouth for 4 seconds, and holding breath for 4 seconds. As one improves this pattern, the amount of time can be increased (i.e., 5–8 count for inhale, hold, and exhale). Another relaxation training technique, *guided imagery*, incorporates deep relaxation with focused attention to envisioning a relaxing scene. In one application of guided imagery among children with functional abdominal pain, patients were asked to envision their pain and then were asked to develop an image that would get rid of the pain [54]. *Progressive muscle relaxation training* seeks to gradually reduce muscle tension and increase mind-body awareness (i.e., how stress can manifest as muscle tightness). This technique involves gentle tensing and releasing of muscles, typically beginning from the feet and moving slowly up the body from one muscle group up to the next, until reaching the head. One consideration for individuals with CRPS is to allow passive progressive muscle relaxation (i.e., no tensing muscles), as tensing some muscles for patients with chronic pain may exacerbate pain symptoms.

Mindfulness-Based Interventions (MBI)

Mindfulness-based interventions (MBIs) involve harnessing a range of techniques to facilitate patients' understanding and application of mindfulness: attention to the present moment

"characterized by nonjudgmental awareness, openness, curiosity, and acceptance of internal and external present experiences." [55, 56] MBIs may incorporate mindful breathing, meditation, mindful walking, and focusing on visual or auditory cues. For example, *mindful breathing* guides one's attention to focus on the act of inhaling and exhaling while allowing negative thoughts to simply just be observed mindfully, rather than attempting to avoid or resist negative thoughts. *Mindful listening* may incorporate noticing sounds surrounding the individual, then noticing the sound of breathing or even one's own heartbeat to help with increasing engagement with the present moment. Music or natural sounds may also be utilized for mindful listening.

Mindfulness-based coping skills have become well-known methods of chronic pain treatment for a variety of pain conditions across pediatric and adult patients, with findings similar to CBT for chronic pain [57–63]. Mindfulness-based strategies help to promote acceptance, which can foster resilience for individuals with CRPS [64]. However, as with other physiological self-regulation interventions, individual patient characteristics should be considered in treatment planning. Some MBI may be contraindicated for some patients with CRPS (e.g., mindful body scans that draw attention to the affected limb may increase pain) [60].

Self-Hypnosis

Self-hypnosis has long been utilized for its beneficial pain management effects and offers individuals suffering from chronic pain a tool for managing pain and the level

of distress associated with pain. Many individuals with CRPS have received messages from providers and their community that "the pain is all in your head" or "there is nothing else we can do for your pain," thus reinforcing the belief that one does not possess the ability to change any aspects of their symptoms, and this will be a lifelong experience without relief. These negative suggestions can be powerful. Self-hypnosis is a technique that may help individuals with CRPS to enhance their ability to capitalize on creative processes to alter perceptions of pain, catastrophic thoughts, negative feelings, avoidant behaviors, and physiological reactions to pain. Self-hypnosis typically includes three components: induction, suggestion, and post-hypnotic suggestion. Inductions are intended to develop a deep relaxation state (e.g., body scan, countdown breathing). Suggestions are made to shift how pain is understood and experienced (e.g., from sharp pain to a dull ache, increasing the sensation of comfort, increase movement from immobile states, and changing from a cold sensation to warm). [65] Posthypnotic suggestions are made to generalize the benefits of self-hypnosis practice beyond the session.

Hypnosis has demonstrated empirical support in the treatment of chronic pain [66–69]. A meta-analysis of 85 experiential trial studies on the use of hypnosis for the treatment of pain identified improvements in analgesic effects as well as optimizing pain relief [65]. In the Eccelston and colleagues Cochrane review, in addition to relaxation training, hypnosis was also found to be a helpful treatment modality for pain and that hypnosis interventions were effective in reducing chronic pain intensity [66]. Furthermore, hypnosis has been an effective method for individuals with CRPS to manage various symptoms (i.e., protective posture, reduced function, immobility, pain, etc.) and fosters increased self-regulation and self-efficacy [70].

Self-hypnosis also combines well with other multidisciplinary interventions to provide a context for disrupting maladaptive patterns and creating more adaptive responses [71, 72]. For example, in one study of adult patients with upper extremity CRPS type I ($n = 20$), self-hypnosis was utilized in combination with physical therapy. The goal of self-hypnosis treatment for CRPS in this study was to "recreate the illusion of movement to disrupt the blockage and exclusion of the affected limb segment, thereby freeing the patient from pain and functional disability." [73] This treatment combination was found to be effective in improving function and return to work for the majority of participants [73].

Biofeedback (BFB)

Biofeedback (BFB) is a skills-based treatment that targets improving patient health and well-being by teaching strategies to change physiological responses. BFB seeks to increase the patient's ability to control their response to pain by increasing the relaxation response and decreasing cognitive and emotional arousal. Simply put "bio" refers to bodily responses and "feedback" is the signal fed back to the patient in real time, usually though a visual or auditory system. With CRPS and other chronic pain conditions, the sympathetic nervous system "fight or flight" response becomes activated by pain. During times of pain and stress, our body secretes stress

hormones that lead to a cascade of physiological changes such as increased heart rate, blood pressure, vasoconstriction and changes in breathing, sweating, and muscle tension. Given the psychophysiological link between stress, dysregulation of the autonomic nervous system and chronic pain, learning self-regulation skills to interrupt the stress response is an important component of any pain management program [74, 75].

BFB involves using one or more physiological sensors to examine the body's physiology, while in real-time, feeding that signal back to the patient. Sensors convert the body's information into a sound and/or an image on a computer or portable electronic device that allows for increased awareness and build/train increased active control of physiological factors that contribute to pain. Common sensors used with BFB to assess physiological factors include electromyography (EMG), heart rate variability (HRV), respiration, skin temperature, and skin conductance (SC). While receiving feedback from sensors, patients learn in real time how to activate their parasympathetic nervous system using a range of techniques that may include diaphragmatic breathing, guided imagery, autogenics, body scan, progressive muscle relaxation, mindfulness, and meditation. EMG biofeedback may be a particularly beneficial sensor when conducting muscle-focused relaxation/retraining procedures [76]. Furthermore, for many patients, the extremity impacted by CRPS is often colder and therefore, thermal BFB is used to enhance the relaxation response and ultimately achieve bilateral balancing of temperature regulation.

The first stage of BFB treatment typically focuses on awareness (i.e., identifying problematic or dysregulated physical and psychological responses via self-report and sensors). Next, physiological self-management strategies are implemented to change the BFB signals from a stressed to relaxed range (e.g., postural training, CBT, mindfulness- and acceptance-based strategies, meditation, progressive muscle relaxation (PMR), body scan, guided imagery, autogenic, and self-hypnosis). BFB training necessitates consistent and regular practice. The final stages of training focus on reducing the reliance on the clinician and equipment by generalizing skills into day-to-day environment with daily independent practice. Often, patients can use recorded scripts from their clinician, their favorite meditations, or self-guided approaches to ensure skills acquisition. Once the patient demonstrates mastery of skills, the therapist reduces reliance on BFB [77].

Biofeedback is an empirically validated treatment for various chronic pain conditions [78] including headache disorders, TMD, and fibromyalgia [79–85]. There is limited research on BFB for CRPS; therefore, we look to the chronic pain literature for treatment options. A meta-analysis found that biofeedback treatments in the chronic pain population can lead to improvements on various pain-related outcomes in the short and long term, as a standalone and an adjunctive treatment intervention [86]. Furthermore, significant small-to-medium effect size has been reported for pain intensity reduction over an average follow-up of 8 months and a reduction in depression, disability, muscle tension, and improved cognitive coping [86].

BFB should only be delivered by trained healthcare professionals competent in using the modalities described above to ensure safety. Contraindications for patients who may not be a good fit for BFB include: severe debilitating depression, severe psychosis, and individuals with a pacemaker or other implantable electrical device. Overall, when used with appropriately, it is considered to be a safe, fun, and engaging intervention. BFB provides a skill that patients can use anytime for any stressor they encounter, making this an important physiological self-management strategy. More information about biofeedback and training in BFB can be found by visiting the Biofeedback Certification Institute of American (BCIA)—http://www.bcia.org.

Acceptance and Commitment Therapy (ACT)

ACT is a 3rd wave therapy, also considered contextual CBT [87], and has been shown to be effective in treating chronic pain [88]. ACT is recognized by the American Psychological Association (APA) as an empirically validated treatment for chronic pain in both the adult and pediatric populations [89]. Pain acceptance has been found to contribute to positive physical and psychosocial adjustment [90, 91, 92] and demonstrate improvements in psychological inflexibility, pain-related functioning, mental health-related quality of life, self-efficacy, depression, and anxiety in the chronic pain population [93]. ACT works specifically through processes related to psychological flexibility [94].

While traditional CBT focuses on identifying and changing the *content* of one's thoughts (cognitive restructuring), ACT promotes psychological flexibility, thus reducing the *influence* that unhelpful thoughts have on one's mood and behaviors highlighting engagement in deliberate *choice* regarding their actions despite what their mind (cognitions) tells them. ACT proposes that psychological inflexibility including experiential avoidance, preoccupation with the past or future, lack of perspective taking, and reduced engagement in values-based behaviors (committed action) are at the heart of all suffering. The opposite of this is psychological flexibility, or a conscious awareness (mindfulness) and emotional distancing (defusion) from painful "private experiences" (or difficult thoughts, feelings, memories, urges, and sensations). The process of emotional distance from restrictive or unhelpful private experiences allows one to make deliberate choices to intentionally engage in value-based activities (committed action) [94]. Acceptance does not involve resignation, rather it is the willingness to accept the experience fully while engaging in behaviors that bring meaning and purpose to one's life [95]. Engagement in living a full life with chronic pain is about decreasing behaviors around controlling pain (when controlling pain means reducing engagement in meaningful life activities) and, instead, focusing on accomplishing valued goals. Acceptance is also known as willingness, the opposite of avoidance or efforts to control painful sensations, emotions, or thoughts [91]. In ACT, the struggle that comes from trying to avoid or change painful thoughts, feelings, memories, sensations, and urges is considered the actual problem, not the experience itself.

ACT's core concepts are represented in the hexaflex and include values, committed action, defusion, contact with the present moment (mindfulness), acceptance, and self-as-context (Fig. 6.3) [96]. Here we describe each concept and its conceptualization using a specific clinical example that a patient with CRPS may experience. Values are personal characteristics and behaviors that are vitally important to an individual; they serve as a guiding force, or a moral compass, that helps inform specific steps or behaviors, known as committed action, one can take in order to move toward restoring meaning and purpose in life. Values are critical to consciously define as they serve as a strong motivator when it comes to reducing avoidance. Mindfulness (focusing one's attention on the present moment) is bringing intentional awareness to internal experiences and observing these thoughts, feelings, and sensations from a stance of curiosity without imparting judgment. Defusion is the act of separating or disentangling from challenging internal experiences and involves enacting exercises which cultivate acceptance, or the intention to willingly lean into inevitable internal discomfort, thus reducing emotional reactivity. These strategies work synergistically to help one realize the self-as-context, or the idea that we are not the content of our experiences (our thoughts, sensations, feelings, or things we see), but rather we are a being that can contain and observe these things and still behave in a way that we choose, rather than, or regardless of, what internal experiences may tell us. Broadly applied, if a patient with CRPS is fearful of walking due to pain, their instinctual response may be to avoid activities that involve walking more than a few minutes. They may engage in avoidance thus reducing engagement in social or recreational life-enhancing events. If time with loved ones is a valued activity, treatment targets would include helping them reduce avoidance and practice meaningful engagement in behaviors by using defusion and mindfulness to address internal conflicts, reducing the impact they have on their behaviors. Experiential exercises and metaphors are used to recognize the power of choice with regard to action rather than being controlled by internal thoughts and feelings. The goal is to build a repertoire of workable behaviors.

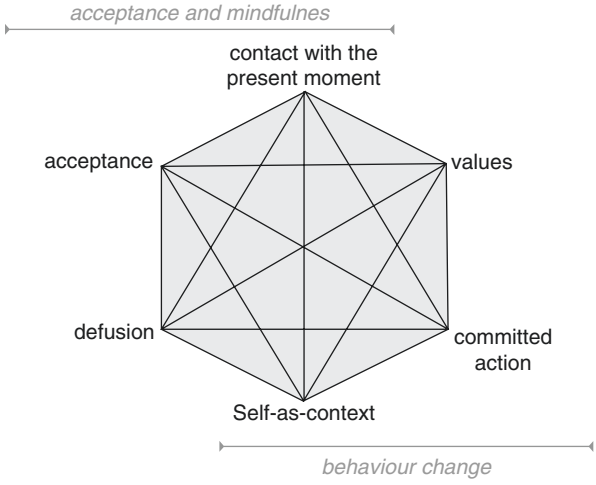

Fig. 6.3 The ACT Hexaflex diagram, illustrating six mid-level constructs often found useful in conceptualizing patient concerns. (Note: Permission to reprint granted from Hulbert-Williams et al. [134])

Case Example of ACT for CRPS

Mary, a 54-year-old woman, loved organizing, advising, connecting, and bringing families together. She was passionate about her job working as a wedding coordinator. She valued her physical, emotional, and spiritual health, friendships, and spending time in nature. She regularly prioritized Sunday morning walks with friends. Unfortunately, she developed lower extremity CRPS after she fractured her ankle. Following the diagnosis of CRPS and subsequent pain, she became very fearful of walking, and started to avoid anything that involved walking more than 10 minutes as it increased her pain levels. As a result, she quit her job as it involved too much movement and told her friends she was no longer able to join them for their weekly walks. Consequently, she spent most of her time at home, rarely engaging with friends, and became depressed and disconnected from the things she once enjoyed. She stopped exercising and became physically deconditioned (disconnection from values, or "values illness"). As a result of these changes, she became more sensitized to pain, walking tolerance decreased to less than 5 minutes, and the quality of her life diminished. Mary felt frustrated, guilty, worthless, hopeless, helpless, and irritable. Treatment utilizing ACT principals, would include: (1) recognition of avoidance behaviors (stopping valued activities) as a result of being fused with distressing internal experiences (fear, sadness, guilt, self-criticism, pain, unhelpful thoughts and rules, and reasons around her behaviors); (2) recognition that she is a person who contains these internal experiences (self as context); and (3) teach strategies (defusion) to recognize (via mindfulness) that her mind may come up with unhelpful thoughts (e.g., "CRPS has ruined my life, I'll never be able to work/exercise or see my friends until this goes away") yet she can choose to engage in valued activities (committed action) that are aligned with her values, even if the activities themselves may evoke some physical and emotional discomfort (acceptance). In Mary's case, modifying her work from on-site wedding coordinator to consultant advising those interested in becoming wedding coordinators may allow her to remain in her area of expertise. Also, she could suggest alternative activities for social engagement, for example, Yoga or Tai Chi classes as a form of movement versus engaging in regular walks which may trigger increased pain. In this way, she is still able to remain engaged in her valued activities by practicing healthy behaviors, spend time with her friends, enjoy her skills of organization, creativity, and bringing others together.

Motivational Interviewing (MI)

As outlined in this chapter, there are many evidence-based behavioral health interventions that are efficient and effective in treating CRPS and chronic pain conditions. However, effect sizes of interventions are often within the low to moderate ranges, which, in part, may be due to suboptimal rates of treatment adherence [97]. Only 50% of pediatric and adult patients with chronic pain referred to psychological interventions actually initiate these services [98–100] For individuals who do initiate treatment, increased engagement translates to better outcomes [98, 99].

Treatment for CRPS hinges on patients learning self-management tools and achieving functional gains (e.g., increased physical activity, work/school attendance, etc.) [101]. For many patients, functional improvements result in short-term elevations in pain and discomfort. The nature of optimal CRPS interventions may undermine patient willingness to adhere to treatment. Thus, within this patient population, there is a particular need to prioritize developing treatment motivation for self-management of symptoms, despite potential for discomfort.

In both the adult and pediatric literatures, readiness to change has emerged as a significant predictor of which patients benefit from multidisciplinary chronic pain interventions [102–104]. Readiness to change refers to one's readiness to adopt a self-management approach to chronic pain [105] and is based on Prochaska and DiClemente's Transtheoretical Model (TTM) of Behavioral Change [106]. The five TTM stages of change, contextualized for patients with chronic pain, include: (1) precontemplation: an individual does not wish to change their behavior; (2) contemplation: an individual is aware of personal responsibility for pain management but is not fully committed to making immediate behavior changes; (3) preparation*:* the individual is taking steps to prepare for behavior change; (4) action*:* the individual engages in the target behaviors and learns self-management of chronic pain; and (5) maintenance*:* the individual continues to engage in target behaviors and pain self-management.

Motivational interviewing (MI) is a person-centered therapeutic approach that is rooted in TTM and seeks to resolve patients' ambivalence about behavior change by strengthening their intrinsic motivation and commitment to change [107]. MI has five overarching treatment principles: (1) express empathy through reflective listening; (2) develop discrepancy between patients' goals or values and their current behavior; (3) avoid argument and direct confrontation; (4) adjust to patient resistance rather than opposing it directly; and (5) support self-efficacy and optimism [107]. Core therapeutic skills utilized include the use of open-ended questions, affirmations (genuinely recognize patient strengths leading to behavior change), reflective listening, and summary statements. In a summary statement, the clinician summarizes the content of what the patient has said, while highlighting the patient's use of "change talk" which refers to signs the patient is interested in committing to the target behavior.

MI was originally developed as treatment for substance dependence (e.g., alcohol use, smoking cessation) but since has expanded to successfully promote a range of health behaviors (e.g., obesity, type 1 diabetes, asthma) [108, 109]. Within the chronic pain literature, one available meta-analysis found that MI significantly increased adherence in adults to prescribed treatments in the short term, with small to moderate effects sizes [110]. However, the effect of MI on adherence was not maintained at a 6-month follow-up. The authors noted that there were only seven published randomized control trials (RCTs) at the time of their report. Though initial findings are promising, there is a need for research to continue to examine the effects of MI on treatment adherence, pain, and function over time, among pediatric and adult patients with CRPS [110, 111].

Group-Delivered Interventions

Although behavioral health interventions for chronic have most often been developed to be administered within the context of individual therapy, group-based interventions have also been developed and evaluated [112, 113]. There are multiple advantages of group-based therapies that may enhance treatment of CRPS. Group-delivered treatment allows clinicians to reach more patients at one time versus individual treatment approaches. This makes them a cost-effective and far-reaching treatment approach. Furthermore, people living with CRPS and other chronic pain conditions can often feel isolated, misunderstood, and invalidated by the people in their life and medical providers. The invisible nature of chronic pain adds to this dynamic. Group therapies provide a shared experience providing validation of the pain experience and the impact it has on one's life, a supportive environment to share and learn strategies to actively self-manage pain and a community of people who understand the impact that chronic pain has on one's identity, relationships, and overall function. The comradery experienced via group therapy is powerful and an integral part of the healing process. There are types of group interventions for CRPS and chronic pain conditions: reviewed here are CBT, mindfulness and acceptance based, and Explain Pain group interventions.

CBT Groups

Group CBT includes psychoeducation, learning pain coping skills, and application of these skills to the chronic pain population. Identifying automatic negative thoughts, cognitive restructuring are often key components to this therapy, in addition to introduction to acute versus chronic pain, the biopsychosocial model, activity pacing, sleep hygiene, pleasant activity scheduling, and constructive communication styles. CBT has been delivered in groups and shown to be effective for patients with depression, chronic pain including lower back pain, neck pain, migraines, and headaches [114]. Research has demonstrated that the groups' success has been correlated to the skill/sense of community that is built by the group instructor, and that CBT for depression has lower dropout rates than individual treatment [115]. One RCT demonstrated that the addition of group-based CBT to an exercise program was more effective for improving disability and quality of life for chronic neck pain compared to exercise alone [116].

Mindfulness- and Acceptance-Based Group Therapies

Unlike CBT's focus on controlling pain and changing unhelpful thoughts, mindfulness- and acceptance-based group therapies focus on increased awareness while changing one's relationship with their painful thoughts, memories, sensations, and urges to allow them to engage in meaningful life-enhancing behaviors. A meta-analysis in 2016, comparing 25 RCT, exploring the efficacy MBIs found small effect sizes on depression, disability and quality of life and moderate effect sizes on anxiety and pain interference [57]. At follow-up, small effect sizes were found on pain intensity and disability and larger effects on pain interference. A recent RTC

demonstrates that group-based MBSR has comparable results to CBT groups for patients with chronic low back pain and is considered an effective treatment option [117]. In addition, an RTC in 2011 found acceptance and commitment therapy groups to be comparable to CBT groups in addressing chronic pain [118].

Patient Education: Explain Pain Groups

Explain Pain differs from CBT in that it does not teach relaxation training, formal cognitive restructuring, or other physiological self-management skills [119]. Explain Pain focuses on education about the biological mechanisms of pain, often using metaphors to apply complex content to the patient's unique pain experience. Several key concepts are that pain is a normal biological process, pain can be overprotective, and pain is always real even when tissue damage is not present [119]. Explain Pain has been delivered via group therapy for various pain conditions including back pain, fibromyalgia, chronic fatigue syndrome, or with surgical procedures (lumbar radiculopathy) [120–122].

Innovative Digital Directions for the Field

Optimal treatment of CRPS includes behavioral health support, though widespread access to these specialized services is limited by treatment-related costs to patients, shortage of programs outside of university centers, and a dearth of pain behavioral health specialists [123]. Unequal access to specialized behavioral health treatment further exacerbates healthcare disparities and underscores the critical need to develop treatment delivery systems that are effective and address current limitations of treatment access. Over the past few decades, advancements in technology have supported the proliferation of virtually delivered care. Electronic health (eHealth) is a broad term that refers to healthcare delivered virtually (e.g., virtual sessions with a clinician [124], Internet treatment). Virtual sessions with clinicians are under the umbrella of eHealth and are commonly referred to as telehealth. Early efficacy findings comparing the benefit of in-person versus telehealth behavioral health suggests equivalency of care on clinical outcomes [125]. eHealth also incorporates the digitization of behavioral health interventions. There are multiple interventions for chronic pain that are now delivered remotely [126–129]. For example, the Web-based Management of Adolescent Pain (WebMAP) is an Internet-delivered CBT program that provides 8 weeks of online training modules completed by children and caregivers. A multicenter RCT revealed that adolescents randomized to the WebMAP group reported greater reductions in pain catastrophizing, functional impairment, and depressive symptoms as compared to youth completing an informational control [126].

In additional to eHealth, mobile health interventions (mHealth) describes the use of mobile devices and wireless technology to deliver healthcare (e.g., smartphone applications, wearable devices, and text messaging) [130]. Access to smartphones has become largely universal for individuals across developmental groups and socioeconomic backgrounds, which may support mHealth modalities as being

uniquely suited for the rapid dissemination of behavioral health interventions across differing healthcare settings [131]. Increasingly sophisticated technology has led to the development of interactive and engaging, game-like programs that are able to adapt to an individual's responses and generate tailored content. Digitally delivered care is rapidly expanding across healthcare and is a promising interventional modality with early evidence suggesting it is primed to enhance behavioral health delivery and patient outcomes. There are numerous smartphone apps that may help to promote physiological self-regulation (i.e., Calm, Headspace, Relax Melodies, and Breathe2Relax). These and many others may be utilized to assist individuals with CRPS to learn to incorporate relaxation training into daily practice. See Table 6.2 for examples of digital resources.

Table 6.2 Digital behavioral health resources

How does your brain respond to pain?: https://www.youtube.com/watch?v=I7wfDenj6CQ
Pain retreat: http://www.painretreat.net/mainbottom.htm
Understanding pain: What to do about it in less than 5 minutes: https://www.youtube.com/watch?v=vdM4dHefA4w
Pain education: http://www.tamethebeast.org/#tame-the-beast
Apps for behavioral health treatment
Deep "belly" breathing:
Breathe2Relax – Free on the App Store – All ages
iBreathe-relax and breathe – Free on the App Store – All ages
BellyBio interactive breathing – Free on the App Store – All ages
General relaxation:
Relax & Rest Guided Meditations – $1.99 on the App Store – Best for adolescents
Simply Being-Guided Meditation for Relaxation & Presence – $1.99 on the App Store – Best for adolescents
Autogenic Training & Progressive Muscle Relaxation – $2.99 on the App Store – Best for adolescents
Calm (simple breath work with great visual imagery) – Free on the App Store
Headspace: Meditation & Sleep (helpful for anxiety, sadness, pain management, self-esteem, and creativity) – Free on the App Store
Stop, Breathe, & Think (helpful for stress, anxiety, sleep, focus, resilience, happiness, yoga, and mindfulness) – Free on the App Store
Insight Timer-Meditation App (timer to help calm the mind, reduce anxiety, manage stress, sleep deeply, and improve happiness) – Free on the App Store
General cognitive-behavioral therapy:
Stress & Anxiety Companion – Free on the App Store – All ages
Moodpath: Depression & Anxiety – Free on the App Store – Best for ages 14+
At Ease: Anxiety & Worry Relief – $2.99 on the App Store – Best for adolescents
Sleep:
CBT-I Coach – Free on the App Store – All ages
Breathe: Meditation & Sleep – Free on the App Store – All ages
iSleep Easy-Meditations for Restful Sleep – $3.99 on the App Store – Best for all ages
Relax Melodies: Sleep Sounds – Free on the App Store – All ages
Sleep Cycle: Smart Alarm Clock – Free in the App Store – All ages

One very relevant application of digital solutions for the treatment of CRPS is virtual reality (VR). Therapeutic VR is an immersive, three-dimensional (3D) experience that grants patients the ability to engage in activities that may seem impossible in real life. VR could be particularly relevant for supporting patients' use of CRPS-affected extremities in a highly engaging and distracting environment. There is emerging evidence that VR can be harnessed to increase movement among patients with chronic pain, yet additional study is needed to better understand the utility of VR with patients who have CRPS [132, 133].

Conclusions

Optimal treatment for CRPS espouses a multidisciplinary approach where pain medicine, physical and occupational therapies, and behavioral health specialists collaborate to facilitate patients' recovery. Behavioral health providers are key members of the treatment team and there are a breadth of efficacious behavioral health interventions that successfully address cognitive distortions, improve patient physiological self-regulation, and encourage motivation to engage in treatment, among other treatment targets. Behavioral health interventions are related to patient improvement across pain, functional disability, and comorbid psychological conditions. Although behavioral health services were designed for individual and in-person delivery, there are emerging and promising trends in the field that seek to harness the power of group interventions and digital solutions to expand the reach of efficacious interventions. Up to this point, most research advancements have not been specific to CRPS, but have been generated within the broader chronic pain literature. To ensure the optimal treatment of CRPS, additional research is needed to better understand patients' unique behavioral health needs. Furthermore, the majority of extant literature reviewing efficacious behavioral health interventions has been conducted with adult patients. Pediatric patients have unique treatment needs not covered in this chapter (e.g., role of caregivers) that could be further explored in the literature. As reviewed in this chapter, there are a number of evidence-based behavioral health interventions that improve pain, pain-related distress, and function associated with chronic pain, yet there is also significant room for the field to grow as we aspire to provide optimal treatment for patients with CRPS.

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Comprehensive Rehabilitation of Patients with Complex Regional Pain Syndrome

7

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"One doesn't ask of one who suffers, 'What is your country and what is your religion?' One merely says, 'You suffer.' This is enough for me. You belong to me and I shall help you."

-Louis Pasteur

Introduction

Complex regional pain syndrome (CRPS) is perhaps the most fascinating and challenging pain syndrome for the rehabilitation specialist. The symptoms of CRPS impact many aspects of a patient's life and are best understood through a biopsychosocial model. In this chapter, we will present guidance for using an interdisciplinary approach for CRPS rehabilitation based primarily on clinical experience. This model seeks to address not only the biological changes involved, but also to intervene in the psychological and social spheres. The use of an interdisciplinary team addressing the broad impact of CRPS presents many challenges but is often needed to address this life-changing diagnosis.

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Interdisciplinary treatment of pain was pioneered by John Bonica, MD, in the mid-to-late twentieth century. Dr. Bonica's leadership led to the establishment of multidisciplinary pain programs in North America and globally. Unfortunately, many of these programs no longer exist because they are expensive and difficult to maintain. As medical science has advanced, interventional pain treatments including myriad pharmacological, neuromanipulative, and surgical treatments have promised resolution of pain within the dominant biomedical model. In traditional biomedical treatment, interventions are aimed at halting or reversing the pathophysiologic mechanisms active in the condition. Treatment modalities have been applied based on various theories of causation and maintenance of the CRPS with limited results.

The biopsychosocial model of care is complex. The lack of uniformity in the design, application, and financing of biopsychosocial treatment programs makes it difficult to compare the effectiveness of one program to another. Components of these programs vary greatly, including different disciplines providing several forms of both interventional and noninterventional treatments. Rehabilitative treatment is focused on functional restoration of a person who is hampered by a condition and does not limit focus on pathophysiology. What we know and learn in rehabilitation often comes from trial and error and is guided by our understanding of the person – their strengths, weaknesses, fears, hopes, and the resources they bring to the fight. Rehabilitation has been strengthened by advances in evidence-based treatment of pain, including a better understanding of the neuroscience of pain. In complex regional pain, experience reported from those across multiple centers affirms that restoration of movement in the face of pain is the critical element in arresting and/or reversing the disease process.

A comprehensive Cochrane review completed in 2013 by O'Connell et al. [1] reported that there was insufficient high-quality evidence on which to base comprehensive clinical guidance on the management of CRPS. However, the authors provided evidence, although low quality, for the use of graded motor imaging programs in improving function and reducing pain compaired to conventional physical therapy. The review also provided low-quality evidence for mirror therapy in improving function and reducing pain in poststroke CRPS when compared to traditional physical therapy. Furthermore, the review demonstrated low-quality evidence that occupational therapy/physical therapy has a small positive effect on pain at 3-, 6-, and 9-month intervals; however, the effect is unlikely to be clinically important at 1 year when compared to passive education and psychological therapy provided by a social worker. It is important to note that there are many cases of CRPS that resolve completely with conservative physical and occupational therapy alone.

Although the Cochrane review did not provide official recommendations for the management of CRPS, various medical institutions have used the same research to develop guidelines. These guidelines support pharmacological management, paired with physical and occupational therapy using mild exposure in a step-by-step fashion

to increase function, while keeping pain at tolerable levels. Harden et al. [2] provided a review of evidence for and against various CRPS treatments. Regarding comprehensive treatment, the authors offered the following interdisciplinary functional restoration treatment algorithm in combination (used with permission) (Fig. 7.1).

As reflected in the algorithm above, the authors emphasized that, from the outset, consideration should be given to use of medications, psychotherapy, and/or injections on an individual basis as may be appropriate, with escalation of these additional interventions if the patient is not progressing in their rehabilitation.

The European Pain Federation established a Pan-European task force of experts in CRPS to produce quality standards surrounding the diagnosis and treatment of CRPS. The results of the task force's efforts were published in the European Journal of Pain in 2019 [3] and put forward "current best practice." Table 7.1 (used with permission) from this seminal article outlines the standards for the diagnosis and management of CRPS.

The Pan-European task force of experts acknowledged that there is significant room for improvement in diagnosing CRPS by accepted criteria in a timely manner and instituting a plan of care that would meet the criteria laid out. The task force also acknowledged the limitation of their methods in the discussion – "that evidence-based support for these standards is incomplete and there is no standard that could not benefit from further study." They recommended regular review of the standards in light of "new and emerging evidence."

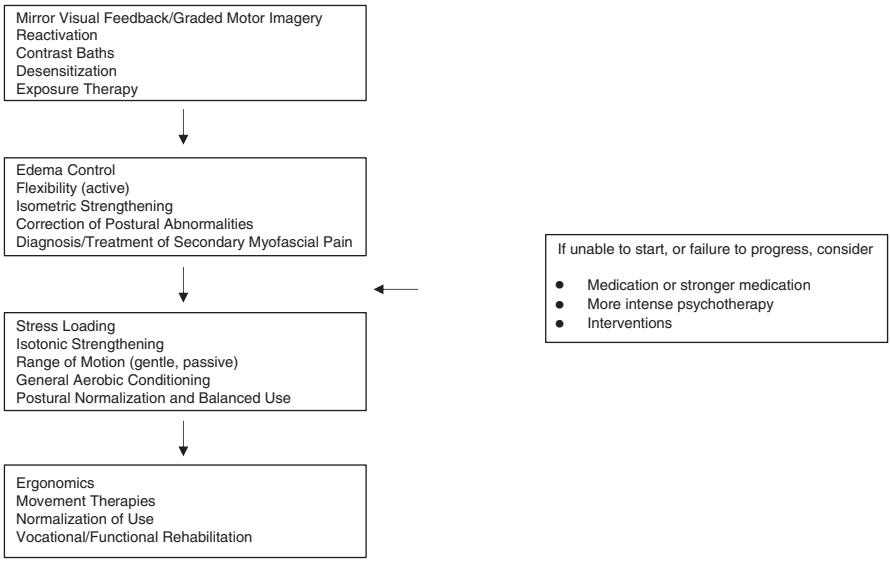

Fig. 7.1 Overall treatment of complex regional pain syndrome algorithm. (Harden et al. [2])

Nevertheless, the publication of their standards allows each country in the European Pain Federation the ability to assess their level of care in relation to this benchmark. The advantages of these standards are that they do not assume availability of specialized and superspecialized care and provide guidelines for referral when they are not provided locally. Establishment and implementation of standards in the United States is difficult because quality measures vary within different states, insurance providers, and even the multitude of Medicare and Medicaid providers. Independent health care systems could establish similar standards and the high cost of mismanagement of CRPS may be the main incentive to move in this direction.

Table 7.1 European pain federation standards for the diagnosis and management of complex regional pain syndrome

Diagnosis	Standard 1	"Budapest" diagnostic criteria for CRPS must be used, as they provide acceptable sensitivity and specificity
	Standard 2	Diagnosing CRPS does not require diagnostic tests, except to exclude other diagnoses
Management and referral	Standard 3	The management of mild (mild pain and mild disability) CRPS may not require a multiprofessional team; however, the degree of severity and complexity of CRPS must dictate the need for appropriately matched multiprofessional care
	Standard 4	Patients diagnosed with CRPS must be appropriately assessed; this assessment must establish any triggering cause of their CRPS, their pain intensity, and the interference their pain causes on their function, their activities of daily living, participation in other activities, quality of life, sleep, and mood
	Standard 5	Referral to specialized care must be initiated for those patients who do not have clearly reducing pain and improving function within 2 months of commencing treatment for their CRPS despite good patient engagement in rehabilitation
	Standard 6	Referral to superspecialized care must be initiated for the small number of patients with complications such as CRPS spread, fixed dystonia, myoclonus, skin ulcerations or infections or malignant edema in the affected limb, and those with extreme psychological distress
	Standard 7	Specialized care facilities must provide advanced treatments for CRPS including multidisciplinary psychologically informed rehabilitative pain management programs (PMP). If they do not provide these treatments, then they must refer for these treatments, if needed, to other specialized care facilities, or to superspecialized care facilities
Prevention	None	No Standards were consistent as having sufficient support to recommend as mandatory
Information and education	Standard 8	Patients and where appropriate their relatives and carers must receive adequate information soon after diagnosis on (a) CRPS, (b) its causation (including the limits of current scientific knowledge), (c) its natural course, (d) signs and symptoms, including body perception abnormalities, (e) typical outcomes, and (f) treatment options. Provision of information is by all therapeutic disciplines and must be repeated as appropriate

Table 7.1 (continued)

Pain management	Standard 9	Patients must have access to pharmacological treatments that are believed to be effective in CRPS. Appropriate pain medication treatments are considered broadly similar with those for neuropathic pains, although high-quality studies in CRPS are not available [4]. All patients with CRPS must receive a pain treatment plan consistent with any geographically relevant guidelines
	Standard 10	Efforts to achieve pain control must be accompanied by a tailored rehabilitation plan
	Standard 11	Medications aiming at pain relief may not be effective in CRPS, while causing important side effects; therefore, stopping rules should be established and a medication reduction plan must be in place if on balance continuation is not warranted
	Standard 12	CRPS assessment (see above) must be repeated as appropriate because both the natural development of the disease and of the treatment may change the clinical picture over time
Physical and vocational rehabilitation	Standard 13	Patient's limb function, overall function, and activity participation, including in the home and at work or school, must be assessed early and repeatedly as appropriate. Patients should have access to vocational rehabilitation (as relevant)
	Standard 14	Patients with CRPS must have access to rehabilitation treatment delivered by physiotherapists and/or occupational therapists as early as possible in their treatment pathway
	Standard 15	Physiotherapists and occupational therapists must have access to training in basic methods of pain rehabilitation and CRPS rehabilitation
Identifying and treating distress	Standard 16	Patients must be screened for distress including depression, anxiety, posttraumatic stress, pain-related fear, and avoidance. This must be repeated where appropriate
	Standard 16	Where required, patients must have access to evidence-based psychological treatment
Long-term care	None	No standards were considered as having sufficient support to recommend as mandatory

Goebel et al. [3]

Background

In this chapter, we present information gained primarily through clinical experience from an outpatient, community-based pain rehabilitation program that utilizes medical providers (medical doctors and nurse practitioners), nurses, psychologists, physical therapists, and occupational therapists who provide interdisciplinary care for a wide variety of chronic pain conditions. The program allows patients to continue to reside at home and, in many cases, maintain employment while participating in treatment. By providing services in the patient's community, we can address environmental contributors to pain in the natural environment. Environmental factors may be harder to assess and treat for individuals participating in destination

programs for a short duration. When patients remain in their community, it allows the intervention to address natural contingencies that influence pain. In our experience, these contingencies often play a major role in how a patient responds to pain and in overall outcome. Factors such as home environment, family dynamics, and employment often strongly influence a patient's experience. This program attempts to provide highly individualized care with a primary focus on the unique needs of each patient. Psychosocial factors, while not always directly related to CRPS symptoms, have the potential to impact a patient's ability to engage in treatment. We attempt to provide support for as many psychosocial challenges as possible by linking patients with other services inlcuding social work or community supports. By assessing and being aware of a patient's overall needs, we feel we can provide additional value to the patient.

In the program, patients participate in intensive treatment, typically attending appointments 2–3 days a week for between 10 and 12 weeks, depending upon the presenting concern. Treatment is typically provided in a one-on-one manner. This includes two hours per week with pain psychology, physical therapy, and occupational therapy each. Patient time with their medical provider is 15–30 minutes once a week for patients on chronic moderate- to high-dose opioids, or those with nonopioid polypharmacy. Those not receiving opioids or presenting with polypharmacy are seen every other week by their medical provider. This standard approach is modified based on patient's need. For those that are high functioning, treatment intensity or duration may be reduced to once a week. The therapists can reduce or expand visits as they and the patients deem necessary. This has been important when treating patients with CRPS as treatment may be extended, with the treatment team often slowly decreasing the frequency of treatment as a patient makes the transition to self-management after treatment.

A key consideration when providing interdisciplinary care, especially when treating CRPS, is provider communication. The program is integrated with all services and providers being housed in the same location. Formal team meetings occur weekly, with all patients being discussed by all team members. Providers can discuss progress as well as concerns. Feedback between providers is encouraged, allowing for different disciplines to support one another on shared goals. The meetings also allow for discussion of the efficacy of interventions being provided, and coordination for changes to treatment, including eventual completion. Informal communication occurs as needed. Providers often meet briefly in between sessions, providing feedback on the patient's concerns or targets for a treatment session. Electronic communication is also common with the team attempting to have all members aware of a patient's status as they progress through the program.

We recognize that this represents only one model of care for CRPS, but is presented in order to provide a framework of interdisciplinary care for CRPS and to share knowledge gained through our experiences. We encourage the reader to compare the possible benefits or deficits to what may be available at other institutions and locations. This chapter presents discipline-specific guidance from each

member of our interdisciplinary team (medical care, physical therapy, occupational therapy, and psychology), including the process of assessment, objective measures, and interventions used to address CRPS symptoms, as well as insights gained in clinical treatment.

Medical Treatment in Interdisciplinary Rehabilitation

Early signs and symptoms of CRPS in a person postinjury, if recognized by an experienced clinician, can often be reversed and resolved by physical activation alone. Physical and occupational therapists or even a surgeon or primary care provider who can motivate the patient to restore movement in the face of pain may be all that is necessary to resolve the problem at an early stage. Recent research by Barnhoorn and colleagues in the Netherlands (2015) demonstrated that pain exposure physical therapy (PEPT) could produce equivalent outcomes when applied voluntarily to CRPS patients of recent onset and limited prior treatment. When this is not successful or the problem is not recognized, resolution and rehabilitation become more difficult and patients are more likely to require multidisciplinary treatment. The effectiveness of multidisciplinary treatment has proven difficult to measure because each program has unique features, time frames, and elements. Further, it is organizationally and ethically difficult to provide a control group for what is a relatively uncommon condition.

The nature of CRPS is such that it can cause high levels of disability, anxiety, catastrophizing, and depression in many patients. The field has long disputed whether preexisting psychological or physical factors play a major role in the onset of CRPS, but best evidence indicates that this is not the case [5]. Nevertheless, many patients present with preexisting conditions that negatively impact their ability to cope with and recover from CRPS and so must be addressed in order to facilitate maximal restoration of function. Multidisciplinary pain treatment programs are usually reserved for the patient who has not responded to "usual care." In the case of chronic benign pain, in general, and CRPS, in particular, there is not a clear recomendation for care. Multidisciplinary treatment is seen as one among many options, despite the ability of multidisplinary treatment to address the complexity patients often present with.

We require a provider referral to evaluate and treat patients with chronic pain. In this, we are in competition with interventional pain treatment clinics, private physical therapy providers, chiropractors, neurologists, orthopedic surgeons, and physiatrists. Certain medical insurers have been requiring consultations at Spine Centers of Excellence before authorizing surgical interventions for spinal pain. These centers of excellence are required to initiate evaluation and treatment by a nonsurgical specialist, usually a physiatrist. Our institution houses one of these centers and they are a major source for referrals to our chronic pain programs. These providers are trained in the diagnosis of CRPS. We are involved with providing continuing medical education presentations for physicians, advanced practice professionals,

physical and occupational therapists, as well as for psychologists, social workers, and nurse case managers. We believe that standardization of treatment for CRPS would be major improvement in the ability to assess quality of care and evaluate components of the treatment of this condition. However, to date, treatment algorithms have been promulgated, and are not routinely followed at most locations.

Interdisciplinary Medical Rehabilitation of CRPS: Assessment

Once a referral is received, our staff offers an evaluation appointment with one of our medical providers and then nursing reviews the referral and makes sure that adequate records have been provided. A 1-hour initial evaluation appointment is undertaken by the provider. This includes a detailed history of the present illness and present medication use, review of past medical history with particular attention to disqualifying conditions such as dementia or significant cognitive impairments, unstable cardiopulmonary disease, unstable psychiatric condition with imminent threat to self or others, or untreated substance use disorder.

When the diagnosis of CRPS is considered, the CRPS: Diagnostic Checklist [6] is completed. We are looking for a clinical diagnosis at this point to determine recommended treatment. Most patients with CRPS have previously undergone a variety of diagnostic and therapeutic interventions, but additional diagnostic testing is pursued when individually indicated.

Patients with severe depression or anxiety and those with prior history of multiple psychiatric hospitalizations are frequently asked to see one of our pain psychologists for an evaluation before a decision is made to offer multidisciplinary treatment. The purpose of this evaluation is to ensure that they are stable enough psychologically to participate in and benefit from our treatment. An important part of the initial evaluation is to begin forming a therapeutic relationship with the patient and begin the education process as to the nature of CRPS and the need to focus on functional restoration and self-management techniques and elimination of ineffective medications and treatments. These patients are often very frustrated with the medical care that they have received and are distrustful of the system. Patience and demonstration of concern when the patient shares their history is key to gaining trust. We then try to normalize the patient's experience by acknowledging that they have every reason to be skeptical that our treatment will be any better than the multiple other attempts they have already tried.

Every member of our team is engaged in gaining trust and helping to restore a feeling of hope in patients who have frequently given up on ever getting any better. If the patients are not treated with respect anywhere along the line, they likely will not come back. Frequently, by the time they get to us, they do not expect to be treated with respect. The time dedicated to this initial evaluation is extremely important.

Patients with CRPS present with pain out of proportion to their observable pathology and typically demonstrate pain behavior proportional to their pain complaints. Guarding, withdrawal, breath holding, and crying are all typically more

common in the CRPS patient than in the low back pain or peripheral neuropathy patient who may also rate their pain at 10/10. For this reason, those of us who treat chronic pain consider CRPS to be one of the most painful maladies we see. We have had patients refuse to see us again because we touched their affected extremity. Consequently, we ask the patient to manipulate their affected extremity while we observe and at times, they will refuse to even attempt this. Although the Budapest diagnostic criteria require assessment of temperature, differences, allodynia, and hyperalgesia, as well as evaluation of dystonia and stiffness, patient trust that may be lost is not worth the gain in diagnostic accuracy in a patient who is this sensitive. Regardless of the diagnosis, this patient is in serious need of rehabilitation and we forgo unwanted examination and manipulation unless the patient agrees. Most patients will allow and tolerate an adequate examination if asked ahead of time and instructed to stop us if the pain is too much. It is most important to the rehabilitation process to establish a working relationship of trust with the patient at the time of the evaluation as there may not be another opportunity.

It is unusual for there not to be a recommendation of multidisciplinary treatment after an evaluation. There are several reasons for this. We have found over many years that we are not very good at predicting who will do well. Some patients who appear to have little hope of improvement at evaluation have shown truly remarkable transformation while others who appear less severely disabled show very little benefit despite our best efforts. It seems that the more miserable the patient, the more likely we are to be able to help them. Incredible suffering is a strong motivator toward change. Patients frequently share that, "This is my last hope." We explain that our pain programs are for people who have pain for which there does not seem to be any cure. We utilize all team members to try to reduce or eliminate their pain if we can, but our primary focus is restoring function. Our patients have usually been through many failed attempts at cure and they end up at our clinic feeling that the pain has won. The first step in the rehabilitation process is restoring enough hope that they will return for treatment. This is by no means a given.

We focus pharmacological treatment on restoring sleep with tricyclic antidepressants, cyclobenzaprine or trazodone, use of gabapentin or pregabalin for neuropathic pain, antidepressants for symptoms of both depression and anxiety, and minimizing or eliminating opiates. Since our primary psychological approach to pain treatment is acceptance and commitment therapy (ACT), we begin at the outset to focus on pain neuroscience education, educating the patient as to the abnormalities in their pain system and the need to learn to react to their pain differently through acceptance of the pain and relaxation. It is important to teach them that hurt does not mean harm. For this reason, we avoid as much as possible identifying pain relief as a major focus. If the patient comes to us on high-potency analgesics, we begin treatment without adjusting these; however, as we see progress, we gradually reduce the medications after educating the patient about lack of evidence for long-term effectiveness of opioids, the risk of hyperalgesia and overdose, and the other common adverse reactions to these medications.

Treating complex regional pain syndrome presents significant challenges. When we encounter a CRPS patient of recent acute onset, we work to begin

active treatment as soon as possible because pain avoidance can quickly lead to complications including progressive involvement of the affected limb, dystonia, muscular atrophy, osteopenia, and depression and/or anxiety. For patients with prolonged history (beyond 1–2 years), we anticipate a prolonged treatment course. We begin with our intensive program; however, unless there is unusually rapid improvement, we decrease the intensity and set progressive activity goals at monthly intervals. It is not unusual to have treatment of these patients extend to a year or longer. Continued treatment is always dependent upon progressive improvements over time. We have had some patients experience full functional recovery and return to full-time employment after years of disability using this approach.

Patients and primary care providers are often left making referral decisions based on in-network versus out-of-network or short-term out-of-pocket expenses and without knowledge of long-term outcomes and costs. The opioid epidemic has resulted in more referrals of patients on chronic opioid. As our program has never endorsed long-term opiate analgesic treatment for chronic benign pain, we are quite confident in our ability to safely taper patients from both high- and low-dose opioids as outpatients. We instruct patients in monitoring their own clinical opiate withdrawal scale and provide them with a direct pager to one of our providers to use for any unexpected problems. Since we see these patients on a weekly basis and prepare them with self-administered nonpharmacologic pain treatment tools, we rarely receive any nighttime or weekend calls.

Treatment Considerations in Medical Rehabilitation of CRPS: Interventions Used

We begin by establishing functional goals: What do you want to do again? What is important to you? What do you miss the most? Asking these questions helps the clinician build rapport and understanding. We are demonstrating that we care about the client as a person and that their goals are what are most important.

Patient education then becomes the priority. It is the foundation that the rest of treatment builds upon. We review basic concepts of CRPS, including peripheral and central changes. We review pain neuroscience with a focus on pain as a complicated, multidimensional response to perceived threat. We discuss the role of the central and peripheral nervous systems and the role of the autonomic nervous system in pain. The client will learn strategies for flare-up management.

We start the education process about CRPS. It is acknowledged that they have a severe and an uncommon pain problem and one that is not well understood. We try to help them understand that the problem is not only in the part of the body that hurts but also in their nervous system. Therefore, the treatments focus on altering nervous system function. Pointing out that pain from CRPS has been known to spread to other parts of the body, including involving the opposite limb or going from an upper limb to a lower limb without any injury to the other extremity, can help them see that it is not a simple, localized process.

We then begin to explain the complexity of the sensation of pain. The use of metaphors as championed by Moseley, Butler, and others has been particularly useful. All of us are familiar with a breadth of pain experiences and some unreasonable fears such as around needles or dentists based on past traumatic experiences, which have uniquely sensitized us to these situations. Thinking about these experiences can allow us to see how fear and other emotions modify our pain experiences, exaggerating some and minimizing others.

We provide links to online resources to expand the information available and allow the patient to hear other sources confirming what we are saying. Pain neuroscience education (PNE), also known as therapeutic neuroscience education (TNE) [7], consists of educational sessions for patients describing in detail the neurobiology and neurophysiology of pain and pain processing by the nervous system. Our physical and occupational therapists receive training in PNE and are the primary educators in our program. Their teaching is reinforced by both medical providers and psychologists on the patient's treatment team. Our psychologists primarily use ACT as the predominant cognitive behavioral approach unless patient characteristics make another approach more desirable.

It is important to explain to the patient at their initial appointment the nature of rehabilitation in CRPS. Progress in treating CRPS is critically dependent on restoring use of the painful extremity and this is most effective when done as early as possible in the disease process. For patients who come to us after years of pain, we make it clear that rehabilitation specialists are familiar with patients who have conditions for which we have no cure – patients with spinal cord injuries, paralysis from strokes, head injuries, and other neurological diseases, people with amputations, children with cerebral palsy, and other congenital defects. None of these people want to have to live with those conditions. They would much rather have us cure them, make them good as new, or better than new. We do not have the ability to do this; therefore, we work to help them become the least disabled as possible. We focus on helping them become the kind of person, spouse, son or daughter, employee, or friend that they can be despite their disability. This approach applies equally well to the 15% of CRPS patients whose pain has become chronic.

Interdisciplinary Rehabilitation of CRPS: Physical Therapy

The physical therapist plays a pivotal role in the treatment of the person with CRPS. The physical therapist evaluates the patient's movement dysfunctions as well as develops a plan for increasing activity tolerance with the goal of patient independence and self-efficacy in physical activity. Additionally, utilizing graded motor imagery (GMI) and other sensory discrimination techniques for those with CRPS is a crucial part of the physical therapist's role. Progressing a patient through this will take time, critical thinking skills, and a significant amount of encouragement to the patient.

The goal of treatment is to improve the patient's quality of life and their functional activity tolerance. This will look different for every patient as each is an

individual person. In addition to GMI, the physical therapist looks at strengthening and flexibility where necessary; coordination; desensitization to aversive stimuli; and aerobic exercise conditioning.

Interdisciplinary Rehabilitation of CRPS: Physical Therapy Assessment

The person with CRPS often has a poor understanding of why they hurt. While a person with chronic low back pain (CLBP) will almost always have misconceptions around "arthritis" and the dreaded "degenerative disc disease," they at least have a mental framework about the low back pain. The person with CLBP will usually know others with CLBP. They will have seen spine specialists who merely treat low back pain. They will have had all the scans and imaging that allow us to "see what is wrong."

Complex regional pain syndrome is different, and the patient will rarely be able to answer the question, "What is CRPS?" with any reasonable accuracy. Since CRPS is a collection of symptoms without a discrete, known cause, there are no scans or tests that allow us to "see" CRPS. The symptoms can vary between patients and can also vary moment to moment within one patient. The person will probably know of others who have had a similar injury but healed up and got back to a normal life. They will ask "Why didn't I?"

The pain can be extreme. A light breeze can be excruciating. The affected body part can feel chronically hot, cold, or fluctuate between the two for no reason. The affected body part may even begin to be perceived as larger or smaller. For the patient with CRPS, there is so much they do not understand. When you combine intense, painful, disabling symptoms with a lack of understanding as to why he/she has the symptoms, there will be emotional distress. Emotional distress is quite possibly the most effective method of making pain worse, whatever the cause.

It is well understood that providing education is a primary responsibility for any patient with chronic pain. With CRPS, the responsibility to educate becomes even greater. The patient must understand the basics of what is going on and what needs to be done about it. Education needs to be realistic. The path forward is not easy, it is not linear, and we do not know where it will end, or even if it ever will [8].

In most respects, obtaining the history from a patient with CRPS is similar to that for an orthopedic patient. However, there are a few differences that are specific to CRPS outlined below.

1. Have they had symptoms that are relevant to CRPS?
   (a) Temperature dysregulation
   (b) Trophic changes – skin, hair, and nail changes
   (c) Motor abnormalities – difficulty actively moving the affected area
   (d) Disproportionate pain – specifically asking about hyperalgesia and allodynia
   (e) Have any of these symptoms come and gone over time?

2. How has this issue changed your life? What are you having difficulty doing that normally would be easy? ADLs? Household tasks? Yard and garden tasks?
3. If we could snap our fingers and you were feeling better, what would you be doing for fun, enjoyment, and recreation?
4. What is your understanding of CRPS? If a friend asked you to explain it to them, what would you say?

The last question is possibly the most important. It is unlikely the patient will have a solid understanding of what CRPS is. If you can help them to understand what the problem is, then the patient can become a partner in treatment.

Interdisciplinary Rehabilitation of CRPS: Physical Therapy Objective Measures

As with obtaining a subjective history, the objective assessment will be like a traditional orthopedic patient, with several exceptions. Those exceptions are noted below. Before we discuss the methods, there is an important point to keep in mind. The person with CRPS typically has high levels of reported pain. It is common for their symptoms to be easily aggravated. One should not push to get all objective measures recorded on the first or even the second visit. The rehabilitation of the person with CRPS takes time. By taking it slow and being patient, you are demonstrating to the patient that you have a solid understanding of CRPS, and you do care about their well-being.

- Observation
  - What is the coloration of the affected area?
  - Where does there appear to be swelling?
  - Is there abnormal hair or nail growth?
- Photography
  - Take a picture of the affected and unaffected areas. Make sure this becomes part of the patient's medical record.
- Edema
  - Use circumferential or volumetric measurements, if appropriate.
- Active and passive range of motion (ROM) measurements.
  - Begin with AROM and then PROM if patient can tolerate it.
  - Note any abnormalities in motor patterns.
- Muscle strength
- Manual muscle testing (MMT) and/or dynamometry.
  - Careful with strength testing as tactile hypersensitivity is common.
- Sensory testing
- Light-touch monofilament testing
- Take care to note whether there seems to be a dermatomal pattern. Lack of this is normal.
- Sensory discrimination testing

- Two-point discrimination testing
- Graphesthesia
- Texture discrimination
- Temperature discrimination
- Pain/pressure threshold
- This will require a dynamometer.
- Laterality testing
- See the graded motor imagery section.
- Neurodynamic testing
- The aim of the neurodynamic testing is to determine the following:
  - Whether there is evidence of reduced neural mobility.
  - Whether you can use structural differentiation to determine if one peripheral nerve is more affected than others.
- Functional outcome measures
  - Lower extremity functional scale
  - Qdash/DASH
  - Foot and ankle ability measure
  - Patient-specific functional scale

Interdisciplinary Rehabilitation of CRPS: Physical Therapy Interventions

Patient education is one of the most important aspects of treatment. The program devotes considerable time to patient education. Typically, patients are interested in learning more about their conditions. The key areas to focus on are flare management, graded exercise/exposure, and pain neuroscience education.

An important part of the treatment of chronic pain is teaching the patient how to deal with pain flare-ups. Normalizing flare-ups is an aspect that people with chronic pain need to understand. Everyone has pain and everyone experiences an increase in symptoms due to physical or emotional stresses. Those with chronic pain often consciously or unconsciously catastrophize about pain flare-ups. Their inner monologue sounds like, “This is only going to get worse!” or “This is going to be worse than last time!”

In the program, a series of steps have been adopted that assist patients in developing their own flare management plan. The goal is to help them be able to cope and maintain their functional abilities through the duration of a flare. This starts with the understanding that a flare can be induced by physical or emotional stresses but does not mean that there is harm or injury to the tissues. Patients are encouraged to come to scheduled appointments even during a flare-up, recommend different ideas to assist in the management of their symptoms, and avoid the tendency for people to rest until they feel better again.

Pain neuroscience education or therapeutic neuroscience education is an intervention that has been found effective for reducing pain and improving patient knowledge of pain, improving function, reducing psychosocial factors, enhancing

movement, and minimizing healthcare utilization in patients with musculoskeletal pain [9, 10]. There are many resources for educational information on pain neuroscience education. Our program consistently uses the Neuro Orthopaedic Institute's (NOI) Explain Pain and the Why You Hurt Flashcards developed by Adriaan Louw, PT, PhD. The focus of pain neuroscience education is centered on increasing the patient's level of understanding in order to reduce the threat of pain.

A basic understanding of the nervous system's role in pain production is essential to establish a foundation of knowledge. One metaphor that helps to explain the nervous system's role in pain production is likening it to the body's alarm system. Our house alarms are used to let us know when something is a threat to our homes and the nervous system does the same thing for our bodies. When something changes in our environment, messages are sent to the brain for interpretation. From there, the brain must decide about what action to take. In the case of pain, a nociceptive/danger message is sent to the brain by the peripheral nerves (touching a hot stove, a nail in foot, hitting head on something, etc.). If the brain recognizes enough potential threat to the physical body, the brain produces the perception of pain to grab attention and produce an adaptive change.

When discussing CRPS, education on homuncular changes is important for the purpose of understanding GMI. These changes are usually referred to as "smudging." Built into the brain, there is a mental picture or representation of the body. An illustration of a homunculus is useful, and each body part has nerves that correspond to it. When taken together, those nerves form a picture of our bodies. A demonstration of this is touching the tip of the nose with eyes closed. Without a picture of the body in the brain, the nose would not be able to be found without seeing it. This picture remains crisp and clear when body parts are utilized and moved; movement in the environment is easy and fluid. Most movements do not require conscious thought; they just happen. Following an injury, even with the simplest of injuries, the picture in the brain can get "smudged" or "smeared." When this happens, the brain can lose track of where that body part is. It is a lot like losing a small child in a crowded room. The first reaction is panic. When the brain is not certain where a body part is, it panics. Pain is an expression of that panic. Gradual exposure to movement is the simplest and most effective method of "un-smudging" the brain. By actively using neural pathways, the homunculus can be refreshed and reinvigorated.

Graded motor imagery is an intervention that proposes the use of movement observation, laterality recognition, explicit motor imagery (visualization), and mirror therapy to "exercise" central motor pathways in a gradual, but progressive fashion [11]. The end goal of GMI is to move the patient to the point where they can do active movement, functional exercise, and other more traditional rehabilitation interventions with less pain. It is important to note that GMI is not the pinnacle of rehabilitative treatment. GMI gives the clinician a starting point for treatment with patients who cannot tolerate any type of active treatment.

The hypothesis supporting GMI is that neural pathways, or "neurotags" [12, 13], for movement and for pain have become intermeshed in such a fashion that activity in the neural pathway for, say, toe flexion concomitantly activates the neural

pathway for pain in the toe. It is as if the two pathways have become one. It is classical conditioning, as in Pavlov's dog. In a normal situation, a bell should not result in salivation from the dog. However, the more the bell is presented with food, the more the dog's neural pathways associate the bell with food. The same thing happens with pain. The more a person expects something to hurt, the less movement is needed for it to hurt. It can reach the point where even thinking about movement creates pain. The physiologic goal of GMI is to normalize the neural pathways for movement such that not only does the movement occur as intended but pain does not automatically coincide with movement.

There are three types of data that the brain uses to make decisions: sensory input, expectations/memories, and contextual cues. In chronic pain, and quite notably in CRPS, expectation and contextual cues are very powerful. The person with CRPS may find their symptoms fluctuate depending on where they are, who is around, what type of sounds they hear, what they are able to smell, and what they can see. Memories of the inciting trauma are well known to increase symptoms [13]. A patient may have considerable pain when attempting to make a fist. While performing their laterality recognition, the patient may need to initially skip or avoid the images of a fist. During mirror therapy, one would commonly begin with the mirror image performing relatively innocuous movements. As the patient improves, gradually add movements that have a greater tendency to elicit symptoms.

Lastly, pain is unpredictable, and this is even more true for CRPS. Despite solid clinical reasoning, a thorough understanding of the pathophysiology of CRPS, and good rapport, there will be patients who do not see improvement. There will be cases where interventions lead to a temporary worsening of symptoms. As a clinician, one must be willing to accept poor outcomes and learn from them. Treating CRPS is not for the fragile ego. The first step in GMI is education. It is our experience that the patient must have some level of understanding of why GMI is necessary, how GMI works, and what GMI will do. Concepts that need to be explained are as follows:

- Basic pathophysiology of CRPS
- Motor and sensory homunculus changes in CRPS
- Motor planning at a central level
- How GMI can reestablish normal movement
- How GMI can lead to success in the future

The best method to explain complicated topics like GMI is through stories, analogies, and metaphors. If you can talk about changes in "nerve sensors," "ruts in the road," and changes to the "body in the brain," you can then educate the patient on these complicated topics. It is important that the stories be flexible and adaptable. Each educational session will need to be molded and modified for the needs, biases, and experiences of the patient sitting in front of you.

Do not attempt to explain everything about CRPS and GMI in one session. That would be too much information for any individual to grasp. Best practice is to

educate in short segments. Each session should build on content presented in the last session. Each session should include a short review of past concepts.

The education will need to be repeated and reinforced frequently. CRPS and GMI are too complicated for the average individual to fully grasp after one educational session. Brief, but frequent reminders of the goals of GMI and how it works are helpful. GMI is a method of graded exposure. Each stage of GMI gradually increases the "intensity" of central neural activity. The first stage is movement observation. This is the least complicated stage of GMI, and it is not necessarily used with every patient. Movement observation is used after a patient attempts laterality recognition but is unsuccessful because of symptom aggravation. Movement observation is the starting point for the most sensitive patients.

The patient watches others perform movements, particularly movements of the affected body part. Instruct the patient to be a "movement detective." The patient should start to analyze basic, everyday movements to see how it happens, when it happens, when the movement seems unusual, and how movements vary from person to person. The patient can take note of when observing other's movements changes their own symptoms. For example, the patient might note that observing movement during their favorite sport aggravates symptoms. Or observing movement in a violent movie could have a different symptomatic effect compared to observed movement in a romantic comedy.

GMI requires steady, consistent, repeated bouts of "exercise." The patient should aim for 1.5–2 hours per day. Short sessions are usually required as the mental effort to focus on other's movements is taxing. While doing movement observation, the patient should periodically test whether laterality recognition continues to aggravate their symptoms. If it does not, they should move immediately to laterality recognition. Laterality recognition is the second stage of GMI. In this stage, the patient will look at a series of images and try to identify whether it is a right or left body part or, if an image of the spine, whether the image is of someone moving to the right or the left. This is most commonly done by using an app on a smartphone (*Recognise* by the *NOI Group*), flashcards (purchased or homemade), or by looking through magazines and attempting to spot specific body parts. Laterality recognition typically begins with several rounds of testing. The Recognise app works best for this, as it can give you immediate data on reaction time and accuracy. At Mary Free Bed Pain Rehabilitation Program, the following testing protocol has been developed:

1. Begin with a round of demonstration where you demonstrate 10–20 images for the patient.
2. Instruct the patient that they are to identify whether the image they see is of a right-sided body part or a left-sided body part.
3. They are to identify the body part as "quickly and instinctively" as possible. "Don't stop and think about it, just react!"
4. Give the patient one practice round of 20 images. Make sure they understand that the first round is practice only.
5. For the first testing round, begin with the 40–50 basic images. Record the speed and accuracy.

6. Ask if there was any symptomatic reaction. If not, repeat with 40–50 vanilla images. Record the speed and accuracy.
7. Ask if there was any symptomatic reaction. If not, repeat with 40–50 context images. Record the speed and accuracy.
8. Ask if there was any symptomatic reaction. If not, repeat with 40–50 abstract images. Record the speed and accuracy.
9. Once testing is complete, the clinician has an opportunity to begin the educational process.
   (a) Begin with an explanation of how movement is created at a central level.
   (b) Explain how their scores, if abnormal, indicate that the areas of the brain that help plan and create movement need some "exercise."
   (c) Explain that "exercising" the brain takes a lot of time and repetition.
   (d) Give the patient written instructions regarding:
      1. Different methods of laterality recognition – *Recognise* app, flashcards, magazines, etc.
      2. Frequency – 1.5–2 hours per day in 3- to 10-minute bouts.
      3. What to look for in accuracy and reaction time (if using the *Recognize* app).

We consider an abnormal score to be below 85% accuracy or above 2 seconds of reaction time. This is based on research on normal subjects [11]. There seems to be a tendency for normal accuracy and reaction time for the spine to be higher (90% and higher and 1.5 seconds and lower) and for recognition of the knee and shoulder to be lower (80% and higher and 2–2.5 seconds and lower). The standards for the spine and knee/shoulder are based on clinical experience and have not been established by research. When looking at the results, any asymmetries are noted. These asymmetries may be in accuracy, reaction time, or both. There are a variety of different patterns (outlined below) that have been noted over time.

1. Lower accuracy/slower reaction time for the affected body part – these fit with the classic "smudging" hypothesis. In other words, changes in the mental representation in the sensory and motor homunculi lead to difficulty recognizing the affected body part.
2. Lower accuracy/slower reaction time for the unaffected body part – the most common hypothesis for this scenario is that pain has so drawn the individual's attention to the affected body part that they are biased toward the affected body part.
3. Lower accuracy/normal reaction time for the affected body part paired with normal accuracy/slower reaction time for the unaffected body part. Note: This is a pattern that has been observed with many patients, possibly 50%. It is as if the brain sees the unaffected body part but must take longer to make sure it is the unaffected side. Meanwhile, the brain has difficulty recognizing the affected body part.

Laterality recognition training progresses as the patient's reaction time and accuracy improve and as symptom aggravates. The patient is instructed to imagine

movement becomes less common or disappears. Generally, the patient moves through the different types of images – basic, followed by vanilla, followed by context, and finally, abstract images.

Explicit motor imagery is the third stage of GMI. Explicit motor imagery is more commonly referred to as visualization. The patient is instructed to imagine movement of their affected body part performing movements, from a first-person perspective. As an example, Sue has CRPS of the right hand. Her laterality scores are good and there is no symptom aggravation. Sue is asked to look at a picture of a right hand in a certain posture. Sue then closes her eyes and imagines her own hand moving in and out of that same posture several times. She imagines this movement as happening from her perspective, not from the perspective of someone watching her.

The patient starts by imagining simple, innocuous movements. As the fluidity of their mental movements improves, the patient can begin to imagine more complicated movements and/or movements that are typically symptom provoking. The progression can continue to include complicated series of movements that happen in specific contexts. For example, a person imagining themselves typing on a computer. The patient is instructed to imagine movement. Not only could they imagine themselves typing, but they could be typing a specific word, sentence, or saying. Regarding frequency and duration, we recommend that same 1.5–2 hours per day in 3- to 10-minute sessions. It is valuable to have the patient continue to perform some maintenance laterality recognition.

It has been our experience that many patients will have difficulty with visualization. They will report to us that no matter how hard they try, they simply cannot visualize their body part moving. In cases like this, we will often move onto the fourth stage of GMI rather than create persistent frustration and feelings of failure.

The fourth stage of GMI is mirror therapy. In mirror therapy, the individual watches the reflection of the contralateral body part as it performs movements ranging from simple to complex. It is important that the patient not be able to see the affected body part while performing mirror therapy. The patient is positioned comfortably with a mirror in place such that the reflection accurately reflects the size and position of the affected body part. The affected body part should be covered or in some way hidden from the view of the patient. Begin with an explanation that includes the following:

- Humans are visually dominant. We tend to believe what our eyes tell us even if we are aware it is an illusion.
- We will begin with simple movements of the unaffected body part while watching the reflection. Do not look at the body part that is moving but look at its reflection.
- Do not judge what you see. Simply watch the movement.

Begin by asking the patient to perform several repetitions of a single joint, uniplanar movement. Ask them if there was any symptomatic reaction. Observe the affected body part for changes in color or any involuntary movements. It is common to see one or both.

If there is no reaction, continue with other simple movements. Take the time to assess the patient's reaction.

If the patient can tolerate simple movements without aggravation or only transient aggravation, you can attempt more complicated movements. At this point, or even earlier, the patient will be ready to move onto more traditional treatment modalities – active and passive ROM, strengthening, stretching, functional activities, etc. Even when a patient has begun traditional treatment, it is valuable to have them continue with maintenance laterality recognition and/or mirror therapy.

Graded exposure to activity is a widely used approach to treating chronic pain and is sometimes referred to as pacing [14]. The key reason for pacing and graded exposure is to retrain the brain and nervous system gradually to help change associations between specific movements or activities and the fear that it will cause onset of pain. When thinking of graded exposure, you can liken it to training after an injury or climbing a mountain. The athlete is not just going to jump back into their game right away or the mountain climber is not going to start with Mount Everest. There is a process of events that needs to occur including rehabilitation for the athlete and training for the mountain climber. Each time in order to progress, the person must do a little bit more than the day before.

The first step for the patient is to understand their baseline. This is the amount of activity that they can do without a flare in their symptoms. Pain may increase slightly but it does not incapacitate the patient for hours or days. The second step is to work to gradually increase tolerance to activity. This is done by working below the flare-up line but increasing challenges often. Instead of just avoiding the pain, a patient is going to be working to increase tolerance to activity without creating a flare of symptoms. This often takes some trial and error in order to understand their unique flare-up level.

Subsequently, guiding the patient through increasing their activity level to improve tolerance. Activity tolerance does not improve in a linear direction. Typically, there are fluctuations in progress when trending in the positive direction. It is imperative that patients are educated on this idea and that this is normal.

Pain exposure therapy is exactly what it sounds like. The patient moves, exercises, and performs everyday tasks despite symptom aggravation. This type of therapy can be very successful when certain criteria (below) are met:

- The patient fully understands and accepts that hurt does not equal harm.
- The patient is willing to aggravate symptoms.
- The patient has the skills necessary to minimize emotional distress.
- The patient has the self-awareness to understand when they are aggravating symptoms beyond a tipping point.
- The patient has the self-discipline to be consistent with treatment, especially on the "bad" days.

While we know pain exposure can be an effective treatment [5, 15], the Netherlands-based group showed that pain exposure physical therapy, defined as a direct exposure to painful stimuli with ignorance of pain, is equal to the standard

guidelines at restoring function and decreasing pain. Our experience is that few patients with CRPS have the skills or temperament for pain exposure therapy to be effective. This is especially true at the outset of treatment. Patients have typically been investing much of their time and energy into preventing and minimizing pain. Later in treatment, after the patient has gained knowledge and understanding and after solid rapport has been established with their treatment team, then pain exposure therapy can be successful.

Interdisciplinary Occupational Rehabilitation of CRPS

Occupations are any role, routine, hobby, or activity/exercise that "occupies" a person's time and holds personal meaning. To differentiate the types of occupations, they are classified under specific headings such as activities of daily living (ADLs), instrumental activities of daily living (IADLs), work/school, leisure, play, and others. Examples of ADLs include self-care such as bathing, toileting, eating, grooming, and dressing. IADLs encompass the level of activity beyond specific focus on the physical body, things such as: community mobility, meal preparation, house chores, shopping, care of others, care of pets, and social engagement. The occupational categories of work and school will depend on the type of work being performed and the age, developmental level, and grade of the student. Leisure occupations include hobbies for those over the age of 18, and play includes developmental milestones and games for children that are instrumental to their growth. When a person encounters a barrier to these occupations, an occupational therapist (OT) works to adapt, compensate, and modify an environment or skill so that the person can be as independent as possible. Function and independence are the OT's focus when working with all clientele.

Occupational therapists' skills in determining current performance in the occupations of ADLs, IADLs, sleep, socialization, leisure and/or recreation, work, and school help them provide additional valuable information regarding client factors (including body functions, body structures, and values and/or beliefs), performance skills, performance patterns, contextual factors, and environmental factors that can help guide realistic, objective, and measurable functional goals for the individual with chronic pain [16].

Occupational therapists aim to support patients in improving functional tolerance and reengaging in these meaningful life tasks. In treating persons with CRPS, the overall goal does not change when compared to a person with chronic pain; however, the education, engagement, and approach to activities may look quite different. The OT will consult with the physical therapist (PT) on the strength, endurance, and flexibility that a patient has in order to participate in their daily occupations. An OT will consult with the psychologist to gather information on the state of their patient's mental health in order to comprehend, carry over, and the ability to mentally attend to daily occupations. The OT will also consult with the physician in order to understand if the patient is on medication that impacts their ability to tolerate activities or exercises. The team relies on the OT for equipment

recommendations, modifying task performance, and pain-related education in occupation for the purpose of increasing patient engagement in their daily life.

An OT is integral to the team in that they are fully in charge of using a patient's meaningful occupations to lead them toward overall success and greater independence. There is no traditional formula that is used because each patient has individual occupations that hold meaning. An OT is going to get to know the patient, understanding that, although there are occupations that are socially and legally required – such as personal hygiene and attendance at school, people also have occupations that have varying levels of personal meaning. If an OT can assist a person with returning to doing something that they care about, or need to perform, then quite often mental and physical health will improve as well.

Accurate pain education, posture, body mechanics, and overall lifestyle redesign are the focus of occupational therapy in treating persons with CRPS. Pain education related to those activities of daily living (ADL), instrumental activities of daily living (IADL), leisure, and recreational activities for reengagement occurs within each session. This education supports patients in understanding of how the nervous system functions during daily activities, including lifting, home tasks, and other IADL, allowing the patient to develop skills to manage nervous system imput more effectively.

Interdisciplinary Occupational Rehabilitation of CRPS: Assessment

At evaluation, the OT secures initial history and context focused on a person's routines, environment, family context, habits, and current pain management tools. Initial education is included by the OT within the program to build rapport with the client and learn the major areas of their life that are viewed as limited due to their pain. A detailed description of their daily habits, responsibilities, home environment, change in performance most recently are gathered, and any initial personal goals for activity performance are identified. Examples of questions posed and conversations in evaluation are as follows:

- When did your symptoms begin? What tasks or activities make your pain worse? What do you typically do to attempt to control the pain or manage?
- Tell me about your current daily routine, what do you do on a typical day?
  - How has pain changed your routine?
- How has this issue changed your life? What are you having difficulty doing that normally would be easy? ADLs? Household tasks? Yard and garden tasks?
- Are you still working?
- What job tasks are required of you? Is this classified as sedentary, light duty, medium, heavy, or very heavy strength classification per Human Resources documents?
- How has work changed due to your diagnosis and has your employer allowed for modifications in your work requirements?
- If No, when was your last employment? What caused you to leave?

- Do you spend a significant amount of time using technology? Cell phone, laptop, desktop, work computer setup, etc.? Describe for me the positioning, posture, and chair use.
- If we magically make you better (which we cannot), how would your life look different than it currently does with your activities?
- What do your pain symptoms or diagnosis mean to you? How would you describe your symptoms and diagnoses?
- Starting conversation on what is pain.

Interdisciplinary Occupational Rehabilitation of CRPS: Objective Measures

Key objective measures for measuring patient function include the Q-DASH, UEFI, and PSFS or patient-specific functional scale. The former two being questionnaire format for upper extremity common daily activities a patient can self-report for their current level of difficulty. The PSFS is an in-depth conversation and discovery of what activities are meaningful to the patient, what truly makes them who they are, and how their diagnosis has affected their ability to participate in those activities. It is a subjective self-report, but one of high value as the large goal of the multidisciplinary pain program is to advance a patient's perceived functional abilities versus pain decrease.

Interdisciplinary Occupational Rehabilitation of CRPS: Interventions

Given the significant focus on pain education within the multidisciplinary team the natural next step is application to activity and occupation. Occupational therapy utilizes occupation within our initial education sessions for body mechanics, spinal anatomy related to daily postures, functional lifting, and overall safe participation strategies for a patient's desired activity.

There are three different types of pain – nociceptive, neural, and central sensitization. Nociceptive pain occurs when there is an actual injury, such as slamming one's finger in a door. What hurts? The finger. Nothing else on the body should hurt and, therefore, the pain is designated to just that one area. Neural pain occurs in the case of, for example, sciatica. The pain stays on the sciatic nerve, but it will travel the length of the nerve and, therefore, pain can be felt in numerous areas of the body. Central sensitization is an umbrella term used to describe what we refer to as a "sensitive" nervous system. A sensitive nervous system can occur when the body has undergone, witnessed, or lived through something that it feels is traumatic, and it goes into protection mode. Whether that be a physical trauma such as a car accident, or an emotional trauma such as an abusive relationship or a childhood of poverty. The brain's job is to protect itself and the body. When the central nervous system, which is the brain and spinal cord, becomes "sensitive," it goes into

overdrive when looking for threats within its environment. These threats can be seen in numerous areas of the body, and for those with central sensitization that pain therefore also moves within the body.

With CRPS, that pain can be felt in the affected limb, but the patients may also report pain in other areas of the body that is not consistent with nociceptive or neural pain. The brain can begin to see common natural body processes as things that need protection against. When the brain detects a threat, it will send off the alarm. The alarm is pain. The alarm can be described as stabbing, shooting, aching, throbbing, etc. but the common theme is that it is disruptive enough for the body to pay attention. An alarm that sounds too quietly would not be much of an alarm. Therefore, when the body of someone who has central sensitization detects a threat, it sends pain. Currently, knowledge on the exact triggers is not specific, but there is a pool of triggers that one can draw from when attempting to understand what threat the brain is detecting. Those include immunity, temperature, repetitive activities, and circulation, and perhaps one of the biggest triggers is stress, anxiety, and overall high negative emotions. Oftentimes, fear of the unknown, which is common in a diagnosis of CRPS, since it is so, well, complex, can ramp up anxiety, stress, and overall high negative emotions which we know can increase the intensity of the alarm.

It is, therefore, imperative that patients receive education about the role of pain, how it manifests in the body, and strategies and techniques to help decrease the pain when performing meaningful occupations. It is also very important to deliver education in a way that is understandable. Not everyone knows what nerves do in the body, what makes up the central and peripheral nervous system, or even the role of the spine. In early occupational therapy sessions, patients receive pain neuroscience education as well as get an overview of spinal anatomy. After all, when one understands how the body works, it is much easier to implement small changes in routines because the "why" has been explained. It is also important to tell patients that there is nothing "wrong" with their brains. Instead of saying "your brain is sending false alarm messages," indicating that there is something faulty or "wrong," rewording the education with: "your brain is doing a great job, it's just doing it a little too well." We have even used the example of one's brain being likened to a "helicopter mom" – stepping in too much, when decreased protection is needed.

For those with CRPS, it can feel as if no one understands them, and often OT's will hear, "no one has this but me." Imagine how isolating and frightening that sounds. By sitting down and discussing the education and telling a person that they are not alone, this can create incredible rapport. When building rapport, an OT must listen and take each hobby, activity, and occupation as seriously as the patient. An OT might think that self-care should be more of the focus, for example, bending down to put on shoes, but the patient may not find that as valuable. Perhaps their spouse or partner does that for them, and instead they would like to focus on knitting or cooking again. It is the OT's job to listen to the patient and work on things that they not only need to do to stay healthy and independent but also the things that they want to do. Assuming things about an individual, whether that be age related, cultural, or even an assumption about gender identity, is a sure way to negatively impact

the rapport building process. For someone who is already feeling frightened and uncertain, making false assumptions about occupational performance or identity can be detrimental. Therefore, in the occupational profile, OT's ask the patient about their lives and what pronouns they prefer to set a tone of acceptance and trust.

Interdisciplinary Psychological Rehabilitation of CRPS

Psychological intervention is an integral component of the rehabilitative approach. Research continues to increasingly support psychologically informed care as an important aspect of treatment [3]. Psychological treatment of CRPS is primarily focused on increasing quality of life and addressing beliefs and behavior that are barriers to recovery. Psychological intervention is helpful for addressing the broad impact of CRPS-related symptomatology and could have a potential benefit on pathology itself as part of multidisciplinary care [17]. This section will provide a general framework of psychological treatment based on our experience. When considering this information, it is extremely important to note that each patient is an individual and should be treated as such. Individual beliefs, history, psychosocial stressors, health, etc. will greatly influence a patient's response to treatment and must be considered for effective care. We have found treatment to be most effective when patients receive interventions based on both the current evidence and individual patient dynamics.

All patients in our interdisciplinary program receive regular psychological intervention. Patients are initially screened by a medical provider to determine appropriateness for interdisciplinary care (see previous section). In addition, all patients participate in a biopsychosocial assessment with a psychologist. We attempt to give patients "the benefit of the doubt," allowing most patients to attempt to participate. Individuals with psychopathology that is untreated or prevents stability may be screened out and referred to community mental health services prior to starting interdisciplinary care. Patients with active psychosis, suicidal or homicidal intent, active substance use disorders, or trauma-related dissociative symptoms may be asked to first address these issues. In addition to talking with a psychologist, patients will complete psychological testing measures which are used for treatment planning and program improvement. Psychological intervention in our model of care is provided through individual therapy sessions. After evaluation, patients are seen for individual therapy two times a week for just under an hour.

Providing individual therapy services allow clinicians to customize treatment to address specific challenges each patient may present with. While each patient's treatment is individualized, certain key components are provided to all patients with CRPS. Treatment is informed by the principles of acceptance and commitment therapy, with pain-specific education and interventions included. Some pain psychology interventions include interdisciplinary care, outpatient psychoeducational groups, support groups, and individual outpatient pain psychology. Patients with CRPS require substantial support from both physical and psychological providers, and interdisciplinary care allows both patients and providers to feel more comfortable

with providing effective treatment. While patients with CRPS are enrolled in the formal program, we have found that the length of treatment must be tailored to the individual. CRPS patients typically require greater periods of care. It is common that frequency of treatment will be reduced after 10–12 weeks, with appointments being slowly titrated down from two times a week to sessions once a month or longer. This slow reduction allows patients to demonstrate consistent use of skills in their home environment, reduces posttreatment anxiety, and encourages long-term follow through. It is our belief that all patients should have exposure to psychology treatment; however, a minority of patients may not respond to psychological interventions. Psychology is viewed as a mandatory component of our treatment.

Many patients are hesitant to engage in psychology, likely due to stigmatization of mental health treatment. If a clinician observes that a patient is not making progress, reduced frequency of sessions or discharge may be appropriate. This often relates to an unwillingness to engage in treatment or those individuals who present with extremely concrete beliefs, both of which tend to be indicators of poor outcome. Patients may also be referred to an eight-week ACT-based support group after completion of interdisciplinary care. This group is facilitated by a program psychologist, and allows program graduates the opportunity to process challenges and review skills in a support group setting.

Interdisciplinary Psychological Rehabilitation of CRPS: Assessment

Psychological treatment for a patient diagnosed with CRPS should begin with a comprehensive biopsychosocial assessment. The assessment serves multiple purposes. It is typically the first-time meeting with a patient and rapport development, while seeking the information needed to formulate a treatment framework should be the primary aim. As with all psychotherapy, the therapeutic alliance between patient and provider is a major factor in patient engagement and subsequent success [18]. For individuals diagnosed with CRPS, it is important to assess their previous involvement with the medical community. Louw and colleagues found that individuals with CRPS are “ill informed, confused, and receive conflicting information” from providers. Therefore, patients may present with frustration regarding previous interactions with medical providers who did not fully understand their symptoms, or who may have provided treatment that exacerbated symptoms [19]. We have encountered patients who interpret that providers believe their symptoms are “all in their head,” or feel that previous medical providers discounted the severity of their symptomology. A referral for psychological intervention may be interpreted as further proof that their symptoms are viewed as strictly psychological in nature. For this reason, we have found discussions of a patient’s previous treatment, acknowledging poor experiences, and openly discussing concerns a patient has to be therapeutic. Brief education regarding the value of behavioral health treatment helps to address this barrier. These discussions are often provided at the start of the assessment, especially if the patient has questions

regarding the role of the psychologist as a part of the interdisciplinary team or appears guarded.

The biopsychosocial assessment then turns to a discussion of the presenting concern. Patients typically present with pain and/or loss of function related to their CRPS diagnosis. Discussing the events surrounding the development of their CRPS symptoms is a natural place to begin. While patients have likely described these events multiple times to other providers, allowing patients to tell "the story of their pain" supports the development of rapport and helps the patient to feel heard. This discussion may help a clinician's understanding of a patient's beliefs related to pain, knowledge of pain science, behavioral response, and reported symptoms. When listening to a patient's history, behavioral health providers are uniquely positioned to ask questions that may not have been previously explored. Psychosocial stressors occurring around the time of injury are extremely important, in that they often influence a patient's interpretation of their injury, their method of coping, and pain-related beliefs. For example, a patient who developed CRPS at a time of financial hardship and housing instability may be more prone to changes in mood and a sense of hopelessness. This financial hardship may also impact their ability to seek treatment, change social relationships, and may limit a patient's engagement in treatment. Evidence has not linked psychosocial stressors to the development of CRPS, however several pathophysiological processes associated with CRPS may be maintained by stress and affective change [2]. Understanding psychosocial factors occurring in a patient's life when pain began as well as in the present are often key components of successful treatment.

We have also found that legal involvement complicates treatment. Patients may have difficulty navigating incongruent goals of the rehabilitation and legal realms. Our experience has been that this is especially relevant to those with CRPS, as patients may have had independent medical evaluations which cast their symptoms in doubt. While legal involvement rarely changes the interventions used in treatment, it is a major stressor for patients to manage, and can influence engagement in treatment, and is therefore discussed as part of the assessment.

Individuals who develop chronic pain often find themselves dealing with decreased social interaction, increased conflict with family, and decreased leisure activities, among other changes [20]. Patients experiencing functional limitations are more prone to psychological distress (anxiety and depression) [21]. For this reason, it is extremely important to assess not only pain ratings but also the wide impact of pain upon the patient's life. Physical limitations are key in treatment planning in a rehabilitation approach, as they provide insight into functional goals. Exploring the development of pain, how a patient currently experiences pain (how it feels), its location, and all related symptoms are important for a patient to communicate and may highlight dysfunctional beliefs. The progression of symptoms may impact a patient's ability to function. Assessing the progression of symptoms and other areas of the body that are impacted is important as progression of symptoms is likely to increase a patient's sense of fear and lead to decreased function. Patients may present with other sources of pain than CRPS. Central sensitization may be present and understanding how this condition may exacerbate CRPS is

needed. In addition to pain-related distress, social factors are often impacted by CRPS. Patients may have changes in work, financial stress, shifting familial roles, and decreased self-view. While these factors may not be directly related to pain, ignoring these issues will prevent progress. In our experience, having a patient identify what aspects of their life they want to address supports treatment. We have observed that when a patient successfully addresses sources of distress in their life, even those that are not directly related to pain, they will often describe either a reduction in pain or an increased ability to tolerate pain.

Research has not established psychopathology as predictive for the development or maintenance of CRPS symptoms [2]. Mood disorders have not been associated with CRPS onset [22, 23], and preliminary evidence indicates that the prevalence of mood disorders in a CRPS sample was not substantially higher than for other pain patients [24]. Research, however, demonstrates that chronic pain and mood conditions have a bidirectional relationship in general [25]. Initial research supports that CRPS pain negatively impacts affect [26]. Assessment for psychopathology, both prior to and after the development of CRPS, is important as a patient may have underlying mental health symptoms that have been made worse by pain or functional limitations [27, 28]. At the current time, it is unclear if CRPS-related pain is more impactful on emotions than other sources of pain. Outcomes have been mixed, at times patients with CRPS may present with higher levels of emotional distress (anxiety and depression) than typical pain patients [29–31], other studies have not supported this concept [27, 28]. Our clinical experience has been that CRPS is highly distressing frequently leading to decreased mood, increased anxiety, and worsening of preexisting mental health symptoms. Psychopathology is explored during the assessment, and the psychologist is responsible for making appropriate mental health diagnoses, as well as communicating the potential impact of these diagnoses with the treatment team. Pain may worsen underlying psychopathology, which can impact the patient's course of treatment. Psychological treatment as a part of interdisciplinary care will attempt to address the interaction between psychopathology and pain. Patients may require additional intervention to address psychopathology, including referral for outpatient psychology/psychiatry at the time of evaluation or during the course of treatment.

Understanding development and early childhood experiences may help elucidate the patient's primary coping style, and help a clinician understand how patterns of thinking and beliefs may have developed. Of specific importance is exploring adverse childhood experiences (ACES) and trauma. Research demonstrates a link between adverse childhood events and patients having an increased likelihood for development of chronic pain [32, 33]. Individuals who have been diagnosed with PTSD are much more likely to develop CRPS when compared to controls [34]. Providing patients with education on the interaction between trauma and chronic pain may help them to be more open to discussing traumatic experiences. If possible, providing concurrent treatment for trauma and pain is beneficial [35]. Our

experience has been that many patients seeking pain-focused treatment may not be open to in-depth trauma processing; for those who are, a referral to trauma-focused treatment may be made. Skills presented in psychology are also helpful managing trauma more effectively. Understanding a patient's trauma history is necessary for effective team-based care. Using a trauma-informed approach that allows for a team to make appropriate changes to treatment based on the patient's needs is imperative. The psychologist is key to communicating these needs to the team throughout treatment.

We have also found that exploring educational history and the presence of learning disorders is important. Patients who have previously struggled with learning may require adaptations to how content is presented, or adjustments to the pace of treatment. Frequent review of content is provided to all patients, but those with learning or intellectual disabilities may require more support or adaptations to content presented.

Beliefs related to both pain and treatment are influenced by a patient's culture, and culture should be discussed during the initial assessment. When possible, talking with a patient directly about cultural considerations is helpful. At times these conversations may be difficult due to cultural norms, and thus cultural variables may need to be explored throughout treatment. We have found this especially true for immigrants, many of whom are navigating complex stressors related to acculturation while also attempting to cope with pain. These individuals have frequently been exposed to trauma which may further complicate treatment. Beliefs regarding effective treatment vary greatly across cultures, and the role of psychological intervention may need to be discussed in more detail based on cultural expectations, especially when medical care is seen as a passive process. We have also found that analogies that are often key components of pain neuroscience education and ACT may not be translated effectively, requiring adaptations. Cultural variables should always be considered, and are likely to require changes to a typical routine.

General health information is also assessed. While this content is more thoroughly addressed in a patient's medical evaluation, basic review of health behavior, diet, exercise, substance use, and sleep is performed. Psychological providers fully assess for the presence of substance use disorder, which may require referral or additional interventions to address. This is especially important when a patient has had exposure to opiate-based treatment because of the risk for dependency. Reviewing health information can help to identify content that will be addressed as treatment progresses, such as sleep hygiene, diet, and the patient's health literacy.

Overall, a thorough psychological assessment helps behavioral health providers to develop rapport, provide education, and formulate a treatment plan. Information gathered in this assessment is then communicated to other treatment team members in weekly case conferences. Working to understand a patient's biopsychosocial history is a key component of successful treatment for CRPS.

Interdisciplinary Psychological Rehabilitation of CRPS: Objective Measures

In addition to an in-person interview, psychological testing materials are provided to each patient. These items, provided via a tablet, are brief screening measures for several psychological constructs relevant to the treatment of chronic pain. While these measures are not diagnostic, they allow for additional information that is relevant to treatment planning. Measures that are provided focus on the following areas:

- Pain intensity (PROMIS)
- Pain behavior (PROMIS)
- Physical functioning (PROMIS)
- Global health (PROMIS)
- Depression (PROMIS)
- Anxiety (PROMIS)
- Chronic pain acceptance (Chronic Pain Acceptance Questionnaire)
- Pain catastrophizing (Pain Catastrophizing Scale)
- Insomnia (Insomnia Severity Index)
- Pain self-efficacy (Pain Self-efficacy Questionnaire)
- Adverse childhood experiences (Adverse Childhood Experience Questionnaire)

Once completed, elevated scores or areas of clinical interest are reviewed with the patient. Having objective scores that can be compared to a wider population is helpful for reducing a patient's defensiveness and fostering conversations regarding beliefs and behavior which are negatively impacting the patient. These measures are provided around the time of discharge as well, allowing for discussions related to progress and continued areas of need. Use of testing materials provides patients with objective measures that are helpful for both patients and providers.

Interdisciplinary Psychological Rehabilitation of CRPS: Interventions

The use of evidence-based practice is recommended in the treatment of chronic pain. While there is limited research into specific interventions for the treatment of CRPS, there is strong evidence for several psychological orientations in the treatment of chronic pain. Cognitive behavioral therapy has the best evidence for the treatment of chronic pain. While most of our providers have experience using CBT, our primary psychological intervention is Acceptance- and Commitment Therapy (ACT). ACT demonstrates evidence for effective treatment of chronic pain [36]. Due to the severity of symptomatology, and substantial limitations associated with CRPS, the framework of ACT, with its focus on accepting symptomology versus struggling to control symptoms, is particularly beneficial. Measures of acceptance, a key target in ACT, have been shown to be helpful in reducing pain-related interference and intensity [37] and improving mood [38]. Initial research indicates that

acceptance of pain in patients with CRPS was associated with decreased pain intensity, increased mood, and increased activity level [39]. Working with patients to accept rather than attempt control their pain supports other therapeutic endeavors which often provide slow improvement and may increase distress at some points in treatment. ACT supports patients in clarifying their values, allowing clinicians to discuss reasons for participating in difficult treatment. Values clarifications also help patients to define how they can engage in valued activity despite ongoing symptomatology. Individuals with CRPS may experience long-term intractable pain increasing the need for acceptance. Acceptance of pain and pain-related distress may help patients to increase use of active coping strategies when pain remains [40]. Patients often respond to chronic pain through a focus on passive coping approaches and sedentary behavior. This is particularly relevant when working to treat CRPS, as reducing movement has been correlated with worse outcomes [41, 42]. Patients are likely to have attempted to eliminate or "control their pain." Patients have likely undergone ineffective treatment that may increase a sense of hopelessness, which in turn can lead to increased depressive symptoms and negative outlook. By introducing the concept of acceptance and focusing on increasing valued behavior, despite pain, as a primary goal, treatment providers can establish realistic functional goals to work toward.

The limits of a patient's ability to control pain is a key component of ACT-based treatment. The more a patient focuses on pain in attempts to control it, the more likely they are to be distressed. This often leads to a negative cycle in which a patient ruminates on controlling pain, and engages in ineffective attempts to reduce pain, which may include decreased use. When attempts to control pain are ineffective, patient distress is increased, leading to psychological and physiological arousal, exacerbating pain, and leading to further attempts to control pain. In this cycle,

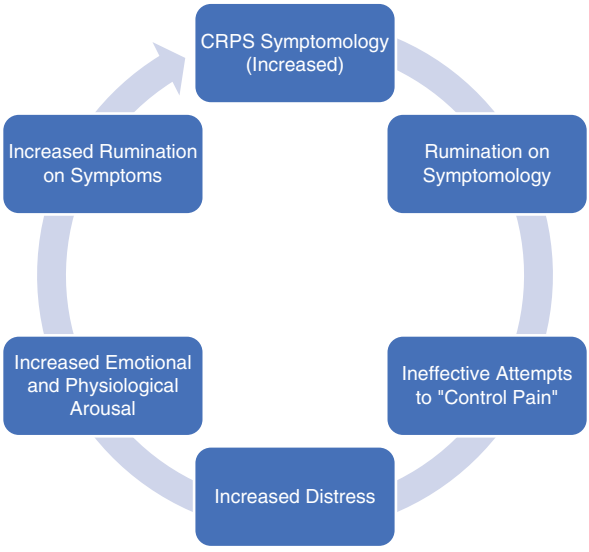

Fig. 7.2 Pain control cycle

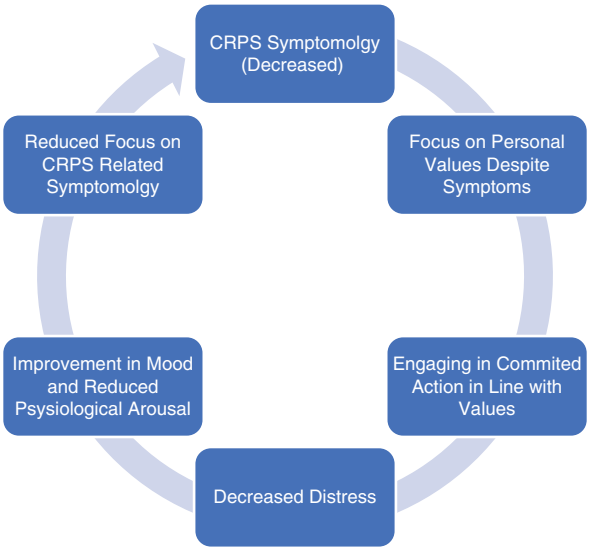

Fig. 7.3 Pain acceptance cycle

attempts to control pain may actually perpetuate pain as well as maladaptive coping (Fig. 7.2).

By helping a patient to shift their focus away from the impact of CRPS and toward personal values, we find patients feel "less stuck," which often leads to improved mood and decreased distress (Fig. 7.3).

One difficulty of utilizing ACT-based treatment in treating CRPS is that symptoms may prevent behavior that the patient once saw as valuable. Time must be spent clarifying values and working to identify alternative ways to engage with personal values. For example, if a patient presents with depression due to inability to work from CRPS-related symptoms, a provider may discuss values that work provided. On the surface this appears to be an easy question. The patient is likely to indicate that work provided income. However, with processing, it becomes clear that a patient's employment also provided healthy social interaction, a sense of purpose, and/or intellectual challenge. While a clinician is not able to have a patient immediately return to work, it is likely that alternative ways to meet these values can be found outside of a work environment. By accepting that the patient is not able to control his or her pain, we may be able to transition effort toward functional, value-based goals that are achievable, even with pain remaining present.

While education is provided by all team members in the interdisciplinary model, psychology will typically focus on the role of the brain in pain (central pain response), the negative effects of disuse, and ways in which mood, stress, and psychosocial factors are likely to influence pain. Education on the self-management approach provided by our rehabilitation center is also highlighted. Education is considered a low-cost intervention that is recommended for all acute and chronic CRPS patients [2]. In these conversations, we attempt to make connections between the patient's experience of pain and outside factors, such as stressors, the environment,

and patient behaviors. Early conversations regarding pain may serve to highlight unhelpful beliefs that a patient has, which may be targets for future sessions. Education can also be used to help patients understand interventions that will be provided and to increase patient engagement in treatment.

In addition to education, relaxation skills are provided early in treatment. Several randomized control trials have demonstrated efficacy in using relaxation-based interventions in the treatment of chronic pain [43–45]. While this connection between relaxation and symptom reduction is less understood in CRPS, preliminary evidence supports the use of relaxation skills in treating CRPS [2]. The relaxation response may be helpful in reducing CRPS symptoms, and is often combined with exposure-based treatment, allowing a patient to better manage uncomfortable sensations stemming from these experiences. Relaxation skills are also helpful for addressing comorbid mental health symptoms including anxiety, depression, and trauma. These skills are presented along with the pain education on concepts including sympathetic nervous system changes, nociceptive hyperarousal, and central sensitization. Relaxation skills are presented as ways in which a patient may "retrain their brain," working to change the central nervous system's unhelpful response to painful CRPS stimuli. Relaxation interventions provided are varied, with selections often based on client response and willingness to engage. Common forms of relaxation presented include diaphragmatic breathing, mindfulness, paced breathing, progressive muscle relaxation, and autonomic relaxation. As treatment progresses, these skills will be paired with biofeedback. Biofeedback provides direct feedback on a patient's efficacy in use of relaxation. A variety of biofeedback measures have been used in the treatment of CRPS, including skin conductance, temperature, heart rate variability, and EMG. The primary goal of including biofeedback is supporting the patients' use of physiological relaxation and reducing emotional arousal. Patients are strongly encouraged to practice relaxation skills outside of the treatment environment, with the psychologist introducing different forms of relaxation and focusing on identification of techniques which are both effective and that the patient is willing to follow through on. Consistently reinforcing a patient's use of relaxation strategies and presenting this topic multiple times with varied intervention appears to support long-term follow through. Other team members frequently reinforce relaxation, having patients actively use these skills when appropriate.

Processing and addressing dysfunctional beliefs about pain constitute a large portion of time spent in psychological intervention. Patient beliefs are informed by individual experience making them extremely varied. Understanding a patient's history is key to understanding patient's beliefs and styles of coping. While it is not possible to address all of the varied forms of unhelpful beliefs a patient may present with, research and clinical experience indicate that addressing fear of pain, including catastrophizing, and avoidance are key treatment targets to be addressed by multidisciplinary teams [3].

Measures of fear have consistently been shown to be strong predictors of disability and other negative outcomes [46]. This appears to relate to patients with CRPS as well, with fear being linked to a worsened disease course [47]. Initial research supports the concept that reducing fear can support increased movement

and, thus, improve function in CRPS [48]. Fear is a normal response to pain and should be presented as such to patients. Patients are likely to experience several forms of fear. The most obvious type being the symptoms of CRPS themselves. Patients often make changes to behavior in attempts to reduce pain. When beginning interdisciplinary care, they may feel apprehensive regarding the tasks they are being asked to engage in. All members of an interdisciplinary team should be aware of the interaction between fear and pain. Physical and occupational therapy providers are likely to ask the patient to engage in behavior that may have elicited pain in the past or that may result in increased pain in the moment. Previous experiences may color a patient's view of treatment resulting in hesitancy to fully engage in a treatment for which they question the efficacy. A thorough assessment of a patient's history can help providers to identify past experiences, as well as beliefs that may hinder treatment engagement. Of note are catastrophic beliefs, such as pain will only get worse and that there is no effective treatment for CRPS. Catastrophic beliefs are likely to have a negative impact on mood and may impact treatment efficacy [49]. Psychological treatment is likely to address these beliefs directly through education as well as discussing the role of catastrophic thinking on physiological arousal and resulting unhelpful behavioral responses, including increased avoidance. It is important to be aware that physical interventions (physical and occupational therapy) are effective in behaviorally addressing fear. Physical intervention can allow a patient to slowly increase physical activity, while all members of the treatment team provide support and encouragement without reinforcing fear or avoidant behavior. Consistent support from all team members is likely to go a long way in reducing fear. Treatment staff also work to normalize pain that may occur. By providing a patient with realistic expectations, symptoms that come up are not met with the same level of anxiety compared to a patient's previous experiences. We have observed that, as patients see functional improvement, willingness to experience discomfort in treatment increases.

It has also been helpful to provide consistent communication regarding pacing. Patients may find a slow pace of improvement to be frustrating. This has especially been true when patients are engaging in graded motor imagery. Patients may feel that the quicker they progress the better, which at times may not be in their interest. Exploration of a patient's fear or apprehension regarding pain is imperative as it allows the interdisciplinary treatment team to provide different modalities to address a patient's fear, supporting recovery from pain.

Avoidance is another important target for multidisciplinary treatment. Avoidant behavior may take many forms but can be viewed basically as reducing behavior in an effort to limit pain or distress. For most individuals, avoidant behavior appears to make sense. In acute pain, we tend to learn that reducing behavior and avoiding things that hurt is an appropriate response. This pattern of coping, however, does not appear to be helpful for chronic pain. This is an especially important consideration when treating CRPS as research demonstrates that disuse is related to poor outcomes [50]. In multidisciplinary treatment, the role of increasing physical movement must be addressed by all team members. While much of the physical aspects of avoidance will be directed by physical health providers (physical and

occupational therapy), psychological intervention is important in helping patients to reduce avoidant coping. Our experience has shown that avoidance is often an established style of coping relevant to many aspects of a patient's life. Patients may have poorly established problem solving or coping skills, leading them to attempt to avoid distress versus dealing with it. Avoidance is often a behavioral representation of fear or anxiety. When individuals with CRPS find that their established coping skills are ineffective, fear, discouragement, and hopelessness often set in. When behaviors are painful, a punishment contingency develops. Aversive stimuli (pain) is elicited by behavior, leading to a reduction (avoidance) of this behavior. While patients are informed that increasing activity is good for them, it can be difficult to consistently engage in behaviors that increase pain or fear. For these individuals, education remains key. Discussions about why avoidant coping is unhelpful are imperative. Support and reinforcement of increasing activity are consistently provided by all treatment team members.

We have found that frank discussions identifying passive coping behavior and processing if these behaviors have been effective are impactful. When patients develop awareness that despite trying to avoid pain it remains present, they are often open to new approaches. Behavioral experimentation can be helpful. Patients often find that beliefs related to pain are not fully accurate and that activities do not elicit as much pain as expected. Effective team communication supports patients in challenging pain-related beliefs. When patients can do more than expected in a discipline, it can be communicated to the team, allowing this success to be reflected to the patient. For example, we have observed patients who report an inability to walk between rooms spend 20 minutes on a treadmill talking to their PT. Patients are often surprised by their ability to cope with pain, especially when dealing with CRPS symptoms for a prolonged period. Clinicians are encouraged to explore a patient's overall pattern of coping to determine a patient's ability to tolerate distress. Distress tolerance can be fostered in psychology through increasing behavioral and cognitive coping skills. Behaviorally, our program focuses on the development of relaxation skills which can be used as a patient reduces avoidance. The ACT framework used by our program frames avoidance of pain as a form of "experiential avoidance" that fits directly into ACT treatment, leading to several ACT-based interventions. Psychologists work with patients to address avoidance through clarification of values and to explore whether avoidant behavior has been functional. We have found that patients often have not considered the effects of their coping style on pain or quality of life. A psychologist may discuss how avoidance may be helpful in the short term but is unlikely to be helpful in the long run. We then utilize interdisciplinary collaboration, attempting to have a patient increase valued behavior despite pain. For example, when attempting to get a patient with CRPS walking more, it may be more helpful to have a patient walk on a golf course than on a treadmill. These adaptations to treatment appear to greatly increase patient engagement and are a key component to effective use of the interdisciplinary team. Helping patients to understand why they are working to reduce avoidance is a key for gaining follow through. Our program works to consistently place patients in the role of active participants, attempting to limit passive intervention and to focus on patient-directed goals toward functional improvement.

While there are countless additional psychological considerations in the treatment of CRPS, avoidant styles of coping and fear have been shown to be primary concerns in treatment and can be effectively addressed through interdisciplinary collaboration. Treatment is most effective when team members work together targeting beliefs and behaviors that may prevent progress through values and functional goals.

As stated earlier, our course of treatment for patients with CRPS is highly variable. Termination may be difficult for patients and there are several things to consider. Interventions are designed to improve self-efficacy, and patients are asked to implement these skills on their own as they progress in treatment. Patients, however, often associate improvement with participation in treatment versus their own changes. This idea is directly discussed with patients, with clinicians providing reinforcement for self-management behavior throughout treatment. Working with patients to develop a concrete relapse prevention plan is of value. Implementation of routine physical and psychological behaviors occurs over the course of treatment, but having patients develop a written plan is important. For those patients who have had significant symptom reduction and/or functional improvement, long-term psychological treatment may not be required. In our experience, this is rare. While many patients will improve, they often continue to experience impactful symptomatology. It is also quite common that psychosocial stressors related to CRPS, including financial concerns, persist. For this reason, patients may benefit from a slow reduction in therapeutic contact. Reducing the frequency of treatment toward termination promotes patients transitioning to more natural supports. Support group intervention has also been helpful, allowing patients to reduce treatment while continuing to feel a sense of support. Referral to outpatient counseling in a patient's community is often appropriate, especially for patients with major psychosocial stressors, psychopathology, or trauma history. Finding a balance between providing patients with appropriate support while not fostering dependence on service can be difficult. Allowing patients to return for "refresher" sessions also allows patients to have more confidence to work to manage symptoms on their own, while providing an option for support should they have difficulty posttreatment. As treatment ends, providing ongoing support and helping patients to maintain confidence are extremely important for effective care.

Key Considerations, Limitations, and Barriers

As with all treatments, limitations to interdisciplinary rehabilitative care should be considered. A primary limitation at the current time is the lack of definitive evidence supporting interdisciplinary care for the treatment of CRPS. Evidence supporting the use of interdisciplinary care in the treatment of pain is well established [51, 52], and initial evidence for interdisciplinary care in treating CRPS appears promising. Clinicians, however, should be aware that additional research is needed to fully support the use of interdisciplinary care, and while interdisciplinary treatment rarely

results in negative side effects, the financial expense and amount of time required can be prohibitive to the patient.

Development of interdisciplinary programs is also difficult. We have referenced the expense and difficulties in establishing and maintaining experienced multidisciplinary programs and we must address the barriers to these programs and the way we have addressed them.

Pain psychologists are in short supply and we have had to provide initial and ongoing training to psychologists with limited prior experience in treating individuals with chronic pain conditions. We have been fortunate to have hired psychologists with fellowship training in pain rehabilitation who have then directed the training and education of additional mental health staff. We have used primarily PhD, fully licensed psychologists and have also had very effective master's psychologists and postdoctoral clinicians on our teams. In addition, we helped to establish a multidisciplinary pain team at a Federally Qualified Health Center using a master's level clinical social worker who successfully provided pain rehabilitation services to a population that had limited care options. We now employ 11 psychologists treating pain in outpatient settings in 6 different locations. This has created a supportive network that enhances the expertise of our psychology staff and provides a very positive work environment that allows us to recruit and replace staff as needed.

Physical and occupational therapists rarely receive training in the treatment of chronic pain in their degree programs and are frequently frustrated with these patients when seen in an outpatient setting without multidisciplinary support. As a teaching hospital, student therapists are offered rotations in our pain center where they are exposed to care done by therapists who are passionate about our programs. This has allowed us to recruit promising candidates as they graduate or attract them from other positions when we have an opening. We have encouraged additional training in postgraduate courses provided by Dr. Adriaan Louw and the NOI Network to enhance their skills particularly with graded motor imagery, mirror box therapy, and pain neuroscience education.

Our programs have also used medical providers, MDs, DOs, PAs, and NPs from various backgrounds. We seek psychologically minded practitioners with interest in mind/body approaches to health care. It is very helpful to have primary care physicians with experience in treating mental health disorders, but it is critical that they work well in teams. Working with patients with chronic pain can be emotionally draining, but having the support of a team of clinicians dedicated to providing excellent care is what makes this type of care rewarding and fascinating.

Ideally, treatment of CRPS should begin as soon as possible and lack of coordination can result in significant delays and lack of a standardized approach. Some patients begin receiving interventional treatments such as sympathetic nerve block injections, high-dose opioids, and ketamine infusions progress to spinal cord stimulation or dorsal root ganglion stimulation, sometimes without the advantage of experienced physical or occupational therapists only to end up at our clinic several years after their diagnosis. This is a weakness of the fee-for-service system, with employer-financed health care insurance, often resulting in competition for patients and discouraging cooperation among health care systems and individual providers.

Patients and primary care providers are often left making referral decisions based on in-network versus out-of-network or short-term out-of-pocket expenses and without knowledge of long-term outcomes and costs.

Future Considerations

The use of interdisciplinary treatment focused on functional restoration addresses the complex set of symptoms associated with CRPS. Addressing CRPS from a biopsychosocial perspective is supported by evidence, and interdisciplinary treatment is uniquely suited to address the multifaceted nature of this disorder. However, there remains much that is unknown about CRPS that impacts the ability to provide effective treatment. While research is advancing, there is no definitive model of care that is deemed most effective. As knowledge of the mechanisms that underlie CRPS pathophysiology is discovered, efficacy of treatment may be improved through linking patients with treatment that is most likely to be successful, including incorporating novel treatments supported by evidence. These advancements may eventually lead to preventative models of care. At the current time, the lack of known cause, standardized diagnosis, and standardized models of care negatively impact patients with CRPS. In addition, the lack of large-scale randomized, controlled treatment trails and comparison research for different treatments are barriers to matching a patient to an appropriate treatment.

In order to effectively address CRPS, a standard diagnostic criterion must be used. The lack of objective tests and a history of diagnostic uncertainty have led to confusion regarding both diagnosis and treatment of CRPS. While the Budapest Criteria appear to be increasingly used (and is now the standard in Europe), they have not been universally adopted and this has resulted in diagnostic uncertainty. Standard diagnostic criteria are likely to support more effective research and collaboration in treating this disorder. In addition, continued research into early warning signs that may predispose someone to development of CRPS is important.

It appears that nonmedical treatment is a valuable tool in the treatment of CRPS. Research has shown that interdisciplinary approaches focusing on functional restoration are effective in reducing the impact and course of those with CPRS [2]. However, there remains a high level of variability in within interdisciplinary care. Programs utilize various types of providers (e.g., physical therapists, occupational therapists, psychologists, and recreational therapists), different intensities (inpatient, intensive outpatient, outpatient, etc.), and different durations. In addition, care within different professional orientations is not standard. For example, one PT may provide manual manipulation, while another may use graded motor imagery. While there will always be variation across providers, continued research and dissemination of a standard treatment model for CRPS that incorporates individual needs would likely benefit patient outcomes. Increased collaboration between behavioral and medical treatment approaches also appears warranted. Collaboration between behavioral and interventional treatment could lead to a stepped model of care that would provide the most appropriate and effective treatment based on patient need.

Behaviorally focused treatment included in interdisciplinary care addresses several clinically relevant targets including increasing movement, addressing psychosocial contributors, and working to increase function. Outside of time and expense, behavioral treatment has few side effects and appears to be a good option for early intervention. Despite this, in our experience, patients often participate in interdisciplinary care as a "last resort." Early identification of CRPS symptomology and expedient participation in interdisciplinary care specific to individual needs may lead to better outcomes. For this to happen, CRPS must be diagnosed early and appropriate referrals must be made. It is likely that front-line clinicians would benefit from additional education and resources to help guide those with CRPS to appropriate, evidence-based treatment, and away from common behavioral responses including avoidance and inactivity that are likely to make symptoms worse.

In addition to a standardized model of diagnosis, adoption of standardized outcome measures would also advance the understanding of effective treatment for CRPS. Due to divergent types of treatment using specific outcome measures, comparing the efficacy of one form of treatment to another is difficult. Attempting to increase standard outcome measures will help in comparing how individual patient characteristics respond to specific treatments.

Additional considerations relate to medical treatment systems. While interdisciplinary care is an effective intervention, there are few systems set up to provide this type of care. The majority of these are housed in universities or hospitals. Even among established providers, the number who have knowledge of CRPS and its treatment is small, further limiting access to care. Financial issues may also be prohibitive. Interdisciplinary care is typically intensive, requiring patients to attend treatment multiple times a week. Even those who are insured may struggle with copay/coinsurance expenses associated with interdisciplinary care. Those who are uninsured or underinsured may not have access to this type of care. In addition, the intensive nature of treatment may impact employment or other responsibilities. In order to effectively treat all patients, these barriers to receiving care need to be addressed.

As research into CRPS advances, there is hope that discovery will lead to more effective targeted treatment. At the current time, interdisciplinary care appears to be an appropriate early treatment for CRPS that is likely to help individuals manage pain effectively and reduce the impact of this disorder on their quality of life. In the future, standardized diagnosis, treatment, and evaluation measures will likely have a positive effect on patient outcomes. It is our belief that a clearly defined stepped model of care would be beneficial to clinicians, allowing patients to receive appropriate care based on their presentation and needs, allowing for incorporation of evidence-based behavioral and interventional treatment, and leading to better outcomes for those suffering with CRPS.

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Adjuvant Treatments for CRPS

8

Jamie Kitzman and Anna Woodbury

Introduction

Adjunct therapies for CRPS include complementary, alternative, and integrative therapies and can be broadly classified into manipulative therapies such as acupuncture and massage, energy therapies such as qigong and reiki, mind-body therapies such as mindfulness meditation and yoga, and biologically based therapies such as herbs and diet modification. Some of these therapies overlap, as in the case of acupuncture, which is both a manipulative therapy and an energy therapy, or in the case of yoga, which is both a mind-body therapy and an energy therapy. Many of these therapies belong to alternative medical systems, such as traditional Chinese medicine or Ayurvedic medicine.

It is particularly necessary for treating clinicians to familiarize themselves with these adjunct therapies, as patients may be seeking out these therapies on their own and will be in need of sound, evidence-based medical advice. According to a 2012 National Health Interview Survey (NHIS) census, the most commonly utilized complementary therapies among adults in the United States were natural products such as fish oil (17.7%) followed by deep breathing (10.9%); yoga, tai chi, or qi going (10.1%); chiropractic or osteopathic manipulation (8.4%); meditation (8%); and massage (6.9%) [20]. A subsequent 2017 NHIS census revealed a dramatic increase in yoga and meditation use with both being utilized by approximately 15% of the US adult population.

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Regardless of the philosophy behind the adjunct techniques, in the treatment of pain syndromes, it is worth examining each of these therapies in depth to assess the risks and benefits for their application to CRPS, a notoriously difficult-to-treat pain condition.

Acupuncture

Acupuncture is a needling technique that has been practiced for thousands of years in China, with the first written documented use dating back to a textbook from 200 B.C. called the *Huang Di Nei Jing*, also known as "The Yellow Emperor's Canon" or "The Yellow Emperor's Classic of Internal Medicine." There is a growing body of medical literature supporting the use of acupuncture for a variety of chronic pain syndromes, including CRPS. In traditional Chinese medicine, acupuncture is used to help restore the flow of energy or *qi* (also spelled *chi* and pronounced chee) through energy highways called meridians with the goal of balancing the body's energy.

In allopathic medicine, the most widely accepted theory for acupuncture's mechanism of action is based on evidence suggesting that acupuncture exerts its analgesic effects by inducing afferent nerve signals that stimulate the release of endogenous opioids and neurotransmitters, modulating signals in the central nervous system [14, 122]. These CNS effects have been appreciated on PET studies, SPECT, and fMRI [51, 154]. Electroacupuncture has been shown to reduce pain by peripheral, spinal, and supraspinal mechanisms [163]. In addition, it may block pain messages by activating the descending inhibitory system [85].

Acupuncture involves the insertion of hair-thin needles into the skin at specific points. Needles can be manually or electrically stimulated. Heat may be applied by moxibustion or an electric heat source. There are various forms of acupuncture including Chinese scalp acupuncture (CSA), Korean hand therapy (KHT), and auriculotherapy or "ear acupuncture." Alternatives to traditional needle treatment are available, including acupuncture beads, adhesive microneedles, and semipermanent ear needles. These allow for longer treatment times and patient participation. This can be particularly useful in CRPS patients, allowing them to regain some sense of control of their symptoms.

The World Health Organization recognized acupuncture as an effective treatment in acute postoperative pain and multiple chronic pain conditions. Multiple literature reviews and meta-analyses have now categorized acupuncture as having an overall positive effect in pain treatment [82, 86, 102, 149, 154]. However, a 2019 Cochrane review of the use of acupuncture in neuropathic pain reported insufficient evidence to support or refute its use compared to sham or other therapies due to the quality of included studies [64]. However, the use of acupuncture in animal models of CRPS shows promise. In rat models, electroacupuncture has anti-allodynic effects in neuropathic pain and induces the production of anti-inflammatory cytokine reducing inflammatory pain [58, 64, 80, 154, 162].

There are some human studies specific to acupuncture in CRPS, though the literature size and quality is not as robust. In a meta-analysis within the Chinese healthcare system in poststroke CRPS patients, traditional manual acupuncture when added to rehabilitation therapy was more effective than conventional rehabilitation therapy alone in decreasing visual analogue scale (VAS) scores, improving limb dysfunction, and improving activities of daily living (ADLs) [117]. Another meta-analysis out of China reported similar findings with the use of electroacupuncture [156]. The authors noted poor reporting quality and considerable heterogeneity in the trials included. In a case report, a patient with CRPS receiving three times a week acupuncture treatments over 6 months reported to be pain free most days of the week. In addition, the patient's depression and disability scores improved considerably. A case series of two patients receiving CSA reported complete resolution of CRPS measured by VAS and skin changes [56]. In a recent Cochrane study, *Jingu* acupuncture was used with *Xingnao Kaiqiao* acupuncture to evaluate the therapeutic effects on poststroke CRPS compared to *Xingnao Kaiqiao* acupuncture alone [155]. Both groups demonstrated improvement in VAS scores, limb movement, and functional independence. Furthermore, there was superior improvement of VAS scores and limb movement in patients that received combination acupuncture treatment. This literature taken together suggests that acupuncture therapy, irrespective of the specific approach, may have beneficial effects in CRPS. However, the existing evidence is lacking and larger, well-designed studies are needed.

In the hands of a trained acupuncturist, acupuncture is very safe. The most common side effects are soreness, bleeding, and bruising at the site on insertion. Dizziness and vasovagal reactions are common, but easily treated. The most serious adverse events related to acupuncture are pneumothorax and cardiac tamponade related to inserting a needle too deeply in the chest area. Again, these issues are easily avoided with proper preparation and training. Allergy to the metal needle or irritation from adhesive is possible.

Movement-Based Mind-Body Practices (Qigong Therapy, Tai Chi, Yoga)

Mind-body practices have been used for centuries. Qigong (pronounced chee-gung) is a form of martial arts that combines exercises and meditation for self-healing. *Qi*, meaning "breath" or "air," represents energy or life's vital force, while *gong* means "effort" or "work." Qigong integrates breathing, posture, movement, and focused intention to balance *qi* in turn improving mental and physical health. Developed originally as a form of self-defense, tai chi (pronounced tie-chee) also uses movement-based mediation to promote the flow of energy and relaxation. Each posture flows gently into the next, keeping the body constantly in motion and harmonizing the circulation of qi. Yoga, meaning "union" in Sanskrit, is a discipline of meditation with roots in India. It has both spiritual and physical components. *Chakra* are the centerpoints of spiritual energy. When energy is blocked in a chakra,

an imbalance occurs causing physical, mental, or emotional symptoms. *Asnas*, or physical postures, are used to rebalance chakra and free energy. These forms of movement-based mind-body practice boost the physical benefits of improved strength, flexibility, and balance. In addition, they appear to improve mood, decreasing depression and anxiety (Fig. 8.1).

There are some studies, admittedly low in quality, supporting the use of movement-based mind-body practices in chronic pain. Investigators report reduced stiffness, decreased pain, and improved daily function [4, 72, 131]. In literature reviews, there appeared to be positive evidence of its use in chronic pain [82, 102]. In a study of 22 patients with late-stage CRPS, 91% of patients reported less pain when trained in Qigong compared to 36% of control trained by a sham master [161]. Though pain relief was transient, they reported long-term relief of anxiety. Although the data for its use in CRPS are scant and of poor quality, it may provide benefit considering that the mainstay of treatment is physical therapy (PT), which is movement-based in nature.

Movement-based mind-body practice is very safe. It is a form of exercise that can be practiced by people of all ages. Modification can be made to adjust for individual skill and comfort levels.

Fig. 8.1 Six basic yoga postures. Dr. Kitzman demonstrates six basic yoga poses that can help to improve flexibility, balance, and stability to decrease pain and improve function. From left to right, top row: Downward dog (Adho mukha svanasana), Warrior II (Virabhadrasana II), Peaceful warrior (Urdhva Virabhadrasana); bottom row: Tree pose (Vrksasana), Warrior I (Virabhadrasana I), and Upward dog (Urdhva Mukha Svanasana)

Relaxation-Based Mind-Body Techniques

Relaxation-based mind-body techniques include deep breathing, progressive muscle relaxation, meditation, and guided imagery. These techniques can reduce stress symptoms, which in turn improves coping and perceived pain. Biofeedback is the use of monitors or electric sensors to track physiologic responses of the body to various stimuli. The patient's physiologic responses are converted to visual and auditory feedback which they can use to augment relaxation training. It is generally accepted that relaxation techniques are helpful in pain treatment. Although low in quality, there is positive evidence supporting the use of relaxation techniques in chronic pain [82, 96, 102]. There are also positive results in CRPS literature when used in combination with a multidisciplinary treatment plan [30]. Relaxation-based techniques are an integral part of the cognitive-behavior component of CRPS treatment.

Herbs and Supplements

Herbs have been used in medicine for centuries. With the rise of the opioid epidemic, they have become increasingly popular in pain management as an adjunct or alternative to prescription medications. Herbs could be beneficial in CRPS not only by mitigating the pathophysiological features of the disease but also by alleviating comorbid conditions. These herbs have not yet been studied specifically for CRPS, but based on their mechanisms, they may be a target for further research. Turmeric, ginger, nutmeg, cinnamon, white willow bark, and feverfew are known for their anti-inflammatory properties. Bromelain, an extract from the stems of pineapple, may benefit trauma-related inflammation and promote healing of muscle and connective tissue. Boswellia, used in Ayurveda medicine, may help with inflammation and have practical applications for CRPS, as well [71]. Kava and St John's wort are used for neuropathic pain. St John's wort is also commonly used to treat depression, which is commonly associated with CRPS. Passion flower and valerian increase GABA levels and can be used to treat coexisting anxiety. However, the literature supporting the use of herbal products is very limited. A 2020 Cochrane systematic review of herbals in treatment of neuropathic pain included two small studies, one investigating nutmeg and the other St John's wort [10]. The reviewers concluded that there was insufficient evidence to determine whether either of these herbs have meaningful efficacy in neuropathic pain.

Cannabis has been used for thousands of years, with archaeological clues of its use in medicine dating back to 2700 B.C. Of the herbs discussed so far, it is the only one that has been specifically studied for CRPS. More recently, it is being approved for medical use throughout the United States and the world. However, there is considerable controversy in its use. This is due, in part, to concerns about potential cognitive, behavioral, and psychiatric sequelae [55, 159]. Furthermore, its efficacy in treating medical conditions is yet to be determined. There are over 540 chemical substances found within the cannabis plant, with the most experimental studies

focusing on two cannabinoids: tetrahydrocannabinol (THC) and cannabidiol (CBD). A 2013 randomized, placebo-controlled crossover trial including eight participants with a diagnosis of CRPS found significant reductions in pain (at least 30%) for those using cannabis low- or medium-dose vaporized cannabis over placebo [160]. Interestingly, high doses (8% THC) may be associated with increased pain sensitivity [153]. A 2018 Cochrane review and meta-analysis evaluated the use of cannabis in chronic neuropathic pain [99]. Compared to placebo, cannabis-based medicine probably increases the number of people achieving 30% or greater relief (moderate-quality evidence) and 50% or greater relief (low-quality evidence). However, there was no difference in health-related quality of life. In a subgroup analysis, the reviewers were unable to determine if herbal cannabis reduced pain intensity. Cannabis-based medicine may increase CNS side events including sleepiness, dizziness, and confusion. These side effects resulted in higher study withdrawal rates in the treatment groups, but there was not enough evidence to conclude an increase in serious adverse events; the tolerability of herbal cannabis did not significantly differ from placebo. In another systematic review, Häuser et al. concluded that there are inconsistencies in the efficacy of cannabis-based medicines in neuropathic pain and inconsistencies in its tolerability and safety in chronic pain [52]. However, other study groups concluded the evidence that supports the safety and efficacy of short-term, low-dose cannabis for the treatment of neuropathic pain [77, 130] (Table 8.1).

Supplements and vitamins have also gained increasing popularity in pain management. Some supplements that have been studied in various pain conditions are discussed here. Most have not been studied specifically for CRPS; they are discussed given their potential to treat chronic pain conditions, but necessitate further investigation.

S-adenosyl-methionine (SAM-e) is a naturally occurring compound in the body that is important to normal body function. In its synthetic form, it is considered a supplement in the United States, while it is a prescription drug in Europe. Small, low-quality studies support its use in depression and osteoarthritis [38, 103]. It has also been studied in fibromyalgia and migraine with trends toward pain improvement in the SAM-e group, but without statistical significance in these small, low-quality studies [40, 63, 152]. It has been speculated that the analgesic effects of SAM-e for migraine sufferers stem from its effects on 5-hydroxytryptamine (5-HT, or serotonin) turnover [40]. 5-HT is a product of decarboxylation from 5-hydroxytryptophan (5-HTP). 5-HTP is a naturally occurring chemical precursor that is involved in the production of serotonin. It may provide benefit in CRPS patients with coexisting depression, anxiety, or insomnia. Interestingly, there is a growing body of evidence for the involvement of 5-HTP receptors and serotonin pathways in nociception [21, 39]. However, there is insufficient evidence to support the efficacy of 5-HTP supplementation.

Vitamins and minerals including vitamin C, D, E, and magnesium have been studied for chronic pain. The use of vitamin C was adopted by US and European medical societies for the prevention of CRPS [81, 118]. However, more recent literature support that this practice is inconsistent [62]. A meta-analysis of the use of vitamin C in the prevention of CRPS in distal arm fracture by Evaniew et al. failed

Table 8.1 Herbs with potential applications for CRPS

Herb	Potential mechanism	Recommended dose	Adverse effects
Anti-inflammatory Bromelain	Modulation of kallikrein-kinin, arachidonic acid pathways, and cell-mediated immunity [100]	*Adults*: 80–320 mg orally 2–3 times per day for 8 days following surgery or trauma. Topical gel also available *Pediatrics*: Not recommended [100]	Allergic reactions; gastrointestinal and menstrual distress[53]
Boswellia	NO/cGMP/ATP-sensitive-K + channel activation and opioid receptor binding [88]; inhibition of 5-lipoxygenase in leukotriene synthesis [137]	*Adults*: 1000–3600 mg/day in patients with osteoarthritis or rheumatoid arthritis [59] *Pediatrics*: N/A	May induce nausea/vomiting and preterm labor [59]
Cinnamon	Activation of TRPA1 cation channel to exert analgesic and anti-inflammatory effects [84, 136]	No established dosing or efficacy. One study for perineal pain used a compounded ointment (2% w/w) applied every 12 hours for 10 days [95]	Potential for allergic reactions in some people; cassia cinnamon may contain coumarin, which may cause or exacerbate liver disease [53]
Feverfew	Inhibits prostaglandin synthesis and cytokine-mediated signaling; may inhibit smooth muscle spasm; inhibits serotonin release from platelets [113]	*Adults*: For arthritis and inflammatory pain in a 70 kg adult, 60–120 drops, 2 times daily of a 1:1 weight-to-volume (w/v) fluid extract, or 60–120 drops twice a day of 1:5 w/v tincture *Pediatrics*: Weight-based dosing (can be calculated based on the above recommendation for a 70-kg adult). Not recommended in children under 2 years old [113]	Digestive issues including nausea and bloating; fresh leaves can cause mouth sores and skin irritation; withdrawal effects may result in difficulty sleeping, anxiety, headaches, and increased musculoskeletal pain; can cause preterm labor and uterine contractions in pregnancy [53]; may result in increased bleeding [113]
Ginger	TRPV1 receptor activity and modulation of the leukotriene pathway [9]; 5-HT receptor modulation [15]; suppression of IL-1β, IL-6, and TNF-α [46]	Clinical trials have used doses of 170–1000 mg, administered 3–4 times daily [44]	Mild gastrointestinal side effects may occur; may increase flow of bile; may increase bleeding [53]

(continued)

Table 8.1 (continued)

Herb	Potential mechanism	Recommended dose	Adverse effects
Nutmeg	Inhibition of COX-2 expression and substance P levels via topical application [164]	No therapeutic dosing has been found, though it has been applied topically as a 125-mL spray containing nutmeg oil 14%, without benefit over placebo for diabetic neuropathy [98]. Oral doses at 1–2 mg/kg result in toxicity	Psychosis, hallucinations, palpitations, resembling anticholinergic toxicity [2]
St. John's wort	Several active components with different mechanisms, including activation of an opioid-dependent pathway and protein kinase C-mediated NF-kB and STAT-1 induced inhibition of iNOS [37]	Weight-based: 5–100 mg/kg associated with analgesia [37]	May cause photosensitivity, fatigue, anxiety, dizziness, headache, gastrointestinal symptoms, dry mouth, sexual dysfunction, serotonin syndrome, multiple drug interactions [53]
White willow bark	11 salicylate compounds found in willow bark may result in the anti-inflammatory and analgesic effects	120–240 mg salicin daily [135]	Allergic reactions in those sensitive to salicylates (aspirin allergy); possibly increased risk of bleeding, gastritis/stomach ulcers, asthma [135]
Gabaergic Kava	Certain Kavain analogues show analgesic potential outside of anxiolytic effects, though the mechanism of action is uncertain [73]. Kavain does have γ-aminobutyric acid (GABA) receptor modulating properties [17]	60–120 mg of kavapyrones or kavalactones daily, no longer than three months [33, 90]	Potential for liver damage, skin changes, heart and eye problems [53], diarrhea, fatigue, depression [157], sedation or motor impairment [33]
Passion flower	GABAergic and opioidergic [3]	Purple passion fruit peel pills (150 mg, daily) for 2 months improved osteoarthritis pain and function [35]. Other formulations including the flower extract have been used (400 mg twice per day) for anxiety [115]	May cause drowsiness; in pregnancy, may cause contractions [53]

(continued)

Table 8.1 (continued)

Herb	Potential mechanism	Recommended dose	Adverse effects
Valerian	GABA reuptake inhibition [158]	For pain related to dysmenorrhea, 255 mg three times per day improved symptoms [94]. For insomnia, doses of 300–600 mg taken before bedtime have been used [49]. Not sufficiently studied in children younger than age 3, pregnant women, or nursing mothers	Very few side effects including dizziness, headache, itching, and gastrointestinal symptoms; possibly sedating [53]
Cannabinoid THC	Modulation of the endocannabinoid system, CB1 and CB2 receptors [54]	Vaporized (1.29–4% THC), 4–8 puffs every 3 hours [160]	Cannabis use disorder; low birth weights in pregnancy; increased risk of injury among older adults; toxicity in children; psychoses and schizophrenia; orthostatic hypotension (dizziness, falls); serious lung injuries linked to vaping; recurrent severe vomiting with long-term use; effects related to contamination with other substances [13]

to demonstrate significant benefit, while Meena et al. found significant reduction in the prevalence of CRPS with its use in the same population [32, 91]. The use of vitamin C is relatively low risk except to those with a history of kidney disease, as excess vitamin C can lead to kidney stones. Vitamin D deficiency has been found to be associated with chronic pain, and its supplementation has been associated with pain relief [87]. Given the association of CRPS with decreased bone density, it would be reasonable to ensure adequate vitamin D and calcium intake. In theory, magnesium could be of benefit as an NMDA antagonist, countering the wind-up phenomenon and central sensitization in chronic pain. However, the current literature is inconsistent [19, 36]. A pilot trial compared eight patients who received 70 mg/kg magnesium sulfate infusions in 4 hours for 5 days to two patients who received equivalent placebo normal saline and found significant improvements in pain, quality of life, and function in the treatment group [19]. However, a subsequent study by this group involving 56 participants found insufficient benefit from magnesium infusion over placebo [36] (Table 8.2).

Table 8.2 Supplements commonly used for CRPS

Supplements	Potential mechanism	Recommended dose	Adverse effects
S-adenosyl-methionine (SAM-e)	Precursor of amino acids and involved in multiple biological reactions	1200 mg/day initially; then maintenance 400 mg/day for osteoarthritis [129]	Nausea, indigestion; interaction with serotonergic and dopaminergic medications; may aggravate mania in bipolar [128]
5-Hydroxytryptophan (5-HTP)	Precursor to serotonin	No established dosing for pain; 200–300 mg/day given in 3–4 divided doses for depression [1]	Nausea, vomiting, diarrhea, sleepiness, serotonin syndrome [1]
Vitamin C	Antioxidant [114, 145]	500 mg daily for 50 days following injury or surgery [60, 165]	Kidney stones, low back pain, nausea and gastrointestinal side effects, hemolysis, migraines [150]
Vitamin D	Neuroactive steroid, prostaglandin and inflammatory pathway modulator, and various other cellular activities [87]	No established dosing for pain. Should be guided by recommended dosing to correct vitamin D deficiency based on serum 25(OH)D concentrations [87]	Anorexia, weight loss, polyuria, heart arrhythmias, kidney stones, increased circulating calcium which leads to vascular and tissue calcification, with subsequent damage to the heart, blood vessels, and kidneys [109]
Vitamin E	Antioxidant [114, 145]	No established dosing for pain. Side effects occur with long-term use of doses greater than 400 units per day [151]	Abdominal pain and diarrhea, bleeding (anticoagulant) including hemorrhagic stroke [110]
Magnesium	NMDA receptor antagonism [36]	For perioperative pain, 30–50 mg/kg intravenous bolus of magnesium sulfate as a loading dose, and maintained at 6–20 mg/kg/h by continuous infusion until the end of surgery or for 4 hours after the initial bolus [101]; 300 mg orally, daily in diabetic polyneuropathy [78]	Nausea, vomiting, diarrhea, urinary retention, drowsiness, confusion, muscle weakness, fatigue, depression, lethargy, hypotension, arrhythmias, cardiac arrest [108]

In utilizing these supplements, it is most important to consider the relative risk vs. benefit. It may be prudent to avoid the use of herbal products and supplements due to lack of evidence for efficacy, freedom from FDA regulation, and potential untoward effects. Larger, more rigorously designed studies are needed to investigate not only the efficacy but also the risks of using herbs, supplements, and cannabis therapy. However, if a patient is already using an herb or supplement, or is extremely interested, there are resources to help guide evidence-based usage. The National Center for Complementary and Integrative Health, a branch of the NIH, provides evidence-based resources on multiple therapies including their website "Herbs At a Glance" [53]. The NIH Office of Dietary Supplements also provides comprehensive fact sheets on an extensive list of vitamins and supplements with separate versions available for consumers and healthcare professionals [28]. For a more comprehensive overview of herbs and supplements, there also exist Physician Desk References for purchase [116].

Transcutaneous Electrical Stimulation

Transcutaneous electrical nerve stimulation (TENS) is a noninvasive modality of pain relief that involves the use of a small battery operated unit with electrodes that produces an electrical current in the skin. Akin to electroacupuncture, TENS activates afferent fibers promoting the release of endogenous opioids in the CNS and the activation of central inhibitory pathways [24, 27, 138]. Despite its universal use in pain management, the efficacy of TENS in reducing chronic pain or neuropathic pain is controversial [42, 43]. Perez and colleagues found insufficient evidence to suggest that it is effective in the treatment of CRPS [118]. It has been shown to reduce analgesic requirements in postoperative pain [8]. TENS reliably reduces hyperalgesia in animal models [34, 61]. In a RCT of 30 patients with CRPS, Bilgili et al. [6] reported significant improvement of pain scores, edema, ROM, and functional capacity when TENS was combined with a PT program.

Considering its low-risk profile, it is reasonable to consider TENS for patients with CRPS, especially those in earlier stages where inflammation and hypersensitivity are dominant. However, more studies are needed to elucidate its efficacy. It may be prudent to first allow a patient to experience a "TENS trial" prior to device purchase, to ensure that the patient feels the type of stimulation is beneficial. Risks of TENS are primarily related to improper usage resulting in burn injury. Placement over the front of the neck near the carotid baroreceptors or over other sensitive structures is also generally discouraged.

Noninvasive Brain Stimulation

There are many types of noninvasive brain stimulation, including repetitive transcranial magnetic stimulation (rTMS), transcranial direct current stimulation (tDCS), and cranial electrotherapy stimulation (CES) (Fig. 8.2). rTMS uses rapidly

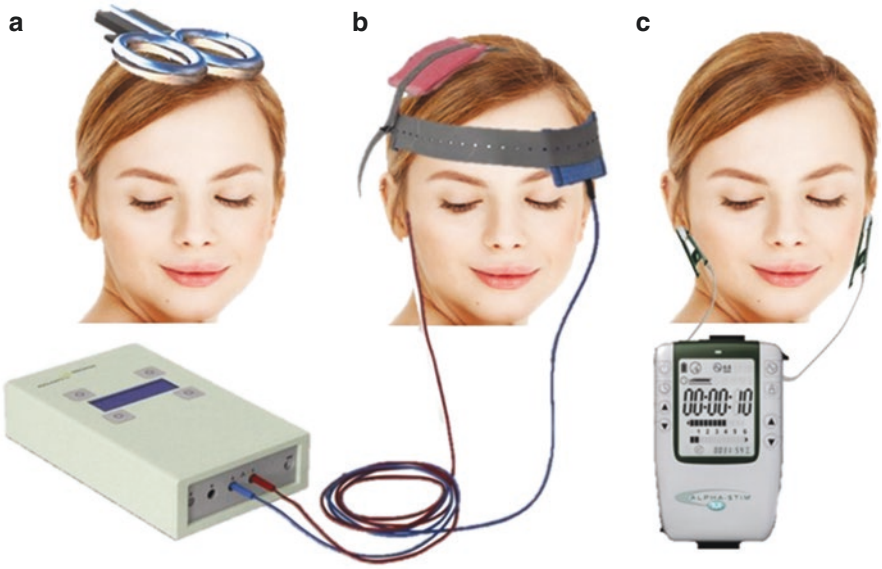

Fig. 8.2 Noninvasive brain stimulation with three modalities. (**a**) In rTMS, a magnet coil is applied over specific areas of the brain to target regions using a magnetic pulse. (**b**) In tDCS, a direct current is applied using a positive and negative electrode applied to the head. (**c**) CES applied using Alpha-Stim product via the ear induces alpha-type brain waves that mimic a meditative state

changing magnetic fields to form an electrical current that targets specific areas of the brain through electromagnetic induction. Granted FDA approval in the treatment of depression, it has been used and well studied for psychiatric disorders refractory to pharmacologic therapy, most commonly depression and anxiety. tDCS delivers constant low direct current through electrodes placed on the head. The British Institute of Health and Care Excellence has deemed it safe and effective in the use of depression. CES is similar to tDCS but uses alternating current (AC) rather than direct current (DC). These currents are thought to induce changes in neuron membrane potentials that can have lasting effects.

In a 2018 Cochrane review and meta-analysis, O'Connell et al. evaluated the efficacy of noninvasive cortical stimulation techniques in the treatment of chronic pain. When applied to the motor cortex, rTMS demonstrated a small decrease in pain scores on short-term follow-up, although the decrease was not deemed to be clinically significant [106]. Self-reported quality of life improved despite lack of evidence for improvement of disability. Interestingly, rTMS to the prefrontal cortex was not found to be effective in reducing pain. tDCS was found to have a clinically significant reduction in pain intensity and improvement in quality of life compared to sham, but the authors did note that these effects may have been exaggerated by a small study bias [106]. CES was not found to be effective with existing low-quality

evidence, though further research is needed [106]. These findings are consistent with the European academy of neurology published guidelines for central neurostimulation therapy in chronic pain [23]. A European task force evaluating neurostimulation therapy for neuropathic pain reports that rTMS, specifically, has efficacy in central and peripheral neuropathic pain, although short-lived in nature [22].

Accordingly, noninvasive brain stimulation may prove to be beneficial in CRPS. Changes in cortical structure and processing have been reported in CRPS [70, 124, 144]. It is thought that the peripheral changes in CRPS, both autonomic and somatosensory, are a manifestation of neuroplastic changes in central processing [104, 144]. Another theory is that abnormal peripheral input induces reorganization of the sensorimotor cortex [11, 104]. In a review of the literature for its use in CRPS, Nardone et al. found most studies utilized transcranial magnetic stimulation for physiological characterization of the brain [104]. Two small studies found the use of rTMS for therapeutic purposes, both reporting a transient decrease in pain [119, 121]. tDCS has been used in conjunction with other modalities, including TENS and graded motor imagery, for the treatment of CRPS with mixed results [57, 76]. Thus, further studies are needed to investigate its therapeutic benefits in CRPS.

Noninvasive brain stimulation is considered safe. However, they are associated with headache, nausea, dizziness, skin irritation, and transient vision changes. Fainting, seizures, hearing loss, cognitive changes, and induction of electrical current in implanted devices (defibrillators, pacemakers) have been reported with rTMS.

Pulsed Electromagnetic Field Therapy

Akin to rTMS, pulsed electromagnetic field therapy (PEMF), also known as low-field magnetic stimulation (LFMS), is a noninvasive treatment that uses electromagnetic fields to induce microcurrents in the body to enhance health and healing. Most PEMF devices come in the form of an electric massager or a full body electric yoga mat. They also come as local pad applicators and pinpoint probes. It has FDA approval for the treatment of fracture nonunions and to promote bone formation after cervical spine fusion surgery. PEMF has been used to reduce postsurgical pain and edema with mixed results [68, 93, 125, 141]. There is evidence for its use in knee osteoarthritis [127].

Though there are no published data of the use of PEMF in CRPS, Pagani et al. explain the rationale through a review of existing literature [112]. These studies demonstrate its ability to decrease pro-inflammatory cytokines and increase antioxidant proteins as well as increase osteoclast apoptosis, osteoblast viability, and bone calcification. Given the osteopenic changes and inflammatory features of CRPS, it is understandable why PEMF is being considered for the treatment of CRPS. However, currently there are no data available.

There are no known adverse side effects of PEMF.

Prism Adaptation Therapy

Prism adaptation therapy (PA) is a noninvasive therapy using prismatic goggles to promote reorganization of sensorimotor coordination. Participants are asked to point to targets while wearing left or right deviated goggles to recalibrate the brain to a new visual-motor alignment. PA has been effective for treating unilateral neglect and visuospatial disorders, particularly in stroke [16]. It is described as having a bottom-up effect, working on coordination at the level of the cerebellum while giving rise to high-order cognitive effects in other parts of the brain [120, 142]. These effects have been shown on fMRI [25].

There is some controversy over neglect-like symptoms on CRPS. Some believe CRPS results in neglect of the affected limb, while others see it as overrepresentation of the affected limb or neglect of the healthy limb [16, 147]. Sumnitani et al. looked at how the visual experience of PA could modify perception of pain in five CRPS patients [142]. They observed reduced pain intensity by about 50% on a NRS within a week of daily PA when trained to have visual displacement *away* from the affected limb. In addition, they reported amelioration of motor neglect. Interestingly, one patient who was trained to have visual displacement *toward* the affected limb experienced worsening pain. In a case report, Bultitude et al. observed a reduction in NRS score and disability after three weeks of PA [12]. Furthermore, the pain returned after a "washout" no treatment period and improved again after subsequent PA treatments. The same trends were seen with other clinical indicators of disease specifically edema, discoloration, temperature to touch, and ROM. Both studies noted the beneficial effects to be brief. In contrast, Christophe et al. reported sustainable pain relief after intensive PA [16]. Furthermore, Moseley et al. demonstrated that autonomic dysfunction in CRPS measured by temperature changes could be modulated with PA [97]. Although these small studies are promising, larger studies are needed to substantiate these findings.

Very few side effects have been reported. Anecdotally, it may cause dizziness and blurry vision temporarily.

Hyperbaric Oxygen Therapy

Hyperbaric oxygen therapy (HBOT) is the use of 100% oxygen at higher than atmospheric pressure to improve tissue oxygen supply. It is more commonly used in the treatment of nonhealing wounds, refractory osteomyelitis, decompression sickness, and carbon monoxide poisoning. The increase in circulating oxygen enhances fibroblast, osteoblast, and leukocyte function [111]. It also promotes angiogenesis and neovascularization (Jain et al. 1999). Anti-inflammatory and antinociceptive effects of HBOT have been seen in animal models [47, 83, 143]. It has been reported to alleviate neuropathic pain, decreasing allodynia and hyperalgesia in rodent and human studies [41, 47, 79, 83, 123, 143].

Though the pathophysiology of CRPS is not completely understood, inflammation and endothelial dysfunction seem to play an important role in the vasomotor

disturbances observed [74]. It is thought that ischemia from microvascular dysfunction contributes to the pathophysiology of CRPS [18]. Impaired macro- and microperfusion in affected arms of patients was observed by Schurmann et al. [132]. Accordingly, HBOT has come of interest in treating CRPS.

There is a growing body of evidence that HBOT is effective in the treatment of chronic pain including chronic headaches, fibromyalgia, and trigeminal neuralgia [47, 143]. However, there is a paucity of literature with regard to its use in CRPS. A case report of CRPS in the lower extremity reported a decrease in swelling and allodynia with improvement of skin color and range of motion after 15 treatments over 3 weeks [65]. In another report, HBOT improved CRPS symptoms allowing for reduction of steroid dose at both initial presentation and subsequent flares [7]. In a double-blinded, randomized controlled study, Kiralp et al. reported a decrease in pain and edema after 15 HBOT sessions compared to placebo [69]. In addition, they observed an increase in range of motion. Given the limited evidence, more RCTs are needed to confirm the efficacy of HBOT in CRPS.

HBOT is safe with few contraindications. These include untreated pneumothorax (risk for conversion to a tension pneumothorax), seizure disorder (oxygen-induced seizures), disulfiram (blocks superoxide dismutase which protects against oxygen toxicity), use of various chemotherapy agents (bleomycin interstitial pneumonitis, doxorubicin cardiotoxicity, cis-platinum-impaired wound healing), COPD with CO_2 retention (may take away respiratory drive), chronic sinusitis and current URI (upper respiratory infection) (causes significant sinus squeeze and possible ear barotrauma), eustachian tube dysfunction (ear barotrauma), claustrophobia (anxiety), congenital spherocytosis (hemolysis), and asthma (air trapping upon ascend leading to pneumothorax). There is a risk of dose-dependent pulmonary toxicity which is rarely seen due to the intermittent nature of HBOT, but is a consideration in patients that are on home oxygen. There is a theoretic risk of cataract maturation, but this has not been observed. Other side effects include myopia from changes in the lens shape and painful tooth squeeze if recent dental work has been done, both of which are temporary. It is not currently FDA approved for the use in CRPS or other chronic pain syndromes. Of note, HBOT may be cost prohibitive and availability to a hyperbaric chamber limits access for patients (Fig. 8.3).

Ozone Therapy

Ozone or O_3 is a naturally occurring, odorless gas with strong oxidizing properties. It was used in medicine by German soldiers during WWI to disinfect wounds [31]. Medical ozone is a mixture of O_2 and O_3, typically 95–99% O_2 and 1–5% O_3. It can be administered directly as an intravenous gas, either locally or systemically, or reinfusion of previously removed aliquot of blood with ozone added. In vivo and in vitro studies have found ozone to have antimicrobial effects and modulate the immune response [133]. Ozone therapy was found to decrease blood viscosity and is superior to HBOT in improving blood rheology [148]. With promising evidence, ozone is most commonly used in chronic pain as an alternative to steroids in local

Fig. 8.3 Portable home hyperbaric chamber. The hyperbaric oxygen chamber shown is portable with three zippers and its costs was approximately $4000 in the year 2020. This particular chamber is meant for home use. There are a wide range of chambers available, with more advanced models costing upwards of $100,000. Wellness and medical centers may have chambers available for therapeutic treatments to be used on an as-needed basis

injections for joint and disc osteoarthritis [5, 26, 105]. In a study of 65 fibromyalgia patients, it was found to improve symptoms by greater than 50% [146]. At the time of this review, there was only one case report involving the use of ozone in CRPS. A pediatric patient with CRPS of the lower extremity had improvement of pain after 10 sessions over 2 weeks with complete resolution of pain after four months [126]. She continued to be symptom free at 1-year follow-up.

Side effects include vein irritation, chest tightness, and cough if given in excess or too rapidly, which would raise concern for air embolism. It has known pulmonary toxicity when inhaled. Due to potentially serious adverse effects, it is recommended to wait for additional studies in its efficacy and safety before proceeding with its use.

Hirudotherapy

Hirudotherapy, also known as medicinal leech therapy (MLT), is the application of medicinal leeches to local sites for various ailments. Initially used for bloodletting centuries ago, it re-emerged in plastic and reconstructive surgery with the advent of microsurgery to relieve venous congestion in skin flaps and salvage revascularized tissue. It has been used throughout the world for DVT, postphlebitic syndrome, tinnitus, and pain reduction in osteoarthritis and epicondylitis. Leech therapy works not only by the physical suction and removal of blood from tissue to which it is attached, but also leech saliva itself contains various bioactive substances that can be of benefit in CRPS. Leech saliva has analgesic and anti-inflammatory properties. It also increases blood flow through secreted substances that cause endothelial muscle relaxation and vasodilation. Leech saliva

extract has been found to improve blood rheology of rats with acute blood stasis, enhancing circulation and decreasing stasis. There are studies showing protective effects of leech saliva extracts in cerebral ischemia-reperfusion injury [29]. Given these qualities, MLT may provide relief to the inflammation and vasomotor disturbances observed in CRPS. Furthermore, it may alleviate the microvascular dysfunction contributing to CRPS pathophysiology.

Though there is a growing body of basic science research, the literature with regard to the use of MLT in CRPS is sparse. One case report was found. A patient with CRPS of hand who received five MLT sessions reported decreased pain scores, swelling, and skin temperature asymmetry immediately after each session [75]. Kulbida et al. also reported improvement of active and passive range of movement.

The most common side effects of MLT are itching and bleeding at the site of application. Vasovagal symptoms have also been reported. Patients should be forewarned that MLT does commonly cause scar formation. Rare, but potential complications of MLT include local infection, bacteremia, and infection with leech-borne illness. Because there is a potential for transmission of blood-borne illness, leeches should not be reused. Allergy to the leech and their secretions is possible.

Physiotherapy-Based Interventions

Physical rehabilitation is the mainstay of treatment for CRPS. It should be initiated as early as possible as it may slow early disease progression. Function of the affected limb and the patient's overall daily function should be assessed early and repeatedly. It is important to have adequate pain control to optimize patient participation in physical therapy [45]. Immobilization of the affected limb should be avoided [107]. Recreational rehabilitation programs have also been developed, targeting patient-specific hobbies and previous pastimes. Frequently, it is through recreational therapy that kinesiophobia is overcome [50]. It provides a form of physical therapy, but also has psychological benefits of reintroducing joyful activities. Vocational rehabilitation provides treatment specific to the patient's occupation with a goal of decreasing time to return to work and improving daily function at work. This can be particularly helpful to encourage adaptation at work and return to normalcy. Specifically, we will touch on the following PT-based techniques: graded motor imagery, fluidotherapy, aquatherapy, and massage.

Graded motor imagery (GMI) is a rehabilitation program that includes three stages or techniques: (1) left/right discrimination – relearning to recognize left and right body parts, (2) explicit motor imagery – imagining moving specific body parts without actually moving it, allowing for pain-free thoughts of movement of the affected body part, and (3) mirror therapy (MT) – using mirrors to create the illusion of movement of the painful body part. By retraining the brain in these techniques, GMI is used for treatment of chronic pain and movement problems. In a Cochrane review, there was very low-quality evidence that GMI may reduce pain scores or improve functional disability in CRPS patients at 6 months compared to

conventional care [139]. In a systematic review, Méndez-Rebolledo et al. [92] noted that GMI and MT can improve pain in CRPS. However, the evidence was insufficient to recommend these therapies over other treatments due to small sample size and heterogeneity.

Fluidotherapy, also known as fluidized therapy, is a dry heat therapy that uses a specialized chamber to provide a suspended air stream of fine sawdust-like particles that take on the characteristics of a liquid. It provides localized pain relief while also improving circulation, stiffness, and hypersensitivity through the use of heat, massage, pressure oscillations, and suspension (Mosby, 2016). Though fluidotherapy is thought to be useful in CRPS, there is little literature about its use in CRPS specifically. We were able to find one study, a randomized controlled trial in patients with poststroke CRPS. One group received fluidotherapy five times a week in addition to conventional rehabilitation, while the other received conventional rehabilitation only [134]. They found significantly more improvement of edema and neuropathic pain graded by PainDETECT questionnaire in the group that received fluidotherapy. It is very safe to use. It should not be used in patients with open wounds, active infections, or severe circulatory disorders. It should be used with caution in patients with heat sensitivity. It is common to see mild erythema after treatment. Aquatherapy, also known as hydrotherapy, is the use of water to assist in physical rehabilitation. Typically, it is used to improve muscle relaxation, increase joint motion, and reduce pain through movement of the body in water. In CRPS, water-based physical therapy can allow for earlier participation in physical therapy, providing a more buoyant medium of exercise allowing less weight bearing on the affected extremity. The hydrostatic pressure produces a mild compressive force on the skin that can reduce the edema seen in CRPS [50]. Water temperature should be tested on the patient and regulated as it could exacerbate pain. Balneotherapy is a type of aquatherapy that uses mineral water for submersion and can involve massage through moving water. Traditionally, hot springs, cold springs, or other natural water sources are used (i.e., Dead Sea, volcanic mud baths, and sulfur springs). Balneotherapy may be helpful in CRPS as it is thought to improve sleep, decrease pain, and provide relaxation. Contrast bath therapy involves immersion of all or part of a body in alternating hot water and ice water, and alternating. It may provide some benefit in mild cases of CRPS to facilitate improved circulation by alternating vasodilation and vasoconstriction. It should be used with caution as it can induce an exacerbation of symptoms or cause pain in patients with hypersensitivity or allodynia. Furthermore, patients with severe CRPS may not benefit from the therapy due to vasomotor changes seen with disease progression [50].

Massage uses hands-on techniques to promote circulation and overall well-being. Manual lymphatic drainage is a type of massage that promotes lymphatic flow and drainage. Massage was not found to be effective in a 2016 Cochrane review in adults with CRPS [139]. Most studies showed no significant difference when massage was added to other PT-base modality. Caution should be taken with the use of massage in patients with allodynia or hyperalgesia. Therefore, it may not be a practical option for many patients with CRPS. It can be considered for patients with mild or resolving CRPS to promote circulation and normalize hands-on contact.

There is a paucity of good-quality literature available investigating which type of PT modalities is effective in reducing pain and disability in CRPS [140]. However,

Gutiérrez-Espinoza et al. [48] reported that a physical therapy program based on hydrotherapy, manual therapy, and exercises improves the function and reduces the pain in older patients with CRPS.

Use of Adjuvants in Children With CRPS

Concurrent with a comprehensive multidisciplinary treatment plan, the following adjuncts may provide benefits to children with CRPS. Acupuncture is a safe treatment modality that is well tolerated in pediatric patients with chronic pain [89]. In fact, in a small retrospective study, Kemper et al. found that 70% of pediatric patients report it as a pleasant and helpful experience [66]. At times, acupuncture can be difficult to perform in children, due to fear of needles and inability to remain still once needles are in place. The acupuncturist should be adaptable to such circumstances. Use of distraction whether it is the form of conversation or an electric device can be very helpful not only for placement of needles but also to maintain stillness during a treatment session. Acupressure and use of non-needles adjunct such as acupuncture beads and adhesive microneedles are reasonable alternatives to traditional acupuncture when needle phobia is a concern. Also, it may be necessary to decrease the length of the treatment session in younger children that have a tendency to fidget. Mind-body practices can be a novel approach to exercise and stress relief in children. Kempert et al. found that that children with chronic pain can benefit from a single yoga session, reporting not only decreased pain but also reduced mental and physical tension [67]. Parent participation can be encouraged and may be particularly helpful in the complex parent-child dyad that frequently accompanies pediatric pain. As a gentle approach to exercise, these practices may disrupt the pain-disability cycle that is commonly ingrained in home life and everyday activities. Having minimal adverse side effects, TENS, massage, and aquatherapy can be used, but depends on the child's tolerability. Prism adaptation therapy may have particular appeal in children as it involves the use of prismatic goggles and interactive tasks. It is reassuring that it has a remarkable safety profile in adults.

The following adjuncts are not recommended for use in children. Parents and practitioners should refrain from using herbal products and supplements in children due to unknown efficacy, side effects, and dosing. Noninvasive brain stimulation and PEMF should be avoided as there is still much to be learned about its benefit and its effect on the growing brain. Hyperbaric oxygen therapy has been used in children safely. However, there are no studies of its use for pediatric CRPS. Children may be at higher risk of middle ear barotrauma and sinus discomfort due to higher incidence of URIs, a relative contraindication to HBOT. Ozone therapy should be avoided in children due its higher safety concerns in the event of air embolism. Hirudotherapy should be used with caution in children due to the nature of the procedure, requiring bloodletting. Furthermore, obtaining assent from the child is particularly important to minimize emotional stress or PTSD from any therapeutic procedure. As with all pediatric medicine, it is imperative to have a family-centered approach to any treatment plan.

Conclusion

Many adjuvants are available for the treatment of chronic pain and may be helpful in CRPS. The level of evidence for the use of acupuncture in CRPS is strongest compared to other modalities discussed. The theory behind less conventional therapies provides the basis for a viable option, but larger more rigorous studies are needed to definitively conclude their efficacy and safety. The use of adjuvants in children reflects that of adults, but greater caution must be used and more emphasis should be placed on guardian involvement. All adjuvants must be used in conjunction with a multidisciplinary treatment plan. They should be a complement, not an alternative, to conventional treatments of CRPS.

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Interventional Treatment of Complex Regional Pain Syndrome

9

Christina Shin and Jianguo Cheng

Introduction

Complex regional pain syndrome (CRPS) is a challenging biopsychosocial condition. As our understanding of the pathophysiology mechanisms underpinning CRPS evolves, so does therapeutic management. The optimal approach to CRPS treatment is multimodal and comprehensive. Previous chapters have discussed pharmacotherapy and physical therapy. Interventional therapies, such as nerve blocks and intravenous infusions, also have long held a role in pain relief, specifically in facilitating a patient's participation in functional rehabilitation. This chapter discusses interventional approaches to the management of CRPS, including intravenous infusion therapies, sympathetic nerve blocks, and neuromodulation therapies. The latter approach includes peripheral nerve block and stimulation, dorsal root ganglion stimulation, spinal cord stimulation, and intrathecal drug delivery systems.

Intravenous Therapies

Compared with other interventional procedures discussed in this chapter, intravenous therapy is often less invasive and less costly. Intravenous regional blockade (IVRB) aims to block the sympathetic innervation or counter local neural inflammation in a single limb affected by CRPS.

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First described in 1974, IVRB with guanethidine was performed for the treatment of CRPS type 1 [1]. The purpose of the technique was to facilitate the fixation of guanethidine to the tissue of the affected limb in order to displace norepinephrine at sympathetic nerve endings and prevent the reuptake of norepinephrine. This technique has since been utilized and explored with a variety of medications with low to moderate level evidence of support for clinical applications [2].

Description of IVRB

The patient is placed in the supine position and vital signs are monitored continuously. Sedation may or may not be utilized. A catheter is placed in a distal vein of the affected limb and another catheter is often placed in a vein of an unaffected limb for the purpose of providing sedation or resuscitation as needed. Once satisfactory intravenous access is established, the affected limb is elevated and/or elastic bandage is placed to facilitate venous drainage. A pneumatic double cuff tourniquet is used. The proximal cuff is inflated first followed by the distal cuff inflated to a pressure approximately 50–100 mmHg above the systolic blood pressure of the affected limb. After inflation, the desired solution is slowly injected into the catheter of the affected arm over about four minutes. After a period of time (typically 20–30 min), the pneumatic tourniquets are deflated intermittently and slowly over a period of five minutes to minimize adverse reactions, including dizziness, lightheadedness, and headache. Continuous monitoring of vital signs, including electrocardiogram, is maintained for about one hour after the block to detect adverse events related to any systemic absorption of the medication. Depending on the patient's tolerance to the procedure, these treatments are often repeated every few days and/or weeks. Treatments are paired with careful evaluation of pain scores, edema, allodynia, temperature, and range of motion.

Intravenous infusion of different classes of medications, including but not limited to sympatholytic agents, anti-inflammatory medications, and N-Methyl-D-aspartate (NMDA) receptor antagonists, has been investigated as a treatment for CRPS [3]. Unlike an IVRB, an intravenous infusion does not utilize tourniquets and requires only intravenous access and continuous monitoring of vital signs.

Complications

Compared with other interventions discussed in this chapter, the IVRB technique has few major side effects but relatively frequent minor effects, including transient burning sensation with injection, nausea, dizziness, and lightheadedness, particularly after tourniquet deflation [2]. A major side effect is orthostatic hypotension requiring resuscitation and prolonged observation with continuous vital sign monitoring.

Intravenous Infusions and IVRB with Sympatholytic Agents

Animal models of CRPS have suggested a role for sympatholysis in mitigating symptoms of CRPS. One such study found a reduction in mechanical allodynia in rats with chronic post-ischemia pain after receiving both sympathetic vasoconstrictor antagonists as well as vasodilators [4]. As such, IVRB with sympatholytics, such as local anesthetics, guanethidine, clonidine, phentolamine, and beta blockers, have been investigated in patients suffering from CRPS.

Intravenous infusions of lidocaine have been studied in randomized controlled trials [5, 6]. In sixteen CRPS patients, Wallace et al. investigated the effect of various plasma concentrations of lidocaine on different thermal pain thresholds using neurosensory testing, compared with the placebo of diphenhydramine infusion [5]. They found that, at the highest studied plasma concentration of 3 mcg/ml, lidocaine significantly increased the hot pain thermal threshold in the painful area. In allodynic regions, intravenous lidocaine also produced a significantly decreased response to cool stimuli and stroking compared with placebo [5]. A separate randomized, placebo-controlled parallel study demonstrated that lidocaine at delivered concentrations of 5 mg/kg/hr was associated with significant relief of neuropathic pain compared with saline [6]. Both studies however studied the immediate effects of pain reduction and no long-term follow-up was performed.

Though initially introduced as a promising medication for IVRB in CRPS [1], recent systematic reviews have provided negative recommendations for IVRB with guanethidine based on literature evidence [2, 7]. Multiple randomized controlled trials found no significant sustained pain relief with guanethidine over placebo [2, 7–10]. Other agents explored for its potential sympatholytic mechanisms include clonidine, phenoxybenzamine, labetalol, ketanserin, and droperidol [2]. However, data supporting the use of these medications are limited and produce mixed results, thereby prompting at best a rating of 2B+ (individual cohort study or low-quality randomized controlled trials) (e.g., <80% follow-up) [2].

Intravenous Infusions and IVRB with Non-sympatholytic Agents

A number of studies found positive results in patients receiving IVRB with bisphosphonates [2]. In one prospective series of 27 patients, a single 60 mg dose of pamidronate was significantly more effective in reducing pain score, global assessment of disease severity score, and physical function at three-month follow-up compared to placebo [11]. A systematic review of four randomized trials found that bisphosphonates reduced intensity of pain at 4 and 12 weeks follow-up with rare adverse effects [12]. The bisphosphonates investigated were pamidronate [11, 13, 14], alendronate [13], and clondronate [14]. In these studies, bisphosphonate therapy (typically administered as a single dose which may or may not have been repeated over several days) was associated with reduced pain severity and swelling and increased range of motion. Furthermore, biochemical analyses found increased bone mineral content in the affected limb without significant changes in the unaffected limb [13].

While the data are limited, quality evidence seems to suggest a potential to reduce CRPS pain, particularly pain related to bone demineralization.

NMDA receptor antagonists, such as ketamine and magnesium, have also been implicated as therapeutically beneficial when administered intravenously in patients with CRPS. A recent systematic review recommended intravenous ketamine infusion as a potential therapy for patients with CRPS refractory to other interventions [2]. Significant and sustained improvement across multiple pain domains were found in a randomized, double-blind placebo-controlled trial of 19 patients with CRPS [15]. The infusion dose of ketamine utilized was 50 mg/hr up to 200 mg/4 hr session [15]. A double-blind randomized placebo-controlled study of 60 patients with CRPS type I found a significant reduction in pain scores early in the follow-up period [16]. However, by week 12, there was no difference between placebo and ketamine [16]. Furthermore, there were no functional improvements in the ketamine group [16]. In contrast, studies investigating the efficacy of intravenous magnesium have produced contradictory results, and thus, magnesium is not recommended as a therapy for CRPS [2].

A small randomized, double-blinded crossover study of ten patients with unilateral lower extremity CRPS received IVRB with lidocaine and varying doses of ketorolac [17]. Significant pain reduction was observed in the ketorolac groups. However, the statistical difference was short-lived, lasting only one day after injection [17].

Finally, intravenous immunoglobulin (IVIG) therapy has been proposed as a potential therapy for long-standing CRPS based on data suggesting the involvement of the immune system. A randomized, double-blind placebo-controlled crossover study in 12 patients found a statistically significant reduction in pain intensity up to 19 days following a one-time dose of 0.5 g/kg IVIG, compared to saline [18]. The mean decrease in pain units was 1.55 [18].

Few studies exist comparing IVRB with more invasive interventions. Nascimento et al. compared IVRB using sympatholytic agents with a sympathetic ganglion block for CRPS type I [19]. Similar pain reduction results were found between the two groups: IVRB using 70 mg lidocaine with 30 mcg clonidine versus sympathetic ganglion block using 70 mg lidocaine [19]. Reductions in pain intensity and duration were observed after the first three iterations of each type of block but both groups failed to have further improvements thereafter [19]. This suggests that, at least for some CRPS patients, IVRB is an option for short-term pain relief to facilitate physical therapy.

Sympathetic Blocks

As previously discussed in earlier chapters, perturbations in the sympathetic nervous system have been implicated as an important mechanism in CRPS. Perhaps one of the most commonly described procedures in the management of CRPS, sympathetic blocks are utilized for diagnostic and therapeutic purposes. In the ascending pathway, such blocks aim to disrupt nociceptive as well as visceral and somatic

afferent fibers. In addition, blockade of sudomotor, visceromotor, and vasomotor efferent fibers may be therapeutic for symptoms of CRPS. The sympathetic blocks used for CRPS are stellate ganglion block, upper thoracic sympathetic block, and lumbar sympathetic block.

Stellate Ganglion Block for Upper Extremity CRPS

In 80% of people, the stellate ganglion, also known as the cervicothoracic ganglion, is formed by the fusion of the inferior cervical ganglion and first thoracic ganglion. It is located at the level of C7, anterior to the C7 transverse process and posterior to the vertebral vessels. The stellate ganglion is located medial to the scalene muscles and lateral to the longus coli muscle, esophagus, and trachea. It is superior to the subclavian artery [20].

The stellate ganglion block (SGB) has been performed by landmark-based technique [20] and under fluoroscopy [21], CT [22], and ultrasound guidance [23]. In this chapter, fluoroscopy guidance and ultrasound guidance will be described.

The patient is positioned supine with the head slightly hyperextended and rotated to the contralateral side. The C6–C7 level is identified by fluoroscopy in the anterior-posterior (AP) view. After sterile preparation and subcutaneous infiltration with a local anesthetic, a needle is inserted at the junction of the transverse process and corresponding C6 or C7 vertebral body. Contact is made with bone and an oblique view is obtained by fluoroscopy to assess needle position and ensure it is anterior to the intervertebral foramen (Fig. 9.1a). Once the needle position is adequate, 0.5 –1 ml of contrast dye is injected to confirm the correct needle tip position and to prevent intravascular or another off-target injection. The contrast dye should spread over the prevertebral sympathetic chain at C6-T1 (Fig. 9.1b). Thereafter, SGB is performed with injection of local anesthetic (often, 1% lidocaine or 0.25% bupivacaine) or a combination of local anesthetic and steroid (dexamethasone 10 mg, for instance) to prolong the blockade (Fig. 9.1c). When clinically indicated, neurolysis of the stellate ganglion can be performed using radiofrequency ablation. The specific radiofrequency protocol may differ between institutions.

In contrast to fluoroscopy, ultrasound imaging aims to identify the prevertebral fascia and allow for the precise deposition of local anesthetic just deep to the prevertebral fascia [23]. The sympathetic chain can be found between the longus colli muscle and longus capitis muscle (Fig. 9.1d–e). Proponents of this approach argue that ultrasound guidance increases the specificity of the procedure in blocking the sympathetic chain alone.

With the guidance of fluoroscopy or ultrasound, inadvertent injury to or injection of medications into nearby structures (i.e., vertebral artery, inferior thyroid vessels, carotid artery, vagus nerve, cervical nerve roots) may be avoided. It is noteworthy that simultaneous bilateral SGB should be avoided because it may compromise breathing by paralyzing the recurrent laryngeal nerves and the vocal cords, leading to airway obstruction. Recurrent laryngeal and phrenic nerve blocks are frequent side effects of SGB, due to local anesthetic diffusion from the area of the ganglion.

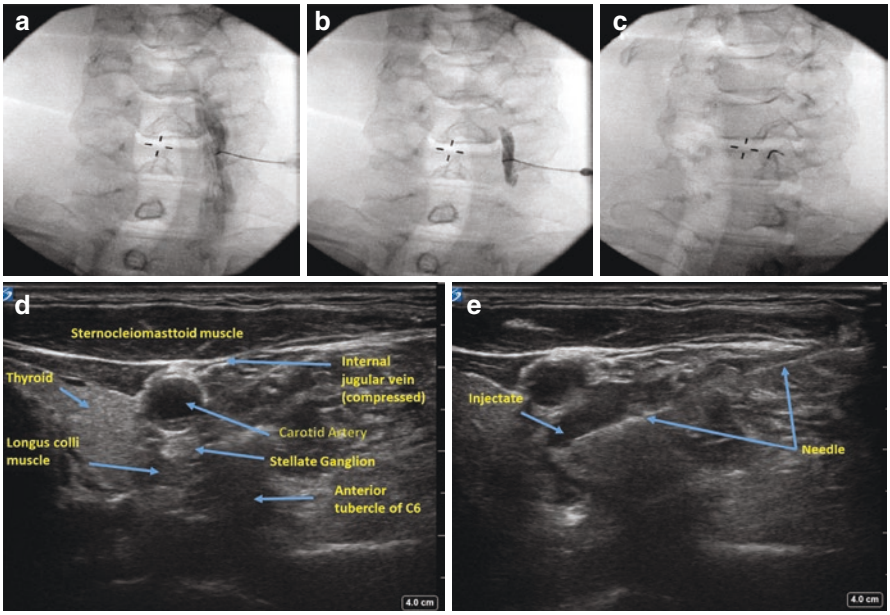

Fig. 9.1 Stellate ganglion block under fluoroscopy (**a**–**c**) or ultrasound (**d–e**) guidance. (**a**) The needle is placed at the base of the C6 transverse process in the oblique view. (**b**) In the anterior-posterior (AP) view, contrast is injected via extension tubing and spreads cephalad and caudad from C6. (**c**) Injection of local anesthetic and steroid in the AP view. (**d**) Ultrasound image of the stellate ganglion and its surrounding structures. (**e**) Needle and injectate targeting the stellate ganglion

Because diffusion of drug is required to obtain a satisfactory block, it is expected that these nerves will often be temporarily blocked.

Thoracic Sympathetic Block for Upper Extremity CRPS

While SGB has been frequently utilized for severe upper extremity pain, studies have found that SGB alone does not achieve sufficient sympatholysis [24]. In some patients, this is due to the direct projection of thoracic sympathetic ganglia to the brachial plexus, bypassing the cervical or stellate ganglia [25]. At the start of the procedure, the patient is placed in the prone position. The skin is infiltrated with a local anesthetic solution and prepared with disinfectant. Under fluoroscopic guidance [26], the spinal needle is inserted into the skin and advanced to the posterior third of the T2 vertebra. Contrast dye is injected and correct positioning is confirmed if the dye outlines the prevertebral sympathetic chain at T1–3. Thereafter, a local anesthetic solution is injected into the T2 sympathetic ganglion (Fig. 9.2).

More recently, the thoracic paravertebral block as an approach to achieving thoracic sympathetic blockade has been described and studied [27]. In comparison to SGB, a T2 paravertebral block significantly increased the incidence of temperature

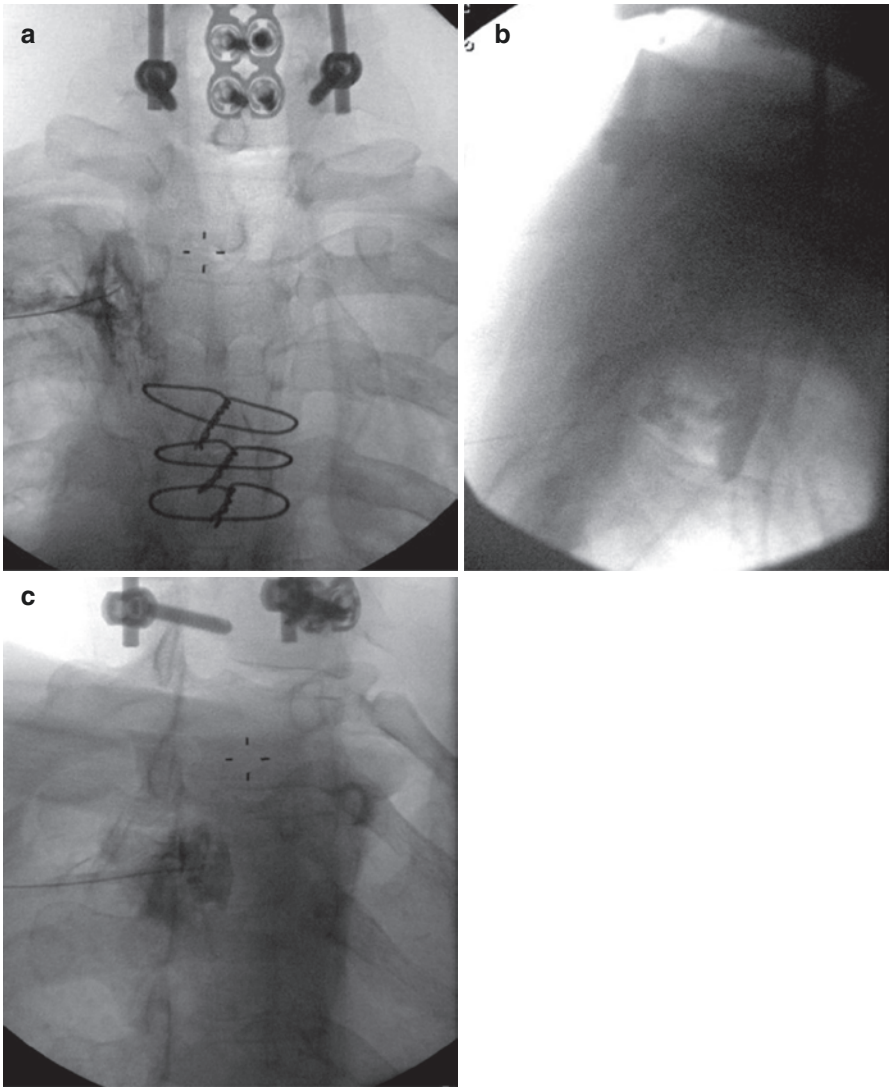

Fig. 9.2 Thoracic sympathetic block under fluoroscopy. Needle placed at level T2. Injection of contrast and local anesthetic/steroid in (**a**) AP view, (**b**) lateral view (tip at posterior one-third of vertebral body), and (**c**) contralateral oblique view

increase by at least 1.5 °C (primary outcome). Additionally, numeric rating scale scores were found to be significantly lower and satisfaction and block duration significantly higher in the paravertebral block group, compared with the group receiving SGB. However, only 20% of patients receiving SGB achieved the primary outcome of increasing the limb temperature of 1.5 °C, raising the question of whether the SGB was properly performed. In addition, the technical difference

between the paravertebral block and the traditional thoracic sympathetic block (described above) was not clearly defined and the depth of the needle tip in the paravertebral block group was not clearly described. It is possible that the paravertebral block was in fact performed in a similar manner as the traditional thoracic sympathetic block. The use of a large volume of injectate (10 ml) for the paravertebral block further increased this possibility. Therefore, it remains to be determined whether the typical paravertebral block approach with the tip of the needle posterior to the posterior spinal line in lateral view is sufficient to achieve thoracic sympathetic block and therefore to replace the traditional thoracic sympathetic block approach (tip at the posterior third of the T2 vertebral body on lateral view). The significance of this difference is that the risk of pneumothorax associated with the traditional thoracic sympathetic block approach due to the unique anatomical features of the upper thoracic spine can be reduced by adopting the paravertebral block approach. Theoretically, T2 paravertebral block should be sufficient to block the upper thoracic sympathetic chain.

Lumbar Sympathetic Block for Lower Extremity CRPS

The lumbar sympathetic ganglia, the convergence of pre- and post- ganglionic fibers, are located at the anterolateral side of the lumbar vertebrae. The lumbar sympathetic block is performed under image guidance. Given the ease of use and efficiency, fluoroscopy, compared with CT and MRI, is most frequently utilized. More recently, ultrasound has emerged as a valuable tool [28].

Under fluoroscopic AP view, the L2–4 levels are identified with the patient in the prone position. Using sterile technique, the skin is infiltrated with local anesthetic and then a needle is advanced toward the anterolateral edge of the target L2 or L3 lumbar vertebra (Fig. 9.3a). The lateral view is then obtained to confirm the needle tip in the anterior two-thirds of the target lumbar vertebra. The needle is further advanced to the anterolateral margin of the vertebral body with the final position confirmed on all three standard views (AP, lateral, oblique) and with contrast dye injection. The contrast dye should outline over the prevertebral sympathetic chain at L2–4 (Fig. 9.3b). Finally, a local anesthetic is injected. A local anesthetic blockade may be followed up, if clinically indicated, with a more definitive block using radiofrequency ablation or neurolysis with phenol. The use of botulinum toxin has also been reported to prolong the blockade and therapeutic effects [29].

Outcomes

The efficacy of sympathetic blocks has undergone the scrutiny by the Cochrane Collaboration and its most recent systematic review was conducted in 2016. This Cochrane analysis considered randomized controlled trials that examined the outcomes of sympathetic blockade with local anesthetics in patients with CRPS compared to placebo versus no treatment versus alternative treatments [30]. At the time

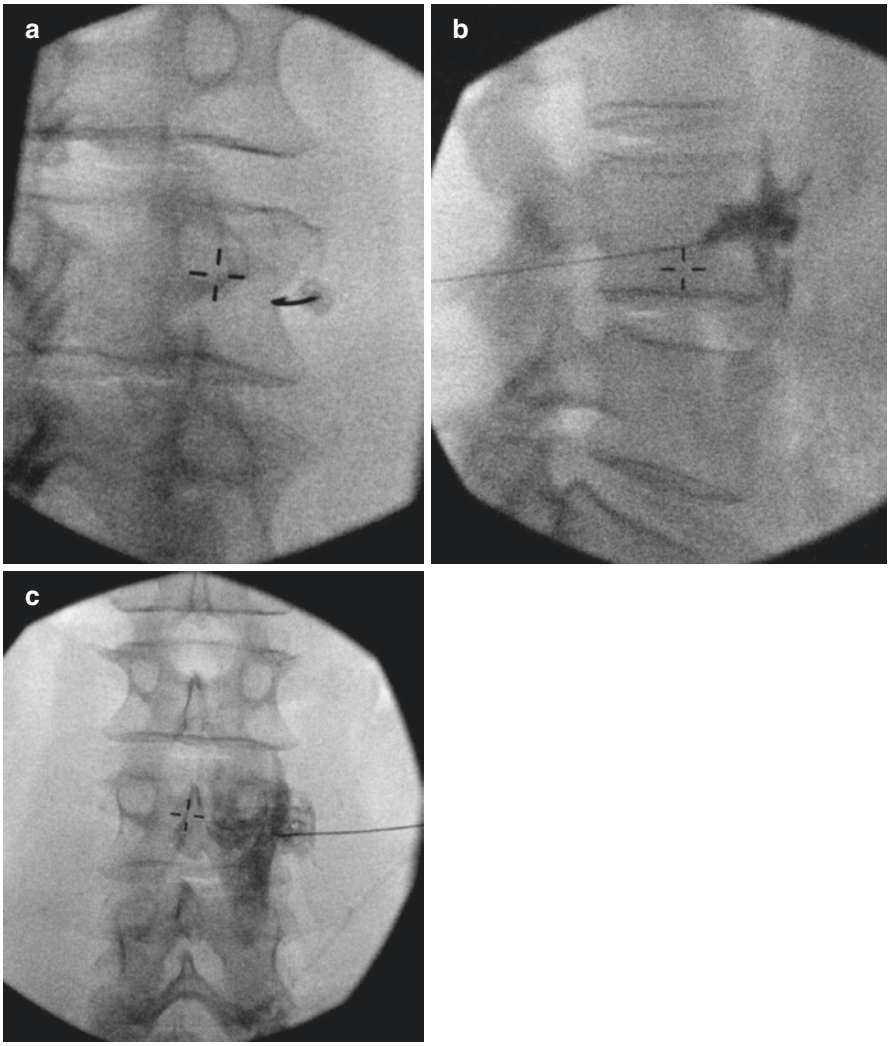

Fig. 9.3 Lumbar sympathetic block at L3 under fluoroscopy. (**a**) Needle placement in oblique view at L3. (**b**) Contrast is injected to confirm needle placement in lateral view. (**c**) Confirmation of contrast spread along the vertebral body in AP view

of the analysis in September 2015, a total of 12 studies were included with a combined patient population of 461 [30]. Despite a few studies reporting pain relief following either SGB or lumbar sympathetic blockade, taken as a whole, authors determined the level of evidence to be limited, low quality and sometimes conflicting, and concluded that sympathetic blockade has yet to be demonstrated superior to placebo in reducing pain in the long-term [30].

A recent cohort study of 225 patients in 2019 shed new light on the efficacy of sympathetic blocks in CRPS [31]. Many studies utilize an immediate increase in skin

temperature (of at least 1.5 degrees Celsius) as a measure of completeness of the sympathetic block [24, 32]. In addition to skin temperature changes, a number of studies have investigated the degree and duration of pain relief associated with sympathetic blockade in the treatment of CRPS. The most recent retrospective cohort study found that 61% of its patients with CRPS had a greater than 50% pain reduction [31]. A majority of those experiencing pain relief reported a duration of relief 1–4+ weeks [31]. In contrast to conventional thought, this study also found no significant association between pre-procedure temperatures of the affected extremity and the pain reduction of sympathetic blockade, suggesting that temperatures were not predictive of successful outcome [31]. In addition, the study found that there was no difference in the success rate of spinal cord stimulation trials between patients with or without more than 50% pain relief after sympathetic blocks. It was concluded that sympathetic blocks may be therapeutic in patients with CRPS regardless of pre-procedure limb temperatures and that the effects of sympathetic blocks do not predict the success of spinal cord stimulation [31]. This study provided level II evidence in support of sympathetic blocks for CRPS in select patients [31].

Neuromodulation Therapies

Neuromodulation typically involves the implantation of a device to achieve long-term therapeutic benefit. Overlapping principles include basic indications, absolute contraindications, and preoperative considerations. The use of peripheral nerve block and/or stimulation, dorsal root ganglion (DRG) stimulation, spinal cord stimulation (SCS), and intrathecal drug delivery systems is warranted in patients with persistent CRPS symptoms despite reasonable attempts at conservative management with medication use and physical rehabilitation. While many would argue that neuromodulation should be considered sooner rather than later in a patient's disease course to achieve longer lasting benefit, it is generally accepted that physical therapy and a trial of pharmacologic agents, including topical and oral agents, is a starting point.

Contraindications vary with each procedure. However, absolute contraindications most often include the following: preexisting infection at operative site, bacteremia and septicemia, hemodynamic instability, therapeutic anticoagulation without the ability to hold anticoagulants, allergy to procedure medications, and patient refusal.

Preoperative Considerations

Patient selection is key to the success of neuromodulation. Preoperative evaluation of the patient begins with a comprehensive history and physical exam, including a thorough review of relevant medical and psychiatric comorbidities. Prior to trial and permanent implantation of stimulators and intrathecal drug delivery systems, all patients are evaluated by a clinical psychologist/psychiatrist to identify factors that

may lead to therapeutic failure, to address cognitive and behavioral concerns, and to set proper expectations for and from the patients.

Specific cardiopulmonary comorbidities will influence the sedation management and positioning of the patient during the procedure. Severe immunodeficiencies, including those caused by chemotherapy, may preclude implantation of permanent devices due to increased risk for infection. A careful review of medications is required and a coordinated plan must be made regarding the safety of withholding anticoagulant medications immediately prior to and after a procedure. Permanent implantation procedures require a dose of perioperative antibiotics to prevent surgical site infections. Choice of antibiotic will depend on the patient's allergies though standard of care is usually a cephalosporin for adequate skin and soft tissue flora coverage. In addition to antibiotic use, proper sterile attire and surgical site skin prep with sterile drape are instrumental. All procedures should occur under continuous vital sign monitoring by a clinician and when appropriate, intravenous access should be established to permit resuscitation as needed by the clinician. When sedation is delivered, supplemental oxygen and noninvasive bag-valve-mask devices should also be available. Intubation is rarely needed for neuromodulation device implant surgeries.

Peripheral Nerve Block and Stimulation

While several frameworks have been put forward to elucidate pain and its origins [33], the mechanism most frequently cited as the rationale behind the use of electrical stimulation is the gate control theory, first described by Melzack and Wall in 1965 [34]. Gate control theory proposes that non-painful sensory input, via large-diameter sensory fibers, closes the "gates" in the spinal cord dorsal horn laminae, thereby preventing transmission of painful input via small-diameter fibers. Thus, the patient would experience less pain. This theory provides a physiological explanation for how nociception may be modified by non-nociceptive stimulation, for example, rubbing or massaging a painful site. However, the true mechanisms of neuromodulation remain to be determined and are likely related to modulation of the conduction, transmission, and perception of pain signals, as well as processes involving non-neuronal cells in the spinal cord that contribute to central sensitization and chronification of pain. Neuromodulation techniques may alter the neurochemical components of the dorsal horn with a decrease in the excitatory neurotransmitters, aspartate, and glutamate, and an increase in the levels of inhibitory neurotransmitters, GABA, and glycine. Based on the above-described principle, techniques for electrical stimulation at both the peripheral and central nervous systems have been developed. We will begin our discussion with peripheral nerve stimulation.

Peripheral nerve stimulation (PNS) is the direct electrical stimulation of nerves outside of the central neuroaxis, such as the median nerve. Distinct from SCS, PNS aims to directly inhibit primary pain afferents, thereby replacing the pain experience with a more pleasant paresthesia.

Indication

The following patient selection criteria have been used for the consideration of PNS in CRPS, along with other chronic pain conditions [35]:

1. Pain within a sensory distribution of a single peripheral nerve.
2. Positive diagnostic peripheral nerve block.
3. Exclusion of nerve entrapment neuropathies.
4. Patient is free of major psychological or psychiatric disease.

Procedure

A PNS may be implanted percutaneously or under direct visualization. This chapter will discuss the implantation of PNS in a percutaneous fashion using ultrasound technology and a 14-gauge or 17-gauge needle. Equipment for the implantation consists of (1) an implantable PNS electrode with 8–16 contacts and (2) a pulse generator (battery), either implanted or external.

Positioning of the patient will depend on the target nerve, and repositioning during the surgery may be necessary. The patient's skin is prepared in sterile fashion and relevant structures are identified using either ultrasound or fluoroscopy. Once the nerve is located, the skin is infiltrated with local anesthetic.

Similar to procedures for other electrical stimulation or devices, the implantation of a PNS is typically a two-stage procedure. The first stage trials the efficacy of electrical stimulation for pain relief via temporary implantation of an electrode near the target nerve. Next, the electrode is sutured in place and then connected to a temporary power source. The patient will then test the temporary peripheral nerve stimulator and assess for symptomatic pain relief. The patient will move ahead with the second stage if the relief is adequate. The temporary electrode will be explanted and replaced with a permanent electrode and typically with an implantable pulse generator (IPG) in a subcutaneous pocket. The permanent electrodes are anchored to the fascia with nonabsorbable suture. The implantable systems may last for up to 10 years or more (Fig. 9.4). More recently, research in PNS has produced devices that allow for pulse generators to communicate wirelessly to the in-situ electrode, thereby avoiding a second incision and foreign body. When a wireless system by Bioness or Stimwave is used, pulse generator implantation is not necessary. In the case of using the PNS system by SPRINT, the electrode is placed near the target nerve under ultrasound guidance and an external pulse generator is connected to the electrode. After about 60 days, the system is removed without incision.

Outcomes

Overall, there is little data on the long-term efficacy of PNS in the treatment of CRPS. One prospective study examined the efficacy of surgically placed plate-type electrodes on affected nerves in 30 patients [36]. About 63% of this cohort reported good or fair relief over a period of 2–4 years with an average reduction in pain from 8.3+/− 0.3 preimplantation to 3.5+/−0.4 at follow-up on a pain scale of 10. The

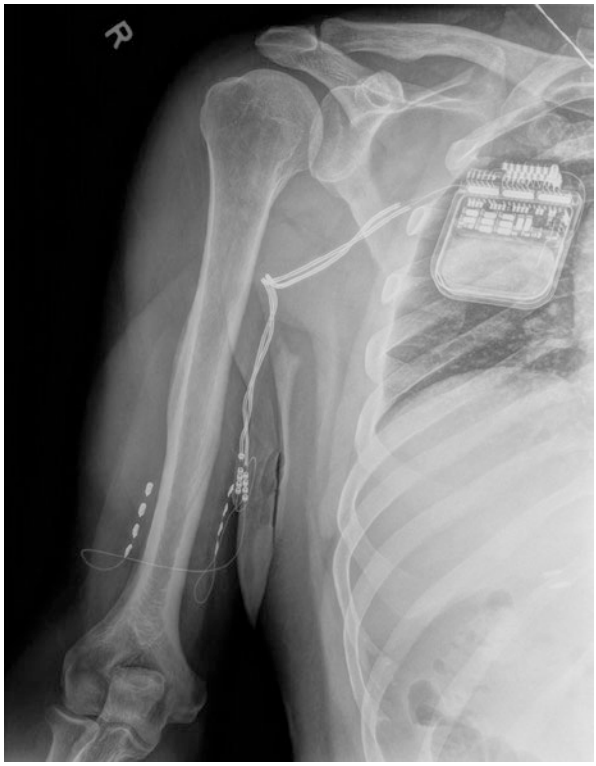

Fig. 9.4 Peripheral nerve stimulator with implantable pulse generator connected by tunneled extension wires. Radial nerve and ulnar nerve PNS leads were implanted to successfully manage complex regional pain syndrome type II involving the right forearm and hand

authors of this study also report improvement in functional activity. One case report found success with peripheral median nerve stimulation for CRPS following multiple carpal tunnel release surgeries [37]. At 36 months, this patient reported good pain relief without the need for additional analgesics [37]. Thus, PNS has the potential to deliver focused stimulation to the target nerve that innervates the painful region of CRPS.

Complications

Potential complications include infection at the surgical site, PNS lead migration or tip erosion requiring explantation, hardware malfunction, pain over device, and tolerance/habituation to stimulation.

Spinal Cord Stimulation

For patients who do not respond to noninvasive conservative therapy, spinal cord stimulation (SCS) may be considered as an effective intervention. Traditionally, providers have utilized a multimodal approach centered on noninvasive therapy, including rehabilitation and analgesics. SCS may be considered an escalation of care and reserved for non-responders. More recent data suggest that delays in more

definitive therapy may be associated with poorer outcomes, including limited improvements in functional status and mental health [38], and thus warrant earlier consideration of SCS in the care of patients with CRPS. Although the dorsal root ganglia (DRG) are part of the peripheral nervous system from an anatomical perspective, DRG stimulation is generally accepted as a form of SCS for regulatory and other reasons and is therefore discussed here in light of level I evidence for CRPS.

SCS has been utilized in a number of chronic pain syndromes, most commonly for CRPS and failed back surgery syndrome [39]. As a reversible intervention, SCS is programmed to deliver low voltage electrical stimulation to decrease pain sensation through implanted leads in the epidural space (Fig. 9.5). Classically, the gate control theory of pain proposed that pain relief arose from competitive inhibition of impulses from nociceptive neurons by SCS-mediated activation of large sensory nerve fibers. Neurophysiology studies in animal models of neuropathic pain have suggested potential biochemical bases for analgesia [40–42]. Electrical stimulation of dorsal columns has been associated with increased GABAergic activity and decreased release of glutamate and aspartate in the dorsal horn. As the latter are excitatory amino acids, it is thought that electrical stimulation mitigates nociceptive transmission via dampened excitatory activity [40]. Recordings of neuronal units in the dorsal horn in cats suggested inhibitory action in the dorsal horn via interneurons in or near the substantia gelatinosa [41].

Procedure

SCS therapy consists of two stages: the trial phase followed by permanent implantation should the trial be successful. Trials typically occur in the clinic setting, where under fluoroscopy, temporary electrodes are introduced into the epidural space in the cervical or thoracic region for upper or low extremity CRPS. First, the patient is positioned prone and standard monitors are applied. Sterile preparation is performed and the skin is infiltrated with local anesthesia. Under direct fluoroscopy, a Tuohy needle is introduced into the epidural space. The electrode is advanced until the tip is at the desired location. For treatment of upper extremity CRPS, the target is typically the superior aspect of the C4 vertebral body (Fig. 9.6). The T9–T12 vertebral bodies are typically targeted for the treatment of lower extremity CRPS (Fig. 9.7). For DRG stimulation, leads are placed in the lateral epidural space near the target DRG at levels from T10 to S2 for CRPS in the lower extremities, depending on the dermatomal target corresponding to the patient's primary region of pain (Fig. 9.8). A special introducer is used to guide the placement of DRG leads, in addition to the needle for epidural access. Depending on the anatomical target, up to 16 contacts can be placed for SCS or DRG stimulation.

Intraoperative testing to determine stimulation overlap with subjects' painful areas is conducted during implantation. Of note, there is no need for intraoperative testing if HF10 (high-frequency (10 kHz) stimulation) by Nevro is used as it is a paresthesia-free mode of stimulation. Depending on the technology, the patient may or may not experience paresthesia in the area covering pain when the electrode is activated. Following satisfactory placement, the Tuohy needle (and introducer for DRG leads) is withdrawn and an external stimulator is connected to the trial

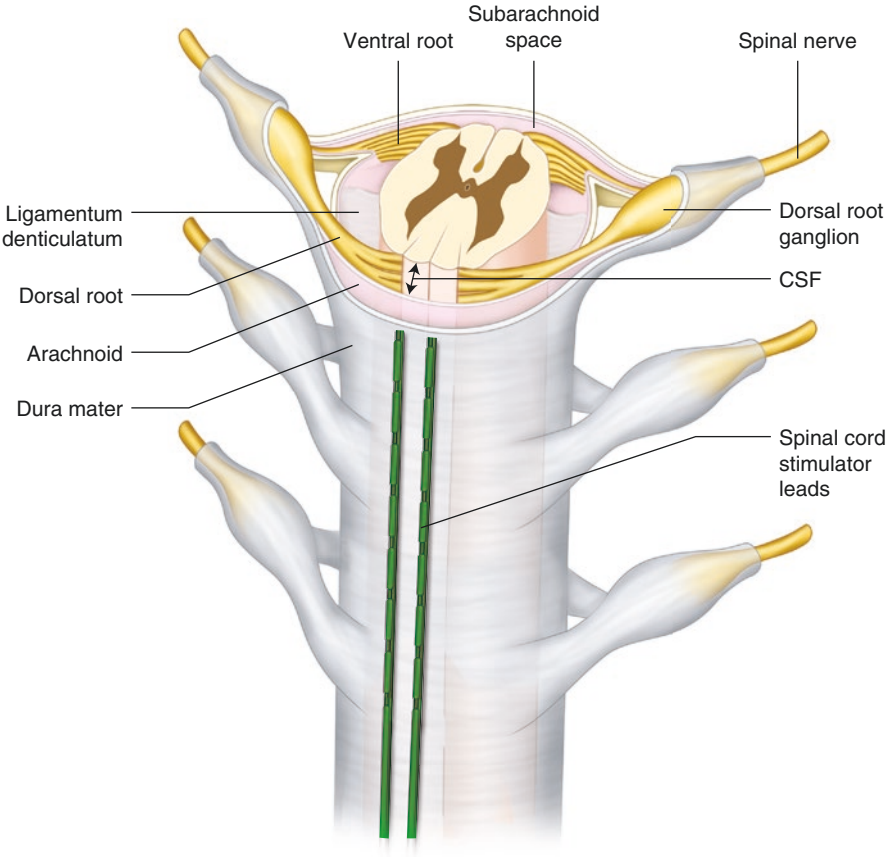

Fig. 9.5 Spinal cord stimulator. Illustration of spinal cord stimulator implanted in epidural space and relevant neuraxial anatomy

electrode. The patient is instructed on how to proceed with the trial stimulation at home over the next 5–10 days. A successful trial is often defined as a 50% or greater reduction in pain.

For the permanent implantation, the patient presents to an operating room where either monitored anesthesia care or general anesthesia is induced. The patient is positioned prone and prepared using the sterile technique. Occasionally, the patient may be positioned in the lateral decubitus position. Fluoroscopy is used to mark anatomical landmarks and decision as to which level of interlaminar space to access is made by the operator. Prior to incision, a local anesthetic is infiltrated into the skin and subcutaneous tissue. A midline longitudinal incision is made and dissection down to the fascia and supraspinous ligament is performed with careful attention to hemostasis using electrocautery. The operator may continue to inject local anesthetic along the desired path of the Tuohy needle. The epidural space is then accessed using the paramedian approach with

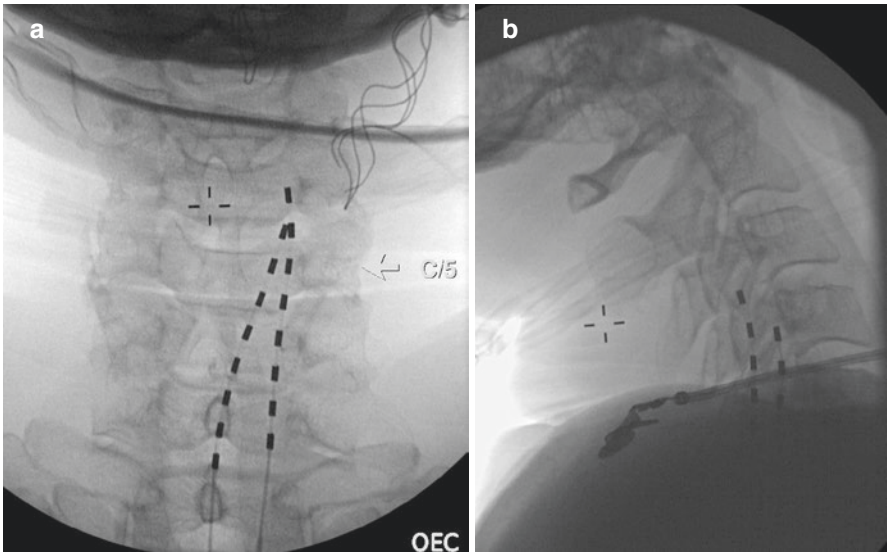

Fig. 9.6 Cervical spinal cord stimulator implantation under fluoroscopy for upper extremity CRPS type I. Needle entry at T2–3 with tips of the leads at C4. (**a**) AP view of dual lead placement, one in the lateral posterior epidural space and the other in the mid-lateral posterior epidural space. C5 is denoted in the image. (**b**) Lateral view of lead placement in the posterior epidural space

a Tuohy needle, through which, an electrode is introduced into the epidural space. Both leads may be placed at the same interlaminar space using a right and left paramedian approach. Under live fluoroscopy guidance, one lead at a time is advanced cephalad until the tip of the electrode is at a satisfactory position. As each lead contains a wired stylet, some degree of lead steering is possible (Figs. 9.6a and 9.7a). A lateral fluoroscopy view may then be obtained to ensure that both leads are in the posterior epidural space (Figs. 9.6b and 9.7b). Both leads are then fixed using small anchors into the deep fascial tissue with further securement using nonabsorbable sutures. After fixation, another fluoroscopic image is obtained to ensure that the leads had not migrated during the fixation process. With the help of an introducer, DRG leads are placed in the lateral epidural space near the target DRG. Fluoroscopy images are taken to confirm lead location underneath the pedicle of respective vertebra in AP view and in the foramen in the lateral view (Fig. 9.9). The introducing sheath is then retracted back to the epidural space and an S-shape curve of the lead is made in the epidural space to relieve the strain. The epidural needle and the introducer are removed without dislodging the electrode.

SCS electrodes can also be placed surgically through laminectomy. In such cases, paddle leads are used for stability to prevent lead migration. This approach can be advantageous for lead placement in the cervical region, where lead migration

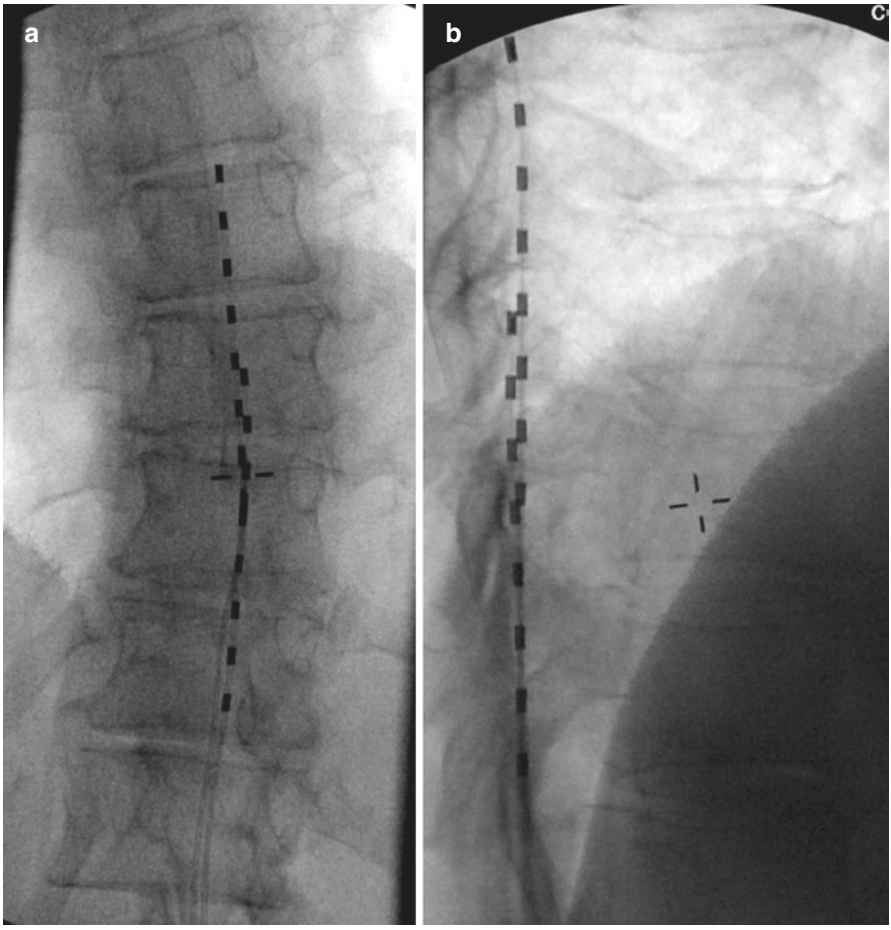

Fig. 9.7 Thoracic spinal cord stimulator leads for lower extremity CRPS under fluoroscopy. Dual lead implantation in (**a**) AP view and (**b**) lateral view. Needle entry at L2–3 with tips of leads at T8 and T9 respectively

is more common. A disadvantage of paddle lead is that revision/replacement can be more challenging when lead fracture occurs.

The IPG is then implanted by a single incision. The location of the IPG is typically at the buttock for both thoracic and cervical stimulation. There are occasions when the IPG may be placed in the subclavicular area or mid-axillary line for cervical leads or abdominal wall for thoracic leads. After an appropriately sized pocket is created, the generator is inserted and the leads carefully tunneled from the anchor site to the pocket using a tunneling device. The leads are then connected to the generator. The IPG is secured with nonabsorbable sutures to the subcutaneous fascia. Once again, fluoroscopic images are obtained to confirm lead positioning. Fascia

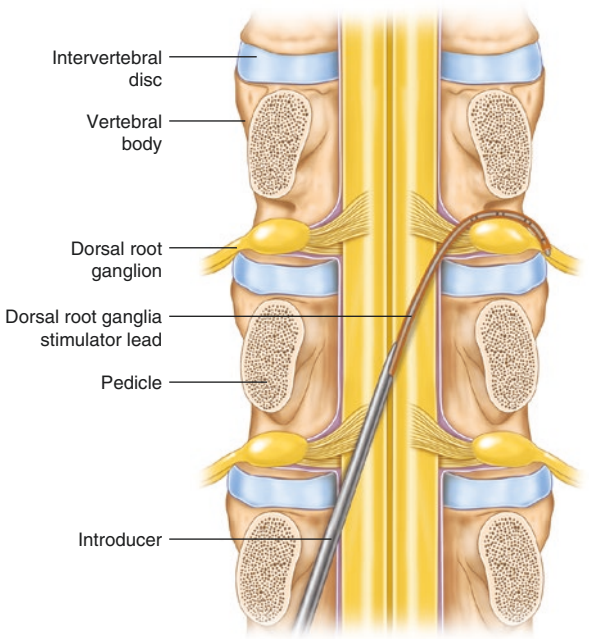

Fig. 9.8 Dorsal root ganglia stimulator. Illustration of dorsal root ganglia stimulator implanted in lateral epidural space and relevant neuraxial anatomy

and skin are meticulously closed. The patient emerges and is brought to the recovery unit.

Complications

Potential device-related complications of SCS implantation include lead migration, lead fracture, and IPG dysfunction. Biological complications include epidural hematoma, spinal cord or peripheral nerve injury, postdural puncture headaches, surgical site infection, and pain at the pocket of the IPG. Most commonly reported side effects include paresthesia in other locations and pain or irritation from the leads or IPG [43].

Outcomes

Recent studies have provided level I evidence to support DRG stimulation for CRPS [44]. The efficacy of SCS for CRPS has been demonstrated by numerous case reports, few randomized controlled trials, and systematic reviews. The first prospective randomized controlled trial compared two arms: physical therapy (PT) only versus SCS + PT [45]. Patients enrolled in the trial had CRPS involving either an upper or lower extremity for at least 6 months. Those randomized to the SCS + PT arm only received a permanent implantation if the trial was successful, defined as a reduction in pain intensity by at least 50% prior to randomization or if the patient rated the global perceived effect of treatment as at least a 6 (“much improved”) on a 7-point scale. Of the 36 patients who received a trial, 24 moved on to receive a permanent implantation. In an intention-to-treat analysis, the SCS + PT group had a

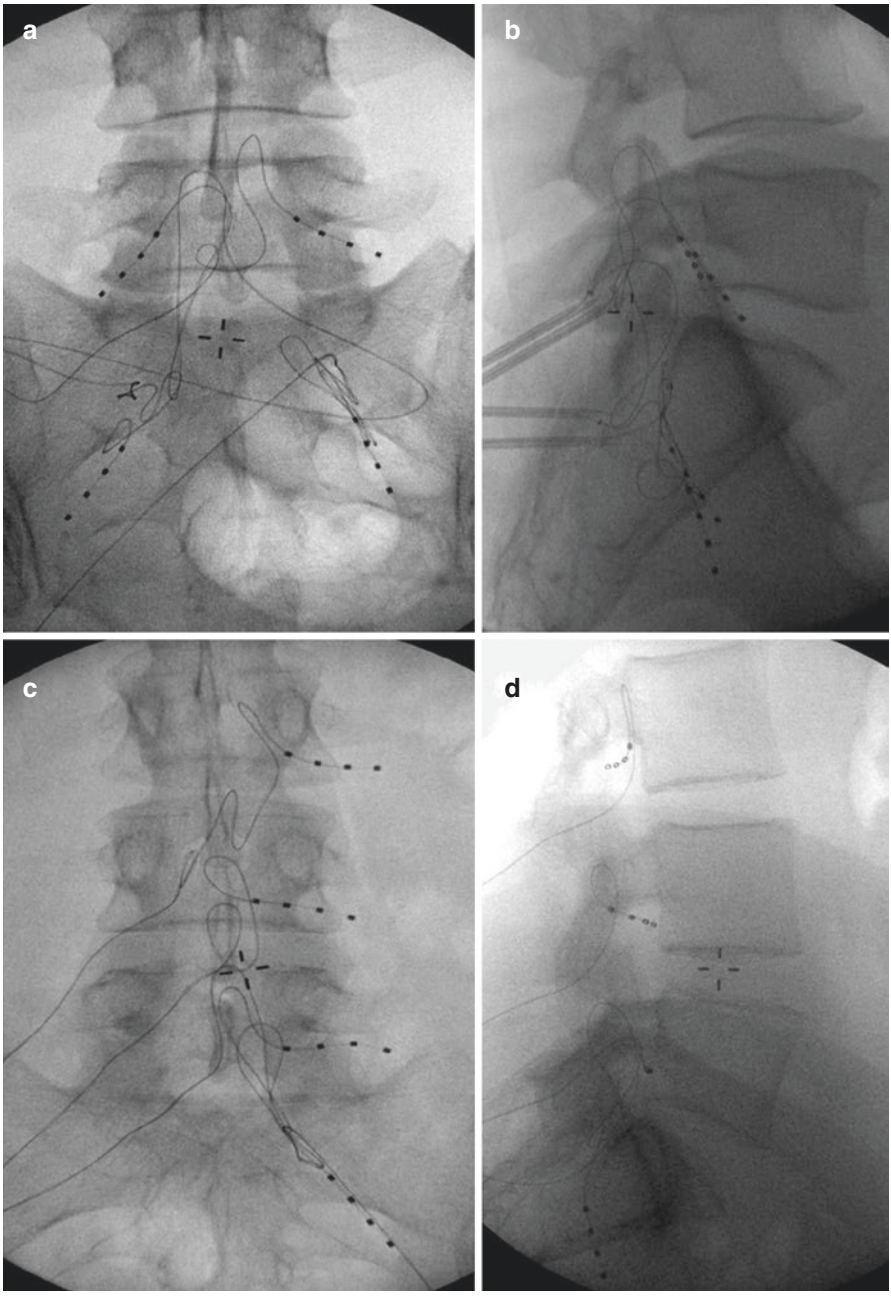

Fig. 9.9 DRG stimulation electrode placement for lower extremity CRPS under fluoroscopy. Bilateral L5 and S1 DRG coverage in (**a**) AP view and (**b**) lateral view. Left side L3, L4, L5, and S1 DRG coverage in (**c**) AP view and (**d**) lateral view

statistically and clinically significant reduction in pain intensity at six months compared with the PT group. Those actually receiving the implantation also reported an improvement in health-related quality of life. These effects were maintained at two-year follow-up in a subsequent study [43]. By five years, pain scores were similar among the two arms however 95% of the patients who had received an SCS implantation reported that they would repeat treatment for the same results [46]. A prospective case series of 19 patients at two centers found significant improvement in pain level (Visual analog scale scores, McGill Pain Rating Index) and in sickness impact profile [47]. A systematic review including the aforementioned randomized controlled trial as well as 25 case studies and one cost-effectiveness study found level I evidence for SCS as an effective intervention for CRPS [48]. A more recent systematic review included a total of 19 studies and found high-level evidence for the use of SCS for CRPS with respect to outcomes of perceived pain relief, pain score improvement, quality of life, and patient satisfaction [49].

Intrathecal Drug Delivery Therapy

Pain management through intrathecal delivery systems began as early as the 1980s and was approved by the U.S. Food and Drug Administration in 1991. Implantable intrathecal systems are used for malignant and non-malignant chronic pain refractory to medical therapy including failed back surgery syndrome, spinal cord injury-induced spasticity, CRPS, and chronic pancreatitis. The goal is to provide a targeted approach to drug delivery, which is especially beneficial to those patients who have been dose limited by medication side effects. Similar to other interventional procedures, absolute contraindications include anticoagulation with the inability to discontinue anticoagulants, coagulopathies, cerebrospinal fluid outflow obstruction, intracranial hypertension, and systemic infection or infection at the site of insertion. Medication choice varies and depends in part on the mechanism of pain. Several medications have been studied, including opioids, baclofen, local anesthetics, clonidine, glycine, and ziconotide.

Procedure

A basic intrathecal drug delivery system consists of 1) indwelling catheter, 2) implanted pump containing a reservoir of drug, and 3) external controller. The catheter is placed percutaneously into the intrathecal space, and the implanted pump is most often placed in a subcutaneous pocket in the abdomen.

Prior to permanent implantation, the patient undergoes a trial to determine whether or not medications delivered intrathecally would alleviate pain. Such trials may take many forms, including single or repeated injections of medication into the intrathecal space and/or an inpatient trial of continuous infusion via intrathecal catheter.

For the permanent implantation of an intrathecal pump, the patient is brought to the operating room. The procedure can be performed under general anesthesia, regional

anesthesia, or local anesthesia with sedation. The advantage of regional and local anesthesia is the ability of the patient to provide any direct feedback during implantation, thereby potentially preventing nerve injury. Following satisfactory induction of anesthesia, the patient is placed in the lateral decubitus position and prepared in a sterile fashion. Using fluoroscopy, the L3–4 intervertebral space is identified. A 3- to 4-cm vertical skin incision is made over the L3–4 space and dissection is performed from skin to lumbodorsal fascia, taking care to ensure hemostasis with electrocautery. Blunt dissection is then used to extend laterally along the lumbodorsal fascia plane to create space for excess catheter length and the anchor. Using a paramedian approach and under fluoroscopic guidance, a 14-gauge Tuohy needle is advanced toward the intrathecal space (Fig. 9.10a). Access to the space is confirmed radiographically and with return of cerebral spinal fluid (CSF) (Fig. 9.10b). After stylet removal, the catheter is inserted into the Tuohy needle and advanced to the desired vertebral level under fluoroscopy. A guidewire in the catheter facilitates cephalad advancement. After satisfactory positioning of the catheter dorsal to the spinal cord, a purse-string nonabsorbable suture is made around the Tuohy needle. The Tuohy needle and catheter guidewire are then removed carefully without retraction or shearing of the catheter. The purse-string suture is tightened to prevent a CSF leak. The catheter position is verified with fluoroscopy before anchoring to the lumbodorsal fascia with a small anchoring device which accompanies the pump.

Once the catheter is secure, attention is then turned to creating a pocket for the intrathecal pump. Prior to presenting to the operating room, the physician identifies and marks an ideal position on the patient's abdomen, taking care to avoid the belt line and the costal margin. An 8 cm horizontal incision is made and then dissected to a depth of 1.5 cm. This incision represents the middle of the pocket. With careful blunt dissection, a pocket is then created which approximates the size of the pump. The intrathecal catheter is then tunneled laterally to the pump pocket using a tunneling device. Four non-absorbable sutures are made at the four corners of the pocket. The pump, which had been filled and primed with medication, is connected to the pump and inserted into the pocket. The pump is secured to the external abdominal fascia by tightening the four sutures (Fig. 9.10c). All incisions are then irrigated and closed.

Complications

Immediately after the procedure, complications may include CSF leak and/or postdural puncture headache. In the days to weeks to years following implantation, potential complications are hematoma, seroma, or infection surrounding the implant. Erosion through the skin may also occur. Device-related complications include displacement, kink, or fractures of the catheter, as well as pump failure. Medication-related complications vary with the type of medication selected for the intrathecal drug delivery system. For example, though less frequent than oral or intravenous delivery of opioids, intrathecal opioids can still lead to respiratory depression, sedation, and constipation. Other complications include the formation

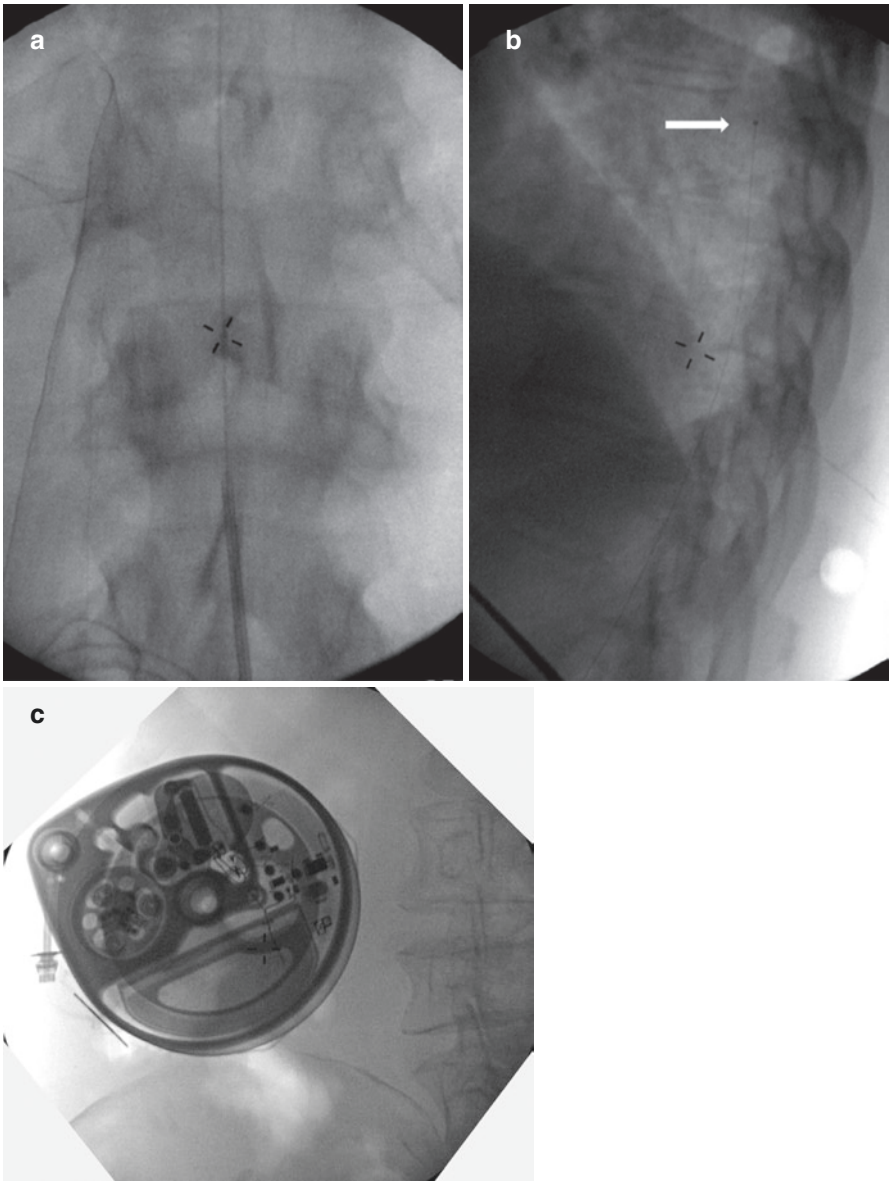

Fig. 9.10 Intrathecal pump implant under fluoroscopy. (**a**) Catheter placement through a spinal needle entry at L2–3 in AP view. (**b**) Lateral view showing the tip of the catheter (white arrow) at T9 in the intrathecal space just behind the spinal cord. (**c**) Pump placement within the right abdominal wall in AP view

of inflammatory mass around the tip of the catheter and possible overdose or withdrawal due to malfunction of the pump or human error during medication preparation or refill.

Pharmacologic Agents

A variety of studies have examined many different types of medications and combinations of medications for intrathecal pharmacologic management of chronic pain. At present, only three medications are approved by the FDA for use in intrathecal pumps: morphine, baclofen, and ziconotide. For the treatment of CRPS, studies have examined the efficacy and safety of clonidine and adenosine [50], baclofen [51, 52], methylprednisolone [53], glycine [54], bupivacaine [55], opioids [56], and ziconotide [57]. Combination of medications has also been studied, such as opiate plus local anesthetic [58].

The Polyanalgesic Consensus Conference (PACC) panel of experts have developed guidelines based on current research, with the most recent update published in 2017 [59]. This panel presented best practices for the use of intrathecal infusion of medications to treat patients with chronic refractory pain, including CRPS. Various treatment statements were ranked by the quality of the evidence, degree of recommendation, and strength of consensus among the panel members.

Through this systematic methodology, the conclusion that intrathecal clonidine decreases pain scores, allodynia, hyperalgesia, and mean arterial blood pressure in CRPS patients was determined to have high-quality evidence, strong recommendation, and strong consensus amongst panel members [44]. In their secondary analysis, investigators found a significant decrease in pain scores over time with intrathecal clonidine infusion [50]. Clonidine is an alpha2 adrenergic agonist and has been found in basic research to inhibit the activation of glial cells, ultimately inhibiting the production of proinflammatory cytokines [60].

Ziconotide, an antagonist of presynaptic N-type calcium channels in the dorsal horn of the spinal cord [61], is a first-line therapy and FDA approved for the intrathecal management of neuropathic and nociceptive pain. The PACC strongly recommends with high-quality evidence that intrathecal therapy with ziconotide be utilized for cancer- and noncancer-related pain [59]. In a series of patients with CRPS, pain scores as well as edema, skin abnormalities, and mobility were found to be markedly improved with ziconotide therapy [57].

Baclofen is also highly recommended but specifically for the indication of spasticity associated with chronic pain [59]. A single-blind, placebo-run-in, dose-escalation study in 36 CRPS patients found significant improvement in dystonia scores, pain disability, and quality of life at 12-month follow-up after implantation of an intrathecal pump administering continuous baclofen [62]. Forty-two patients with CRPS and dystonia symptoms received baclofen via intrathecal pump and

investigators found a significant improvement in multiple dimensions of pain, including global intense pain, sharp pain, dull pain, and deep pain [63]. Unlike the symptom of dystonia, however, the degree of pain improvement did seem to plateau after about 6 months of follow-up [63]. A randomized-controlled, double-blind crossover study found no differences in fast versus slower infusion rates of baclofen on dystonia and pain [52]. In fact, there was an increase in adverse events with a faster infusion rate, which included headache, drowsiness, short-term amnesia, and light-headedness [52].

Local anesthetics, steroids, and other medications have been studied. A randomized, double-blind placebo-controlled cross-over study found no improvement in pain or dystonia with intrathecal glycine in CRPS patients [54]. Similarly, methylprednisolone, delivered as a single 60 mg dose, was ineffective in improving pain intensity in a double-blind, randomized controlled trial of 20 CRPS patients [53]. Intrathecal bupivacaine monotherapy was trialed in a woman with CRPS of her lower extremity, whose condition was refractory to local blocks and SCS [55]. Initial trials found intrathecal morphine to offer minimal relief [55]. Clonidine was trialed thereafter and found to provide excellent pain relief for several days however was limited by significant adverse events, including headaches, weakness, and hypotension [55]. A trial of bupivacaine ensued and produced complete pain relief with minimal perineal anesthesia and extremity motor block at an infusion of 3 mg/day with additional self-administered boluses [55].

Intrathecal opioids have been utilized for pain management for as long as intrathecal drug therapy has been approved. Compared with systemically delivered opioids, intrathecal opioids typically confer the advantage of fewer side effects. An early prospective series of 15 patients with reflex sympathetic dystrophy following spinal surgery found excellent pain relief in a little more than half of its patients and good-to-fair pain relief in the remaining study population over a 44-month follow-up period [56]. The studies discussed thus far tracked patients, on average, over a 1- to 2-year time frame. Herring et al. sought to better understand the long-term outcomes of intrathecal drug delivery systems in patients with CRPS at a single institution who had at least four years of continuous follow-up [64]. They found that intrathecal opioid dose was not associated with long-term decreases in oral opioid consumption; ziconotide was associated with a decrease in oral opioid intake over the four-year follow-up; and bupivacaine was associated with an increase in oral opioid intake [64].

Concluding Remarks

In summary, interventional therapy is a critical component of multidisciplinary and multimodal management of CRPS, particularly for refractory cases. There is level I evidence to support DRG stimulation and SCS, level II evidence to support intrathecal drug therapy and sympathetic blocks, and substantial and variable evidence to support PNS and intravenous therapies with specific treatment regimens. It is important to emphasize a comprehensive and holistic approach to the management of

CRPS based on the biopsychosocial model of patient-centered care. When interventional therapies are indicated, it is essential for practicing physicians to have the training and competence to appropriately select suitable candidates, proficiently perform the procedures, closely monitor patients' outcomes, and promptly identify and manage potential complications.

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Interventional Treatments for CRPS in Children

10

Andrew Dinh and Genevieve D'souza

Known at the time as reflex sympathetic dystrophy, one of the first cases of complex regional pain syndrome (CRPS) in the pediatric population was recorded as early as the 1970s [1]. Interestingly, there were several case reports of spontaneous resolution of symptoms in the pediatric population which then prompted the notion that sympathetic blocks carried a certain amount of risks that did not meet the benefit for what was considered, at the time, a self-resolving syndrome [2, 3]. Whether or not interventional treatment was used in the pediatric population, a multimodal approach to CRPS centered on physical therapy, medication management, and psychosocial intervention remains to be the most beneficial approach in children to this day [4, 14, 17].

When considering interventional therapies in CRPS in children, two modalities of treatment should be considered – invasive and noninvasive. Noninvasive options entail transcutaneous electrical nerve stimulation (TENS) while invasive options include, but are not limited to:

- Trigger point injections
- Bier blocks or intravenous regional anesthesia (IVRA)
- Peripheral nerve stimulation
- Sympathetic nerve blocks and neuraxial blockade
- Spinal cord and dorsal root ganglion stimulation

The use of TENS units in the setting of CRPS in the pediatric population has been described in multiple case reports and case series with variable efficacy [4–6]. While the use of rat models has shown the benefit of decreased risk in developing allodynia [7], prospective trials in the pediatric population have yet to be completed

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to evaluate the efficacy in the treatment of CRPS. Because of these devices tend to be well tolerated in children and have a low financial burden to patient's families, a trial of its addition to a multimodal treatment plan may be worthwhile.

Trigger point injections have shown potential benefits mainly in the upper extremity pathology of adults suffering from CRPS-like symptoms [13–15]. In the pediatric population, data remain limited in showing efficacy. Further, prospective and controlled studies in large cohorts are needed to determine the benefits of these low-risk procedures. Intuitively, myofascial tender point injections are difficult to perform in children without sedation and would inherently make it difficult to show a clear benefit. While medical risks are relatively low, the lack of tolerability of the procedure may outweigh any benefit seen from its use.

Bier blocks have been used since the early 1900s for the use of surgical analgesia in extremity surgeries. More recently, it has come to gain utility in the treatment of CRPS in adults as a chemical sympathectomy as an alternative to repeated sympathetic blocks. There is evidence that the use of local anesthetic solutions can decrease neurogenic modulation if used early in the disease process [21]. Several studies have shown the use of intravenous regional block with local anesthetic and another medication to be superior to placebo if used early in disease progression [21]. In the pediatric population, there have been a few trials and case reports detailing the use of intravenous regional anesthesia in the setting of CRPS. A case study in 2003 noted complete resolution of symptoms with use of intravenous regional anesthesia with lidocaine and ketorolac [22]. A prospective trial in 13 children showed complete resolution after a 2-month follow-up with the use of Bier Block techniques in the setting of early CRPS [25]. Pediatric administration of intravenous regional anesthesia does have some difficulty, including the need for heavy sedation and/or general anesthesia and extremely cautious dosing, especially in smaller children. A well-described, classic Bier-block technique has been showing promise in the pediatric population [23].

Peripheral nerve stimulation has been used in the treatment of many chronic pain conditions that do not respond to conventional treatment regimens. The most prevalent theory behind its use in conditions related to peripheral nerve injuries is the gate-theory of neuromodulation. This approach has been used in both children and adults with positive results [24]. A drawback to the conventional sequence of peripheral nerve stimulator insertions is the need for multiple anesthetics: one anesthetic to implant the electrodes as a trial and a subsequent anesthetic for permanent implantation of the generator once clinical efficacy has been proven. These implants are also not MRI safe, which will have to be taken into consideration. More recently, the development of wireless generators in the delivery of peripheral nerve stimulation has made it more attractive in reducing the number of anesthetics. Wireless generators, that negate the need for a second anesthetic and tissue pocket for implantation, have shown promising results over control groups [23]. Use in the pediatric population continues to require further studies but its inherent reduction of anesthetic risks remains attractive to both patients and their families.

The use of sympathetic blocks and neuraxial blockade has shown benefit as an adjunct to diagnosis [4, 8–11]. With the notion of sympathetically dependent pain as a spectrum in CRPS patients, there is a potential diagnostic and therapeutic benefit

to trialing sympathetic blockade in the pediatric population. While the technique is comparable to that in adults, performing sympathetic blockade in the pediatric population has the additional risk of general anesthesia for the majority of pediatric cases. This risk must be considered and included when deciding the cost-benefit ratio on an individualized basis. The necessity of general anesthesia removes the benefit of a responsive patient and places the patient at a greater risk of complications of the procedure. It is critical that the practitioner has a concrete understanding of the anatomy and physiology before proceeding with each procedure.

One potential difference between the use of sympathetic blockades between children and adults, as described by Wilder et al. [1, 12], is the use of catheters versus a series of injections. Benefits of this approach stem from the potential reduction in the number of overall procedures for the child over a relatively short period of time: less total number of anesthetics, less exposure to radiation, and overall more patient compliance are all benefits that are noted by this author. The most important aspect of this approach is that it can help facilitate the engagement of physical therapy. The use of indwelling catheters typically requires inpatient admission in pediatric patients in order to monitor for potential side effects from the sympathetic blockade. One benefit of the inpatient setting is the possibility of a more rigorous physical therapy. Ideal blockade would be motor-sparing to allow a child who is unable to engage in physical therapy due to pain to participate throughout the admission period.

Spinal cord stimulation and dorsal root ganglion therapy have seen positive results in the CRPS population and have been gaining traction as a favorable treatment modality over the past 10 years [18–20]. Benefits are postulated to be related to neuromodulation and the multiple functional improvements noted in both the adult and pediatric populations. Not only do patients perceive improved pain scores and quality of life but analgesic sparing, sleep hygiene and psychosocial impacts are well documented. Implementation in the pediatric population again carries the same risks in terms of the need for heavy sedation or general anesthesia for its deployment. Again, these therapies are most effective in a multimodal therapeutic model in the treatment of pediatric CRPS [1, 4, 12, 18, 20].

Critics of invasive procedures in the pediatric population state that the lack of efficacy is not worth the risk of multiple procedures and potential side effects and complications following anesthetics [16]. There continues to be a lack of strong evidence for routine use of invasive procedures as a single modality to treat CRPS in the pediatric population. Invasive procedures should be reserved for use in a multimodal approach for patients that fail to respond to conservative therapies. While some studies note complete resolution of symptoms with the use of invasive procedures in children, it is critical to emphasize that the goal of procedural therapy is to achieve enough pain relief for the patient to participate in physical therapy and other forms of nonpharmacological treatment regimens. To date, due to both ethical and practical reasons, blinded, randomized controlled trials comparing invasive and noninvasive therapies in the pediatric population suffering from CRPS are very limited and may continue to be a barrier to adequate reporting and evidence-based recommendations.

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Emerging Therapies for the Treatment of Complex Regional Pain Syndrome

11

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Introduction

The treatment of complex regional pain syndrome (CRPS) is challenging due to the complexity of the underlying pathophysiology. The focus of treatment emphasizes functionality and requires an interdisciplinary approach [1]. Patients who do not respond timely to interdisciplinary treatment may require advanced interventional pain therapy including neuromodulation, which involves electrical stimulation of the nervous system [2]. Distinct from conventional nerve blocks with local anesthetic that indiscriminately halts neurotransmission, neuromodulation at different levels of the nervous system interferes with what is believed to be maladapted nociceptive transmission and processing. High-level evidence from randomized, controlled trials demonstrates improved pain severity, quality of life, and satisfaction with various forms of neuromodulation over physical therapy alone [3–6]. To date, our current iteration of neuromodulation does not guarantee success or sustained efficacy; however, neuromodulation has cast a new light onto our current understanding and research into CRPS. The current treatment options for CRPS are described elsewhere. Here, we discuss both advancements in technology and emerging concepts in the future of CRPS therapies with a focus on stimulation of the spinal dorsal columns, dorsal root ganglia, peripheral nerves, and brain.

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Neuromodulation

Cost Efficacy

Given the benefits of neuromodulation, some advocate for earlier consideration of this therapy in the treatment algorithm of CRPS rather than a therapy of last resort [7]. The historically reported high up-front cost continues to be a barrier to neuromodulation; however, the diminished annual cost of CRPS care thereafter from decreased healthcare utilization is often forgotten. The cost-effectiveness of spinal dorsal column stimulation (SCS) has been studied, while the cost-effectiveness of the more recent dorsal root ganglion stimulation (DRG) has yet to be reported [8–11]. Treatment of CRPS with SCS breaks even with conservative management at 3 years, and becomes more cost-effective thereafter [10]. Factoring the additional net economic cost recovered per quality adjusted-life years from the benefit of SCS, the expense falls well within a price point regarded as representing good value and appropriate use of societal and healthcare system resources [8]. Four variables exert the largest impacts on the cost-effectiveness of SCS: (1) the cost of adjunct pain regimen with spinal cord stimulation, (2) the probability of no pain relief from SCS, which is inversely proportional to the cost efficacy, (3) the cost of conservative management, which is directly proportional to the cost, and (4) the time interval between implantable pulse generator (IPG) replacements, which also is directly proportional to the cost [11]. Innovations in SCS and DRG technology impact the cost-efficacy by directly affecting the aforementioned variables.

Dorsal Column Stimulation

Since the first successful report of dorsal column stimulation by Shealy et al. in 1967 [12], over 30, 000 individuals each year receive SCS therapy for various chronic pain conditions. The efficacy of SCS for the treatment of CRPS is supported by a randomized control trial by Kemler et al. [4]. Subjects were randomized to receive SCS plus physical therapy or physical therapy alone. In this study, the SCS participants demonstrated a statistically and clinically significant reduction in mean pain intensity and improvement in global perceived effect in as early as 1 month and persisted through 2-year follow-up [5]. The triumphant success of SCS also exposed the areas in need for improvement. Responders to SCS therapy is low; only 67% of the subjects randomized to the SCS arm reported successful trial stimulation and proceeded to implantation [4]. Furthermore, 5-year follow-up to the initial SCS randomized trial uncovered the diminutive pain-alleviating effects of SCS with time, the SCS and control groups became comparable after 3 years of therapy [13]. Subsequent prospective long-term follow-up studies echoed a similar loss of SCS efficacy with time [14]. Habituation describes this phenomenon of loss of efficacy, after initial success, despite having appropriate stimulation coverage and absence of hardware-related malfunctions [14–16]. The underlying mechanism behind habituation to SCS therapy is not completely understood. It is hypothesized to be in part

from the progression of underlying disease, plasticity of the pain circuitry, or other physiological or psychological factors (e.g., hawthorne effect, patients may over romanticize the results of the trial in order to undergo permanent implantation). Habituation to SCS therapy is seen not only with CRPS, but across other pain conditions.

Innovations in SCS technology have focused on manipulating the electrical stimulus delivered to the dorsal columns: amplitude, pulse width, pulse repetition frequency, and electrode geometry [17–21]. However, the success is limited by wide variabilities in efficacy. An analysis of clinical studies and case series from 1972 through 2013 reveals only 58% of patients experienced at least 50% or greater improvement in pain [18–23], and the success rates did not correlate with study year, which suggests no improvement with clinical experience or innovation [24]. Burst pattern and high-frequency (10 kHz) stimulation represent widely adopted developments in SCS programming capable of suppressing neuropathic pain without eliciting paresthesia [25, 26]. Burst pattern SCS is comparable to conventional waveform SCS in the treatment of CRPS and selection of one stimulation waveform over another is also influenced by patient preference [27]. Case series support high-frequency waveform as another viable option in the treatment of CRPS; [28, 29] however, higher level evidence for this therapy for CRPS is needed. Despite the most recent innovations in SCS programming, habituation continues to be the top reason for SCS explantation [30–32].

An incomplete understanding of the mechanism of SCS and its interaction with the pathophysiology of chronic pain may account for the stagnation in clinical success. Despite an emphasis on neuronal circuitry, glial cells constitute the majority of the cellular components in the nervous system [33]. The disruption in the balance of neuroglial interactions contributes to chronic pain [34]. Interestingly, glial cells are also responsive to electrical fields. Preclinical experiments illustrate that targeted electrical modulation of glial components has beneficial outcomes on animal models of neuropathic pain [35]. The most recent emerging SCS program is the first to be developed from preclinical science and is designed to deliver a multiplex of waveforms to enhance the neuroglial interactions in the spinal cord. A clinical trial is currently underway in non-CRPS patients with chronic leg and back pain and is demonstrating promising early results with efficacy in reducing pain severity as well as high responder rates [36].

Modern neural circuitry hypothesis of SCS incorporates inhibitory interneurons, local and supra-spinal neurocircuits, and cortical pain matrices into the preexisting gate control theory that inspired the development of SCS [24]. Although neuronal recordings have been a classical tool in neuroscience, it is not until recently that advancements in SCS technology have allowed for human recordings of spinal cord axonal responses in close proximity to the applied electrical stimulus [36]. Electrical stimulus above the threshold potential of a neuron cause depolarization and generation of an action potential in an antidromic and orthodromic fashion along the axon from the electrical stimulus. The summation of numerous action potentials comprises the evoked compound action potential (ECAP). The ability to record ECAP in response to SCS opens the door to the next level of SCS innovation.

Researchers now have the ability to study the ECAP in response to SCS. ECAP represents real-time responses and provides information about the characteristics of the underlying nerve fibers. For example, the speed of propagation of the ECAP reflects the type of nerve fibers (sensory Aβ, nociceptive Aδ, and C fibers). The characteristics of the ECAP as it relates to specific SCS parameters can be used to study mechanism of action and provide insight into the pathophysiology of chronic pain.

Another major milestone from ECAP recordings is the ability to incorporate closed-loop feedback into SCS therapy. Closed-loop feedback governs most physiologic processes to allow for maintenance of homeostasis such as in the control of blood sugar. In cardiac electrophysiology, closed-loop feedback mechanism allows implanted pacemakers to deliver electrical stimulus to the heart only in response to the native heart rhythm. All preexisting spinal neuromodulation systems are classified as open loop—that is, the SCS stimulus is independent from the neural response to that stimulus. SCS leads are fixed in the epidural space, yet the distance between the spinal cord suspended in the cerebral spinal fluid and the electrodes fluctuates with cardiac and respiratory cycle, let alone patient movement [37–39]. Small changes in distance between the electrode and the spinal cord magnify into large variations in the electrical field strength and the area of stimulation. The consequence of open-loop, fixed-output SCS is best illustrated clinically by overstimulation, stimulation in unwanted areas, and even muscle activation that can occur with coughing or changes in body position (e.g., standing, sitting, and supine positioning) [38]. The inverse is true regarding under-stimulation and the reduction in therapeutic effect. Therapy habituation may be in part due to over- and/or understimulation.

The goal of closed-loop SCS in this paradigm is to allow for variable SCS stimulation to target a goal ECAP—in effect, to maintain a near consistent spinal cord activation (Fig. 11.1). The initial studies of closed-loop SCS are conducted on patients with chronic back and/or leg pain [40–42]. In a double-blind, randomized

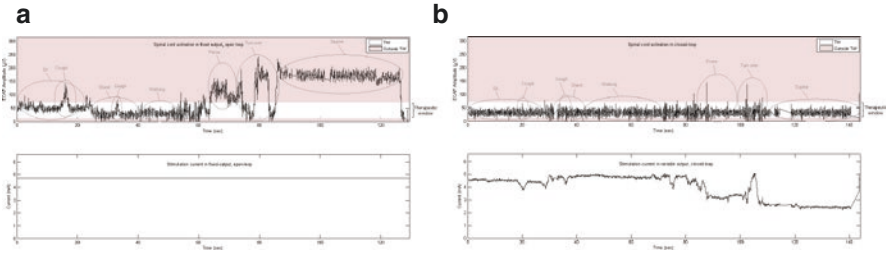

Fig. 11.1 Measured ECAP in the spinal cord in response to fixed-output, open-loop SCS versus variable-output, closed-looped SCS. (**a**) In fixed-output, open-loop stimulation, changes in body position or normal physiologic (i.e., heartbeat, cough) results in variable spinal cord activation (over- and under-stimulation) as measured by variations in ECAP amplitude outside the desired therapeutic window. (**b**) In variable-output, close-loop stimulation, stimulation current is adjusted based on previous ECAP measurements to maintain a target spinal cord activation. TW, therapeutic window; ECAP, evoked compound action potential

fashion, subjects with the same SCS hardware are randomized to receive paresthesia-based, open-loop SCS programming or paresthesia-based, targeted ECAP closed-loop SCS settings. Target ECAPs are personalized to each individual by titrating spinal cord activation in response to patient feedback. The result of the clinical trial suggests the closed-loop group to be superior to the open-loop group with regard to many outcomes: the number of responders with 50% or greater reduction in pain, improvements in pain intensity, functional disability, quality of life and sleep, patient satisfaction and decrease in opioid usage [40]. The findings are sustained through the 12-month follow-up. The responder rates with the closed-loop system is among the highest of all the randomized control trials of spinal cord stimulation [26, 40, 43, 44].

Closed-loop technology is spearheading the next frontier in spinal cord stimulation. It is able to achieve the highest efficacy and response rates by keeping the ECAP within a target therapeutic window more than 80% of the time [40, 42]. Whether targeting an optimal spinal cord response can address therapy habituation is yet to be determined with longer follow-up periods. The findings in chronic back and/or leg pain are promising for translation to the treatment of CRPS—but needs further investigation. Lastly, having the ability to record spinal cord responses presents an opportunity to reexamine the effects of preexisting SCS programs (e.g., high frequency, burst pattern waveforms) on spinal cord activation, and begs the question of whether harmonizing these parameters can produce synergistic improvements to SCS therapy for CRPS and other chronic pain conditions.

Dorsal Root Ganglion Stimulation

Despite the innovations in SCS for treating chronic pain conditions, the lack of precision and inability for selective targeting has prevented successful treatment of focal pain conditions such as CRPS. In addition, SCS complication rates are high, reflecting largely the pragmatic challenges associated with the SCS internal pulse generator and the leads. Furthermore, the loss of therapeutic efficacy plagues the long-term sustainability of SCS therapy; this habituation accounts for the majority of the published explant rates (9–23%) [16, 45]. This has, in part, stimulated interest in exploring the dorsal root ganglia (DRG) as target for neuromodulation, especially for CRPS, which is currently the sole FDA-approved indication for DRGS.

The pseudounipolar primary sensory neurons, spanning from their peripheral receptive fields to the dorsal horn, have a T-shaped split of a single axon that emerges from their soma housed in the DRG. It is well accepted that the DRG is an important site for signal modulation because of highly unique and specialized features like the T-junction (which can filter, enhance, or impede signals from the periphery), and a microenvironment interacting with surrounding satellite glial cells [46–48]. The neuroimmune interface plays an important chemosensory role in responding to nerve injury as well as development of central sensitization and neuropathic pain states [49]. A comprehensive discussion of the neuropathologic changes that occur in the DRG following axonal injury is beyond the scope of the current chapter.

Nevertheless, the DRG is a prime target for selective neuromodulation given its specific anatomic location and its critical function in the nociceptive circuitry.

SCS involves placement of leads in the epidural space to generate an electrical field over the spinal dorsal column. The overall principle behind DRG stimulation is similarly based on the gate theory of transmission, but the site of electrical field application is different. The distinct anatomic approach to the DRG has solved some practical limitations seen in SCS neuromodulation but has introduced its own special considerations. The DRG is enclosed within the dural sheath, surrounded by only a small volume of CSF, which contrasts favorably with SCS, where a thicker CSF layer between the leads and dorsal column acts as an energy sink [50]. The energy required to create an effective electrical field around the DRG is 92.5% less than SCS therapy [51]. This has a desirable impact on the longevity and smaller size of the internal pulse generator. The lead placement involves positioning of the electrodes close to the DRG within the neuroforamen, surrounded by ligaments posteriorly, inferiorly, and superiorly. In theory, this lead stabilization contrasts with SCS, making DRG leads less susceptible to positional changes and potentially reducing likelihood of lead migration; though a better assessment of the incidence of these complications is needed [52, 53]. A retrospective analysis of DRG-related complications, as noted in the FDA database (Manufacturer and User Facility Device Experience) shows lead migration is the most common device-related complication, similar to SCS [46]. Additionally, 9% of all complications reported new neurological symptoms (most commonly, new or worsening radiculopathy), which is not common in SCS. If this is indeed true, it could be unique to the technique of lead placement (steeper angle of approach) or neural tissue compression within the limited neural foraminal space.

Europe approved the stimulation of the DRG as a therapy for chronic pain in 2011, and the United States followed in 2016, after early prospective studies showed efficacy for treatment of a wide variety of chronic pain conditions such as postlaminectomy syndrome, thoracic and lower extremity neuropathy, postherpetic neuralgia, phantom limb pain, and CRPS [54–56]. This was promising because some of these conditions, such as axial low back pain, groin or perineum pain, phantom limb pain, and CRPS, have been underserved with SCS therapy [56–59]. The first direct head-to-head comparison between conventional SCS and the emerging DRG techniques for the treatment of CRPS came with the landmark ACCURATE trial, which was a prospective, randomized controlled, multi-site non-inferiority study ($N = 152$) [60]. The results, however, ended up meeting criteria for superiority when the DRG arm noted greater pain relief and treatment success throughout the 12-month follow-up. Additionally, the DRG group reported higher quality-of-life and mood, less positional effect on paresthesia intensity, and better stimulation specificity to the pain areas. Subsequently, a systematic analysis of evidence by the Neuromodulation Appropriateness Consensus Committee (NACC) led to the strong consensus (level I) recommendation on the use of DRG for focal neuropathic pain and CRPS (type I or type II) of lower extremity [61].

Habituation to therapy is a known treatment-limiting complication of dorsal column stimulation. Loss of therapeutic effect secondary to presumed habituation is

the most common cause for hardware removal, seen in 41% of all explants [16]. The median time until explant in a retrospective study of 234 patients was 19.6 months. Can targeting the DRG circumvent the development of therapy habituation? A recent substudy of the ACCURATE trial attempted to answer this question by comparing the percentage pain relief (PPR) over time in the DRG versus SCS arms in a modified intention-to-treat analysis [62]. In comparison to the trial stimulation period, a drop in PPR at 1 month after permanent implant was seen in both DRG (82–70%) and SCS (77–67%) groups. However, the DRG arm did not see any further drops in PPR over the remaining duration of the 12 months while the SCS arm continued to see a decline in pain relief (77–58% at 12 months). This underpowered, retrospective, nonblinded substudy has several important limitations; but it does lend support to DRG stimulation potentially maintaining therapy efficacy over time. However, given that therapy habituation typically occurs 2–3 years after SCS treatment, appropriately powered studies with longer follow-up periods to examine the sustainability of DRG therapy is needed to better address the critical questions regarding habituation [5].

Despite the promising results from the ACCURATE trial and other studies discussed previously, DRG stimulation for treatment of CRPS currently has significant limitations, the most important being the paucity of evidence for the safety and efficacy in upper extremity pain conditions. This is largely due to anatomic challenges associated with lead and generator placement. Cervical and high thoracic DRG implantation can be challenging due anatomic challenges to access the epidural and DRG space, the limited neuroforaminal space, and the presence of critical vascular supplies to name a few. Cervical lead placement incurs the same risks as cervical transforaminal procedures such as the potential for vascular injury or spasm to reticular and cervical arteries resulting in devastating neurologic consequences. Also, the cervical spine may be prone to lead dislocation due to high mobility. Current FDA approval for DRG stimulation therapy in the United States is limited to lead placement between T10 and S2 spinal levels, though no such anatomic restriction exists in many other parts of the world. Some recent small and largely uncontrolled studies illustrate that DRG stimulation may be safe and effective for upper extremity chronic pain conditions including CRPS [63–65]. The overall complication rate ranges from none to very low. In a cohort study of patients who underwent cervical/upper thoracic DRG placement ($N = 20$), one patient reported transient paresis of the arm and hand with spontaneous eventual resolution. Of interest in this study, five patients in the cohort underwent DRG implantation for cervicothoracic CRPS, all of them endorsed >50% pain relief at 3-month follow-up compared to baseline [3]. However, until we have better safety and efficacy studies, adaptation of DRG for upper extremity CRPS remains an emerging area for innovation with great promise.

In summary, DRG stimulation can be superior to conventional SCS for lower extremity CRPS. Further iterations of this technology will likely herald improvements in clinical outcome. Just as innovations in refining the electrical field and stimulation parameters in SCS have led to improved clinical results, there is great curiosity to see how refining of the DRG electrical stimulus can impact the

modulation of chronic pain. In preclinical rat models of peripheral diabetic neuropathy, burst and conventional stimulation of the DRG were equally efficacious in reversing mechanical hypersensitivity [66]. Interestingly, a residual benefit on mechanical hypersensitivity was seen up to 15 minutes after cessation of burst DRG stimulation, which was not reported in conventional DRG stimulation. The findings above support the hypothesis of distinct neuromodulatory effects of burst pattern stimulation on the DRG target [67]. As seen in the SCS industry, incremental hardware improvements over the last 50 years have resulted in smaller batteries, introduction of wireless connectivity, and broader MRI compatibility, among others. Similar technologic innovations are welcomed in DRG stimulation. Specifically, implementation of safe application of DRG stimulation for upper extremity CRPS. And in line with the push toward demand-based neuromodulation, technical improvements that allow recognition of pain signals (within the DRG) are highly desirable in a move toward a closed-loop circuit and a clinical tool to research chronic pain.

Peripheral Nerve Stimulation

Peripheral nerve stimulation (PNS) is the application of an electric field to a nerve group distal to the DRG or the trigeminal ganglion [22]. The theoretical foundation is again based on the gate control theory. PNS is a treatment option for peripheral neuralgia and type II CRPS (causalgia) [68, 69]. Historically, surgeons performed PNS implantations using an open approach, with a reported success rates between 60% and 80% (based on case series) for the treatment of CRPS [69]. However, due to the complexity of the surgeries and the associated complications, percutaneous approach with leads largely replaced the open surgeries by 1999. It was not until 2016 that the FDA approved a novel PNS system comprising of a small percutaneously implantable tin lead with a small external peripheral pulse generator. Prospective studies demonstrate safety and efficacy of the new PNS technology for chronic neuropathic pain—however, the efficacy for CRPS treatment has yet to be examined [70, 71]. CRPS-related case reports using this novel technology reveal promising outlooks for short-term and sustained efficacy [72–74]. Modernized PNS has the potential to re-emerge as a treatment option for CRPS.

Brain Stimulation

Contemporary brain stimulation for pain relief includes both invasive (deep brain (DBS) and motor cortex stimulation (MCS)) and noninvasive (transcranial magnetic stimulation (TMS)) modalities, although none are currently FDA approved for any pain indication in the United States. In practice, DBS and MCS have been reserved as experimental treatments for refractory pain and are "therapies of last resort," while TMS is often short lived and often used to study basic circuit mechanisms of brain disease or to help identify candidates for MCS. While relatively little

information is available about treating CRPS with DBS, there are relatively more data available regarding MCS and TMS.

Deep Brain Stimulation

The first reported case series using DBS for analgesia targeted the internal capsule in four patients with facial deafferentation pain in 1974 [75]. Since then, over 600 subjects in the literature have undergone DBS for various pain syndromes, most commonly for post-laminectomy syndrome and central pain syndromes [76–79]. Based on the initial identification of key brain circuits involved in somatosensation and opioidergic signaling, historical brain targets for pain DBS have most commonly been the ventral (somatosensory) thalamus (vTh) and periaqueductal gray (PAG), respectively [79]. Few case series include cohorts of patients that carry an explicit diagnosis of CRPS (or the older term reflex sympathetic dystrophy) though it is likely that other tested patients may have met CRPS criteria (e.g., Brachial plexus avulsion, "pain related to accident") [80, 81]. Of the eight identified CRPS patients treated with DBS in the literature, all had leads placed in the vTh and PAG bilaterally. Two of these eight patients were enrolled in a large, unblinded, multicenter, industry sponsored trial in the early 1990s [80], of which only one achieved sufficient relief during an externalized electrode trial to proceed to permanent implant, but no additional data is available on analgesic outcome. Another large case series reported results of DBS targeting vTh (lateral) and PAG in six patients with CRPS II, of which four advanced past the 7-day trial period to obtain permanent DBS implant (by having reported ≥50% pain relief during the trial) [81]. Over a mean follow-up duration of 4.9 years, pain relief with DBS ranged from 50% to 100% on the visual analog scale (VAS) for pain intensity. Of note, all of these patients had previously been failed by SCS therapy. The authors surmised that DBS was effective for CRPS II due to their "rather circumscribed area of pain," though patients were not blinded to treatment. While limited data may point to potential promise of vTh/PAG DBS for CRPS-related pain, comparatively more data are available for motor cortex stimulation.

Motor Cortex Stimulation

Early attempts to provide analgesia with direct somatosensory cortical stimulation failed to provide pain relief [82]. Instead, stimulation of the adjacent primary motor cortex (M1) directly (subdural) or epidurally has shown efficacy for many refractory pain syndromes in small trials [83]. Small case reports using unblinded MCS to treat CRPS I and II of the hand and forearm demonstrated significant analgesia, reduced mechanical and thermal allodynia and improved motor function up to 12 months (longest duration measured) in three subjects [84, 85]. More recently, a small case series in five patients with CRPS demonstrated similar improvements in four of the five patients [86]. These four patients were then tested in a single-blinded

cross-over trial and further demonstrated rapid improvement of pain (70–80% decrease of VAS) and sympathetic dysfunction only days after commencement of stimulation. One further report suggests that MCS could provide significant relief for CRPS even after the development of tolerance to previously successful treatment with SCS [87]. Although the mechanism of action of MCS for analgesia is still controversial, imaging studies point to altered metabolism in the cingulate, orbitofrontal cortex, and sensory thalamus as potential key regulators of the pain response [83, 85]. Despite the lack of mechanistic understanding, MCS remains a viable last-line therapy for CRPS. However, before undergoing invasive treatment with MCS, it is common clinical practice to first demonstrate some analgesic response to motor cortical stimulation using TMS [88].

Transcranial Magnetic Stimulation

TMS involves modulating cortical electrical activity through the application of electric fields that are noninvasively induced by external magnetic fields over the scalp. European consensus recommendations categorize M1 TMS for the treatment of CRPS as Category C, in favor of a possible analgesic affect [88]. Two sham-controlled studies studying the effect of high-frequency repetitive TMS of M1 in 32 patients with CRPS I demonstrated significant pain relief in many patients, though there was a large variability between patient responses [89, 90]. Although analgesic effect of TMS was similarly rapid as MCS (~30 sec), therapeutic effect waned over minutes and was absent 45 minutes after a single session. Even when TMS was repeated daily for 10 days, some subjects showed enduring benefit for up to 3 months, while others lost benefit over hours after stopping stimulation. Predicting which patients may respond to TMS remains uncertain and is an active area of study. Further, TMS for CRPS II has not been studied as extensively as for CRPS I, limiting generalizability.

Ultimately, DBS and MCS may be appropriate therapeutic options for patients with CRPS that have been failed by all other treatments including other forms of neuromodulation. TMS may help to identify appropriate candidates for MCS, before committing to an invasive and currently off-label procedure.

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Treatment Algorithm for Complex Regional Pain Syndrome

12

En Lin Goh, Swathikan Chidambaram, and Daqing Ma

Introduction

Definition and Terminology

Complex regional pain syndrome (CRPS) is a chronic neurological disorder of a body region, usually involving the limbs that is characterized by severe pain associated with sensory, autonomic, motor, and trophic impairment [1, 2]. According to the International Association for the Study of Pain (IASP) consensus definition [3], "CRPS describes an array of painful conditions that are characterized by a continuing (spontaneous and/or evoked) regional pain that is seemingly disproportionate in time or degree to the usual course of any known trauma or other lesions. The pain is regional (not in a specific nerve territory or dermatome) and usually has a distal predominance of abnormal sensory, motor, sudomotor, vasomotor, and/or trophic findings. The syndrome shows variable progression over time."

A variety of alternative names have been used to describe CRPS in the past including reflex sympathetic dystrophy, algodystrophy, causalgia, Sudeck's atrophy, shoulder-hand syndrome, and transient osteoporosis [4, 5]. In current practice, these are

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now grouped under the single heading of CRPS, which can be classified into two subtypes, based on the presence or absence of identifiable nerve injury [3, 4]. CRPS Type I, formerly known as reflex sympathetic dystrophy, refers to patients with CRPS without peripheral nerve injury, while CRPS Type II, formerly known as causalgia, refers to patients with CRPS with peripheral nerve injury. It is estimated that CRPS Type I contributes to approximately 90% of all diagnoses using this classification [3]. Warm and cold subtypes of CRPS are recognized as well [6]. Warm CRPS is characterized by increased skin temperature at the onset of symptoms, whereas cold CRPS is characterized by decreased skin temperature at the onset of symptoms.

In recent years, a new subtype of CRPS, termed CRPS-not otherwise specified (NOS), has become increasingly recognized by clinicians [7]. As a result of the increased specificity and decreased sensitivity of newer diagnostic criteria, approximately 15% of patients previously diagnosed with CRPS would have been without a diagnosis [3, 8]. Thus, a third diagnostic subtype, CRPS-NOS, was recommended to categorize these patients. The aim of this recommendation was to improve the identification of CRPS, without creating a reduced rate of clinical diagnosis that could be harmful to patients and deny them access to treatment [9]. CRPS-NOS can be considered in patients with abnormalities in less than three Budapest symptom categories or two Budapest sign categories if the current clinical features are still felt to be best explained by CRPS [10].

Clinical Presentation

The main symptoms of CRPS are pain, sensory alterations, motor impairment, autonomic disturbance, and trophic changes of the affected limb [11]. Pain is the most prominent and debilitating symptom and is typically described as a continuous burning, stinging, or tearing sensation within the affected limb that is worse at night and exacerbated by movement, touch, temperature, or stress [12, 13]. Often, there are associated sensory changes including allodynia, hyperalgesia, or hypesthesia in the distal aspect of the affected limb [12]. A degree of functional motor impairment is found in a large proportion of patients [12, 13]. This presents as a reduction of complex muscle strength and range of movement, related to pain, edema, or contractures. There may be evidence of central motor manifestations including tremor, myoclonus, or dystonia. Autonomic features such as changes in skin temperature or color, sweating, and edema are commonly reported [11]. Skin color changes occur most frequently (74%), followed by edema (70%) and excessive sweating (40%). The affected limb also displays trophic changes including increased hair growth, changes in nail growth, joint contractures, fibrosis of fascia, and skin atrophy [11].

Early descriptions of CRPS reported three sequential clinical stages of this condition [14–19]. In Stage 1, burning and throbbing pain develops in a limb either with or without an inciting cause, associated with diffuse aching, sensitivity to touch or cold temperature, and localized edema [20]. Stage 2 is characterized by the progression of soft tissue edema, skin and articular soft tissue thickening and muscle

wasting, which occurs over three to 6 months. Stage 3 refers to the most severe stage, with marked limitation of movement of the limb, joint contractures, skin atrophy, nail changes, and demineralization of bone. In recent years, the utility of this concept has been questioned due to the lack of evidence supporting the existence of three discrete stages [9, 21].

Diagnosis and Evaluation

Diagnostic Criteria

CRPS is a clinical diagnosis made based on the findings from the history and physical examination [22]. There should be a high index of suspicion in cases where symptoms develop following limb trauma (within four to 6 weeks), which are no longer fully explained by the inciting event, which affect the distal limb or extend beyond the region involved in the trauma, or which extend outside the territory innervated by a single nerve or nerve root. In 1994, a consensus conference was held by a working group for the IASP to define this condition [1]. This led to the use of CRPS as an officially endorsed term, classification of CRPS into Types I and II, and the development of the first diagnostic criteria for CRPS, known as the Orlando Criteria (Table 12.1) [1, 4]. Further iterations of this diagnostic criteria resulted in the development of the Budapest Criteria in 2003 to improve diagnostic accuracy [2]. Compared to the Orlando Criteria, the Budapest Criteria have demonstrated comparable sensitivity and greater specificity in differentiating between CRPS and other forms of neuropathic pain, with an estimated sensitivity and specificity of 82% and 68%, respectively [2, 13].

Investigations

There is no gold standard investigation to confirm the diagnosis of CRPS. However, some investigations are useful adjuncts in the diagnostic workup of patients, especially in cases of diagnostic uncertainty.

Plain radiographs can demonstrate marked demineralization of bone in the affected limb that may worsen in severity as the disease progresses [9, 11]. This usually starts at the ends of the bones and gradually becomes more homogeneous. The sensitivity of this finding remains very low [11]. Imaging of both hands on the same radiograph is recommended to identify areas of bone demineralization of the affected hand, which is supportive of the diagnosis. Three-phase bone scintigraphy has demonstrated utility in diagnosing CRPS, especially in the early stage of disease, with positive findings noted in up to 90% of patients [11, 23]. When performed within the first 5 months following the onset of symptoms, increased radiotracer uptake in the articular and periarticular structures of the affected limb during the third phase is supportive of the diagnosis. It must be noted that a negative test does

Table 12.1 Orlando and Budapest clinical diagnostic criteria for complex regional pain syndrome (CRPS)

Orlando criteria	Budapest criteria
1. The presence of an initiating noxious event or a cause of immobilization 2. Continuing pain, allodynia, or hyperalgesia in which the pain is disproportionate to any known inciting event 3. Evidence at some time of edema, changes in skin blood flow, or abnormal sudomotor activity in the region or pain (can be a sign or a symptom) 4. Excludes the existence of other conditions that would otherwise account for the degree of pain and dysfunction	1. Continuing pain, which is disproportionate to any inciting event 2. Must report at least one symptom in three of the four following categories: Sensory – Reports of hyperesthesia and/or allodynia Vasomotor – Reports of temperature asymmetry and/or skin color changes and/or skin color asymmetry Sudomotor/edema – Reports of edema and/or sweating changes and/or sweating asymmetry Motor/trophic – Reports of decreased range of motion and/or motor dysfunction (weakness, tremor, dystonia) and/or trophic changes (hair, nail, skin) 3. Must display at least one sign at time of evaluation in two or more of the following categories: Sensory – Evidence of hyperalgesia (to pinprick) and/or allodynia (to light touch and/or temperature sensation and/or deep somatic pressure and/or joint movement) Vasomotor – Evidence of temperature asymmetry (>1 °C) and/or skin color changes and/or asymmetry. Sudomotor/edema – Evidence of edema and/or sweating changes and/or sweating asymmetry Motor/trophic – Evidence of decreased range of motion and/or motor dysfunction (weakness, tremor, dystonia) and/or trophic changes (hair, nail, skin) 4. No other diagnosis better explains the signs and symptoms

not rule out the diagnosis of CRPS. In the later stages of the disease, bone scintigraphy may be normal but plain radiographs will demonstrate profound bone demineralization in the affected limb.

Autonomic tests have been used as part of the diagnostic work-up for patients with CRPS [24]. These include resting sweat output (RSO), resting skin temperature (RST), and quantitative sudomotor axon reflex test (QSART).

Epidemiology

Incidence and Risk Factors

In 2003, when the first population-based study on CRPS was conducted, the incidence rate of CRPS Type I was estimated at 5.46 per 100,000 person-years, and the incidence rate of CRPS type II was 0.82 per 100,000 person-years, giving rise to a combined incidence rate for both CRPS Types I and II of 6.28 per 100,000 person-years [25]. A subsequent population-based study estimated the combined incidence

rate of CRPS to be approximately four times greater at 26.2 per 100,000 person-years [26]. Such variations in the incidence of CRPS can be attributed to differences in socio-economic background and diagnostic criteria used. CRPS occurs most frequently in individuals aged between 61 and 70 years and affects females three times more than males [26]. There appears to be an increased preponderance for the upper limbs with a ratio of 3:2 compared to the lower limbs. Several risk factors have been identified including menopause; heavy smoking history; history of migraine, osteoporosis, asthma, angiotensin-converting enzyme (ACE) inhibitor therapy; and elevated intra-cast pressure due to a tight case or extreme positions [27–30].

Surgery

Surgery is commonly cited as an inciting event for CRPS and can complicate post-operative recovery. Operative procedures of the shoulder, distal radius, carpal tunnel, and Dupuytren's contracture have been reported to be associated with the manifestation of CRPS. The incidence of CRPS following shoulder, distal radius, carpal tunnel, and Dupuytren's contracture surgery is estimated to be between 0.9 and 11%, 22–39%, 2– 5%, and 4.5–40%, respectively [31–39]. Compared to upper limbs, CRPS is reported less frequently in operations of the lower limbs. In a prospective study of patients with tibial fractures, the incidence of CRPS following surgical repair was documented at 31%; 33.3% of patients treated with intramedullary nailing, 28.6% of patients treated with nails and screws, and 28.6% of patients treated with external fixation [40]. In another retrospective study, the incidence of CRPS Type I and II in patients undergoing elective ankle and foot surgery was reported at 3.6% and 1.8%, respectively, giving an overall incidence of 4.4% [41]. The major limitation in these data is the small cohort sizes and high susceptibility to a type I error due to the lack of gold standard diagnostic criteria.

Fracture

Fractures appear to be a common inciting event for the development of CRPS. The overall incidence of CRPS Type I 1 year after a fracture in a study was 7.0, with 15.2% of cases occurring after ankle fracture, 2.9% following fifth metatarsal fracture, and 7.9% after wrist fracture [42]. In contrast to fractures of the upper extremity, there is limited evidence regarding the incidence of CRPS following fractures of the lower extremity. Furthermore, there is wide variation in the reported incidence, mainly due to inconsistencies in the diagnostic criteria used. For instance, the development of CRPS following fractures of the distal radius is reported to range between 1 and 37% [40, 42–46]. Moreover, data available from these studies have been limited solely to CRPS Type I, and as such, more work is needed to elucidate the incidence of CRPS Type II.

Pathophysiology

The acute phase of CRPS is proposed to be an exaggerated inflammatory response to trauma, involving central and peripheral sensitization. Repetitive episodes of these processes lead to abnormally increased pain sensations as well as misinterpretation of normal somatosensory stimuli as pain stimuli, leading to allodynia and hyperalgesia. The pathophysiology of CRPS is still poorly understood; however, there is evidence to support the proposed underlying mechanisms.

Inflammation

The acute phase of CRPS presents with the cardinal signs of inflammation including pain, edema, erythema, warmth in the affected area, and impaired function [47]. Typically, in response to tissue trauma, there is activation of the inflammatory pathways that results in the production of pro-inflammatory cytokines such as interleukin(IL)-1β, IL-2, IL-6, and tumor necrosis factor-α (TNF-α) along with neuropeptides including calcitonin gene-related peptide, bradykinin, and substance P [48]. These cause increased plasma extravasation and vasodilation, producing the characteristic features of acute CRPS [49, 50]. Studies aimed at characterizing the inflammatory profile of acute CRPS have identified raised levels of pro-inflammatory cytokines. Similar mechanisms can also be seen underlying chronic CRPS. Recent meta-analyses have shown a pro-inflammatory drive, especially involving cytokines such as IL-1 and IL-6 [48]. However, these studies also show that the inflammatory profile is different between patients at different stages of the condition, suggesting that inflammatory pathways must evolve with duration and severity. Hence, it is evident that there is an inflammatory component in the etiology of acute CRPS.

Central and Peripheral Sensitization

Following tissue damage and/or neuronal injury, alterations in the central and peripheral nervous systems lead to increased inflammation and enhanced responsiveness to pain. In the central nervous system (CNS), persistent and intense noxious input from peripheral nociceptive neurons increases the excitability of nociceptive neurons in the spinal cord, namely, central sensitization [51]. The release of neuropeptides such as substance P, bradykinin, and glutamate by the peripheral terminals of sensory nerve fibers in the skin, muscle, and joints sensitize and increase the activity of local peripheral and secondary central nociceptive neurons resulting in increased pain from noxious stimuli (hyperalgesia) and pain in response to non-noxious stimuli (allodynia) [51, 52]. Within the spinal cord, the neurons display greater excitability by repeated brief non-noxious stimuli at a comparable rate to noxious stimuli [53]. Often, this phenomenon is seen preferentially in neurons innervating the CRPS-affected limb compared to the unaffected limb [54, 55].

In most patients, central sensitization results in the peripheral sensitization of tissue, but at times, the initial trauma can result in peripheral sensitization directly through the localized release of neuropeptides such as substance P and bradykinin [49]. Neuropeptides not only increase the activity of nociceptors at baseline but also exaggerate their response to nociceptive input, resulting in hyperalgesia [49, 56, 57]. Neuropeptides also decrease the firing threshold for thermal and nociceptive input, leading to allodynia [58]. Together, this leads to the classical symptoms that CRPS patients exhibit. Thus, central and peripheral sensitization are important mechanisms underlying the pathophysiology of CRPS.

Altered Cutaneous Innervation

Initial neuronal injury, however, imperceptible has been implicated as an important trigger in the development of both CRPS Types I and II [50, 59]. Compared to the unaffected limb, there is usually a reduction in C-type and Aδ-type cutaneous afferent neuron fiber density in the CRPS-affected limb, specifically within the nociceptive fibers [59, 60]. There is also abnormal innervation of hair follicles and sweat glands in the skin among patients with reduced nociceptive fiber density [60]. The altered function of these nerve fibers may account for the hyperalgesia seen in these patients. One animal study in rats has shown a causal relationship between the neuronal trigger caused by trauma and a reduction in neuron fiber density, highlighting the possibility that altered cutaneous innervation of the CRPS-affected limbs may be a result of an initial neuronal injury [61]. Human studies, however, have been unable to replicate this causative effect, thus, suggesting that the reduction in neuron fiber density may be an epiphenomenon.

Altered Sympathetic Nervous System Function

Traditionally, CRPS was thought to be a result of an overdriven sympathetic nervous system (SNS) [62]. Indeed, symptoms such as peripheral cyanosis and sweating seen in chronic CRPS are due to peripheral vasoconstriction that is mediated by the SNS [63]. However, recent evidence has suggested that the mechanism is less direct than proposed, and a coupling between sympathetic and afferent pathways that maintains the pain symptoms in CRPS [64].

In normal physiology, there is little communication between sympathetic and peripheral afferent nociceptive neurons, so it cannot be that the SNS is responsible for the pain symptoms. However, animal studies have suggested that adrenergic receptor expression on nociceptive fibers following nerve trauma leads to sympathetically induced pain [65]. Similar findings were seen in patients with sympathetically mediated CRPS pain where high sympathetic nervous system activity increased spontaneous pain by 22% and increased the spatial extent of dynamic and punctate hyperalgesia by 42 and 27% respectively [66]. In addition, there is a reduction in circulating catecholamines such as noradrenaline in the CRPS-affected limb

compared to the unaffected limb [67]. This reduction causes negative feedback compensatory upregulation of peripheral adrenergic receptors and super-sensitivity to circulating catecholamines, as is supported by laboratory work showing increased transcription of a_2-receptors in the dorsal root ganglion in rat models of CRPS [68]. Taken together, the generation of SNS receptors on nociceptive fibers and increased catecholamines imply a coupling between both systems that maintain the pain symptoms seen in CRPS.

Autoimmunity

Initial evidence for an autoimmune component emerged when patients treated with intravenous immunoglobulins (IVIG) showed improvement in CRPS symptoms. This observation was further strengthened in a small randomized clinical trial (RCT) involving IVIG and another study involving plasma exchange therapy [69, 70]. The presence of immunoglobulin G (IgG) autoantibodies against surface antigens on autonomic neurons in the serum of patients with CRPS suggests that autoimmunity may play a role in the development of this condition [71, 72]. Passive transfer of IgG from CRPS patients to healthy mice led to the development of CRPS symptoms [73]. Unlike other peripheral neuropathies, immunohistochemical techniques and cytometric analysis have identified the generation of autoantibodies against alpha-1 and beta-2-adrenergic receptors in CRPS models [71]. Many patients with CRPS often have IgM and IgG profiles consistent with previous infections with Campylobacter, Chlamydia, and Parvovirus, suggesting an element of cross-reactivity from antibodies generated against these pathogens similar to the antigenic mimicry seen in Guillian-Barre syndrome, systemic lupus erythematosus, and Sjogren's syndrome [74, 75].

A major limitation of the autoimmune theory was that regional symptoms classically seen in CRPS could not be explained by ubiquitous immunoglobulins present throughout the serum. Recently, mouse models of fractures and cast immobilization, immunoglobulins, and Langerhans cells were more prevalent in ipsilateral limbs [76]. This has given rise to the concept of regional autoimmunity. In CRPS, not only could new antigens be selectively expressed in affected tissues, there may also be post-translational modification of existing proteins leading to a compartmentalization of the tissues affected [77]. The accumulation of immunoglobulins in the ipsilateral limb in the fracture/immobilization mouse model is dependent on NK1 receptor signaling, suggesting an element of neural control [77]. Further work is necessary to fully delineate the underlying mechanisms of regional autoimmunity.

Brain Plasticity

Brain plasticity has been widely reported in CRPS, and studies have shown changes in brain patterns with duration and severity of symptoms. Compared to patients with late CRPS, early stages of CRPS are associated with greater disruption in motor

control regulators and reduced perfusion in the somatosensory cortex, limbic system, and regions involved in spatial body perception suggesting that brain plasticity is a more active process in the early stages of CRPS [78]. Neuroimaging has identified a decrease in the area representing the CRPS-affected limb in the somatosensory cortex compared to the unaffected limb, indicating a lesser sensory representation of the affected limb on the Penfield homunculus [79, 80]. Previously, the degree of reorganization was shown to correlate with the severity of pain symptoms. However, recent studies demonstrated that the brain patterns are actually preserved and attributed the findings of former work to the low resolution of neuroimaging available [81]. Conversely, other studies have shown the normalization of these changes, if CRPS is successfully treated [1, 82]. Graded motor imagery is an example of effective therapeutic intervention that relies on rewiring the networks in CRPS. Further work is necessary to refute these contradictory findings.

Genetic Factors

Genetic factors have been proposed to contribute to CRPS, although there is a lack of consensus on the exact genes involved. Much of the evidence for this stems from family studies of patients with CRPS. Siblings of CRPS patients under 50 years were found to have a threefold increase in the risk of developing the condition [83]. One case study illustrated an association between CRPS and mitochondrial disease in seven families, suggesting a maternal inheritance pattern [83, 84]. The genes of the major histocompatibility complex encoding the human leukocyte antigen (HLA) molecules, HLA-B62 and HLA-DQ8 alleles, were found to strongly correlate with the development of CRPS [85]. Polymorphisms in inflammatory cytokines such as TNF-alpha and adrenergic receptors have also been identified in some CRPS patients [86–88]. A major limitation of work evaluating the genetic contribution to CRPS is the small sample size, which decreases the strength of any probable associations. Thus, while studies have provided evidence to recognize the genetic contribution to CRPS, further work involving genome-wide association studies may identify individual genetic associations [86].

Psychological Factors

In the past, symptoms of CRPS have been categorized as psychogenic. Although studies have uncovered the aforementioned pathological mechanisms, the role of psychological factors is still immense. Any psychiatric input that increases the release of catecholamines, including anxiety and depression, can lead to CRPS symptoms. The incidence of CRPS after trauma is higher in patients with preexisting psychological and/or psychiatric illness [89]. Conversely, there is a huge negative impact on the mental health of CRPS patients, with higher occurrence of anxiety, depression, and body-image concerns, which may, in turn, result in a vicious cycle that can exacerbate CRPS symptoms [90].

Management

The management of CRPS is usually symptomatic and can be carried out in primary and subspecialty care involving a multi-disciplinary team. Broadly, this involves physiotherapy; analgesia and anesthesia; interventional procedures; and psychological therapy. Treatment should be guided by the severity of symptoms and response to treatment.

Physiotherapy

Physiotherapy and occupational therapy are recommended for all patients with CRPS as the first-line treatment for mild CRPS. Engaging in physiotherapy can improve pain and functioning as well as help patients overcome the fear of pain. The program must be tailored to each patient and may involve elevation, massage, contrast baths, transcutaneous electrical nerve stimulation, gentle range of motion, isometric strengthening exercise, and stress loading of the affected limb. There may be a role for graded motor imagery and mirror therapy in reducing neuropathic pain and improving two-point sensation in the affected limb [91]. One review by the Cochrane collaboration reported a paucity of high-quality data supporting the effectiveness of physiotherapy based on eighteen clinical trials [92]. There are also no clear positive data on the effectiveness of multimodal physiotherapy, electrotherapy, and manual lymphatic drainage for treating CRPS. Further research to determine the effectiveness of these conservative therapies is needed.

Psychological Therapy

CRPS is a chronic condition that places a huge emotional and psychological burden on patients and dramatically impacts their quality of life [93]. Hence, psychological support is an important component to multi-disciplinary management [94]. This is especially important since some patients may also have concomitant psychiatric conditions, including major depression, generalized anxiety disorder, and post-traumatic stress disorder. Psychological therapies may include cognitive behavioral therapy, relaxation skills, and biofeedback. Graded-exposure treatment can help manage fear-triggering situations and stimuli. This involves gradually exposing the patient to such situations so that they develop resilience. The efficacy of graded exposure therapy in reducing pain and improving function has been concluded in a large case series as well as small single-center RCT [95]. Further work is necessary in evaluating the direct effect of other psychological therapies on CRPS.

Medical Management

There are a range of pharmaceutical treatments that are currently used in clinical practice. Non-steroidal anti-inflammatory drugs (NSAIDs) and corticosteroids are commonly used to reduce inflammation. Steroids have shown significant improvements in pain and functionality in the affected limb in case series and RCTs. However, this beneficial effect is not seen in all patients, which may be attributable to the heterogeneous and multifactorial nature of the condition [96–101]. Although both NSAIDs and corticosteroids work in the same way of reducing inflammation, studies have shown that NSAIDS do not show a similar clinical benefit.

Opioid therapy is useful in the acute phase of tissue injury, although long-term use for both peripheral and central neuropathic pain is less efficacious and requires larger doses [102]. The long-term use of these agents should be carefully weighed up due to the risks of tolerance, addiction, and overdoses leading to death.

Tricyclic antidepressants (TCAs) such as amitriptyline and antiepileptics including gabapentin or pregabalin have demonstrated effectiveness in managing chronic pain syndromes that have a neuropathic component [103–105]. Despite their effectiveness, TCAs exhibit a wide range of adverse effects and are dangerous in overdose compared to the latter two agents. Studies investigating the efficacy of gabapentin in CRPS Type I have reported marked improvements in pain reduction and long-term sensory deficits [106]. However, there are no data evaluating its long-term safety and efficacy profiles with adequate follow-up of patients treated with gabapentin. Similarly, pregabalin is effective in managing pain associated with diabetic neuropathy and post-herpetic neuralgia but its use in CRPS has been anecdotal so far. A discussion with patients regarding the benefits and risks of using these agents in managing the pain associated with CRPS should take place due to the possibility of experiencing adverse effects without any therapeutic benefit.

In other studies, the NMDA antagonist ketamine was shown to alleviate pain and induce complete remission in treatment-resistant patients, possibly through central sensitization and neuroplasticity [107, 108]. However, patients have reported side effects commonly seen with ketamine use, including nausea, vomiting, headaches, and psychomimetic effects [109]. Some studies have been devoted to identifying the use of adrenergic receptor antagonists or alpha-2 adrenergic agonists to reduce sympathetically mediated pain in CRPS. For example, phenoxybenzamine has shown promising results in pain remission in the acute stage while clonidine has led to reduction in localized hyperalgesia [110, 111]. In managing chronic CRPS, medications such as nifedipine and baclofen have been shown to be effective, especially if combined with other strategies such as neuromodulation [112–114]. However, these observations are based on case series with small cohort sizes that will need stronger evidence with more rigorous methodology.

The inflammatory process underlying CRPS has been shown to generate free radical oxygen species, and this led to the use of antioxidants such as vitamin C and dimethyl sulfoxide to treat CRPS [115–117]. So far, vitamin C has been established as the most efficacious preventative therapy for the development of CRPS and is commonly used perioperatively following extremity surgery [118, 119].

Surgical Management

There are several surgical options that are typically reserved for patients with disease not responding to medical management. These include neuromodulation, sympathectomy, and amputation of the affected limb.

Of these, neuromodulation techniques such as spinal cord stimulation (SCS) combined with physiotherapy have been shown to be superior to physiotherapy on its own at 6 months and 2 years, although this effectiveness diminished after a long-term follow-up of 5 years [120]. Although SCS can improve functionality and pain symptoms, possible complications include lead displacement, pulse-generator pocket revision, pulse-generator failure, and infection [121–123].

Sympathectomy is another technique that can be used to manage CRPS. The responsible sympathetic chai, such as the stellate ganglion, may be lysed using chemicals, ablated with radiofrequency or resected surgically. Compared to chemical sympathectomy which has variable effectiveness, radiofrequency sympathectomy provides analgesia for a longer time period [124, 125]. However, complications that can result include neuralgia, anhidrosis, and Horner's syndrome, and given that it is a permanent procedure, it should be only considered when other treatment options have failed.

In some cases, amputation of the affected limb may be indicated due to pain, limb dysfunction, gangrene, infection, or ulcers [126]. While this may reduce the pain experienced and improve mobility, phantom pain and recurrence in the residual limb are possible. Hence, this should be a last resort option reserved for a few extreme cases [127].

Novel Therapeutic Approaches

A major field of research will be harnessing immune modulators in treating CRPS. Recent work has established an autoimmune component to CRPS, which serves as the basis for using intravenous immunoglobulin (IVIG). However, there have been mixed results and this can be attributed to methodological differences. For example, one RCT of 13 patients with chronic CRPS showed adequate pain relief in 12 patients after 6–19 days after treatment [69]. However, the recent low-dose intravenous immunoglobulin treatment for long-standing complex regional pain syndrome (LIPS) trial showed no benefit in moderate to severe chronic

CRPS. This lack of benefit may largely be due to its patient selection, cohort size, and inadequate power to detect subgroup differences [128]. In other autoimmune conditions, plasma exchange therapy which removes the antibodies generating the disease process has been very useful, specifically in conditions such as Guillain-Barre syndrome. A retrospective analysis has extended this to CRPS and shown that 91% of patients reported a significant median pain reduction of 64% following therapy, thus supporting larger large, randomized placebo-controlled trials to validate this finding [70].

The role of inflammatory mechanisms in CRPS is well-established and has been reviewed extensively [22]. Consequently, this has led to studies exploring the use of immunotherapy targeting specific cytokines albeit, with mixed results. One study reported pain relief in one-third of the participants within 4–6 weeks of starting them on thalidomide [129]. However, another phase IIb trial evaluating lenalidomide showed no added benefit [130]. Nevertheless, this could be attributed to methodological differences between the studies that are very similar to the varied results obtained with IVIG therapy. Furthermore, when used in other medical conditions, immunotherapies are often only applicable to selected populations within a disease category, and this may be true for the CRPS population as well. This raises the need for further studies evaluating patient characteristics that may make immunotherapy more suitable for specific patient groups.

Treatment Algorithm

Based on the various treatment modalities discussed, we propose the following treatment algorithm for patients presenting with clinical features suggestive of CRPS (Fig. 12.1). Following confirmation of the diagnosis, patients should be stratified according to the severity of symptoms to guide the management setting. Patients with mild to moderate symptoms can be safely managed in primary care or the community, while those with moderate to severe symptoms should be referred to a pain service for multidisciplinary team assessment. All patients should receive education and support on their diagnosis and prognosis and a combination of physiotherapy, occupational therapy, and simple analgesia with NSAIDs or weak opioids. Treatments for neuropathic pain such as amitriptyline, gabapentin, or pregabalin should be considered in patients in whom the analgesic response cannot be sustained or is inadequate. Psychological therapy should be offered as a subset of patients may benefit from this. Patients managed in the community should be referred early to a pain service if they experience treatment failure or unacceptable treatment response. These patients, in addition to those with moderate to severe symptoms, should receive CRPS-specific rehabilitation such as graded motor imagery delivered at CRPS rehabilitation centers. Patients resistant to combined treatment modalities can be considered for surgical review, albeit with the involvement of the multidisciplinary team in the discussion.

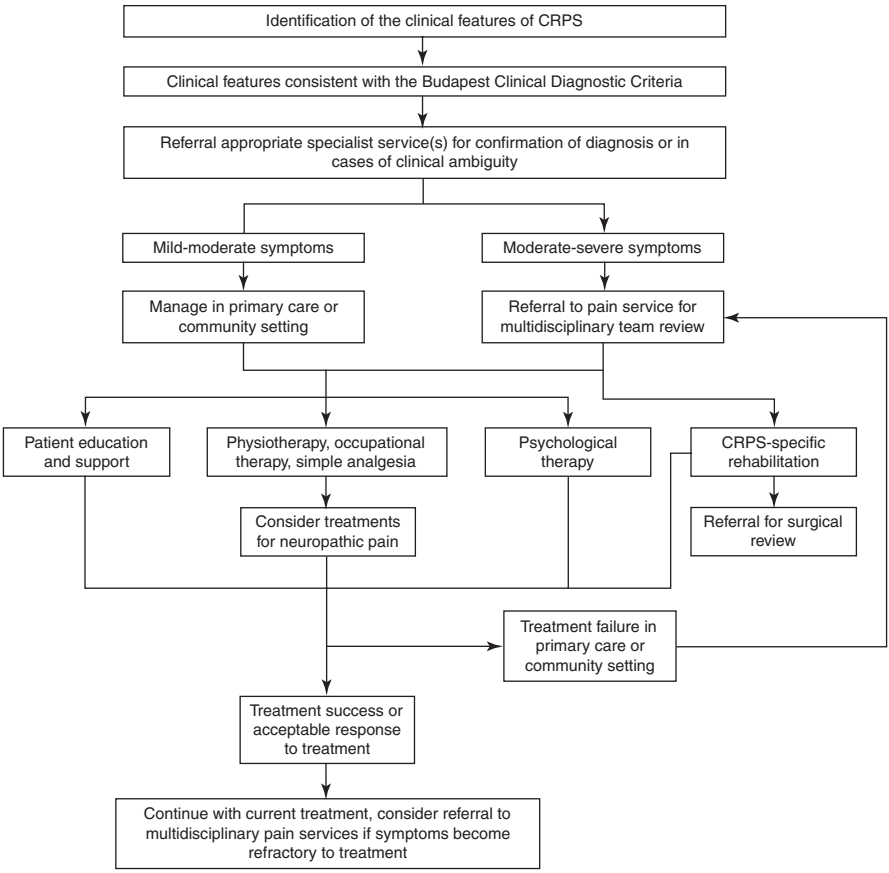

Fig. 12.1 Treatment algorithm for complex regional pain syndrome (CRPS)

Conclusion

The pathophysiology of CRPS is complex and multifactorial, involving localized inflammation; altered central and peripheral sensitization; and autoimmunity. Despite recent advancements, it remains poorly understood to an extent where guidelines can be established to inform clinical practice. Hence, management is largely carried out based on a trial and error approach, and has been successful in providing control of the condition in several cases. Existing work supporting and refuting conventional therapies tends to be case series or small cohort studies that have produced conflicting results. Continued work to better understand the complex mechanisms underlying CRPS will ultimately lead to the development of better therapies.

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Part III

Special Considerations in CRPS

Children and Adolescents with CRPS

13

Joshua Lee and Shalini Shah

Background

It is a guiding adage in pediatrics that "Children are not small adults." This is also true in cases of pediatric complex regional pain syndrome (CRPS). This chapter highlights where pediatric CRPS differs from adult CRPS, based on the growing body of pediatric CRPS research.

Epidemiology

CRPS was previously thought to be extremely rare in children [1]. Case reports in the 1970s and 1980s brought greater awareness of pediatric CRPS to the medical community [2–9]. CRPS is more likely to affect adolescent females, with the average age range being 12–13 [10–12]. There is also a female predominance in adult CRPS patients; however, the female predominance in pediatric CRPS appears to be higher [13, 14]. Incidence data on CRPS are limited in adults, and even more scarce in kids.

The incidence of CRPS in adults was found to be 5.5 per 100,000 in Olmsted County, Minnesota, and 26.2 per 100,000 in the Netherlands [15, 16]. Using subset analysis on this data, the incidence of CRPS in pediatric patients was estimated to be 1.58 per 100,000 in Minnesota and 5.2 per 100,000 in the Netherlands [17]. Abu-Arafeh and Abu-Arafeh studied the incidence of CRPS in children in Scotland based on the voluntary reporting of general pediatricians and pediatric subspecialists. They estimate the incidence of pediatric CRPS to be 1.2 per 100,000. As these

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data depend on voluntary reporting by physicians, it is likely an underestimate. To our knowledge, this is the only epidemiological study to be published to date specifically studying the incidence of pediatric CRPS. Of the 26 cases of CRPS reported, only 1 was a case of CRPS type 2 (3.8%) [17]. This is similar to the adult data shown in the study by de Mos et al. in which 2.9% of the patients had CRPS type 2 [16].

Etiology and Pathogenesis

A clear mechanism of how CRPS develops is still not well understood. In adult literature, it is generally accepted that CRPS develops as a result of a combination of pathologic processes involving nerve injury, abnormal central and peripheral nervous system sensitization, autonomic dysregulation, inflammation, and autoimmunity [18, 19]. The clinical features of CRPS in pediatrics differ from those in adults and children typically have a better prognosis, which may suggest a different pathophysiological mechanism. However, it may be that the differences in clinical presentation are due to unique environmental, endocrine, and developmental factors in children [20]. The high treatment success rate in children with CRPS relative to adults has been attributed to greater brain plasticity [21]. Wilder has argued that CRPS in children is not intrinsically different from CRPS in adults, and that the apparent better outcomes are due to children's greater willingness to participate in appropriate physical therapy [22].

fMRI Data

Though there are very few pediatric studies on the pathogenesis of CRPS, the P.A.I.N. group at Boston Children's Hospital has published multiple studies using functional MRI data from pediatric CRPS patients. Given that pediatric CRPS patients tend to have a quicker recovery, they were able to obtain fMRI images of CRPS patients before they were treated and after they had treatment leading to symptomatic recovery. They found that pediatric CRPS patients exposed to stimuli which evoke mechanical or cold allodynia activate CNS patterns which are similar to those which are seen in adults. In addition, BOLD (blood oxygen level dependent) changes were found in brain areas that possibly correlate with non-pain CRPS symptoms found in adults, such as hemi-inattention, altered cognition, and movement disorders. They also noted that differences in CNS activation persisted even after patients were treated and they no longer had painful symptoms. This evidence suggests that pediatric and adult CRPS may have similar underlying mechanisms, and that CNS changes can persist in children even after symptomatic recovery [23].

The same group later analyzed the same data looking at functional connectivity between brain regions (compared to functional activation previously studied), and found brain alterations in the cortical, limbic, and basal ganglia systems that

persisted even after symptomatic recovery [24]. In adult patients with CRPS, alterations in functional connectivity have also been found [25].

The P.A.I.N. group also studied functional resting-state connectivity of the habenula in pediatric CRPS using fMRI images. They found that compared to controls, pediatric patients with CRPS had decreased habenula resting-state functional connectivity to brain areas that have been associated with motor, affective, cognitive, and pain regulatory processes, and this may be associated with CRPS symptoms [26]. The habenula has been shown to be activated in response to acute pain in adult subjects [27].

This group also used fMRI images to study brain resting state networks in pediatric CRPS patients. They found that pediatric CRPS patients have differences in resting-state networks compared to controls, and that these differences are reversible with treatment. They also noted differences between adult and pediatric patients. Whereas adult CRPS patients compared to controls had reduced connectivity of the default mode network, in pediatric patients it was increased. In addition, in adult CRPS patients, the frontoparietal network had increased connectivity whereas in pediatric patients, the left frontoparietal network had reduced connectivity. These differences may be explained by differences in development, treatments, and disease duration from children to adults [28].

In addition, the P.A.I.N. group showed pediatric patients with CRPS also have structural brain changes. Pediatric patients with CRPS were found to have decreased gray matter in various brain regions, and gray matter increased after treatment. Gray matter alterations have also been found in adult CRPS patients; however, these changes did not always correlate with the changes found in the pediatric patients in this study. The differences were attributed to differences in duration of symptoms and medication use between adult and pediatric CRPS patients, as well as the higher plasticity of the pediatric brain [21].

Genetics

There have been several studies that suggest a genetic predisposition to CRPS, though specific genes or inheritance patterns have not clearly been identified. Higashimoto et al. identified eight children from seven different families with CRPS in their pediatric genetics clinic. All eight of these patients met criteria for having a mitochondrial dysautonomic disorder, and these patients anecdotally responded well to a treatment for mitochondrial dysfunction involving nutritional supplements. Pedigree analysis revealed that six of the seven families met criteria for maternal inheritance. This suggests a possible genetic predisposition due to maternally inherited mitochondrial dysfunction [29].

The adult literature also suggests the possibility of a genetic component to CRPS. CRPS has been noted to occur in families, and data suggest that siblings younger than age 50 of CRPS patients may have a higher risk of CRPS [30–32]. Also, CRPS both with and without dystonia has been associated with certain HLA alleles [33–37]. Jin et al. conducted genome-wide expression profiling in CRPS

patients compared to controls and identified genes that were preferentially expressed in CRPS patients, though their sample size was small [38].

Psychological Factors

Historically, psychological disorders have long been thought to play the primary role in the development of CRPS in both adults and children [39, 40]. Many have thought that certain patients are psychologically predisposed to developing CRPS, which would explain why some develop pain out of extreme proportion to an injury and others who sustain much more severe injuries do not suffer CRPS at all [39].

In 1990, Egle and Hoffman, reflecting a common view of CRPS from this era, describe the typical psychological profile of a CRPS patient which includes anxiety, depression, and emotional instability. In their own case series of 12 patients, Egle and Hoffman identified common characteristics of stressful life events, history of chronic pain, and signs of "pain proneness." They use their case series results to support a view of CRPS as a psychosomatic disease [41].

Emotional distress has often been extensively described in pediatric CRPS patients as well. Some have suggested that in pediatric patients, psychological factors may play a greater role than in adult CRPS patients [42, 43]. Bayle-Iniguez et al. studied psychological characteristics of 73 pediatric patients with 92 controls. They found that anxiety was very strongly associated with CRPS. However, it is not clear if the anxiety in these patients existed prior to the CRPS [44].

Sherry and Weisman analyzed psychosocial factors in 21 families with children affected with CRPS. The majority of the families (71%) were described as having "high internal cohesion, expressiveness, and organization and low levels of conflict." Also, 12 of the 21 families (57%) had marital conflict. In this context, they describe a typical psychological profile of a child who suffers with CRPS as "a compliant, overachieving child, usually a preadolescent girl, who has undue stress placed upon her by both her family psychodynamics and school. Usually this is a stable but overly close, cohesive family." They go on to describe that they observed inappropriate levels of enmeshment, particularly between mother and daughter, often in the context of parental marital conflict. In this context, the child is burdened with being a mediator which supplants their previous role as a child. They believe that in this setting, the child's CRPS allows them to take on the "sick role" and it is a means of infantilizing, restoring the nurturing behavior they were missing [45].

Though there is clearly a strong relation between psychological dysfunction and CRPS, many have doubted whether the evidence is strong enough to support a causal link. Both Lynch and Wilder caution that Sherry and Weisman's study did not include a control group, and caution against drawing conclusions to a psychological origin for CRPS [22, 40]. Also, though Sherry and Weisman found significant levels of enmeshment during their psychological interviews, they did not identify significant abnormalities when patients were assessed with the Child Behavior Checklist (which is a standardized measure that identifies depression, anxiety, as well as social problems) [45]. Vieyra et al. assessed the family functioning of 28 children

with CRPS and included comparisons to children with migraine headaches as well as healthy controls. In contrast to Sherry and Wiseman's conclusions, they found no differences in family functioning among the three groups [46].

In case reports of pediatric CRPS, a significant amount of children with CRPS were found to have psychological dysfunction [11, 42, 47–49]. Cases have also been reported in which CRPS is a comorbid condition in children with anorexia, somatization, and conversion disorder [49–51]. Some case reports state explicitly that psychological factors were what induced CRPS to occur [43, 49].

Despite the multitude of case studies describing the prevalence of psychological dysfunction in children with CRPS, many have stated that the evidence for a psychological etiology of CRPS is weak. Bruehl and Carlson point out that many case series do not use a systematic method to evaluate psychosocial dysfunction, have a small sample size, and do not evaluate patients' psychological states prior to having CRPS [39]. Lynch has expressed similar concerns, citing lack of control groups, no blinding of psychological evaluators, and the need for clearly defined and uniform psychological criteria [40].

Lee et al. used validated, reliable depression and anxiety tools (The Children's Depression Inventory and The Revised Children's Manifest Anxiety Scale) to assess children undergoing physical therapy and cognitive behavioral therapy for CRPS. They found that children with CRPS did not have elevated depression or anxiety scores [52].

Logan et al. assessed depression and anxiety using standardized tools in pediatric patients with CRPS compared to pediatric patients with chronic headaches and abdominal pain. They found that children with CRPS had depression and anxiety scores that were within normal ranges, and their scores did not differ significantly from those of children with headaches or abdominal pain. They had a relatively large sample size (101) and used rigorous CRPS diagnostic criteria [53].

In a similar study, Wager et al. also used validated tools to compare depression and anxiety scores of children with CRPS to children with abdominal pain and headaches. They found that pediatric patients with CRPS had lower depression and anxiety scores than children with abdominal pain, and they had similar scores to children with headaches. Taking their data together with data from the study of Logan et al., they state that the results "dispute the idea that severe psychological distress is a specific vulnerability factor for CRPS" [54].

Wager et al. found that children with CRPS had more stressful life events prior to the onset of pain compared to patients with chronic primary headaches. They state stressful life events may be one of the etiological factors in the development and maintenance of CRPS. Stressful life events have also been described in other studies of both pediatric and adult patients with CRPS [45, 55, 56].

In a recent retrospective review of pediatric patients with CRPS, Mesaroli et al. assessed for depression and anxiety using the BASC-2 scale. Similar to other researchers, they found that patients with CRPS had self-reported scores within normal ranges. However, they also noted that 39% were clinically diagnosed with an anxiety disorder, 12% with a depression disorder, and 13% with a somatic symptom disorder. Given a discrepancy between patient self-report and clinical

diagnosis, they conclude that multiple modes of assessment should be used when evaluating psychological features. The patients in this study were not compared to other chronic pain patients or to healthy controls [57].

In adult studies, there have been conflicting reports as to whether or not CRPS patients have more psychological issues compared to non-CRPS patients [58]. However, in a systematic review, Beerthuizen et al. report that studies of higher methodological quality and prospective studies do not report a relationship between CRPS and psychological factors [59].

Though evidence may not suggest a psychologic etiology for CRPS, it is clear that psychologic and family distress is present in many pediatric CRPS patients. Whether or not this distress is the cause or the result of CRPS, it clearly needs to be taken into account when CRPS patients are evaluated and treated. Many advocate the biopsychosocial approach to CRPS, which has increasingly become more prominent in the approach to chronic pain in general [53, 60–62]. The biopsychosocial model, which views illness as a complex and dynamic interaction between biological, psychological, and social factors, allows for nuances in the interactions between pain and emotional symptoms and is the foundation for a multidisciplinary approach to pain management which has shown to be effective in the treatment of chronic pain [63–65].

Other

Though the mechanisms are not clear, case studies have shown interesting associations between CRPS and other illnesses. The development of CRPS in children has been reported after vaccination for rubella, DTaP, and HPV [66–69]. Case reports have also suggested associations between pediatric CRPS and Ehlers Danlos [70], factor VIII deficiency [71], von Willebrand disease [72], and even scurvy [73]. Having an atopic background was also found to be associated with CRPS [44]. An association between allergies and CRPS has also been demonstrated in adults [74].

Clinical Features

Common clinical features include pain, decreased range of motion, allodynia, hyperesthesia, skin color changes, edema, temperature asymmetry, and an increase in complaints after exercise [13, 14, 57]. Neurologic findings that have been observed include paresis, decreased sensation, dyscoordination, tremors, spasms, and involuntary movements [14]. Abnormal sweating, muscle atrophy, as well as trophic changes of the hair, nails and skin have also been observed [14, 57]. Pediatric CRPS patients have been found to have allodynia to both cold and heat [75]. One key difference between pediatric and adult CRPS patients is that pediatric CRPS tends to affect the lower extremities, in sharp contrast to adult CRPS which has preferentially affects the upper extremities [13–15, 76]. While in adults and children, the affected limb can be both more cold or more hot than unaffected

extremities, in children, the affected limb is disproportionately more cold as compared to adult patients (72% compared to 45%) [14]. Also, in pediatric patients, while a significant percentage present with edema (40%), it is much lower than in adults (78%) [14]. Mesaroli et al. found that children are more likely to present with sensory (hyperesthesia and allodynia) and motor (weakness, decreased range of motion) signs, and less likely to have trophic changes such as nail and skin abnormalities [57]. In Abu-Arafeh and Abu-Arafeh's systematic review, they found that about one-third of pediatric patients with CRPS have movement disorders or dystonia, which is similar to the frequency seen in the adult CRPS population [77].

Though CRPS in children classically occurs after a minor injury (such as an ankle sprain), in children, the percentage of patients with no history of trauma is higher than in adults. In Abu-Arafeh and Abu-Arafeh's pediatric epidemiological study, 74% had a clear preceding traumatic event [17], and in Tan et al.'s chart review, 92% of pediatric patients had an inciting traumatic event [14]. However, in multiple case series, only about one-half of patients remember a preceding incident of trauma [10, 78, 79]. This contrasts with adult data; In Sandroni et al.'s study, all 74 patients had an inciting event, and in de Mos et al.'s study 89.2% of the 238 patients with CRPS reporting a preceding trauma [15, 16]. Adults with CRPS are also more likely to have a history of a traumatic event that is severe (such as a fracture or after surgery), whereas pediatric patients are more likely to have experienced minor trauma such as a sprain or strain [14].

Many children with CRPS find their functional ability to be severely impaired. In Sherry et al.'s case series of 103 patients, 50 (49%) required crutches to ambulate, 12 (12%) were bedridden or required a wheelchair, and only 20 (19%) were still able to perform most activities [48].

Diagnosis

Diagnosis of pediatric CRPS is largely clinical. A careful history and physical are vital to rule out other neurological, rheumatological, or orthopedic conditions. Labs and imaging may be used to rule out other differential diagnoses. There are no laboratory tests that can definitively confirm or rule out CRPS, and routine labs (including inflammatory markers) are typically within normal ranges [22, 80, 81]. Physical exam may reveal signs such as allodynia, temperature asymmetry, skin color changes, edema, or dystonia [57].

Imaging results in pediatric CRPS are generally normal [13, 80, 81]. When radiographs are performed later in the disease, osteopenia is often seen [13]. Bone scans can show normal, decreased, or increased uptake; however, decreased uptake is generally considered the most common result in pediatric CRPS [11, 81–84]. This differs from adults where increased intake is generally characteristic of CRPS [85]. MRI may show edema [84].

Standardized criteria for the diagnosis of CRPS include the International Association for the Study of Pain (IASP) criteria as well the more updated Budapest criteria [86]. The Budapest criteria has been shown to have a similar sensitivity but

higher specificity than the IASP criteria [87]. However, these criteria have not been validated in the pediatric population [57, 80, 81, 87]. Friedrich et al. retrospectively applied the Budapest criteria to 174 pediatric patients who were clinically diagnosed with CRPS. They found that the Budapest criteria was positive in only 64% of patients with clinical CRPS. They noted that their pediatric CRPS patients who did not meet Budapest criteria presented with fewer signs and symptoms. Their results suggest that for pediatric patients, alternative cutoffs may be more appropriate and there is a need for more extensive validation of the Budapest criteria in the pediatric population [88].

Treatment

Physical and Occupational Therapy

The goals of treatment in pediatric CRPS are to restore function, and to treat pain. As in adult CRPS, physical therapy is considered the cornerstone of treatment [22, 81, 89]. Physical therapy also has the most supporting evidence among treatments for pediatric CRPS [90]. Many case series have demonstrated success in treating pediatric CRPS with intensive multimodal regimens which have combined physical, occupational, and psychological therapy.

In an early case series, Bernstein et al. treated 23 patients with physical therapy in 2–3 daily session over an average of 21 days. Therapy consisted of weight bearing, vigorous toweling, and active exercise. All patients at follow-up had restored function, and most had no or only occasional to moderate pain. A few of the patients received psychotherapy and some received aspirin or acetaminophen, but no other pain medication or interventional treatments were used [78].

Murray et al. in their case series treated 46 pediatric patients with physical therapy. The duration, frequency, and type of therapy were not specified. Many also received NSAIDs or acetaminophen, but invasive treatments were not used. The child and adolescent psychiatry team was consulted on 20% of the patients. 87% of the patients made a full recovery. 11 of these 40 patients who fully recovered experienced recurrence [10].

In a larger study, Sherry et al. treated 103 children with CRPS with intensive physical and occupational therapy. The therapy consisted of 5–6 hours a day of jumping, running up and down stairs, sports drills, handwriting, and hydrotherapy. Patients also participated in desensitization therapy including towel rubbing, hand massage, and textured fabric baths. The average duration of therapy was 14 days. 77% of patients also received psychologic counseling. Though acetaminophen was given occasionally for headaches, no other mediations were given and those already on medications at the start of the treatment were weaned off. At completion of the treatment, 92% were symptom-free, and of those followed for more than 2 years, 88% were symptom-free at the time of follow-up. A high rate of recurrence, 31%, was also noted [48].

Lee et al. performed a small randomized controlled trial of 28 patients, who were randomized to either receive physical therapy once a week or three times a week, along with weekly cognitive behavioral therapy for 6 weeks. The treatment consisted of transcutaneous electrical nerve stimulation, progressive weight bearing, tactile desensitization, massage, and contrast baths. Significant improvement was seen in both pain and function at the initial 10-week follow-up, and these results were maintained at long-term follow-up (mean of 66 weeks). Of note, 50% of patients experienced recurrence, and 10 patients eventually received a sympathetic blockade [52].

Brooke et al. examined the effectiveness of an interdisciplinary inpatient therapy program for 32 children with CRPS, which included physical and occupational therapy as well as psychological counseling, art therapy, recreational therapy, and child life specialists. The program included therapy for 5 hours a day over 5 days a week, over a mean duration of 19 days. Therapy consisted of strengthening and aerobic exercise, as well as desensitization and stress management techniques. At follow-up, 89% had resolution of pain and 95% had restoration of function. 37% experienced recurrence [91].

Logan et al. used physical, occupational, and cognitive behavioral therapy for 56 pediatric patients with CRPS in an outpatient day hospital program. This program involved therapy for 8 hours a day, 5 days a week for a median duration of 3 weeks. One hour of CBT involved deep breathing, relaxation, guided imagery, and biofeedback, problem solving, and developing coping strategies for stressful life events. Physical therapy had the goal of increasing weight bearing through stress-loading, strength, flexibility, and cardiovascular fitness. Occupational therapy aimed to maximize independence and participation in self-care, school, and leisure activities. They were also given a home exercise program. Functional outcomes were assessed with validated tools. Upon discharge, 93% showed clinically significant improvement in function. Of the 45 patients who were followed long-term (mean time of 10 months), 95% had significant improvement at time of follow-up [92].

Dietz et al. published a case series involving 83 patients who were instructed in a home, patient-directed regimen involving massage and mobilization. Of the 51 patients who were followed until symptoms resolved or treatment failed, 89% had no functional limitations and minimal or no pain [93].

The quality of the evidence for physical therapy was criticized in a systematic review by Bialocerkowski et al. Specific therapy regimens were noted to be poorly defined or highly variable. Also, many of the case series they analyzed combined other modalities, including medications and invasive procedures, making it difficult to know if therapy alone is effective [94]. However, the studies mentioned above all use therapy (physical, occupational, and psychological) as the primary modality, with minimal to no use of medications or interventional procedures. Although there is significant variation in intensity, duration, and setting of therapy, these case series all show excellent results with multimodal therapy for pediatric patients with CRPS.

Psychological Therapy

Psychological therapy has not been studied alone in pediatric CRPS but has been successfully incorporated into many interdisciplinary treatment programs [13, 42, 48, 52, 55, 91, 92]. As psychological distress is present in many pediatric patients with CRPS, it is important to offer psychological therapy as part of an interdisciplinary, biopsychosocial approach to treatment. Interventions includes relaxation training, breathing exercises, biofeedback, guided imagery, and coping skills [52, 91, 92]. Family therapy can be helpful when family relationships are identified as a source of stress [45].

Medications

To the authors' knowledge, there are no large, prospective randomized controlled trials for medications in pediatric CRPS. Case reports exist which report success with gabapentin, pregabalin, and oxcarbazepine; however, they only involve one patient each [95–97]. Many case series evaluating interdisciplinary therapy also incorporated medications; however, the number of simultaneous treatment modalities, as well as the variety of medications used, makes it difficult to draw conclusions [13, 55, 98]. Brown et al. randomized 34 pediatric CRPS patients to either receive gabapentin or amitriptyline, and both groups reported significantly decreased pain. However, there was no placebo control group and no significant difference was observed between the two treatment groups, so the benefit could be due to regression to the mean or to placebo effect [99]. In a small case series by Ruggeri et al. in the 1970s, dexamethasone did not show any effect [6].

There is some controversy regarding the use of medications in pediatric CRPS [22]. Some emphasize the need for intensive physical therapy and do not recommend medications [22, 48]. Others see the potential benefit from therapies that have shown some benefit in adult CRPS but have not been as extensively studied in the pediatric population, such as vitamin C, topical ketamine, and gabapentin [76]. Bisphosphonates (which have strong evidence to support their efficacy in adults) have not been studied extensively in children, though a case report exists of a pediatric CRPS patient successfully treated with pamidronate [90, 100, 101]. Calcitonin, which has had mixed results in adult CRPS patients, has not been studied in children [90, 100]. Ketamine has been shown to be beneficial in adult CRPS patients, and there have been limited studies showing that it is effective in children as well [90, 100]. Sheehy et al. found that subanesthetic outpatient ketamine infusions may be more effective in pediatric CRPS patients than in pediatric patients with other chronic pain conditions [102]. A pilot study by Bredlau et al. suggests that oral ketamine is safe in pediatric patients with CRPS [103].

In many case series of intensive multimodal therapy, NSAIDs or acetaminophen were used as adjuncts. However, in these cases, they were used to relieve soreness and headaches and not as the mainstay of treatment [10, 48, 78, 91]. There is not good evidence for the use of opioids in adults or children with CRPS, and their use

is not recommended given side effects and potential consequences of long-term use [104]. Relative to adult CRPS, there is an overall paucity of evidence regarding the use of medication for pediatric CRPS [90].

Invasive Treatments

Interventional therapies for CRPS are used often in adults, though there is less evidence for their use in children. The most commonly used interventions are sympathetic blocks, spinal drug infusions, and regional anesthesia [105, 106]. Other interventions that have been reported include intravenous lidocaine, spinal cord stimulation, and both chemical and surgical sympathectomy [105, 106]. Numerous case studies report success in pediatric CRPS using these techniques [107–114]. These studies tend to be of low methodological quality. There is a placebo-controlled, blinded, crossover trial, in which Meier et al. studied lidocaine injected via a lumber sympathetic blockade, along with saline injected intravenously, compared with saline injected via a lumbar sympathetic blockade with lidocaine injected intravenously. The lidocaine lumbar sympathetic blockade group resulted in a significant reduction in pain intensity compared to the saline sympathetic blockade with intravenous lidocaine group [115].

Zernikow et al. in their review of invasive studies on pediatric patients with CRPS, comment that studies of invasive procedures in pediatric CRPS rarely reported results using validated tools, had many atypical cases who may have had diagnoses other than CRS, and often the patients simultaneously underwent conservative treatments making it difficult to draw conclusions about a specific treatment. They conclude that there is weak evidence of invasive therapies and that high-quality multimodal conservative treatment should be attempted first [106].

Some experts are similarly cautious regarding invasive treatments and do not recommend them [10, 48]. Others, while they agree that high-quality therapy is the foundation of treatment, recommend procedures to help facilitate participation in therapy [116]. Donado et al. found that patients who did not show improvement with 4 months of conservative treatment, had improvements in pain and function with inpatient admission that involved continuous regional anesthesia. Though Donado et al. agrees with Zernikow that most pediatric CRPS patients will improve with conservative multimodal therapy, they conclude that continuous regional anesthesia may help to facilitate inpatient therapy in a small subset of patients that do not initially respond to conservative therapy [117]. Dadure et al. performed peripheral nerve blocks and Bier blocks on 13 children with pediatric CRPS, all of whom did not initially respond to at least 6 months of conservative treatment. Ropivacaine was continuously infused through pumps that were continued at home for a total of 96 hours of infusion. This was given in conjunction with intensive physical therapy which started at the hospital and continued at home. All the children had pain relief and functional improvement at 2-month follow-up [118]. This study has been criticized for not having a control group and for not having long-term follow-up [119].

Cucchiaro et al. used a combination of peripheral and epidural catheters in combination with a rigorous multimodal therapy regimen for 31 pediatric CRPS patients, and found a significant improvement in pain and function. Of note, the average length of hospital stay was 8 days, compared to an average of 14 days noted in children who had inpatient therapy but no regional anesthesia [48, 120].

Spinal Cord Stimulation

Spinal cord stimulation, which has shown to be effective for reducing pain and improving quality of life in adult CRPS patients, has only been studied in small case series in children [90]. Rodriguez-Lopez et al. advocate an approach involving conservative treatment including physical and psychological therapy, oral medications, and capsaicin patches. In patients who fail to respond in 3–5 weeks, bupivacaine infusions via lumbar epidural catheters are used for 2 weeks. If pain still persists, spinal cord stimulators are placed. In their case series of ten patients, six required lumbar epidural bupivacaine infusions, and three required spinal cord stimulators. All had zero or minimal pain and only minor functional limitation at 12-month follow-up [121].

Olsson et al. published a case series in which seven adolescents with CRPS with symptoms refractory to physical therapy and sympathetic blocks received treatment with spinal cord stimulation. Five patients had complete pain relief and two had partial but significant pain reduction. At follow-up interview which ranged from 1 to 19 years since the spinal cord stimulator had been removed, all had either no pain or minor pain [122].

Stanton-Hicks et al. report a case in which an adolescent girl with CRPS was successfully treated with spinal cord stimulation. However, she developed recurrence with further injuries which did not respond to spinal cord stimulation [112].

Alternative Treatments

Acupuncture, which in systematic reviews has been shown to be safe in children, may have some value in treating pediatric CRPS [123, 124]. In Zeltzer et al.'s study, they found that acupuncture and hypnosis was well tolerated and improved pain in a group of pediatric chronic pain patients which included some patients with CRPS [125]. A small case series by Lin et al. showed acupuncture in pediatric CRPS patients reduced pain, improved function, and was well tolerated [126].

Graded motor imagery is a therapy that uses recognition of hand laterality, imagined movements, and mirror therapy in order to gradually activate cortical motor networks without triggering a protective pain response [127]. This has shown promise in studies of CRPS in adults, though not all studies have shown improvement in pain [127–129]. Despite a lack of studies and evidence supporting the use of graded motor imagery in children, some therapists have applied adult protocols to treating children [130]. Heeger et al. have advised caution in this, given that children may

not be developmentally ready to distinguish between left and right extremities or to appropriately generate motor imagery [130]. Also, Johnson et al. noted some patients had an increase in pain with graded motor imagery [129]. Heeger et al. emphasize a need to establish of age-appropriate protocols to use graded motor imagery in children, rather than applying adult protocols to children [130].

Transcutaneous electrical nerve stimulation (TENS) has been described as effective in case reports of pediatric CRPS [4, 9]. TENS was included as a therapy by Wesdock et al.'s study of multimodal therapy, but it did not provide benefit [98]. Though there is not high-quality evidence to recommend its use, Wilder recommends a trial of TENS given its safety, modest cost, and acceptance by children [22].

Summary table of evidence for treatments

Multimodal (physical, occupational, and psychological) therapy	Shows benefit in pediatric CRPS. The most effective regimens, duration, frequency, and settings of therapy are not well defined
Invasive treatments	Overall, not good evidence to support the use of invasive treatments. May have benefit in cases refractory to conservative treatment
Medication	There is not good evidence to support the use of medication in pediatric CRPS

Prognosis

The prognosis of pediatric CRPS is generally considered to be favorable compared to adults. Studies using physical, occupational, and psychological therapy, with only minimal medication use and no invasive therapies, report success rates of 80% or higher of treating pain and restoring function [10, 48, 52, 78, 91–93]. However, many of these studies showed significant recurrence rates, with some reporting a 30–50% chance of recurrence, which is significantly higher than the 1.8% per year risk of recurrence reported in adults [48, 52, 91, 131].

Goldschneider has questioned whether the prognosis of children is really that much better than adults, citing a lack of studies on long-term outcomes and also a bias toward positive results as patients who do not respond to treatment tend to be lost to follow-up [132]. Wilder has argued that the greater success rates seen with multidisciplinary therapy in children compared to adults may be because of the greater willingness of children to participate in intensive therapy, rather than differences in the disease itself [22].

When Tan et al. followed pediatric patients with CRPS into adulthood, they found that though pain and other symptoms were decreased from the time they were first seen as children, 52% continued to continue to complain of pain. Of 12 signs and symptoms surveyed at time of initial consult and at follow-up (on average 12 years later), only 4 had improved, 1 had worsened, and the rest were not significantly different. They conclude that the prognosis of childhood-onset CRPS may be closer to adult-onset CRPS than what is reported in other studies [133].

Conclusion

Pediatric complex regional pain syndrome differs from adult complex regional pain syndrome in several respects. There is a larger female predominance and the lower limb is disproportionately affected. Also, there is a higher percentage of cases that present after no known trauma. As in adults, the precise pathophysiology is not well understood. While many CRPS patients have psychological comorbidities, evidence does not suggest a psychological origin of pediatric CRPS. Diagnosis is clinical, with laboratory tests and imaging serving to rule out other differential diagnoses. Adult criteria for diagnosis is used, although many recognize the need for pediatric-specific criteria. Multidisciplinary therapy, including physical, occupational, and psychological therapy, is the foundation of treatment for pediatric complex regional pain syndrome. Though case reports have reported benefit with medications, there is not good evidence for pharmacologic therapies. Invasive procedures are controversial in pediatric CRPS, with some arguing that they have no role, and others using them for cases that are refractory to conservative treatment. The prognosis is generally favorable, though recurrence is very common. Despite a tremendous growth in research on pediatric CRPS in the recent decades, there is a still a great need for more high-quality evidence in the treatment of pediatric CRPS.

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Review and Management of Complex Regional Pain Syndrome in Pregnancy

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Introduction

Complex regional pain syndrome (CRPS) is a chronic neuropathic condition characterized by a spontaneous or evoked, continuous pain in a specific region that is disproportionate in severity and time to the expected course of the causative insult [1]. In up to 90% of cases, the cause is felt to be identifiable and is most often related to a recent trauma, such as fracture, sprain, strain, other soft tissue injury (burns and scrapes), surgery, or minor procedure, and is thought to affect the upper extremity more than the lower [2]. Sometimes, however, there is no known cause. The pain is typically accompanied by edema, sensory, vasomotor, sudomotor, and/or tropic changes [3].

The estimated annual incidence of CRPS is about 5.46–26.2 cases per 100,000 persons in the general population [4, 5]. Women are more commonly affected than men with a ratio of up to 4:1 [5] and with a peak age range 40–50 years old [3, 5, 6]. While the postmenopausal time period, in particular, appears to be a risk factor for CRPS, there have been several cases about CRPS occurring during pregnancy, which in itself has been suggested to serve as a protective factor [7]. The data behind that theory, however, are limited.

The relative prevalence of CRPS among pregnant women is unknown given that research has been limited to case reports. According to several studies, pregnancy

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accounts for 0.5–33% of the reported CRPS cases in women and appears to be the most frequently found etiology among them [8]. A review of nine cases of pregnant women with CRPS by Poncelet et al. reported an average patient age of 36 ± 3.5 years old, with symptom initiation occurring at 28.1 ± 2.2 weeks following conception and with six of the patients experiencing excessive weight gain (>12 kg) prior to onset [8]. The most common location affected in this review was the hip, although no side appeared to be predominant; and in four of nine cases, bilateral hips were involved [8]. Extensive involvement of the disease appears to be rare [9]. The above findings have been echoed in more recent studies. In particular, Mansouri et al. summarized that among a review of 57 reported cases of CRPS in pregnant women, there was an increased incidence of the disorder within the third trimester in young primiparas and a decreased incidence during the first and second trimesters and postpartum period [10]; 159 sites were involved and broken down as follows: 54% hip, 25% knee, 21% ankle or foot, and 8% entire lower extremity [10]. CRPS also tends to affect women more so during their first pregnancy as new onset and has the possibility to relapse during subsequent pregnancies, sometimes in the contralateral joint [11]. This chapter focuses specifically on the development of CRPS in pregnancy rather than on its relapse or remission during the pregnancy.

Pathophysiology

The pathophysiology of CRPS is not well understood but likely represents a combination of multiple mechanisms, each of which is thought to affect different patients in varying proportions. This variability in the underlying causative mechanism contributes to the heterogeneity of presenting symptoms among the CRPS population. Proposed mechanisms include disruption of small density nerve fibers, increased sensitivity of the central and peripheral nervous system, increased inflammatory markers (proinflammatory cytokines TNF-α and interleukin-1, -2, and-6), genetic factors (HLA-B62 and HLA-DQ8), and psychological disorders (depression and anxiety) [2, 3, 6].

In pregnant patients, changes in body posture, hormones, metabolites, psychological components, and other factors may contribute to the unique pathophysiology. As mentioned previously, CRPS is seen more commonly within the third trimester of pregnancy and can preferentially affect the hip joints. It is unlikely that the association of CRPS of the hip and pregnancy is purely coincidental, and multiple studies have proposed hypotheses regarding the specific mechanism behind this trend. Curtiss et al. proposed that intermittent compression by the fetus of the femoral and obturator nerve could be responsible for pain and decalcification seen in the hip joint of affected pregnant women [11, 12]. Further, during pregnancy, women experience significant weight gain and increased lordosis, which in combination with the weight of the fetus, contributes to trauma experienced at the femoral head and neck [8]. This increase in mechanical stress and microtrauma as well as obstruction of venous return by the fetus on the inferior vena cava are thought to result in microthrombi and phlebitis in the bone as well as irritation of the

autonomic nervous system [8, 12, 13]. While bilateral involvement of hip joints has been reported [8], there appears to be a preference for left hip, possibly related to the increased frequency of left occiput position of fetus at term [14].

Hypertriglyceridemia has been recognized as an independent risk factor for development of CRPS in the lower extremity [15, 16]. Although the association is not fully understood, there is a significant inflammatory response to hypertriglyceridemia that involves both the innate and adaptive immune systems, which could explain its role in contributing to increased symptom burden in CRPS patients [17, 18]. In fact, simvastatin in particular has been shown to have antinociceptive effects in the management of CRPS, although more research needs to be done investigating its exact mechanism of action [18]. Hypertriglyceridemia is common in pregnancy, especially during the first trimester [8], as the rising progesterone during this time leads to increased intestinal lipid synthesis, which allows for the transfer of other nutrients across the placenta and to the fetus for healthy development [19].

There has been some research done exploring the effect of estrogens on CRPS. Hormones, especially estrogen, play a critical but complex role in pain modulation. Thus, it is important to consider this association when looking at pain in the pregnant population given the rise in both estrogen and progesterone as pregnancy progresses. Many pain syndromes, such as arthritis and migraine, actually improve during pregnancy with the thought being that these syndromes worsen with periods of rapid drops in estrogen and improve with steady states of the hormone [20, 21]. This theory is supported by research showing increased pain surrounding menstruation, the postpartum period, and with abrupt withdrawal of estrogen-based hormone supplementation [20]. The exact mechanism of action of estrogens in these situations is unclear but thought to be related to multiple factors, including estrogen receptor-α-mediated vasodilatation via increased nitric oxide synthesis, enhanced serotonergic signaling, and altered endogenous opioid tone [20, 22]. Conversely, it also appears that women with chronic pain may have exacerbated pain or new pains during pregnancy, but there is no current relationship to any one hormone to explain this phenomenon [23]. Increased pain may be better attributed to mechanical changes in the setting of uterine growth, such as increased lumbar lordosis, increased joint forces, and laxity of joints [24].

The relationship between inflammatory pain and estrogens has also been analyzed in multiple animal studies and is possibly related to modulation of cytokine production and release in granulomatous tissue [25, 26]. In one study by Yamasaki, et al., estrogen replacement therapy was shown to decrease the severity of arthritis and bone loss in rats [27]. These animal studies have additionally shown that estradiol likely decreases or tempers the immediate effects of inflammation but may worsen the long-term postinflammatory process [25]. Women with CRPS type I were found to have the lowest level of E2 compared to other healthy women of different ages in a study done by Buryanov et al. [7]. However, research thus far has not been revealing for any association between cumulative endogenous estrogen exposure and risk of CRPS [28].

The presence of psychological disorders such as depression and anxiety can contribute to the development of CRPS, possibly due to the effects on alpha-adrenergic

activity and overall sympathetic arousal [29]. CRPS is hypothesized to cause upregulation of peripheral catecholaminergic receptors in the affected extremity causing hypersensitivity to the circulating catecholamines and leading to vasoconstriction of the extremity. Primary afferent fibers can become sensitive to adrenergic excitation as well, causing increased nociceptive firing in response to sympathetic discharge and can lead to central sensitization. Central sensitization leads to increased pain and can lead to further catecholamine release, creating a vicious cycle. Increased emotional stress leading to anxiety and anger can be associated with increased catecholamine release [30]. Catastrophic thinking as related to pain has also been associated with proinflammatory cytokine activity. It has, therefore, been postulated that CRPS can be directly linked to greater feelings of depression in patients, and increased psychological stress can worsen CRPS symptoms [30]. Prospective studies have shown conflicting results; however, there are data that have shown that increased anxiety preprocedure was more likely to lead to CRPS postprocedure in total knee replacement [30]. Retrospective studies have linked the cause of CRPS to a significant life stressor. There is also an increase in these disorders in the perinatal period, which could help explain the association between CRPS and pregnancy. Anxiety, in particular, has been shown to be a risk factor for developing CRPS type I [31] and has a perinatal prevalence ranging from 9 to 22% [32]. Women of childbearing age are also at higher risk for developing major depression, with the prevalence of perinatal major and minor depression specifically ranging from 8.5% to 11% and the incidence of perinatal major or minor depression reaching up to 14.5% according to a 2005 Agency for Healthcare Research and Quality Report [33]. More recently, Becker et al. presented that up to 70% of pregnant women report symptoms of depression and 10–16% of women meet criteria for major depressive disorder [34]. Depression during pregnancy has been associated with preterm birth, low birth weight, fetal growth restriction, postnatal cognitive and emotional complications, and in the mother, it has been linked to preeclampsia and gestational diabetes [34]. The reason for these complications is postulated to be related to increased stress hormones that cause vasoconstriction and lead to hypoperfusion, as well as epigenetic changes in the fetus that can lead to HPA axis changes, all of which could theoretically contribute to development of CRPS in this population [34]. Sleep disturbance and resulting fatigue are other important considerations for a pregnant patient which might contribute to mental health conditions and trigger CRPS. One meta-analysis presented that 46% of pregnant women report poor sleep, which increases throughout pregnancy [35]. Poor sleep and fatigue are known to be predictors of pain, and pain also contributes to poor sleep and fatigue [36]. Importantly, poor sleep and fatigue, as well as chronic pain are related to mood disturbances, which require special treatment in this patient population and will be discussed in a later section [36].

Clinical Symptoms

As described above, CRPS typically presents as severe, continuous pain in a specific region that can be accompanied by additional symptoms. These symptoms could include sensory, vasomotor, sudomotor, and motor categories, and the patients may

present with hyperalgesia, allodynia, sweating, skin temperature and color differences, focal dystonia, and disruption of nail and hair growth [3, 4, 37]. Patients may also have impaired range of motion of the affected extremity [4] and exacerbation of symptoms following exercise [37].

The presenting features of CRPS in pregnancy can be easily misleading and nonspecific, which accounts for the likely underestimated incidence and prevalence among this population. As previously reported, when compared to the general population, CRPS in pregnancy tends to involve the pelvic girdle and lower extremity, particularly the hip joint, more frequently than the upper extremity. Patients have reported gradual, sciatic-type pain and phlebitis pain, usually located in the inguinal area and sometimes radiating to the anterior thigh or knee [8, 10]. The pain may be accompanied by limping and functional impairments which may worsen with standing and improve in the decubitus position, and in severe forms, it may even be difficult to walk with crutches [8]. There often is slight limitation of passive range of motion, especially at the extremes [8]. Marked edema and cutaneous vasomotor dysfunction can be observed in more distal involvement in knees, ankles, and foot, and these are often the primary symptoms [8, 12, 15]. CRPS in pregnancy can be complicated by fractures of the femoral head, femoral neck, or the pelvis and seldom require surgery [8]. Fractures can be displaced, nondisplaced, or impacted, and are not necessarily a result of trauma but could be related to demineralization of bone seen in the syndrome [8]. Additional factors may increase the risk of fracture, including forced abduction during delivery and underlying bony abnormalities, both of which must be taken account during labor to avoid injury [10]. Breastfeeding in the postpartum period in these patients is typically avoided due to its increased association with bone demineralization in the setting of the growing baby's need for calcium [38, 39].

Overall, symptoms of CRPS in pregnancy typically improve within several weeks or months, although when the syndrome is uncomplicated, delivery appears to result in rapid recovery [8]. Specific pregnancy outcomes related to CRPS have not been explored extensively, although there does not appear to be an association with increase in premature births or dystocia, nor does CRPS present as an indication for cesarean section [8]. Although no reports on the discussion of obstetric implications have been identified, Poncelet et al. reported that 26 of 33 patients had vaginal deliveries and the remaining 7 had cesarean sections for cephalopelvic disproportion, orthopedic indications, or unspecified reasons [8].

Diagnosis

For standardization purposes, the Budapest consensus criteria have been established and validated as being superior to the former International Association for the Study of Pain (IASP) criteria for diagnosing CRPS [40, 41]. There are two recognized forms of CRPS that are distinguished by presence of identifiable nerve lesion. CRPS type I, also referred to as reflex sympathetic dystrophy, is more common and does not involve a known peripheral nerve injury, whereas CRPS type II, also known as

causalgia, has evidence of nerve injury [42]. Other than assessing for hypertriglyceridemia as discussed previously, lab testing in CRPS is of low yield, as results are typically unremarkable or nonspecific, such as elevated erythrocyte sedimentation rate or hydroxyprolinuria. However, given that the differential diagnosis of CRPS includes other life-threatening conditions such as tuberculosis, neoplasm, infection, and vasculitis, it is important to assess appropriately for those disorders using lab tests such as complete blood count, C-reactive protein, antinuclear antibody, rheumatoid factor, complement levels, and serum immunoelectrophoresis [43]. While there is no imaging gold standard for diagnosing CRPS, there are certain studies that can be helpful in providing a diagnosis. One of these studies is three-phase bone scintigraphy, which has shown increased radiotracer uptake in all three phases in joints distant from the trauma site if obtained within the first 5 months of symptom onset; it is especially specific for use in the upper extremity [42]. The pathogenesis for bone loss specifically is not clear but could possibly be related to tissue hypoxia from microvascular compromise, which produces a low local pH and causes a dissolution of hydroxyapatite crystals to the area. There has not been a link to increased osteoclastic activity in CRPS [44, 45]. Plain radiographs have also been used during workup and may show patchy osteoporosis or even a "ghostly" appearance of the femoral head but have low sensitivity for detecting CRPS [8, 46]. When used for diagnosis in eight pregnant patients, most findings did not show up on initial exam and usually did not appear until 3–6 weeks after clinical symptoms [8]. While both of these studies likely would not result in fetal harm per the American College of Obstetricians and Gynecologists' committee opinion, they are typically avoided in pregnant patients given the increased risk of birth defects such as growth restriction, microcephaly, and intellectual disability compared to other imaging modalities [47]. In the general population, CT and MRI have not been shown to be useful. However, for safety purposes mentioned above, MRI is the diagnostic imaging method of choice for early and differential diagnosis in the pregnant population, with positive findings of low signal intensity on T1-weighted images and high signal intensity on T2-weighted images of the affected joints [8, 48]. These findings typically appear within 48 hours of symptom onset and normalize within 6–8 months [8]. Mansouri et al. reported characteristic MRI findings of bone marrow edema in the presence of no collapse or erosion of the subchondral bone in their patients [10]. Joint space is typically not changed throughout pregnancy [11]. Ultimately, the diagnosis of CRPS in pregnant patients appears to be underreported due to its complex mechanism, nonspecific symptoms, and misdiagnosis, and is based primarily on clinical signs/symptoms and exam. An early diagnosis and an interdisciplinary approach are fundamental factors for an optimal and successful treatment.

Management

Given the complex nature and unclear pathophysiology of CRPS, treatment is quite challenging and requires an interdisciplinary approach. The options for safely treating the symptoms of CRPS become much more limited when pregnancy is involved.

Conducting well-controlled, randomized studies to assess the safety of medications and various interventions is extremely controversial and likely not to occur if there is a possibility of maternal or fetal harm. Unless otherwise well documented, most recommendations for management of chronic pain conditions such as CRPS in pregnancy are based on case reports and anecdotal evidence. The interdisciplinary approach to chronic pain conditions involves medications, therapies, behavioral strategies, interventional procedures, and at times surgery. This approach is no different in CRPS, and the careful utilization of these strategies becomes especially important in pregnancy. Medications must be proven to be safe to the mother and the fetus throughout pregnancy and effectively treat the pain. Therapies are widely considered benign and safe for most patients. However, there are certain modalities involving heat and exercise that must be deliberated when applied to a pregnant patient. Interventional procedures must be safe and appropriate when considering exposure to radiation. Finally, behavioral strategies are crucial for management of chronic pain conditions. Given the stressors of pregnancy, changes in anatomy, and increased fatigue and sleep deprivation that can occur, behavioral and cognitive strategies that can combat these changes can become more important. All of these modalities have a specific role in treatment of pain, and their safety and efficacy will be discussed further in this section. Ultimately, a combination of medication, therapies, and if necessary, interventional procedures may be needed to manage CRPS in pregnancy appropriately.

Pharmacotherapy

Based on the chronic nature of CRPS, medications are often given as the initial treatment so patients can better tolerate therapies and are more likely to engage in their work and activities of daily living. Medication management of CRPS is largely limited to case reports and case series. Because CPRS is four times more likely to occur in women, research should be dedicated to the medications that can be used safely and effectively in pregnancy and the young female population [49]. Commonly used medications for chronic pain including acetaminophen, anti-inflammatories, antiepileptics, antispasmodics, tricyclic antidepressants (TCAs), and opioids are discussed here, though their use in CRPS specifically is not well studied. More recent literature has demonstrated growing interest in immunomodulators, newer generations of bisphosphonates, alpha-adrenergic agonists, and ketamine as possible treatment options. These medications as well as other commonly used pain medications used in chronic pain will be discussed here as they relate to management of CRPS pain and if they can be used in a pregnant patient.

Of note, in 2015, the Food and Drug Administration (FDA) introduced the Pregnancy and Lactation Labeling Rule (PLLR) that changed the content and format for medications pertaining to pregnant and lactating women. The traditional letter categories A, B, C, D, and X were not to be used in any medications produced after 2015 and were to be removed from any existing medications by 2020. Drug companies are now reporting any risks reported based on the use of their medication

in pregnant or lactating patients, and if there are any risks to males and females with reproductive potential. These risks are to be reported in Pregnancy Exposure Registries by drug companies and are not endorsed by the FDA. Information on medications is now reported in summary form regarding if and what adverse events occur [50].

Antipyretics

Acetaminophen is one of the most commonly used pain medications given its cost, availability, and overall low side effect profile. Its use in treatment of chronic pain conditions has been hallmarked as a first-line medication in many conditions including arthritis and chronic low back pain [51]. Though there are no studies suggesting its use in CRPS [30], The American College of Obstetrics and Gynecologists recommends acetaminophen as a primary pain medication during pregnancy [52].

Surveys have reported anywhere from 40 to 65% of pregnant women use acetaminophen for pain some time during their pregnancy, most commonly for headache and fever [52]. Due to the better side effect profile and lower risk of fetal harm compared to nonsteroidal anti-inflammatories (NSAIDs), it is the preferred medication for pain, especially during the third trimester. Adverse neurological and behavioral outcomes in children when taken during pregnancy were reported in recent studies [52]. Studies also report that perinatal use of acetaminophen has been linked to attention deficit hyperactivity disorder (ADHD) as well as autistic spectrum disorder (ASD) in the children who were exposed [52]. The FDA concluded that the studies reporting increased incidence of ADHD and ASD had significant flaws and were inconclusive as to whether acetaminophen was correlated with these disorders [52].

Anti-Inflammatories

NSAIDs and corticosteroids are often used to treat the inflammatory component of pain. They work by inhibiting the synthesis of prostaglandins which play a role in inflammation and increase pain as a peripheral process. NSAIDs have been trialed in individuals with CRPS; however, the inflammatory component of CRPS is largely neurogenic in nature. There have been no recent trials of NSAIDs in the management of CRPS, though prior small studies have shown either mixed results or no improvement in CRPS symptoms [30].

In pregnancy, NSAIDs should be avoided in the third trimester as they can cause premature closure of the patent ductus arteriosus [53]. Aspirin has been studied extensively in pregnancy, and FDA access data continue to recommend that aspirin not be used in the third trimester of pregnancy because of its NSAID qualities; therefore, it could cause fetal complications [54]. However, the American College of Obstetrics and Gynecologists have released their expert opinion in 2018: low-dose aspirin (81 mg/day) can be used safely throughout the entirety of pregnancy

without adverse events. Moreover, low-dose aspirin should be started at least 12–28 weeks into the pregnancy in any woman with high risk of preeclampsia and then continued until delivery. High risk of preeclampsia risk factors include a history of preeclampsia, chronic hypertension, type 1 or type 2 diabetes, renal disease, autoimmune disease, and multifetal gestation [55].

Oral corticosteroids have been shown to be effective in acute CRPS when inflammation is thought to be more pronounced [30]. Both oral and intravenous steroids have been studied over several decades, all with predominantly positive results, though sample size has often been small, and results were generally more favorable in the patients with symptoms more acute than chronic in nature [56]. Steroid use in pregnancy may be necessary for chronic conditions such as rheumatologic disorders. There are currently not enough studies to implicate fetal harm with chronic steroid use, though symptoms of hypoadrenalism should be monitored in an infant if high doses of steroids were used during pregnancy [57].

Tricyclic Antidepressants (TCAs)

Though known originally for their antidepressant effects, there is ample scientific evidence to support the use of TCAs in neuropathic pain due to the augmentation of descending inhibition by blocking presynaptic reuptake of neurotransmitters such as norepinephrine. The use of these medications in CRPS is primarily anecdotal; very little research exists on the utilization of TCAs for symptom management. Currently, there is only one case report of amitriptyline being used in CRPS [30]. There are no well-controlled studies done in pregnancy to demonstrate the safety of amitriptyline. There have been a few reports of CNS abnormalities, limb deformities, and developmental delay in infants born to mothers taking amitriptyline, but there is insufficient evidence to say that this medication is not safe to use [58].

Antiepileptics

Medications that are first line for seizures often have sodium or calcium channel blocking properties. Since pain is thought to be related to the excitability of neurons, these medications have been hypothesized to work on pain by blocking ion channels [59]. The use of gabapentin has been well studied in neuropathic conditions, though its specific use in CRPS has only been seen in case series [60]. No reports have been documented for pregabalin use in CRPS [30]. There has been one study that evaluated carbamazepine as an effective medication for CRPS; other antiepileptics such as phenytoin, lamotrigine, and oxcarbazepine have not been studied in adults [30]. There are no well-controlled studies that have been performed in pregnant women to determine if gabapentin is safe in pregnancy. Studies in animals have demonstrated birth defects and abnormal brain formation [61]. The use of pregabalin in pregnancy is also not well studied and, therefore, has not been determined to be safe [62]. A cohort study by Patorno et al. assessed infants who

were exposed to pregabalin during the first trimester did not confirm an increased risk of congenital malformation with pregabalin use compared to infants without pregabalin exposure [63]. Animal models have demonstrated birth defects such as skeletal malformations, but the dose of the medication use was much greater than normal human dosing [62]. Comparatively, carbamazepine has been demonstrated to cause congenital malformations including spina bifida during pregnancy [64]. Craniofacial defects, cardiovascular malformations, and developmental delay have also been seen. If being used for seizures, carbamazepine should be weaned, and a new antiepileptic should be started prior to pregnancy. Though no studies have been done in CRPS with other antiepileptics, it is worth noting that phenytoin also has known teratogenic effects and should not be used during pregnancy [65], and oxcarbazepine is structurally similar to carbamazepine and, therefore, should be used with caution during pregnancy, though there are no significant studies of its use in pregnancy [66]. There are no significant studies of lamotrigine in pregnancy either [67].

Muscle Relaxants

Intrathecal baclofen has been suggested to mediate dystonia-type symptoms that can be related to CRPS [60]. Oral antispasmodics are not recommended and often result in significant side effects such as dizziness and drowsiness. Intrathecal baclofen safety in pregnancy has not been studied, and oral baclofen has been shown to cause fetal structural abnormalities in animal models only. There are no well-controlled studies of baclofen in human pregnancy [68]. Although there are other muscle relaxants that are used for chronic pain such as tizanidine, cyclobenzaprine, and benzodiazepines, these medications have not been studied in CRPS. Benzodiazepines such as diazepam have been documented to increase the risk of congenital malformations and other developmental abnormalities and have similar associated risks to infants being born on opioids, such as neonatal flaccidity, respiratory and feeding difficulties, and hypothermia [69]. Tizanidine and cyclobenzaprine both have not been well studied in pregnancy [70, 71].

Alpha-Adrenergic Agonists

Clonidine is an alpha2-adrenergic agonist thought to help with the more autonomic components of pain [30]. Application has been trialed via oral, transdermal, and more recently, intrathecal routes. Oral clonidine has not been supported for its use in CRPS. Transdermal clonidine has been shown to reduce hyperalgesia and allodynia in a case series; however, larger, randomized controlled trials in other neuropathic conditions have not shown significant success [72]. Intrathecal clonidine has been studied against placebo and adenosine with no long-term benefits on pain and a significant side effect of lowering blood pressure [60]. There are no well-controlled studies of clonidine in pregnancy to determine if it is safe to use for the management

of pain; however, its use for management of hypertension in pregnancy is well studied and frequent [73, 74].

Immunomodulators

More recently, immunomodulators have been studied in CRPS, particularly, tumor necrosis factor alpha (TNF-α) inhibitors. TNF-α is a cytokine that promotes an inflammatory response that is secreted predominantly by macrophages but can be found in other cells. Anti-TNF agents are thought to cause inhibition of the inflammatory cytokine cascade, alter leukocyte recruitment and endothelial activation, and reduce neovascularization, among other anti-inflammatory mechanisms [56]. Case reports have shown promising results with the TNF-α inhibitors thalidomide and infliximab, though these studies have only involved very small patient populations [56]. Unfortunately, thalidomide is a powerful teratogen that has been reported to cause mortality in about 40% of infants and results in significant birth defects even after one dose [75]. There is insufficient evidence to conclude if infliximab is safe to use in pregnancy, though no significant adverse events have been reported thus far [76]. Intravenous immune globulin (IVIG) is thought to cause an interference with activation of the complement and cytokine network. There have been case reports and one randomized controlled trial that showed improvement in CRPS symptoms after IVIG compared to placebo with no significant adverse events [56]. There is no current data on the safety of IVIG during pregnancy and no well-controlled studies have been done [77].

Opioids

Opioids remain a controversial medication class for management of any chronic pain condition due to their significant adverse effects and risk of addiction. There has been no recent research or case reports investigating opioid use in CRPS. There is some evidence for its use in neuropathic pain, though dose escalation is common, and the need to use acute "rescue" doses for a pain crisis tends to escalate [30]. Tramadol, a partial serotonin and norepinephrine reuptake blocker, and methadone, an N-methyl-D-aspartate receptor (NMDA) antagonist, have been suggested to manage neuropathic pain such as in CRPS, but the risks of their use persist. Hyperalgesia with prolonged opioid use must be considered as well [30]. Morphine, oxycodone, Percocet (oxycodone and acetaminophen), Vicodin (hydrocodone and acetaminophen), dilaudid (hydromorphone), tramadol, and methadone were reviewed for their safety and use in pregnancy. All opioids are linked to neonatal opioid withdrawal syndrome (NOWS). This syndrome presents as irritability, hyperactivity, tremor, vomiting, diarrhea, failure to gain weight, abnormal sleep, and high-pitched cry in the newborn. This syndrome may be life threatening; the severity and duration of symptoms depend on the amount and timing of opioids used during pregnancy [78, 79]. Controlled studies of various opioids have been done in animal models. The

manufacturers of morphine, tramadol, dilaudid, and methadone have noted skeletal, neural tube, and external defects with toxic doses of these medications [78, 80–82]. These defects were not seen with oxycodone [83]. Nonteratogenic effects seen in animal models have included low birth weight, difficulty with breathing, delayed motor maturation, decreased offspring fertility, as well as decreased fertility in the mother and father if taking opioids. Behavior problems including increased stress, anxiety, and altered learning and memory have been suggested as well [80–84]. Methadone has been studied more so in pregnant women as it is a medication commonly used in those with a history of opioid dependence and abuse. Currently, the data show there are unlikely teratogenic risks associated with methadone and no increased risk of miscarriage. There may be decreased fetal growth, weight, and height at birth, though these deficits do not appear to persist. Other studies that have looked at behavioral or cognitive development have not been conclusive in their findings due to possible confounding factors. Overall, women who are on methadone maintenance programs have improved prenatal care leading to significantly reduced obstetric and fetal complications compared to women using illicit drugs, so the risk of discontinuing methadone should be strongly considered in a woman on methadone who would like to become pregnant [78]. There are no well-controlled studies in humans during pregnancy to assess the abovementioned risks. Additionally, extensive monitoring of the infant while breast feeding may need to continue if the mother is taking opioids since all forms of opioids are found in breast milk and, therefore, can be transferred to the infant.

Other Oral Medications

Bisphosphonates are a well-studied class of medications for management of CRPS. Those with CRPS who show active bone resorption on triple-phase bone scan may benefit from medications that alter bone resorption. As mentioned previously, within the first 5 months of onset of CRPS, there can be increased activity seen in all three phases of the bone scan [42]. Bisphosphonates inhibit osteoclasts and reduce osteoblast activity to help slow down the rate of bone turnover especially at active remodeling sites and become activated in an acidic environment [45]. Bisphosphonates also reduce acidosis, which can be a cause of pain in both the tissues and the bone and have been shown to decrease production of proinflammatory mediators [45]. Varenna et al. explained several ways that bisphosphonates could work to alleviate symptoms of CRPS [45]. To date, there have been several randomized controlled trials and case reports of both oral and intravenous treatments with older generation bisphosphonates that have shown promising results in reducing pain [44, 56, 60]. There were no reported adverse events (notably osteonecrosis) in these trials [56]. The intravenous bisphosphonate neridronate had shown initial good results for management of CRPS [85]; however, the clinical trial was halted in 2018. Bisphosphonates may cause fetal harm if used during pregnancy. There have been significant skeletal, visceral, and external abnormalities noted in animal models, though there are no well-controlled studies or data in humans to support these findings [86, 87].

Calcitonin is an oral or intranasal medication that is thought to have antinociceptive effects independent of its effect on bone. Randomized controlled trials have been done investigating calcitonin, one of which showed improvements in pain, and the others, which have involved both oral and intranasal formulations, did not show significant benefit [60]. There are no significant human studies to support if calcitonin is safe to use in pregnancy [88].

Vitamin C (ascorbic acid) has been studied in clinical trials as a preventative intervention after a soft tissue injury to a limb. Its role is to inhibit proinflammatory cascades as an antioxidant [89]. Given the significant inflammatory state of CRPS and the known microcirculatory effects CRPS causes to a limb, Vitamin C has been trialed as a stabilizing medication to prevent CRPS from developing. Its use has been studied in orthopedic literature, which describes Vitamin C as an appropriate adjunct for prevention of pain following wrist fracture [90]. A meta-analysis of randomized controlled trials of distal radius fracture treatment with Vitamin C to prevent CRPS showed conflicting results [89]. A follow-up meta-analysis looked at three upper extremity and one lower extremity study of utilizing daily high-dose (500 mg) Vitamin C after surgical intervention to the wrist or ankle and found that the results were statistically significant in preventing CRPS [90]. Given that Vitamin C is inexpensive and easy to obtain, its use is being encouraged in patients who may develop CRPS. Toxicity with Vitamin C has only been seen in extreme doses (intravenous doses in renal failure and overall doses greater than 50 times the regular dose) [91]. Vitamin C has been used for decades in pregnancy. A published meta-analysis looked at women who took daily Vitamin C between the 9th and 16th weeks of pregnancy and showed no adverse outcomes; however, there are no enough data to rule out the possibility of any negative effects. The dose of Vitamin C should not exceed the daily recommended dose [92].

Topicals

The 5% lidocaine patch is FDA approved for treatment of postherpetic neuralgia and has been helpful in the management of allodynia [30]. Given these findings, it may have some efficacy in treating CRPS [30]. There are no known side effects to using lidocaine patches during pregnancy; however, there have been no well-controlled studies on its use in pregnancy [93]. Capsaicin is a compound found in chili peppers that is an agonist for receptors on central and peripheral terminals of nociceptive primary sensory neurons [30]. When topical capsaicin is used, it causes dying back of nociceptive nerve endings, though use of it can be user limited due to the burning sensation at the site of application until that area becomes denervated [30]. Capsaicin has been found to be helpful in postherpetic neuralgia, and in patch form has been used in peripheral neuropathic pain with success; however, its use is significantly limited by the painful burning [30]. There are no known risk factors for its use in pregnancy, and there is currently insufficient evidence regarding whether or not capsaicin is safe in pregnancy [94]. Free radical scavengers have also been studied in CRPS patients due to the tendency of inflammation to cause an increase

in free radical formation. Dimethyl sulfoxide N-acetylcysteine (DMSO) cream has been studied and shown to decrease pain and increase range of motion compared to placebo [60].

Ketamine has also been tried as a topical, though its effects were quite short lasting and have not been studied independently since 2009 [60]. In 2015, a compound cream of ketamine, DMSO, clonidine, and pentoxifylline was created and trialed on 13 CRPS patients: nine reported symptom reduction and six reported continued reduction after 2 months [95]. Both topical DMSO and ketamine have not been studied in pregnant women and, therefore, cannot be concluded to be safe in pregnancy.

Botulinum Toxin

Botulinum toxin A (Botox) works by blocking acetylcholine release at the synapse to help ease spasticity and has been shown to inhibit glutamate and substance P, which may explain its role in easing neuropathic pain [30]. Trials have assessed botulinum toxin A for pain management in CRPS; however, it was not found to be beneficial and the procedure itself was found to be both painful and expensive [60]. When used in conjunction with bupivacaine in lumbar sympathetic blocks, the duration of analgesia was significantly longer [30]. Botulinum toxin A has not been adequately studied for use during pregnancy. In some animal models, decreased skeletal ossification, reduced growth, early delivery, and maternal death occurred. However, other animal models did not demonstrate any adverse events [96].

Ketamine

Intravenous ketamine has been more recently studied for management of CRPS due to its effects on central sensitization and hyperalgesia. Glutamate is thought to be upregulated due to inflammatory factors and has an affinity to NMDA receptors, which causes an increase in synaptic pain signal transmission [60]. Ketamine is an NMDA antagonist and is, therefore, thought to block this response. Up until 2019, trials have mostly been underpowered, and there have been no clinical guidelines for dosage or duration of infusion, and there were no safety parameters for monitoring patients during infusion. Xu et al. have since released guidelines for the use of ketamine in 2019 [97]. There are many serious side effects to consider with its use especially if used in too high of a dose, including cardiac, psychiatric, and gastrointestinal effects [98]. Randomized controlled trials thus far have shown promising and prolonged results with management of pain and quality of life, though the abuse potential and possible side effects make this treatment complicated. Intrathecal ketamine has been tried without significant benefit [30].

There are no well-controlled studies of intravenous ketamine done in pregnancy. Animal models have demonstrated developmental delay when used [98].

Cannabis (Marijuana)

As legislation changes and research continues, cannabis has become a popular medication for management of central pain. Currently, its legal use is determined on a state-by-state basis and is FDA approved for management of certain seizure disorders, spasticity and pain in multiple sclerosis, severe cancer-related pain, an appetite stimulant in cancer and HIV patients, as well as an antiemetic for those receiving chemotherapy. Given the complexity of CRPS, the use of cannabis for pain management will likely come into question. THC (delta-9-tetrahydrocannabinol) is the component of cannabis that can cause both excitatory and inhibitory effects, leading to relaxation and enjoyment and the feeling of being "high" as well as anxiety, psychotic symptoms, depression, apathy, and impairment of memory, concentration, executive function, and coordination. The degree of these symptoms and how long they last vary widely from person to person and by route of administration [99]. CBD (cannabidiol) on the other hand does not have acute effects on motor or cognitive performance, and acts more as an anxiolytic and sedative, as well as an anticonvulsant [99]. In a study performed by Martín-Santos et al., subjects were given a dose of THC, CBD, or placebo in a double-blind fashion and their effects were documented by the subjects for the next 3 hours. The psychotic symptoms documented in the THC group varied significantly among subjects, and the CBD group showed significantly few differences from the placebo group when measuring anxiety levels. However, the study does note that prior studies have shown CBD being most effective for decreasing anxiety for subjects who had a history of anxiety [99]. Given these findings, a lower THC dose in cannabis products is preferred to prevent possible psychotic symptoms in patients.

There is no current literature on cannabis being used in patients with CRPS; however, there is extensive literature on its use in other chronic pain conditions. The cannabinoid system is important to the development, homeostasis, and neuroplasticity of the central nervous system [100]. Endogenous opioids are produced and act on cannabinoid receptors to decrease pain in the central and peripheral nervous system. Nerve injury can cause sensitization to the pain pathway, and cannabinoids are thought to help mitigate this effect [100]. There have been many randomized controlled trials on neuropathic pain and cannabis use. A review by Modesto-Lowe et al. documented several trials that assessed patients with peripheral neuropathy due to HIV, diabetes, trauma, or undetermined etiology who smoked or inhaled vaporized cannabis, utilizing various levels of THC. All studies suggested that pain improved significantly in the cannabis groups compared to placebo and that a higher THC percentage likely resulted in more pain improved; however, the higher THC group also reported the most negative side effects [100]. Different forms of cannabis are available for treatment of conditions and include smoked, vaporized, edible, and sublingual. A cross-sectional study by Hazekamp et al. provided an international, web-based survey to cannabis users to document their reasons for cannabis use, the method they use, and to comment on their experience with cannabis. The most common reason for cannabis use was management of pain, and the side effects were

more prevalent in the pharmaceutical cannabis than the herbal cannabis. Users preferred to smoke or used vaporized forms of cannabis compared to pill form or edibles [101].

There have been several studies that have looked at brain development, behavior, structural abnormalities, and fetal mortality rates as related to marijuana use in pregnancy. In utero exposure has been linked to impaired cognition and increased sensitivity to drugs of abuse, lower test scores with visual problem solving, and decreased attention spans compared to those not exposed. There are no studies that show structural abnormalities in humans following marijuana exposure to a fetus. The rate of stillbirth appears to be increased with marijuana use in some studies; however, this could be confounded by cigarette smoking, which had not been controlled. There have been studies demonstrating low birth weights in newborns who were exposed to marijuana in utero; however, preterm birth did not seem to be associated. Overall, it is difficult to determine the effects of recreational marijuana, medical marijuana, or the different modalities of marijuana use (inhalation vs. edibles vs. sublingual) on the pregnant woman and there are no current studies that fully support if medical marijuana is safe to use in pregnancy [102].

Medications utilized in CRPS and recommendations for use in pregnancy

Medications	Recommendations for use in pregnancy
Antipyretics	
Acetaminophen	Safe to use throughout pregnancy if taken appropriately
Anti-inflammatories	
NSAIDs	NSAIDs should not be used during third trimester and can cause premature pulmonary ductus arteriosus closure
Aspirin	Same recommendations as NSAIDs Low-dose (81 mg/day) aspirin is recommended for all high-risk preeclampsia women. Should be started as soon as possible in pregnancy, at least between 12 and 28 weeks, and continued through pregnancy
Corticosteroids	No well-controlled studies done in pregnancy, its safety cannot be determined May cause hypoadrenalism in newborn if high doses are used during pregnancy
Tricyclic antidepressants	
Amitriptyline	No well-controlled studies done in pregnancy and its safety cannot be determined CNS abnormalities, limb deformities, and developmental delay have been reported
Antiepileptics	
Gabapentin	Gabapentin has no well-controlled studies done in pregnancy and its safety cannot be determined
Pregabalin	Pregabalin has demonstrated fetal abnormalities in animal models. There are no well-controlled studies done in human pregnancy
Carbamazepine	Carbamazepine is a known teratogen, notably causing spina bifida, craniofacial defects, and cardiovascular abnormalities It should not be used in pregnancy
Oxcarbazepine	Oxcarbazepine may not be safe in pregnancy; however, there are no well-controlled studies to determine its safety

Medications	Recommendations for use in pregnancy
Phenytoin	Phenytoin is a known teratogen, it should not be used in pregnancy
Lamotrigine	Lamotrigine has no well-controlled studies done in pregnancy
Muscle relaxants	
Baclofen	No well-controlled studies done in pregnancy for both intrathecal baclofen and oral baclofen Oral baclofen has demonstrated fetal abnormalities in animal models
Benzodiazepines	No current literature on the use of benzodiazepines, tizanidine, or cyclobenzaprine in CRPS Benzodiazepines linked to congenital malformations and neonatal flaccidity, and respiratory and feeding difficulties
Tizanidine Cyclobenzaprine	No well-controlled studies done in pregnancy for tizanidine or cyclobenzaprine, and their safety cannot be determined
Alpha adrenergic agonist	
Clonidine	No well-controlled studies done in pregnancy for management of pain; however, it is a common medication for treatment of hypertension in pregnancy
Immunomodulators	
Thalidomide	Significant fetal mortality rate with use and a known teratogen. Should not be used in pregnancy
Infliximab	No well-controlled studies done in pregnancy and its safety cannot be determined
IVIG	No well-controlled studies done in pregnancy and its safety cannot be determined
Opioids	
Morphine Oxycodone Percocet (oxycodone and acetaminophen) Vicodin (hydrocodone and acetaminophen) Dilaudid (hydromorphone) Tramadol Methadone	Risk of opioid dependency and NOWS in infants with exposure to any opioid during pregnancy No well-controlled studies done in pregnancy and its safety cannot be determined Risks versus benefits of opioids in pregnancy should be considered, especially in patients on methadone for history of opioid abuse
Bisphosphonates	No well-controlled studies done in pregnancy and its safety cannot be determined
Calcitonin	No well-controlled studies done in pregnancy and its safety cannot be determined
Vitamin C (ascorbic acid)	No significant adverse events reported. Do not exceed recommended daily dose
Topicals	
Lidocaine patch Capsaicin cream DMSO Ketamine cream	No well-controlled studies done in pregnancy and its safety cannot be determined in the listed topicals
Botulinum toxin	No well-controlled studies done in pregnancy and its safety cannot be determined
Ketamine	No well-controlled studies done in pregnancy and its safety cannot be determined
Cannabis (marijuana)	Behavior problems and low birth weight were linked to cannabis use Insufficient data on medical use of marijuana or other forms of marijuana/CBD/THC in pregnancy

Interventional Therapies

Interventional procedures for the management of CRPS are frequently used if conservative treatments are not effective. Commonly used procedures include trigger point injections, nerve blocks, implantable devices, and even surgical intervention. The safety of these procedures in pregnancy is discussed below.

Trigger Point Injection

Trigger points are thought to be localized taut bands of muscle fibers which cause pain when manipulated [103]. Trigger point injections have been well studied as a means to manage muscular/fascial pain related to trigger points [103, 104]. It has been proven in multiple studies that the injectate is not important in the trigger point injection, but rather that the needle manipulation itself is sufficient to cause pain relief [100, 105]. The conventional trigger point injection involves an anesthetic and/or corticosteroid. The use of these medications is not without risks, especially if the medication is injected intravascularly or if an allergic reaction occurs [103]. The use of trigger point injections has not been well studied in CRPS and is currently limited to case reports [106, 107]. Trigger point injections have not been specifically studied in pregnancy either. As previously discussed, steroid use in pregnancy has not been well studied and comes with the risk of hypoadrenalism in the newborn if used in high doses. Localized lidocaine injections have not been well studied to indicate if they are safe to use in pregnancy [108].

Sympathetic Nerve Block

The sympathetic nerve block (stellate ganglion block for the upper extremity and lumbar sympathetic block for the lower extremity) serves as a diagnostic and therapeutic intervention for CRPS [30]. Pain relief following a successful sympathetic block with either anesthetic or botulinum toxin can be long term and generally outlasts local anesthetic blocks. A successful block can be determined by a change in temperature in the affected limb (usually by about 2–3 degrees Celsius), an increase in blood flow to the limb, decreased electrical conductance of the skin, and, in the upper extremity, Horner's Syndrome should be present, though not all patients experience all of these changes [30, 109]. There have been studies that have shown no difference and even an inferior effect of sympathetic blockade versus intravenous regional anesthesia (discussed below) [30]. Though the role of sympathetic nerve blockade is largely empirical, its use does become significantly important if pain is relieved in an individual so that other rehabilitation techniques can be used for treatment during that pain-free time [30].

Lumbar sympathetic blocks have been used for decades in the first stage of labor for pregnant patients, especially if the patient has a history of spine pathology or

lumbar spine surgery making epidural placement more difficult [48]. However, this procedure has more risks than a traditional epidural [110].

There are no known reports of lumbar sympathetic blocks being performed for pain management in pregnancy. However, it is worth mentioning the risks of radiation exposure secondary to procedures. Ultrasound and MRI are considered safe modalities during pregnancy. If any other imaging modality is deemed necessary for the care of a pregnant patient (such as CT scan and X-ray) and the benefit of the study outweighs the risk of fetal exposure, the imaging should be done. The dose of radiation from CT, X-ray, or nuclear medicine scans are overall much lower than the amount needed to cause harm to a fetus [47]. If fluoroscopy needs to be used for procedures during pregnancy (such as nephrostomy, cholecystostomy, or suprapubic cystostomy, to name a few), precautions are taken such as placing a lead apron on the patient's pelvis, maximizing the distance between the X-ray source and the image receptor, using pulsed fluoroscopy at the lowest rate, and minimizing the amount of pictures taken. The posteroanterior approach is preferred over oblique or lateral imaging due to the shorter distance the beam needs to travel through the patient [111]. All imaging procedures should be performed only if necessary, and radiation exposure should always be minimized, especially in the pregnant patient.

Bier Block

Intravenous regional anesthesia, otherwise known as a Bier block, has been used to provide anesthesia for local procedures for many years. In CRPS, sympatholytic, antihypertensives, anesthetic, and anti-inflammatory medications have been used frequently [112]. Clonidine has been a more recent medication used for management [113]. The procedure is done with an application of a tourniquet to the proximal aspect of the affected limb and an IV is inserted distally. The solution of choice is injected slowly, and the cuff is deflated gradually after a specified amount of time. Vitals are monitored and pain scores recorded [112]. Randomized controlled trials have been done with many different medications. The trials have demonstrated varying degrees of success: one trial utilizing clonidine over multiple sessions demonstrated good long-term relief of symptoms in the lower extremity [113]. Studies utilizing NSAIDs or steroid paired with anesthetic have shown intermittent short-term success [112, 114, 115]. A systematic review performed in 2016 evaluated retrospective studies on intravenous blocks with methylprednisolone and lidocaine. Those that received doses of the medication multiple times over several weeks were much more likely to have good long-term benefits than those that received a single intravenous infusion [115–117]. Intravenous lidocaine alone has been proven to be affective for symptoms that are thermal (significant heat or coolness to the limb) and for allodynia [117, 118]. Antihypertensives, such as guanethidine and reserpine (among others), have been frequently used with anesthetic and/or steroid for regional anesthesia and have been successful in case reports; however, several double-blinded, randomized controlled trials have shown no significant benefit with

using these antihypertensives compared to controls, and high doses of these medications can cause significant side effects [112]. Other intravenous medications utilized for pain in CRPS have been discussed previously. Up to 2% of pregnant patients will undergo a nonobstetric surgery while pregnant. Operations are most likely to be for pregnancy-related complications but also involve laparoscopic procedures (appendectomy, cholecystectomy, ovarian disorders, etc.). Regional anesthesia is preferred over general anesthesia if safe and possible [119]. Though the utilization of regional anesthesia is commonly used for operative procedures in pregnancy, its use in pain management as a Bier block has not been well studied. Medications used commonly in the Bier block mentioned above have been described in pregnancy previously in this chapter.

Dorsal Root Ganglion Stimulation

The dorsal root ganglion (DRG) is located between every spinal nerve and the spinal cord and contains the primary sensory neurons. Animal models have shown pathophysiologic changes in the DRG in the setting of chronic pain. Because of these findings and its ease of access, it has become a more popular target for stimulation to control neuropathic pain. Procedures targeting the DRG (radiofrequency ablation, steroid injection, and ganglionectomy) have been thought to be more effective in managing CRPS symptoms than spinal cord stimulators since the signal from the spinal cord stimulator (SCS) can be augmented in cerebral spinal fluid, stimulator leads can migrate, and position changes can affect stimulation [120]. A randomized controlled trial in 2017 of CRPS patient who underwent DRG stimulation versus SCS implantation was performed: those who underwent DRG stimulation had an 81.2% success rate in treating CRPS pain compared to the 56.7% success rate in those who received a stimulator [120]. Stimulators used for DRG stimulation have not been proven to be safe during pregnancy [121]. There are no apparent case reports of its use in pregnancy in the current literature.

Radiofrequency Ablation

Ablation and neurodestructive techniques for sympathectomy have been discussed and utilized for many years for management of CRPS, though they have fallen out of favor as they have not been shown to cause significant improvement in symptoms and there is an increased rate of recurrence after such invasive techniques [30]. Radiofrequency ablation (RFA) to cause sympatholysis has been compared to phenol neurolysis and was not proven to be more effective [60]. Pulsed RFA was compared to conventional block in the lumbar sympathetic chain and was not found to be more effective as well [122]. However, case reports have shown benefit for some patients who received pulse RFA, even years later [123]. RFA in pregnancy is not well described. One case report of pulsed RFA to the piriformis in a pregnant patient with a malignant mesenchymal tumor has been reported: the ablation

provided significant relief without adverse events [124]. There does not appear to be other significant literature currently on the use of ablation for pain during pregnancy. As stated above, any radiation exposure in pregnancy should be minimized and should only be used if necessary.

Spinal Cord Stimulator

The use of SCS in management of CRPS pain has been shown not just to be effective in controlling pain but has also improved quality of life and reduced health care costs [125, 126]. The SCS mechanism of action is not fully understood, though there may be a relationship to the suppression of dorsal horn signals within the spinal cord. Dorsal horn neurons are thought to undergo long-term potentiation and lead to central sensitization, which is a hallmark of chronic pain [127]. Patients with spinal cord stimulators have access to a handheld programmer to adjust or turn on/off their spinal cord stimulator, making its use more convenient for the patient.

Though SCS use is currently not recommended in pregnancy due to theoretical complications including possible lead migration, exposure to an electromagnetic field to the mother and fetus, as well as possible implications on neonatal health, several case reports have been published that have acknowledged successful pregnancies with concurrent SCS use for management of CRPS [49]. There have been no reported miscarriages secondary to SCS use [49]. There have been reported cases of preterm labor while SCS has been in use; however, because these incidents are reported in a noncontrolled fashion, it is inconclusive if the SCS was a contributing factor to preterm labor. Case report studies showed that there have been no reported negative health effects to either a mother or fetus with SCS use [49, 128–132].

Acupuncture

Acupuncture has been used for thousands of years to treat chronic conditions including pain; however, its use is still controversial. A recently updated meta-analysis confirmed the significant effect that acupuncture has on the management of chronic pain compared to controls [133]. Acupuncture in the management of CRPS has been discussed in case reports [134, 135]. Given the overall safety profile of acupuncture, pregnant women have trialed acupuncture for management of pelvic pain as well as nausea/vomiting throughout pregnancy [136]. A meta-analysis in 2008 was only able to elucidate three randomized controlled trials of acupuncture for management of back and pelvic pain in women in their second and third trimesters. Despite the small sample size, there was a small positive effect on pain management when acupuncture was used. The authors did note that placebo effect and the role of the patient believing in the effectiveness of acupuncture could be a confounding factor [136]. There were no adverse effects noted in the analyzed trials [136]. A systematic review of the safety of acupuncture in pregnancy was performed in 2014. Of the 22,283 sessions of acupuncture performed across 105 articles, the

incidence of adverse events was determined to be 1.3%, with the risk of mild-to-moderate adverse events being 1.5% and no serious adverse events or death causally related to acupuncture [137]. Bleeding, hematoma, pain at the site of needling, dizziness, headache, and worsened pain have been the most widely reported adverse events [137].

Therapy and Modalities

CRPS is best managed with an interdisciplinary approach given the complexity of the symptoms and the potential for significant disability. While the above medications and interventional procedures play an important role in acute pain relief, therapy (physical, occupational, recreational, and vocational) as well as the modalities utilized during therapy are essential for long-term relief and prevention of pain in any patient with a chronic pain condition. Fortunately, many of the described modalities are used to treat the significant pain complaints that can occur during pregnancy.

Physical Therapy

One of the cornerstones for treatment of any complex pain condition is physical therapy (PT). Through PT, patients focus on strengthening, range of motion, flexibility, and are introduced to modalities otherwise not available to them at home (ultrasound, hydrotherapy, mirror therapy, etc.). PT in the setting of CRPS focuses on increasing the ability of the affected limb, which may have restricted movement or edema secondary to the CRPS. Following a successful interventional procedure to reduce pain, patients can better tolerate these manipulations. Another component of physical therapy that becomes important in CRPS is relaxation techniques and managing pain once it does return. Education is essential for all patients with chronic pain conditions.

Myofascial release and massage are frequently used in physical therapy to help loosen muscles and provide pain relief, sometimes decreasing edema to the area [30]. Myofascial pain can be a significant component of CRPS and may help relieve the other autonomic symptoms of CRPS if treated in therapy [30]. Tactile discrimination and desensitization therapy are utilized by physical therapists when treating patients with hypersensitivity and allodynia. Studies done in CRPS have shown that patients will have less awareness of their affected limb in space compared to the unaffected limb, and it takes longer for a person to respond to stimuli when applied to the affected limb [138]. Incorporating two-point discrimination and having the patient locate and determine the stimuli to the affected limb has been shown to help reduce pain in CRPS [138]. Desensitization is the process involving increasing sensory stimuli to the affected area with different textures, starting with very light and smooth objects and progressing to gradually heavier and more abrasive materials. The theory is that desensitization alters the central processing of the nervous system

and resets "normal" feeling to the area [30]. Aquatic therapy is a good option for patients who have a difficult time with weight bearing and have significant edema from CRPS. Working through range of motion and activities that would normally be painful on ground may be improved with the addition of water if the water is at the appropriate temperature so as not to exacerbate symptoms. Contrast bath utilizes variations in water temperatures and is further discussed below.

The above modalities are frequently used in pregnancy, especially in the setting of low back pain [30]. Strengthening, range of motion, myofascial release, and bracing are frequently used for patients who are unable to make lifestyle changes on their own [139]. Aquatic therapy is frequently utilized in pregnancy given the buoyancy and decreased load on the patient. The water can help dissipate heat as well when exercising, though care should be taken in extreme hot and cold water so as not to alter heart rate and blood pressure drastically [140].

Modalities

TENS

Transcutaneous electrical nerve stimulation (TENS) has been used for both acute and chronic pain. The proposed theories of its use are gate theory, induction of local vasodilation, and stimulation of acupuncture points [141]. A study by Bilgili et al. demonstrated significant improvement in neuropathic and spontaneous pain scores as well as range of motion among patients utilizing TENS in conjunction with hydrotherapy and exercise compared to those who did not receive TENS [141]. Of note, the TENS was not used alone for management, which is consistent with the general practice of modalities being used as an adjunct rather than a solo treatment. In a small prospective study, pregnant patients at greater than 32 weeks were assigned to nothing, exercise, acetaminophen, and TENS for treatment of low back pain. The TENS group showed significant improvement in pain compared to other groups [142]. The use of TENS has been studied late in pregnancy as well, and no adverse events during pregnancy or labor and delivery were observed [143]. Although there is a theoretical risk of inducing contractions if a TENS is applied over certain acupuncture points, this risk has not been proven and any induced contractions would stop as soon as stimulation from the TENS is stopped. There have been no reported fetal anomalies or changes in fetal heart rate with TENS use as well. The current density from the TENS should be low and the electrodes are recommended not to be placed around the pelvis in a mother who is thin and if the fetus is lying in the occipitoposterior position [144]. In the case of CRPS, the TENS would be applied over the affected limb, therefore, not involving the abdominal area. TENS is likely an acceptable modality for pain relief in a pregnant patient with CRPS.

Contrast Bath

Contrast baths utilize hot and cold water to help improve circulation to the affected area by theoretically promoting alternating vasodilation and vasoconstriction [30]. Depending on the patient, the significant change in temperature may exacerbate

CRPS symptoms and may not be well tolerated. Typically, contrast baths involve two buckets, one with warm water and one with cold water, and the affected area is submerged for a certain amount of time. Martins et al. utilized a 4:1 minutes hot-to-cold ratio for submersion with success and this has been used in prior studies [145]. As previously discussed, large variation in the temperature of water for a pregnant patient can cause significant effects on heart rate and blood pressure and is generally not advised in pregnancy [141]. However, since contrast baths only apply to the affected limb and involve relatively little water, this practice is unlikely to have significant effects on the fetus or mother. There are no significant studies of contrast baths used in pregnancy.

Fluidotherapy

Fluidotherapy is a dry heat modality that creates a convection-formed vortex with heated air and finely ground particles. The heated air circulates the particles and encases the area in what feels like fluid. Its use in CRPS has been shown to be helpful with range of motion and decreasing pain sensitivity. A study from 2019 randomized upper extremity CRPS patients to combined fluidotherapy with a conventional rehab program or to only a conventional rehab program. Those who received fluidotherapy had improved neuropathic pain and decreased edema after treatment [146]. Fluidotherapy does not appear to be studied in pregnancy. The application of fluidotherapy is only applied to the affected limb, limiting the exposure of increased heat centrally or to the fetus. Though safety is not determined, it is unlikely this modality would cause harm to the fetus or the mother.

Ultrasound

Ultrasound has been a therapeutic modality for treatment of musculoskeletal or ligamentous injuries for many years. It induces its effects through heating as well as other nonthermal processes such as mechanical stress [147]. In PT sessions, higher intensity settings are used compared to diagnostic ultrasound to produce heat to the tissue. The amount of heat should be kept within safe parameters to avoid burning and necrosis. The goal is to improve blood flow to the area to help accelerate healing. Ultrasound can be coupled with promoting transport of compounds into the skin as well in a process called phonophoresis [147]. There is a modest level of efficacy with ultrasound in the PT literature, though its significance remains uncertain [142].

Ultrasound is not well studied in CRPS, and trials that have been done have not shown its use to be effective [148]. Other small case studies have shown its effectiveness with daily use [149]. In pregnancy, exposure to any imaging modality or radiation, even ultrasound, should be limited to when necessary. The amount of heat absorbed in tissues of the abdomen during ultrasound evaluation of the fetus is not significant enough and too quickly dissipated to cause any harm [150]. The World Health Organization conducted a systematic review and a Cochrane review that assessed birth weight, perinatal mortality, neurological development, school performance, and handedness. Only handedness has shown any association with ultrasound exposure in utero [150]. CRPS would involve ultrasound of the limb involved

and be far removed from the pelvis and fetus, and therefore may be an acceptable modality for a physical therapist to try to help alleviate pain.

Occupational Therapy

Occupational therapy (OT) primarily focuses on returning patients to independently performing activities of daily living, such as eating, bathing, and grooming. Range of motion, dexterity, proprioception, as well as pain control are important for accomplishing these tasks. There is overlap with modalities provided by PT and OT including edema management, mirror therapy, and graded motor imagery. Splinting for hands and arms may be necessary if there is reduced range of motion or contracture from CRPS. Stretching and carrying exercises become important for weight shifting and weight bearing in the upper extremity [30]. Compression gloves can be considered for edema control. Modalities as discussed above could be applied in OT as well to treat CRPS in pregnancy.

Mirror Therapy

Mirror therapy was first utilized for treatment of phantom limb pain as a way for patients to control and move the phantom limb by focusing on the reflection of the normal limb. Being able to relax the phantom limb then leads to pain relief. Mirror therapy has been introduced as a way to treat CRPS and other chronic pain conditions. One study looked at two patients with CRPS type II of the upper extremity who were taught to do mirror therapy from home. The patients performed mirror therapy three to five times per day, each session lasting about 15 minutes. One patient did mirror therapy for 3 weeks, the other for 5 months. Both patients reported pain improvement between and during sessions and even long term [151]. A literature review on CRPS and mirror therapy assessed nine studies that all showed positive effects on pain and motor function after mirror therapy. These results were seen in both acute and chronic phases of CRPS as well as a modality by itself or paired with other modalities [152]. Mirror therapy itself appears to be a safe modality.

Chiropractic Care

Doctors who practice chiropractic care often perform multiple treatments to patients depending on their presentation. Manipulative therapy is most common; however, teaching exercise, nutrition, and prevention are mainstays of their treatment [153]. Most patients use chiropractic care for back or neck pain; however, there are numerous conditions chiropractors are asked to treat. CRPS has not been specifically studied with chiropractic care; however, treatment has been studied in patients with limb pain and vasomotor reflexes [154]. These studies showed improved symptoms in limbs that presented like CRPS, as well as improved vasomotor regulation.

Chiropractic care is safe in pregnancy and has been used for management of low back pain. In fact, it has been reported that 11% of pregnant women with low back pain will have at least one chiropractic treatment [155]. A systematic analysis performed in 2008 reviewed six studies about chiropractic care in pregnancy. All studies showed decreased pain following chiropractic care; however, the quality of evidence was questioned. There were no adverse events reported in any study, and most chiropractors feel that it is safe to perform spinal manipulation therapy on pregnant women [155].

Psychological and Behavioral Therapy

Chronic pain frequently impacts mental health and well-being. Therefore, utilizing psychological and behavioral interventions as a part of the treatment plan is often necessary. There are significant physiologic changes in CRPS that are thought to be linked to behavioral disturbances as mentioned previously. Therefore, psychological/behavioral treatments may help both the physical symptoms of CRPS and address the underlying emotional disturbances and stressors that the patient might have [30]. In pregnancy especially, depression can be a common complication and is best predicted by a history of depression prior to pregnancy. Antidepressants have been linked to preterm birth, low birth weight, pulmonary hypertension, and postnatal adaptation syndrome, making their use more complicated during pregnancy [34]. Because of the severity of the complications that can arise if depression is undertreated or not treated, depression is screened for during and throughout pregnancy and difficult decisions must be made in terms of treatment. If the benefit of staying on an antidepressant medication outweighs the risk (i.e., history of psychosis or suicidality), medications should be continued, and the pregnancy should be monitored closely. Psychotherapy is recommended as the initial treatment for mild-to-moderate depression especially as a new diagnosis or if medications were not required for treatment prior to pregnancy.

Below are common psychological and behavioral interventions used to manage chronic pain and are implicated in the treatment of CRPS.

Cognitive Behavioral Therapy (CBT) and Other Behavioral Therapy

An important aspect of managing pain in a patient with CRPS is reintroducing control to the patient's life. By teaching the patient how to better understand their condition and how it affects their thinking and behavior, they may be able to help themselves control pain flare ups and the emotional component that comes with increased pain [30]. As discussed previously, increased pain or a fear of increased pain can cause significant distress, leading to a surge in catecholamine release and, therefore, increasing CRPS symptoms. By engaging in CBT and other cognitive-based interventions, patients can learn to stop the cycle of physical and emotional distress. Behavioral intervention also includes goal setting and managing realistic expectations with patients, which is often discussed with physical therapists and with psychologists during treatment. Reactivating and using the affected limb involves

behavioral change, cognitive restructuring, additional psychotherapy tools, and conventional physical and occupational therapy [156]. Additionally, CBT becomes important for patients who are more likely to have a difficult time managing chronic pain which includes those with previous psychological diagnoses including depression and anxiety, who many have experienced significant life stressors especially if the CRPS was caused by a stressful event, and those who have a previous history of chronic pain conditions [156].

CBT itself focuses on assessing thoughts associated with pain, avoidance behaviors, and assessment of painful experiences. The behavior that is linked to pain is identified and uncoupled. Reviews on this topic have shown that those who engage in cognitive behavior therapy have improved disability posttreatment and improved pain, disability, and mood at follow-up [157]. Another review by Williams et al. assessed randomized controlled trials that analyzed patients with chronic pain who received either CBT or behavioral therapy. Thirty-five studies were assessed with nearly 5000 patients, the majority of which engaged in CBT: Of the outcomes measured, there were improvements seen in disability immediately posttreatment and at follow-up and catastrophic thinking posttreatment as well as small effects on pain and on mood at follow-up. Behavioral therapy had much weaker results [157].

Pregnant females who either have a history of depression or experience depression during pregnancy would likely benefit from psychotherapy. As previously mentioned, it is the treatment of choice for mild-to-moderate depression in pregnancy. Changes in anatomy, sleep patterns, pain, and the anxiety of pregnancy can lead to significant behavioral disturbances that should be adequately addressed.

Most studies in pregnancy focus on mindfulness (see below) or integrating CBT with other therapies. A meta-analysis performed in 2018 identified patients who used CBT in the perinatal period in order to combat anxiety. The study showed improvement in perinatal anxiety in those who received CBT versus control groups and from pretreatment to follow-up, although significant heterogeneity was noted and overall only a small amount of studies was identified [158].

Biofeedback

Studies related to CRPS patients receiving biofeedback have been quite small and limited to case reports; however, these case reports have demonstrated favorable results [30]. Thermal biofeedback and EMG biofeedback are primarily used in this patient population [156]. Patients with chronic pain are known to receive benefit from biofeedback. One meta-analysis looked at patients with chronic low back pain who received biofeedback as part of their treatment. Most studies utilized EMG biofeedback. All analyzed studies concluded that patients who received biofeedback in conjunction with other treatments or alone had improvements in pain intensity, depression, coping, and reduction in muscle tension, even at long-term follow-up [159]. In pregnancy, biofeedback has been used in different conditions including hypertension, migraine management, and pelvic floor muscle training. In terms of pain management, biofeedback has been studied primarily in labor pain, which has not shown significant benefit in randomized controlled trials [160]. Though no

significant research exists on using biofeedback in pregnant patients with chronic pain, it would be a reasonable therapeutic option to try given the low risk.

Meditation and Relaxation

The goal of meditation and relaxation especially for patients with chronic pain is to reduce emotional arousal in the setting of pain. Therapy often includes breathing-focused relaxation, progressive muscle relaxation, relaxing imagery, and autogenic training [30]. Progressive muscle relaxation can be particularly appropriate for CRPS as the protocol is to include the area affected by CRPS progressively to move through range of motion that initially avoids the tension-release cycle of movement. After being able to engage the affected area fully, a more proximal site of pain may be located to be a contributing factor to their chronic pain, which can be myofascial in nature and, therefore, be treated differently and appropriately [156]. Several randomized controlled trials have been performed to assess the efficacy of relaxation techniques in patients with CRPS. One study had a cohort of 18 patients, of which half were randomized to PT alone to address their symptoms and half were randomized to PT and autogenic relaxation. Both groups improved equally, and interestingly skin temperature improved more in the relaxation group [161]. In another randomized controlled trial with 135 patients, one-third were placed in a group that received PT, relaxation training and cognitive interventions, one-third received OT, and one-third were a control group. There were significantly greater improvements at 1-year follow-up for the PT and relaxation group in terms of pain, range of motion, and impairment levels [162]. Though the available data and research on relaxation in CRPS patients are small, there is significant evidence of its use in chronic pain patients [30].

Mindfulness, much in line with CBT and other behavioral interventions, has been studied in pregnant patients to manage the stressors that come with pregnancy. One randomized controlled trial placed one group of pregnant patients into a mindfulness training track that involved a 3-hour mindfulness session weekly over 8 weeks, and one group who received standard of care. The group who learned mindfulness reported significantly less stress and depression as well as more self-awareness compared to the standard group. These results were reflected during pregnancy and 3 months after delivery [163]. A similar randomized controlled trial assigned women to an 8-week mindfulness intervention group during pregnancy and compared them to controls who received standard of care. Results showed those who received mindfulness training had significantly fewer symptoms of anxiety and depression during pregnancy and during the postpartum period compared to controls [164]. Although neither of these studies commented on the patients having chronic pain conditions, it can be assumed that mindfulness would be beneficial to any patient who may experience stress or anxiety during pregnancy that may pervade into the postpartum period.

Hypnotherapy

Hypnotherapy has been studied over the years as an alternative treatment for pain management. A growing number of studies have suggested that hypnotherapy can

adequately treat pain conditions; however, the mechanism behind these effects is not well understood. Furthermore, what is considered "hypnosis" is not always clear; however, all treatments seem to have an "induction" phase during which the patient is introduced to a subjective experience and will be suggested to change their behavior and engage in different thoughts, not just during the treatment but also after the treatment is over. The goal is to teach the patient how to perform self-hypnosis so that they may be able to control their experiences long term after treatment has ended. Experiences are obviously subjective, and the amount of practice needed to achieve benefit varies widely. A review performed by Jensen et al. evaluated 19 studies that assessed hypnosis as a means to treat chronic pain, including cancer-related pain. They found that in 18 of the studies, hypnosis was considered effective in reducing pain, and some studies even reported continued pain relief 1 year after treatment [165]. Hypnosis compared to other treatments that implement suggestion (relaxation training, progressive muscle relaxation, etc.) yielded similar results. It is important to note that these studies are limited in number of patients, and the heterogeneity between studies and the types of patients evaluated makes their applicability challenging.

There are very few studies that assess hypnosis in CRPS alone. One study by Lebon et al. assessed patients who underwent hypnotherapy for CRPS of the upper extremity that occurred primarily after surgery. All patients underwent a hypnotherapy session followed by a PT session that focused on pain-relieving modalities, mobilization, and massage. These sessions were done weekly, interspersed with regular rehabilitation sessions 3 days per week. All patients reported significant benefit from hypnotherapy-PT sessions, and the researchers reported decreased time to achieve significant benefit compared to standard of care. Patients were also quicker to respond if their symptoms were more acute [166]. The author suggested that hypnotherapy reduces activity of certain brain areas that are active during painful treatments and activates areas that are involved in voluntary movement, which coincide with areas that are activated in CRPS [166]. The literature on hypnotherapy in pregnancy is largely limited to reducing pain during labor and delivery. A Cochrane review from 2016 assessed randomized controlled trials of utilizing hypnosis prior to or during labor with or without pharmacologic intervention. Women who received hypnosis were less likely to use pharmacological pain relief than the control groups; however, there was no difference between groups in most other primary outcomes, including sense of coping with labor, spontaneous vaginal birth, or satisfaction with pain relief. There was no difference between hypnosis group and groups that received standard care, counseling, or relaxation training. The number of epidurals used did not vary between groups either [167].

In summary, treatment of CRPS in pregnancy is challenging. An early and multifaceted, interdisciplinary approach is suggested by reasearchers. Common medications used for management of CRPS have not been well studied in pregnant women, and therefore must be used with caution. Acetaminophen can be considered as a first-line treatment for a pregnant woman with CRPS. Interventional procedures are not commonly performed in pregnancy, and the risk of radiation exposure must be considered. PT and OT can help teach patients to control their symptoms and use

safe modalities. Therefore, both are recommended for management. Psychotherapy and behavioral intervention-based therapy are imperative in chronic pain conditions and could become more important in a patient dealing with the stressors of pregnancy and the possible increase in pain that can occur while pregnant. In the future, well-studied protocols and guidelines are needed for a safe and effective treatment of CRPS in pregnancy.

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Chronic Regional Pain Syndrome in the Geriatric Patient

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Introduction

Complex regional pain syndrome (CRPS) is a chronic pain condition characterized by pain out of proportion in time and severity to the inciting stimulus. The pain usually occurs after major or minor injury secondary to physical trauma or surgery [1]. It most commonly affects the extremities and likely occurs as a result of dysfunction in the central or peripheral nervous systems [2, 3]. Chronic pain conditions are very common in the elderly and pose a significant economic burden on health care, especially with an increasing number of older aged individuals in our population. Chronic pain is defined as the pain that lasts for 3–6 months and chronic pain lasting for more than 6 months can then transition into the classification of CRPS.

CRPS in the geriatric population poses an interesting challenge to healthcare providers. There are very few published reports that focus specifically on CRPS in the geriatric population, yet of those that are published, many state that CRPS is

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quite common in the elderly [4]. And interestingly, CRPS typically develops after an injury, a surgery, a stroke or a heart attack, all of which are more commonly occurring as a person ages [5]. In fact, falls are the leading injury among older adults and every year, 1 out of 3 older adults falls, yet less than half tell their doctor [6].

Clearly, this gap in the literature involving this patient population which makes it challenging to both collect relevant information and to find new information to help treat these patients. Furthermore, there is known discrepancy in the definition and diagnosis of CRPS in the literature, which likely adds to the paucity of studies involving geriatric patients and CRPS [7]. There are two types of CRPS that also have alternative nomenclature which further adds to the confusion. **Type 1:** A trivial injury, for example, fractured or sprained ankle, with no confirmed nerve damage. This type was previously known as reflex sympathetic dystrophy (RDS). **Type 2:** This may emerge after breaking a bone, having surgery, or after a serious infection and there is clear evidence of nerve damage. This type was previously known as Causalgia [8].Comorbidities and physical ailments in the older population may also lead to underreported chronic pain or misdiagnosed CRPS. However, as the baby boomer generation is continuing to increase in age, healthcare providers must be aware of CRPS occurring within this population. This chapter will attempt to extrapolate relevant information involving the elderly and relevant chronic pain syndromes, as well as explain what has been published involving CRPS in geriatric patients.

Epidemiology

It is well known that chronic pain states increase as we age; however, the literature on the epidemiology of CRPS is limited, making it difficult to adequately assess the socioeconomic burden of the condition. One retrospective population-based study found the incidence of CRPS in the general population peaks in incidence at 50–70 years of age [9]. Furthermore, another study further suggested that the peak incidence of CRPS is 55–75 years of age, however, noting that CRPS may be considered more benign in this age group than in younger patients [10]. Finally, a study of National Health Insurance Service data in Korea determined that the prevalence of CRPS had an increased prevalence in females, and found that prevalence was greatest in elderly patients (>70 years old) [4].

Pathophysiology

The basic pathophysiology of CRPS remains unclear, including the mechanism of disease onset and progression [11]. CRPS most likely does not have a single cause, but rather results from multiple causes that produce similar symptoms. With regard to the elderly, one prospective study suggested that increased psychological distress in conjunction with physical injury might affect the later development of CRPS, or

at least the condition's severity [12]. CRPS occurring after fractures of distal radius is also more common in elderly patients with psychological or psychiatric conditions [13] but not all authors agree regarding physiological factors as predictors of CRPS incidence [14]. Interestingly, one study found that patients who developed CRPS from trauma were on average 46.8 (+/− 15.8) years of age, compared to those patients who developed it spontaneously (38.2 years +/− 15.3) [15], suggesting that spontaneous development of CRPS following trauma is more prevalent in older populations. However, it seems as though the pathophysiology of CRPS is not distinct from that of CRPS in other populations. In fact, one study that investigated cerebral pain processing in children with CRPS found similar underlying mechanisms as in adults [16] with persisting aberrations of pain processing even after recovery.

Clinical Diagnosis

Clinical Presentation

Geriatric pain assessment, in general, is a complicated clinical process affected by a multitude of factors. Complicating factors can include cognitive or language impairments that reduce communicative abilities, coexisting diseases, concomitant medications, and inability to pay for drug regimens. Assessment can be challenges in geriatric patients who may also suffer from depression, anxiety, psychosocial issues, poor memory, side effects of medications, and failing overall health. As a group, elderly patients often underreport discomfort and pain states, thinking pain is a consequence of aging. The national trend by healthcare providers limit or entirely avoid the use of opioids related to government monitoring and nationwide opioid epidemic also limits options for treatment. As such more reliable and valid methods of identifying, diagnosing, and understanding pain in older individuals are needed. These challenges in assessing pain in older adults have been the focus of an increasing number of papers related to pain measurement in patients with dementia and pain assessment more generally. Patients with CRPS can sometimes present similarly to patients experiencing neuropathic pain, reporting allodynia, hyperalgesia, and intense burning pain, which can make diagnosis of CRPS difficult [3]. However, CRPS is also characterized by the added symptoms of local tissue edema, autonomic dysfunction, motor weakness, decreased range of motion, tremor, and trophic changes to the hair, nails, and skin [3]. These symptoms are common across all age groups diagnosed with CRPS including geriatrics. CRPS is also characterized by abnormalities in sensory function, including changes in thermal sensitivity, pressure hyperalgesia, and light touch threshold hypoesthesia [17]. Interestingly, light touch threshold has been shown to be correlated with perceived pain, suggesting that it may be useful for clinical assessment [17]. Given the significant similarities between CRPS and neuropathic pain, a retrospective cross-sectional study was conducted at a tertiary pain center to compare presenting phenotypes of CRPS patients to neuropathic pain patients [3]. All included CRPS patients met Budapest

Criteria [3]. The groups filled out questionnaires to rate qualities, such as pain severity, physical functioning, and anxiety [3]. It was determined that CRPS patients had higher rates of neuropathic pain and physical disability than their counterparts [3]. CRPS patients also appeared more neuropathically sensitive, more frequently reporting sudden pain attacks, pain with extreme temperature, and pain with slight pressure or light touch [3]. Beyond these domains, there were no other significant differences in perceived pain severity or overall distress, suggesting that patients with CRPS are similar to others with chronic pain [3]. There was no distinction made between age groups in these studies.

Budapest Criteria

Currently, there is no specific diagnostic test for CRPS, or CRPS in geriatrics, and physicians must rely entirely on clinical findings to make the diagnosis. Per the Budapest Criteria, CRPS was defined by regional pain disproportionate in time and degree to the inciting event; a distal predominance of sensory, vasomotor, sudomotor/edema, and/or motor/trophic findings; and an inability to better explain symptoms with other diagnoses [18, 19]. Patients must endorse at least one symptom in three of the four listed symptom groups and exhibit at least one symptom in two or more of these groups at the time of presentation [19]. The Budapest Criteria increased specificity of diagnosing CRPS from 0.41 with the IASP criteria to 0.79 [20]. In 2017, diagnosis of CRPS was further augmented by the development of the CRPS Severity Score (CSS) used to continuously measure symptom severity to assess disease progression [21]. Harden et al. demonstrated the validity of the CSS in clinical practice by showing that improvements in CSS corresponded to improvements in patient-reported pain intensity, daily functioning, and overall well-being [21].

Unfortunately, given the heterogenous presentation of CRPS, even the combined use of the Budapest Criteria and the CSS makes it difficult to diagnose and subclassify affected patients [19]. For example, it has been demonstrated that the Budapest Criteria have low diagnostic validity in patients with poststroke CRPS (PS-CRPS), which causes patients to suffer immense pain, swelling, and nonuse of the affected arm [22]. Inability to accurately diagnose PS-CRPS increases morbidity in affected patients since nonuse can lead to permanent loss of function of the arm [22]. A multicenter study that analyzed data from three large, independent samples of patients with CRPS determined that patients could be grouped into two major phenotypes: central and peripheral [19]. The peripheral phenotype refers to patients with prevalent inflammatory signs such as edema, diaphoresis, temperature asymmetry, and trophic changes [19]. The central phenotype reflects maladaptive cortical plasticity and includes patients who present with sensory-motor processing dysfunction, such as allodynia and general motor and sensory deficits [19]. To group patients, peripheral signs are coded with a −1 while central signs are coded with a +1 with scores <0 pointing to the peripheral phenotype and scores >0 to the central phenotype [19]. The authors also describe a method of clustering to allow the coding of mixed

phenotypes [19]. This method of classification has implications for diagnosis and treatment of CRPS, especially given the fact that these two clusters of disease appear to develop in parallel and do not differ in duration [19].

Assessing Pain in the Elderly

The criteria of CRPS diagnosis are discussed at length in this book and since the literature does not differentiate CRPS criteria with age, these criteria can be extrapolated to assess elderly patients. Therefore, here we will focus on assessing chronic pain in elderly patients. Assessing pain in elderly individuals is challenging for several reasons. An elderly individual may not report their pain to their healthcare provider because they view it as a part of the aging process, or because they are fearful of more diagnostic testing or medication [23, 24]. There may also be miscommunication between the elderly individual and their healthcare provider in the terminology used to describe their pain. They may refer to the pain as aches or hurting rather than pain, which can cause confusion [25]. Cognitive disturbances may also cause further complications if a patient has dementia, Alzheimer's, or other age-related cognitive decline [26]. Therefore, the healthcare provider should focus on gathering a comprehensive patient history with a goal of identifying the precise etiology of pain [27], including intensity of pain, frequency of pain, and location of pain. Furthermore, geriatric assessment tools to assess cognition, function, gait, and affect should also be used [28]. The 0–10 verbal scale of pain intensity may also be used (0 being no pain, 10 being worst pain), but this may be challenging for patient with cognitive disturbances. Healthcare providers should be equipped with several methods for assessing pain including visual analog scale, numerical scale, pain thermometer scale, and/or the pain faces scale, the latter having been established as a good tool to use for elderly individuals [23, 29–31].

Treatment

Treatment of CRPS has proven difficult given the fact that its unverified pathophysiology and variable presentation make accurate clinical diagnosis challenging. It is believed that treating CRPS requires a multimodal approach that involves a combination of medical management with potential for interventional procedures, physical therapy, and psychiatric therapy. Unfortunately, despite the fact that delaying treatment or providing inadequate therapy has the potential to worsen symptoms and negative impact prognosis, a gold standard framework for treatment of the condition is lacking. This obstacle is amplified by the fact that the heterogenous presentation and course of CRPS makes it very difficult to monitor the disease process over time even in individual patients. Given these circumstances, even those patients with diagnoses of CRPS are often subject to lack of consistent symptom monitoring and effective treatment.

Nonpharmacologic Treatments

Nonpharmacologic treatments in conjunction with pharmacological treatments are an effective way to treat chronic pain in the elderly. Treatments including physical therapy, acupuncture, chiropractic manipulation, massage, and low impact exercises, such as swimming, walking, and yoga are all beneficial [32]. Physical and occupational therapy are some of the most widely prescribed interventions for CRPS [33–35]. It has also been shown that physiotherapy can be augmented with the addition of fluidotherapy, which facilitates improvements in edema and pain ratings [36]. These treatments, especially when used in conjunction, have the potential to decrease pain and to improve patient mobility. The literature lacks high-quality evaluations of the impact of specific forms of physiotherapy on the disease process [33–35, 37]. There are data, however, suggesting that excessive physical therapy may in some cases worsen pain and associated symptoms [38]. Of additional importance, these treatments have minimal side effects, can be done as a part of normal activities of daily living, or are available at a low cost, which make them ideal for the elderly [32]. A 2018 systematic review and meta-analysis that determined the efficacy of psychological interventions in older adults with chronic pain found that psychological interventions for the treatment of chronic pain in older adults have small benefits, including reducing pain and catastrophizing beliefs and improving pain self-efficacy for managing pain. These results were strongest when delivered using group-based approaches, rather than individual approaches [39].

For patients in whom physiotherapy provides either inadequate or inappropriate relief, spinal cord stimulation (SCS) is an option. It has been demonstrated that CRPS patients treated with SCS experience improved tissue hypoxia in affected regions, indicated by decreases in angiogenic growth factors such as VEGF [40]. Retrospective studies have also shown that SCS is effective in reducing pain and improving quality of life by reducing psychological distress [41]. SCS implantation in the elderly, however, does have risks. The AIPP suggest a conservative approach for neuraxial interventional procedures in anticoagulated patients [42]. Heparins are associated with the greatest risk of epidural hematoma and combinations of heparin and vitamin K antagonists (VKA) are strictly prohibited immediately following epidural procedures [43]. Many elderly individuals also take aspirin, and while aspirin is associated with a low risk of epidural hematoma, when it is in combination with other antiplatelet medications, this increases the risk of adverse outcomes [43]. The elderly are also at a greater risk of bleeding during the procedure due to comorbidities such as cerebrovascular disease, ischemic stroke, serious heart disease, diabetes, renal insufficiency, and liver disease [44]. Recently, advances in neuromodulation have determined that high-frequency SCS (10 kHz, also known as HF10-SCS) is, in many patients, a more effective and affordable option compared to traditional low-frequency treatment (40–60 Hz) [45]. With HF10-SCS, the spinal cord is not stimulated with the aim of inducing a paresthesia that blocks out pain since neurons are stimulated below the threshold for sensitive perception [45]. In fact, the dorsal root ganglia (DRG) has been shown to be an effective target for treatment of chronic pain in part due to the reduced cerebrospinal fluid layer surrounding the DRG

compared to the areas of the spinal cord typically targeted by SCS [46]. Pain reduction with HF10-SCS has been shown to be long lasting and has the potential to decrease opioid requirements [45]. The procedure can be performed under general anesthesia without needing to wake the patient (unlike LF SCS) and with fluoroscopy guidance to optimize lead placement [45]. Given these advantages, it has also been shown that HF10-SCS is efficacious in achieving pain relief in patients with CRPS who have previously been exposed to LF SCS with suboptimal response [47].

In some patients, SCS is used in combination with intrathecal baclofen (ITB), which stimulates a gamma-aminobutyric-acid B receptor on primary afferent fibers and inhibits neuronal transmission in the dorsal horns [48–50]. Review of studies conducted in the last three decades suggests that SCS has the potential to produce improvements in perceived pain, functional status, and overall quality of life [51, 52]. Retrospective studies show that patients under the age of 40 years who are treated with SCS within a year of disease onset experience the best outcomes [52]. However, many patients outside of this specific cohort also see improvements of their disease, citing decreased usage of anticonvulsants, antidepressants, and/or NSAIDs by 25% [52]. The combination of SCS with ITB has been shown to further decrease refractory pain and improve dystonia [50]. Of note, SCS has not been shown to prevent progression of CRPS, and in some patients has been reported to cause contiguous spread of pain with progressive enlargement of the affected region [52, 53].

Pharmacologic Treatments

Pharmacological treatment for pain is justified when the patient is experiencing functional impairment or a decreased quality of life. This becomes an especially important consideration in the elderly who are already at a greater risk for functional impairment and decrease quality of life. Pharmacologic of CRPS in the geriatric population also requires additional considerations. Pharmacologic management may involve a multimodal approach where multiple medications from different categories are prescribed together to treat pain. Potential drug interactions as well as increased sensitivity to medication side effects in the geriatric population make medical management challenging in these patients. Healthcare providers are advised to start with nonopioid medications due to the high incidence of side effects associated with opioids. Furthermore, patients should also start at the lowest dose of medication possible to achieve pain relief, also to minimize side effects, which requires more intensive patient monitoring [54]. It may also be beneficial to prove local pain relief with nerve blocks.

NSAIDs are usually a first-line treatment for pain; however, they are contraindicated in elderly patients with chronic pain due to increased risk of side effects in the geriatric populations. Healthcare providers should also be cognizant of route of administration. Elderly patients may not be able to easily administer oral medication and may require another alternative. Inhalation of ketamine is one possibility [55]. A 2019 randomized controlled trial study of intravenous subdissociative dose

of ketamine versus morphine for acute geriatric pain in the Emergency Department found that SDK administered at 0.3 mg/kg over 15 min provides analgesic efficacy comparable to morphine for short-term treatment of acute pain in the geriatric ED patients but results in higher rates of psychoperceptual adverse effects [56]. Thus far, evidence for successful use of ketamine to treat CRPS is weak with patients reporting only short-term improvements in pain [57]. Furthermore, ketamine is associated with psychotomimetic and dissociative side effects, which can be exasperated in the presence of other medications, increasing the concern for cognitive disturbances, balance issues, and falling in the elderly [58]. Bisphosphonates, the most commonly prescribed medication for osteoporosis, reduces pain in both human and rat patients with CRPS; however, the mechanism of action of pain reduction is unclear [59, 60]. Further exploration is needed, but it is thought that bisphosphonates may exhibit an antalgic effect in CRPS by modulating concentrations of inflammatory mediators [59]. Bisphosphonates are commonly prescribed to elderly individuals for osteoporosis and are well tolerated.

Conclusion

The pathogenesis of CRPS has proven challenging to elucidate while the variable etiologies and presentation have made it difficult to develop a framework for diagnosis. Persistent pain is highly prevalent in the elderly population. It is important to appreciate how to manage pain effectively in general in this group. CRPS presents an additional challenge for treatment. Currently, the literature lacks high-quality evidence to guide treatment of the condition in geriatric patients. Even patients with a known CRPS diagnosis suffer refractory pain with significant consequences from depression, insomnia, anxiety, and suicide. There is a clear need for better understanding of the disease process in the geriatric population and development of a classification system to streamline relevant research. This classification system may account for different CRPS phenotypes that may reflect distinctive pathophysiological mechanisms. Continued study of the disease process will aid the development of clinical trials that will allow for the development of more targeted and effective treatments.

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Challenges and Controversies in Complex Regional Pain Syndrome (CRPS) Treatment

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Treating patients with complex regional pain syndrome (CRPS) is a big clinical challenge. We have observed many exciting advances and improvements in CRPS treatment over the last several decades [1, 2]. On the other hand, controversies remain in many aspects of CRPS management. In this chapter, we focus on the role of sympathetic blocks, IV ketamine infusions, and peripheral nerve stimulation in the treatment of CRPS.

Sympathetic Blocks in CRPS

There are two types of CRPS: type I, formerly known as reflex sympathetic dystrophy (RSD) [3], and type II, formerly known as causalgia. Both CRPS types I and II have been regarded as the result of a dysregulation of the central and autonomic nervous system, and some CRPS pain is sympathetically mediated. For these reasons, sympathetic blocks have been a widely used treatment for CRPS [2]. The

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stellate and lumbar sympathetic ganglia are responsible for the sympathetic innervation of the upper and lower limb, respectively, and many clinicians have sought to interrupt these sympathetic pathways through local anesthetic blocks, chemical neurolysis, and/or radiofrequency neurotomy to treat CRPS. Other techniques, such as T2 thoracic sympathetic block (TSB) and thoracic erector spinae plane (ESP) block, have been reported with variable therapeutic success [4].

Which Sympathetic Blocks Can be Used and How Are They Performed?

Stellate Ganglia Block (SGB)

The stellate ganglion is formed by the fusion of the inferior cervical ganglion and the first thoracic ganglion and provides sympathetic innervation to the ipsilateral upper extremity, chest, face, and head. The location of the stellate ganglion is at the level of C7, anterior to the transverse process of C7 and the neck of the first rib, superior to the cervical pleura and just below the subclavian artery [5]. In early work, the paratracheal tissue displacement approach was utilized to perform the stellate ganglion block at the C7 transverse process [6]. However, a high incidence of brachial plexus block, recurrent laryngeal nerve paralysis, and systemic effects from large volumes of local anesthetic solution and/or intravertebral artery injection at C7 level were noted. Therefore, Carron et al. introduced a modified low-dose paratracheal approach to do SGBs at the C6 level by palpating the anterior transverse process of C6, or the Chassaignac tubercle, and injecting the local anesthetic (LA) medially [7]. For safety reasons, placement of an intravenous catheter is recommended prior to performing the SGB. Vital signs, including a three-channel electrocardiogram, blood pressure, and pulse oximetry, should be monitored during and for 30 minutes after the block. Currently, most SGBs are being done with ultrasound, fluoroscopic, or CT guidance [5] [8].

Ultrasound-Guided Technique

The patient is positioned supine, with the neck slightly extended and the head turned slightly away from the injection side. The skin is prepared and draped in the usual sterile fashion, and the transducer is placed perpendicular to the tracheal axis at the level of the cricoid cartilage and is moved inferiorly, until the superior aspect of the thyroid gland is visualized. The transducer is then relocated laterally to visualize the anterior aspect of the Chassaignac tubercle on the C6 transverse process. The position of the vessels can be identified with color Doppler. With an in-plane approach, the needle is inserted from lateral to medial to direct the tip to the prevertebral fascia of the longus colli muscle located between the posterior aspect of the carotid artery and the tip of C6 anterior tubercle. An aspiration test must be done to look for blood or cerebrospinal fluid (CSF), then a local anesthetic is injected in small, intermittent volumes and the spread of the local anesthetic can be observed in real time. A total of 5–10 ml of a local anesthetic is injected, until the fluid spreads along the prevertebral fascia to the stellate ganglion [9]. Other techniques have also been described.

For example, Bael et al. performed SGB with the lateral paracarotid approach using an out-of-plane needle insertion at the C7 level under ultrasound guidance, which was feasible and more effective at elevating skin temperature in the upper extremity than SGB at C6 [10].

A block is considered successful by observing the development of a Horner syndrome, increase in skin temperature in the ipsilateral limb of at least 2 degrees centigrade, increase in blood flow, and loss of the galvanic skin response. The ultrasound (US)-guided technique may provide greater accuracy and reduce the volume of local anesthetic required for sympathetic block of the upper extremity, as compared to the landmark-based techniques. Yoo et al. did an interesting study regarding the impact of injection volume during SGB. The definition of successful injection was based on the hand temperature change before and after SGB. There was no difference in success rate between the 4-, 6-, and 8-ml injection groups [11].

Fluoroscopically Guided Technique

The patient is positioned supine, and an anteroposterior view is obtained with the C-arm to identify C6 by counting up from T1. The C-arm is then tilted to line up the superior aspect of the C6 vertebral body and is rotated obliquely at approximately 25–30 degrees ipsilaterally to obtain a foraminal view. The target is the junction of the vertebral body and the C6 transverse process. Under an oblique view, the needle is directed toward the C6 anterior tubercle and advanced under real-time imaging to contact the bony target. The position needs to be checked with both anteroposterior and lateral views. A small amount of contrast media (0.5–1 ml) can be injected first to visualize injectate spread. A small test dose of local anesthetic is then administered to reduce the risk of intravascular injection further. Following this, 5–10 ml of a local anesthetic is injected in incremental doses with aspiration between each injection. The same procedure can be performed at the C7 level if needed, but the physician must be aware of the higher risks of vascular puncture at the C7 level [9].

CT-Guided Technique

The patient was placed in supine position. A safe route was chosen to avoid injury to the vessel, and the puncture point and puncture angle were clearly defined. After disinfecting the area, a safe step-by-step progression of the needle was then carried out under CT guidance, until the needle tip was accurately placed at one of the two defined targets: either between the vertebral artery and the C7 transverse process or the neck of the first rib facing the T1 vertebral body [12].

Lumbar Sympathetic Block (LSB)

The lumbar sympathetic trunk is located along the anterolateral aspect of the first through fourth lumbar vertebra. The preganglionic neurons exit the spinal cord via white rami of the ventral roots of spinal nerves L1 to L4 and then synapse at the appropriate lumbar sympathetic ganglion. From there, the postganglionic neurons extend distally and innervate specific sites. The densest portion of lumbar sympathetic ganglia resides along L2 and L3. Because of this, lumbar sympathetic blocks are most commonly performed along the lower third of L2 or the upper third of L3

[13] [14]. Fluoroscopically guided blocks are most commonly used in practice, although US-guided and CT-guided techniques are also described.

Fluoroscopically Guided Technique

The patient is positioned prone. The C-arm is centered over the midlumbar region and then rotated obliquely 20–30 degrees, until the tip of the transverse process of L3 overlies the anterolateral margin of the L3 vertebral body. The skin is prepared and draped in the usual sterile fashion, a 22-gauge spinal needle is advanced using a coaxial technique toward the anterolateral surface of the L3 vertebral body. The needle tip should be kept over the lateral margin of the vertebral body until the needle gently contacts bone, then walked laterally off the bony margin. Once the trajectory has been confirmed, the C-arm should be returned to an anteroposterior (AP) view. Proper needle position should lie medially to the lateral margin of the vertebral body verified with an AP view. A lateral image should also be obtained to confirm that the needle tip does not lie anterior to the vertebral body. Radiopaque contrast should be injected to confirm proper spread and the absence of vascular uptake. After aspiration to exclude intravascular needle placement, 15–20 ml of 0.25% bupivacaine is injected in divided doses. Signs of successful sympathetic blocked in the lower extremities include venodilation and a temperature rise toward core temperature [15].

Ultrasound-Guided Technique

The patient lies prone with a pillow under the lower abdomen and iliac crest to reduce the lumbar lordosis. After sterile preparation of the skin and draping, the LSB should be performed at the upper third of the L3 vertebra, which is identified by counting the lamina and transverse processes from the L5 to L3 with paramedian sagittal scanning. After marking the level of the L3 vertebra, the transducer should be rotated transversely to obtain a short-axis view showing the transverse process and facet joint. Then, the modified transverse scan of the lumbar paravertebral region through lumbar intertransverse space may be obtained by positioning the transducer 4–6 cm lateral to the midline in the transverse orientation at the L2-L3 or L3-L4 intervertebral level. The transducer should also be directed medially to insolate the anterior fascia of the psoas major muscle, the target of the needle tip, through the lumbar intertransverse space. Color Doppler is utilized to determine the presence of vascular structures and to plan the needle trajectory. The needle is then advanced toward the anterolateral edge of the target vertebral body using a posterolateral approach. The needle is inserted from a lateral to medial direction using the in-plane technique so as to monitor it in real time as it is advanced, using a hydrolocalization technique with 1.5 ml of normal saline. The target of the needle tip is the anterior fascia of the psoas major muscle close to the paravertebral space. After evaluating the location of the needle tip under US and verifying negative aspiration for blood or CSF, 3 ml of contrast dye is administered incrementally to exclude vascular injection by a C-arm image [16]. Ultrasound-guided lumbar plexus block in the supine position is described in one study. This approach could be an option for patients who are unsuitable for prone position. In addition, it may minimize the

risk of intrathecal injection. However, kidney and bowel injuries are potential complications with this approach [17].

Thoracic Sympathetic Block

SGB is the most commonly used technique to treat CRPS in the upper limbs. Anatomical and clinical studies have suggested that it may not be the most effective technique [18] [19] because of the presence of anatomical variations. In a certain percentage of individuals, nerves from the thoracic sympathetic ganglia can project directly to the brachial plexus, bypassing the upper stellate and middle cervical ganglia [20]. This anatomical variation may also partly explain why not all CRPS patients respond to SGB [19]. Thus, all of the sympathetic fibers could be affected by blocking the T2 and T3 ganglia, rather than the SGB. Rocha et al. performed a long-term randomized, double-blinded active-control study to evaluate the efficacy of thoracic sympathetic block (TSB) for upper limb type I CRPS [21]. The data showed that the pain reduction, improvement in evoked pain, and amelioration of depressive symptoms, were significantly superior to the control treatment (control group: the needle was positioned subcutaneously at the T2 level, with solution injected subcutaneously). They concluded that TSB is a safe procedure and has both short- (1-month) and long- (12-month) term positive impact on upper limb type I CRPS as an add-on treatment to a standardized rehabilitation and pharmacological treatment program. Gungor et al. described a TSB of the upper extremity via thoracic epidural approach with advancement of a catheter through neural foramen and positioning the catheter tip in the upper thoracic paravertebral space on a patient with upper extremity CRPS [22]. TSB was also reported to improve pain in a CRPS patient who failed SGB, paravertebral block, and ketamine infusion [23].

Erector Spinae Plane Block

A high thoracic erector spinae plane (ESP) block was performed as a sympathetic block in patients with upper extremity CRPS [24]. In this technique, a 20-gauge epidural catheter was inserted through an 18-gauge Tuohy needle, the catheter tip was placed between the transverse process and erector spinae muscle group at the level of T1–2. Local anesthetic was continuously infused for 14 days. During the local anesthetic infusion, the overall numeric pain rating scale (NRS) of the patients was reduced to 3/10, and all patients reported significantly decreased cold sensation of the affected upper extremities. The frequency of breakthrough pain was also reduced by half, and the consumption of narcotics was decreased.

ESP block was also used to treat lower extremity CRPS. Chung et al. reported their experience of a continuous ESP block at the L4 level in a patient with left lower extremity CRPS, in which lumbar plexus blocks and peripheral nerve blocks had insufficient effects [25]. After a good response to a single ESP block, a continuous ESP block was performed with a ropivacaine infusion maintained for 12 days without any complications. This patient received significant improvement in pain intensity.

Intravenous Sympathetic Block

Sympathetic blocking agents such as reserpine, guanethidine, or alpha-1 adrenergic receptor antagonists (phenoxybenzamine and labetalol), have been prescribed in treating CRPS patients. Reserpine depletes storage of norepinephrine and guanethidine inhibits presynaptic release of norepinephrine in the sympathetic nerve terminal. Both regional intravenous guanethidine and reserpine have been reported in the treatment of RSD. Results from case reports are inconsistent and a RCT failed to support the effectiveness of IVRB with guanethidine, reserpine, or droperidol in CRPS management. Only case studies showed effective responses with phenoxybenzamine and labetalol, but there is no RCT investigating this medication in CRPS [26].

Is One Sympathetic Block Technique Superior to Another?

To answer the question of which image-guided technique is superior in SGB, Imani et al. did a small randomized clinical trial to compare the effectiveness of ultrasound-guided SGB versus fluoroscopically guided SGB in the upper extremities of CRPS patients in reducing pain and dysfunction of the affected limb. Fourteen patients were enrolled and randomized into two equal groups who received SGB under the guidance either with ultrasound or with fluoroscopy. From this study, they observed that both blocks significantly improved pan intensity until 6 months after block. In comparison with fluoroscopic guidance, the ultrasound-guided technique has lower complications and better improvement in the patient's disability indexes [27].

What Agents Can Be Used for Sympathetic Blocks?

Local anesthetics are commonly used in sympathetic block. In addition to local anesthetics, several other agents have been applied in sympathetic blocks. In order to prolong the sympathetic blockade, botulinum toxin was injected in two patients with CRPS in the lower extremity during the LSB procedure [28]. The injection significantly improved the pain intensity at 2-months' follow-up and allodynia and coldness disappeared and skin color came back to normal. Lee et al. also observed that the addition of botulinum toxin prolonged the analgesia of the LSB. They also found that the effects were more in type II than in type I CRPS [29]. Carroll et al. conducted a randomized controlled trial to compare the duration of analgesia in nine CRPS patients who underwent LSB with bupivacaine with or without botulinum toxin A (BTA) [30]. They found that BTA prolonged the mean analgesia time from fewer than 10 days to up to 71 days. Following the BTA injection, one patient developed significant nausea and emesis that lasted two days and resolved spontaneously [30]. No severe adverse events were reported. Dysarthria was reported after sympathetic injection with botulinum which disappeared spontaneously after 3 weeks [31].

Are Sympathetic Blocks Effective in Treating CRPS Pain?

Even though SGB has been used for CRPS since the 1950s [32], the literature mostly consisted of case reports or observational studies [33]. Yucel et al. performed a study, in which 22 CRPS patients received three SGBs at weekly intervals. The patients were evaluated before and 2 weeks after the last of three SGBs. They found that SGB successfully decreased VAS and increased the range of motion of the wrist joints. Further, the postblock VAS value in short duration of symptom onset group (<28 weeks) is significantly lower than the value in long duration of symptom onset group [34]. Early intervention may provide better outcomes.

In 2012, Yoo et al. did a randomized clinical trial (RCT) to evaluate the efficacy of ultrasound-guided SGB (US-SGB), compared with that of blind SGB in the management of CRPS for stroke patients [35]. In this study, every patient received two SGBs at a 7-day interval and was followed for 4 weeks. US-SGB and blind SGB both significantly decreased patients' VAS and the amount of hand swelling at 2- and 4-weeks' follow-up. The US-SGB group showed a more significant improvement in mean change of VAS compared to the blind SGB group, but no advantage in the reduction of hand swelling was observed during follow-ups. They also observed that US-SGB can achieve therapeutic effect with less volume of local anesthetic, compared with blind SGB. This study did not observe adverse effects during the procedure or follow-up period in the US-guided group, while two patients from the blind group experienced hematoma formation at the injection site.

A double-blinded placebo-controlled study approach is ideal to help exclude the impact of psychological factors on the outcome of sympathetic block. In 1998, Price et al. did the only placebo-controlled crossover RCT of sympathetic blocks in CRPS [36]. In this study, seven patients were recruited, where four patients with upper extremity CRPS underwent SGB and three patients with lower extremity CRPS received lumbar sympathetic block (LSB). Each patient received two blocks, normal saline (NS) and local anesthetic (LA), and served as his own control. The two blocks were randomized and separated by an interval of seven to ten days. The median duration of pain relief was significantly greater with LA treatment (5 days 12 hours for return to 50% of the difference between baseline and peak effect) than for NS (6 hours for 50% return). Interestingly, both NS and LA blocks of the relevant sympathetic ganglia resulted in more than 50% peak pain reduction 30 minutes after the block. There was no statistical difference in peak analgesic effects between NS and LA sympathetic blocks. It is possible that saline may have produced a small local anesthetic effect on sympathetic ganglia, as suggested by Urban and McKain [37]. Conversely, Haddox et al. observed normal saline injection of the stellate ganglion in normal volunteers failed to produce block of sympathetic efferent activity [38]. Nevertheless, it is important to address the potential placebo effect in sympathetic block studies should always be considered.

LSB is widely utilized to treat lower extremity CRPS with disruption of the nerve supply from the sympathetic chain to the lower extremities [39]. Gungor et al. observed that their patients achieved a very favorable response after LSB with an almost complete resolution of pain, symptoms and signs, were able to wean their

pain medications and achieve normal activities of daily living without any significant limitation [40]. LSB also produced a significant reduction in pain intensity in children with CRPS [41]. In this double-blinded placebo-controlled crossover designed study, 23 pediatric patients, ages 10–18 years with unilateral lower limb CRPS, received intravenous lidocaine and lumbar sympathetic saline, or lumbar sympathetic lidocaine and intravenous saline. A significant reduction in pain intensity, allodynia to brush, pinprick, and punctuate temporal summation, as well as verbal pain scores, was observed after lidocaine sympathetic block that was not found with IV lidocaine.

Does the Response to Sympathetic Blocks Predict Success of Other Treatment Modality Such as Spinal Cord Stimulation?

Recently, Cheng et al. performed a retrospective study to investigate the therapeutic and predictive values of sympathetic blocks in CRPS [42]. In this study, 84% of CRPS patients (n = 255) achieved successful pain reduction, defined as more than 50% pain relief, after sympathetic blocks. The duration of successful pain reduction was fewer than 7 days in 15%, 1–4 weeks in 71%, 1–3 months in 9%, and 3–6 months in 5% of these patients. Since only a portion of CRPS patients are likely respond to sympathetic blocks, the ability to distinguish those patients who may derive significant benefit from sympathetic block is therefore of considerable medical and economic importance. Unlike the conventional notion that sympathetic blocks are likely beneficial for patients with cold CRPS, this study did not observe an association between long-term effects and temperature parameters. This finding is consistent with several other studies [43] [44]. This study also did not observe the association between the response to sympathetic block and outcomes of spinal cord stimulation. Based on this large retrospective study, the authors concluded that sympathetic block provided a clinically significant pain reduction for 1–4 weeks or beyond in a majority of CRPS patients.

Should Sympathetic Neurolysis Be Used to Treat CRPS Pain?

Because nerve blocks usually only have a transient effect, neurolysis of sympathetic ganglia has been tried to prolong the analgesic effect. Dev et al. treated CRPS patients using lumbar sympathetic neurolysis with alcohol, and about 50% of patients responded [45]. In a case report, a patient received complete pain relief with normal function during follow-up for a period of 12 months after radiofrequency ablation of stellate ganglion [46]. Manjunath et al. [47] randomized 20 CRPS I patients to receive either percutaneous radiofrequency lumbar sympathectomy (90 seconds at 80 °C, n = 10) or lumbar sympathetic neurolysis with 3 ml of 7% phenol (n = 10) each level at L2, 3, and 4. All patients were admitted for 24 h observation. There were statistically significant reductions from baseline in

various pain scores after the procedure, but there was no statistically significant difference in mean pain scores between the groups. One of the 10 patients in the phenol group had postsympathectomy neuralgia. No evidence of nerve injury was observed during follow-up in any of the patients. The authors concluded that radiofrequency lumbar sympathectomy may be comparable to phenol lumbar sympathectomy, but they stated that larger trials are required to confirm these findings.

Pulsed radiofrequency (PRF) has also been evaluated to treat CRPS. Djuric et al. observed substantial pain relief (>50%) in 91.7% of PRF applications at 3 months and 83.3% at 6 months, with some treatments resulting in persistent relief well beyond 12 months [48]. Further, Freitas et al. compared the efficiency between PRF and LSB on CRPS [49]. In this study, patients were randomized and received either PRF or LSB treatment. The evaluation with VAS scores, neuropathic pain scale, and RAND SF-36 scale was done in a follow-up of 1 day, 7 days, 2–4 and 6 months. PRF appears to show a similar benefit in the treatment of lower limb CRPS, compared with the sympathetic block. Only hot pain sensation was significantly improved at 4- and 6-months' follow-up in the PRF group. Kim et al. [50] investigated the efficacy of pulsed radiofrequency (PRF) on the cervical sympathetic chain under ultrasound guidance in 12 CRPS patients. Under ultrasound guidance, PRF was performed for 420 seconds at 42 degrees C on the C6- and C7-level sympathetic chain. The pain intensity decreased significantly at 1 week after the procedure. Eleven patients experienced at least moderate improvement, and the reduction in symptoms was maintained for a mean of 31.41 +/− 26.07 days after PRF. There were no complications associated with this procedure. Park et al. [51] retrospectively compared the clinical effects of PRF to those of the thoracic sympathetic ganglion (TSG PRF, $n = 7$) and to those of the cervical sympathetic chain (CSC PRF, n = 10) in patients with upper-extremity CRPS. Seven TSG PRF cases and 10 CSC PRF cases were enrolled in the present analysis. The postprocedure temperature was significantly higher in the TSG PRF group than in the CSC PRF group. NRS pain values 1 week after the procedure were significantly lower, and the effect duration was significantly longer, after TSG PRF than after CSC PRF. The authors concluded that TSG PRF is a more effective procedure than CSC PRF for managing chronic upper-extremity CRPS.

Despite the possible efficacy provided by sympathetic neurolysis which was advocated by some experts [52], the association with a higher risk of dysesthesia, hyperesthesia, deafferentation pain, and bothersome sweating remains a big concern [53]. Prior to radiofrequency lesioning of the sympathetic trunk, sensory and motor stimulation must be used to verify that the active needle tip is not adjacent to a spinal nerve to avoid unwanted neural injury. However, the value and the accuracy of sensory stimulation to aid in precise needle positioning at the desired target remains controversial [54]. Lumbar sympathetic neurolysis is generally reserved for patients with refractory ischemic rest pain secondary to arterial occlusive disease that is nonreconstructable [55]. The level of evidence for using sympathetic neurolysis in CRPS is low.

Summary of Sympathetic Block for CRPS

Sympathetic block provides a clinically significant pain reduction in some CRPS patients with a sympathetically maintained pain. No particular sympathetic block technique is superior to another. Botox A may be added to the block injectate to prolong the analgesic effect. Patients not responding to sympathetic block may still benefit from other treatment modalities such as spinal cord stimulation. Use of sympathetic neurolysis to treat CRPS remains controversial. The quality of the available studies on sympathetic block and neurolysis in CRPS is low (case series, small sample size, retrospective, etc.). Further studies with better quality are warranted.

Intravenous Ketamine Infusion for CRPS

N-Methyl-D-aspartate (NMDA) receptors have been implicated in the maintenance of amplified noxious signals, namely central sensitization, induced by repetitive stimuli in rats [56]. Ketamine, primarily an NMDA receptor inhibitor, has therefore been used to treat many chronic pain syndromes including CRPS [57].

Is IV Ketamine Infusion Effective in Managing CRPS Pain?

Since the 1990s, many case series have showed that ketamine infusion is effective in reducing pain in CRPS/RSD [58–66]. These reports are limited by having only one or two patients in each report and the International Association for the Study of Pain (IASP) diagnostic criteria were not mentioned.

Observational studies with a higher number of patients (with or without the IASP diagnosis criteria) also demonstrated the efficacy of ketamine infusion in CRPS. IV anesthetic doses of ketamine (starting at 3 mg/kg/h, followed by a gradual daily titration up to a final dose of 7 mg/kg/h) were used in a nonrandomized, open-label, phase II trial in 20 patients with severe refractory CRPS meeting the IASP diagnosis criteria [67]. Complete pain relief was observed at 1 month in all patients, at 3 months in 17, and at 6 months in 16 patients. Movement impairment, quality of life, and ability of work were also improved. In another open-label prospective study, IV ketamine infusion at 250–300 μg/dl for at least 4.5 days provided significant pain reduction. All patients were able to withdraw from narcotics at 6 weeks following completion of the treatment [68]. A retrospective chart review [69] analyzed a total of 33 patients with CRPS who had undergone ketamine infusion (dose range 10–50 mg/hr) at least once. There was complete pain relief in 25/33 (76%) and partial pain relief in six (18%) patients following the initial course of therapy. All 12 patients who received second courses of treatment experienced complete relief of their CRPS pain. The most frequent side effects observed were a feeling of inebriation and hallucinations. Less frequent side effects included complaints of lightheadedness, dizziness, and nausea. A four-hour ketamine infusion escalated from 40 to 80 mg over a 10-day period resulted in a significant reduction of pain in

an open-labeled, prospective study on 40 CRPS I and II patients who met the IASP diagnosis criteria [70]. Analgesia persisting beyond the ketamine infusion period was reported in an observational study on 10 CRPS I patients [71]. A recent longitudinal cohort study [72] on 63 children and adolescents (21 patients with CRPS I and 2 with CRPS II) showed that IV subanesthetic ketamine infusion on an outpatient basis significantly reduced pain intensity. The pain reduction was greater in patients with CRPS than in patients with other chronic pain syndromes. The treatment was safe and not associated with psychotropic or hemodynamic perturbations, but did not change the overall morphine-equivalent intake.

Only a few RCTs have studied IV ketamine infusion in CRPS. The first RCT was reported by Sigtermans et al. in 60 CRPS-I patients who met the IASP criteria [73]. Patients were admitted for 5 days. IV ketamine was started at 1.2 μg/kg/min (or 5 mg/hr. for a 70-kg patient) on day 1 and was titrated to a maximal dose at 7.2 μg/kg/min (or 30 mg/hr. for a 70-kg patient). Ketamine ($n = 30$) provided significant pain relief compared to placebo ($n = 30$) but the significance was lost at week 12 ($p = 0.07$). Ketamine did not produce functional improvement but did result in mild to moderate psychomimetic side effects. A secondary analysis of these data found that significant pain relief was achieved for up to 6 weeks, but there is no direct effect on the motor function [74]. A pharmacokinetic-pharmacodynamic (PK-PD) modeling study on these data showed that 100-h infusion of S(+)-ketamine treatment is more effective in pain relief than placebo in CRPS-1 patients with analgesia outlasting the treatment period by 50 days, despite rapid plasma concentration reduction following infusion discontinuation [75]. Schwartzman reported the second RCT in 19 patients [76]. IV ketamine (0.35 mg/kg/h, not to exceed 25 mg/h over a 4-h period daily for 10 days, diagnosis met the revised IASP criteria, $n = 9$) but not normal saline ($n = 10$) resulted in a statistically significant ($p < 0.05$) reduction in weekly pain assessments (a 7-question pain questionnaire and the short-form McGill Pain Questionnaire) for the full 12 weeks of the study. The quantitative sensory testing and quality of life were insignificantly improved. Subjects in both the ketamine and placebo groups were administered clonidine and midazolam.

Systematic reviews [26, 77–79] evaluated IV ketamine in CRPS and concluded that although ketamine is promising in the treatment of CRPS, there is no sufficient evidence to recommend the routine use of ketamine and large, well-designed RCTs are needed.

What IV Ketamine Infusion Protocol Is Optimal?

Ketamine infusion has gradually gained popularity in CRPS, but no consensus protocol exists. We surveyed more than 300 international health providers who treated CRPS patients with ketamine. The infusion protocol varies among clinicians, clinical settings (outpatient or inpatient), dose and duration, etc. [80]. Based on these findings, expert practitioners convened at the RSDSA Annual Meeting in 2016 and a consensus protocol was proposed as follows [80].

Inpatient Infusion

Initial rate: 10 mg/h (approximately 0.15 mg/kg/h based on the ideal body weight), increased every two hours in 5–10-mg increments.

Maximum rate: 40 mg/h.

Titrate to "drowsy to moderate sedation" (e.g., Richmond Agitation-Sedation Scale [RASS] score of −1 to −3) (See Table 16.1) or pain reduction of 50% using the numeric pain rating scale (verbal), whichever is achieved first.

Duration: 24 hours for three to five days.

Outpatient Infusion

Initial rate on day 1: 0.4–0.7 mg/kg/h; then titrated to a RASS score of −1 to −3 or pain reduction of 50% using the numeric pain rating scale (verbal), whichever is achieved first. If the patient becomes oversedated or the dissociation is too great or not tolerated, then reduce the infusion by 25%.

Maximum rate: 50 mg/h.

Total dose: 200 mg on day 1.

In subsequent sessions, dosing is 30% more than the previous day's maximum dose. The routine target dose is 150 mg/h or 600 mg over four hours (some participants suggested that carefully selected patients may receive up to 1200 mg over four hours).

Duration: Four hours for each of five to 10 sessions.

Clinical trials are needed to validate this consensus protocol.

Which Patients Are Likely to Respond to IV Ketamine Infusion?

Using resting-state functional magnetic resonance imaging (rs-fMRI), Motoyama et al. reported that if the neuronal connectivity between the medial prefrontal cortex (mPFC) and precuneus is low, the patient is likely to respond to subanesthetic-dose ketamine [81]. This has not been validated in large-scale CRPS cohorts.

Table 16.1 Richmond Agitation and Sedation Scale (RASS)

+4	Combative	Violent, immediate danger to staff
+3	Very Agitated	Pulls or removes tube(s) or catheter(s); aggressive
+2	Agitated	Frequent nonpurposeful movement, fights ventilator
+1	Restless	Anxious, apprehensive but movements not aggressive or vigorous
0	Alert and calm	
−1	Drowsy	Not fully alert but has sustained awakening to *voice* (eye opening and contact ≥ 10 sec)
−2	Light sedation	Briefly awakens to *voice* (eye opening and contact < 10 sec)
−3	Moderate sedation	Movement or eye opening to *voice* (but no eye contact)
−4	Deep sedation	No response to voice but movement or eye opening to *physical* stimulation
−5	Unarousable	No response to *voice or physical* stimulation

What Are the Short- and Long-Term Consequences of IV Ketamine Infusion?

Patient safety is a major concern of IV ketamine infusion. Adverse effects from IV ketamine may include central nervous system (CNS)-related, cardiovascular, and hepatic effects [82]. The most important CNS effects mediated by ketamine are psychotropic. Patients receiving ketamine more often experienced mild to moderate psychomimetic side effects during drug infusion (76% versus 18%, $P < 0.001$) [71]. Psychotropic side effects such as anxiety and dysphoria, as well as difficulty in sleeping, nightmares, and muscular weakness were reported with an anesthetic dose of ketamine infusion for 5 days [67]. Ketamine impairs memory functions in healthy volunteers [83], but the effects of long-term use of ketamine for the treatment of CRPS are not clear. Koffler (68) reported no severe cognitive defects after a 5-day IV ketamine infusion at 6 weeks, but long-term cognitive function was not investigated.

Ketamine has indirect stimulatory effects on the cardiovascular system through an increase in catecholamines. Once catecholamines are depleted, ketamine can cause myocardial depression [82]. S(+)-ketamine demonstrated dose-dependent effect on cardiac output that was similar between healthy volunteers and CRPS patients [84]. These data indicate that hemodynamic monitoring is required when ketamine infusion is used to treat CRPS.

Several studies reported elevated liver enzymes following ketamine treatment. Anesthetic dose ketamine infusions caused liver enzyme elevation in 16 out of 20 patients (80%) that returned to normal within 2 weeks [67]. In a case series of six patients [85], who received two continuous IV 100-hour ketamine infusions separated by 16 days, three patients had a transient increase in liver enzymes to three times the upper limit of normal. The enzyme levels slowly returned to the normal range within 2 months, once the infusion was promptly discontinued. This observation may suggest that there is an increased risk of ketamine-induced liver injury if the infusion is prolonged and/or repeated within a short period of time.

A retrospective chart review studied the safety of prolonged (minimum 5 days and maximum 55 days) IV ketamine infusion in an outpatient setting in 13 patients (8 CRPS, 1 migraine, 3 neuropathy, and 1 phantom limb) [86]. Fatigue developed in 4 patients (31%), dizziness in 3 (23%), confusion in 2 (15%), and spinal pain in 2 (15%) patients. No patients reported hallucination.

Clinical literature on long-term effects of ketamine infusion is scarce. Tolerance to ketamine-mediated analgesia developed following repeated administration of the drug in animals [87–90] and humans [91–93]. Bonnet [94] reported a clinical case of tolerance to ketamine's antidepressant action accompanied by the development of ketamine addiction, loss of consciousness, dissociative immobility, and amnesia. Ketamine-induced neurotoxicity has also been reported [95].

Summary of IV Ketamine Infusion for CRPS

IV ketamine infusion has been reported to be effective in managing refractory pain in some CRPS patients. Optimal infusion protocol remains controversial. Ideal patient selection is unclear, and longer term effects (tolerance, neurodegeneration, etc.) of IV ketamine infusion are unknown.

Peripheral Nerve Stimulation for CRPS

The use of peripheral nerve stimulation (PNS) for the treatment of CRPS pain has been implemented since the late 1960s following the findings of Wall and Sweet in 1967.

Is PNS Effective in Treating CRPS? Which Patient Is Likely to Respond to PNS?

Hassenbusch et al. [96] performed peripheral nerve stimulator implants in 30 patients with CRPS in the distribution of one or two nerves and followed these patients to assess their response. Nineteen (63%) patients experienced good or fair relief on a consistent basis. These patients not only had improvements in their pain but were found to have improvements in vasomotor tone and functional activity, hallmarks of dysfunction in CRPS. Those who did not respond to the therapy were more likely to have pain in the distribution of more than one major peripheral nerve, and they were not seen to have any change in vasomotor tone, trophic changes, pain control, or motor strength. Buschmann et al. [97] obtained even more impressive results, having performed PNS in 48 patients with CRPS type II and 4 patients with phantom limb pain. Forty-seven patients underwent permanent implantation following a successful trial and 43 (91%) of them had good to excellent lasting relief. Mirone et al. reported a successful case using median nerve stimulation to treat an iatrogenic CRPS after multiple carpal tunnel surgeries [98]. Yet, despite the benefit touted in these reports, the use of PNS has not been implemented routinely in CRPS patients. Reasons for not using PNS have been the historical design and use of equipment ill suited for peripheral nerve application. Originally, the electrodes used for peripheral nerve stimulation were cuff shaped [99] and were placed surrounding the target nerve. This approach caused significant scarring and fibrosis as well as nerve constriction and unwanted muscle contractions [99, 100]. Then, button-type electrodes were introduced [101]. This new technique allowed the electrode to be sutured to the perineurium and allowed for a more focal targeting of the nerve fascicles. The introduction of flat “paddle” or “plate” electrodes containing four electrode contacts occurred in the late 1980s [100]. Then, in the early 1990s, the first FDA approved lead to be used specifically for peripheral nerve application was introduced (Model 3987A On-Point, Medtronic Inc., Minneapolis, MN, USA). It contains an integrated mesh for improved positioning [101] with hopes of reducing

migration, fibrosis, and to allow greater programming versatility [100]. Despite improvements in lead design, the hardware was still borrowed from designs intended for spinal cord stimulation. In fact, no implantable pulse generator (IPG) was manufactured or approved specifically for peripheral nerve application [100]. As a result, complications with peripheral nerve stimulators were frequent. These included improper electrode selection, cuff rotation requiring repositioning of the cuff on the same nerve, or requiring the addition of another stimulating system. In the 19 patients reported by Hassenbusch et al. who had positive outcomes following peripheral nerve stimulation, 7 (37%) required subsequent revision for generator displacement or discomfort, lead malfunction, or for the addition of an additional electrode [96]. Similar revisions were historically reported in other studies largely owing to the deficiencies in the equipment for use on peripheral nerve anatomy [100, 101]. In addition to nerve-electrode interface issues, implantation of the permanent IPG often occurred in more proximal locations in the body, requiring extension wires and cables to be tunneled across joint lines [102]. This, alongside the mechanically dynamic nature of the areas of lead placement, imposed inherent stress on the system contributing to lead migration, fracture, or disconnection [99, 100]. Finally, the spread of CRPS into a proximal area or into another extremity has been reported in up to 10% of individuals. As a result, the addition of another lead and IPG were occasionally required, adding further risks associated with subsequent surgery [96, 103]. With the lack of regulatory approval of implantable devices for peripheral nerve stimulation, a lack of push from device manufacturers, and historically limited interest from practitioners, most implantable peripheral nerve stimulators continue to be used off-label [100].

However, with the advent of percutaneous approaches, there has been a resurgence of interest in PNS. Eight or 16 contact leads on a cylindrical electrode can be implanted near the targeted nerve and attached to an internal or external generator. Deer et al. [104] demonstrated in a multicenter randomized, double-blinded trial that a novel percutaneous PNS device with an external generator implanted in 94 patients with chronic pain of peripheral nerve origin achieved a mean pain reduction of 27.2% from baseline to month 3, compared to a 2.3% reduction in the control group. The presence of external generators reduces the risk of infection compared with traditional surgical implantation of an IPG and the discomfort associated with its localization. Moreover, a percutaneous approach does not predispose the lead or connection cables to the same forces as when the device was tunneled and connected to a generator across joint lines. In addition, with a percutaneous approach and external generator, multiple electrodes can be placed quickly and easily to target one or more nerves.

There is still much to be desired with regard to the application of PNS in the treatment of CRPS. CRPS remains a complex disorder characterized by a multifactorial pathophysiology involving the peripheral, central, and autonomic nervous system, and patient presentation is heterogeneous. Pathological changes have been localized in the periphery, within the dorsal root ganglion, spinal levels, and within the brain of CRPS patients, highlighting the complex nature of the disease. The heterogeneity of the disease process makes patient selection difficult. Patients with

CRPS do not present uniformly but typically with a constellation of symptoms, ranging from classic neuropathic pain characteristics including burning, allodynia, dysesthesias, motor changes, to autonomic features including skin color changes, changes in sweating, and with skin and nailbed deformities [1]. Identifying the ideal candidate at a specific course in their disease progression for neuromodulation is currently unknown. While the Budapest Criteria introduced by the International Association for the Study of Pain (IASP) in 2004 did provide clinicians with a sensitive and specific method of identifying patients with CRPS, there is currently no good predictor for the monitoring of response or for identifying the progression of CRPS [105]. During the 2002 IASP meeting, the consensus was that if a patient did not respond to 12–16 weeks of conventional therapy, a trial of neuromodulation including spinal cord or peripheral nerve stimulation may be warranted [103]. It has been well known that early, aggressive, multidisciplinary treatment provides improved outcomes in patients with CRPS [2, 103]. It is possible that early intervention may prevent central sensitization before chronic conditions can form.

Clinical approaches to neuromodulation differ greatly. A survey of 100 pain physicians in 2004 revealed that only 35% considered neurostimulation in their treatment algorithm of CRPS [106]. Of these, 71% considered SCS, while only 4% considered PNS [106]. In another article, many practitioners were found to perform a targeted nerve block, prior to the implementation of peripheral neuromodulation. However, a negative result to a nerve block may not necessarily predict the response to neurostimulation [107]. Identifying an ideal candidate for neuromodulation based on history and examination and proceeding with a trial may be performed, irrespective of the response to previous injections or nerve blocks.

Is PNS Cost-Effective in Treating CRPS?

Despite the benefits, neuromodulation as a treatment modality may incur significant costs associated with the device and operative time for implantation. While metrics such as patient satisfaction and pain scores may represent the patient response, third-party payers for such treatments often observe other metrics when determining cost/benefit analyses and reimbursement. A study conducted in 2004 by Mekhail et al. used a cost-benefit analysis of SCS and PNS systems implanted in 196 patients for the treatment of chronic neuropathic intractable pain. They determined that marked savings in direct medical costs occurred 3.1 years after implantation with an average annual cost saving of $30,221 per patient [108]. However, these were patients with chronic symptoms unresponsive to conservative therapies. If PNS would be considered earlier in patients' clinical presentations, perhaps the clinical course and chronicity of CRPS symptoms would decrease, thus contributing to further cost savings and resource benefit.

PNS continues to evolve 50 years after its first use was described. Alongside improvements in peripheral nerve stimulation, advancement has been made in the domains of spinal cord stimulation and dorsal root ganglion stimulation. The ACCURATE trial, a prospective multicenter randomized comparative effectiveness

trial on 152 patients with CRPS of the lower extremities, demonstrated that DRG stimulation provided a higher rate of treatment success (81.2% vs. 55.7%) with less postural variation in paresthesia intensity compared to SCS [109]. However, no direct comparison between peripheral nerve stimulation and spinal cord or dorsal root ganglion stimulation has been conducted to date. Further research into the pathophysiology of CRPS is needed to ensure an appropriate patient selection and to obtain optimal success with neuromodulation.

Summary of PNS for CRPS

Using PNS to help manage intractable pain in patients with CRPS is gaining increasing popularity. Pain limited to single a nerve distribution might be one of the most important factors in identifying an appropriate patient for PNS. There is Level I evidence of DRG stimulation in patients with CRPS in lower extremities. Whether PNS or DRG stimulation for CRPS is cost-effective remains to be determined by further studies.

Summary and Future Directions

The complex pathophysiology of CRPS makes treatment challenging. Studies of varied quality have reported that sympathetic block, IV ketamine infusion, and PNS provide clinically significant pain reduction in patients with CRPS. Appropriate patient selection and early intervention may improve the effects of sympathetic block or PNS on CRPS. Major controversies exist as to whether sympathetic neurolysis should be used in CRPS, whether intermittent IV ketamine infusions could cause tolerance or neurotoxicity, and when PNS should be utilized during the course of CRPS. There is a clear need for further better quality research to address these controversies and guide future treatments for improved outcomes.

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