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REVIEW ARTICLE

Complex regional pain syndrome: a narrative review for the practising clinician

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Summary

Complex regional pain syndrome (CRPS) is a life-altering condition that usually affects the extremities after a trauma or nerve injury. The physiologic changes that occur as a result of the inciting injury are complex, as the name of the syndrome implies. The pain and disability associated with CRPS often lead to psychological co-morbidities that create a vicious cycle of pain, isolation, and depression. We review recent developments in the understanding of CRPS and advancements in management of this syndrome. Further research in targeting specific mechanisms involved in the pathophysiology of CRPS should lead to prevention of this condition.

Keywords: causalgia; chronic pain; CRPS; reflex sympathetic dystrophy

Editor's key points

- The diagnosis and treatment of Complex Regional Pain Syndrome has been a challenge to health care providers since its recognition.
- As a result of the devastating impact on those afflicted, both functionally and psychologically, much effort has been made to understand this enigmatic disease.
- This literature review summarizes these efforts, including the history, current understanding of the pathophysiology and available treatments for CRPS. This is done to enable providers to help their patients manage pain and improve their quality of life.
- Comprehension of this syndrome is constantly evolving, and evidence-based treatments for favourable outcomes are lacking, mandating further research into its mechanisms and treatment.

Complex regional pain syndrome (CRPS) is a chronic neurologic condition resulting from a traumatic insult, with a prevalence of approximately 5.4–26.2 per 100 000 person years.[1] It can be further divided into two subtypes, based on the absence (CRPS I, previously known as reflex sympathetic dystrophy) or presence (CRPS II, previously known as causalgia) of a major nerve injury. It is distinct from other pain syndromes by the presence of autonomic dysfunction, persistent regional inflammatory changes, and a lack of dermatomal distribution. It commonly presents with allodynia, hyperalgesia, skin temperature changes, and oedema. Epidemiologic trends suggest that being female, having an upper extremity injury, and suffering high-energy trauma places patients at an increased risk of developing this disorder.[1]

This condition is enigmatic in nature. It has been historically difficult to diagnose, arduous to treat, and the

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pathophysiologic mechanism behind its development has not been clearly defined. Here, we provide a current review of the medical literature involving CRPS, including patient presentation, pathophysiology, diagnostic criteria, and current treatment strategies.

History

Cases of CRPS are evident as early as the 16th century. Ambrose Paré, a barber and surgeon during the reign of French King Charles IX, made reference to the treatment of a severe and persistent pain syndrome after limb phlebotomy, or 'bloodletting.'[2] One of the earliest cases of CRPS in North America was likely described in 1864 by a physician named Silas Weir Mitchell, who was characterising a specific type of pain resulting from gunshot wounds during the Civil War.[2] His patients complained of a severe burning pain associated with shinning red skin.[3] In 1872, he went on to coin the condition 'causalgia', which he associated with pain in excess of the inciting injury.[2] In 1946, James A. Evans, a physician from Massachusetts, described a similar condition to Mitchell.[2] He reported on patients who experienced intense suffering associated with abnormalities of the sympathetic nervous system, which he designated 'reflex sympathetic dystrophy.'[4]

Throughout the past century, this disorder has been known by many different names, including Sudeck's atrophy, sympathetically mediated pain, and sympathetically independent pain. It was not until 1994 that a task force under the International Association for the Study of Pain (IASP) developed its current designation, Complex Regional Pain Syndrome, which they published in the second edition of the Classification of Chronic Pain.[2] CRPS I, previously known as reflex sympathetic dystrophy, is thought to be caused by trauma with the absence of major nerve injury, and it accounts for the majority of cases.[5–7] CRPS II, previously known as causalgia, involves an identifiable nerve injury related to major trauma or surgical insult.

Pathophysiology

A singular linear mechanism behind the development of CRPS is unlikely to be discovered. Under the most widely accepted pathologic model, CRPS is thought to be an elaborate combination of different factors that begin to take place at the time of initial injury, including nervous system sensitisation, autonomic dysfunction, and inflammatory changes. It is also believed that there may be some evidence of a genetic predisposition to this syndrome, and psychological factors may influence development as well.

Peripheral nervous system

The development of CRPS likely starts subsequent to an inciting or traumatic event, leading to distinct changes in the peripheral nervous system. Nociceptive sensitisation occurs early on, driven by the release of pro-inflammatory mediators such as tumor necrosis factor-alpha (TNF-α) and prostaglandin E2.[8] This sensitisation leads to a decrease in the depolarisation threshold locally,[8] likely contributing to hyperalgesia in these patients.

It is also believed that a coupling between the sympathetic and peripheral nociceptive nervous systems may develop over time, leading to the distinct symptomatology of CRPS.[9] Aδ and C afferent neurons are thought to engage the autonomic nervous system after persistent synaptic firing, linking the two.[8] Additionally, peripheral nociceptive nerves have been shown to develop catecholamine sensitivity after injury in CRPS.[9]

There is also a probable chronological change in peripheral nervous system morphology. In a recent case study, the peripheral nerve fibres of a chronic CRPS patient were examined using transmission electron microscopy.[10] The researchers reported a significant degeneration of large somatomotor Aα nerve fibres, while Aδ nerve fibres were spared.[10] They hypothesised that an imbalance of nerve signalling may occur peripherally, increasing Aδ nociceptive activity and enhancing pain. Regardless, it appears likely that long-term changes in the peripheral nervous system play an important role.

CNS

CNS sensitisation is also fundamental to the development of CRPS. Continuous peripheral nerve activation after injury has been shown to increase the efficacy of synaptic nociceptive firing in the dorsal horn.[11] This sensitisation is thought to be mediated by neuropeptides such as glutamate and substance P, decreasing the threshold for response to mechanical and thermal stimuli, and leading to hyperpathia and allodynia.[8] This has also been demonstrated in animal models, where antagonism of substance P intrathecally lead to decreased allodynia.[12]

Chronically, much like the peripheral nervous system, structural CNS changes may take place. For example there are reports that the affected limbs of CRPS patients make up a smaller representation in the somatosensory cortex than unaffected limbs.[13] This may lead to increasing CNS symptomatology as the disease continues, such as motor dysfunction, neglect, and impaired recognition. There is also decreased range of motion and dystonia with flexion of fingers, toes, and wrists in some patients.[14] Favourable clinical response to intrathecal baclofen suggests a central gamma-aminobutyric acid mechanism is involved.[14] While not fully elucidated, there is likely central reorganisation of motor and nociceptive pathways that occur in CRPS patients.

Autonomic dysregulation

As stated previously, it is believed that coupling between adrenergic and nociceptive neurons occurs in CRPS, leading to increased pain after sympathetic stimulation.[8 15] For example there is increased expression of α1-adenergic receptors in CRPS affected limbs,[16] and pain can be induced through injecting phenylephrine intradermally in these patients.[17] Physical restructuring may take place as well, as experimental models suggest an increased linkage between the autonomic nervous system and the Aδ and C nerve fibres responsible for pain.[8]

Distinct aspects of CRPS symptomatology can be explained by autonomic dysfunction as well. For example alterations in the circulating catecholamines can explain the progression of warm limbs to cold. During the acute phase, studies have shown a decrease in circulating norepinephrine, potentially leading to vasodilation, oedema, and increase in limb temperature.[18] It is believed that over time this leads to increased peripheral catecholamine sensitivity, and the subsequent excessive vasoconstriction and hyperhidrosis that develops, leads to the cold, clammy extremities seen in the chronic phase of

the disease.[18] Undoubtedly, there is a strong underlying adrenergic component to CRPS pathophysiology.

Immunologic

Immunologic influences are likely fundamental to CRPS development. Specifically, an increase in neuropeptides such as substance P and calcitonin gene-related peptide (CGRP) leads to the release of pro-inflammatory mediators, such as TNF-α, interleukin (IL)-1β, IL-6, and nerve growth factor (NGF), some of which potentiate peripheral sensitisation to noxious stimuli.[19–21] Cytokine production is partially driven by innate immune cells, and at the time of the initial insult, increased mast cell accumulation has been shown.[20] Moreover, the release of cytokines and neuropeptides (substance P and CGRP) cause an increase in tissue permeability and vasodilation, clinically presenting as oedema and increased warmth.[22]

However, while it has been shown that mast cells and inflammatory cytokines are increased acutely, this trend is not necessarily sustained, and mast cells may not be increased in chronic disease.[23] In a recent study, mast cells were shown to be diminished immediately surrounding the atrophied dermal nerve fibres in the limbs of CRPS patients.[24] The researchers hypothesised that a dysregulation between normal neural-mast cell interaction takes place, leading to prolonged inflammation and delayed tissue repair in CRPS.

There is also evidence implicating autoimmunisation in CRPS development. It is believed that autoantibodies form against autonomic nervous system structures, potentiating inflammation and exacerbating symptoms.[25] In fact, investigative studies have shown that up to 70% of these patients have anti-autonomic immunoglobulin G antibodies in their serum.[19] The importance of these findings has yet to be clearly defined.

Genetic influence

The genetic impact on CRPS development is currently under investigation. A study in 2009 examined familial inheritance in a Dutch patient population with the disorder.[26] The researchers identified 31 families with multiple affected members, and concluded that a familial linkage is associated with an earlier onset and a higher incidence of multiple limb involvement.[26] However, they were not able to determine a specific inheritance pattern.

Despite this, efforts to identify specific genotypes associated with CRPS are showing promise. Human leukocyte antigen (HLA) subtypes B62 and DQ8 were found to be significantly associated with disease development with fixed dystonia.[27] A more extensive investigation in 2013 performed a genome-wide profile of patients with CRPS.[28] The researchers found that HLA-A29.1, matrix metalloproteinase 9 (MMP9), alanine aminopeptidase N (ANPEP), l-histidine decarboxylase (HDC), granulocyte colony-stimulating factor 3 receptor (G-CSF3R), and signal transducer and activator of transcription 3 (STAT3) gene expression were significantly increased in CRPS patients compared with controls.[28] Many of these genes are involved in signal transduction, cell motility, and immunity.

The exploration of specific microRNA (miRNA) signatures is another interesting avenue of genetic study. These small non-coding segments of RNA have been shown to directly alter gene expression.[19] A 2011 study found 18 distinct miRNA signatures that were significantly elevated in CRPS patients compared with controls, potentially indicating a new target for therapy.[19,29] However, a genetic link is not certain. A conflicting study in 2016 looked at >200 000 single nucleotide polymorphisms between CRPS patients and control groups, and found no significant difference in expression between the two.[30] More investigation is needed to determine if there is a genetic link to developing CRPS.

Psychological stress

There is some evidence that certain psychological states can make a patient more susceptible to disease development. Patients with post-traumatic stress disorder (PTSD) have a significantly increased incidence of CRPS when compared with controls.[31] In many of those patients, PTSD began before the onset of CRPS, suggesting a predisposition. What is more certain is that psychological stress seems to influence disease progression. Patients with higher levels of anxiety, perception of disability, and pain-related fear have been shown to have a worsened disease course.[32] This is likely secondary to an increase in anxiety-associated catecholamine release, leading to increased nociceptive sensitisation and adrenergic symptoms.

Catastrophising, an exaggerated negative psychological response to noxious stimuli,[33] may also have a significant impact in the development of CRPS. It has been shown to lead to increased proinflammatory cytokine activity in response to painful stimuli, and the level of catastrophising has been correlated to future pain scores in patients.[34] Catastrophising is also correlated to altered grey matter volume in paediatric patients, possible affecting chronic motor function and pain development.[35]

Presentation

Epidemiology

Many epidemiologic studies have been conducted, and there seem to be regional variations in terms of presentation. The first major survey was conducted by Sandroni and colleagues[7] in 2003. This survey became the baseline for identifying risk factors and disease prevalence of CRPS; however, it was somewhat limited. Over a 10 yr period, the researchers examined fewer than 100 patients from a small community in the USA, and they primarily focused on describing CRPS I patients.[7] More recently, two other major epidemiologic surveys were conducted examining a much larger population. The epidemiologic study by Ott and Maihofner[6] was conducted near Nuremberg, Germany in 2018. Their results mirrored the study by Sandroni and colleagues,[7] reporting an incidence disparity between women and men as high as 71% and 29%, respectively.[6] They also showed that the upper limb was more prone to CRPS development (70% of patients), and that CRPS I occurs much more frequently than CRPS II (88% and 12%, respectively).[6]

The epidemiologic survey by Kim and colleagues,[5] however, showed some important differences. Utilising data from the Korean National Health Insurance Service, investigators looked at patient data from more than 74 000 patients, a much larger survey than the previous two.[5] They reported that the female to male disparity was much narrower, and the age of highest incidence was much higher than previously reported.[5] They also determined that the pelvis, thigh, and lower limb were more likely to be affected than the upper limb in their patient population.[5]

The variability in these studies highlights the challenges of CRPS diagnosis. Because it is a clinical determination,

physicians using different criteria will often have different results. For example in legal disability claims, many clinicians surveyed in the study be Kim and colleagues[5] utilised the Persistent Disability and Assessment Guidelines by the American Medical Association instead of the IASP or Budapest criteria. These guidelines focus more on objective findings than subjective symptoms, and older patients who are more likely to be disabled from injury may better fit the criteria, increasing the overall age of incidence. Interestingly, a correlation may exist between the increased age of onset and the higher likelihood of lower limb involvement in the study by Kim and colleagues,[5] as elderly patients are more prone to hip and pelvic fractures than their younger counterparts.

How reflective these studies are of the general population depends on the diagnostic criteria utilised. If objective symptoms and diagnostic testing are emphasised, the survey by Kim and colleagues[5] is likely to be more reflective. If clinical criteria are emphasised, the surveys by Ott and Maihofner[6] and Sandroni and colleagues[7] are likely more representative. A comparison of the three surveys can be seen in Table 1.

Inciting event

Certain injuries have been shown to lead to a higher incidence of developing CRPS. Fractures involving the upper extremities, especially antebrachial fractures, seem to be the most vulnerable.[1] When CRPS develops in the lower extremities, injuries of the ankle and intra-articular injuries may enhance patient risk.[15] Regardless of limb, proximal fractures seem to have a very low disease incidence, suggesting that patients suffering from distal injuries are more susceptible.[1] The presence of a concurrent musculoskeletal disease, such as rheumatoid arthritis, may also increase the risk.[19]

High energy injuries, severe fractures, and prolonged general anaesthesia times during repair are positively associated with disease development.[19] Interestingly, the length of time spent under regional anaesthesia did not show a similar correlation.[19] Regardless, patients whose fractures were treated surgically may be more susceptible to developing CRPS.[1]

Common pain presentation

CRPS patients exhibit a constellation of symptoms, including sensory abnormalities, autonomic signs, and motor dysfunction throughout the disease course.[36] The characteristic symptom initially is strong, burning pain, usually out of proportion to the inciting event. This pain begins at the site of the initial trauma, and then spreads regionally without specific dermatomal distribution.[1 37] Increases in skin temperature, nail and hair growth, and erythema can be seen.[36] As the disease progresses, hair growth tends to slow, nails become more brittle, and muscle weakness begins.[36] Skin temperature can also decrease, resulting in a 'cold limb'.[37] Eventually, irreversible changes in muscle weakness, decreased muscle mass, and intractable pain can develop.[36] While pain is usually triggered mechanically, thermal stimuli and psychological factors can exacerbate symptoms as well.[37,38]

Diagnostic criteria

There is no definitive confirmatory test for CRPS, and diagnosis remains difficult. In 1994, the first set of diagnostic criteria emerged for CRPS from the IASP, which are listed in Table 2.[32] However, problems soon became evident. The diagnostic criteria had a low specificity, and often led to misdiagnosis.[32] In 2003, a new set of diagnostic criteria was developed, now known as the Budapest criteria, which is the current standard in CRPS diagnosis (Table 3).[32,39] These criteria still maintained a high sensitivity for CRPS (0.99), however, they greatly improved upon the specificity of the IASP diagnostic criteria (0.41–0.68).[39]

In order to further quantify the severity of disease, in 2010, Harden and colleagues[40,41] developed the CRPS severity score (CSS). It included 17 different symptoms of CRPS, giving one point for the presence of each. Higher scores were not only shown to positively correlate with increased pain and functional limitation, but have also been used as a measure to track the response to treatment in patients with CRPS.[41] These criteria are listed below in Table 4.

Other diagnostic tools

No diagnostic test is considered definitive for CRPS; however, other modalities can help support the diagnosis. Thermography may be the most common and basic diagnostic method utilised, and temperature differences are a component of the CSS.[40] Changes of 1°C or more are considered to be significant; however, larger temperature differences do not seem to correlate with the subjective degree of pain experienced.[42]

Bone scintigraphy is another common diagnostic test for CRPS, but it is controversial. When utilised for evaluating CRPS I, bone scintigraphy imparts a high specificity, but sensitivity

Table 1 Comparison of epidemiologic surveys for CRPS.[5–7] *Data extrapolated from study. †Reported as highest incidence per decade ranges. ‡CRPS I only. ¶Reported as a percentage. CRPS, complex regional pain syndrome.

Survey details	Sandroni and colleagues[7] (2003)	Kim and colleagues[5] (2018)	Ott and Maihofner[6] (2018)
Location of study	MN, USA	Korean National Health Insurance Database	Erlangen-Nuremberg regional area
Years surveyed	1989–1999	2011–2015	1993–2014
Number of cases surveyed	85*	74 349	1043
Average age of onset (yr)	46	70–79†	50.1
Incidence of CRPS 1:2 (percentage of total)	87:13*	63:37	88:12
Incidence between female:male (per 100 000 person years)	8.57:2.16‡	10.2:8.0	71:29¶
Most common limb affected	Upper limb	Lower limb/pelvis	Upper limb

Table 2 Initial International Association for the Study of Pain (IASP) criteria for complex regional pain syndrome, 1994[32].

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

was found to be decreased when using the Budapest criteria as a reference.[43] Another recent meta-analysis concluded that scintigraphy has no benefit in the management of CRPS, as it should not be used as a confirmatory measure.[44]

Electromyography has shown some validity in specific patient populations. Myoclonus that presents in CRPS patients is thought to be distinct from other types of myoclonus, and this may be able to be characterised through electromyography.[45] However, only 11–36% of patients demonstrate myoclonus, greatly limiting its sensitivity as a diagnostic tool.[45]

In a small observational study in 2016, musculoskeletal ultrasonography (MSK US) was used to characterise physical differences in muscle tissue in CRPS patients.[46] This study concluded that muscles affected by CRPS have significant myoglobular distortion, while muscles affected by chronic neuropathic pain were structurally normal.[46] However, a much larger study would be needed to validate using MSK US as a useful diagnostic modality. Ultimately, a singular definitive diagnostic test for CRPS is not currently within reach.

Treatment

The treatment for CRPS is mainly dealt symptomatically with a combination of physical/occupational therapies, psychological therapy, neuropathic pain medications, anti-inflammatories and interventional procedures.[32 34] Many of the medications utilised for the treatment of CRPS are based on their efficacies in treatment of neuropathic pain.[47] Medications that underwent trials for CRPS are limited and the evidence is discussed in this review. The neuromodulation trial data on spinal cord stimulation (SCS) and dorsal root ganglion (DRG) stimulation are also discussed in this review. The evidence for the effectiveness of many of the treatment modalities for CRPS is lacking strength, and further research is required.

Table 3 Budapest Criteria for CRPS, 2003.[32] CRPS, complex regional pain syndrome.

Continued pain that is disproportionate to any inciting event
Patient must report one symptom in three of the following four categories:
Sensory: allodynia or hyperalgesia
Vasomotor: temperature asymmetry, skin colour changes
Sudomotor: oedema, changes in sweating
Motor/trophic: decreased range of motion, motor dysfunction, changes in hair and nail growth
Must display one sign at the time of evaluation in at least two of the following categories:
Sensory: evidence of hyperalgesia and allodynia
Vasomotor: evidence of temperature asymmetry or skin colour changes
Sudomotor: evidence of oedema or swelling
Motor: motor weakness/dysfunction
There is no other diagnosis that explains the patient's signs or symptoms
CRPS 1 - Without evidence of major nerve damage
CRPS 2 - With evidence of major nerve damage

Table 4 Symptoms included in the CRPS Severity Score, 2010.[40] CRPS, complex regional pain syndrome.

Symptoms that were self-reported
Allodynia
Temperature asymmetry
Skin colour asymmetry
Sweating asymmetry
Trophic changes
Motor changes
Decreased range of motion
Asymmetric oedema
Symptoms observed at the time of examination
Hyperpathia to pinprick
Allodynia
Temperature asymmetry to palpation
Skin colour asymmetry
Sweating asymmetry
Asymmetric oedema
Trophic changes
Motor changes
Decreased active range of motion

Physical/occupational/psychological therapy

CRPS treatment guidelines recommend a multidisciplinary approach including rehabilitation with physical (PT), occupational (OT), and psychological therapy.[34,48] Because of the extremity pain in CRPS, patients tend to avoid the use of the affected limb. With the use of PT and OT, the goal is to have the patient improve the functionality and the range of motion of the extremity, and achieve reduction in pain and increased mobility.[34] A Cochrane review published in 2016 examined 18 randomised controlled trials (RCTs) (n=739) on physiotherapy-based interventions.[49] Most of the trials examined were of 'low' quality or at 'high' risk of bias. However, despite these drawbacks, the Cochrane review described two therapies with the best available data that could provide improvements in pain and function in CRPS I patients.[49] The two therapies, which are very similar, are graded motor imagery (GMI) and mirror therapy.[49]

GMI involves three stages: first, patients start identifying limb laterality with images, second, patients progress to imagining moving their limb into a position based on an image, and then finally, patients view the unaffected limb moving reflected on a mirror.[50] Two trials with GMI (n=49) showed improved pain and functional disability at 6 months with CRPS I patients.[49] Mirror therapy, which was first described in phantom limb pain,[51] has been utilised for CRPS.[52] Patients in mirror therapy programs will start by describing both the affected and unaffected limb, followed by imagined movements of both extremities, and then finally patients will look at the mirrored limb without movement.[52] Two trials with mirror

therapy (n=72) also showed improvements in pain and functionality at 6 months in CRPS I patients.[49]

CRPS can lead to an emotional toll on patients. Because of the pain of CRPS, patients will tend to avoid the use of the affected limb and generate fear associated with the pain in the affected limb. With severe pain, patients will take on significant emotional stress. Psychological therapy can be helpful in this regard to assist patients with coping mechanisms for pain, relaxation training, thermal biofeedback, and graded exposure therapy.[34] A small RCT was conducted involving 18 patients who received either PT or PT with relaxation training. Both groups had similar improvements in pain, range of motion, and oedema, but the PT with relaxation training had better limb temperature improvements. A number of case reports have been published involving thermal biofeedback with complete resolution of symptoms.[34]

Ultimately the role of PT/OT and psychological therapy is to improve functionality, mobility, quality of life, and the ability to manage one's own pain. In CRPS, these therapies should be utilised early and are considered by many pain physicians to be first-line treatments.[34]

Neuropathic pain medications

Neuropathic pain medications have not been extensively studied for CRPS. The basis of using neuropathic pain medications to treat CRPS is on their usefulness in treating other neuropathic conditions.[47] The evidence for their use in CRPS is limited. Gabapentin, which binds to the α2-δ subunit of voltage-dependent calcium channels, has some RCT evidence that demonstrates efficacy in reducing pain in patients with CRPS.[53,54] Recently, in 2016, an RCT of amitriptyline *vs* gabapentin for CRPS I in the paediatric population (ages 7–18 yr old) was published.[55] Thirty-four patients were randomly assigned to receive amitriptyline 10 mg day^{-1} or gabapentin 900 mg day^{-1} and were followed for 6 weeks. Both drugs were effective in reducing pain intensity and improving sleep, with no statistical significant difference between the two drugs.[55] No other tricyclic antidepressants have been studied in RCTs involving the CRPS population. An anticonvulsant drug, carbamazepine, which blocks sodium channels, has been studied in a small trial with CRPS patients given 600 mg day^{-1} over 8 days, and the trial showed pain reductions.[56] The use of other neuropathic pain medications by pain physicians to treat CRPS is empirical and based on each provider's preference and experience.

Anti-inflammatory medications

The efficacy of NSAIDs in decreasing pain in certain neuropathic conditions has not been well demonstrated.[57] However, inflammation has a role in CRPS, particularly in the early months of the syndrome. NSAIDs are a class of drugs which work by inhibiting cyclooxygenase-1 and -2, resulting in an overall decrease in prostaglandins that promote inflammation. This can lead to an overall anti-inflammatory effect and reduction in pain. NSAIDs, as a class of non-opioid pain reliever medications, may possibly be used by clinicians as part of an initial therapy. Many of the studies involving the use of NSAIDs in CRPS have been small and results have been mixed.[58 59] An RCT involving 12 patients published in 2011 used i.v. regional blocks (IVRBs) for CRPS type I affecting the lower extremity.[59] Four consecutive IVRBs were provided to patients 1 week apart in random order, with lidocaine 0.5%, 50 ml, with ketorolac 0, 30, 60, or 120 mg. Only 1 day of significant pain relief was shown in the ketorolac group.[59] In 2014, a group investigated the short term use of the cyclooxygenase-2 specific inhibitor parecoxib on CRPS pain intensity and oedema.[58] Twenty patients with CRPS of the upper extremity were recruited and randomised to either receive 2 days of i.v. parecoxib 80 mg or placebo each day.[58] There were no differences in the outcomes studied between the two groups.[58] An RCT in 2006 (n=60), which compared the efficacy of the corticosteroid prednisolone (40 mg day^{-1}) *vs* the NSAID piroxicam (20 mg day^{-1}) in patients with CRPS type I after stroke, showed at 1 month that the prednisolone group had significant improvements in signs and symptoms of CRPS compared with the piroxicam group.[60] Both groups showed significant improvements in the Barthel index activity of daily living score.[60] NSAID targeting of cyclooxygenases may potentially provide some relief for the inflammation in CRPS, but corticosteroids may be able to decrease inflammation by targeting various other inflammatory pathways. Systemic corticosteroids have been studied in various trials and generally had positive results for CRPS. A 1982 study, commonly cited in various reviews on CRPS and corticosteroids, involved 23 patients placed into two treatment groups of prednisone or placebo.[61] The prednisone group was given 10 mg three times a day until clinical remission or a maximum of 12 weeks. The 13 patients in the prednisone group had more than 75% improvement in clinical symptoms.[61] Two of the 10 patients in the placebo group also reported improvement. A critical review of the clinical trial evidence published in 1997 showed that corticosteroids had consistent support in providing analgesia and long-term effectiveness.[62] A recent open-labelled randomised study in 2016 involving 58 patients with CRPS type I post-stroke was published, which showed that prednisolone was safe and effective for use up to 2 months.[63] Fifty-eight patients with post-stroke CRPS type I were all given prednisolone 40 mg day^{-1} for 2 weeks then tapered into two groups: one group would be continued on prednisolone 10 mg day^{-1} and the other group would be off prednisolone. The initial dose of prednisolone helped 56/58 patients, and the group that continued prednisolone therapy continued to have further improvement in symptoms. About one-half of the patients in the discontinuation group experienced worsening of symptoms after initial improvement, and were placed back on prednisolone, with about 77% subsequent improvement in the following month.[63] Patient selection and length of corticosteroid therapy is important, as systemic treatment can have effects on fasting blood sugar and body weight. Long-term chronic steroid use and its long-term adverse effects have been well documented. Interestingly, a small (n=21), double-blind, randomised study in 2010 studied whether a single dose of intrathecal methylprednisolone 60 mg in chronic CRPS patients could have an effect on pain intensity. The trial was stopped, as the interim analysis showed that the treatment had no effect.[64] Steroids given intrathecally were not effective, possibly because the patients selected for the study had longstanding chronic CRPS with severe pain.[64] The data support that a short course of corticosteroids could be beneficial for patients in early CRPS with a prominent inflammatory component.

Bisphosphonates

Bisphosphonates are a class of medications that are widely used for the treatment of osteoporosis because of their ability to inhibit osteoclast bone resorption. Because of this

mechanism of action, bisphosphonates have been used also to treat pain associated with a number of bone-related pathologies including Paget's disease and metastatic cancer. Bisphosphonates have been proposed to be a treatment for CRPS, but the mechanism of pain reduction is not clear.[65] Some theories involve the ability of bisphosphonates to modulate inflammation, inhibiting bone marrow cell growth and migration, reducing the acidity of the bone microenvironment.[66] Patients with CRPS that are bone scan negative, either because of having chronic CRPS or predominantly cold disease, are potentially less responsive to treatment.

A Cochrane review published in 2013 indicated that the evidence for bisphosphonates being effective for pain in CRPS was of low quality.[67] A more recent meta-analysis of all RCTs to assess bisphosphonates for treatment efficacy for CRPS I was conducted.[66] Four trials were included (n=181) with the following bisphosphonate regimens: oral alendronate 40 mg day^{-1} for 8 weeks, i.v. pamidronate 60 mg once, i.v. clodronate 300 mg day^{-1} for 10 days, or i.v. neridronate 100 mg on 1, 4, 7, and 10 days. The VAS pain score was statistically reduced in the bisphosphonate group compared with placebo at 30–40 days.[66] At 2–3 months, the VAS pain score continued to be reduced in the bisphosphonate group.[66] Some adverse events reported were mild fever for <3 days, gastrointestinal intolerance, erythema at the site of infusion that resolved within 2 days, subclinical hypocalcaemia, and polyarthralgia.[66] There were no reports of serious side-effects. Based on the meta-analysis, the authors concluded that bisphosphonates reduce pain in patients with CRPS I, but also indicated that further research was needed.

Sympathetic nerve block

Part of the pathophysiology of CRPS is thought to be related to autonomic dysregulation in the affected limb and an exaggerated response to catecholamines, which contributes to pain. Interventional pain physicians will typically use sympathetic nerve blocks (SNBs) as a means of decreasing pain for their patients with CRPS. Patients with CRPS of the lower extremity will have a lumbar sympathetic block performed and patients with CRPS of the upper extremity will have a stellate ganglion block. A successful block will be monitored typically with an increase in temperature of the affected extremity. A Cochrane review, last updated in 2016, examined a multitude of clinical trials for the efficacy of sympathetic blocks for the treatment of pain in CRPS. Despite including 12 studies with n=461, because of the overall quality of evidence and lack of evidence, the review could not 'support or refute' the use of these blocks for the treatment of CRPS.[68] There are only two small RCTs (n=32) comparing SNBs with placebo, and those two studies demonstrated no significant difference between the groups. Most of the other studies in the Cochrane review found no difference in pain outcomes comparing SNBs against other active treatments.

Despite the low quality of evidence on the use of SNBs for CRPS, they are commonly performed by interventional pain physicians, as patients who respond to this treatment will commonly want to have the procedure when in severe pain. Larger RCTs need to be conducted to fully understand the efficacy of SNBs in CRPS.

Spinal cord stimulation

Spinal cord stimulation (SCS) is the process of sending electrical stimulation on the dorsal column of the spinal cord. Electrodes are placed into the epidural space percutaneously, with the electrodes attached to a power source/pulse generator. Patients first undergo a trial of SCS and have the electrodes attached to an external pulse generator. After a successful trial, the pulse generator is implanted subcutaneously. The electrical stimulation on the dorsal column is thought to mask the sensation of pain, and perceived pain is reduced. The evidence for SCS for treating mixed neuropathic/nociceptive and neuropathic/radicular pain conditions, such as in failed back surgery syndrome and CRPS, is particularly strong.[69] A recent systematic review published in 2017 examined the effects of SCS on specific outcomes in patients with CRPS.[70] Nineteen studies were evaluated and high-level evidence of improvements in perceived pain relief, pain score, and quality of life, and satisfaction with SCS were present. The data on functional status and psychological effects were inconclusive.[70] Further studies need to be conducted to determine the efficacies of these outcomes.

A review published in 2013 examined the pain care algorithm to determine when SCS would be appropriate for patients with CRPS. Based on their analysis with considerations of safety, efficacy, and cost, the authors determined that SCS should be utilised earlier and 'not be considered a therapy of last resort.'[71]

Dorsal root ganglion stimulation

Dorsal root ganglion (DRG) stimulation is a relatively new and developing technology where the electrical stimulation is applied to the DRG. The DRG is the location of the cell bodies of peripheral sensory neurons. A case series published in 2015 showed the promise of DRG stimulation in patients with CRPS.[72] In the eight patients that had successful trials, after DRG implantation, patients had improvements in pain, and subjective improvement in functionality. At 1 month, self-reported pain reduction was approximately 62%, and relief persisted to 12 months.[72] At 12 months, the quality of life improved for all of the patients, and six of eight patients had greater than 50% reduction in pain compared with baseline.[72] More recently, the ACCURATE study was published in 2017, which was a prospective, randomised multicenter trial with n=152 patients with CRPS of the lower extremity.[73] Patients were randomised to either receive SCS (dorsal column) or DRG stimulation. At 3 months, the number of patients with greater than 50% pain relief was statistically higher in the DRG group (81.2%) compared with the SCS group (55.7%). At 12 months, patients in the DRG group continued to have greater statistical pain relief (74.2% *vs* 53.0%) compared with the SCS group. No difference was seen in serious adverse events in the two groups.[73]

DRG stimulation may prove to be the more superior neuromodulation option for CRPS, as DRG can target specific painful areas of limbs. Safety and efficacy appear to be similar, if not superior, to SCS.[73] However, further studies on DRG stimulation as a treatment for CRPS will continue to strengthen the evidence.

Prevention of CRPS: vitamin C?

Up to 10% of patients with distal radial fractures are thought to develop CRPS.[74] A prospective, double-blind study published in *Lancet* in 1999 had patients with wrist fractures either take a capsule of vitamin C 500 mg or placebo as a prophylactic antioxidant drug for 50 days.[75] At 1 yr follow-up, patients in the vitamin C group were associated with a lower risk of developing CRPS.[75] Vitamin C is thought to be a low-risk

intervention that acts by inhibiting pro-inflammatory pathways mediated through antioxidant mechanisms.[75] A follow-up prospective, double-blind, dose-response study in 2007 examined vitamin C at 200, 500, and 1500 mg compared with placebo taken as a prophylactic antioxidant drug for 50 days after a wrist fracture.[76] The prevalence of CRPS in the vitamin C group was lower compared with placebo (2.4% *vs* 10.1%, $P=0.002$).[76] Analysis of the different doses suggested that vitamin C 500 mg would be the recommended dose for possibly reducing the prevalence of CRPS in these patients.[76] However, in 2014 a prospective RCT was conducted to look at the effect of vitamin C on functional outcomes after a wrist fracture.[77] Patients were randomised to receive vitamin C 500 mg or placebo for 50 days. In this study, there was no significant difference in functional outcomes studied, the rate of CRPS, or bone healing.[77] A recent meta-analysis in 2015 was conducted to determine whether vitamin C was effective in preventing CRPS in patients with distal radial fractures.[78] In the meta-analysis, data were combined from across the three trials, and vitamin C appeared not to reduce the risk of developing CRPS (risk ratio=0.45; 95% confidence interval, 0.18–1.13; $I^2=70\%$).[78] Further study of the effectiveness of vitamin C in the prevention of CRPS after distal radial fracture is required.

Of note, a group studied whether vitamin C was effective in preventing CRPS in foot and ankle surgery.[79] Control and intervention groups were chronologically separated and a vitamin C dose of 1000 mg was used. In their study, vitamin C seemed to be effective in preventing CRPS after foot and ankle surgery.[79] The authors in the study recommended the use of vitamin C for prevention.[79] Because of mixed outcomes and the overall quality of evidence, it is unclear whether vitamin C overall has effectiveness in reducing the prevalence of CRPS after certain fractures and limb surgeries. However, because of the low risk of intervention, and some positive results in certain studies, the use of vitamin C by physicians for patients with distal radial fractures or after foot or ankle surgeries could still be a possible intervention that could be safely utilised and recommended with moderate strength in some guidelines.[80]

Future directions

CRPS is a life-altering condition and can be very difficult for the patient and the treating physician. The pathophysiology of CRPS is still unclear; however, based on recent literature, progress is being made. The treatment for CRPS is generally still driven by clinician experience, as evidence-based recommendations are lacking. Initial treatments, not based on strong evidence, would be to incorporate PT/OT/psychological therapies early with neuropathic medications. The strongest evidence for successful treatment would be to introduce neuromodulation early if other treatments fail, as long as the patient is an appropriate candidate. There are frequently small studies being published, which make incremental advancements in our knowledge of CRPS, but larger RCTs are needed in the field.

Authors' contributions

Major contributors in drafting the review: HS, JR.
Study conception and design: PS.
Revising paper critically for important intellectual content: PS, SH.
Read and approved the final review: all authors.

Declaration of interest

The authors declare that they have no conflicts of interest.

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