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Review Article

A review of waveform and paradigm variations of spinal cord stimulation for the treatment of complex regional pain syndrome

Vahid Mohabbati (MD, FRACGP, FFPMANZCA, FAChPM, AFRACMA)[1,2,3,4,*], Parsa Mohabbati[1,2], Mohammadkazem Papan, Ph.D.[1,2]

[1]Sydney Pain Research Centre, Sydney, NSW, Australia

[2]Sydney Pain Management Centre, Sydney, NSW, Australia

[3]Associate Professor at Faculty of Engineering at the University of New South Wales (UNSW), Australia

[4]Clinical Senior Lecturer at the School of Medicine and Psychology (SMP), Australian National University, Canberra, Australia

*Author for correspondence: Email: director@sydneypaincentre.com, research@sydneypaincentre.com

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Abstract

Complex Regional Pain Syndrome (CRPS) is a challenging condition marked by intense and often long-lasting pain, typically occurring in a limb following an injury. Traditional treatment approaches might not always offer significant pain relief, prompting the investigation of advanced treatments like Spinal Cord Stimulation (SCS). This review delves into the significance of SCS therapy for CRPS, focusing on the utilization of different waveforms and paradigms in its management. Spinal Cord Stimulation is a treatment modality that utilizes a medical device to send electrical impulses to the spinal cord, aiming to alter pain signals and provide relief. For patients with CRPS, this therapy has become a focus of interest due to its ability to reduce pain and enhance overall quality of life, particularly in cases where other interventions have proven ineffective.

Introduction

Complex Regional Pain Syndrome (CRPS) is a neuropathic pain disorder often initiated by an injury to an extremity or a peripheral nerve. The pain experienced in CRPS is often disproportionate in intensity or duration compared to the expected course of pain following similar tissue injuries. Clinical definitions and understanding of CRPS are still evolving, but it appears to involve functional central abnormalities and peripheral inflammation [1]. It can be challenging to diagnose CRPS, but The Budapest criteria, established in 2003, have greatly improved specificity. There are four components to these criteria: (1) persistent pain that is significantly more severe than would be expected from the initial inciting event, (2) at least one symptom presents in three of the four categories: sensory, vasomotor, sudomotor/edema, and motor/trophic, (3) evidence of a past or present causative event, and (4) exclusion of other possible causes [2]. Complex Regional Pain Syndrome (CRPS) is classified into two subtypes: Reflex Sympathetic Dystrophy (RSD), also known as type I CRPS, causes neuropathic pain without overt nerve damage. Type II CRPS, or causalgia, occurs when nerves are injured. CRPS is treated to reduce pain, restore function, and enhance overall quality of life. A collaborative, multidisciplinary approach is often used, including physical therapy, medications, and psychological interventions. CRPS can be treated with spinal cord stimulation (SCS) which is a procedure that entails placing electrodes in the epidural space to modulate pain signals. Patients with CRPS who undergo SCS have reported experiencing decreased pain levels and improved function [3]. Several studies have investigated the incidence and prevalence of Complex Regional Pain Syndrome (CRPS). Allen *et al.* carried out a retrospective analysis of medical records involving 134 patients and provided insights into the epidemiology of CRPS. They highlighted factors such as fractures, bone diseases, and chronic pain as relevant to the understanding of CRPS incidence [4]. A study in the Netherlands observed a declining trend in the incidence of Complex Regional Pain Syndrome (CRPS) following distal radius fractures between 2014 and 2018. Hospital cases declined from 520 to 223,

with a notable drop in national annual incidence from 23.2 to 16.1 per 100,000 person years. This decline is linked to evolving CRPS and fracture management strategies emphasizing prevention and psychological factors in posttraumatic pain [5]. CRPS is commonly associated with the extremities, but rare cases have been reported in the trunk. These cases are less common than those with CRPS in the extremities. Trunkal CRPS has not been extensively studied in terms of incidence and prevalence [6]. CRPS is also thought to have a familial occurrence, although that is fairly rare. There have been familial cases of CRPS, suggesting a genetic predisposition. The overall prevalence of familial CRPS is unclear [7]. The incidence and prevalence of CRPS have been studied in varying degrees. Trunkal CRPS is considered rare and reported in few cases. Familial CRPS is relatively rare, but documented. CRPS incidence and prevalence in different populations should be examined in greater depth. In conclusion, the incidence and prevalence of CRPS are influenced by various factors such as fractures, systemic conditions, and demographic variables. Understanding these factors is crucial for improving the management and outcomes of individuals affected by CRPS. CRPS diagnostic criteria have evolved over time to improve accuracy and completeness in patient assessment. Prior to the introduction of the Budapest criteria, the diagnostic criteria for Complex Regional Pain Syndrome (CRPS) were based on the differentiation of CRPS from other neuropathic pain conditions by the presence of edema, vasomotor changes, and sudomotor disturbances [8]. The diagnostic process for CRPS involved a thorough evaluation to ensure prompt and aggressive treatment interventions, continuous assessment of the patient's clinical and psychological well-being, along with striving for maximal pain relief and functional improvement [9]. CRPS diagnosis hinges on meticulous history-taking and clinical examination, assessing sensory, autonomic, and motor symptoms. Ancillary tests such as bone scintigraphy, plain radiographs, and quantitative sensory testing (QST) complement diagnosis. Autonomic function evaluation, including infrared thermometry and quantitative sudomotor axon reflex testing (QSART), can further confirm CRPS. Diagnostic testing for CRPS often includes bone scans, X-rays, CT scans, and autonomic testing. These assessments are crucial in establishing the diagnosis and excluding other potential conditions.

The use of autonomic testing, in particular, can help in assessing the autonomic nervous system's involvement in CRPS. Bone scintigraphy offers insight into vascular bone changes, especially within the first year of symptoms.

Abnormal uptake in the metacarpophalangeal joints and metacarpal bones during the third phase of the scan is a strong indicator of CRPS. However, there's no universally accepted gold standard for comparison. Plain radiographs primarily evaluate mineralization status, typically revealing changes in chronic CRPS cases. Quantitative sensory testing (QST) evaluates thermal and pain thresholds, offering insights into the function of sensory nerve fibres. Despite lacking a distinct sensory profile for CRPS, QST aids in diagnosis. Autonomic function evaluation, including infrared thermometry and Quantitative sudomotor axon reflex testing (QSART) is a tool used to evaluate the function of the sympathetic nervous system. Skin temperature differences, particularly dynamic changes in response to sympathetic activity, are prominent features, enhancing diagnostic accuracy. Swelling can be measured using water displacement techniques, which provide additional diagnostic insight [10]. Based on the guidelines set forth by the International Association for the Study of Pain (IASP), the criteria focus on bedside testing and are intended to be accessible to any clinician. This approach relies heavily on subjective assessments, both from patients and clinicians [11]. CRPS is diagnosed clinically, meaning that its identification relies mainly on the patient's symptoms and clinical evaluation, rather than by specific laboratory tests or imaging findings. In CRPS, patients commonly experience changes in sensory and motor function, along with autonomic system abnormalities.

Pain from CRPS is usually spontaneous and out of proportion [12]. To conclude, prior to the Budapest criteria, the diagnostic guidelines for CRPS cantered on distinguishing CRPS from other pain syndromes based on specific clinical features. A comprehensive assessment was essential to ensure an accurate diagnosis. Diagnostic testing, including bone scans, X-rays, CT scans, and autonomic testing, play an important role in confirming CRPS. The evolution of diagnostic criteria, such as those proposed by the IASP, has aimed to improve the accuracy and efficiency of diagnosing CRPS. CRPS differential diagnosis involves distinguishing CRPS from other chronic pain disorders, such as algodystrophy and various neuropathic pain conditions. Clinical evaluation, additional tests, and a thorough evaluation of the patient's clinical presentation and symptom along with medical history are essential for an accurate diagnosis. A diagnosis of CRPS is primarily based on clinical signs and symptoms, as there is no diagnostic procedure. Algodystrophy, another term for CRPS, can be considered in the differential diagnosis. There are many similarities between algodystrophy and CRPS, including erythema, edema, and functional impairment, sensory and vasomotor disturbances. However, careful clinical evaluation and additional tests can help differentiate the two conditions [13]. The diagnostic challenge lies in distinguishing CRPS from other chronic pain conditions with overlapping clinical features and symptoms.

Neuropathic pain syndromes are another chronic pain condition to distinguish from CRPS. Similar to CRPS, these conditions can cause peripheral and central sensitization. Differentiating CRPS from other neuropathic pain conditions requires a thorough evaluation of symptoms, medical history, and physical examination [14]. CRPS dermatologic manifestations may encompass symptoms such as allodynia, swelling, redness, changes in skin pigmentation (hypopigmentation or hyperpigmentation), and the presence of petechiae. These skin changes often serve as the initial indicators of the syndrome [15]. Besides pain, CRPS may also result in trophic alterations and impaired motor function [16].

The condition is often characterized by multiple symptoms, including chronic persistent pain, autonomic, sensory, motor, and trophic symptoms following trauma that cannot be explained by the trauma itself [17]. Complex Regional Pain Syndrome (CRPS) Type 1 typically develops following a harmful or traumatic event. CRPS may result from peripheral and central sensitization, neurogenic inflammation and disturbances in autonomic function.

CRPS management involves a multidisciplinary approach, including physical therapy, medications, and psychological interventions. Timely diagnosis and intervention are essential for enhancing outcomes and avoiding prolonged complications. However, management of CRPS can be challenging, and there is no universally effective treatment [18]. Two CRPS subtypes have been proposed by the International Association for the Study of Pain (IASP) to aid in clinical research and targeted treatments.

One subtype of CRPS is CRPS-I, also known as reflex sympathetic dystrophy. CRPS-I clinical presentation includes symptoms such as muscle atrophy and muscular disorders. A study by Hulsman *et al.* [19] suggests that the myopathy observed in CRPS-I may be due to disuse or neurogenic factors.

Nevertheless, additional research is required to fully elucidate the mechanisms underlying CRPS-I. Another form of CRPS, known as CRPS-II or causalgia, is characterized by symptoms such as intense burning pain, allodynia, and heightened sensitivity to painful stimuli (hyperalgesia [19]. Ultrasonography offers valuable insights into the anatomy, movement mechanics, and visible pathological changes of muscles. This imaging technique can aid in understanding motor dysfunction linked to CRPS-1 and serves as a cost-effective bedside diagnostic tool. Additionally, it holds potential in guiding physical therapy interventions for CRPS-1 patients [20].

Pathophysiology and Etiology of Complex Regional Pain Syndrome

CRPS pathophysiology involves various mechanisms **(Figure 1)**, including inflammation, central reorganization, neurogenic inflammation, nociceptive sensitization, impaired vasomotor response, and maladaptive neuroplasticity [21]. Inflammation plays a significant role in CRPS pathophysiology. Injury or trauma triggers an inflammatory response, releasing pro-inflammatory mediators and cytokines. Central reorganization is another important aspect of CRPS pathophysiology. Chronic pain causes changes in the central nervous system, particularly the somatosensory cortex. These changes can lead to altered sensory processing and abnormal pain perceptions [22]. There is evidence suggesting a potential overlap in the pathophysiology of CRPS and trigeminal autonomic cephalalgias (TACs). Central sensitization and disruption of inhibitory pain modulation in CRPS may trigger ipsilateral cranial symptoms and increase vulnerability to TACs. This suggests that these conditions may share mechanisms [23].

Recent studies have shed light on the neuro-inflammatory mechanisms underlying this pain disorder. The imbalance between pro- inflammation and anti-inflammatory cytokines further contributes to the inflammatory state and pain perpetuation in CRPS [24]. Acute Complex regional Pain Syndrome (CRPS) is associated with signs of inflammation such as increased skin temperature, edema, skin colour changes, and pain. Pro-inflammatory cytokines are up-regulated, while anti-inflammatory cytokines are diminished. CRPS involves both adaptive immunity and neurogenic inflammation, with autoantibodies directed against certain receptors and neuropeptides playing a role. The sympathetic nervous system is also involved, resulting in cool skin, increased sweating, and sympathetically-maintained pain [25].

The sympathetic nervous system (SNS) is believed to play a significant role in the pathophysiology of Complex Regional Pain Syndrome (CRPS). Chronic pain conditions such as CRPS, Reflex Sympathetic Dystrophy (RSD), and sympathetically maintained pain (SMP) may be caused by the SNS. Researchers have explored the interaction between sympathetic fibres and nociceptors in CRPS as one aspect of SNS involvement. In CRPS, sympathetic fibres may activate C nociceptors directly, causing pain generation and maintenance. This interaction between sympathetic fibres and nociceptors may contribute to the hyperalgesia and allodynia observed in CRPS [26]. One proposed mechanism for CRPS development is facilitated neurogenic inflammation, which involves the release of inflammatory mediators from sensory nerves. Also, neuroplastic changes within the central nervous system may contribute to CRPS [27]. Sympatho-afferent coupling, which involves the interaction between sympathetic efferent and afferent sensory nerves, is a significant aspect in understanding CRPS. Psychological distress can impact the sympathetic nervous system and catecholamine release, affecting CRPS pain through sympatho-afferent coupling. Prospective studies show a link between increased psychological distress and physical injury with the development

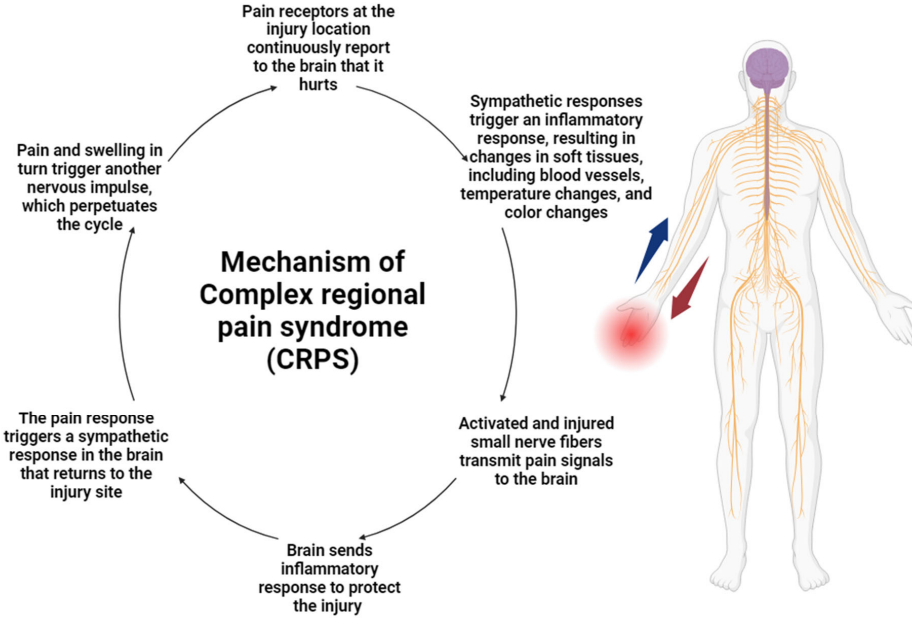

Figure 1. Mechanism of complex regional pain syndrome (CRPS).

and severity of CRPS, as seen in older patients undergoing knee arthroplasty [28]. It is crucial to acknowledge that CRPS involves not only sympatho-afferent coupling but also peripheral and central sensitization, brain changes, genetic factors, and psychological influences [29]. Neuroplasticity refers to the nervous system's ability to adapt to different stimuli and experiences. Neural plasticity plays an important role in the development and maintenance of complex regional pain syndrome (CRPS). CNS neuroplastic changes occur in CRPS. The changes can occur as a result of peripheral nerve injury or trauma, resulting in altered pain signal processing. A key aspect of neural plasticity in CRPS is central sensitization. An increase in CNS neurons' responsiveness to nociceptive stimuli is known as central sensitization. A condition characterized by heightened pain sensitivity and lowered pain thresholds resulting in allodynia (pain in response to normally non-painful stimuli) and hyperalgesia (increased sensitivity to painful stimuli). A key mechanism underlying CRPS persistent pain is central sensitization. Central sensitization occurs not only in CRPS but also in fibromyalgia, osteoarthritis, musculoskeletal disorders, headaches, and neuropathic pain. This suggests that central sensitization contributes to pain hypersensitivity through neural plasticity. The role of neural plasticity and central sensitization in CRPS is crucial. Targeting neuroplastic changes in the CNS may normalize hyperexcitable neural activity and alleviate pain in CRPS patients. Neuroplasticity treatment would be more effective if there were objective biomarkers of central sensitization [30].

CRPS etiology is complex and involves multiple factors. Trauma or injury to the affected limb, neurogenic inflammation, psychological distress, genetic predisposition, immune system dysfunction, and autonomic dysfunction are all potential factors that may contribute to CRPS. CRPS may arise from trauma to the affected limb, including fractures, sprains, or surgery, triggering abnormal responses in the nervous system. Neurogenic inflammation also plays a role, with abnormal inflammatory responses in the limb contributing to pain, swelling, and skin changes, mediated by released inflammatory mediators and neuropeptides from damaged nerves [31]. Psychological factors, including depression and anxiety, are linked to CRPS development and persistence. Stressful life events correlate with CRPS onset in children. However, while psychological factors are unlikely to solely cause CRPS, they can influence its emergence and worsening [32]. The autonomic and somatic nervous systems are both implicated in CRPS pathology, and neurogenic inflammation and hypoxia might play a role. Psychological factors may also contribute to CRPS development and maintenance. Understanding CRPS risk factors is important for early diagnosis and tailored treatment. Identifying risk factors may also provide clues for further research into CRPS causes [31]. Further research is needed to fully understand these factors' underlying mechanisms and interactions in CRPS etiology. CRPS has multifaceted triggers and causes, with trauma being a common initiator, including fractures, limb trauma, surgeries, immobilization, and strokes. Trauma can induce abnormal responses in both peripheral and central nervous systems, precipitating CRPS. Inflammation is also pivotal, with aberrant and neurogenic inflammation implicated in CRPS onset and persistence. Recent medical insights highlight CRPS's association with abnormal inflammation, vasomotor dysfunction, and maladaptive neuroplasticity, underscoring its profound impact on severe and chronic pain and disability [33,34]. One study compares the psychological characteristics of patients with chronic complex regional pain syndrome (CRPS), major depressive disorder (MDD), and other types of chronic pain, Patients with CRPS had higher scores on certain scales of the Minnesota Multiphasic Personality Inventory (MMPI-2) in comparison to healthy controls, but lower scores compared to the MDD group. Pain severity was associated with depression and scores on the Masculinity-Femininity scale, suggesting the need to evaluate depressive symptoms in CRPS patients [35]. A study investigated whether increased pro-inflammatory cytokine levels following a fracture correlated with CRPS. Baseline data from 702 participants with wrist and/or hand fractures were gathered, with follow-up at 16 weeks. The study concluded that there was no indication supporting the theory that early systemic cytokine expression post-injury relates to CRPS diagnosis. These findings imply that innate immune activation likely does not significantly contribute to CRPS development [36]. Various predisposing factors and patient traits are linked to heightened CRPS risk. Demographics like age and gender play a role; most patients are middle-aged females. Etiological factors such as orthopedic surgery, trauma, stroke, immobilization, and cast usage are associated with increased risk, likely due to tissue damage and inflammation. Comorbidities like smoking, menopause, migraines, osteoporosis, asthma, and anxiety disorders also heighten CRPS risk, possibly via mechanisms like vascular dysfunction and hormonal changes. An analysis of 88 CRPS patients revealed upper extremity predominance, with soft tissue trauma as the primary cause. Menopause in females and smoking in males were common risk factors. Understanding these epidemiological features aids in identifying high-risk patients for early intervention [37]. CRPS is associated with shoulder pain and lower Brunnstrom hand stages in stroke patients, indicating that pain severity and motor impairments could impact CRPS development or progression post-stroke. This study explored clinical factors affecting motor recovery and ambulation in stroke patients, finding that females had lower Brunnstrom hand and upper extremity values, along with a higher CRPS prevalence [38]. In addition, bisphosphonates, a class of medications commonly used to treat osteoporosis, have been explored as a potential therapeutic approach for CRPS. One research conducted a retrospective case series of children and adolescents with CRPS and found that treatment with bisphosphonates was associated with improvements in pain and functional outcomes. This suggests that osteoporosis and bone health may be relevant factors in CRPS development and management [39]. The multifactorial nature of CRPS suggests that there are multiple contributing factors that vary from patient to patient [40]. CRPS may have a genetic aspect. A case study highlighted a young athlete with both CRPS and Von Willebrand disease, suggesting genetic factors could play a role in CRPS development. This implies certain individuals might be genetically predisposed to CRPS. The case involved a 17-year-old female with Von Willebrand Disease who developed CRPS type 1, initially misdiagnosed by various medical specialties. Aggressive inpatient rehabilitation led to significant improvements in mobility and weight-bearing tolerance. This case represents the first documented link between a bleeding disorder and CRPS, hinting at an underlying microvascular pathology [41].

Available Treatments for Complex Regional Pain Syndrome

CRPS is difficult to treat due to its various symptoms and difficulty identifying causative lesions. There are limited trials of controlled treatment for CRPS. Physical therapy is a standard

treatment approach for CRPS, aiming to improve function, reduce pain, and enhance quality of life for individuals suffering from this condition. Physical therapy interventions for CRPS typically involve a multidisciplinary approach, including a combination of exercises, manual therapy, modalities such as heat or cold therapy, and education on pain management strategies. The goals of physical therapy in CRPS management include restoring range of motion, improving strength and flexibility, desensitizing the affected limb, and promoting functional independence. A systematic review by O'Connell NE *et al.* [42] evaluated the effectiveness of physical therapy interventions for CRPS and found evidence supporting the use of graded motor imagery, mirror therapy, and desensitization techniques in reducing pain and improving function in individuals with CRPS. These findings highlight the importance of tailored physical therapy programs in addressing the complex nature of CRPS [41-43]. There are various pharmacological interventions used in CRPS management. One class of medications that shows efficacy in neuropathic pain syndromes, including CRPS, are tricyclic antidepressants (TCAs). TCAs have antihyperalgesic effects and enhance noradrenergic descending inhibitory pathways and partially blocking sodium channels. These mechanisms contribute to their analgesic properties in neuropathic pain conditions. Tricyclic antidepressants have been shown to treat neuropathic pain by enhancing noradrenergic pathways and partially blocking sodium channels [44]. In addition to TCAs, other pharmacological treatments may be considered for CRPS. For example, certain drug combinations, including opioids, anticonvulsants, and topical agents, have been used to manage neuropathic pain, such as CRPS. These medications target different pain pathways and can relieve some patients. Pain experts can help treat difficult types of pain, such as neuropathic pain and complex regional pain syndrome. They can provide interventions and pharmacological treatments, including drug combinations and invasive procedures, to improve pain relief. Interventional procedures, such as sympathetic ganglion blocks and spinal cordotomy, have also been used in CRPS management. These procedures aim to interrupt abnormal sympathetic activity associated with CRPS and provide pain relief [45]. It is important to note that pharmacological interventions alone may not manage CRPS. Multimodal approaches that combine pharmacotherapy with other treatment modalities, such as physical therapy, psychological interventions, and interventional procedures, may improve pain control and functional outcomes. Sympathetic blocks were successfully used to treat three patients with complex regional pain syndrome type-1, resulting in significant pain relief and symptoms resolution within six months [46]. Lumbar sympathetic blocks are also used for CRPS. These blocks involve injecting a local anaesthetic into the sympathetic ganglia in the lumbar region to block the sympathetic nerves and reduce pain. Sympathetic blocks were studied for their analgesic effects on complex regional pain syndrome patients. A retrospective study on 318 patients showed a 61% success rate in achieving more than 50% pain reduction with sympathetic blocks, lasting 1 to 4 weeks or longer. The authors suggest that sympathetic blocks are beneficial for complex regional pain syndrome patients [43]. Sympathetic dysfunction may occur in complex regional pain syndromes, and sympathetic blocks are routinely performed. Cheng *et al.* test the hypothesis that sympathetic blocks provide analgesic effects that may be related to temperature differences between the extremities before and after the blocks, and that the effects of sympathetic blocks may predict spinal cord stimulation success. Their study examined the effects of sympathetic blocks on CRPS. A study of CRPS patients examined the association between pain reduction and SCS trial success. Patients who received sympathetic blocks and those without experienced no difference in success rates in SCS trials. Therefore, sympathetic blocks don't predict SCS success [43]. Sympathetic blocks have been used both as diagnostic and therapeutic tools for CRPS, but the evidence supporting their effectiveness is largely anecdotal. The difficulty in evaluating the efficacy of sympathetic blocks is attributed to inconsistent terminology, challenges in objectively quantifying physical findings, and the failure to control for co-morbid psychological factors. A study by aimed to examine the predictive factors of outcome following sympathetic block in the treatment of CRPS. The study found that the relative contribution of physical and psychometric features as prospective predictors of outcome was unclear. This highlights the need for further research to establish the efficacy of sympathetic blocks in CRPS treatment. The efficacy of sympathetic blocks in treating complex regional pain syndrome (CRPS) is still uncertain due to inconsistent terminology and difficulties quantifying physical findings. Anxiety negatively affects pain relief and functional improvement in CRPS patients treated with sympathetic blocks. Positive response to initial sympathetic block is predicted by higher sensitivity scores on the Neuropathic Pain Scale, C fiber allodynia, Adelta-fiber allodynia, and pretreatment-reported dynamic mechanical allodynia [47,48]. Another study evaluated the outcomes of sympathetic blocks in CRPS management. 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. This suggests that sympathetic blocks do not predict the success of spinal cord stimulation, indicating that sympathetic blocks may have therapeutic benefits regardless of pre-procedure limb temperatures. A retrospective study of 318 patients found that sympathetic blocks provided more than 50% pain relief in 61% of patients with complex regional pain syndrome. The degree and duration of pain relief were not associated with pre-procedure temperature differences between the limbs. The success rate of spinal cord stimulation trials was unaffected by sympathetic blocks [43]. Surgical intervention is one of the treatment modalities used in severe CRPS cases. A systematic review and meta-analysis study focused on CRPS treatment modalities after hand surgery. The study aimed to analyse the outcomes of different treatment modalities in recent literature. The study found that surgical intervention and other treatments such as physical/occupational therapy, psychiatric counseling, neuropathic pain medicines, and anti-inflammatory drugs can manage CRPS after hand surgery [49].

Efficacy of Spinal Cord Stimulation in Complex Regional Pain Syndrome

The use of spinal cord stimulation (SCS) has been shown to be effective in the treatment of chronic pain, particularly chronic back pain and neuropathic pain. SCS works by reducing chronic pain intensity, improving quality of life, and reducing the need for narcotic analgesics. When other standard treatment methods fail and the pain persists for more than six months, it is considered [50]. SCS's mechanism of action is unclear. Gate control theory suggests that SCS reduces pain by activating A beta fibres and inhibiting A delta and C fibres. Some researchers propose that SCS may reduce pain by directly inhibiting pain pathways in the spinothalamic tract, but this theory has not been proven [51]. Multiple studies have demonstrated SCS efficacy in CRPS treatment. Clinical studies have

shown success rates ranging from 50% to 70% with SCS, with decreased pain intensity scores, functional improvement, and decreased medication usage. Additionally, SCS has been shown to benefit other chronic pain conditions such as peripheral vascular disease and ischemic heart disease. SCS's mechanism of action in treating CRPS is not fully understood. However, there are several theories proposed. One theory suggests that SCS may suppress tactile allodynia, a common CRPS symptom [52]. Another theory suggests that SCS may increase the inhibitory action of gamma-aminobutyric acid (GABA) in the dorsal horn of the spinal cord, which can reduce pain. Additionally, SCS may affect human brain activity, contributing to its analgesic effects. While SCS in CRPS treatment is well-supported by the literature, there are some controversial aspects. The use of SCS in postherpetic neuralgia, diabetic neuropathy, deafferentation pain, and spinal cord injury pain is still debated. Further research is needed to determine SCS efficacy in these conditions [53,54]. In a randomized comparative trial conducted by Timothy R. Deer and his team, they found that dorsal root ganglion stimulation (DRG stimulation) achieved higher treatment success rates for complex regional pain syndrome and causalgia at both 3 and 12 months in comparison to spinal cord stimulation (SCS). Also, DRG stimulation resulted in less variation in paresthesia intensity with posture changes compared to SCS. These findings indicate that DRG stimulation is a more effective treatment option for managing complex regional pain syndrome and causalgia, providing better and more consistent pain relief for patients over the course of the study [50]. Researchers examined if certain factors in a patient's clinical history correlated with opioid reduction or cessation after spinal cord stimulation (SCS). The analysis included 214 patients who had undergone SCS implantation, with the only factor associated with complete cessation of opioid use being a median dose of 30 mg of morphine per day. The study concluded that the elimination of opioid dependence after SCS therapy is highly dependent on the daily opioid dose [55]. A systematic review assessed the clinical and cost-effectiveness of SCS in CRPS patients, highlighting its effectiveness in managing both CRPS type I and type II. it is reported that 67% of CRPS patients experienced at least 50% pain relief with SCS, and it was cost-effective compared to physical therapy alone. No significant predictors of SCS outcome were identified, and economic analysis indicated cost savings and quality-adjusted life-year benefits with SCS therapy. This review provides valuable insights into the positive impact of SCS on CRPS patients [56]. Additionally, a retrospective case series study evaluated the clinical outcomes of SCS in patients with severe, intractable CRPS. The study provided insights into the real-world effectiveness of SCS in managing severe CRPS cases. In this article, SCS is recommended for CRPS patients after conservative treatments fail, and early SCS intervention is crucial for pain relief, functional restoration, and psychological stabilization in CRPS patients [57]. High-frequency spinal cord stimulation at 10 kHz (HF10-SCS) provides enhanced and durable pain relief for patients with chronic back pain and leg pain. A retrospective case series of 13 patients with complex regional pain syndrome (CRPS) showed that HF10-SCS resulted in a 67% pain-relieving response rate. HF10-SCS may be viable for patients with CRPS with chronic intractable pain, including those with suboptimal results from traditional spinal cord stimulation (SCS) [58]. A prospective multi-centre study conducted in 2014 investigated the long-term efficacy and safety of HF10 SCS for chronic low back pain. The study found that after a trial period, 88% of patients reported a significant improvement in pain scores and underwent permanent implantation of the system. At 24-month follow-up, 90% of patients still reported pain relief and other improvements in disability, sleep disturbances, and opioid use reduction. These results support the long-term safety and sustained efficacy of HF10 SCS in managing chronic low back pain. The potential impact of these innovations in SCS technology on CRPS management is significant. HF10 SCS has shown sustained effectiveness in reducing pain, improving function, and reducing opioid use in patients with chronic low back pain [59]. Another innovation in SCS technology is dorsal root ganglion (DRG) stimulation. A randomized comparative trial conducted by compared the effectiveness of DRG stimulation and traditional SCS for the treatment of complex regional pain syndrome and causalgia. The trial found that DRG stimulation yielded a higher rate of treatment success with less postural variation in paresthesia intensity than traditional SCS. This suggests that DRG stimulation may be a more targeted and effective approach for managing CRPS [60]. Spinal cord stimulation (SCS) can effectively treat complex regional pain syndrome (CRPS) by activating inhibitory spinal interneurons and reducing pain behaviors. SCS can also alleviate the vascular symptoms of CRPS through antidromic activation of spinal afferent neurons and inhibition of sympathetic efferents. The involvement of neurotransmitters like calcitonin gene-related peptide and nitric oxide in SCS-induced cutaneous vasodilation has been observed in animal models [54]. A retrospective cohort study analysed the long-term effects of SCS on CRPS patients, showing significant pain relief, improved quality of life, and high patient satisfaction rates. SCS had a beneficial impact on pain intensity, depression, pain catastrophizing, and pain medication consumption. The study supports the continued use of SCS in treating severe CRPS, expanding the evidence for its effectiveness [61]. A retrospective study of 35 CRPS patients who underwent SCS trials showed that 77% had permanent SCS implanted, with a median follow-up of 8 years. While SCS did not lead to discontinuation or reduction of strong opioids or neuropathic pain medication, 70% of patients continued to use their SCS device during the follow-up period [62]. Peripheral nerve and dorsal root ganglion stimulation (DRG-s) are effective treatments for focal neuropathic pain, including complex regional pain syndrome (CRPS) limited to one or two dermatomes, but in rare cases, patients may seek amputation as a last resort for CRPS that is unresponsive to treatment [63,64]. Multiple studies have demonstrated the long-term effectiveness and sustainability of SCS treatment for CRPS. A study reported successful pain reduction and improved quality of life and function in CRPS patients who underwent SCS treatment [65]. SCS' sympatholytic effect is considered one of its therapeutic properties contributing to its effectiveness in treating CRPS. This effect is believed to be responsible for the positive outcomes observed in peripheral ischemia and CRPS. By modulating sympathetic activity, SCS can alleviate pain and improve blood flow in affected areas, leading to pain relief and improved function [66]. Furthermore, SCS has been shown to reduce opioid use in patients with chronic pain conditions, including CRPS. This is particularly important given the current opioid crisis and the need for alternative pain management strategies. SCS provides a non-pharmacological approach to pain relief, reducing opioid dependence and associated risks [67]. The interaction between spinal cord stimulation (SCS) and the sympathetic nervous system (SNS) in the context of Complex Regional Pain Syndrome (CRPS) is an important area of study. CRPS is a chronic pain condition characterized by sensory, motor, and autonomic

disturbances. The SNS plays a significant role in CRPS, as it regulates pain and autonomic responses. A study investigated pain and autonomic responses to ambiguous visual stimuli in chronic CRPS patients. Cortical reorganization in CRPS can lead to dysfunctional central integrative control, causing pain. Autonomic responses to visual stimuli were investigated in CRPS patients, showing diminished vasoconstrictor responses and asymmetric vasomotor responses. Some CRPS patients experienced enhanced pain and dystonic reactions when viewing ambiguous visual stimuli, indicating abnormal pain networks and somatomotor pathways. The results showed that patients with CRPS exhibited enhanced pain and autonomic responses compared to healthy controls. CRPS may result from an abnormal interaction between visual perception and SNS [68]. SCS is thought to exert its therapeutic effects by modulating the SNS activity, leading to pain relief. The exact mechanisms underlying this modulation are not fully understood, but it is believed that SCS may influence the release of neurotransmitters and neuromodulators involved in pain processing and autonomic regulation. Fibromyalgia is characterized by hyperalgesia and allodynia, with no consistent tissue abnormalities. Central nervous system pain processing abnormalities, such as abnormal temporal summation of pain, play a key role in fibromyalgia and other chronic pain syndromes. They highlighted the role of neuroplastic changes and the SNS in chronic pain maintenance. SCS has been used as a treatment option for fibromyalgia, and it has been suggested that its effects may be mediated through the modulation of the SNS [69]. Spinal cord stimulation offers cost-effectiveness, improved quality of life, and reduced need for pain medications, with evidence from randomized controlled trials showing its superiority over conservative treatment for pain improvement and functional outcomes, particularly in failed back surgery syndrome [70]. Spinal cord stimulation (SCS) has been used for over five decades to provide effective pain relief for chronic conditions, such as failed back surgery syndrome, regional pain syndromes, and neuralgias, reducing the need for opioids and improving pain scores, disability scores, and quality of life scales. Measurable outcomes such as pain scores, disability scores, and quality of life scales consistently show improvement with SCS in back and leg pain patients [71].

A recent systematic review by Ryan Mattie *et al.* [72] analysed randomized controlled trials investigating SCS for CRPS, focusing on different waveforms and frequencies. Across six studies with 329 patients, SCS showed initial pain relief, particularly in CRPS-I patients, though long-term efficacy diminished. Multiple SCS frequencies (40 Hz, 500 Hz, 1200 Hz, burst) and found high-frequency SCS (HF-SCS) provided superior pain relief over low-frequency SCS (LF-SCS) and placebo. However, patient preferences varied, emphasizing the need for personalized SCS settings. The review underscores SCS's potential for CRPS but highlights complications and diminishing benefits over time. Traditional SCS operates on the gate control theory, and advancements in waveform technology, including high-frequency and burst stimulation, have improved clinical outcomes by reducing paresthesia and enhancing neuromodulatory effects. Long-term studies show mixed results, with some reporting sustained pain relief while others note diminishing effects. Optimizing waveform selection based on patient characteristics remains key to maximizing therapeutic benefits [64,73].

Promising Areas of Research and Unmet Needs in CRPS Treatment

Neuromodulation economic considerations, particularly spinal cord stimulation (SCS), are also important areas of research. SCS is highlighted as a widely studied and implemented modality for persistent spinal pain syndrome and CRPS. Understanding neuromodulation therapies' cost-effectiveness and long-term economic impact can inform treatment decisions and resource allocation. The impact of recent research, patient needs, and insurance coverage on treatment options for chronic pain conditions, focusing on the cost-effectiveness of neuromodulation, specifically spinal cord stimulation, for persistent spinal pain syndrome and complex regional pain syndrome are promising areas of Research [74].

Different waveforms in SCS therapy

Figure 2 shows diverse Spinal Cord Stimulation Waveforms including, tonic, burst, High-Frequency, along with Advanced Strategies including Differential Target Multiplexed, and ECAP Controlled waveform. **Table 1** presents a concise timeline of significant advancements in Spinal Cord Stimulation (SCS) devices for chronic pain management, highlighting key milestones in the evolution of this technology.

Conventional (Traditional) waveform: This waveform involves the delivery of a constant and unchanging frequency and amplitude of electrical impulses [75]. This waveform delivers continuous electrical pulses to the spinal cord at a low frequency (typically around 40 to 60 Hz). It has been shown to provide pain relief and improve functional outcomes in patients with CRPS [76]. The mechanism of action of conventional waveform SCS in CRPS is not fully understood, but several theories have been proposed. One theory suggests that SCS modulates the transmission of pain signals by activating inhibitory pathways in the spinal cord, such as the release of gamma-aminobutyric acid (GABA) from inhibitory interneurons in the spinal dorsal horn [77]. Additionally, functional magnetic resonance imaging (fMRI) studies showed that tonic SCS altered the activation of supraspinal areas associated with the lateral spinothalamic tract. Therefore, tonic SCS activates supraspinal areas and modulates incoming nociceptive signaling at spinal levels [78]. While conventional waveform SCS has shown promising outcomes in the treatment of CRPS, there are some limitations. Some studies have reported that conventional waveform SCS may not be effective in certain cases, such as spinal cord injury or post-amputation pain. Previous studies have shown that conventional tonic waveform SCS failed in 80% of patients with amputation-related pain and 65% of patients with cord neuropathy. Guidelines regarding SCS application for different indications do not strongly recommend the use of SCS for spinal cord injury or postamputation pain [75].

Burst waveform: De Ridder *et al.* have described a burst stimulation application of spinal cord stimulation that may be able to operate in a supraspinal manner. The modality uses bursts of five pulses with an intraburst frequency of 500 hertz and a repetition frequency of 40 Hertz [79]. Burst SCS delivers a series of closely spaced electrical pulses in bursts, mimicking the natural firing patterns of neurons. This approach can provide more effective pain relief with lower overall energy consumption, potentially extending the longevity of the device's battery. Burst SCS delivers groups of closely spaced pulses. This waveform's unique ability to

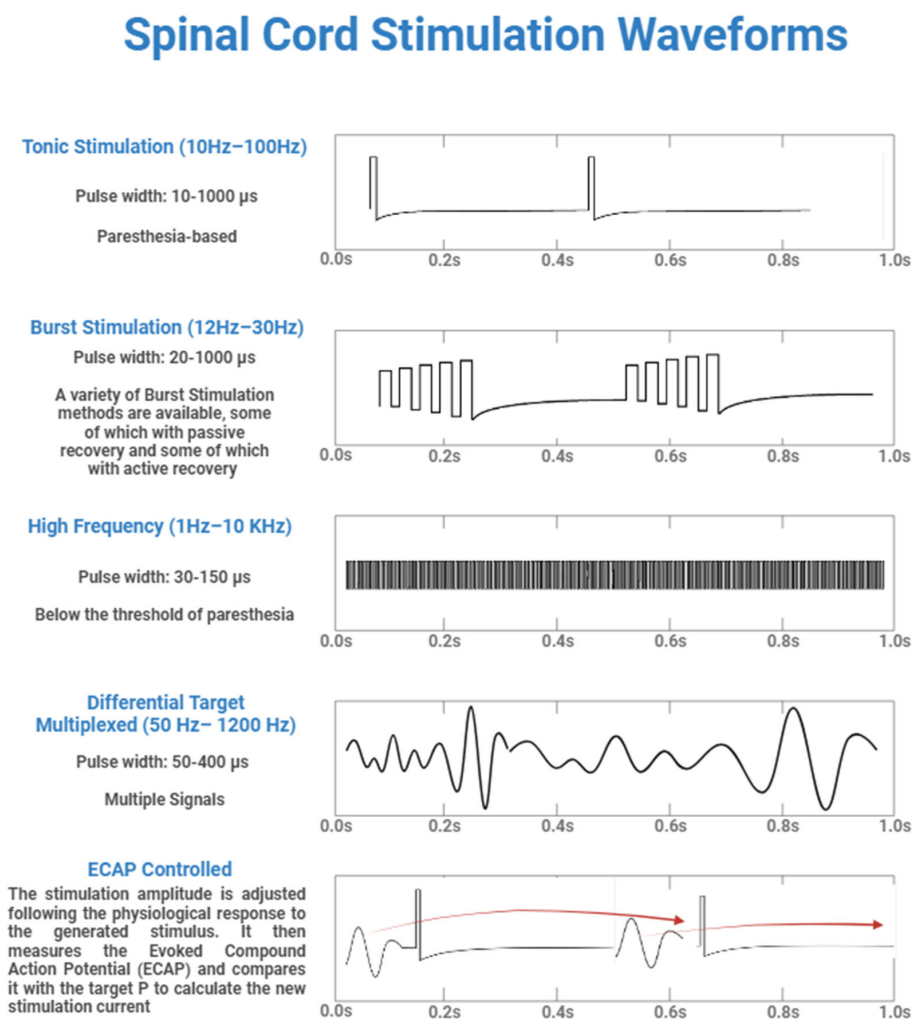

Figure 2. Different waveform for spinal cord stimulation.

Table 1. Evolution of spinal cord stimulation devices for chronic pain management.

Year	Manufacturer	Product Name	Waveform	Mode of Action	Efficacy	Potential Benefits for CRPS	Key Features / Innovations	Key References
1967	Medtronic	First SCS Device	Conventional/ Tonic	Delivers continuous mild electrical pulses to the spinal cord	Significant pain relief in many patients	Generalized pain relief	Marked the initiation of spinal cord stimulation technology. Operates with constant frequency and pulse width.	Doe JP, *et al.* (2020)
1989	Medtronic	Pisces Quad	Conventional/ Tonic	Delivers continuous mild electrical pulses to the spinal cord	Significant pain relief in many patients	Generalized pain relief	Introduced the Quadripolar Lead.	Doe JP, *et al.* (2020)
2004	Boston Scientific	Precision	Conventional/ Tonic	Delivers continuous mild electrical pulses to the spinal cord	Significant pain relief in many patients	Generalized pain relief	Introduced rechargeable systems and smaller size.	Doe JP, *et al.* (2020)

2015	Nevro	Senza	High-Frequency	Avoids paresthesia with higher frequency stimulation	Substantial pain reduction	Effective for certain neuropathic pain	Offers pain relief without paresthesia; operates at 10 kHz frequency.	Smith A, *et al.* (2019)
2016	Abbott	Axium DRG	Low Frequency Dorsal Root Ganglion stimulation	Targets specific sensory nerves (dorsal root ganglia) and pulsed waveform to stimulate neural tissue	Localized therapy beneficial for focal pain areas and Recharge-Free	Beneficial in selected CRPS cases	Targets the dorsal root ganglion to affect specific nerves associated with pain areas. Localized therapy beneficial for focal pain areas and Recharge-Free, and beneficial in selected CRPS cases	Williams M, *et al.* (2018)
2018	Medtronic	Intellis	DTM	Specific algorithm delivers a unique pattern of signals	Improved pain relief and outcomes	Provides real-time neural feedback	Introduced Differential Target Multiplexed (DTM) stimulation; combination of standard and high frequency.	Davis R, *et al.* (2020)
2021	Boston Scientific	WaveWriter Alpha	Combinational	Mimics natural nerve impulse patterns with burst pulses	Automatically rotates through waveforms	Paresthesia and sub-perception therapies	Offers a combination of waveforms, allowing personalized therapy and featuring Contour™ and Subperception™ technologies.	
2022	Saluda Medical	Evoke	Closed-Loop	Adjusts stimulation in real-time based on patient's responses	Potential in managing chronic pain	Customizable to patient needs	Provides real-time, closed-loop feedback adjusting stimulation levels in response to spinal cord's reaction.	Thompson Y, *et al.* (2022)
2016	Abbott	Axium DRG	Low Frequency Dorsal Root Ganglion stimulation	Targets specific sensory nerves (dorsal root ganglia) and pulsed waveform to stimulate neural tissue	Localized therapy beneficial for focal pain areas and Recharge-Free	Beneficial in selected CRPS cases	Targets the dorsal root ganglion to affect specific nerves associated with pain areas. Localized therapy beneficial for focal pain areas and Recharge-Free, and beneficial in selected CRPS cases	Williams M, *et al.* (2018)

mimic natural neural firing patterns holds promise for enhancing pain relief in CRPS patients, potentially reducing tolerance and extending battery life. Burst waveform spinal cord stimulation (SCS) has shown promise in the treatment of complex regional pain syndrome (CRPS) and other chronic pain conditions. Several studies have investigated the efficacy of burst waveform SCS compared to other waveforms, such as tonic waveform SCS, in the management of chronic pain. Burst waveform SCS delivers a series of closely spaced electrical pulses followed by a period of no stimulation, mimicking the natural firing pattern of neurons in the spinal cord. This waveform has shown promising results in relieving pain in patients with refractory upper limb pain after spinal cord injury and upper limb amputation [75]. One study by Deer *et al.* (2016) compared dorsal root ganglion (DRG) stimulation, which utilizes burst waveform SCS, to spinal cord stimulation in the treatment of CRPS and causalgia. The study found that DRG stimulation yielded a higher treatment success rate with less postural variation in paresthesia intensity compared to spinal cord stimulation [60]. As Complex regional pain syndrome is a chronic debilitating disease characterized by sensory abnormalities, this study investigated the effects of SCS on sensory characteristics allodynia and hyperalgesia in CRPS and concluded that SCS significantly reduces CRPS pain, diminishes allodynia and hyperalgesia, and can be used to monitor the effect of SCS over time [80].

High-Frequency waveform: Frequency changes are a useful parameter for modulating a patient's sensory perception. An adjustment of frequency may be effective in modifying the subjective sensations of patients and adjusting the quality of their paresthesias. It has been demonstrated that the patient's satisfaction with the perceived sensation decreases as the frequency increases. This suggests that a higher Frequency may need to be set up at subthreshold amplitude to achieve a positive response. High-frequency SCS employs higher pulse rates compared to conventional SCS. It's believed to modulate the dorsal horn of the spinal cord, which can lead to pain relief by inhibiting pain signals' transmission.

High-frequency SCS uses stimulation frequencies of 10 kHz, which is below the neuronal threshold for sensitive perceptions, resulting in the absence of paresthesia. The data highlighted that high-frequency SCS follows a different mechanism of action compared to conventional SCS [81]. Several studies have demonstrated the efficacy of HF10-SCS in the treatment of CRPS. One case series reported pain alleviation with HF10-SCS suggest that HF10-SCS may be a viable and effective treatment option for CRPS. Traditional SCS typically uses low-frequency stimulation, but recent studies have investigated the use of high-frequency spinal cord stimulation at 10 kHz (HF10-SCS) for the treatment of CRPS [58]. The underlying mechanism of action of HF10-SCS in the treatment of CRPS is not fully understood. Another theory proposes that HF10-SCS may have supraspinal effects in addition to its spinal or segmental effects. Resting state functional magnetic resonance imaging (fMRI) studies have been conducted to explore the brain connectivity patterns during HF10-SCS, providing insights into the potential mechanisms of action. Based on the results of the study, there has been an increase in connectivity between the anterior insula (affective salience network) and regions of the frontoparietal network and the central executive network. HF-SCS at 10 kHz might influence the salience network, and therefore, also the emotional perception of pain, according to these findings [82]. Another study reported the long-term efficacy of 10 kHz SCS in reducing chronic pain, improving disability, reducing opioid consumption, and improving quality of life [59]. Additionally, the mechanisms of kHz frequency stimulation, including HF10-SCS, are still under investigation, and further research is needed to fully understand its effects. Understanding the cellular mechanisms of kilohertz electrical stimulation is important in neuromodulation. The hippocampal brain slice model was used to study the effects of high-frequency electric fields. No significant changes were observed in the paired-pulse field EPSPs (fEPSP) in response to kHz stimulation, suggesting the need for further investigation into the mechanisms of action [83].

Differential target multiplexed (DTM) waveform: DTM is an advanced waveform that combines multiple types of electrical pulses, optimizing pain relief and minimizing paresthesia. By targeting different pain pathways simultaneously, DTM aims to provide more consistent and effective pain management for CRPS patients. One type of SCS that has shown promise for the treatment of CRPS is differential target multiplexed (DTM) waveform stimulation. DTM stimulation is a paresthesia-free SCS pattern that has been found to be superior to conventional tonic stimulation. Transcriptomics-based results show that differential target multiplexed programming modulates neuronal-glial interactions and gene expression towards a healthy state. DTM stimulation works by modulating neuron-glial interactions, which play a role in the development and maintenance of chronic pain. By targeting these interactions, DTM stimulation can help restore the balance of neurotransmission and reduce pain [84]. Chronic neuropathic pain involves distorted neuroglial interactions, immune and inflammatory response perturbations, and disrupted synapses and cellular interactions. Spinal cord stimulation (SCS) has been effective for over 40 years, but its mode of action is not fully understood. Differential target multiplexed programming (DTMP) uses multiple electrical signals to modulate glial cells and neurons, providing better results in reducing mechanical and thermal hypersensitivity compared to low rate and high-rate programming. DTMP effectively modulates the expression of genes involved in pain-related processes and neuroglial interactions, returning their expression to levels observed in non-injured animals [85]. It is important to note that while DTM stimulation shows promise as a treatment for CRPS, further research is needed to fully understand its mechanisms of action and optimize its use. Studies evaluating the long-term outcomes and durability of pain relief with DTM stimulation are warranted. Additionally, more research is needed to compare DTM stimulation with other treatment modalities, such as pharmacological interventions and other forms of neuromodulation. DTM stimulation has been found to provide superior pain relief compared to conventional stimulation and has the potential to improve functional outcomes for patients with CRPS. By modulating neuron-glial interactions and influencing gene expression, DTM stimulation can help restore the balance of neurotransmission and reduce pain. However, further research is needed to fully understand the mechanisms of action and optimize the use of DTM stimulation for CRPS. One study investigated the effectiveness of different frequencies of SCS (40, 500, 1200 Hz, burst, and placebo stimulation) in reducing pain in patients with CRPS, using visual analogue scale (VAS), McGill Pain Questionnaire (MPQ), and Global Perceived Effect (GPE) as outcome measures. Standard frequency spinal cord stimulation (SCS) is effective for patients with complex regional pain syndrome (CRPS), but non-standard frequencies can provide even better pain reduction, and the preferred stimulation setting is influenced by comfort and user-friendliness, so individualized patient care with customized frequencies and waveforms is recommended to maximize therapeutic effects [86].

Different paradigms in SCS therapy

Conventional (Paresthesia-Based) paradigm: This paradigm relies on inducing a tingling sensation (paresthesia) in the painful area. The patient adjusts the stimulation settings to overlap the pain with the paresthesia, effectively masking the pain signals. The effectiveness of different SCS stimulation patterns has also been investigated. Compared the interference effects on somatosensory evoked potentials (SEPs) from tonic, burst, and high-dose SCS. The study found that burst stimulation with a similar energy to tonic stimulation did not reduce SEP amplitude as much as tonic stimulation, suggesting different effects on the spinal cord. According to the study results, conventional tonic spinal cord stimulations and burst or high-dose spinal cord stimulations have different sites of action and effects on the spinal cord [87]. Similarly, Goebel *et al.* reported the successful use of dorsal root ganglion (DRG) stimulation for CRPS recurrence after amputation and failure of conventional SCS. DRG stimulation has been suggested as a potentially effective treatment for CRPS when conventional SCS fails [88].

Paraesthesia-Free paradigm (Sub-Threshold): In this approach, the goal is to provide pain relief without inducing paresthesia. This is particularly useful for patients who find paresthesia uncomfortable or for areas where paresthesia cannot cover the entire pain region effectively. High-frequency SCS (HF10 therapy) is another approach that has been explored for the treatment of chronic low back and leg pain, including neuropathic pain syndromes. HF10 therapy uses high-frequency stimulation (10 kHz) that is below the neuronal threshold for sensitive perceptions, thus eliminating paresthesia [81]. The mechanism of action of SCS in the treatment of CRPS is not fully understood. However, several theories have been proposed. One theory suggests that SCS suppresses the electroencephalographic evoked pain response in CRPS patients, indicating a modulation of

pain processing at the spinal cord level. Another theory suggests that SCS may reduce glial activation at the spinal cord level and activate opioid receptors, leading to pain relief [89]. While SCS has shown efficacy in the treatment of CRPS, it is important to note that the clinical outcome data is limited to a small number of studies and case reports. Further research is needed to better understand the optimal patient selection criteria, stimulation parameters, and long-term outcomes of SCS in the treatment of CRPS.

Closed-Loop SCS systems: Closed-loop SCS systems, also known as adaptive or responsive systems, represent a paradigm shift in SCS therapy. These systems use real-time feedback to adjust stimulation parameters based on the patient's pain levels, ensuring more personalized and dynamic pain management. For CRPS patients, whose pain intensity can vary widely, closed-loop systems offer the potential for improved efficacy and reduced reliance on manual adjustments.

ECAP (Evoked Compound Action Potential) technology: ECAP technology is a significant advancement in SCS therapy, allowing clinicians to directly measure the spinal cord's response to stimulation. By assessing the ECAP threshold, clinicians can optimize stimulation settings for each patient, improving pain relief accuracy and reducing the chances of uncomfortable paresthesia.

Dorsal root ganglion stimulation: Dorsal root ganglion, offering potential advantages in terms of improved target control. One significant factor is the cerebrospinal fluid layer that surrounds the DRG, which has a considerably smaller volume compared to the layer surrounding the spinal cord. As a result, DRG stimulation necessitates lower stimulation amplitudes compared to traditional SCS. The DRG houses the cell bodies of sensory neurons and is an active participant in the development of certain forms of chronic pain. The cerebrospinal fluid layer surrounding the DRG has much lower volume than the one that surrounds the spinal cord. Therefore, lower stimulation amplitudes are required with DRG stimulation compared with SCS, resulting in less postural variation [90].

Conclusion

Spinal cord stimulation (SCS) has emerged as a pivotal neuromodulation therapy for managing chronic pain conditions such as Complex Regional Pain Syndrome (CRPS) and persistent spinal pain syndrome. Over the past five decades, advancements in waveform technology, including high-frequency, burst, Differential Target Multiplexed (DTM) waveforms, and dorsal root ganglion (DRG) stimulation, have significantly improved clinical outcomes by enhancing neuromodulatory effects and reducing paresthesia. SCS exerts its therapeutic effects by modulating the sympathetic nervous system (SNS), leading to improved pain processing, autonomic regulation, and functional recovery. Research into cortical reorganization and autonomic responses in CRPS patients suggests that SCS may play a crucial role in restoring dysfunctional pain networks. Furthermore, economic considerations highlight the cost-effectiveness of SCS compared to long-term pharmacological interventions, making it a viable alternative for chronic pain management.

The field of SCS for CRPS is advancing rapidly, driven by innovative research and technological advancements. Emerging strategies focus on enhancing pain relief and minimizing side effects through novel waveform designs, such as Burst and DTM waveforms, and hybrid waveforms combining multiple types. Frequency modulation and patterned stimulation aim to target specific pain pathways more effectively, while closed-loop systems incorporating AI offer adaptive, real-time adjustments for optimized relief. Individualized treatment approaches are evolving to tailor therapies to unique patient profiles, and experimental techniques like optogenetics promise precise control over neural activity. Addressing habituation and tolerance is crucial for extending therapy effectiveness, and combining SCS with other treatments could yield synergistic benefits. Long-term studies will be essential to evaluate the safety, durability, and overall risk-benefit ratio of these advancements, paving the way for a new era of personalized pain management.

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Conflict of Interest

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