Interventional Pain Medicine 3 (2024) 100527

Contents lists available at ScienceDirect

Interventional Pain Medicine

journal homepage: www.journals.elsevier.com/interventional-pain-medicine

Spinal cord stimulation for the treatment of complex regional pain syndrome: A systematic review of randomized controlled trials

Ryan Mattie [a], Alan Bingtao Lin [b,*], Harjot Bhandal [c], Benjamin Gill [d], Jennifer Tram [e], Samamtha Braun [f], Nitin Prabakar [g], Claire Tian Yin [h], Nick Brar [i], Andrew Fox [j], Mikhail Saltychev [k]

[a] *Interventional Pain Management, Total Spine Institute, Los Angeles, CA, USA*
[b] *Ortho-Gen Pain Management and Sports Medicine, Folsom, CA, USA*
[c] *Evolve Restorative Center, Santa Rosa, CA, USA*
[d] *Omaha Pain Physicians, Omaha, NE, USA*
[e] *Department of Physical Medicine and Rehabilitation, VA Greater LA Health Care System/UCLA, Los Angeles, CA, USA*
[f] *Department of Physical Medicine and Rehabilitation, University of Texas, San Antonio, San Antonio, TX, USA*
[g] *Department of Anesthesia and Perioperative Care, University of California, San Francisco, San Francisco, CA, USA*
[h] *SUNY Downstate College of Medicine, Brooklyn, NY, USA*
[i] *Providence St. Joseph Health, Los Angeles, CA, USA*
[j] *Director of Spine Surgery, Total Spine Institute, Los Angeles, CA, USA*
[k] *Department of Physical and Rehabilitation Medicine, University of Turku, Turku, Finland*

ARTICLE INFO

Keywords:
Complex regional pain syndrome (CRPS)
Spinal cord stimulation (SCS)
Pain management
Neuromodulation
SCS waveforms

ABSTRACT AND KEYWORDS

Background: Spinal Cord Stimulation (SCS) is a widely recognized treatment for Complex Regional Pain Syndrome (CRPS), particularly in cases where traditional methods are ineffective. This paper systematically reviews randomized controlled trials to analyze the efficacy of SCS, as well as Dorsal Root Ganglion (DRG) Stimulation in treating CRPS, focusing on its long-term effectiveness.

Methods: This systematic review focused exclusively on randomized controlled trials to assess a primary outcome of improvement in pain symptoms in patients diagnosed with CRPS. The primary outcomes assessed were pain reduction and patient satisfaction, with attention to functional improvement, quality of life improvement, preference for waveform settings, and complications when such data was made available.

Results: The results showed significant pain reduction in CRPS patients treated with SCS and DRG. Preference for specific SCS settings varied among patients, with no clear superiority of one setting over another. Innovations in SCS technology, including novel waveforms and frequencies, demonstrated potential for enhanced efficacy and patient comfort.

Conclusions: The review underscores the importance of SCS and DRG as significant treatment options to reduce pain for patients suffering from CRPS. It highlights the need for ongoing research to optimize SCS therapy, focusing on individual patient preferences and responses to different stimulation parameters. This personalized approach could lead to improved patient outcomes in CRPS management. Additionally, as this study only contained data from Randomized Controlled Trials, inclusion of well-conducted observational studies may help to provide stronger evidence for use of this therapy in CRPS patients.

1. Introduction

Complex regional pain syndrome (CRPS) is a debilitating and multifaceted neuropathic pain condition characterized by hyperalgesia and allodynia that exceed the intensity and duration of the initial inciting event. The pathophysiology of CRPS is poorly understood, but has long been proposed to be due to a multifactorial, sympathetic dysregulation in response to extremity trauma or peripheral nerve lesion that includes: neurogenic inflammation, nociceptive sensitization, vasomotor dysfunction, and maladaptive neuroplasticity [1–3].

* Corresponding author.
E-mail address: drlin@ortho-gen.com (A.B. Lin).

https://doi.org/10.1016/j.inpm.2024.100527
Received 15 September 2024; Received in revised form 8 November 2024; Accepted 10 November 2024

CRPS is broadly categorized into two types: CRPS-I, which occurs with injury or illness that does not directly damage an identifiable nerve, and CRPS-II, which is concurrent to confirmed nerve damage [4]. The Budapest Criteria, introduced in 2003, outlines four main categories of symptomatology in CRPS (sensory, vasomotor, sudomotor/oedema, and motor/trophic) and remains the current standard for CRPS diagnosis [4].

Treatment modalities for CRPS include conservative regimens, of which physical and occupational therapies are key initial components, as well as pharmacotherapy, and interventional procedures like sympathetic blocks and transcranial magnetic stimulation [1,5–9].

Spinal cord stimulation (SCS) may be indicated for patients with refractory symptoms despite conservative therapy. Clinically described in the 1960s, SCS has become a prominent treatment for chronic pain globally over the last 50 years [12]. The historical evidence for the efficacy of SCS in treating CRPS is compounded by the current discussion on how to best maximize its therapeutic effects, making SCS a growing field of clinical study. While the use of SCS in treating chronic pain is a thoroughly reviewed topic, the existing literature lacks a scoping review of the use of SCS for CRPS specifically. Although chronic pain is one of the diagnostic criteria for CRPS, there are multiple aspects of this complex disease that distinguish CRPS from other pain disorders. Therefore, this pathology necessitates independent analysis of treatment efficacy. This study provides a systematic review of the use of SCS in the treatment of CRPS.

2. Methods

2.1. Framing of research strategy (PICO)

2.1.1. Population

· Adults (>16 years) with CRPS-I or II.

· Excluding case reports, case series (≤10 subjects), conference proceedings, theses.

2.1.2. Intervention

- Spinal cord stimulation (="neuromodulation") - technique of applying a mild electrical current to stimulate nerve fibers in the select areas of the spinal cord (dorsal columns) for the treatment of CRPS
- Dorsal root ganglion stimulation (="neuromodulation") - respective to SCS technique applying stimulation to the dorsal root ganglion

2.1.3. Control

- Conservative medical management

2.1.4. Outcome

- Any numerical data concerning pain severity and the level of functioning before and after the intervention

2.1.5. Inclusion criteria

Only studies that defined the index diagnosis of CRPS based on the Budapest Criteria were included in the review. The definition and criteria are as follows:

Complex regional pain syndrome is understood as an array of painful conditions that are characterized by a continuing (spontaneous and/or evoked) regional pain that is seemingly disproportionate in time or degree to the usual course of any known trauma or other lesion. The pain should be regional (not in a specific nerve territory or dermatome) and usually has a distal predominance of abnormal sensory, motor, sudomotor, vasomotor, and/or trophic findings. The syndrome shows variable progression over time. The diagnosis of CRPS is clinical and it is based on the following criteria.

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

2.2. Data sources and search strategy

Articles were considered only if they were published in English in academic peer-reviewed journals with available abstracts, published any time prior to April 2023, when the search was initiated. Databases searched included Medline, Embase, CINAHL, CENTRAL, Scopus. The search strategy is presented in Table 1. The references of identified articles and reviews were also checked for relevancy.

2.3. Selection strategy

The records identified from the data sources were stored in the Endnote software (Endnote X7.8, Thomson Reuters). Using a built-in search engine of the Endnote software, duplicates, conference proceedings, theses, reviews, and case reports were removed. Two independent reviewers screened the titles and abstracts of the remaining articles and assessed the full texts of potentially relevant papers (Fig. 1). Disagreements between the reviewers were resolved by consensus or by the third reviewer.

2.4. Extraction strategy

The data needed for a quantitative assessment were extracted using a standardized form based on recommendations by the Cochrane Handbook for Systematic Reviews of Interventions. The minimal set of extracted data included.

- First author
- Year
- Country
- Design
- Settings
- Sample size
- Age distribution
- Gender distribution
- Follow-up
- Intervention
- Notes
- The original conclusions in brief
- Main outcome estimates

Table 1
Search strategy.

Database	Clause
Medline via PubMed	("complex regional pain syndromes"[Mesh] OR (crps [TIAB] OR "complex regional pain syndrom" [TIAB] OR causalgia [TIAB] OR deafferentation [TIAB] OR (sympath* [TIAB] AND distro* [TIAB]) OR sudek* [TIAB] OR Algodystroph* [TIAB])) AND ("spinal cord stimulation"[Mesh] OR "Ganglia, Spinal"[Mesh] OR "spinal cord stimulation" [TIAB] OR "Spinal Ganglion" [TIAB] OR "Dorsal Root" [TIAB] OR neuromodulation [TIAB]) NOT transcutaneous [TIAB] Filters applied: Abstract, Clinical Study, Clinical Trial, Comparative Study, Controlled Clinical Trial, Evaluation Study, Observational Study, Randomized Controlled Trial, English
Embase	('complex regional pain syndrome'/mj OR "complex regional pain":ti OR (sympath*:ti AND distro*:ti) OR sudek*:ti OR Algodystroph*:ti OR "complex regional pain":ab OR (sympath*:ab AND distro*:ab) OR sudek*:ab OR Algodystroph*:ab) AND (('spinal cord stimulation'/mj OR 'spinal cord stimulator'/mj) OR (('spinal ganglion'/exp OR "Spinal Ganglion":ti OR "Dorsal Root":ti) AND stimulation:ti) OR "spinal cord stimulation":ti OR "spinal cord stimulation":ab OR (("Spinal Ganglion":ab OR "Dorsal Root":ab) AND stimulation:ab)) AND 'article'/it AND ('clinical article'/de OR 'clinical trial'/de OR 'clinical trial topic'/de OR 'cohort analysis'/de OR 'comparative study'/de OR 'controlled clinical trial'/de OR 'controlled study'/de OR 'cross sectional study'/de OR 'intervention study'/de OR 'longitudinal study'/de OR 'major clinical study'/de OR 'multicenter study'/de OR 'multicenter study topic'/de OR 'observational study'/de OR 'prospective study'/de OR 'randomized controlled trial'/de OR 'randomized controlled trial topic'/de OR 'retrospective study'/de OR 'trend study'/de)
CINHAL	(MH Complex Regional Pain Syndromes OR TI "crps" OR TI "complex regional pain syndrom" OR TI causalgia OR TI sympath* AD dsitroph* OR TI sudek OR TI Algodystroph* OR AB "crps" OR AB "complex regional pain syndrom" OR AB causalgia OR AB sympath* AD dsitroph* OR AB sudek) AND (MH Spinal Cord Stimulation OR (MH Spinal Nerve Roots + AND (TI stimulation OR AB stimulation)) OR TI "spinal cord stimulation" OR TI "Spinal Ganglion" OR "Dorsal Root" OR "neuromodulation" OR AB "spinal cord stimulation" OR neuromodulation) Limiters - Abstract Available Narrow by Subject Age: all adult Narrow by Language: English Source type: Academic Journals
Scopus	((TITLE ("spinal cord stimulation" OR (("spinal ganglion"/exp OR "Spinal Ganglion":ti OR "Dorsal Root":ti) AND stimulation:ti)) OR ABS ("spinal cord stimulation" OR (("spinal ganglion"/exp OR "Spinal Ganglion":ti OR "Dorsal Root":ti) AND stimulation:ti)))) AND ((TITLE ("complex regional pain" OR (sympath*:ti AND distro*) OR sudek* OR algodystroph*) OR ABS ("complex regional pain" OR (sympath*:ti AND distro*) OR sudek* OR algodystroph*))) AND (LIMIT-TO (DOCTYPE, "ar")) AND (LIMIT-TO (SRCTYPE, "j"))
CENTRAL	#1 MeSH descriptor: [Spinal Cord Stimulation] explode all trees 176 #2 MeSH descriptor: [Ganglia, Spinal] explode all trees 52 #3 MeSH descriptor: [Spinal Nerve Roots] explode all trees 221 #4 MeSH descriptor: [Complex Regional Pain Syndromes] explode all trees 365 #5 ("spinal ganglion" OR "Spinal Ganglion"):ti,ab,kw 122 #6 (stimulation):ti,ab,kw 58237 #7 ("complex regional pain" OR (sympath* AND distro*) OR sudek* OR algodystroph*):ti,ab,kw 712 #8 ("spinal cord stimulation" OR "dorsal root stimulation" OR "spinal ganglion stimulation"):ti,ab,kw 946 #9 #5 AND #6 59 #10 #1 OR ((#2 OR #3) AND #6) 209 #11 #4 OR #7 OR #9837 #12 #10 AND #11 27

2.5. Assessment of risk of systematic bias

The Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies by National Heart, Lung, and Blood Institute (https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools) was used. Each of the 14 criteria was graded by an independent reviewer as "low," "high," or "unclear" risk of systematic bias. The reviewers were also asked to judge the total risk as "low"or "high."

2.6. Statistical analysis (meta-analysis)

The planned meta-analysis was impossible for several reasons. Most importantly, there was a great number of crossover and heterogeneous study designs. The complexity of results disallowed extraction of numeric data. Ultimately only two studies were potentially useful for the meta-synthetic purposes – studies by Kemler et al. and Canós-Verdecho et al. [13–16] These relatively small samples with apriori heterogeneity were considered insufficient to conduct data pooling.

3. Results

This review identified 216 records appropriate for abstract screening (Fig. 1). After abstract screening, six studies were included for full review. Five of the six studies were determined to have a low risk of systemic bias by both independent reviewers (see Table 2). The study by Kriek et al., in 2017 was determined to have a high risk of systemic bias by one reviewer and in 2017 was determined to have a high risk of systemic bias by one reviewer and a low risk of a low risk of systemic bias by the other reviewer, due in part to concerns regarding the poorly defined study population [17]. Overall, it was determined that there is little risk of systemic bias found across these six studies.

Across all six studies, a total of 329 unique patients were included. Most of the studies focused on CRPS-I. However, Kriek et al. (2017) and Deer et al. (2017) included both CRPS-I and CRPS-II [17,18]. Time of follow-up varied from 1 month in the initial Kemler et al. and Canós-Verdecho et al. papers to 5 years in the final Kemler et al. report in 2008 [13,15,16].

Kemler, 2000 [13]

Kemler et al. (2000) published the results of a RCT that explored the effects of SCS combined with PT for patients with CRPS. Fifty-four patients were randomized into two treatment cohorts: PT alone (n = 18) or combined SCS and PT (n = 36). The study included individuals aged 18–65 years diagnosed with CRPS for a minimum of 6 months who demonstrated significant pain intensity (minimum of 5 cm on visual-analogue scale (VAS)) despite other conventional therapies.

The results revealed a significant reduction in pain intensity, showing a mean decrease of 2.4 cm in the SCS group compared to a 0.2 cm increase in the control group over a six-month period, a statistically significant difference ($p < 0.001$). Additionally, the GPE significantly favored the SCS group, with 39 % of patients reporting substantial improvement against just 6 % in the control group ($p = 0.01$). However, the study revealed no significant enhancement in functional status across either group, a crucial aspect of patient recovery and well-being.

The investigation further highlighted improvements in health-related quality of life (HRQoL) among patients who received SCS in addition to PT compared to those who underwent PT alone. These improvements encompassed pain relief, psychological well-being, and physical and social functioning. Specifically, HRQoL enhancements were observed only in the subset of 24 patients who proceeded with SCS implantation, providing a focused snapshot of HRQoL enhancement within a six-month frame. However, the research did not extend beyond this period, leaving the long-term sustainability of these HRQoL improvements open to future exploration.

Complications within the SCS cohort necessitated additional interventions in 6 patients, including one device removal. The methodology and data presentation of this study facilitated understanding the

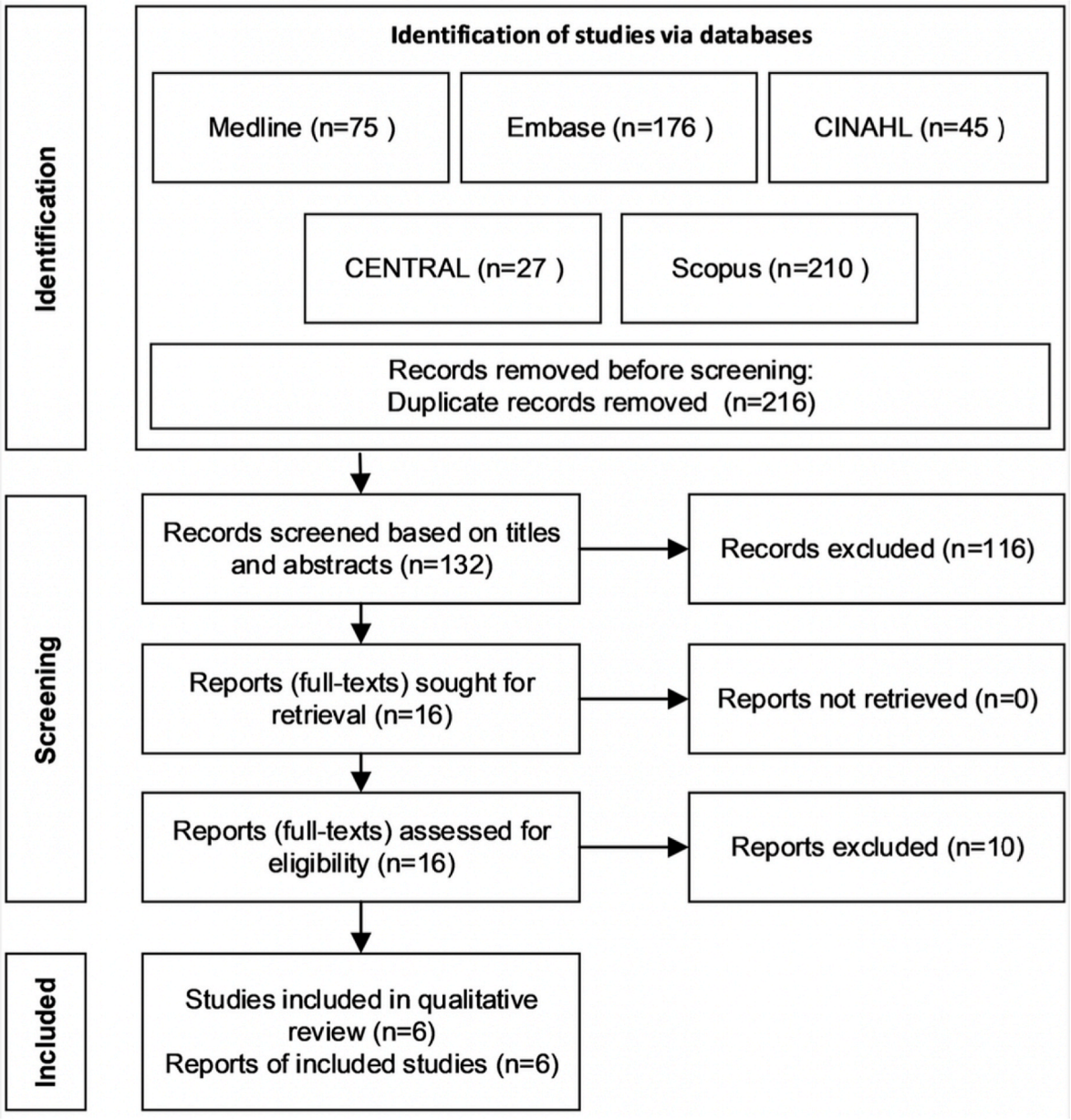

Fig. 1. Selection strategy.

role of SCS in CRPS. The results encourage consideration for patients who have found little relief through conventional treatments. Nevertheless, the exclusion of individuals with specific comorbid conditions could potentially limit the generalizability of these findings to a broader CRPS patient population.

Kemler, 2004 [14]

Kemler et al. (2004) extended previous findings by examining the efficacy and sustainability of SCS combined with PT over a two-year period in patients diagnosed with CRPS. This randomized controlled trial included 36 patients assigned to the SCS + PT group and 18 patients to the control group receiving PT alone, maintaining a 2:1 randomization ratio.

The study assessed several critical dimensions, including pain intensity, GPE, functional status, and health-related quality of life, at baseline and at various intervals up to two years. Results indicated a significant reduction in pain intensity within the SCS + PT group, with a mean decrease of 2.1 cm on the VAS, while no change was observed in the PT-only group. Furthermore, 43 % of the SCS + PT group reported "much improvement" in GPE, compared to 6 % in the PT group. However, there was no clinically significant improvement in functional status.

Improvements in health-related quality of life were noted among patients in the SCS + PT group. At the two-year follow-up, 57 % of the SCS group reported significant benefits, with 20 out of 35 patients showing notable improvements. Specifically, 15 patients reported "much improvement," and 13 exhibited a 50 % reduction in baseline pain intensity.

Despite these positive outcomes, complications were observed in the SCS group, with 9 out of 24 patients (37.5 %) requiring surgical intervention. The study concluded that SCS, following careful patient selection and successful test stimulation, is a viable long-term solution for pain relief and quality of life enhancement in CRPS patients.

Kemler, 2008 [15]

The five-year final follow-up study from Kemler et al. (2008) examined the long-term efficacy of SCS combined with PT for patients with chronic CRPS-I. The study included a prospective randomized

Table 2
Assessment of risk of systemic bias outcome.

#	Criteria	1		2		3		4		5		6		7		8		9		10		11		12		13		14		Overall	
	Reviewer	#1	#2	#1	#2	#1	#2	#1	#2	#1	#2	#1	#2	#1	#2	#1	#2	#1	#2	#1	#2	#1	#2	#1	#2	#1	#2	#1	#2	#1	#2
	Study																														
1	Kemler, 2000 [13]	Y	Y	y	Y	y	Y	y	Y	y	Y	y	Y	y	Y	NA	NA	y	Y	y	Y	y	Y	NR	NR	y	Y	y	Y	LOW	LOW
2	Kemler, 2004 [14]	Y	Y	y	Y	y	Y	y	Y	y	Y	y	Y	y	Y	NA	NA	y	Y	y	Y	y	Y	NR	NR	y	Y	y	Y	LOW	LOW
3	Kemler, 2008 [15]	Y	Y	y	Y	y	Y	y	Y	y	Y	y	Y	y	Y	NA	NA	y	Y	y	Y	y	Y	NR	NR	y	Y	y	Y	LOW	LOW
4	Deer, 201718	Y	Y	y	Y	y	Y	y	Y	y	Y	y	Y	y	Y	NA	NA	y	Y	y	Y	y	Y	NR	NR	y	Y	y	Y	LOW	LOW
5	Kriek, 2017 [17]	Y	Y	n	Y	y	Y	NR	Y	y	Y	y	Y	y	Y	NA	NA	y	Y	y	Y	y	Y	NR	Y	y	Y	y	NA	HIGH	LOW
6	Canos-Verdecho, 2021 [16]	Y	Y	y	Y	y	Y	y	Y	y	Y	y	Y	y	Y	NA	NA	y	Y	y	Y	y	Y	NR	NR	y	Y	y	NR	LOW	LOW

Y = yes; N = no; CD = Cannot Determine; NA = not applicable; NR = not reported. For Overall: H= High risk; L = low risk; U = unclear.
Criteria.
1. Was the research question or objective in this paper clearly stated?.
2. Was the study population clearly specified and defined?.
3. Was the participation rate of eligible persons at least 50 %?.
4. Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants?.
5. Was a sample size justification, power description, or variance and effect estimates provided?.
6. For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured?.
7. Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed?.
8. For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (e.g., categories of exposure, or exposure measured as continuous variable)?.
9. Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?.
10. Was the exposure(s) assessed more than once over time?.
11. Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?.
12. Were the outcome assessors blinded to the exposure status of participants?.
13. Was loss to follow-up after baseline 20 % or less?.
14. Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?.

controlled trial with 36 patients allocated to receive SCS + PT and 18 to receive PT alone. Among those, 10 patients were excluded from the final analysis, leading to a comparative evaluation of 31 patients in the SCS + PT group versus 13 in the PT group.

Over the five-year period, the results showed a diminishing effectiveness of SCS in controlling pain, with similar outcomes between the SCS + PT and PT-alone groups for most measured variables. However, a subgroup analysis revealed that 20 patients who received an implant showed better outcomes in terms of GPE and pain relief compared to the 13 receiving PT alone. Despite the reduced effectiveness over time and a high complication rate (42 % undergoing reoperation), 95 % of patients with the implant reported they would choose to undergo the treatment again.

This study highlighted the complex role of SCS in treating CRPS-I, suggesting that while initial results were promising in terms of pain relief and patient satisfaction, the long-term effectiveness wanes, and the high rate of complications necessitates careful patient selection and counseling. The research indicated that SCS was successful in approximately 35 % (11 out of 31) of patients based on predefined criteria. These findings underscore the need to balance patient-reported outcomes with clinical efficacy and the burden of surgical complications.

Kriek, 2016 [17]

Kriek et al. (2016) investigated the optimal frequencies and waveforms of SCS for patients with CRPS in a multicenter, double-blind, randomized, placebo-controlled crossover trial. The study enrolled 43 participants with a confirmed diagnosis of CRPS, predominantly type I (93.1 %). These participants underwent a trial phase of SCS, with 35 of 40 participants progressing from trial to implant. 29 patients completed the 10-week crossover trial.

The trial assessed five SCS settings: 40 Hz, 500 Hz, 1200 Hz, burst SCS, and placebo. These settings were randomized to determine which offered superior pain relief. The primary outcome measures included the VAS, McGill pain questionnaire (MPQ), and global perceived effect (GPE). Success criteria required a significant pain reduction of at least 50 % on the VAS compared to baseline, alongside a GPE score of at least 5 on satisfaction and improvement scales, and a preference for the tested SCS setting during the crossover period.

Results indicated that high-frequency SCS (HF-SCS) demonstrated marked superiority in pain mitigation and quality of life enhancement over both low-frequency SCS (LF-SCS) and placebo. There was no significant difference in efficacy among the four active SCS settings, suggesting a potentially universal mechanism of action for SCS in managing CRPS pain, regardless of frequency or waveform.

Patient preferences varied, with 48 % favoring the 40 Hz SCS setting, highlighting individual variability in response to SCS therapy. Other SCS settings provided additional pain reduction for most patients, suggesting that customized SCS settings could optimize therapeutic outcomes.

Safety data indicated no significant adverse effects across the varied

Table 3
Summary of included studies.

Study	Number	Clinical Condition	Definition of Success	Time of Follow up	Success Rate
Kemler 2000 [13]	– 54 patients – 36 patients for spinal cord stimulation with physical therapy, 24 got SCS, remaining 12 patients continue physical therapy – 18 patients only physical therapy	I	- pain intensity - global perceived effect - health-related quality of life - functional status determined based on two measures: 14 patients achieved a score of 6 for the global perceived effect, and 18 patients had a visual-analogue score that was at least 50 percent lower than their baseline score	1,3,6 months	Success rate of 56 %. 20 out of the 36 patients who received spinal cord stimulation combined with physical therapy.
Kemler 2004 [14]	Same as the Kemler 2000 paper	I	(See Kemler, 2000)	2 years	Success rate of 57 % (20 out of 35 patients),. – 15 (43 %) reported "much improvement" compared to only 1 (6 %) of the 16 patients who received only physical therapy (PT). – 13 patients showed a 50 % decrease in the visual analog score for pain intensity from the start of treatmen
Kemler 2008 [15]	– 44 patients – 10 patients were excluded from the final analysis, - the main analysis compared 31 patients in the SCS + PT group with 13 patients in the PT group.	I	(See Kemler, 2000)	5 years	Success rate of 35 % (11 of 31 patients)
Kriek 2017 [17]	29 patients analyzed – 89 patients screened, 43 were included at baseline. – 40 underwent trials and 35 had successful trials. – 3 patients exited the trial before the crossover period, 4 patients discontinued the crossover for various reasons.	I and II (majority in I since 93.1 % of cases)	- A significant pain reduction of at least 50 % on the VAS compared with baseline pain scores. - A positive GPE score of at least 5 on both the satisfaction and improvement scales. - A patient preference for continuing with the stimulation setting that was tested during the crossover period1.	6 months	Success rate of 69 % (Out of the 29 patients who completed the crossover trial, 20 patients preferred high-frequency stimulation, while 9 patients (approximately 31 %) had no preference
Deer 2017 [18]	152	I and II	Primary - >50 % reduction in VAS score at trial end and 3-month follow-up and no stimulation-related adverse neurological events	Trial end, 3,6,9,12 months	DRG success rate 81.2 % SCS success rate 55.7 % at 3 months
Canós-Verdecho 2021 [16]	50	I	Primary end point at 12 months, Minimal Clinical Important Difference in NRS and DN4 scores	1,3,6,12 months	**Conventional Medical Treatment** - 3.0 decrease NRS, 2.1 decrease DN4 **LF-SCS** - 5.6 decrease NRS, 2.9 decrease DN4 **10 kHz SCS** - 4.8 decrease in NRS, 2.8 in DN4

GPE = Global Perceived Effect; VAS = Visual Analog Scale; NRS = Numeric Rating Scale; DN4 = Douleur Neuropathique en 4 Questions; LF = low frequency.

frequencies and waveforms tested, reinforcing SCS as a safe option for a broad range of CRPS presentations. Despite limitations, such as pre-treatment with standard stimulation and potential biases, this study's findings advocate for a personalized approach to SCS therapy, tailoring treatment to individual patient needs and preferences to maximize pain relief and enhance the quality of life for patients with CRPS.

Deer, 2017 [18]

The ACCURATE study, published by Deer et al. (2017), was a prospective, randomized, controlled, multicenter investigation device exemption study to evaluate the safety and efficacy of dorsal root ganglion (DRG) stimulation compared to dorsal column SCS for patients with CRPS-I or CRPS-II (see Table 3). The study was conducted at 22 sites across the United States. Patients diagnosed with CRPS-I or CRPS-II, were eligible for the study.

In total, 152 patients were enrolled and randomized in a 1:1 ration to either the DRG or the SCS arm (76 in each arm). Patients were considered to have a successful trial if they achieved at least a 50 % reduction in lower limb pain during the trial. A total of 61 DRG patients and 54 SCS patients met the success criteria at the end of their trial phase and continued to permanent therapy. Patients who proceeded with implantation were followed at 3,6,9, and 12 months post-implantation. Postoperative reprogramming was allowed for both groups at any time during the study and was performed by their respective companies (Medtronic and Spinal Modulation). By the 12-month visit, 55 DRG and 50 SCS patients had evaluable data.

The primary composite endpoint of the study was treatment success rates for the DRG patients compared to the SCS patients. Treatment success was defined as a >50 % reduction in the VAS score at end of the trial and at 3-month follow-up, as well no stimulation-related neurological deficits during either the trial phase or after permanent implantation. Secondary endpoints in the study included postural variation in paresthesia intensity, Short-Form-36 (SF-36) health-related quality-of-life scale, Profile of Mood States (POMS) scale, Brief Pain Inventory (BPI), patient satisfaction, stimulation specificity, percentage change in VAS score from baseline, and safety analysis.

At the 3-month mark 81.2 % (56/69) patients in the DRG arm achieved treatment success, which was statistically greater than the SCS arm (55.7 %; 39/70). Similar results were observed at the 12-month mark, where 74.2 % (49/66) patients in the DRG arm achieved treatment success, which was greater than in the SCS arm (53 %; 35/66). These results demonstrated both non-inferiority and superiority at the 3 and 12-month follow-up visits. No neurological deficits were reported in ether groups in the study.

Patients treated with DRG experienced significantly less postural variation in perceived paresthesia intensity than the SCS subjects at both the 3- and 12-month visits. SF-36 scores were improved in both the DRG and SCS groups. The general health scale was not significantly improved at 12 months in the SCS group. Both groups also experienced improvements in all domains of the POMS from baseline to 3 months. At the 12-month visit, the SCS group did not have statically significant improvement in the depression and confusion scales compared to baseline. BPI scales showed improvement from baseline in both groups at 3 and 12 months. DRG patients did show statistically greater improvements on the interference, activity, and affective scale when compared to SCS patients at 3 and 12 months. The majority of patients in both groups reported high degrees of satisfaction, with no statistical significance found between the groups. SCS patients were 2.3 times (3 months) and 7.1 times (12 months) more likely to report feeling paresthesia in one or more non painful areas when compared with the DRG cohort. The DRG group also experienced a greater mean percent reduction in VAS scores than SCS patients (84.1 vs. 70.9 %, respectively), persisting to 6 and 12 months. Finally, severe adverse events were not statistically different between the two groups. The rate of non-serious procedure events was higher for the DRG group (46 %) compared with the SCS group (26 %). This was attributed to the longer procedure time and a greater number of leads placed for some DRG patients.

The researchers concluded that DRG stimulation provides enhanced pain relief compared to traditional SCS therapy for patients with CRPS-I or II-affecting the lower extremities. DRG stimulation also resulted in significantly greater improvements in total mood disturbance, physical function, general health, and social function. There were some limitations to the study. The patients were not blinded, and thus subjects treated with SCS might have been less motivated to remain in the study. Any dropouts were counted as failures. The SCS device also had limitations placed on the programming so that the comparison between the devices was not confounded by unique SCS programming features.

Canos-Verdecho, 2021 [16]

Canós-Verdecho et al. (2021) conducted a prospective, randomized study to evaluate the efficacy of treatment with LF-SCS and HF-SCS for patients diagnosed with CRPS-I with upper limb involvement (see Table 3). The study included 50 patients who were randomly assigned to receive either conventional medical treatment (medication, PT, nerve blocks), SCS therapy with a LF-SCS system (Medtronic), or with a 10-kHz HF-SCS system (Nevro). Patients in the SCS group underwent a two-week trial phase. A successful trial was achieved if the patient had at least a 50 % improvement of symptoms or two-point decrease on VAS. After implantation, patients had follow-up visits at the 1, 3, 6, and 12-months. Nineteen patients were randomly assigned to the conventional treatment group, 12 to the LF-SCS group, and 10 to the HF-SCS group. Patients in the LF-SCS group were implanted with either one 8-pole electrode for unilateral pathology or two electrodes for bilateral cases. Intraoperative paresthesia mapping ensured coverage of >80 % of the affected pain area. All LF-SCS group patients received tonic programming with leads placed at either C3, C4, or C5 levels based on paresthesia mapping. Patients in the HF-SCS group were implanted with two electrodes, the first with its most cephalic contact at the level of the upper third of the body of C2 and the second electrode with its most cephalic contact at the level of the body of C3. No intraoperative mapping was performed for the HF-SCS device.

The primary endpoint of the study was 12 months post-implantation. Outcomes measured included the numerical rating scale (NRS), 12-Item Short-Form Health Survey, Oswestry Disability Index (ODI), Study Sleep Scale medical outcomes (MOSS-SS), DN4 neuropathic pain questionnaire, Patient Global Impression Scale on the impact of treatment improvement (PGI-I), and clinical Global Impression Scale on the impact of improving the patient (CGI-I).

At the 3-month follow-up, patients in the LF-SCS group achieved an average decrease of 5.7 points in NRS scores and 2.9 points in DN4 scores. Patients treated with HF-SCS achieved an average decrease of 5.9 points in NRS scores and an average decrease of 3 points in DN4 scores. These met the minimal clinically important difference (MCID) for both LF-SCS and HF-SCS groups but not for the conventional treatment group. At the primary endpoint one year after treatment, patients in the LF-SCS group achieved an average decrease of 5.6 points in NRS scores and 2.9 points in DN4 scores. Patients treated with HF-SCS achieved an average decrease of 4.8 points in NRS scores and an average decrease of 2.8 points in DN4 scores. No significant long-term differences were observed between LF-SCS and HF-SCS groups. Both SCS groups showed around 60 % improvement in NRS scores and 40 % improvement in DN4 scores at the 12-month follow-up visit. The conventional treatment group achieved a 40 % improvement in NRS scores and 30 % improvement in DN4, which still exceeded the MCID threshold.

Five patients in the LF-SCS group perceived bothersome paresthesias with postural changes such as flexing the cervical spine or when lying down. The device amplitude was decreased until this discomfort was no longer perceived. One patient in the HF-SCS group presented with an occipital headache three months after implantation.

The researchers concluded that patients with CRPS experienced considerable improvements at 12 months after the initiation of both conventional treatment and treatment with SCS systems. HF-SCS systems could be considered as an alternative to LF-SCS systems in the cervical spine due to the absence of paresthesias. However, this study

was limited by a small sample size and lacked 1:1 randomization.

4. Discussion

SCS is a well-documented therapy with established techniques that have shown benefit in the treatment of patients with CRPS. Among the six studies included in this systematic review, four studies found a positive effect of spinal cord stimulation on reducing pain intensity or improving quality of life in patients with Complex Regional Pain Syndrome. These studies demonstrated significant pain reduction, increased general perceived effect, or improved health-related quality of life following SCS intervention compared to control groups or physical therapy alone. Specifically, the studies by Kemler et al. (2000, 2004), Deer et al. (2017), and Canós-Verdecho et al. (2021) reported favorable outcomes, indicating the effectiveness of SCS or dorsal root ganglion (DRG) stimulation in treating CRPS [13,14,16,18].

The Kemler et al. studies evaluated response of patients with CRPS-I to spinal cord stimulation with PT versus PT alone [13–15]. The initial study by Kemler et al., in 2000 reported a 56 % success rate based on GPE and VAS difference from baseline.13 The subsequent study by Kemler et al., in 2004 reported a success rate of 57 %, at two-year follow-up suggesting that SCS may provide durable, long-term pain relief for patients with CRPS within this time frame [14].

One study in this group did not find a significant long-term effect, as evidenced by the findings from Kemler et al. (2008) [15]. Subsequent 5-year data by Kemler et al., in 2008 demonstrated attenuation of patient response to 35 %, although notably the overwhelming majority of patients reported that they would repeat the same treatment for the same outcome [15]. Patient tolerance may contribute to decreased pain relief at five years; it may be reasonable to offer a trial of different frequencies or waveforms to patients in these situations. However, high reported patient satisfaction with the procedure even with comparable pain relief scores to the control group suggests that SCS may offer further benefit to the patient beyond the measured outcome variables in the study.

One study was deemed inconclusive. The study by Kriek et al. (2017), which investigated various stimulation frequencies and waveforms, found no significant differences in efficacy between the four active SCS settings [17]. This study demonstrated that HF-SCS was more effective than LF-SCS and placebo in reducing pain intensity and improving quality of life in patients with CRPS-I and CRPS-II. This study also reported that nearly 70 % of patients preferred the HF-SCS while approximately 30 % of patients expressed no preference. The study did not report any significant difference in outcomes between the four active SCS settings (40 Hz, 500 Hz, 1200 Hz and burst SCS), suggesting that the mechanism of pain relief underlying these different frequencies and waveforms may be similar. While high-frequency stimulation was generally preferred, the lack of consistent differentiation in pain relief across various settings led to inconclusive results regarding which specific frequency or waveform is superior for treating CRPS. However, giving patients the opportunity to trial different frequencies and waveforms may increase patient participation in their care and responsiveness to treatment.

DRG stimulation, which uses a similar hardware as SCS but targets the DRG on the posterior roots of each spinal nerve, was the subject of the study by Deer et al. [18] The soma of primary sensory neurons are located in the DRG which process and transmit sensory information from the periphery to the central nervous system. Thus, targeting the specific dorsal root ganglia associated with the painful dermatome in DRG stimulation offers a level of precision above SCS. The Deer et al. study in 2017 was a large, randomized trial that reported a success rate of 81 % in the DRG group and 55.7 % in the SCS group, as measured by a primary outcome of >50 % reduction in VAS at trial end and 3 month follow-up [18]. Overall, this study concluded that in comparison to SCS, DRG stimulation showed higher rates of treatment success over a longer period of time, with significantly less postural-related changes in paresthesia. This study also demonstrated that DRG stimulation results in significantly improved mood as well as social and physical function compared to SCS. This suggests that DRG stimulation may offer additional mood and psychological benefits that may be advantageous in patients with concurrent psychological disorders.

Finally, the Canós-Verdecho et al. study in 2021 concluded that SCS treatment, specifically LF-SCS and HF-SCS, improved NRS scores and DN4 neuropathic pain questionnaire scores when compared to conservative treatment [16]. This study also notably reported that HF-SCS may be more suitable in the cervical spine due to lack of induced paresthesia as opposed to LF-SCS.

Out of the six studies, four found a significant effect, one did not find an effect, and one was inconclusive regarding the specific parameters of SCS efficacy. This distribution underscores the mixed evidence regarding long-term outcomes and the need for further research into optimizing SCS parameters for CRPS treatment.

There are several limitations to this review. First, with regard to the study selection process, this review focused only on Randomized Controlled Trials. While it is true that well conducted RCTs provide better evidence than observational studies, research has shown that well conducted observational studies may provide better evidence in comparison to poorly conducted RCTs [19,20].

A prior systematic review and meta-analysis was published in 2022 by Ho et al. assessing parameters in spinal cord stimulation in complex regional pain syndrome [21]. The review concluded that low frequency spinal cord stimulation was superior to conventional therapy and placebo SCS stimulation [21]. While this offers valuable insight that may benefit patients with more personalized programming parameters, it differs from this analysis where the focus is on the potential pain relief from spinal cord and dorsal root ganglion stimulation regardless of stimulation parameters.

One study included in the review by Ho et al. that was not identified by the search strategy used for this review was a paper by Sokal et al. [21,22] The study focused on the difference in stimulation patterns and frequency applied and patient response, with a follow up time point after only 2 weeks of applied stimulation [22]. This is by no means an evaluation of the long term success of SCS/DRG for CRPS. Moreover, this study addressed treatment for chronic pain syndrome, and not specifically CRPS. While some patients with CRPS may fall into the category of chronic pain syndrome, this is not necessarily true of the chronic pain population at large. It is important to distinguish that while SCS is used to manage both CRPS and chronic pain syndrome, the underlying pathology, mechanisms, and treatment goals differ significantly between these two conditions.

Second, with regard to the included studies, there was considerable variability in trial process or patient selection for SCS implantation, involvement of the device representative, follow-up time, and outcome measures. The variability in these factors pose a limitation to the generalizability of the conclusions. As mentioned previously, the planned meta-analysis was challenging due in part to lack of RCTs, large number of crossovers, and complex design complicating data extraction. There was also considerable heterogeneity of the outcome measures included, although all but one study evaluated pain response using VAS. AS is inherently patient-dependent. The VAS may be more useful for identifying changes in pain score, but the inclusion of a categorical pain outcome may be beneficial in providing an alternative way for patients to express their pain level.

Most studies evaluated the mean pain response, which may not necessarily reflect individual patient responses. Furthermore, the Deer et al. study in 2017 included 152 patients, but the other studies had a significantly smaller patient size, with only 29 patients included for final analysis in the Kriek et al. paper [17,18].

The variability in primary and secondary outcomes between the papers should be noted as well. The Kemler et al. studies assessed pain response using the VAS, GPE, functional status, and quality of life as related to healthcare [13–15]. The primary outcomes of the Kriek et al.

study were pain response using the VAS, MPQ and GPE [17]. The Deer et al. study evaluated pain response using the VAS and neurological deficits associated with the stimulation [18]. The outcome measures of the Canós-Verdecho et al. study were the NRS, 12-Item Short-Format Health Survey, ODI, Study Sleep Scale medical outcomes, Douleur Neuropathique 4 questions pain questionnaire, PGI-I and CGI-I [16]. While the Canós-Verdecho et al. study did not include the VAS as a primary measure of outcome, it did use VAS scores to determine eligibility for SCS implantation during the trial period. The Canós-Verdecho et al. study was also the only study evaluated that included an outcome evaluating the clinicians' perception of the SCS treatment [16].

Overall, the studies evaluated in this review consistently suggest that SCS may be effective at improving pain in patients with CRPS, specifically CRPS-I which was primarily evaluated in most studies. DRG stimulation as evaluated by the Deer et al. study in 2017 may offer a promising, more precise way to target the dorsal root ganglion [18]. These findings are in accordance with other studies suggesting that SCS therapy should not be withheld from patients who suffer from allodynia and hyperalgesia, which contradicts previous findings derived from retrospective analysis and animal research [23].

The added value of this study lies in its focused and systematic review of SCS specifically for the treatment of CRPS. Although SCS has been widely researched as a therapy for chronic pain conditions, the complex nature of CRPS - distinguished by its multifactorial pathophysiology involving neurogenic inflammation, nociceptive sensitization, and maladaptive neuroplasticity - necessitated an independent, disease-specific evaluation of treatment efficacy. By consolidating and assessing the efficacy of SCS specifically in CRPS patients, this study provides insights that can guide clinical decision-making, particularly in optimizing patient selection, and identifying effective stimulation parameters. Moreover, this review highlights the potential advantages of newer SCS technologies such as paresthesia-free systems, and DRG stimulation, which may offer more targeted, effective, and patient-specific approaches for managing CRPS symptoms. Ultimately this may help enhance clinical outcomes for a challenging condition that lacks a universally effective treatment modality.

Further research is certainly needed to explore outcomes with novel stimulation patterns and further elucidate the benefits of various SCS and DRG stimulations. Additional studies may also help identify patient characteristics that predict better clinical response to Low Frequency-SCS, High Frequency-SCS, or burst stimulation.

5. Conclusion

CRPS is a disabling chronic pain condition that is thought to arise from nociceptive sensitization, sympathetic dysregulation, and maladaptive neuroplastic changes. Given its varied clinical presentation that may involve sensory, vasomotor, and/or sudomotor symptoms, CRPS is challenging to both diagnose and treat. The literature has demonstrated that SCS may be effective in reducing pain associated with CRPS by inducing paresthesias at the dorsal columns. Recent innovations in SCS have included the development of novel waveforms and paresthesia-free stimulation. DRG stimulation may also more precisely target the dorsal root ganglion of interest. SCS and DRG stimulation should be considered in the treatment of CRPS refractory to conservative treatment modalities.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

[1] Taylor SS, Noor N, Urits I, et al. Complex regional pain syndrome: a comprehensive review. Pain Ther 2021;10(2):875–92. https://doi.org/10.1007/s40122-021-00279-4 [published correction appears in Pain Ther. 2021 Dec;10(2):893-894. doi: 10.1007/s40122-021-00291-8].

[2] Knudsen LF, Terkelsen AJ, Drummond PD, Birklein F. Complex regional pain syndrome: a focus on the autonomic nervous system. Clin Auton Res 2019;29(4):457–67. https://doi.org/10.1007/s10286-019-00612-0.

[3] Marinus J, Moseley GL, Birklein F, et al. Clinical features and pathophysiology of complex regional pain syndrome. Lancet Neurol 2011;10(7):637–48. https://doi.org/10.1016/S1474-4422(11)70106-5.

[4] Harden NR, Bruehl S, Perez RSGM, et al. Validation of proposed diagnostic criteria (the "budapest criteria") for complex regional pain syndrome. Pain 2010;150(2):268–74. https://doi.org/10.1016/j.pain.2010.04.030.

[5] Eun Young H, Hyeyun K, Sang Hee I. Pamidronate effect compared with a steroid on complex regional pain syndrome type I: pilot randomised trial. Neth J Med 2016;74(1):30–5.

[6] Wiffen PJ, Derry S, Bell RF, et al. Gabapentin for chronic neuropathic pain in adults. Cochrane Database Syst Rev 2017;6(6):CD007938. https://doi.org/10.1002/14651858.CD007938.pub4. Published 2017 Jun 9.

[7] Wertli MM, Kessels AG, Perez RS, Bachmann LM, Brunner F. Rational pain management in complex regional pain syndrome 1 (CRPS 1)–a network meta-analysis. Pain Med 2014;15(9):1575–89. https://doi.org/10.1111/pme.12466.

[8] Zhao J, Wang Y, Wang D. The effect of ketamine infusion in the treatment of complex regional pain syndrome: a systemic review and meta-analysis. Curr Pain Headache Rep 2018;22(2):12. https://doi.org/10.1007/s11916-018-0664-x. Published 2018 Feb 5.

[9] Aïm F, Klouche S, Frison A, Bauer T, Hardy P. Efficacy of vitamin C in preventing complex regional pain syndrome after wrist fracture: a systematic review and meta-analysis. Orthop Traumatol Surg Res 2017;103(3):465–70. https://doi.org/10.1016/j.otsr.2016.12.021.

[12] Isagulyan E, Slavin K, Konovalov N, et al. Spinal cord stimulation in chronic pain: technical advances. Korean J Pain 2020;33(2):99–107. https://doi.org/10.3344/kjp.2020.33.2.99.

[13] Kemler MA, Barendse GA, van Kleef M, et al. Spinal cord stimulation in patients with chronic reflex sympathetic dystrophy. N Engl J Med 2000;343(9):618–24. https://doi.org/10.1056/NEJM200008313430904.

[14] Kemler MA, De Vet HC, Barendse GA, Van Den Wildenberg FA, Van Kleef M. The effect of spinal cord stimulation in patients with chronic reflex sympathetic dystrophy: two years' follow-up of the randomized controlled trial. Ann Neurol 2004;55(1):13–8. https://doi.org/10.1002/ana.10996.

[15] Kemler MA, de Vet HC, Barendse GA, van den Wildenberg FA, van Kleef M. Effect of spinal cord stimulation for chronic complex regional pain syndrome Type I: five-year final follow-up of patients in a randomized controlled trial. J Neurosurg 2008;108(2):292–8. https://doi.org/10.3171/JNS/2008/108/2/0292.

[16] Canós-Verdecho A, Abejón D, Robledo R, et al. Randomized prospective study in patients with complex regional pain syndrome of the upper limb with high-frequency spinal cord stimulation (10-kHz) and low-frequency spinal cord stimulation. Neuromodulation 2021;24(3):448–58. https://doi.org/10.1111/ner.13358.

[17] Kriek N, Groeneweg JG, Stronks DL, de Ridder D, Huygen FJ. Preferred frequencies and waveforms for spinal cord stimulation in patients with complex regional pain syndrome: a multicentre, double-blind, randomized and placebo-controlled crossover trial. Eur J Pain 2017;21(3):507–19. https://doi.org/10.1002/ejp.944.

[18] Deer TR, Levy RM, Kramer J, et al. Dorsal root ganglion stimulation yielded higher treatment success rate for complex regional pain syndrome and causalgia at 3 and 12 months: a randomized comparative trial. Pain 2017;158(4):669–81. https://doi.org/10.1097/j.pain.0000000000000814.

[19] Fogarty AE, et al. Systematic reviews: not always a pain. Interv Pain Med 2022 Aug 15;1(Suppl 2):100128. https://doi.org/10.1016/j.inpm.2022.100128. eCollection2022.

[20] Shrier I, Boivin JF, Steele RJ, et al. Should meta-analyses of interventions include observational studies in addition to randomized controlled trials? A critical examination of underlying principles. Am J Epidemiol 2007;166(10):1203–9.

[21] Ho E, Yazdanpanah N, Ho J, Drukman B, Chang A, Agarwal S. Parameters of spinal cord stimulation in complex regional pain syndrome: systematic review and meta-analysis of randomized controlled trials. Pain Physician 2022 Nov;25(8):521–30. PMID: 36375180.

[22] Sokal P, Malukiewicz A, Kierońska S, Murawska J, Guzowski C, Rudaś M, Paczkowski D, Rusinek M, Krakowiak M. Sub-perception and supra-perception spinal cord stimulation in chronic pain syndrome: a randomized, semi-double-blind, crossover, placebo-controlled trial. J Clin Med 2020 Aug 31;9(9):2810. https://doi.org/10.3390/jcm9092810. PMID: 32878061; PMCID: PMC7563558.

[23] Kriek N, de Vos CC, Groeneweg JG, Baart SJ, Huygen FJPM. Allodynia, hyperalgesia, (quantitative) sensory testing and conditioned pain modulation in patients with complex regional pain syndrome before and after spinal cord stimulation therapy. Neuromodulation 2023 Jan;26(1):78–86. https://doi.org/10.1016/j.neurom.2022.06.009. Epub 2022 Aug 30. PMID: 36050204.