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Spinal Cord Stimulation for Complex Regional Pain Syndrome: An Evidence-Based Medicine Review of the Literature

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Abstract:

Objectives: The purpose of this investigation is to assess the evidence for efficacy of SCS in the management of pain in patients with CRPS.

Methods: *Search strategy:* Electronic databases such as Medline and Cochrane Library were queried using key words such as "spinal cord stimulation," "reflex sympathetic dystrophy (RSD)," and "complex regional pain syndrome (CRPS)."

Selection criteria: Relevant published randomized controlled trials (RCT), cohort studies, case-control studies, case series, and case reports that described SCS as the primary treatment modality for patients with CRPS were eligible for inclusion.

Data collection and analysis: Data extracted from qualified studies were summarized in sections of methodology, demographics, SCS equipment, primary and secondary outcomes, and complications.

Results: Thirteen studies using the primary search strategy and 7 studies from their reference lists were considered. Five of these 20 studies were discarded. One RCT, 2 prospective observational, and 12 retrospective observational studies were eventually considered. The methodological quality of all studies was poor except for the single RCT study.

Discussion: Although limited in quality and quantity, available evidence from the examined literature suggests that SCS is effective in the management of pain in patients with CRPS (grade B/C). Clinically useful information extracted from the available studies is very limited in guiding clinicians in the rational use of SCS for pain management in CRPS patients. Future attempts to investigate the efficacy of SCS in CRPS patients should involve methodologically robust designs such as randomized studies that have sufficient power.

Key Words: spinal cord stimulation (SCS), complex regional pain syndrome (CRPS), reflex sympathetic dystrophy (RSD), evidence-based medicine (EBM)

Complex regional pain syndrome (CRPS) is a neuropathic pain condition characterized by disturbances of sensory, motor, and autonomic function that may be associated with trophic changes.[1] The hallmark of the disease is intractable burning pain that often is exacerbated by emotional distress, light touch, movement of the affected extremity, or changes in ambient temperature. The treatment consists of concurrent utilization of pharmaco-, psycho-, and physio-therapeutic modalities to restore function and health. To date, no scientifically validated cure exists. The primary objective of this investigation was to critically examine the published literature for evidence concerning the efficacy of spinal cord stimulation (SCS) for CRPS using the principles of evidence-based medicine (EBM).

SCS has gained widespread popularity for the treatment of chronic pain of diverse etiology. Since its initial

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application,[2] there has been considerable investigation directed at elucidating its mechanisms of action. In general, SCS exerts multiple biologic effects at both spinal and supraspinal sites. These effects involve a diverse array of neurochemical changes and are associated with a decrease in sympathetic outflow. In neuropathic pain, SCS may have an inhibitory effect on A-β fiber-mediated hyperexcitability of dorsal horn neurons via a γ-aminobutyric acid (GABA)-mediated mechanism.[3] However, SCS has no long-term effect on experimental pain thresholds (thermal or mechanical allodynia) and only limited effect (decrease of 0.5 on VAS) on dynamic and static hyperalgesia in patients with CRPS.[4] To date, there is little scientific evidence concerning which of the known mechanisms might be responsible (either solely or in part) for its analgesic effect. Although SCS can reduce sympathetic outflow, this effect may not be critical to the production of analgesia for patients with CRPS.[5] The reader is referred to a recent review for a more detailed discussion of postulated mechanisms of action.[3]

In general, there is convincing evidence from randomized controlled trials (RCTs) that SCS is effective for the long-term management of pain in patients with peripheral vascular disease[6] and failed back surgery syndrome with radicular symptoms.[7] A panel of experts recently released a consensus statement that addresses important issues such as indications, patient selection, and surgical technique for SCS.[8]

The use of SCS for the treatment of pain in CRPS (including RSD and causalgia) has been reported in the literature for over 25 years. The consensus opinion from experts suggests that SCS should be considered in the treatment algorithm when conservative or traditional therapies have failed.[9] However, such considerations are not based on reliable evidence generated through well-designed randomized controlled trials. To date, there has not been a systemic evaluation of the existing literature concerning the efficacy of SCS for patients with CRPS. Thus, the primary aim of this investigation was to use the principles of EBM to examine critically the published literature for evidence concerning the efficacy of SCS in CRPS. Inclusion criteria were broad enough to allow inclusion of as many studies as possible that described SCS as the primary treatment modality for patients with CRPS. The secondary aim of this investigation was to scrutinize the rationale behind the widespread use of SCS as a therapeutic modality in the management of CRPS.

Whenever possible, we attempted to extract any available information that could be used to guide clinicians who contemplate SCS for patients with CRPS. Thus, the studies were examined for relevant patient clinical and demographic characteristics as well as pertinent SCS stimulation parameters and equipment characteristics associated with improved efficacy. In addition, we searched for information regarding the long-term efficacy of SCS in patients with CRPS and the appropriate timing of SCS in the treatment algorithm for CRPS. Finally, we searched for information regarding objective evidence of disease remission following SCS implementation and whether there was any relationship between the effectiveness of SCS and its ability to modulate sympathetic nervous system (SNS) function.

MATERIALS AND METHODS

Search strategy

A number of electronic databases were queried, such as Medline (1966–2002), Cochrane Library (on-line version 2002), ISI's Web of Science (1945–2002), and WebSpirs from Silver Platter (1976–2002). The most recent search was done in April 2002. Key words used for the search (singly or in combination) included the following: "spinal cord stimulation," "dorsal column stimulation," "reflex sympathetic dystrophy (RSD)," "causalgia," "complex regional pain syndrome (CRPS)," "neuropathic pain," "chronic pain," "neuromodulation," and "neuroaugmentation." In addition, the search included personal files, textbooks, bibliographies of retrieved reports, and literature supplied by manufacturers of the spinal cord stimulators (Medtronic Inc., Minneapolis, MN; ANS-Quest, Allen, TX).

Selection criteria

Types of studies

All published RCTs, clinical trials, case-control studies, cohort studies, case series, and case reports were considered eligible for analysis. Data from unpublished studies, review articles, letters, un-referenced abstracts, un-referenced proceedings from meetings, and duplicate publications were excluded. Only articles written in English were included in the analysis. In addition, articles with mixed data from patients with diseases other than CRPS that could not be separated from data from patients with CRPS were excluded.

Types of participants

Studies of adult patients with the clinical diagnosis of CRPS types I and II, formerly known as RSD and causalgia, respectively, were included in the data analysis. Since the taxonomy and nomenclature of this clinical disorder has changed during the period of publication review, studies were not excluded if they did not meet the current IASP definition of disease.[1] Instead, this distinction was tracked and is summarized in the Results.

Types of interventions

All reports that described SCS as the primary treatment modality for patients with CRPS were included. Since SCS technology has evolved over the years during which the articles under review were published, none of the studies was excluded on the basis of type of equipment, technical parameters, or surgical techniques used to implant SCSs. Rather, information on these distinctions was tracked and is summarized in the Results.

Types of outcome measures

Primary outcome measures for either pain intensity or pain relief, or a combined measures score for the treatment effect, were sought and identified for data analysis. These measures included the 10-cm horizontal visual analog scale (VAS), categorical scores for pain intensity or pain relief, and end-of-treatment global ratings of treatment efficacy (such as combined measures scores of treatment effect). In addition, secondary outcome measures were identified whenever possible. These included reduction of analgesic use, return to work, objective improvement in physiology or function, cost effectiveness, health-related quality of life (HRQOL), improvement in sleep, and improvement in psychometric measures. All studies were included regardless of the source of follow-up data, such as patient questionnaires, chart reviews, in-person interviews, phone interviews, and ratings of pain or treatment efficacy by the investigators or a disinterested third party.

Data collection and analysis

Data extraction

Data was extracted and summarized into 5 general categories: methodology, clinical characteristics (patient demographics), SCS equipment characteristics, outcome measures, and complications. The first category included the following methodological issues: study design, primary and secondary outcome measures, outcome assessment intervals, sources and methods of data collection, and statistical analysis. The second category included the following clinical characteristics: criteria for diagnosis, sex, age, initiating factors, characteristics of pain, baseline VAS pain scores, duration of symptoms, and previous therapies. The third category included the following SCS equipment characteristics: trial SCS equipment, trial SCS parameters, length of trial, success of trial, proportion of internalized patients, implanted SCS equipment, implanted SCS parameters, location of lead placement, and pattern of use. The fourth category included the following primary outcome measures: VAS at end of follow-up period, percent improvement, patient satisfaction, and global perceived effect. In addition, the following secondary outcome measures were sought: quantifiable objective physiological changes, return to work, reduction in medication use, improvement in sleep, improvement in function or activities of daily living (ADL), cost effectiveness, decrease in health-care utilization, and HRQOL. Finally, the fifth category included the following adverse events: reoperation rate, infection rate, technical or mechanical failure, biologic complications such as wound dehiscence, and complications during the trial.

The data were extracted independently by 2 separate reviewers (TSG and PT). Discrepancies in data coding were resolved by formal discussion. A decision was made as to whether the overall conclusion of each report was positive or negative. A positive report for an RCT required a reported statistically significant difference in at least 1 primary outcome measure between the treatment and control groups. In the case of non-controlled studies, a positive report was based on the authors' conclusions supported by evidence derived from the described methodology and reported results.

Statistical analysis

Due to the presence of only one RCT, quantitative analysis (meta-analysis) could not be performed and summary measures of effect, such as relative risk (RR) or an odds ratio (OR) could not be calculated. Alternative indices of SCS efficacy, such as number needed to treat (NNT), or SCS safety, such as number needed to harm (NNH), could be derived for only 1 study. However, the available qualitative evidence is presented descriptively.

Description of studies

Based on the previously mentioned selection criteria, a total of 20 studies were considered initially for inclusion. Five studies[10–14] out of the initial 20 studies did not meet the inclusion criteria and were excluded, while the remaining 15 studies,[15–29] which also included an RCT, were considered for analysis.

Excluded reports

Five studies were removed after initial identification because either information from patients with CRPS could not be separated from patients with other diseases or because sufficient information regarding methodology, patient demographics, SCS equipment, complications, and outcomes could not be extracted. Excluded studies did not include any RCTs. Out of the 5 excluded studies, 1 was prospective[10] while 4 were retrospective.[11–14] All were observational and descriptive. Two of the excluded reports were published abstracts.[12,13]

Included reports

Fifteen studies that met all the inclusion criteria were used in this review. Of the included studies, 1 study was experimental, analytical, and prospective (ie, a RCT).[23]

The 14 remaining studies were observational and descriptive (ie, case series and case reports). Of these 14 studies, 12 were retrospective[15–20,22,24,25,27–29] and 2 were prospective in design.[21,26] Data from these 15 studies were extracted and are summarized in Tables 1–5.

Study subjects

The studies were published between 1974 and 2000. The studies involved a total of 399 patients. Of these, 314 patients met either the diagnostic criteria published by the IASP for patients with CRPS or comparable criteria according to the judgment of 2 independent reviewers (TSG and PT). Criteria were considered comparable to the IASP diagnostic criteria if the authors included statements regarding ongoing pain, abnormal sensory or motor signs and symptoms, and autonomic disturbance.

Treatment group size

There was only one RCT[23] that used an intention-to-treat analysis in 54 patients. A randomization ratio of 2:1 was used for the treatment (36 patients) and control (18 patients) groups, respectively.

Study sponsorship

Only 1 study[16] reported manufacturer sponsorship in the form of grant support.

Country of origin and language of publication

Studies were conducted in centers throughout Europe and North America (Italy, Netherlands, Spain, UK, and USA) and were published in English.

Methodological quality

The methodological quality of the single RCT was independently evaluated and scored by 2 reviewers using the criteria outlined in the widely used CONSORT statement regarding the reporting of RCTs.[31] Of the 22-item checklist, the RCT analyzed in our review met 19 out of the 22 criteria. In addition, we applied the scoring criteria for RCTs published by Kingery.[43] The RCT in our analysis scored 68 out of 100 and ranked comparably to the scores for RCTs for pharmacological therapies for CRPS (mean 57.2 ± 2.9: range 27–82). We are unaware of any available valid method of rating observational–descriptive study designs such as case series and case reports.

RESULTS

Due to the lack of consistent extractable data from RCTs, quantitative data analysis by means of meta-analysis was not possible. Therefore, results are presented qualitatively and descriptively for 15 studies that satisfied the inclusion criteria.

Methodology (Table 1)

Fifteen studies were included in the analysis. One study was an RCT (experimental, analytical, prospective). The remaining 14 studies were observational, descriptive, and predominantly retrospective (12 of 14) versus prospective (2 of 14) in design. Twelve studies explicitly used changes in VAS as the primary outcome

TABLE 1. *Methodology*

Study (citation)	Study design	CRPS patients with SCS	Diagnosis (comparable to IASP's definition)	Primary outcome	Secondary outcome(s)
Barolat[15]	Retrospective case series	18	Yes	CS	AR
Barolat[16]	Retrospective case series	44	Yes	VAS, CS	NE
Bennett[17]	Retrospective case series	101	Yes	VAS	Satisfaction scores; Revision rate
Broggi[18]	Retrospective case series	6	NA	VAS	NA
Broggi[19]	Retrospective case series	54	NA	VAS, CS	NA
Broseta[20]	Retrospective case series	11	Yes	CS	AR; RTW
Calvillo[21]	Prospective case series	36	Yes	VAS	AR; RTW(QOL)
Kemler[22]	Retrospective case series	23	Yes	VAS	GPE
Kemler[23]	Randomized controlled trial	36	Yes	VAS	McGill; HRQL; GPE; Functional status; Complications
Kumar[24]	Retrospective case series	12	Yes	VAS, CS	AR, McGill, VAS
Miles[25]	Retrospective case report	1	NA	CS	AR
Oakley[26]	Prospective case series	19	Yes	VAS	QOL (McGill Beck, Depression Inventory, Sickness Impact Profile, Oswestry Disability)
Robaina[27]	Retrospective case series	8	Yes	VAS	PPL/Thermography; McGill; Sleep; AR, Activity level; Pain Index
Robaina[28]	Retrospective case series	6	Yes	VAS	McGill; AR; Sleep, activity level; QOL; Pain Index
Sanchez-Ledesma[29]	Retrospective case series	24	Yes	VAS, CS	RTW; AR; Vasomotor improvement

AR, analgesic reduction; CS, categorical score for pain relief (good, moderate, minimal, none); GPE, global perceived effect; IASP, International Association for the Study of Pain; NA, not available or not described; NE, not extractable or incomplete information; PPL, photoplethysmography; QOL, quality of life; RTW, return to work; VAS, Visual Analog Scale.

measure to determine the effectiveness of SCS for CRPS.[16–19,21–24,26–29] Eleven studies reported the use of secondary outcome measures,[15,17,20–24,26–29] the majority of which were not validated. Three studies reported the use of multiple assessment intervals for primary or secondary outcomes but failed to either report or discuss the results of these assessment intervals.[19,21,22] Only the RCT reported the use of multiple assessment intervals and reported results analyzed from these intervals.[23] Information regarding the source of data reporting, data collection, and data analysis was reported in only 3 studies.[16,22,24] Only 4 studies included a section that described statistical methods.[17,21–23] One study reported *P* values but did not describe the statistical tests or methods used.[26]

Patient demographics (Table 2)

Diagnostic criteria

Twelve of the 15 studies reported the specific criteria that was used to establish the diagnosis of CRPS.[15–17,20–24,26–29] Six[17,21–24,26] of the 7 studies[16,17,21–24,26] conducted after the publication of the IASP diagnostic criteria also referenced the guidelines. However, only 1 study[17] explicitly stated that the official IASP diagnostic criteria were used as inclusion criteria in the methods section. Two studies used guidelines that were similar to, but more stringent than, the original IASP guidelines.[22,23] Unfortunately, the internal and external validity of these guidelines have not been tested scientifically.

Initiating event

In 7 studies,[15,20,22–24,27,29] trauma or surgery was identified as the specific noxious event antecedent to the development of CRPS (range: 54–100% of patients).

Location of pain

Ten studies reported the location of pain.[15,17,20–27] Of the 265 patients involved in these 10 studies, 98 (37%) had upper extremity CRPS, 165 (62%) had lower extremity CRPS, and 8 (3%) had mixed upper and lower extremity symptoms.

Sex

Twelve studies reported demographic information about sex.[15,17,18,20–28] Of the 355 patients reported in these 12 studies, 122 (34.4%) were male and 233 (65.6%) were female.

Age

Ten studies reported information about patient age.[15,17,20–27] The mean age ranged from 32 to 58 years. The youngest age reported ranged from 18 to 29 years, and the oldest age reported ranged from 50 to 80 years.

TABLE 2. *Demographics (patient characteristics)*

Study (citation)	Age mean (range)	Sex (% male)	Mean duration of symptoms months (range)	Location (% of total)	Previous therapies
Barolat[15]	32 (18–50)	22	33.5 (4–96)	22 UE 67 LE	Symp, PH, IT pump, opioid, IVRA, Sx
Barolat[16]	NA	NA	NA	NA	Symp, Sx
Bennett[17]	44 (26–80) 43 (23–77)	22 44	NA	29 UE 65 LE 6 UE/LE	PT, blocks, PH, PE ANPD
Broggi[18]	NA	17	NA	NA	NE
Broggi[19]	NA	NA	NA	NA	PH
Broseta[20]	48 (29–72)	63	30.6 (8–72)	73 UE 27 LE	Sx, Cons, PE, TENS
Calvillo[21]	49.4 (20–61)	22	24–36	100 UE	PS, PT, Symp, PH, PE, Sx, opioids, ANPD
Kemler[22]	39 (24–54)	35	44 (9–179)	43 UE 57 LE	Symp, PH, opioids, TENS, PT, mannitol, DMSO, ANPD
Kemler[23]	40	39	40 (NA)	61 UE 39 LE	PE; PT, Symp, TENS, PH
Kumar[24]	38.2 (22–82)	75	NA	42 UE 58 LE	Symp, PT, PH, Sx, opioid
Miles[25]	58	100	384 (32 yrs)	100 UE	PE, Acupuncture
Oakley[26]	43.5 (26–80)	26	7.5 (2–60)	53 UE 47 LE	PE
Robaina[27]	43	62	NA	100 UE	Sx, Symp, PE, TENS
Robaina[28]	NE	63	NA	NA	TENS, PE
Sanchez-Ledesma[29]	NE	NE	NE	NA	PE, PH, nerve blocks, Sx, PNS

ANPD, anti-neuropathic pain drugs; Cons, conservative therapies; IT, intrathecal; IVRA, IV regional anesthesia; LE, lower extremity; NA, not available or not described; NE, not extractable or incomplete information; PH, pharmacotherapy; PE, psychological evaluation (formal); PS, psychotherapy; PT, physical therapy; Sx, surgical therapies; Symp, sympathetic block; TENS, transcutaneous electrical nerve stimulation; UE, upper extremity.

Symptom duration

Seven studies reported duration of patient symptoms prior to receiving SCS.[15,20–23,25,26] The mean duration of symptoms ranged from 7.5 to 44 months. The single patient in the case report had duration of symptoms for 32 years. All patients in the RCT reported symptom duration of at least 6 months.

Baseline VAS

Only 7 studies reported baseline visual analog scale (VAS) scores for pain.[17,21–23,26–28] The mean baseline VAS for pain ranged from 6.7 to 8.3.

Previous therapy

All 15 studies reported that patients had tried previous therapies without success prior to SCS. Nine studies reported that their subjects failed to respond to conventional pharmacological treatments before being considered for SCS.[15,17,19–24,29] The specific use of opioids[15,21,22,24] and anti-neuropathic pain medications[17,21,22] such as tricyclic antidepressants or anticonvulsants was mentioned in only 4 and 3 studies, respectively. Six studies[15,16,21–23,27] reported the use of pharmacological interventions designed to interrupt sympathetic nervous system function (ie, intravenous regional anesthesia, stellate ganglion block, lumbar sympathetic block). Seven studies[15,16,20,21,24,27,29] reported the prior use of surgical interventions that sometimes included surgical sympathectomy. Five studies reported previous use of physical therapy[17,21–24] and TENS therapy.[20,22,23,27,28] Prior use of psychologic modalities or formal psychologic screening prior to SCS trial was reported in 9 studies.[17,20,21,23,25–29] Other miscellaneous treatments included peripheral nerve blocks,[17,29] intrathecal pump,[15] peripheral nerve stimulation,[29] antioxidant therapy,[22] and acupuncture.[25]

Equipment characteristics

Trial stimulation equipment and procedures

Ten studies[15,17,18,20–23,26–29] reported the use of externalized percutaneous lead placement, and one study[27] reported the additional use of laminotomy lead placement for trial stimulation (Table 3). Lead configuration varied considerably and studies reported the use of either monopolar, bipolar, quadripolar, or octapolar configurations. The number of leads placed for trial stimulation also varied but was not universally reported. Four studies reported the use of a single lead,[21–23,26] 2 studies reported the use of dual leads,[20,28] and 3 studies reported the use of either single or dual leads.[15,17,29] Only 1 study reported the precise anatomic location of the trial lead.[28] Nine studies reported that the trial stimulation produced a paresthesia that covered the painful area.[15,20–25,27–29]

Trial stimulation parameters

Trial stimulation parameters such as amplitude, pulse width, and frequency were reported in only 4 studies.[15,18,20,29] In these four studies, pulse width ranged from 100 to 500 microseconds and frequency ranged from 70 to 120 Hz. Stimulation amplitude was reported at 1–3 volts[15] or at "paresthesia threshold",[29] "pain relief",[15] or "patient comfort",[20] without stating the actual values. Only 1 study reported the pattern of use of the trial stimulation.[20]

Length of trial stimulation

Eleven studies reported the duration of the stimulation trial period that ranged from 3 to 30 days.[15,18,20–24,26–29] Six of these studies reported trial stimulation that lasted 7 days or less.[15,20–22,24,26] The remaining 5 studies reported trial stimulation of greater than 7 days.[18,23,27–29]

Trial success rate

Eleven studies reported the success rate (ie, the proportion of patients initially screened that later received permanent implants) of the trial device.[15,18,20–24,26–29] The reported success rate ranged from 66.6% to 100%. There was considerable variability in the criteria used to determine successful trial stimulation. Quantitative and validated measures of pain relief were not used by all studies to determine trial success. A 50% decrease in VAS score for pain or a rating of 6 on the global perceived effect (GPE) scale was necessary to define success in 2 studies.[22,23] Three studies used 50% pain relief from baseline VAS scores[21,26,29] while 1 study used walking distance along with 70% pain relief[18] as the primary outcome measure. Other studies used nonspecific outcomes such as "patient satisfied",[19] "acceptable degree of analgesia",[27,28] "patient benefited",[20] or "pain relief to avoid heavy analgesic use."[24]

Implanted equipment and procedures

There was considerable variability with regard to the type of stimulation equipment that was implanted. In general, studies did not provide actual numbers of patients receiving the different types of stimulation equipment. SCS equipment included both internalized pulse generators and externalized radio frequency transmitter-antenna systems. Patients received either single or dual leads that consisted of unipolar, bipolar, quadripolar, or octapolar electrodes. Four studies reported the use of paddle-type electrodes requiring laminotomy for lead placement.[15,16,24,27] The dates of the stimulator implants ranged from 1982 to 2000 (median: 1990). Only 1 study reported the rationale for choosing the type of SCS equipment that was used in the study.[24]

Seven studies reported the precise anatomic location (vertebral level) of the SCS leads.[15,17,18,20,23,24,27] Leads

TABLE 3. *Equipment characteristics*

Study (citation)	Trial stimulation equipment	Trial stimulation parameters	Trial stimulation (days)	Implant criteria	Trial success (%)	Implanted equipment	Implanted equipment parameters
Barolat[15]	Ext; 1 or 2 leads	250–450 μsec, 1–3 V; paresthesia	5–7	"pain relief"	76.5	1 or 2 leads; Lami, Perc; Quad; C3/4-T1/2, T4/5-T10; IPG	NA
Barolat[16]	NA	NA	NA	NA	NA	IPG; Lami	NE
Bennett[17]	Quad; 1 lead	NA	NA	NA	NA	RF, IPG; Quad; C2–C6; T10–T11; IOT	NE 2.1–240 Hz, 0–12 V, 50–500 μsec
	Octrode; 2 leads			NA		RF; Dual octrode; C2–C6, T10–T11; IOT	10–1500 Hz, 0–12 V, 50–500 μsec
Broggi[18]	Ext; monopolar	500 μsec; 70–85 Hz	7–30	70% pain relief plus walking distance test & subjective report	66.6	IOT; C6–T1, T5–7	500 μsec, 70–85 Hz, amplitude to paresthesia
Broggi[19]	NE	NA	NE	"satisfied"	NA	NE	NE
Broseta[20]	Ext; 2 leads; unipolar, bipolar	500 μsec, 80–120 Hz, patient comfort; paresthesia; pattern of use	7	"benefited"	100	RF; C3–T1, T9–T12; paresthesia in painful area	Unipolar, Bipolar, 1–4x daily versus as needed
Calvillo[21]	Ext; bipolar; 1 lead; Quad	paresthesia	5–7	50% pain relief	66.6	NE (used trial parameters)	NA
Kemler[22]	Ext; quad- and bipolar; single or dual stage; 1 lead	paresthesia	7	50% VAS reduction or 6 on GPE	78	IPG; Quad; 1 lead; paresthesia for dual stage	210 μsec, 85 Hz, 0–10 V versus high/low amplitude
Kemler[23]	Ext; bipolar lead; 1 lead	paresthesia	>7	50% VAS reduction or 6 on GPE	66.7	IPG; C4, T12; Quad	210 μsec, 85 Hz, 0–10 V
Kumar[24]	NE	paresthesia	4–7	"pain relief to avoid heavy analgesics"	100	IPG; C4–C5, T9–T11; IOT; Quad	210–300 μsec, 55–60 Hz, 2.5–5.0 V; cycling mode; 1 min on 15–20 min off, 24 hrs/day, Bipolar combinations
Miles[25]	NA	paresthesia	NA	1	NA	RF; 1 lead; Thoracic	NA
Oakley[26]	Ext; 1 lead	NA	3–7	50% pain relief	100	IPG, RF; Quad; 1 lead; IOT	NA
Robaina[27]	Ext; Lami; quad; unipolar; two-stage procedure in at least 1 pt	paresthesia	10	"acceptable degree of analgesia"	100	C5–C7; Quad, Monopolar, Lami electrodes	50–200 μsec, 80–100 Hz, paresthesia threshold; Bi/Uni-polar stimulation
Robaina[28]	Ext, unipolar, bipolar; C5, 2 leads	paresthesia	15	"acceptable analgesia"	100	NA; NE	50–200 μsec, 80–120 Hz, intensity at paresthesia threshold; 30–60 min 2–5 ×/day
Sanchez-Ledesma[29]	Ext, 1 or 2 lead	100–200 μsec, 80–120 Hz, paresthesia threshold; paresthesia	14	50% pain remission	79.2	IPG, RF	1–4 ×/d for 30 min

C, cervical; Ext, externalized percutaneous lead; Hz, hertz; IPG, internal pulse generator; IOT, intra-operative trial for paresthesia coverage; Lami, surgical laminotomy or laminectomy; NA, not available or not described; NE, not extractable or incomplete information; Paresthesia, paresthesia coverage of affected area; Quad, quadripolar lead; RF, radiofrequency-antenna system; Res, resume/laminotomy lead; T, thoracic; VAS, Visual Analog Scale; V, volts.

for upper extremity CRPS were placed between C2 and T1/2, and leads for lower extremity CRPS were placed between T4/5 and T12. SCS lead placement was performed either under direct vision requiring laminotomy or by percutaneous needle technique. Nine studies reported the use of fluoroscopy to guide lead placement.[15,18,21–24,27–29] Six studies reported the use of intraoperative evaluation and verification of appropriate paresthesia coverage during the surgical implantation.[17,18,20,22,24,26] One study reported SCS lead placement on the ventral dura as well as lead placement in proximity to a cervical nerve root.[20] Another study reported the placement of an intrathecal SCS electrode.[25]

Implanted equipment parameters

A complete or near-complete set of stimulation parameters was provided in 7 studies.[17,18,22–24,27,28] In these studies, pulse width ranged from 50 to 500 microseconds, frequency ranged from 10 to 1500 Hz, and amplitude ranged from 0 to 10 volts. Four studies provided information about the pattern of use of SCS,[20,24,28,29] which varied considerably between studies. None of the studies correlated SCS parameters or pattern of use with any outcome variable.

Follow-up interval

The duration of the follow-up period was reported in 13 studies.[15–17,20–29] The range of average follow-up periods across studies was from 6 to 45.6 months. The actual follow-up interval ranged from 1 to 11 months at the shortest and from 14 to 96 months at the longest. Four studies[19,21–23] reported follow-up assessment at regular intervals (ie, 1, 3, and 6 months). Two of these studies reported long-term (>12 month) follow-up assessment intervals.[19,21] Only 3 studies[16,22,24] reported information about the source of the follow-up data (ie, patient visit, phone interview, or questionnaire) or how follow-up data was collected and analyzed (ie, person blinded to treatment intervention, disinterested third party). Only 1 study[26] explicitly reported the number of patients who received follow-up and the number of patients who dropped out of the study.

Outcomes (Table 4)

Assessment intervals

The length of the follow-up period was reported in 12 studies. The range of average follow-up periods across studies was from 6 to 45.6 months. In general, follow-up intervals were variable in length and inconsistent between studies. Studies that reported the use of regular assessment intervals (ie, 1, 3, and 6 months) did not mention relevant data analysis or discuss any results related to these intervals[19,21,22] with the exception of the 1 RCT.[23] As a result, we were unable to choose a standard follow-up interval for data pooling. Thus, outcome measures were pooled at the end of the follow-up period regardless of length.

Primary outcome measure

Twelve studies reported that VAS was used to measure pain relief.[16–19,21–24,26–29] Nevertheless, only 7 of these studies[17,21–23,26–28] reported baseline VAS, and only 5 of these studies[17,23,26–28] reported VAS at the end of the follow-up period. In these 5 studies, the range of average VAS at the end of follow-up was from 1.3 to 4.5. The range of average baseline VAS values for pain was from 6.7 to 8.3. Four of the 5 studies that reported baseline and end of follow-up VAS used statistical tests to determine significance of the results.[17,21–23] Other than VAS, 2 studies[15,25] used categorical pain rating scales (such as 0 = none, 1 = minimal, 2 = moderate, or 3 = good) to measure pain relief. One study likely used VAS but did not explicitly use the term.[20]

Considerable variability existed in the criteria used to determine the success of SCS. Nevertheless, 12 studies reported that SCS was successful and concluded that SCS was effective therapy for patients with CRPS.[15,17,19–24,26–29] The percentage of patients with CRPS that received successful SCS ranged between 53.7% and 100% in different studies. In 1 study (case report), SCS was reported to be unsuccessful.[25] In 2 studies, the authors' conclusions regarding SCS for CRPS were unclear.[16,18]

Secondary outcome measures

Eleven studies[15,17,20–24,26–29] reported secondary outcome measures that were diverse and inconsistent between studies. Six studies[15,20,21,24,28,29] measured reduction in medication use, and 1 of these studies[21] reported that as many as 44.4% of patients had a 50% reduction in analgesic use. The other 5 studies either failed to quantify or discuss these results. Three studies measured "return to work" as a secondary outcome.[20,21,29] One of these studies reported that 27.2% of patients returned to work,[20] while another study reported that 41% of patients returned to work.[21] The third study failed to discuss the results. One study[27] used photoplethysomography and thermography to measure objective indices that were construed to correlate with physiological disease, and reported improvement in both measures. Two of the 3 studies that measured GPE reported successful improvement (57% and 58% of patients had a GPE of 6, respectively).[22,23] One study measured and reported improvement in the Sickness Impact Profile (SIP).[26] Five studies[23,24,26–28] used the McGill pain questionnaire, and 2 studies[23,26] reported improvement in the McGill pain rating index. Other outcome measures that were used

TABLE 4. *Outcomes*

Study (citation)	Baseline VAS	VAS (range) at end of follow-up	Mean follow-up months (range)	Success rate* (%)	Objective changes in disease	Other outcomes	Authors' conclusions
Barolat[15]	NA	NA	6.6 (3–14)	61.1	Reduction of swelling and subjective temp normalization	AR; pain relief (good, mod, min, none)	Positive for SCS
Barolat[16]	NA	NA	3.8 yrs (6–96)	NE	NA	AR; RTW (NE)	NE (not clear)
Bennett[17]	8.0	4.3	18.7 (11–33)	70	NA	Satisfaction scores; Revision rate	Positive for SCS
	8.2	2.2	23.5 (8–44)	91			
Broggi[18]	NA	NA	NA	75	NA	None	NE (not clear)
Broggi[19]	NA	NA	NA	75	NE	NE	Positive for SCS
Broseta[20]	NA	NA	11.9 (3–20)	72.7	NA	AR; RTW in 27.2% of pts	Positive for SCS
Calvillo[21]	8.2	NE	36	45.3	Thermography (NA)	AR by 50% in 44.4% of pts; RTW 41%	Positive for SCS
Kemler[22]	7.9	5.4 (1–8.4)	32 (6–79)	57	30.4% with functional improvement	57% GPE of 6	Positive for SCS
Kemler[23]	7.1	3.5	6	56	No improvement in functional status, ROM, strength, or progression	58% GPE of 6; improvement in pain-rating index and HRQL (pain component)	Positive for SCS
Kumar[24]	NA	NA	41 (7–89)	100	Self reported improvement in edema and temp	AR	Positive for SCS
Miles[25]	NA	NA	18	0	NA	NA	Not effective
Oakley[26]	6.7	4.5	7.9 (1–26.6)	80	Disease resolution in some patients	QOL (improved SIP and McGill)	Positive for SCS
Robaina[27]	8.3	1.4	27	87.5	Improvement in trophic changes in nails and skin	PPL increase in pulse wave; 4° C increase with Thermography	Positive for SCS
Robaina[28]	7.8	1.33	NA (10–36)	83.2	Improvement in edema, sweating, and skin pigment changes (NA); no improvement in trophic parameters	AR, sleep, and activity (NA)	Positive for SCS
Sanchez-Ledesma[29]	NE	NE	NE	91	Vasomotor improvement incorporated into pain index (NA)	RTW and AR incorporated into pain index (NA)	Positive for SCS

AR, analgesic reduction; GPE, global perceived effect; HRQL, health-related quality of life; NA, not available or not described; NE, not extractable or incomplete information; PPL, photoplethysmography; QOL, quality of life; RTW, return to work; SIP, sickness impact profile; VAS, Visual Analog Scale.

*Success rate as defined by the authors.

included functional status,[23] activity level,[27,28] Health-Related Quality of Life (HRQL),[23] Beck Depression Inventory (BDI),[26] Oswestry Disability Assessment,[26] and improvement in sleep[27,28] or vasomotor function.[29] However, it was unclear how these outcomes were assessed, and studies rarely analyzed or discussed the results of these measurements. The reviewed RCT reported improvement in 1 measure of HRQL (pain component of the Nottingham Health Profile) but no improvement in physical function following SCS.[23]

Complications (Table 5)

Ten studies reported information on the rate and types of complications.[15,17,20–26,28] The reported complications were primarily either biologic or technical and varied greatly among studies. The proportion of patients with at least one complication ranged from 9% to 50%. The infection rate (percentage of patients who developed infection) ranged from 1.4% to 11.1%. The rate of complication due to technical problems (percentage of patients with at least 1 technical problem) such as equipment failure, lead migration, or lost coverage ranged from 8.3% to 42.8%. The rate of reoperation (percentage of patients receiving at least one reoperation) ranged from 11.1% to 50%. Only 1 study[28] specifically mentioned that there was no mortality, and only 2 studies[15,24] specifically mentioned that there was no permanent neurologic injury from the SCS device. None of the

TABLE 5. *Complications*

Study (citation)	Total complications (% of patients)	Biological complications (% of patients)	Equipment complications (% of patients)	Re-operation rate (% of patients)	Trial complications (% of patients)
Barolat[15]	50; M	7.1 (allergy)	42.8	50; M	NA
Barolat[16]	NA	NA	NA	NA	NA
Bennett[17]	40; 11.3	none; 1.4	13.3; none	40; 11.3	NA
Broggi[18]	NA	NA	NA	NA	NA
Broggi[19]	NE	NE	NE	NE	NA
Broseta[20]	9	none	11.1	11.1	NA
Calvillo[21]	20.8	8.3	8.3	20.8	NA
Kemler[22]	50; M	11.1	27.8	50	13
Kemler[23]	25; M	4.2	25; M	25; M	11
Kumar[24]	41.7	none	41.7	41.7	NA
Miles[25]	100	NA	100	100	NA
Oakley[26]	31.6	none	26.3	31.6	none
Robaina[27]	NE	NE	NE	NE	NA
Robaina[28]	16.7	none	16.7	NE	NA
Sanchez-Ledesma[29]	NE	NE	NE	NE	NA

M, multiple complications or procedures for the same patient; NA, not available or not described; NE, not extractable or incomplete information.

studies reported the average duration of time between stimulator placement and reoperation (revision). Two studies[15,23] reported that some patients had multiple complications that required several re-operations. Finally, only 3 studies[22,23,26] reported complication rates (percentage of patients with a complication) for the trial stimulation, which ranged from 0 to 13%.

DISCUSSION

Several recent reviews have suggested that SCS should be incorporated into the treatment algorithm for patients with CRPS.[9,30] However, a systematic review of the efficacy of SCS specifically for patients with CRPS that utilizes EBM guidelines has never been published. Our primary aim was to review the available literature, collate existing evidence, and determine the appropriate level and grade of evidence supporting or refuting the use of SCS for CRPS. The goal of this EBM review was to sufficiently weigh all of the available evidence. Hence, the inclusion criteria were broad to allow evaluation of as many studies as possible.

As with any systematic review, our appraisal of the English literature may not have been comprehensive. Studies with an unfavorable outcome may not have been published, leading to publication bias, and it is also possible that we may have missed important published studies despite our best efforts. Thus, our interpretation and inferences should be considered in the light of these limitations. Our search yielded only 1 RCT supporting the use of SCS in CRPS. In general, this study conformed to the CONSORT[31] recommendations for reporting RCTs and had a good methodological score. The rest of the included studies were observational and descriptive, such as case series or case reports, and were predominantly retrospective designs. The observational studies were of poor methodological quality and failed to consistently report patient demographic information, SCS equipment characteristics, validated outcome measures, and complications. Mention of statistical methods that were used for data analysis was commonly absent, and very few studies reported how follow-up data were obtained or analyzed.

Demographic information was reported with moderate consistency across all the studies. In general, demographic data in these studies was representative of the known demographics of CRPS patients.[30] Unfortunately, none of the studies attempted to assess if the use of patient demographic information could determine appropriateness of patient selection or predict which patients would have a successful trial leading to implantation. However, the authors of the RCT concluded that there was no evidence that the use of SCS early in the course of disease could improve function.

The criteria used to establish the diagnosis of CRPS varied considerably between studies. The lack of a uniform definition for CRPS during the years of publication of the reviewed studies may have been responsible for the variation observed in the criteria used for diagnosis by different investigators. In fact, we acknowledge that time-limited understanding in CRPS taxonomy, nomenclature, and pathophysiology may have influenced the methodological design of these studies. For example, some studies reported that a previous trial and response[24] (negative[21] or transient[23]) to sympathetic block was required prior to the eventual use of SCS. To date, there is little scientific information available to support any one

of these requirements. In fact, it is now commonly understood that only a subset of patients with CRPS has sympathetically maintained pain.[32] Recently, it has been proposed to revise the original IASP diagnostic criteria for CRPS for research purposes to improve disease recognition and facilitate outcomes research.[33,34] Until the revised criteria are validated, and newer guidelines issued, studies should continue to use the original diagnostic criteria published by the IASP. Importantly, the use of sympathetic blockade or the results thereof are not required to establish the diagnosis of CRPS according to current IASP criteria for the diagnosis of CRPS.

In general, equipment characteristics were reported inconsistently and inadequately to draw meaningful conclusions. For example, only one study reported the pattern of SCS use in the trial.[20] In addition, only one study reported that the SCS implantation parameters were similar to and based upon the trial parameters.[21] Furthermore, none of the studies explicitly stated whether the choice of implantation equipment was based on trial equipment or whether anatomic placement of the surgical lead was based on anatomic placement of the trial lead. One study claimed that the length of the stimulation trial had no correlation with outcome.[26] However, no study used statistical methods or appropriate study designs to determine whether SCS characteristics had any effect on the outcomes.

During the period of literature publication for this analysis (1974–2000), SCS device manufacturers have refined their products to improve the pattern of coverage and minimize reoperation due to device (technical) failure. We acknowledge that evolution in the surgical techniques and the SCS equipment technology complicates our analysis of equipment characteristics. Nevertheless, serious inadequacies in equipment reporting and methodological design were pervasive across studies. Consequently, no conclusions can be made regarding whether the introduction and use of more modern SCS equipment (and complex stimulation parameters) was more or less effective compared with more primitive SCS technologies.

The criteria used to determine successful SCS trial varied considerably between studies. Most of the studies used a quantifiable and valid measure of pain intensity or pain relief as the primary outcome measure (such as change in VAS or percentage pain reduction). These outcome measures may have greater utility in light of the fact that it has been demonstrated in RCTs of pharmacological therapies that a change in VAS of three or a reduction in pain intensity of 30% is needed to signify a statistically meaningful and clinically relevant treatment effect.[35] Whether these guidelines are applicable to SCS implantation for treating CRPS is uncertain. Several studies also reported secondary outcome measures. In the observational studies, these measures were non-uniform, lacked appropriate validation, and were reported inconsistently such that firm conclusions cannot be made. However, the RCT reported improvement in the McGill pain rating index and the pain component of the Nottingham Health Profile, which is one way to measure HRQOL. The same study did not report any improvement with regard to functional status, range of motion (ROM), or strength.

The one RCT that was reviewed allowed us to compare the efficacy of SCS for CRPS to other established treatments by calculating the NNT (number needed to treat).[36] Since VAS data could not be extracted for this purpose, we defined the NNT as the number of patients with CRPS treated with SCS to obtain at least 1 patient with a rating of 6 on the GPE scale. Based on this analysis, the point estimate of the NNT for SCS was calculated to be 3.0 (95% CI 1.9–7.0), and this compares to the NNT reported for established pharmacological treatments for neuropathic pain, which ranges between 1.4 and 10 but generally falls between 2 and 4.[37]

Although several studies concluded that SCS was effective for treatment of CRPS, none of the studies evaluated the pattern of use of SCS or the association between use and the signs and/or symptoms of disease. In addition, no study reported reliable information on disease progression or remission after SCS use, which in part reflected the fact that outcomes were not assessed over standardized lengths of time.

Reporting the nature and incidence of complications varied considerably among studies. One study concluded that the revision rate was less for patients with dual octrode configurations (less incidence of failed paresthesia coverage) compared with a single quadrode lead. Reoperation was performed commonly due to biologic and technical problems. None of the studies reported mortality or permanent neurologic injury from the SCS device. In general, the overall complication rate in these studies (9–50%) was comparable to the reported complication rate of SCS for low back pain (20–75%).[38]

REVIEWERS' CONCLUSIONS

Implications for clinical practice

The primary aim of this review was to determine the efficacy of SCS for patients with CRPS. In general, we were able to formulate an answer to this question based on the best available evidence. This evidence included information from 1 experimental study (RCT) and 14 observational studies (case series and case reports). We used the guidelines published by the NHS R&D Center for Evidence-Based Medicine (http://cebm.jr2.ox.ac.uk/docs/levels.html) to determine the validity of the evidence by assigning the level (1a–5) and grade (A–D).

The 14 observational studies received level 4, and the single RCT received level 1b. On the basis of this approach, we conclude that available evidence suggests that SCS is effective for the management of pain for patients with CRPS who did not respond to more conservative medical management (grade B/C).

Definitive conclusions cannot be made with regard to any of the secondary outcome measures, in part due to poor methodological design and in part due to inadequate reporting by the authors. In addition, limited useful information can be extracted from the available studies to help clinicians use SCS in the management of patients with CRPS. For example, no firm conclusions can be drawn regarding which stimulation parameters and devices are most effective, the long-term efficacy of SCS in patients with CRPS, the proper timing of SCS in the treatment algorithm in CRPS, relevant patient clinical or demographic characteristics associated with improved efficacy, or the relationship between the efficacy of SCS and the presence of sympathetic nervous system (SNS) dysfunction or the response to sympathetic blocks.

The secondary aim of this investigation was to examine critically the rationale behind the widespread use of SCS as a therapeutic modality in the management of CRPS. The available evidence, although not of the best quality, does support the use of SCS in refractory cases of CRPS. However, this observation exposes the vital need for evidence of higher quality. The lack of well-designed controlled studies that assess the efficacy of SCS in CRPS seriously undermines the wisdom behind the extensive use of this procedure.

Implications for clinical research

Unfortunately, several other important questions remain unanswered by this review. For example, the following considerations are unknown regarding the use of SCS for CRPS: the underlying mechanism of analgesia, the appropriate timing of the therapy in the treatment algorithm, the long-term efficacy, the effect on the natural course of disease, the prognostic value of sympathetic blocks to determine the effectiveness of SCS, the association of SCS with objective physiological improvements, and the criteria required to determine a successful trial. In addition, it is not clear which stimulation parameters, algorithms, or equipment is more effective for CRPS. Moreover, the cost-effectiveness and therapeutic efficacy of SCS compared with conventional therapies has not been established. Recently, however, an economic evaluation concluded that SCS was more effective at 1-year follow-up and less costly by projection analysis after 3 years compared with a standard treatment protocol for CRPS.[39] Finally, the effect of SCS on secondary outcomes other than pain relief is relatively unknown. RCTs of sufficient power and appropriate methodology are required to answer these questions.

Although the authors of the single RCT and the majority of the non-randomized trials reached similar conclusions regarding the efficacy of SCS, non-randomized studies can exaggerate the estimate of treatment effect by as much as 40%.[40] Accordingly, including non-randomized trials in reviews such as this may lead to erroneous conclusions regarding treatment effect. An additional concern in the evaluation of physical treatment modalities is ensuring the adequacy of blinding since inadequate blinding can lead to an overestimation of treatment effect by as much as 17%.[40] Since SCS is an active treatment whose mechanism of action theoretically is based on counter-stimulation, it is difficult to blind subjects to stimulation or to provide them with an alternative, similarly-looking, sham device that produces paresthesia not associated with pain relief. Administration of sham SCS with imperceptible stimulation does not qualify as a true placebo. In general, the major barrier in performing such trials is in designing the "placebo" component of the study. Moreover, the study patient population should have no prior experience with SCS to avoid bias from knowledge of previous stimulation and possibly its efficacy. In addition, a cross-over design with SCS and a sham intervention may have limited utility since eventually the design itself will lead to exposure of the sham and thus negate adequate blinding. Nevertheless, methods to partially blind subjects by use of sham (inactive) or active (but physiologically ineffective) SCS as control groups and methods to measure the success of adequacy of blinding should be undertaken.[41]

Finally, studies should incorporate valid and reliable measures of primary and secondary outcomes and should incorporate long-term follow-up assessments into the methodology. Outcome measures should include indices of physical function as well as objective measures of physiological disease. In addition, studies should determine whether SCS has a sparing effect on more expensive, invasive, or potentially harmful therapies, such as surgical sympathectomy. Many of the concerns identified in this review were similar to those identified in similar analyses of the efficacy of SCS for chronic low back pain[38] or the efficacy of TENS for chronic pain.[42]

SUMMARY STATEMENT

The goal of this review was to critically examine the literature and collate information regarding the usefulness of SCS for CRPS. Limited evidence exists in the English literature to support or refute the usefulness of SCS in CRPS. A single RCT provides the best supporting evidence to date. It is imperative that the pain management community acknowledge the dearth of vital

information regarding the efficacy of SCS and devise ingenious methodologies to investigate this issue with an aim not only to advance evidence-based pain medicine but also to protect patients.

REFERENCES

1. Stanton-Hicks M, Janig W, Hassenbusch S, et al. Reflex sympathetic dystrophy: changing concepts and taxonomy. *Pain*. 1995;63: 127–133.
2. Shealy CN, Mortimer JT, Reswick JB. Electrical inhibition of pain by stimulation of the dorsal columns: preliminary clinical report. *Anesth Analg*. 1967;46:489–491.
3. Meyerson B, Linderoth B. Spinal cord stimulation. In: Loeser JD, Butler SD, Chapman CR, et al. eds. *Bonica's Management of Pain*. 3rd ed. Philadelphia: Lippincott Williams & Wilkins; 2001:1857–1876.
4. Kemler MA, Reulen JP, Barendse GA, et al. Impact of spinal cord stimulation on sensory characteristics in complex regional pain syndrome type I: a randomized trial. *Anesthesiology*. 2001;95:72–80.
5. Kemler MA, Barendse GA, van Kleef M, et al. Pain relief in complex regional pain syndrome due to spinal cord stimulation does not depend on vasodilation. *Anesthesiology*. 2000;92: 1653–1660.
6. Jivegard LE, Augustinsson LE, Holm J, et al. Effects of spinal cord stimulation (SCS) in patients with inoperable severe lower limb ischaemia: a prospective randomised controlled study. *Eur J Vasc Endovasc Surg*. 1995;9:421–425.
7. North RB, Kidd DH, Lee MS, et al. A prospective, randomized study of spinal cord stimulation versus reoperation for failed back surgery syndrome: initial results. *Stereotact Funct Neurosurg*. 1994;62:267–272.
8. Gybels J, Erdine S, Maeyaert J, et al. Neuromodulation of Pain A consensus statement prepared in Brussels 16–18 January 1998 by the following Task Force of the European Federation of IASP Chapters (EFIC). *Eur J Pain*. 1998;2:203–209.
9. Stanton-Hicks M, Baron R, Boas R, et al. Complex Regional Pain Syndromes: guidelines for therapy. *Clin J Pain*. 1998;14:155–166.
10. Alo K, Yland M, Kramer D, et al. Computer assisted and patient interactive programming of dual octrode spinal cord stimulation in the treatment of chronic pain. *Neuromodulation*. 1998;1:30–45.
11. Barolat G. Experience with 509 plate electrodes implanted epidurally from C1 to L1. *Stereotact Funct Neurosurg*. 1993;61:60–79.
12. Mekhail N, Haider N, Androjna C, et al. Spinal cord stimulation for chronic pain. The Cleveland Clinic experience: a preliminary report. *Reg Anesth Pain Med.* 1999;24:71.
13. Pallares J, Pallares M, Fenollosa P, et al. Treatment of reflex sympathetic dystrophy (r.s.d.) of the upper limb by means of spinal cord stimulation (s.c.s). *Pain.* 1990;(Suppl 5):578.
14. Segal R, Stacey BR, Rudy TE, et al. Spinal cord stimulation revisited. *Neurol Res*. 1998;20:391–396.
15. Barolat G, Schwartzman R, Woo R. Epidural spinal cord stimulation in the management of reflex sympathetic dystrophy. *Stereotact Funct Neurosurg*. 1989;53:29–39.
16. Barolat G, Ketci B, He B. Long-term outcome of spinal cord stimulation for chronic pain management. *Neuromodulation*. 1998; 1:19–29.
17. Bennett D, Alo K, Oakley J, et al. Spinal cord stimulation for complex regional pain syndrome I (rsd). *Neuromodulation*. 1999; 2:202–210.
18. Broggi G, Servello D, Franzini A, et al. Spinal cord stimulation for treatment of peripheral vascular disease. *Appl Neurophysiol*. 1987; 50:439–441.
19. Broggi G, Servello D, Dones I, et al. Italian multicentric study on pain treatment with epidural spinal cord stimulation. *Stereotact Funct Neurosurg*. 1994;62:273–278.
20. Broseta J, Roldan P, Gonzalez-Darder J, et al. Chronic epidural dorsal column stimulation in the treatment of causalgia pain. *Appl Neurophysiol*. 1982;45:190–194.
21. Calvillo O, Racz G, Didie J, et al. Neuroaugmentation in the treatment of complex regional pain syndrome of the upper extremity. *Acta Orthop Belg*. 1998;64:57–63.
22. Kemler MA, Barendse GA, van Kleef M, et al. Electrical spinal cord stimulation in reflex sympathetic dystrophy: retrospective analysis of 23 patients. *J Neurosurg*. 1999;90:79–83.
23. Kemler MA, Barendse GA, van Kleef M, et al. Spinal cord stimulation in patients with chronic reflex sympathetic dystrophy. *N Engl J Med*. 2000;343:618–624.
24. Kumar K, Nath RK, Toth C. Spinal cord stimulation is effective in the management of reflex sympathetic dystrophy. *Neurosurgery*. 1997;40:503–508.
25. Miles J, Lipton S, Hayward M, et al. Pain relief by implanted electrical stimulators. *Lancet*. 1974;1:777–779.
26. Oakley J, Weiner R. Spinal cord stimulation for complex regional pain syndrome: a prospective study of 19 patients at two centers. *Neuromodulation*. 1999;2:47–50.
27. Robaina FJ, Dominguez M, Diaz M, et al. Spinal cord stimulation for relief of chronic pain in vasospastic disorders of the upper limbs. *Neurosurgery*. 1989;24:63–67.
28. Robaina FJ, Rodriguez JL, de Vera JA, et al. Transcutaneous electrical nerve stimulation and spinal cord stimulation for pain relief in reflex sympathetic dystrophy. *Stereotact Funct Neurosurg*. 1989;52:53–62.
29. Sanchez-Ledesma MJ, Garcia-March G, Diaz-Cascajo P, et al. Spinal cord stimulation in deafferentation pain. *Stereotact Funct Neurosurg*. 1989;53:40–45.
30. Galer B, Schwartz L, Allen R. Complex regional pain syndromes—type I: reflex sympathetic dystrophy, and type II: causalgia. In: Loeser JD, Butler SD, Chapman CR, et al. eds. *Bonica's Management of Pain*. 3rd ed. Philadelphia: Lippincott Williams & Wilkins; 2001:388–411.
31. Altman DG, Schulz KF, Moher D, et al. The revised CONSORT statement for reporting randomized trials: explanation and elaboration. *Ann Intern Med*. 2001;134:663–694.
32. Boas RA. Sympathetic nerve blocks: in search of a role. *Reg Anesth Pain Med*. 1998;23:292–305.
33. Bruehl S, Harden RN, Galer BS, et al. External validation of IASP diagnostic criteria for Complex Regional Pain Syndrome and proposed research diagnostic criteria. International Association for the Study of Pain. *Pain*. 1999;81:147–154.
34. Harden RN, Bruehl S, Galer BS, et al. Complex regional pain syndrome: are the IASP diagnostic criteria valid and sufficiently comprehensive? *Pain*. 1999;83:211–219.
35. Farrar JT, Young JP Jr, LaMoreaux L, et al. Clinical importance of changes in chronic pain intensity measured on an 11-point numerical pain rating scale. *Pain*. 2001;94:149–158.
36. Cook RJ, Sackett DL. The number needed to treat: a clinically useful measure of treatment effect. *BMJ*. 1995;310:452–454.
37. Sindrup SH, Jensen TS. Efficacy of pharmacological treatments of neuropathic pain: an update and effect related to mechanism of drug action. *Pain*. 1999;83:389–400.
38. Turner JA, Loeser JD, Bell KG. Spinal cord stimulation for chronic low back pain: a systematic literature synthesis. *Neurosurgery*. 1995;37:1088–1095.
39. Kemler MA, Furnee CA. Economic evaluation of spinal cord stimulation for chronic reflex sympathetic dystrophy. *Neurology*. 2002;59:1203–1209.
40. Schultz KF, Chalmers I, Hayes RJ, et al. Empirical evidence of bias. Dimensions of methodological quality associated with estimates of treatment effects in controlled trials. *JAMA*. 1995;273:408–412.
41. Deyo RA, Walsh NE, Schoenfeld LS, et al. Can trials of physical treatments be blinded? The example of transcutaneous electrical nerve stimulation for chronic pain. *Am J Phys Med Rehabil*. 1990; 69:6–10.
42. Carroll D, Moore R, McQuay H, et al. Transcutaneous electrical nerve stimulation (TENS) for chronic pain. *Cochrane Database Syst Rev.* 2001;CD.03222. Review.
43. Kingery WS. A critical review of controlled clinical trials for peripheral neuropathic pair and complex regional pain syndromes. *Pain*. 1997;73:123–139.