



# Spinal cord stimulation for complex regional pain syndrome: A systematic review of the clinical and cost-effectiveness literature and assessment of prognostic factors

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## Abstract

**Objective:** To review the clinical and cost-effectiveness of spinal cord stimulation (SCS) in the management of patients with complex regional pain syndrome (CRPS) and identify the potential predictors of SCS outcome.

**Design:** Systematic review of the literature and meta-regression.

**Methods:** Electronic databases were searched for controlled and uncontrolled studies and economic evaluations relating to the use of SCS in patients with either CRPS type I or II.

**Results:** One randomised controlled trial, 25 case series and one cost-effectiveness study were included. In the randomised controlled trial in type I CRPS patients, SCS therapy lead to a reduction in pain intensity at 24 months of follow-up (mean change in VAS score  $-2.0$ ), whereas pain was unchanged in the control group (mean change in VAS score  $0.0$ ) ( $p < 0.001$ ). In the case series studies, 67% (95% CI 51%, 84%) of type I and type II CRPS patients implanted with SCS reported pain relief of at least 50% over a median follow-up period of 33 months. No statistically significant predictors of pain relief with SCS were observed in multivariate meta-regression analysis across studies. An economic analysis based on the randomised controlled trial showed a lifetime cost saving of approximately €58,470 (US\$60,800) with SCS plus physical therapy compared with physical therapy alone. The mean cost per quality-adjusted life-year at 12-month follow-up was €22,580 (US\$23,480).

**Conclusions:** SCS appears to be an effective therapy in the management of patients with CRPS type I (Level A evidence) and type II (Level D evidence). Moreover, there is evidence to demonstrate that SCS is a cost-effective treatment for CRPS type I.

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**Keywords:** Complex regional pain syndrome; Regression; Spinal cord stimulation; Systematic review

## 1. Introduction

Complex regional pain syndrome (CRPS) is a condition characterised by extreme pain (neuropathic or noci-

ceptive) and dysfunction of the sympathetic nervous system in one region of the body, usually an extremity (Harden, 2001). CRPS encompasses two distinct conditions: CRPS type I (previously called reflex sympathetic dystrophy) and CRPS type II (causalgia). Reflex sympathetic dystrophy and causalgia were renamed as CRPS because this term more adequately describes both conditions as having varied clinical features (complex),

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usually involving a specific region of the body (regional) and involving pain as the primary diagnostic symptom (pain) (Stanton-Hicks et al., 1998). The International Association for the Study of Pain (IASP) has defined CRPS type I based on the following clinical findings: regional pain, sensory changes, abnormality of temperature, sudomotor activity and skin colour, oedema and onset after a noxious event (Merskey and Bogduk, 1994). CRPS type II includes all of the above plus peripheral nerve lesion (Merskey and Bogduk, 1994). Many patients with CRPS will also experience tremor, dystonia and weakness in the affected limb (Stanton-Hicks et al., 1998).

Figures from Sweden indicate an incidence (hospitalised patients) of 40–80 cases of CRPS type I per year between 1990 and 1993 and 27–40 cases of CRPS type II per year in this same period (national population 8.6 million) (Stanton-Hicks et al., 1998). Based on these numbers, CRPS can be seen as a relatively rare yet significant medical condition (Stanton-Hicks et al., 1998). In the USA, the incidence of CRPS appears to be increasing, although this may be due to increased reporting of the condition encouraged by personal injury lawyers (Harden, 2001).

Current treatments for CRPS are primarily focused on restoration of function. Recognised therapies include a combination of pharmacotherapy, nerve blocks and psychotherapy where appropriate (Harden, 2001). In patients who experience symptoms that prevent function-restoring therapy such as severe allodynic pain or fear of movement of the affected limb, additional therapies can be proposed (Harden, 2001).

This interdisciplinary approach is supported by a recently published algorithm to optimise the treatment of CRPS, proposed by Stanton-Hicks et al. (2002) in an update to the current guidelines. This algorithm integrates rehabilitation with psychological treatment and interventional pain management as required throughout the course of therapy. This concurrent use of physical therapy, pain management and psychotherapy should facilitate the patient's progression through the stages of rehabilitation (Stanton-Hicks et al., 2002).

Patients who fail to progress with physical therapy may require additional or more aggressive pain therapy, such as spinal cord stimulation (SCS) (Stanton-Hicks et al., 2002). SCS, a neurostimulation therapy, offers an alternative treatment for chronic pain in cases when less invasive procedures have failed or are contraindicated. SCS therapy has been available since the 1970s and has grown in acceptance over the past three decades for the treatment of many types of non-malignant pain (Barolat and Sharan, 2000). It is based on the Gate Theory, introduced by Melzack and Wall in 1965, which suggests that stimulation of large afferent fibres can inhibit pain transmission at the level of the dorsal horns (Melzack and Wall,

1965). More recent studies indicate that SCS releases substance P, serotonin, noradrenaline, glycin and GABA in the dorsal horns; activation of the GABA-B receptor may be linked to a decrease in the release of glutamate and other excitatory amino acids, resulting in a decrease of neuropathic pain. SCS may also suppress sympathetic activity (Linderoth and Meyerson, 2002). As the pain syndrome in CRPS is related to sympathetic overactivity, SCS could induce pain relief and decrease sympathetic overactivity.

SCS is performed using an implantable pulse generator connected to leads with electrodes positioned in the dorsal epidural space, which are then used to stimulate the ascending and descending dorsal column fibres and/or dorsal root fibres to achieve paresthesia covering the area of pain (Holsheimer and Barolat, 1998). If a positive response to an initial trial period is demonstrated, surgical implantation of the SCS hardware is performed.

CRPS is the second-largest indication for the use of SCS in the USA, and high success rates (up to 70%) in pain relief have been reported in CRPS patients treated with neurostimulation (i.e. SCS or peripheral nerve stimulation) when properly selected (Stanton-Hicks et al., 1998; Barolat and Sharan, 2000).

The purposes of this paper are to undertake a systematic literature review of the clinical and cost-effectiveness literature of use of SCS in the management of CRPS and to examine the potential predictors of outcome following SCS.

## 2. Methods

### 2.1. Search strategy

Several electronic databases were searched for studies relating to the use of SCS in CRPS: Medline, CINAHL, EMBASE, Cochrane Database of Systematic Reviews, Cochrane Controlled Trials Register, the NHS Centre for Reviews and Dissemination HTA database; on-going trials register (e.g. National Research Register, MRC Clinical Trials Register, US National Institutes of Health Clinical Trials Register); specialist economic databases (NHS Centre for Reviews and Dissemination Economic Evaluation Database and Health Economics Evaluation Database).

The searches were conducted up to 1 January 2002. Search terms were selected in order to maximise both the sensitivity and specificity of the search. There was no language restriction. The reference lists in studies and reviews meeting the inclusion criteria were hand searched for further studies. Experts in the field were contacted to identify any studies that may have been missed, or any ongoing or unpublished research.

## 2.2. Inclusion criteria

### 2.2.1. Study design

Although widely accepted that randomised controlled trials provide 'gold standard' evidence of the effectiveness of therapies, non-randomised and uncontrolled studies were also sought in this review to enable exploration of the factors that may predict SCS outcome.

### 2.2.2. Population

Studies including patients diagnosed with CRPS type I or type II were included in the review.

### 2.2.3. Intervention

The intervention performed must have included unilateral or bilateral SCS, either as a single therapy or in combination with other therapies for studies to be included in the review. Studies of subdural SCS were not included, as this technique does not represent current practice.

### 2.2.4. Outcomes

Outcome data reflecting both the benefits and adverse effects of SCS were considered, i.e. pain relief, analgesic consumption, return to work, functional disability, health-related quality of life, patient satisfaction/preference, complications and health service utilisation. Studies assessing healthcare utilisation (e.g. drug usage and physician consultations) and/or costs of SCS were also included.

## 2.3. Exclusion criteria

Studies were excluded from the review if they reported only technical outcomes (i.e. device settings or stimulation protocols), were mixed case series reporting only aggregated results (rather than reporting by indication) or were multiple reports that included results of same patient case series. In the latter instance, only the study with the largest series was included. Single case reports were also excluded.

## 2.4. Study selection

Study selection was carried out independently by two reviewers using a standardised inclusion and exclusion form. Information was extracted from the papers by a single reviewer based on a standardised data extraction form.

## 2.5. Quality assessment

Quality assessment was undertaken by a single reviewer based on a standardised form. Controlled trials were assessed using a modified version of the Jadad

checklist for assessing bias within clinical trials (Jadad et al., 1998). As there is no accepted instrument for or standard approach to the assessment of the quality of case series, a quality-assessment tool was specifically developed for this review, adapted from previously used checklists (Hyde et al., 2002; Wake et al., 2002). This assessment tool was intended to capture information relevant to the four principle categories of study bias: selection bias (i.e. were the baseline characteristics of the intervention and control groups the same?); attrition bias (i.e. was there acceptable loss of patients at follow-up?); performance bias (other than the intervention were the groups treated in the same way?); and detection bias (i.e. were outcomes assessed by a blinded [or independent] assessor in a prospective way using validated outcome measures?) (Clarke and Oxman, 2001). The methodological quality of economic studies was assessed using the *British Medical Journal* guidelines (Drummond and Jefferson, 1996). Based on methodological quality, the evidence was formally graded (Harbour and Miller, 2001 and Appendix 1).

## 2.6. Data handling and analysis

Results of experimental and observational study designs are reported separately. Given the potential limitation of pooling observational studies a conservative random-effects model was used to combine results across case series studies (DerSimonian and Laird, 1986; Egger et al., 1997). Pooling of continuous outcomes, for example pain visual analogue scale (VAS) score, was performed where both a mean and a standard deviation (SD) was reported.

The extent to which study and patient related factors (subgroups) were associated with pain outcome following SCS was analyzed using meta-regression methods (Egger et al., 1997). Eight study level subgroups were defined pre hoc: patient age and sex; type of CRPS (type I versus type II); duration of CRPS; country and years of data collection and publication and overall methodological quality score.

Data are expressed as either the mean with 95% confidence interval (CI) or median with the range. All analyses were performed using Stata v.6 (Stata Corp., College Station, TX, USA).

## 3. Results

In total, one randomised controlled trial, 25 case series and one economic evaluation met the inclusion criteria of this review. The most common reason for exclusion of studies was the reporting of outcomes not disaggregated by indication. Other reasons for exclusion included reporting of only technical outcomes, inappropriate indication, inappropriate outcomes, reporting of

a case report and unobtainable publication. A good level of agreement on inclusion of studies was obtained between reviewers (Kappa score for agreement: 0.81, 95% CI 0.71, 0.91).

### 3.1. Randomised controlled trial

The randomised controlled trial of SCS in the treatment of CRPS was carried out in a single centre in The Netherlands during 1997–1998 by Kemler et al. (2000a, 2001). Patients with CRPS type I with symptoms of at least 6 months' duration were randomised (2:1) to either an 'experimental' group ( $n = 36$ ), receiving SCS plus physical therapy, or a control group ( $n = 18$ ), receiving physical therapy alone. Patients were followed up for up to 6 months. The outcomes assessed were pain, functional capacity, quality of life and complications. After 6 months, patients were allowed to cross over and observational follow-up continued to 24 months.

The trial appeared to be well conducted and had a Jadad score of 3 out of a maximum of 5. This trial was not blinded but, as it is accepted that blinding of both caregivers and patients in neurostimulatory interventions is not possible because the patients will know by the presence of paresthesia that the stimulator is switched on, this was not considered an appropriate criterion to apply. The absence of outcome blinding in this study was considered unlikely to be a substantial source of assessment bias, as the majority of outcomes involved patient self-assessment. The assessment of levels of selection, performance, detection and attrition bias are given in Table 1.

There were no significant differences in baseline demographic and clinical characteristics between groups, with the exception of sex and age. In the experimental group, 39% of patients were males, compared

with 17% in the control group. The mean age was 35 years (SD 8 years) in the experimental group and 40 years (SD 12 years) in the control group.

In this study, SCS therapy led to a reduction in pain intensity, the primary cause of distress for patients, at 12 months of follow-up (mean change in VAS score  $-2.7$ ), whereas pain increased in the control group (mean change in VAS score  $+0.4$ ), and this difference was statistically significant ( $p < 0.001$ ) (Table 2). The result was similar in the intention-to-treat analysis: mean change in VAS score  $-2.4$  for the SCS plus physical therapy group versus  $0.2$  for the physical therapy group ( $p < 0.001$ ).

No significant difference in functional capacity (Jebesen hand assessment) was observed between the two treatment groups.

In the SCS plus physical therapy group, the overall health-related quality-of-life score improved by a mean of 6 (SD 22), which was greater than the improvement with physical therapy alone (mean 3; SD 18), although the difference was not significant ( $p = 0.58$ ) (Table 2).

Six of the 36 patients receiving SCS plus physical therapy experienced complications ( $n = 11$ ) at 6 months but only one complication (infection) was reported at 12 months.

A 2-year follow-up results of this trial have recently been published and demonstrate that the benefits in pain outcome were maintained (VAS mean change  $-2.1$  versus  $0.0$  cm,  $p < 0.001$ ) as well as the improvement in health related quality of life with SCS. A total of 9 of the 24 patients (38%) experienced 22 complications needing operation during the 2-years after implantation (Kemler et al., 2004). None of these complications were associated with neurological or other severe adverse sequelae.

The authors of this study reported that there were no factors other than treatment allocation that influenced the treatment effect.

Table 1  
Assessment of study quality: randomised controlled trial (SCS for Type I CRPS) by Kemler et al. (2000a, 2001)

Possible bias	Assessment of impact
Selection bias and confounding	Not present
Randomisation	Randomisation undertaken by computer-generated means
Allocation concealment	Allocation concealed from study investigators
Performance bias	Unlikely
Groups treated equivalently (excluding the comparison in question)	Standard protocol of physical therapy applied to both groups; however, details of other therapies, such as drug therapy, not discussed
Detection bias	Unlikely
Observer blinding	Not stated
Validated outcomes	Yes
Attrition bias	Not present
Loss to follow-up $\leq 20\%$	No loss to follow-up reported; intention-to-treat analysis performed; 'per implant' analysis also performed
Jadad score	3/5

Table 2

Main results of the randomised controlled trial (SCS for Type I CRPS) and associated cost analysis by Kemler et al. (2000a, 2001, 2002)

Parameter	SCS + PT (n = 36)	PT alone (n = 18)	p value
Change in mean pain VAS score (6 months) ± SD	-2.4 ± 2.5	0.2 ± 1.6	<0.001 <sup>a</sup>
Health-related quality-of-life score (6 months) ± SD	6 ± 22	3 ± 18	0.58
Change in mean VAS score (12 months) ± SD	-2.7 ± 2.8	0.4 ± 1.8	<0.001 <sup>a</sup>
Utility score (EQ-5D) (12 months) ± SD	0.22 ± 0.33	0.03 ± 0.13	0.004 <sup>a</sup>
Cost per patient (12 months)	€9805	€5741	
Lifetime cost saving per patient over PT alone	€58,466		
Mean cost per quality-adjusted life-year	€22,582		

SCS, spinal cord stimulation; PT, physical therapy.

<sup>a</sup> Statistically significant.

### 3.2. Case series

In the 25 case series (Nielsen et al., 1975; Broseta et al., 1982; Mundinger and Neumuller, 1982; Ray et al., 1982; Barolat et al., 1989; Robaina et al., 1989a,b; Sanchez-Ledesma et al., 1989; Devulder et al., 1990, 1991; Pallares et al., 1990; Spiegelmann and Friedman, 1991; Kumar et al., 1991, 1996, 1997, 1998; Shimoji et al., 1993; Hassenbusch et al., 1995; Spincemaille et al., 1995; Calvillo et al., 1998; Bennett et al., 1999; Kemler et al., 2000b; Oakley, 1999; Dario et al., 2001; Kay et al., 2001; Kim et al., 2001) that were included in this review, there were a total of 500 patients with type I or II CRPS. The majority of case series were single-centre studies of relatively small sample size and were conducted and reported in the past 10 years. All studies reported pain relief together with a range of other outcomes. The characteristics of these studies are given in Table 3. Detailed tabular summaries of the characteristics and quality of individual studies are available from the first author.

The overall quality of the case series was judged to be poor (Table 4), with a median overall quality score of 2 (range 0–4) on a 0–7 scale. Few studies provided details of the selection of patients included in their series, potential co-interventions received (e.g. drug therapy), methods of outcome assessment (e.g. blinding, use of validated outcomes) or losses to follow-up.

On average, 67% (95% CI 51%, 84%) of implanted patients with CRPS who received SCS achieved pain relief of at least 50%. Seven of the case series studies (Robaina et al., 1989a,b; Spincemaille et al., 1995; Calvillo et al., 1998; Bennett et al., 1999; Kemler et al., 2000b; Oakley, 1999) assessed pain reduction using the VAS score. In these studies, there was a significant reduction in VAS score following SCS; the pooled mean reduction of VAS score was 4.7 (95% CI 3.4, 6.0).

Functional capacity was reported in three studies (Robaina et al., 1989a,b; Oakley, 1999), using the Oswestry Questionnaire, the McGill Pain Questionnaire or both. There appeared to be improvement across all scales

Table 3

Characteristics of case series

Characteristic	Median (range)	Frequency (%)
Average <sup>a</sup> age (years)	47 (32–64)	–
Sex (% male)	51 (18–85)	–
Duration of pain (years)	5.7 (0.33–14.5)	–
Sample size		
Patients tested <sup>b</sup>	16 (3–42)	–
Patients implanted	20 (1–189)	–
Duration of follow-up (months)	33 (1–87)	–
Year of study publication <sup>c</sup>	1992 (1975–2001)	–
Year of data collection <sup>c</sup>	1986 (1972–1997)	–
Indications <sup>a</sup>		
CRPS type I	–	12 (48)
CRPS type II	–	8 (32)
Both CRPS type I and type II	–	5 (20)
Country of data collection		
USA and Canada	–	12 (48)
Europe	–	10 (40)
Other	–	1 (4)
Not reported	–	2 (8)
Non-English language studies	–	1 (4)
Study setting		
Single center	–	11 (44)
Multicenter	–	1 (4)
Not reported	–	13 (52)
Type of series		
Mixed	–	16 (64)
CRPS only	–	9 (36)
Outcomes reported <sup>d</sup>		
Pain relief	–	25 (100)
Functional capacity	–	5 (20)
Quality of life	–	2 (8)
Drug utilisation	–	1 (4)
Patient satisfaction/preference	–	0
Return to work	–	1 (4)
Complications	–	11 (44)

<sup>a</sup> Age reported in some studies as mean and in others as median.<sup>b</sup> Reported in only nine case series.<sup>c</sup> Middle year and range given.<sup>d</sup> Outcomes often not reported in usable form.

and subscales following SCS implantation (Table 5). Variations in reporting of these outcomes between studies precluded any pooling of these data.

Table 4  
Assessment of bias: case series

Possible biases	Frequency, <i>N</i> (%)		
	Yes	No	Not reported
<b>Selection bias</b>			
Consecutive or representative sample	1 (4)	–	24 (96)
<b>Performance bias</b>			
Absence of co-interventions	–	10 (40)	15 (60)
<b>Detection bias</b>			
Prospective or before/after study	3 (12)	22 (88)	–
Blinded or independent assessment	3 (12)	1 (4)	21 (84)
Validated/objective outcomes	10 (40)	15 (60)	–
<b>Attrition bias</b>			
Loss to follow-up $\leq 20\%$	11 (44)	1 (4)	13 (52)

Two of the case series (Spincemaille et al., 1995; Oakley, 1999) assessed health-related quality of life, one using the Sickness Impact Profile and one using the Nottingham Health Profile. Both studies reported significant improvements in health-related quality of life (Table 6). No case series were identified that reported the level of patient satisfaction or work status following SCS.

Complications in CRPS following SCS were reported in eight of the studies (Barolat et al., 1989; Robaina

et al., 1989b; Spincemaille et al., 1995; Kumar et al., 1997; Calvillo et al., 1998; Bennett et al., 1999; Kemler et al., 2000b; Oakley, 1999). Overall, in these eight studies, 33.0% (22/66) of patients reported at least one complication with SCS. The majority of complications were related to electrode issues (20% of patients), infections (4% of patients), generator issues (2% of patients) or extension cable issues (1% of patients). A further 6% of patients had other complications such as haematomas. No neurological complications were reported in any of the studies, and none of the complications were considered to be serious.

Four case series (Bennett et al., 1999; Kumar et al., 1996; Shimoji et al., 1993; Burchiel et al., 1993) in CRPS included subgroup analyses (Table 7). The subgroup analyses done in these studies indicated that better outcomes were achieved with dual versus single leads (Bennett et al., 1999), better psychological and functional status patients (Burchiel et al., 1993), shorter time from first operation to implant (Kumar et al., 1996) and younger age of patients (Kumar et al., 1996). Outcome was also seen to be associated with the site of electrode placement. Despite these results, there were no consistent predictors across the four studies. Univariate regression analysis across all studies indicated the type of CRPS patients to be a predictor ( $p = 0.005$ ) of SCS success [i.e. on average a greater proportion of pain

Table 5  
Functional capacity of CRPS before and after SCS implantation in case series

Study	<i>N</i>	Questionnaire	Outcome measure	Mean (SD)	
				Before	After
Oakley (1999)	16	McGill-Melzack Pain Questionnaire	Pain rating index	32.97 (NR)	19.18 <sup>a</sup> (NR)
			Number of words chosen	14.2 (NR)	8.09 <sup>a</sup> (NR)
				0.40 (NR)	0.27 <sup>a</sup> (NR)
Robaina (1989a)	6	Oswestry McGill-Melzack Pain Questionnaire	Present pain intensity	14.5 (3.3)	13.8 (3.1)
			Pain rating index	29.1 (10.5)	1.7 <sup>a</sup> (5.8)
			Number of words chosen	12.3 (5.6)	6.8 <sup>a</sup> (2.4)
Robaina (1989b)	8	McGill-Melzack Pain Questionnaire		12.1 (5.1)	6.6 <sup>a</sup> (2.3)

NR, not reported.

<sup>a</sup> Significant reduction ( $p \leq 0.05$ ).

Table 6  
Health-related quality of life (HRQoL) in patients with CRPS before and after SCS in case series

Study	Profile	<i>N</i>	HRQoL domain	Mean (SD)	
				Before	After
Oakley (1999)	Sickness Impact Profile	16	Physical	16.83 (NR)	6.99 <sup>a</sup> (NR)
			Psychosocial	10.07 (NR)	8.68 <sup>a</sup> (NR)
			Total	20.31 (NR)	10.91 <sup>a</sup> (NR)
Spincemaille (1995)	Nottingham Health Profile	NR	Pain	100.0 (NR)	26.0 <sup>a</sup> (NR)
			Mobility	66.0 (NR)	43.7 <sup>a</sup> (NR)
			Energy	63.2 (NR)	24.0 <sup>a</sup> (NR)

NR, not reported.

<sup>a</sup> Significant reduction ( $p \leq 0.05$ ).

Table 7  
CRPS and SCS within-case study subgroup analysis

Study	Subgroup(s)	Outcome measure	Analysis method	Conclusions
Bennett (1999)	Two types of stimulator	Pain VAS score	Stratified design	Dual leads are better than single leads
Burchiel (1993)	Psychological and functional measures	>50% pain relief	Correlation/multiple regression	Both factors predict pain relief (regression equation provided)
Kumar (1996)	Number of operations; time between first operation and implant; age; sex	>50% pain relief; pre-implant work status	Cross tabulations	More operations, shorter time from first operation to implant, younger age and no depression are all associated with better outcomes; also no association with pre-implant work status
Shimoji (1993)	Sex; site of electrode placement	>50% pain relief	Chi-squared test	Sex is not significant, but site of placement is ( $p < 0.05$ )

relief with SCS type was experienced in the case series of CRPS type II patients (mean 69%) compared to those case series with type I CRPS patients (mean 51%)] (Table 8). However, no predictors were found to be statistically significant in the multivariate analysis.

### 3.3. Cost-effectiveness

One well-conducted economic analysis of SCS in the treatment of CRPS, based on the randomised controlled trial of Kemler et al. (2000a, 2001) was identified. This study included both patient and health service costs at 12 months follow-up and an extrapolation (using decision analysis modelling) of these costs over the lifetime of a patient (Table 2) (Kemler and Furnee, 2002). The authors reported that although the costs for SCS plus physical therapy (€9805/patient, US\$10,200/patient at 1998 exchange rate of 1.04) exceeded those of physical therapy alone (€5741/patient, US\$6,000/patient) at 12 months, this difference was reversed over a lifetime analysis. Over a lifetime period there was a cost saving of approximately €58,470 (US\$60,800) with SCS plus physical therapy compared with control patients, although the lifetime costs excluded patient costs as the investiga-

tors reported them as 'low' and not different between the two groups.

The authors of this study concluded that the clinical benefits of SCS plus physical therapy are greater than physical therapy alone, and the lifetime costs are less, making SCS plus physical therapy a 'dominant' therapy.

A cost utility analysis at 1 year of follow-up was also performed, based on EQ-5D quality-of-life utility index (Table 2) (Kemler et al., 2000a, 2001; Kemler and Furnee, 2002). Although patients were allowed to cross over at 6 months in this study, the 12-month cost analysis was based on intention-to-treat, so patients were assessed according to their initial therapy. There was a significant difference between the utility index for patients assigned to SCS and physical therapy at baseline (0.21) and at 12 months (0.43), with a gain of 0.22 ( $p < 0.002$ ) (Table 2). For control patients, the score was 0.19 at baseline and 0.22 at 12 months, a gain of only 0.03 ( $p =$  not significant). Thus, the incremental utility gain for SCS plus physical therapy versus physical therapy alone was +0.19 ( $p = 0.004$ ). The corresponding mean cost per quality-adjusted life-year was approximately €22,580 (US\$23,480) (Table 2).

Table 8  
Between-study subgroup analysis of CRPS case series

Characteristic	Univariate value		Multivariate value	
	Mean (95% CI)	<i>p</i> value	Mean (95% CI)	<i>p</i> value
Average age (years)	-0.71 (-3.49, 2.05)	0.587	-1.61 (-3.91, 0.75)	0.157
Sex (% male)	0.15 (-0.90, 1.20)	0.767	0.23 (-0.94, 2.40)	0.447
Duration of pain	2.00 (-9.31, 13.33)	0.608	<sup>b</sup>	
Duration of follow-up (months)	0.39 (-0.16, 0.95)	0.155	<sup>b</sup>	
Year of study publication	1.81 (-0.18, 3.80)	0.07	1.82 (-0.43, 4.09)	0.100
Year of data collection	1.67 (-2.80, 6.13)	0.396	<sup>b</sup>	
Indications	24.12 (8.25, 40.1)	0.005	10.42 (-1.90, 40.74)	0.07
Country of data collection	5.48 (-19.64, 30.59)	0.65	<sup>b</sup>	
Study setting	<sup>a</sup>		<sup>b</sup>	
Quality score	11.34 (-1.16, 23.85)	0.07	2.77 (-20.24, 14.87)	0.733

<sup>a</sup> Not computable.

<sup>b</sup> Insufficient cases to be entered into multivariate mode.

#### 4. Discussion

This review of the literature identified one randomised controlled trial of SCS in the treatment of CRPS, 25 case series studies and one economic evaluation.

The randomised controlled trial reported a significant long-term benefit of SCS plus physical therapy over physical therapy alone for pain relief in CRPS type I. The main criticism of this trial has been that the comparator treatment (physical therapy alone) may not reflect best practice (Claeys, 2000). However, the use of physical therapy alone for the treatment of CRPS is supported by current guidelines (Stanton-Hicks et al., 2002). Economic analysis from this randomised controlled trial indicated a cost per quality-adjusted life-year (QALY) for SCS of €22,580 (US\$23,480), a value consistent with an acceptable cost-effectiveness (Bryan et al., 2002; Taylor et al., 2004).

Data from the case series included in the review demonstrate the consistent benefit of SCS for CRPS. On average, 67% (95% confidence interval: 51% to 84%) of implanted patients experienced at least 50% pain relief. Although approximately 33% of patients in these studies experienced complications with SCS, no serious adverse sequelae were reported.

##### 4.1. Comparison with other reviews

A number of reviews of the role of SCS in the management of CRPS have been written. Recently three systematic reviews (i.e. included an explicit statement of their literature search strategy) have been published (Grabow et al., 2003; Cameron, 2004; Turner et al., 2004). Because of more restrictive electronic biographic searches, exclusion of foreign language studies, and limitations to studies of a given sample size or follow-up, all were less comprehensive in their evidence identification and inclusion than the present systematic review. None of the previous reviews considered economic consequences of SCS and the study by Turner and colleagues (2004) only included one case series study. Nevertheless, the conclusions and implications of the previous reviews are broadly concordant with the present study (see below).

##### 4.2. Potential limitations of this review

Any review of case series can be affected by publication bias towards positive results and benefits. However, this review was designed to incorporate procedures that would minimise such bias. Where possible, efforts were made to identify case series that included the same patients, and any duplicate reports were excluded. In addition, all relevant results that were available in study

reports were sought, not just those highlighted by the study authors.

The greatest limitation of this review was the relatively small amount of high-quality evidence (only one randomised controlled trial was found). Although 25 case series were identified, the majority of these were poorly conducted. In many of these, only selected outcomes were reported, with the possibility of introducing bias.

Finally, not all studies reported key outcomes in the same way, and not all reported the same outcomes, making direct comparisons difficult.

##### 4.3. Implications for policy

The data from the randomised controlled trial and the economic analysis of this trial support the conclusion that SCS, combined with physical therapy, is both clinically effective and cost effective for the treatment of patients with CRPS type I (Level A evidence, see Appendix). Interestingly, only two of the case series in this review (Bennett et al., 1999; Kim et al., 2001) included only patients with CRPS type I. The majority of the case series focused on CRPS type II (Level D evidence, see Appendix). Notwithstanding the diagnostic difficulties in differentiation of CRPS type I and II, until a similar level of evidence in type II patients is available, caution should be applied in the routine use of SCS in this indication.

Current guidelines for the management of CRPS (Stanton-Hicks et al., 2002) recommend that the routine use of SCS should be applied to patients with CRPS who have failed previous medical (i.e. pharmacological) therapy. The entry criteria for the randomised controlled trial and the majority of case series were in line with these guidelines. Current guidelines (Gybels et al., 1998; Stanton-Hicks et al., 2002) also recommend that patients considered for SCS must be psychologically appropriate, and should have responded well to a test period of neurostimulation prior to permanent implantation.

##### 4.4. Implications for further research

The majority of studies identified for this review were case series. Although providing a poor level of evidence for demonstrating efficacy of SCS, case series can be used to explore the factors that may influence the treatment effect (Guyatt et al., 1995). Given the likelihood that clinicians will continue undertake case series, it is of great importance that the conduct and reporting of such future studies improve. Areas in which improvement is warranted are recruitment of consecutive patients, assessment of outcomes using independent assessors, better reporting of methodology and the complete reporting of



results for all outcomes, including adverse events and/or complications. In addition, for those case series that recruit for more than one patient indication, results should be reported for each indication separately.

In order to provide high-quality evidence, a randomised controlled trial of SCS in the management of CRPS type II is needed.

## 5. Conclusion

SCS appears to be an effective therapy in the management of patients with CRPS type I (Level A evidence) and type CRPS II (Level D evidence). Moreover, there is evidence to demonstrate that SCS is a cost-effective treatment for CRPS type I.

## Declaration of interests

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## Appendix

### Levels of evidence:

- 1++ High quality meta-analyses, systematic reviews of RCTs, or RCTs of very low risk of bias.
- 1+ High quality meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias.
- 1– Meta-analyses, systematic reviews of RCTs, or RCTs with high risk of bias.
- 2++ High quality systematic reviews of case-control or cohort studies. High quality case-control or cohort studies with a very low risk of confounding, bias, or chance and a high probability that the relationship is causal.

- 2+ Well-conducted case-control or cohort studies with a low risk of confounding, bias, or chance and a moderate probability that the relationship is causal.
- 2– Case-control or cohort studies with a high low risk of confounding, bias, or chance and significant risk that the relationship is causal.
- 3 Non-analytic studies, e.g. case reports, case series.
- 4 Expert opinion.

### Grades of recommendation:

- A At least one meta-analysis, systematic review, of RCT rated as 1++, and directly applicable to the target population, or a systematic review of RCTs or a body of evidence rated as 1+, directly applicable to the target population, and demonstrating overall consistency of results.
- B A body of evidence rated as 2++, directly applicable to the target population, and demonstrating overall consistency of results or extrapolated evidence from studies rated as 1++ or 1+.
- C A body of evidence rated as 2+, directly applicable to the target population, and demonstrating overall consistency of results or extrapolated evidence from studies rated as 2++.
- D Evidence level 3 or 4, or extrapolated evidence from studies rated as 2+.

From Harbour and Miller, 2001.

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