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Systematic Literature Review

A Systematic Review of Economic Evaluations Reporting the Cost-Effectiveness of Spinal Cord Stimulation

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ABSTRACT

Objectives: Spinal cord stimulation (SCS) is a recognized treatment for chronic pain. This systematic review aims to assess economic evaluations of SCS for the management of all chronic pain conditions, summarize key findings, and assess the quality of studies to inform healthcare resource allocation decisions and future research.

Methods: Economic evaluations were identified by searching general medical and economic databases complemented with screening of reference lists of identified studies. No restrictions on language or treatment comparators were applied. Relevant data were extracted. The quality of included studies was assessed using the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) checklist.

Results: Fourteen studies met the inclusion criteria and were judged to be of acceptable quality. Economic evaluations assessed SCS for the management of refractory angina pectoris, failed back surgery syndrome (FBSS), complex regional pain syndrome (CRPS), diabetic peripheral neuropathy (DPN), and peripheral arterial disease. Model-based studies typically applied a 2-stage model, i.e. decision tree followed by Markov model. Time horizon varied from 1 year to lifetime. Cost-effectiveness ranged widely from dominant (SCS cost-saving and more effective) to incremental cost-effectiveness ratio of >£100,000 per quality-adjusted life-year. Cost-effectiveness appeared to depend on the time horizon, choice of comparator, and indication. Ten of the studies indicated SCS as cost-saving or cost-effective compared with the alternative strategies.

Conclusion: The results consistently suggest that SCS is cost-effective when considering a long-term time horizon, particularly for the management of FBSS and CRPS. Further studies are needed to assess the cost-effectiveness of SCS for ischemic pain and DPN.

Keywords: chronic pain, full economic evaluations, spinal cord stimulation, systematic review.

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Introduction

Chronic pain imposes a significant economic burden. The cost of back pain alone has been estimated at around one-fifth the total healthcare expenditure in a country or 1.5% of annual gross domestic product.[1] In 2017, the direct medical costs of chronic pain in the United Kingdom were approximately £580 million calculated from the total prescription of analgesic medication and pain-related primary care appointments.[2] Nevertheless, the impact on direct medical costs is relatively small compared with the societal economic burden of chronic pain. Chronic pain causes long-term disability leading to work absence, with productivity costs having a significant impact on economic burden. Indirect costs of back pain in the United Kingdom are estimated at about £11 billion using the human capital approach and £5 billion using the friction cost method.[3]

Spinal cord stimulation (SCS) is considered for patients with chronic pain unresponsive to more conservative treatment. SCS is commonly used for management of neuropathic conditions such as failed back surgery syndrome (FBSS), complex regional pain

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syndrome (CRPS), diabetic peripheral neuropathy (DPN), and ischemic conditions such as peripheral arterial disease (PAD) and refractory angina pectoris (RAP). SCS has been the subject of economic evaluations since the 1990s.[4] Previous systematic reviews of economic evaluations of SCS have focused on results of studies rather than methodologies.[5,6] Furthermore, previous reviews included only economic evaluations of conventional SCS (Con-SCS). With the introduction of a number of new SCS modalities including high-frequency SCS (HF-SCS), burst SCS, and dorsal root ganglion stimulation, the cost-effectiveness of these alternatives warrants review.

The aims of this systematic review are to assess the current state of economic evaluations of SCS for all chronic pain conditions, appraise the quality of this literature, and summarize key findings to support healthcare policy decision making for SCS.

Methods

The protocol for this systematic review is registered on the International Perspectives Register of Systematic Reviews as CRD42018090412. This review is reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA).[7]

Search Strategy

Electronic databases MEDLINE (including epub ahead of print and MEDLINE in process), EMBASE, Cochrane Central Register of Controlled Trials, National Health Service Economic Evaluation Database, Health Technology Assessment Database, Database of Abstracts of Reviews of Effects, EconLit, and Cost-Effectiveness Analysis Registry (CEA Registry) were searched from inception until July 12, 2019. The MEDLINE search strategy is presented in Supplementary Material 1 of this article (found at https://doi.org/10.1016/j.jval.2020.02.005) and was adapted to enable similar searches of the other databases. The reference lists of relevant systematic reviews and eligible studies were hand searched to identify potentially relevant studies. No language restrictions were applied.

Study Selection

Identified citations were assessed for inclusion using a 2-stage process. First, 2 reviewers (S.N., R.V.D.) independently screened the titles and abstracts to identify potentially relevant articles. Second, the full-text articles were independently screened by 2 reviewers (S.N., R.V.D.) using the eligibility criteria in Table 1. Any disagreements were resolved through discussion, and, if necessary, in consultation with a third reviewer (R.S.T.).

Data Extraction

A data extraction form was developed to enable data extraction relating to bibliographic information and general information, methodological characteristics (type of economic evaluation, perspective, time horizon, discount rate, costs and resource use, model assumptions, primary economic outcomes, and sensitivity analyses), and main findings. Data were extracted by one reviewer (S.N.) and checked for accuracy by a second reviewer (R.V.D.). Any disagreements were resolved through discussion with a third reviewer if required (R.S.T.).

Quality Assessment

The methodological quality of included evaluations was assessed using the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) checklist.[8] The CHEERS checklist comprises 24 items and scores each study dichotomously as having met the criteria in full or not. Quality assessment of included studies was performed by 1 reviewer (R.V.D.) and checked by a second reviewer (S.N.). Any disagreements were resolved through discussion, and, if necessary, in consultation with a third reviewer (R.S.T.). The results of the quality assessment based on the CHEERS checklist are provided in Supplementary Material 2 (found at https://doi.org/10.1016/j.jval.2020.02.005).

Data Synthesis

A narrative synthesis and structured tables were used to present information from the economic evaluations identified. The results are reported in line with good practice recommendations for narrative summaries of health economic studies as outlined in the Cochrane Handbook for Systematic Reviews.[9]

To facilitate the comparison of estimates reported from different study settings and time frames, results from the economic evaluation (incremental cost-effectiveness ratio [ICER], incremental cost-utility ratio [ICUR]) were adjusted and converted to 2019 UK pounds (£). Conversion of cost estimates was performed using the CCEMG-EPPI-Centre Cost Converter web-based tool version 1.6, which takes into consideration international exchange rates across currencies and years based on gross domestic product deflator index values and purchasing power parities as recommended in the Cochrane Handbook.[9]

Results

The searches identified 574 citations with 457 remaining after the removal of duplicates. After initial screening of titles and abstracts, 18 were considered to be potentially relevant and were

Table 1. Eligibility criteria.

Inclusion criteria	Exclusion criteria
1. Intervention was SCS (all stimulation protocols) or DRGS for all indications	1. Economic evaluations related to neurostimulation intervention other than SCS or DRGS
2. Full economic evaluations (cost-effectiveness, cost-utility, or cost-benefit) with incremental analysis to a comparator therapy	2. Partial economic evaluations (cost analysis, cost description, cost outcome description)
3. Both costs and clinical or utility outcomes were analyzed or ICER/ICUR were reported as a result of a trial-based or model-based economic analysis	3. Protocol paper, methodological paper, systematic review or meta-analysis, reviews or editorial reports of original studies
	4. No comparator group
	5. Insufficient information available (e.g. conference abstracts)

DRGS indicates dorsal root ganglion stimulation; ICER, incremental cost-effectiveness ratio; ICUR, incremental cost-utility ratio; SCS, spinal cord stimulation.

retrieved to allow assessment of the full text. After full-text review, 14 studies were included.[10–23] Four studies did not meet the eligibility criteria and were excluded.[24–27] The PRISMA flow chart detailing the screening process is shown in Figure 1.

Table 2 presents the characteristics of the included economic evaluations. Chronic pain conditions assessed included RAP (n = 3), FBSS (n = 8), CRPS (n = 4), DPN (n = 1), and PAD (n = 2). One study included 3 conditions (FBSS, CRPS, ischemic pain)[20] and another study 4 conditions (FBSS, CRPS, PAD, RAP).[18] Six of the studies assessed the costs of interventions in the United Kingdom,[11,12,15,20,22,23] 3 in The Netherlands,[14,16,21] 2 in the United States,[13,19] 2 in Canada,[17,18] and 1 in Sweden.[10]

Type of Economic Evaluation and Comparators

Most studies applied CEA or cost-utility analysis. Six studies conducted trial-based evaluations[10,12,14,16,19,21] whereas 6 used model-based analysis.[11,15,18,20,22,23] Seven studies compared SCS for neuropathic pain versus conventional medical management (CMM).[11,15,17,18,20,22,23] Four used reoperation as the comparator in patients with FBSS.[11,19,20,23] One used observational data and compared SCS with pre-SCS (ie, usual care and pain clinic) in FBSS.[13] Physical therapy was considered as the comparator for patients with CRPS[14] and best medical treatment (BMT) the comparator for patients with DPN.[21]

For ischemic pain, coronary artery bypass graft (CABG), percutaneous myocardial laser revascularization and percutaneous coronary intervention were used as comparators to SCS in angina pectoris.[10,12,20] Two studies assessed CMM or BMT as the alternative in patients with PAD.[16,18]

Choice of Model

Six studies were model-based analyses.[11,15,18,20,22,23] Most studies used data from randomized controlled trials (RCTs) as key input parameters. One study used case-series data and developed a Markov model.[18] All model-based studies evaluating SCS for neuropathic pain applied a 2-stage model (ie, decision tree followed by a Markov model). One study applied models for neuropathic pain and ischemic pain separately.[20] A 2-stage model was employed for neuropathic pain, and a mathematical model was applied to ischemic pain.[20] A mathematical model was used for ischemic pain owing to lack of information for input variables.

Economic Perspective

Ten studies adopted a healthcare perspective,[11,12,15,17–23] and 3 adopted a societal viewpoint.[14,16,21] Results were also presented from the perspectives of the health insurance council[14] and Department of Labor and Industries.[13] The perspective of the economic evaluation was not clearly stated in 1 study, although hospital care cost data presented suggest a healthcare perspective.[10]

Time Horizon and Discount Rates

The time horizons ranged from 1 year to lifetime. One study described the mean follow-up period as the time horizon.[19]

Figure 1. PRISMA flow chart.

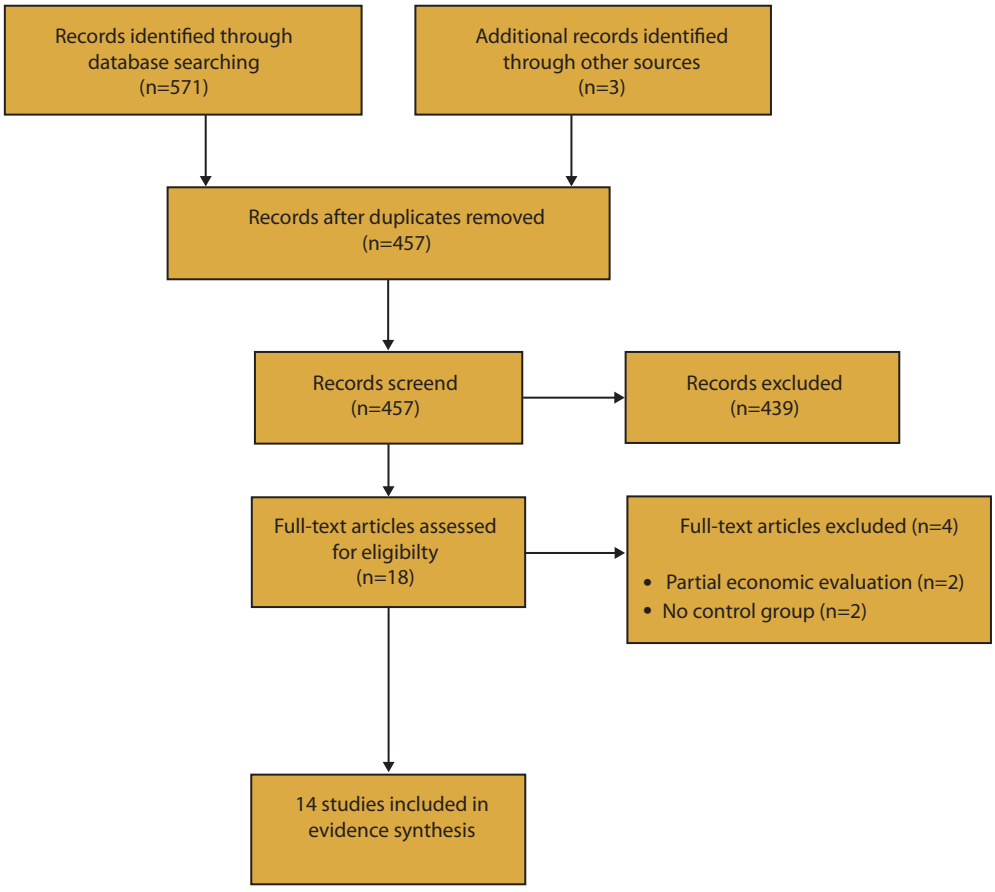


Table 2. Characteristics of the economic evaluations included in the review.

Author and year	Setting	Indication	Time horizon	Intervention	Data source	Trial- or model-based EE	Comparator(s)	Perspective
Andrell 2003[10]	Sweden	Angina pectoris	2 y	SCS	RCT	Trial-based	CABG	Not stated
Annemans 2014[11]	UK	FBSS	15 y	HF-SCS	Case series (HF-SCS) RCT (SCS)	Model based	1) CMM 2) Reoperation 3) TNR-SCS 4) TR-SCS	Healthcare perspective
Dyer 2008[12]	UK	Angina pectoris	2 y	SCS	RCT	Trial based	PMR	Healthcare perspective
Hollingworth 2011[13]	US	FBSS	2 y	SCS	Observational study	Other*	1) Pain clinic 2) Usual care	Department of Labor and Industries
Kemler 2002[14]	The Netherlands	CRPS	1 y, lifetime	SCS with PT	RCT	Trial based	PT	Health insurance council and societal
Kemler 2010[15]	UK	CRPS	15 y	SCS with CMM	RCT	Model based	CMM	Healthcare perspective
Klomp 2006[16]	The Netherlands	CLI	2 y	SCS with BMT	RCT	Trial based	BMT	Societal
Kumar 2002[17]	Canada	FBSS	5 y	SCS	Case series	Other*	BMT	Healthcare perspective
Kumar 2013[18]	Canada	FBSS CRPS PAD RAP	20 y	SCS with CMM	Case series	Model based	CMM	Healthcare perspective
North 2007[19]	US	FBSS	3 y	SCS	RCT	Trial based	Reoperation	Healthcare perspective
Simpson 2009[20]	UK	FBSS CRPS Ischemic pain	15 y	Neuropathic pain SCS + CMM Ischemic pain SCS alone	RCT	Model based	Neuropathic pain 1) CMM alone or 2) reoperation Ischemic pain 1) CABG 2) PCI 3) CMM	Healthcare perspective
Slangen 2017[21]	The Netherlands	DPN	1 y	SCS with BMT	RCT	Trial based	BMT	Societal and healthcare perspective
Taylor 2005[22]	UK	FBSS	2 y, lifetime	SCS	RCT	Model based	CMM	Healthcare perspective
Taylor 2010[23]	UK	FBSS	15 y	SCS with CMM	RCT	Model based	1) CMM 2) reoperation	Healthcare perspective

BMT indicates best medical treatment; CABG, coronary artery bypass surgery; CLI, critical limb ischemia; CMM, conventional medical management; CRPS, complex regional pain syndrome; DPN, diabetic peripheral neuropathy; EE, economic evaluation; FBSS, failed back surgery syndrome; HF-SCS, high-frequency spinal cord stimulation; PAD, peripheral arterial disease; PCI, percutaneous coronary intervention; PMR, percutaneous myocardial laser revascularization; PT, physical therapy; RAP, refractory angina pectoris; RCT, randomized controlled trial; SCS, spinal cord stimulation; TNR, traditional nonrechargeable spinal cord stimulation; TR-SCS, traditional rechargeable spinal cord stimulation.
*Economic evaluation based on effectiveness data from case series only.

Nine studies reported use of discount rates.[12–16,18,20,22,23] For 1 study, discount rates were not applicable as the main analysis considered a time horizon of 12 months.[21] The choice of discount rate in 7 of the studies was informed by National Institute for Health and Care Excellence (NICE) reference case recommendation at the time of the study (ie, 6% for costs and 1.5% for benefits[22] or discount rate of 3.5% for both costs and benefits).[11,12,15,18,20,23] One study discounted both costs and benefits at 3% as recommended by the US Panel on Cost-Effectiveness in Health and Medicine.[14] One study discounted costs at 3% without discounting benefits.[13] Four studies did not report discounting.[10,16,17,19]

Reporting of Costs

Table 3 shows the costs included in each of the economic evaluations assessing SCS. Incremental costs ranged from cost-saving to £24 892. Included costs can be grouped into 3 main categories: direct medical, nondirect medical, and indirect. All the costs evaluated depended on the study perspective. Studies

Table 3. Reporting of costs and cost-effectiveness of SCS.

Author and year	Indication	Costs included in analyses	Source of costs	Incremental costs in 2019 GBP*	Incremental effects/QALYs	ICER/ICUR in 2019 GBP	WTP threshold	Conclusion of economic evaluation
Andrell 2003[10]	Angina pectoris	Direct medical costs Primary intervention Hospitalizations during the follow-up Interventions owing to CHD (during follow-up)	Not stated	CABG more expensive than SCS	SCS group had fewer hospitalization days owing to cardiac morbidity ($P < .05$)	SCS dominant	Not stated	Cost saving
Annemans 2014[11]	FBSS	Direct medical costs Screening costs Implantation and surgery costs Medication costs Complications Removal costs	Simpson et al[20] Taylor et al[23]	CMM as comparator CMM versus TNR-SCS £12 813 827 (£11 787 068) CMM versus TR-SCS £7 430 496 (£6 835 098) CMM versus HF-SCS £6 318 134 (£5 811 868) Reoperation as comparator Reoperation versus TNR-SCS £11 277 226 (£10 373 593) Reoperation versus TR-SCS £5 711 006 (£5 253 389) Reoperation versus HF-SCS £4 598 643 (£4 230 158) TNR-SCS as comparator TNR-SCS versus TR-SCS –£5 383 331 (–£4 951 970) TNR-SCS versus HF-SCS –£6 495 694 (–£5 975 201) TR-SCS as comparator TR-SCS versus TNR-SCS –£5 566 220 (–£5 120 204) TR-SCS versus HF-SCS –£1 112 364 (–£1 023 231)	CMM as comparator CMM versus TNR-SCS 1339 CMM versus TR-SCS 1340 CMM versus HF-SCS 1843 Reoperation as comparator Reoperation versus TNR-SCS 874 Reoperation versus TR-SCS 1083 Reoperation versus HF-SCS 1587 TNR-SCS as comparator TNR-SCS versus TR-SCS 1 TNR-SCS versus HF-SCS 504 TR-SCS as comparator TR-SCS versus TNR-SCS 209 TR-SCS versus HF-SCS 712	CMM as comparator CMM versus TNR-SCS £9569 (£8802) CMM versus TR-SCS £5545 (£5101) CMM versus HF-SCS £3428 (£3153) Reoperation as comparator Reoperation versus TNR-SCS £12,897 (£11,864) Reoperation versus TR-SCS £5271 (£4849) Reoperation versus HF-SCS £2898 (£2666) TNR-SCS as comparator TNR-SCS versus TR-SCS Dominant TNR-SCS versus HF-SCS Dominant TR-SCS as comparator TR-SCS versus TNR-SCS Dominant TR-SCS versus HF-SCS Dominant	£20 000 to £30 000 per QALY	Cost-effective as compared with CMM and reoperation Cost saving as compared with TNR-SCS and TR-SCS
Dyer 2008[12]	Angina pectoris	Direct medical costs Implantation costs Hospitalizations (cardiac ward bed day after procedure) Cardiac-related medications Inpatient and outpatient episodes (for cardiac and noncardiac)	HRG by NHS BNF 2006 Hospital prices (adjusted by National Reference Cost Index)	£7003 (£5520) (95% CI: £1966 to £8613; $P<.01$)	0.12 (95% CI: –0.04 to 0.30; $P = .96$)	£58 356 (£46 000)	£20 000 to £30 000 per QALY	Not cost-effective
Hollingworth 2011[13]	FBSS	Direct medical costs (injury-related medical costs) Implantation costs SCS revision/removal costs Medications Hospitalizations Outpatient and home healthcare Indirect costs Productivity loss costs	Reimbursements based on administrative database	SCS versus usual care £24 892 ($29 358) (95% CI: $16 070 to $43 790) SCS versus pain clinic £17 020 ($20 074) (95% CI: $3840 to $35 990)	SCS versus usual care 10% in SCS and 10% in UC groups on achieving primary outcome SCS versus pain clinic 10% in SCS and 3% in PC groups on achieving primary outcome	SCS versus usual care £283 788 ($334 704) (95% CI: $142 203 to $489 243) SCS versus pain clinic £111 196 ($131 146) (95% CI: SCS dominates to $271 075)	Not stated	Not cost-effective
Kemler 2002[14]	CRPS	Direct medical costs Screening costs Implantation costs Outpatient visit Reposition and replacement Complication costs (including removal and reimplantation) Medications Direct nonmedical costs Cost of aids Transport Out-of-pocket payment	1998 financial and service data The Netherlands health insurance Patient's cost diaries	1-y base case £5063 (€4065) Lifetime base case –£22 330 (–€17 927)	1-y base case 0.18 Lifetime base case 2.33	1-y base case £28 128 (€22 582) Lifetime base case Dominant	Not stated	1-y base case Cost-effective Lifetime base case Cost saving
Kemler 2010[15]	CRPS	Direct medical costs Screening costs Implantation costs SCS revision/explantation/related complication Medications Nonmedication treatment	Manca et al[28] Medtronic, Inc	£8413 (£6994)	1.96	£4285 (£3562)	£20 000 to £30 000 per QALY	Cost-effective
Klomp 2006[16]	CLI	Direct medical costs Hospitalizations Implantation costs Complication costs Medications Other procedure (amputation) Outpatient and home healthcare Other medical costs (GP/rehabilitation/professional care) Direct nonmedical costs Travel expenses Out-of-pocket payment Indirect costs Nonprofessional help	Department-based cost registration Estimates based on reimbursement fees National Hospital Institute report Ministry of Health report Public Health Service prices Manufacturer's prices Institute of Medical Technology Assessment, Rotterdam	Costs of SCS £10 837 (€7900) higher versus BMT	No significant difference in patient and limb survival between 2 treatment groups	Not performed (considered there were no long-term benefits SCS and SCS considerably more expensive than BMT)	Not stated	Not cost-effective

continued on next page

Table 3. Continued

Author and year	Indication	Costs included in analyses	Source of costs	Incremental costs in 2019 GBP*	Incremental effects/QALYs	ICER/ICUR in 2019 GBP	WTP threshold	Conclusion of economic evaluation
Kumar 2002[17]	FBSS	Direct medical costs Hardware used in SCS Professional fees Radiological investigations Drugs Nursing contacts Electrode or pulse generator replacement Alternative therapies (massage/physiotherapy/ chiropractic treatments) Hospital admissions for treatment of breakthrough pain	Price list of device provided by the manufacturer as charged to Canadian hospitals Saskatchewan Medical Association Saskatchewan Health Formulary Hospital Finance Department	Costs of SCS £7407 (CAN$8906) lower versus BMT	Improvement in disability as measured by the Oswestry disability questionnaire of 27% for the SCS group, compared with 12% improvement for the BMT group	SCS dominant	Not stated	Cost saving
Kumar 2013[18]	FBSS CRPS PAD RAP	Direct medical costs Preimplantation costs Implantation costs Complication costs Maintenance costs (nursing/ physician/hospitalization for acute exacerbation of pain) Adjunctive therapy/alternative therapy (acupuncture/ physiotherapy/massage/ chiropractic therapy) Pharmacotherapy Follow-up and evaluations	Hospital Finance Department Neuromodulation clinic Patient database	FBSS £8209 (CAN$12 917) CRPS £15 111 (CAN$23 778) PAD £9890 (CAN$15 563) RAP £14 022 (CAN$22 064)	FBSS 1.39 CRPS 2.12 PAD 1.67 RAP 2.21	FBSS £5906 (CAN$9293) CRPS £7128 (CAN$11 216) PAD £5922 (CAN$9319) RAP £6345 (CAN$9984)	Canada and US WTP threshold $50 000 per QALY and NICE threshold £20 000 to £30 000 per QALY	Cost-effective
North 2007[19]	FBSS	Direct medical costs Hospitalization-related costs	The John Hopkins Hospital billing department	–£2151 (–$1971) (95% CI: –$14 045 to –$10 696; P = .754)	The difference in the proportion of patients achieving a successful outcome for each procedure 29% (2% to 56%; P = .07) Mean QALYs 0.18 (–0.03 to –0.35; P = .09)	SCS dominant	Not stated	Cost saving
Simpson 2009[20]	FBSS CRPS Ischemic pain	Direct medical costs Preimplantation costs Implantation costs Complication costs SCS revision/removal costs Medication costs Reoperation costs	BNF 2007 Curtis and Netten[29] NHS reference costs NHS National Tariff R09	FBSS SCS+CMM versus CMM alone £12 415 (£10 035) SCS + CMM versus reoperation £11 666 (£9430) CRPS SCS + CMM versus CMM alone £10 856 (£8775) Ischemic pain Not performed	FBSS SCS + CMM versus CMM alone 1.26 SCS + CMM versus reoperation 1.34 CRPS SCS + CMM versus CMM alone 0.35 Ischemic pain Not performed	FBSS SCS + CMM versus CMM alone £9892 (£7996) SCS + CMM versus reoperation £8713 (£7043) CRPS SCS + CMM versus CMM alone £31 046 (£25 095) Ischemic pain Not performed	£20 000 to £30 000 per QALY	Neuropathic pain Cost-effective for FBSS and CRPS (at time of appraisal <£30k per QALY for CRPS) Ischemic pain Favors SCS from threshold analysis
Slangen 2017[21]	DPN	Direct medical costs Costs related to the intervention Costs incurred for other reasons attributable to painful DPN Direct nonmedical costs Paid domestic help Informal caregiving Over the counter medications Indirect costs Productivity loss Loss of daily activities	Hospital information system Mean costs questionnaires by patients	Societal perspective £20 102 (€21 226) Healthcare perspective £15 692 (€16 569.05)	Societal perspective 0.22 QALYs Healthcare perspective 48% more successfully treated patients with SCS	Societal perspective £89 173 (€94 160) Healthcare perspective £32 691 (€34 519)	€20 000 to €80 000 per QALY	Not cost-effective
Taylor 2005[22]	FBSS	Direct medical costs Implantation costs Complication costs SCS revision/ reimplantation costs Maintenance costs Medication costs	Kumar et al[17]	2-y base case £3220 (€3002) Lifetime base case –£50 382 (–€46 967)	2-y base case 0.066 Lifetime base case 1.12	2-y base case £49 151 (€45 819) Lifetime base case SCS dominant	Not stated	2-y base case Not cost-effective Lifetime base case Cost saving
Taylor 2010[23]	FBSS	Direct medical costs Screening costs Implantation costs SCS revision/ explantation/removal Complications Medications Reoperation	Rivero-Arias O et al[30] NHS England, totals report for procedure A483 Medtronic, Inc. NHS National Tariff R09	SCS versus CMM £8693 (£7027) SCS versus reoperation £7741 (£6257)	SCS versus CMM 1.25 SCS versus reoperation 0.98	SCS versus CMM £6958 (£5624) SCS versus reoperation £7908 (£6392)	£20 000 to £30 000 per QALY	Cost-effective

BMT indicates best medical treatment; BNF, British National Formulary; CABG, coronary artery bypass surgery; CHD, coronary heart disease; CI, confidence interval; CLI, critical limb ischemia; CMM, conventional medical management; CRPS, complex regional pain syndrome; DPN, diabetic peripheral neuropathy; FBSS, failed back surgery syndrome; GBP, British pound sterling; GP, general practitioner; HRG, Health Resource Group; ICER, incremental cost-effectiveness ratio; ICUR, incremental cost-utility ratio; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; PAD, peripheral arterial disease; QALY, quality-adjusted life-year; RAP, refractory angina pectoris; SCS, spinal cord stimulation; TNR-SCS, traditional nonrechargeable spinal cord stimulation; TR-SCS, traditional rechargeable spinal cord stimulation; UC, usual care; WTP, willingness to pay.
*Costs reported in 2019 GBP. The values in parentheses represent the costs originally reported.

inconsistently evaluated the cost of the SCS intervention because various types of costs were applied. Direct medical costs were evaluated in all studies and were the key inputs for the cost analysis. Direct medical costs can be grouped into 3 types depending on the SCS treatment period: initial costs, that is, (1) preimplantation costs (or testing and screening costs), (2) surgery or implantation costs (mainly covered in device and surgery hospitalization costs), and (3) post-implantation costs (costs for device maintenance, complications, reimplantation, or removal). For the initial SCS costs, 1 study applied only implantation or procedure costs,[10] whereas 2 studies did not clearly state the type of medical costs assessed.[12,19] Most studies considered post-implantation costs, which varied between studies although mostly included costs of complications, reimplantation, or device removal. One study applied annual SCS maintenance costs separated from reimplantation costs.[22]

Costing of resource use data was derived from different sources. Twelve studies described the approach used to estimate unit costs and cost calculations.[12–23] One study did not report the method used to calculate the unit costs.[11] One study did not state sources of cost or unit cost calculation.[10] Three studies used national data to calculate costs.[12,20,23] Costs were derived from previous cost-analysis and economic evaluations in 3 studies.[11,15,22] Three studies applied SCS device costs from manufacturers.[15,16,23] Methods to assess productivity loss included work time-loss compensation payments to workers[13] and the friction method.[21]

Reporting of Effectiveness

All studies provided the choice of outcome measurement. Eleven studies reported the measurement of effectiveness and valuation of preference-based outcomes.[11,12,14,15,18–23] One study did not report the data source of effect.[10] Most of the effectiveness data were collected from RCT and observational data. One study estimated effectiveness data based on a literature review.[20] Pain outcome measurement varied from the proportion of patients achieving 50% pain relief, pain exacerbation, and patient satisfaction. Two studies analyzed the final outcome as mortality.[10,16] The health-related quality of life measured by using a generic measurement with multi-attributes such as the EQ-5D, was reported in 10 studies.[11,12,14,15,18–23] One short-term study estimated missing EQ-5D data by interpolation between adjacent visits or valuing from the last visit and extrapolating to the time horizon.[12]

Economic Evaluation Results

Economic evaluation results are illustrated in Table 3. Eleven studies reported ICERs/ICURs as the final economic evaluation outcome. Three studies performed full economic evaluations by comparing costs and outcomes but did not calculate ICER/ICUR as SCS was found to be dominant or dominated.[10,16,17] Seven of the studies stated the willingness-to-pay threshold based on study setting and used the NICE threshold, which ranges from £20 000 to £30 000 per quality-adjusted life-year (QALY) gained.[11,12,15,18,20,21,23] One Canadian study used both NICE and Canadian ($50 000 per QALY) thresholds.[18]

The ICERs/ICURs varied widely from cost-saving to more than £100 000 per QALY depending on the indication, time horizon, and comparator. SCS was estimated to be cost-saving and cost-effective over long-time periods, from 15 years to lifetime, for most chronic pain conditions considered. The results of studies with a long time horizon are shown in Figure 2A. Eight studies evaluated SCS for FBSS pain.[11,13,17–20,22,23] The ICER/ICUR in FBSS ranged from cost-saving to £283 788 per additional QALY gained. The overall trend was toward SCS being cost-effective compared with CMM alone, especially in longer time horizons. SCS therapy was cost-saving compared with reoperation when used for FBSS.[19] In contrast, 1 observational study of SCS for FBSS patients compared with usual care and pain clinic found that SCS was not cost-effective, reporting an ICER of £283 788 per additional QALY gained (Figure 2B).[13] Four studies considered SCS as highly cost-effective compared with reoperation regardless of time horizon. Nevertheless, SCS was not cost-effective in the short-term (ie, 2-year time horizon) when compared with CMM,[22] pain clinic,[13] or usual care.[13]

Four studies assessed the cost-effectiveness of SCS for patients with CRPS. One short horizon study evaluating SCS for CRPS considered SCS cost-effective per the NICE threshold.[14] One study found SCS to be cost saving compared with physiotherapy alone considering a lifetime time horizon and also cost-effective in the short-term from the first year of SCS therapy.[14] Two studies of SCS versus CMM over a 15-year time horizon reported different results, with ICURs of £4285[15] and £31 046[20] per additional QALY.

One study assessed SCS versus BMT in patients with DPN and found that SCS was not cost effective over 1 year.[21]

Three studies evaluated SCS for RAP with different comparators and time horizons. SCS for persistent pain after CABG was cost-effective over a 20-year follow-up when compared with CMM, with an ICER/ICUR of £6345 per QALY.[18] On the other hand, SCS was not cost-effective compared with percutaneous myocardial laser revascularization at 2-year follow-up.[12] One study of SCS versus CABG reported lower costs and higher effectiveness for SCS (ie, SCS dominant).[10]

One study showed SCS to be cost-effective for PAD over 20 years, with an ICER/ICUR of £6345 per additional QALY gained.[18] Nevertheless, another study with a 2-year analysis period concluded that SCS was not cost-effective for the management of critical limb ischemia.[16]

Sensitivity Analysis

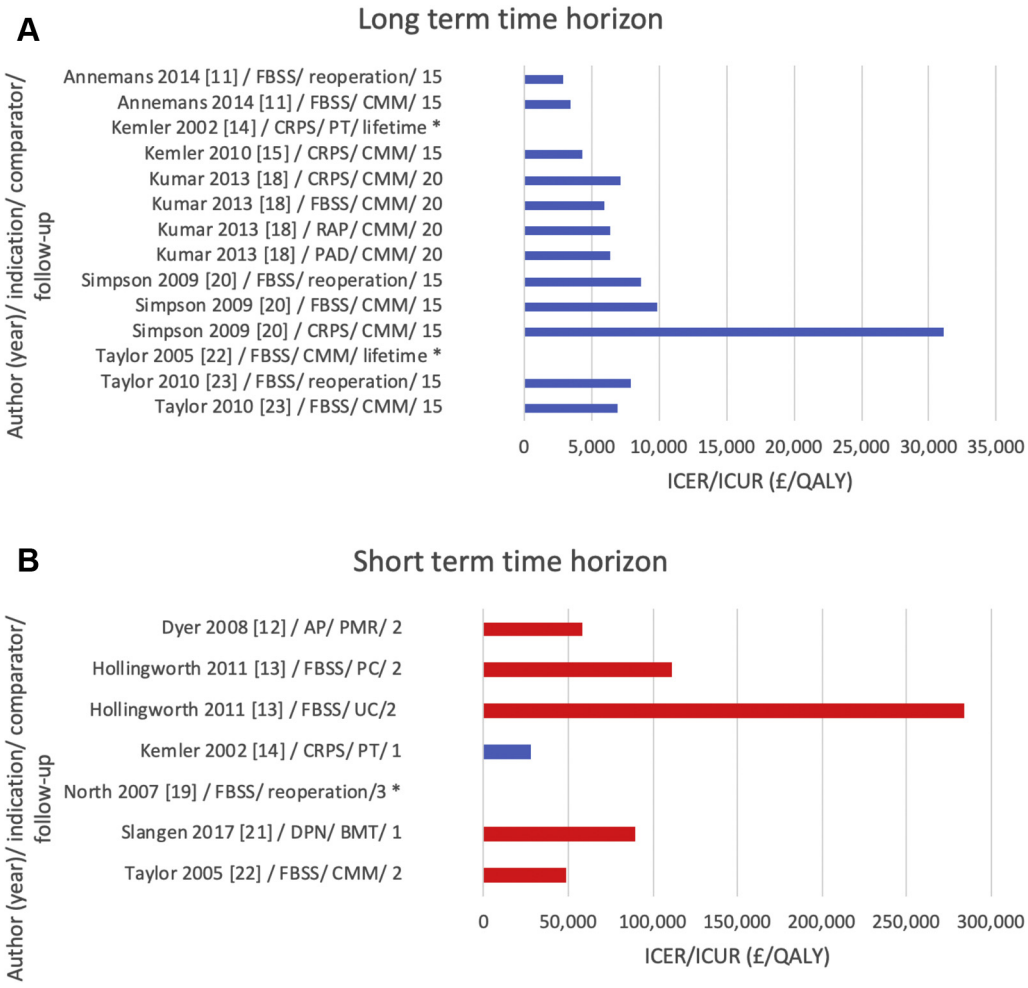
To assess the generalizability and uncertainty of the results, deterministic and probabilistic sensitivity analyses were performed in most studies. One-way sensitivity analysis and/or probabilistic sensitivity analysis were reported in 10 studies.[11–15,18,20–23] Two studies used nonparametric bootstrapping and multiway analysis.[19,22] Supplementary Material 3 (found at https://doi.org/10.1016/j.jval.2020.02.005) presents the types of input parameters affecting the ICER/ICUR and the probability of SCS being cost-effective. For the studies that conducted sensitivity analysis, all of the input parameters were analyzed with discounted costs and outcomes. The ICERs/ICURs were found to be sensitive to the change in SCS equipment costs, costs of pain medication, probability of optimal and suboptimal pain relief, costs, and QALY gain from optimal and suboptimal health states with SCS.

The probability of SCS being cost-effective, at the appropriate range of the cost-effectiveness willingness-to-pay threshold, was more than 70% in 5 studies.[15,18–20,23] One study found that the probability of SCS being cost-effective was below 20%.[13] One study performed expected value of perfect information; the expected value of perfect information result for SCS estimate per patient was relatively low compared with the total cost per patient.[18]

Type of SCS Devices and Battery Longevity

All of the studies considered traditional nonrechargeable SCS (TNR-SCS) devices. Two studies extended the analysis to traditional rechargeable SCS (TR-SCS) and compared it with TNR-SCS in patients with FBSS and CRPS.[15,23] The studies assumed a fixed

Figure 2. Incremental cost-effectiveness ratio/incremental cost-utility ratio when considering a long-term (A) or short-term (B) time horizon.



*Spinal cord stimulation dominant (ie, less costly and more effective).

battery life of 9 years for TR-SCS and varied the battery longevity up to 16 years for TNR-SCS. When all other parameters were fixed, TR-SCS was more cost-effective than TNR-SCS, for which the expected longevity of TNR-SCS was less than 4 years. One study assessed HF-SCS in patients with FBSS compared with CMM, reoperation, TR-SCS, and TNR-SCS.[11] The results showed that HF-SCS was cost-effective with ICERs of £3153 and £2666 per QALY gained versus CMM and reoperation, respectively. TR-SCS was more cost-effective than TNR-SCS; however, HF-SCS dominated both TNR-SCS and TR-SCS.[11]

Discussion

The focus of this systematic review was on full economic evaluations. Fourteen studies met the eligibility criteria. SCS was mostly considered to be cost-effective; however, this depended on the chronic pain condition, comparator treatments, time horizon, and willingness-to-pay threshold.

Previous systematic reviews of cost-effectiveness of SCS found a limited number of economic evaluations. A systematic review of SCS therapy in patients with FBSS included 3 studies, of which 2 studies were full economic evaluations and another study was a cost-consequences analysis.[6] A systematic review of SCS therapy for CRPS found only 1 well-conducted economic evaluation.[5] Besides the limited number of studies identified, both of these reviews did not include detailed evaluation of the methods employed, were mostly focused on the results, and did not perform adjustment of costs from different prices, years, and settings.

Although this systematic review shows that the average costs of SCS tend to be higher than the alternative options, especially at the initial stages of the treatment, the improvement in health-related quality of life compensates this in the long-term. Hence, the time horizon to evaluate SCS interventions should be long enough to capture the differences between treatment and comparator. The results of trial-based studies were limited to a short period of time and may neglect relevant events that can occur later and have a potential impact on costs and health outcomes. Nevertheless, the analytical models were limited by a lack of some long-term data or missing follow-up costs. Therefore, even though a lifetime horizon is preferable, the assumptions of the model when extrapolating into the long-term should be made explicit to increase model transparency and strengthen the cost-

effectiveness evidence. One study, which assessed SCS in patients with FBSS, used a conservative value for pain relief over time and assumed a complication rate of 0% with CMM. The 1-way sensitivity analysis found that the results were sensitive to SCS annual complication rate and may underestimate the cost-effectiveness of SCS compared with CMM.[22]

Preimplantation costs such as screening and testing for response should be included in the analysis. All studies included SCS-related complication costs after surgery, for instance, costs for explantation of the device, revision costs, and follow-up costs. Economic evaluations with a time horizon longer than 1 year should discount future costs and benefits. Although the discount rates for costs and benefits vary between and even within countries (eg, NICE and HM Treasury in the United Kingdom), an appropriate discount rate should be applied in the base case, with sensitivity analyses carried out to examine the impact of other relevant discount rates.

The rationale for choosing the comparator should be clearly presented. Alternative options for the management of FBSS included CMM or reoperation; however, from an evidence-based approach, medication management and reoperation provide weak evidence of clinical improvement in patients with FBSS.[6,31] The study comparator should be based on current practice or clinical guidelines with the adequacy of the comparator clearly presented. Another limitation observed from included studies is the unclear characterization of uncertainty, particularly in trial-based economic evaluations. The statistical uncertainty of CEA can be analyzed using confidence intervals or Bayesian credibility intervals and presented in the form of cost-effectiveness planes or cost-effectiveness acceptability curves.[8]

Neuropathic Pain

FBSS

The use of SCS for the management of patients with FBSS can be considered as cost-effective, particularly when considering long-term time horizons. SCS intervention versus CMM alone was found to be cost-effective from the first 2 years and cost-saving over a lifetime time horizon.[11,17,18,20,22,23] SCS was also estimated as cost-effective or cost-saving when compared with reoperation.[11,19,20,23]

Regarding these 2 strategies (ie, comparison of SCS with CMM or reoperation), CMM data were collected from an international RCT,[32] which can be considered as having high internal validity and well-controlled, making CEA more robust, whereas the data from reoperation were based on case series and a small RCT.[33] Importantly, in the model-based analysis of SCS, data on the complications of CMM and reoperation were unavailable, and assumed "conservative" values were used in the models. These conservative assumptions might lead to unpredictably biased cost-effectiveness results. Although CMM and reoperation are recommended as a standard treatment for FBSS, recent evidence suggests that medication management and reoperation yielded inferior efficacy when compared with other treatment options such as epidural injection or adhesiolysis.[31] Therefore, further analysis of SCS compared with these alternatives would be welcome as well as utility values associated with complications resulting from pain management with CMM and reoperation.

CRPS

Because there is no curative treatment available for CRPS, current practice is to combine medication management and physical and occupational therapy. SCS treatment has been shown to reduce pain significantly in patients experiencing CRPS.[34] In this systematic review, it was observed that SCS for CRPS is cost-effective. Nevertheless, similar to economic evaluations of SCS for patients with FBSS, there was no direct estimation of utility values associated with complications from CMM or alternative treatment strategies. One study compared SCS with PT and demonstrated that SCS was cost-effective from year 1 and became cost-saving over the lifetime.[14] Nevertheless, this study was based on data from a clinical trial, and unit prices were calculated via microcosting from the Dutch population. Hence, the applicability of the results to the UK population should be considered.

Diabetic Peripheral Neuropathy

One published study assessed the cost-effectiveness of SCS in patients with painful DPN comparing SCS with BMT over 1 year.[21] Because of the high initial treatment costs on the SCS arm, SCS was not considered to be cost-effective from either a healthcare or societal perspective, even though SCS yielded more QALYs than BMT did. Nevertheless, it was suggested that SCS is likely to become more cost-effective in the long-term considering the depreciation of SCS material and extrapolating the data for up to 4 years.

Ischemic Pain

The clinical evidence available on the use of SCS for the management of ischemic pain is limited, with SCS used less frequently in this patient group. The results of economic evaluations of SCS for ischemic conditions range from cost-saving to ICERs of £230 000 per additional QALY gained. One study has suggested that the ICER could range from £18 000 to £230 000 per QALY gained considering the clinician's experience.[12]

Strengths and Limitations of the Review

The review methods, including study identification, selection, quality assessment, and data extraction, were carried out in line with PRISMA recommendations.[7] No constraints were set on the type of SCS device studied or population of interest. All types of full economic evaluations[35] were considered relevant, including both trial- and model-based economic evaluations.

Our review can be considered limited by focusing on full economic evaluations, which means that partial economic evaluations (such as cost analyses) were not included. Nevertheless, although such partial evaluation studies can offer detailed information into the costs associated with a treatment, they do not provide information to aide resource allocation decisions and therefore are less valuable for decision making.[35,36]

Policy Implications and Future Research

The findings from this review have important implications for healthcare policy makers. This systematic review found that SCS is considered economically favorable in neuropathic pain of FBSS and CRPS. The review highlights the benefit from the reduction in healthcare expenditure in long-term treatment. Nevertheless, further evidence is required to definitively determine the cost-effectiveness of SCS for ischemic pain. This review also reports the information available on the cost-effectiveness of the several types of SCS device systems, with suggestions that HF-SCS is more cost-effective than conventional TR-SCS and TNR-SCS. The results of HF-SCS should be interpreted with caution as current evidence is limited to 1 economic evaluation making several assumptions (eg, complication rates assumed to be the same for HF-SCS and comparators), the effectiveness data for HF-SCS derived from 1 case series with a 6-month follow-up (validated with data from a case series with 24-month follow-up), and with no utility data (ie,

utility values assumed to be the same for HF-SCS as for conventional SCS). There is a lack of evidence for the cost-effectiveness of dorsal root ganglion stimulation.

Chronic pain may be a lifelong condition; therefore, it is important to assess long-term clinical outcomes and the quality of life of patients with SCS. Most of the studies applied short-term data and extrapolated to lifetime analysis because of the unavailability of long-term data. SCS needs to be compared with treatment options based on current recommendations and clinical guidelines. Moreover, more research is needed on the use of SCS for other chronic pain conditions such as phantom limb pain or peripheral neuralgia.

Conclusion

The results of this review show that SCS is a cost-effective therapy when considering long-term treatment for patients with neuropathic pain (ie, FBSS and CRPS). The results from economic evaluations assessing SCS for patients with ischemic pain require further evaluation because of the lack of clinical data. HF-SCS may be more cost-effective than conventional SCS. Nevertheless, these results are limited to the indications of FBSS and CRPS, with additional research required for other chronic pain conditions.

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Supplemental Material

Supplementary data associated with this article can be found in the online version at https://doi.org/10.1016/j.jval.2020.02.005.

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