Washington State Health Care Authority

Spinal Cord Stimulation

Assessing signals for update

January 9, 2014

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Spinal Cord Stimulation
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Jan 9, 2014

Previous Coverage Decision

A Comparative Effectiveness Review (CER) titled: SPINAL CORD STIMULATION, was originally released in July 2010 by the Health Technology Clinical Committee and summarized below.

Health Technology Clinical Committee
Findings and Coverage Decision

Topic: Spinal cord stimulation

Meeting Date: August 20, 2010

Final Adoption: October 22, 2010

HTCC Coverage Determination

Spinal Cord Stimulation for chronic neuropathic pain is **not a covered benefit**.

HTCC Reimbursement Determination

- **Limitations of Coverage**
  Not Applicable
- **Non-Covered Indicators**
  Not applicable

Health Technology Background

The Spinal Cord Stimulation topic was selected and published in December 2009 to undergo an evidence review process. Spinal Cord Stimulation (SCS) is an alternative treatment proposed for patients with chronic neuropathic pain who have not responded to conventional therapies such as medication, physical and/or psychological therapy, and in some case, re-operation. Current best evidence is available primarily from four trials on 375 patients; which are rated at a Level 1 or 2 (good quality), which is a better level of evidence than some interventions. However, total patient sample size is small, comparators were weak or inappropriate, reported outcomes are mostly subjective and not consistently reported, industry funding and management may have an impact, and no trial included a sham stimulation/procedure arm. The overall body of evidence was inconsistent, with several trials showing benefits on some outcomes at generally shorter follow up periods and others showing no difference. SCS is an implanted, long term treatment, but no evidence exists on either long term efficacy or safety.

The committee agreed that SCS is less safe than alternatives, is an invasive procedure, and has many adverse events. While conventional medical management is not invasive, so would generally have a lower risk profile, re-operation is also a comparator and had less complications. SCS device related complications can be serious and include dural punctures, amplitude by bodily movements; paresthesia in other body parts, pain, disturbed urination, lead fracture, loss of effect, infection. Indications for SCS (FDA): Chronic intractable pain in the trunk and/or limbs including unilateral or bilateral pain associated with FBSS and intractable low back and leg pain, and for some devices: CRPS, radicular pain syndrome or radiculopathies resulting in pain, post-laminectomy pain, unsuccessful disc surgery, degenerative disc disease or herniated disc pain refractory to conservative or surgical interventions, peripheral causalgia, epidural fibrosis, arachnoiditis or lumbar adhesive arachnoiditis, and multiple back surgeries. Potential patients should undergo a period of trial stimulation prior to

permanent SCS implantation. Contraindications for SCS (FDA): Failed trial stimulation due to ineffective pain relief; poor surgical risks; pregnancy; active general infections or multiple illnesses; inability to operate the SCS system; and cardiac pacemakers (with specific exceptions and precautions) or cardioverter defibrillators.

In June 2010, the HTA posted a draft and then followed with a final report from a contracted research organization that reviewed publicly submitted information; searched, summarized, and evaluated trials, articles, and other evidence about the topic. The comprehensive, public and peer reviewed Spinal Cord Stimulation report is 164 pages, and identified a relatively large amount of literature.

An independent group of eleven clinicians who practice medicine locally meet in public to decide whether state agencies should pay for the health technology based on whether the evidence report and other presented information shows it is safe, effective and has value. The committee met on August 20, reviewed the report, including peer and public feedback, and heard public and agency comments. Meeting minutes detailing the discussion are available through the HTA program or online at http://www.hta.hca.wa.gov under the committee section.

Committee Conclusions

Having made findings as to the most significant and relevant evidence regarding health outcomes, key factors and identified evidence related to those factors, primarily based on the evidence based technology assessment report, the committee concludes:

(1) Evidence availability and technology features

The committee concludes that the best available evidence on Spinal Cord Stimulation has been collected and summarized.

- Spinal Cord Stimulation (SCS) is an alternative treatment proposed for patients with chronic neuropathic pain who have not responded to conventional therapies such as medication, physical and/or psychological therapy, and in some case, re-operation.
- Current best evidence is available primarily from four trials on 375 patients; which are rated at a Level 1 or 2 (good quality), which is a better level of evidence than some interventions. However, total patient sample size is small, comparators were weak or inappropriate, reported outcomes are mostly subjective and not consistently reported, industry funding and management may have an impact, and no trial included a sham stimulation/procedure arm. The overall body of evidence was inconsistent, with several trials showing benefits on some outcomes at generally shorter follow up periods and others showing no difference.

  SCS is an implanted, long term treatment, but no evidence exists on either long term efficacy or safety.

(2) Is it safe?

The committee concludes that the comprehensive evidence indicates that Spinal Cord Stimulation is less safe than alternative treatments. Key factors to the committee's conclusion included:

- The committee agreed that SCS is less safe than alternatives, is an invasive procedure, and has many adverse events. While conventional medical management is not invasive, so would generally have a lower risk profile, re-operation is also a comparator and had less complications. SCS device related complications can be serious and include dural punctures, amplitude by bodily

movements; paresthesia in other body parts, pain, disturbed urination, lead fracture, loss of effect, infection.

- The committee agreed that safety was a significant factor: the number of trial reported complications ranged from 8 to 100%. Device related complication requiring revision ranged from 25% to 38% of patients in short term and 42% to 60% in up to 5 years (not including 54% of patients undergoing pulse generator replacements due to battery life).
- The committee agreed that there were currently no reported mortality rates, but that the FDA data was not available and the small sample size is likely underpowered to detect.
- The committee agreed that the removal rate could be considered an efficacy or safety issue, but the rates ranging from 4% to 17% were concerning, especially considering that trial stimulation is done first on all patients.

(3) Is it effective?

The majority of the committee concludes that the comprehensive evidence about Spinal Cord Stimulation effectiveness is unproven.

- The committee agreed that the studies had serious limitations in design, low patient sample sizes, and weak or inadequate comparators. Additionally, placebo effects of a new intervention for patients with chronic pain who have already failed multiple therapies is a serious concern and no study involved sham stimulation or procedures and outcome measures were generally subjective.
- The committee found that evidence overall on important patient outcomes was limited. For all outcomes, there is no evidence of longer term improvement, particularly important when there are significant risks (including 1/3 revision and high removal rate) and the device is intended for permanent implant.
- Given the serious limitations of the studies, the committee agreed that, at best, weak evidence exists that SCS may provide temporary improvement of pain in some patients, but there is no evidence of mid or long term pain improvement.
- While pain is a critical patient outcome, evidence about other important patient outcomes was either not available or not consistent with the pain findings.
    - For instance, for reduction in pain medication in short term: Kumar and Turner found no difference, while North found SCS patients did have reduction.
    - For functional improvements, 1 trial found short term functional improvement, but 2 others did not; and there was no reliable evidence of functional improvement at mid (or long) term.
- For all other outcomes, including improvement in quality of life, there is no reliable evidence of effect.

(4) Evidence about the technology's special populations, patient characteristics and adjunct treatment

The committee agreed that no compelling evidence exists to differentiate sub groups or special populations.

- The committee agreed with the evidence based report that there is inadequate evidence to identify characteristics that either enhance or reduce the efficacy of SCS such as age, sex, workers' compensation or other disability payments, duration of pain, pain intensity, time since first lumbar surgery, number of prior operations for pain, pain location, laterality of pain, allodynia or

hypoesthesia at baseline, McGill Pain Questionnaire or the Minnesota Multiphasic Personality Inventory (MMPI)

(5) Is the technology cost-effective?

- The committee concludes that SCS is unproven to be cost effective.
- The committee agreed that the cost of SCS is substantial, averaging $27,000 per patient.
- The committee agreed that overall value cannot be ascertained without evidence of net benefit of effectiveness and reduced harm. Reliable cost-effectiveness analysis cannot be performed.

Committee Decision

Based on the deliberations of key health outcomes, the committee decided that it had the most complete information: a comprehensive and current evidence report, public comments, and agency and state utilization information. The committee concluded that the current evidence on Spinal Cord Stimulation demonstrates that there isn't sufficient evidence to cover the use of Spinal Cord Stimulation for chronic neuropathic pain. The committee considered all the evidence and gave greatest weight to the evidence it determined, based on objective factors, to be the most valid and reliable. Based on these findings, the committee voted 8 to 1 to not cover Spinal Cord Stimulation.

The committee reviewed the Clinical guidelines and Medicare decision. The Medicare decision was did not cite evidence and was decided prior to any of the studies reviewed by the committee. The guidelines recommendations conflict and not all have reviewed the latest trials included in this report.

1. Purpose of Report

The purpose of this literature update is to determine whether or not there is sufficient evidence published after the original report to conduct a re-review of this technology.

2. Methods

2.1 Literature Searches

We conducted a limited literature search for articles published between May 1, 2010 and December 6, 2013 using the identical search strategy used for the original report. This search included four main databases: PubMed, Medline, Cochrane Library, and EMBASE. Appendix A includes the search methodology for this topic.

2.2 Study selection

In general, we used the same inclusion and exclusion criteria as the original CER.

2.4 Compilation of Findings and Conclusions

For this assessment we abstracted the data from the included studies and constructed a demographics table, Table 3 (Appendix C). We also constructed a summary table that included the key questions, the original conclusions, new sources of evidence, new findings, and conclusions based on available signals, Table 2. To assess whether the conclusions might need updating, we used an algorithm based on a modification of the Ottawa method, Figure 2.

3. Results

3.1 Search

A systematic review was undertaken for articles published between May 1, 2010 and December 6, 2013. We used two search strategies to identify articles from MEDLINE, EMBASE and the Cochrane Library. We used key words to detect articles that used the terms “spinal cord stimulation”, “spinal cord stimulator”, or “spinal cord stimulation”. Among the articles describing the efficacy and/or safety of spinal cord stimulation, we evaluated the full text to determine if the studies met our inclusion criteria. Full text of potential articles meeting the inclusion criteria by both methods were reviewed by two independent investigators to obtain the final collection of included studies, Figure 1.

The literature search identified 213 titles. After title and abstract review, we further reviewed the full text of 22 journal articles. The remaining 191 titles were rejected because they were case reports, commentary, or did not include topics of interest. Among the 22 articles that went on to full text review, 17 were rejected because subjects did not meet the inclusion criteria and/or did not include a comparison of interest, Table 1. No new systematic reviews of relevant literature were identified. Of the five articles that were further reviewed, all five[1-5] were abstracted into an evidence table (Appendix C).

3.2 Identifying signals for re-review

Table 2 shows the original key questions, the conclusions of the original report, the new sources of evidence, the new findings, and the recommendations of Spectrum Research, Inc. (SRI) regarding the need for update.

4. Conclusions (Appendix B, Table 2)

4.1 *Key Question 1:* What is the evidence of efficacy and effectiveness of spinal cord stimulation?

Efficacy: All conclusions are still valid and this portion of the CER does not need updating.

Effectiveness: All conclusions are still valid and this portion of the CER does not need updating.

4.2 *Key Question 2:* What is the evidence of the safety of spinal cord stimulation?

All conclusions are still valid and this portion of the CER does not need updating.

4.3 *Key Question 3:* What is the evidence that spinal cord stimulation has differential efficacy or safety issues in sub populations?

All conclusions are still valid and this portion of the CER does not need updating.

4.4 *Key Question 4:* What is the evidence of cost implications and cost-effectiveness of spinal cord stimulators?

- This section of the report could be updated with the results of the cost-effectiveness analysis of the cohort of Washington State workers' compensation patients with FBSS (Hollingworth (2011)[4].
- However, the addition of this analysis (which suggests that SCS is not cost-effective in this patient population compared with pain clinic or usual care) would not affect the coverage decision (SCS is not covered).

References:

1. Falowski SM, Celii A, Sestokas AK, Schwartz DM, Matsumoto C, Sharan A. Awake vs. asleep placement of spinal cord stimulators: a cohort analysis of complications associated with placement. Neuromodulation 2011;14:130-4; discussion 4-5.
2. Kumar K, Rizvi S, Bnurs SB. Spinal cord stimulation is effective in management of complex regional pain syndrome I: fact or fiction. Neurosurgery 2011;69:566-78; discussion 5578-80.
3. Wolter T, Kieselbach K. Cervical spinal cord stimulation: an analysis of 23 patients with long-term follow-up. Pain Physician 2012;15:203-12.
4. Hollingworth W, Turner JA, Welton NJ, Comstock BA, Deyo RA. Costs and cost-effectiveness of spinal cord stimulation (SCS) for failed back surgery syndrome: an observational study in a workers' compensation population. Spine (Phila Pa 1976) 2011;36:2076-83.
5. Kemler MA, Raphael JH, Bentley A, Taylor RS. The cost-effectiveness of spinal cord stimulation for complex regional pain syndrome. Value Health 2010;13:735-42.

Figure 1. Flow chart showing results of literature search

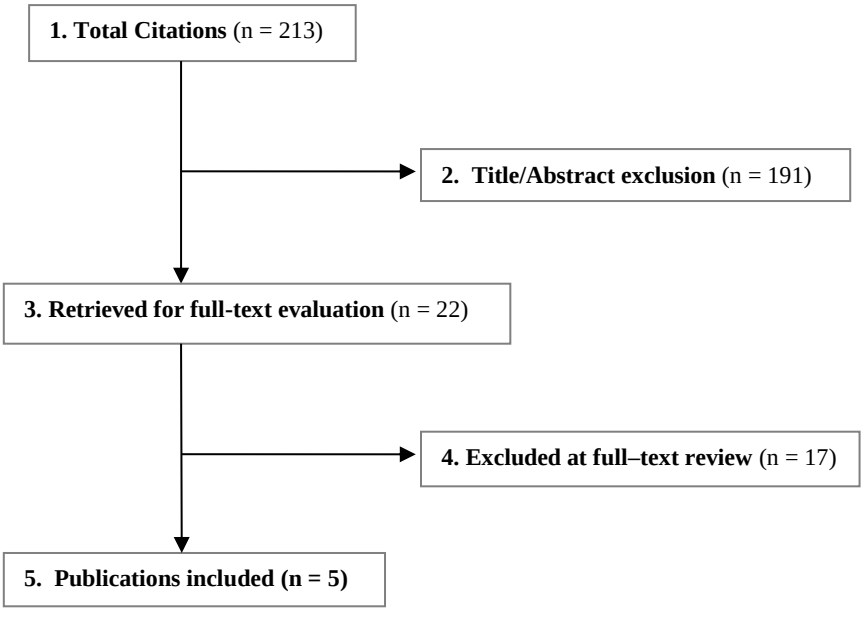
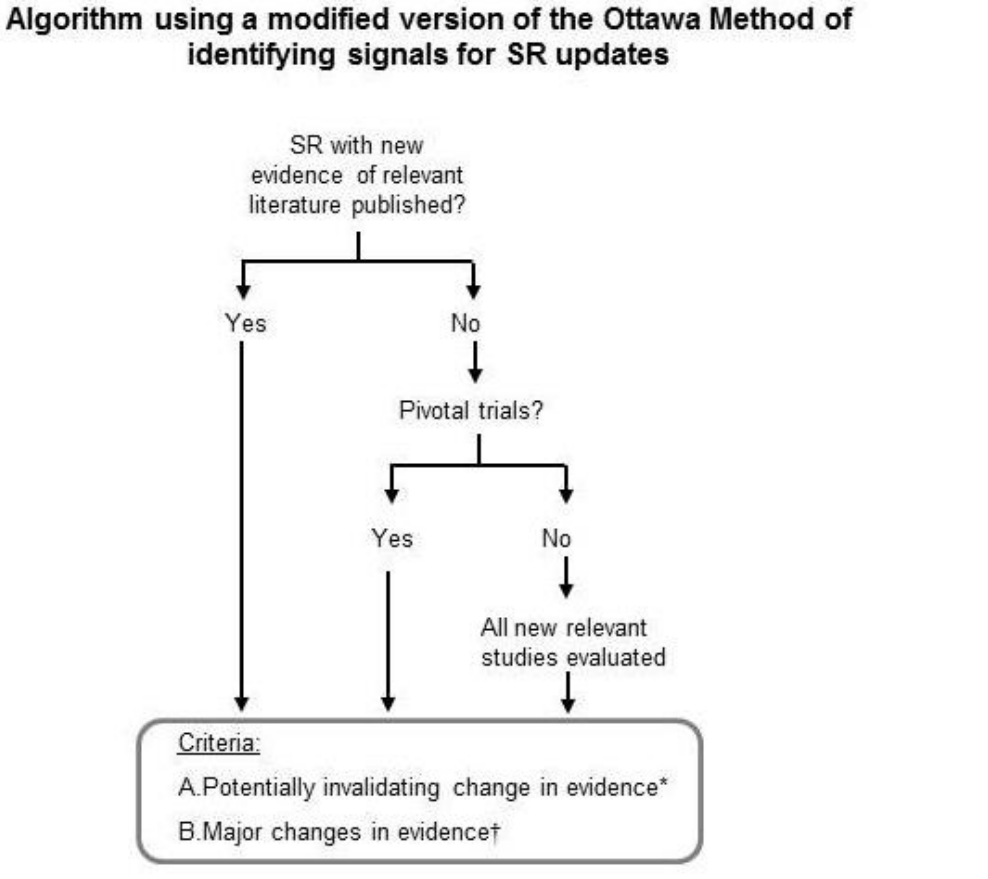


Figure 2. Algorithm of the Ottawa Method of Identifying Signals for SR Updates



*A-1. Opposing findings: Pivotal trial or SR including at least one new trial that characterized the treatment in terms opposite to those used earlier

A-2. Substantial harm: Pivotal trial or SR whose results called into question the use of the treatment based on evidence of harm or that did not proscribe use entirely but did potentially affect clinical decision making

A-3. Superior new treatment: Pivotal trial or SR whose results identified another treatment as significantly superior to the one evaluated in the original review, based on efficacy or harm.

†B-1. Important changes in effectiveness short of "opposing findings"

B-2. Clinically important expansion of treatment

B-3. Clinically important caveat

B-4. Opposing findings from discordant meta-analysis or nonpivotal trial

Table 1. List of excluded articles after full-text review

Study	Reason for Exclusion:
Systematic reviews	
Kelly GA, Blake C, Power CK, O'Keeffe D, Fullen BM. The impact of spinal cord stimulation on physical function and sleep quality in individuals with failed back surgery syndrome: a systematic review. Eur J Pain 2012;16:793-802.	Systematic review does not contain any studies published after the search period of the original HTA.
Krames ES, Monis S, Poree L, Deer T, Levy R. Using the SAFE principles when evaluating electrical stimulation therapies for the pain of failed back surgery syndrome. Neuromodulation 2011;14:299-311; discussion	Not a systematic review.
Levy R, Henderson J, Slavin K, et al. Incidence and avoidance of neurologic complications with paddle type spinal cord stimulation leads. Neuromodulation 2011;14:412-22; discussion 22.	Systematic review does not contain any relevant studies published after the search period of the original Washington State HTA.
Lihua P, Su M, Zejun Z, Ke W, Bennett MI. Spinal cord stimulation for cancer-related pain in adults. Cochrane Database Syst Rev 2013;2:CD009389	Systematic review does not contain any relevant studies published after the search period of the original HTA (SR included 4 case series, two of which were published after the search of the original HTA, and neither of these reported on adverse events following SCS).
Mailis A, Taenzer P. Evidence-based guideline for neuropathic pain interventional treatments: spinal cord stimulation, intravenous infusions, epidural injections and nerve blocks. Pain Res Manag 2012;17:150-8.	Systematic review does not contain any relevant studies published after the search period of the original HTA.
Manchikanti L, Abdi S, Atluri S, et al. An update of comprehensive evidence-based guidelines for interventional techniques in chronic spinal pain. Part II: guidance and recommendations. Pain Physician 2013;16:S49-283.	Systematic review does not contain any relevant studies published after the search period of the original HTA.
Pluijms WA, Slangen R, Joosten EA, et al. Electrical spinal cord stimulation in painful diabetic polyneuropathy, a systematic review on treatment efficacy and safety. Eur J Pain 2011;15:783-8.	Systematic review does not contain any relevant studies published after the search period of the original Washington State HTA.
Poree L, Krames E, Pope J, Deer TR, Levy R, Schultz L. Spinal cord stimulation as treatment for complex regional pain syndrome should be considered earlier than last resort therapy. Neuromodulation 2013;16:12	Not a systematic review.
Raff M, Melvill R, Coetzee G, Smuts J. Spinal cord stimulation for the management of pain: Recommendations for best clinical practice. S Afr Med J 2013;103:423-30.	Search period of systematic review portion does not extend beyond the search period of the original Washington State HTA.
Sparkes E, Raphael JH, Duarte RV, LeMarchand K, Jackson C, Ashford RL. A systematic literature review of psychological characteristics as determinants of outcome for spinal cord stimulation therapy. Pain 2010;150:284-9.	Search period does not extend beyond the search period of the original Washington State HTA.
van Wijck AJ, Wallace M, Mekhail N, van Kleef M. Evidence-based interventional pain medicine according to clinical diagnoses. 17. Herpes zoster and post-herpetic neuralgia. Pain Pract 2011;11:88-97.	Not a systematic review.

KQ1	
North RB, Kumar K, Wallace MS, et al. Spinal cord stimulation versus re-operation in patients with failed back surgery syndrome: an international multicenter randomized controlled trial (EVIDENCE study). Neuromodulation 2011;14:330-5; discussion 5-6.	Study protocol only; excluded as the trial has been terminated due to slow enrollment: http://clinicaltrials.gov/show/NCT01036529
KQ2	
Kim DD, Vakharyia R, Kroll HR, Shuster A. Rates of lead migration and stimulation loss in spinal cord stimulation: a retrospective comparison of laminotomy versus percutaneous implantation. Pain Physician 2011;14:513-24.	Case series with less than five years' follow-up.
Mekhail NA, Mathews M, Nageeb F, Guirguis M, Mekhail MN, Cheng J. Retrospective review of 707 cases of spinal cord stimulation: indications and complications. Pain Pract 2011;11:148-53.	Case series with less than five years' follow-up.
Zan E, Kurt KN, Yousem DM, Christo PJ. Spinal cord stimulators: typical positioning and postsurgical complications. AJR Am J Roentgenol 2011;196:437-45.	Case series with length of follow-up not reported.
KQ3	
Williams KA, Gonzalez-Fernandez M, Hamzehzadeh S, et al. A multi-center analysis evaluating factors associated with spinal cord stimulation outcome in chronic pain patients. Pain Med 2011;12:1142-53.	Case series, so LoE of IV (not I or II as specified in the inclusion criteria of the original HTA).
KQ4	
Taylor RS, Ryan J, O'Donnell R, Eldabe S, Kumar K, North RB. The cost-effectiveness of spinal cord stimulation in the treatment of failed back surgery syndrome. Clin J Pain 2010;26:463-9.	Article provides "previously unavailable details of the NICE cost-effectiveness analysis", which was included in the original HTA. This article reaches similar conclusions as those of the NICE analysis, that is, that SCS is cost-effective compared to CMM or re-operation in FBSS patients.

Appendix A.

The detailed strategy below is presented in Medline and EMBASE syntax.

Search Strategy
(May 2010 – December 6, 2013)
Limited to English language, human population

Database: MEDLINE

1.	"Spinal cord stimulation" OR "Spinal cord stimulation"[MeSH] OR "spinal cord stimulator" OR "spinal cord stimulators"
2.	#1 NOT "Case Reports"[Publication Type]

Database: EMBASE

'spinal cord stimulation'/exp OR 'spinal cord stimulator'/exp AND [humans]/lim AND [English]/lim AND [abstracts]/lim AND [5-1-2013]/sd NOT [12-1-2013]/sd AND [2010-2014]/py

Parallel strategies were used to search the Cochrane Library and others listed below. Keyword searches were conducted in the other listed resources.

Electronic Database Searches
The following databases have been searched for relevant information:

Agency for Healthcare Research and Quality (AHRQ)
Cumulative Index to Nursing and Allied Health (CINAHL)
Cochrane Database of Systematic Reviews (through 2009, Issue 2)
Cochrane Registry of Clinical Trials (CENTRAL) (through 2009, Issue 2)
Cochrane Review Methodology Database (through 2009, Issue 2)
Computer Retrieval of Information on Scientific Projects (CRISP)
Database of Reviews of Effectiveness (Cochrane Library) (through 2009, Issue 2)
EMBASE (1985 through July 23, 2009)
PubMed (1975 through July 23, 2009)
Informational Network of Agencies for Health Technology Assessment (INAHTA)
NHS Economic Evaluation Database (Cochrane Library through 2009, Issue 2)
HSTAT (Health Services/Technology Assessment Text)
EconLIT

Additional Economics, Clinical Guideline and Gray Literature Databases

AHRQ- Healthcare Cost and Utilization Project
Canadian Agency for Drugs and Technologies in Health
Centers for Medicare and Medicaid Services (CMS)
Food and Drug Administration (FDA)
Google
Institute for Clinical Systems Improvement (ICSI)
National Guideline Clearinghouse

Appendix B

Table 2. Spinal Cord Stimulation Summary Table

Conclusions from CER Executive Summary	New Sources of Evidence	New Findings	Conclusion from SRI
Key Question 1: What is the evidence of efficacy and effectiveness of spinal cord stimulation?			
1. a) Efficacy (Short-term, <5 years): **Pain, perceived effect of treatment/patient satisfaction:** There is moderate evidence from three small randomized controlled trials that SCS is superior to conventional therapies (CMM, physical therapy or re-operation) in patients with chronic neuropathic pain during the first 2–3 years with respect to patient reported outcomes of pain, and perceived effect of treatment/patient satisfaction. In the only RCT that measured outcomes for a longer period of time, the benefit of SCS decreased over time and was not significantly different than controls for leg pain after 3 years of treatment (see mid-term below). **Function, quality of life:** The effect on quality of life outcomes is less clear with one RCT reporting substantial benefit of SCS compared with CMM at 6 months follow-up, while another study found quality of life outcomes to be similar between SCS + physical therapy and physical therapy alone at 2 years follow-up. Similarly, function as measured by the Oswestry Disability Index score was better in the SCS group at 6 months versus CMM in one study but the ability to perform daily activities after 3 years was not different in a second study. The strength of this evidence is low. **b) Efficacy (Mid-term, 5-10 years):** **Pain, quality of life, perceived effect of treatment:** There is low evidence from one small randomized controlled trial that SCS is no different from conventional therapy (physical therapy) in patients with chronic neuropathic pain 5-10 years following implant with respect to pain, quality of life, and patient-reported global perceived effect. **c) Efficacy (Long-term, ≥10 years):** There are no data available to assess long-term efficacy.	None	None	• This section of the report is still valid and does not need updating

Conclusions from CER Executive Summary	New Sources of Evidence	New Findings	Conclusion from SRI
2. a) Effectiveness (Short-term, <5 years): **Composite of pain, function, and opioid use:** One prospective cohort study on workers' compensation patients reported similar success on a composite score that includes pain, function and opioid use between SCS and either Pain Clinic or Usual Care treatment groups. There was a modest improvement in leg pain in the SCS group compared with the control groups at 6 months follow-up but this did not persist at the 12 month or 24 month evaluation. **b) Effectiveness (Mid- and long-term, ≥5 years):** **T**here are no data available to assess mid- or long-term effectiveness.			
Key Question 2: What is the evidence of the safety of spinal cord stimulation?			
1. Revision There is high evidence from three randomized controlled trials, one prospective comparative cohort study and six case series that revision of SCS components is not uncommon. Overall short-term revision rates ranged from 12–38% of patients. Mid-term revision rates were 42% in one RCT and 60% in one case series. Reasons for revision include electrode repositioning or replacement, generator revision or replacement, revision of the connecting cable, and total removal and replacement of the system due to infection. There are no long-term data available. **2. Other SCS-related side effects** Side effects reported varied widely among studies and included infection, change in amplitude by bodily movements, paresthesia in other body parts, pain/irritation from the pulse generator, transient neurological defects, severe wound-related pain at the stimulator implantation site, cerebrospinal fluid leak, and subcutaneous hematoma. The rate of side effects could not be determined from the papers reviewed; however, one RCT reported that all patients experienced at least one side effect. **3. Mortality** There is high evidence that the rate of mortality due to SCS is low. Among the four comparative studies, 2 deaths were reported in patients receiving	3 case series: Falowski (2011)[1] Kumar (2011)[2] Wolter (2012)[3]	• There is very low evidence from three case series[1-3] of a total of 305 patients that revision rates from device failure, injection, device/electrode repositioning, electrode fracture, electrode replacement, battery end of life, or pain at the implantation site) range from 14% to 50% of patients. The mean length follow-up was >5 to 7.3 years. • There is very low evidence from one small case series of 25 patients that there were no bleeding complications; this series had a mean length follow-up of 7.3 years.[2] • There is very low evidence from one small case series of 18 patients that there were no severe neurological deficits; this series had a mean length follow-up of 5.8 years.[3]	• This section of the report is still valid and does not need updating

Conclusions from CER Executive Summary	New Sources of Evidence	New Findings	Conclusion from SRI
SCS (2/139); one as a result of a cardiac event six months following SCS implantation, and the cause of one was not reported. No deaths were recorded in the control groups during the same time period (0/179). Two additional deaths were identified in three case series with five year follow-up; one from a cerebrovascular accident in a patient implanted for cardiac ischemic pain, one as a result of suicide. No death was attributed to SCS; however one patient nearly died as a result of complications that arose following trial stimulation.		• There is very low evidence from one small case series of 18 patients that 22% of patients had pain at the implant site; this series had a mean length follow-up of 5.8 years.[3]	
Key Question 3: What is the evidence that spinal cord stimulation has differential efficacy or safety issues in sub populations?			
1. Age There is conflicting evidence whether patient age at baseline is associated with outcome. Two studies found that age did not correlate with either pain relief or success (combination of pain relief and patient satisfaction), while one study found that younger age was correlated with pain relief of at least 50%. One of these studies also reported no correlation between age and SF-36 or GPE scores. **2. Sex** There are mixed results regarding whether patient sex is associated with outcome following SCS. Three studies found that sex was not associated with pain relief, one showed no correlation between sex and SF-36 or GPE scores. In contrast, one study found that females had a significantly higher rate of success (pain relief and patient satisfaction), improved function and activity, and decreased medication usage at five years compared with males. **3. Workers' compensation or other disability payments** One prospective study suggests that whether patients receive workers' compensation/other disability payments or no compensation has no effect on pain relief among patients receiving SCS. Another prospective study found that among patients on workers' compensation, successful outcomes of pain relief, improved function and reduced opioid use was similar between SCS and two control treatment groups. The percentages of success were low in all groups.	None	None	• This section of the report is still valid and does not need updating

Conclusions from CER Executive Summary	New Sources of Evidence	New Findings	Conclusion from SRI
4. Duration of pain There is moderate evidence from three cohort studies that duration of pain prior to SCS implantation is not associated with pain relief or success within the first year after implantation. **5. Pain intensity** There is low evidence from one cohort study to suggest that pain intensity at baseline is not associated with success. **6. Time since first lumbar surgery** There is low evidence from one cohort study to suggest that time since first lumbar surgery is not predictive of success. **7. Number of prior surgeries for pain** There is moderate evidence from two cohort studies to suggest that the number of prior of operations for pain is not associated with pain relief (or success). One study additionally found no correlation between prior operations for pain and function/activity/medication usage at five years. **8. Pain location** There is low evidence from four cohort studies that pain location does not affect outcomes. **9. Laterality of pain** There is low evidence from one cohort study on FBSS patients with open workers' compensation claims that patients with unilateral pain have better pain relief and functional outcomes (as measured by the RDQ) at 12 months compared with patients with bilateral pain. **10. Allodynia or hypoesthesia at baseline** There is low evidence from one cohort study that the presence of allodynia at baseline negatively correlates with success at one year, while the presence of hypoesthesia at baseline was not predictive of success. **11. McGill Pain Questionnaire**			

Conclusions from CER Executive Summary	New Sources of Evidence	New Findings	Conclusion from SRI
There is conflicting evidence from two studies that the McGill Pain Questionnaire is associated with pain relief or success at follow-up with conflicting results. One study found an association between the evaluative subscale while the other study found no association with any subscale and outcome. **12. Minnesota Multiphasic Personality Inventory (MMPI)** There is conflicting evidence from two studies that the MMPI is associated with pain relief or success at follow-up with conflicting results. One study found an association between the depression subscale while the other study found no association with any subscale and outcome. **13. SF-36 Mental Health scores** There is low evidence from one cohort study on FBSS patients with open workers' compensation claims that patients with baseline SF-36 Mental Health scores in the top third have better pain relief and functional outcomes (as measured by the RDQ) at 12 months than do those patients who scored in the bottom third at baseline.			
Key Question 4: What is the evidence of cost implications and cost-effectiveness of spinal cord stimulation?			
Cost Effectiveness There is moderate evidence from three complete economic evaluations that in the short-term, SCS is associated with improved outcomes and increased costs compared with CMM and/or re-operation for the treatment of neuropathic pain. In the long-term, SCS appears to be dominant over the control treatments; however, only one study included in this assessment was conducted in a U.S. setting. More specifically, we found that there is some evidence that SCS is cost-effective at moderate (<$20,000) incremental cost effectiveness ratio (ICER) levels compared with CMM or re-operation, and that SCS cost-effectiveness increases and may be dominant over time compared with control treatments (i.e., CMM or re-operation) assuming device longevity of 4 years and at least a 30% pain threshold criteria. However, the assumption of continued efficacy past 3 years is questionable from the only RCT reporting pain 5-10 years after implantation. Furthermore, only one study was conducted in a US setting.	2 cost-effectiveness analyses: Hollingworth (2011)[4] Kemler (2010)[5]	• Hollingworth (2011)[4] evaluated the cost-effectiveness of SCS compared to pain clinic or usual care in a cohort of Washington State workers' compensation patients with FBSS. SCS was not cost-effective compared with usual care or pain clinic treatment. • Kemler (2010) conducted a re-analysis of the data used in the NHS/NICE cost-effectiveness analysis of CRPS I patients, though the update was not published by NHS/NICE. The NHS/NICE analysis was included in the original HTA.	• This section of the report could be updated with the results of the cost-effectiveness analysis of the cohort of Washington State workers' compensation patients with FBSS. • However, the addition of this analysis (which suggests that SCS is not cost-effective in

Conclusions from CER Executive Summary	New Sources of Evidence	New Findings	Conclusion from SRI
		This analysis arrived at similar conclusions as the original NHS/NICE evaluation, where SCS plus CMM is cost-effective compared to CMM alone. • The ICER of £3562 per QALY for SCS compared with CMM was lower than that reported in the NHS/NICE report (£25,095 per QALY) (and included in the original HTA).	this patient population compared with pain clinic or usual care) would not affect the coverage decision (SCS is not covered).

Appendix C. Demographic table

Table 3. Spinal cord stimulation studies demographic table

Author (Year) Study type	Key Question	Demographics	Results	Conclusion

Falowski 2011
 	
Case series
	KQ2	N = 259
		(167 new device implantations, 220 re-operations for device failure, device repositioning, battery end of life, infection)
		Male: NR
		Age: NR
		F/U: >5 years (details NR)
		
		Diagnosis:
		Neuropathic pain
		
		Intervention:
		SCS implanted while patient awake (76 first-time procedures) or under general anesthesia (91 first-time procedures)
			Safety:
			• Device failure (including multiple surgeries); f/u: > 5 years (*Failure*: any re-operation secondary to a traumatic break in the SCS system, a device malfunction requiring re-exploration, or a device removal secondary to lack of efficacy)
			  • Range: 14.9% - 29.7% of procedures
			  • SCS implanted while patient awake: 29.7%
			  • SCS implanted while patient asleep: 14.9%
			• Infection requiring device explantation; f/u: NR (details NR)
			  • Range: 4.5% - 5.7% of procedures
			  • SCS implanted while patient awake: 4.5%
			  • SCS implanted while patient asleep: 5.7%
			• Electrode repositioning; f/u: NR (details NR)
			  • Range: 14.9 – 17.9% of procedures
			  • SCS implanted while patient awake: 17.9%
			  • SCS implanted while patient asleep: 14.9%
				Safety:
				• Device failure occurred in 14.9% to 29.7% of procedures (exact number not calculable)
				• Infection requiring device explantation occurred in 4.5% to 5.7% of procedures (exact number not calculable)
				• Electrode repositioning occurred in 4.5% to 5.7% of procedures (exact number not calculable)

Kumar (2011) Case series	KQ2	N = 28 Male: 43% Age: 51 (32-82) years F/U: 7.3 (1.5-19.6) years Diagnosis: CRPS I	**Safety:** • Device repositioning: 20% (5/25) • Electrode fracture: 5% (1/25) • Electrode repositioning:20% (5/25) • Electrode replacement: 44% (11/25) • Battery end of life: 40% (10/25) • Hardware malfunction: 0% (0/25)	• This small case series suggested that when followed in the long-term (mean follow-up: 7.3 years), patients have a relatively high rate of hardware complications requiring re-operation (ranging from 0% to 44% of patients). The incidence of

Author (Year) Study type	Key Question	Demographics	Results	Conclusion
		Intervention: SCS	• Infection requiring explantation and re-implantation: 5% (1/25) (occurred 3 times) • Bleeding: 0% (0/25)	infection and bleeding were low (5% and 0%, respectively).

Wolter (2012)
 	
Case series
	KQ2	N = 18
		Male: 3%
		Age: 54 (34-78) years
		F/U: 5.8 (0.4-21) years
		
		Diagnosis:
		Various types of cervical neuropathic pain
		
		Intervention:
		SCS
			Safety:
			• Total "unscheduled" re-operations: 50% (9/18) patients (14 procedures), including but not limited to:
			  • Lead dislocation: 28% (5/18)
			  • Lead breakage: 28% (5/18)
			  • Revision or relocation due to pain at the pocket site: 11% (2/18)
			  • Battery end of life: 11% (2/18)
			• Infection ("severe complication"): 0% (0/18)
			• Neurological deficit ("severe complication"): 0% (0/18)
			• Pain at IPG site: 22% (4/18)
				• This small case series reported that when followed in the long-term (mean follow-up: 5.8 years), 50% of patients had at least one hardware complication requiring re-operation. Further, 22% of patients had pain at the IPG site. There were no cases of infection or neurological deficit.

Hollingworth (2011)
 	
Cost-effectiveness study
	KQ4	Population: FBSS patients in the published Turner 2010 prospective cohort study of Washington State workers' compensation patients*
		
		Diagnosis:
		FBSS
		
		Intervention:
		SCS (n = 51)
		
		Comparators:
		1. Pain clinic (PC)
			Recap of effectiveness results†:
			• Effectiveness results used for this analysis were included in the original HTA†
			• Primary outcome (24 months):
			  • SCS: 5%
			  • PC: 3%
			  • UC: 10%
			  • No significant differences between any groups.
			
			Cost-effectiveness results:
			• Incremental cost per success (i.e., achieving the primary outcome):
			SCS (n = 43) vs. UC (n = 61) (patients who completed 24 month f/u for primary outcome):
			  • Unadjusted incremental cost per patient achieving success on primary outcome: UC less
				• In a cohort of Washington State workers' compensation patients with FBSS, SCS was not cost-effective compared with usual care or pain clinic treatment.

Author (Year) Study type	Key Question	Demographics	Results	Conclusion
		(n = 39) 2. Usual care (UC) (n = 68) <u>Cost-effectiveness analysis</u>: • Costs converted into 2007 US dollars • After first year of enrollment, costs discounted 3% • Incremental cost-effectiveness defined as cost per successful outcome (i.e., additional cost of SCS/additional percentage of SCS patients achieving the primary outcome at 24 months) • Primary outcome: composite of ≥ 50% leg pain relief relative to baseline, a 2-point or greater improvement in the Roland-Morris Disability Questionnaire, and less than daily opioid medication use	costly, more effective ($632,067: UC dominates) • Adjusted‡ incremental cost per patient achieving success on primary outcome: $334,704 (95% credible intervals, $142,203 - $489,243) <u>SCS (n = 43) vs. PC (n = 34) (patients who completed 24 month f/u for primary outcome):</u> • Unadjusted incremental cost per patient achieving success on primary outcome:: $846,977 • Adjusted‡ incremental cost per patient achieving success on primary outcome: $131,146 (95% credible intervals: $271,075) (SCS dominates) <u>Permanent SCS implantation (n = 27) vs. PC (n = 22) (patients who completed 24 month f/u for cost data and primary outcome):</u> • Unadjusted incremental cost per patient achieving success on primary outcome:: $520,315 (PC dominates) • Unadjusted incremental cost per patient achieving success on leg pain outcome: $436,512 (PC dominates) • Unadjusted incremental cost per patient achieving success on Roland Morris Disability Score: $140,049 (PC dominates)	

Author (Year) Study type	Key Question	Demographics	Results	Conclusion
Kemler (2010) Re-analysis of the data used in the NHS/NICE cost-effectiveness analysis of CRPS patients§ (update not published by NHS/NICE) Study sponsored by Medtronic	KQ4	Population: CRPS I patients as included in the Kemler 2000 RCT** (patient-level data available here but not in NHS analysis) Diagnosis: CRPS I Intervention: SCS + CMM Comparator: CMM alone Cost-effectiveness analysis: • NHS perspective • Time period: 15 years • Two-stage decision analytic tree and Markov model used • Primary outcome: ≥ 50% pain relief at 6 months	**Cost-effectiveness results (SCS + CMM versus CMM):** • Cost difference: £6,994 higher with SCS • QALY difference: 1.96 higher with SCS • ICER (SCS relative to CMM): £3562 per QALY	• SCS + CMM is cost-effective compared to CMM alone, with an 87% probability that SCS is cost-effective at a willingness to pay threshold of £30,000. • The ICER of £3562 per QALY for SCS compared with CMM was lower than that reported in the NHS/NICE report (£25,095 per QALY) (and included in the original HTA)

Abbreviations: CMM: conventional medical management; CRPS I: chronic regional pain syndrome I; FBSS: failed back surgery syndrome; F/U: follow-up; ICER: incremental cost-effectiveness ratio; IPG: implantable pulse generator; KQ: key question; NA: not applicable; NS: not statistically significant; RCT: randomized controlled trial; SCS: spinal cord stimulation; UC: usual care

* This study was included in the original HTA report to evaluate effectiveness of SCS versus pain clinic versus usual care. Reference: Turner JA, Hollingworth W, Comstock BA, Deyo RA. Spinal cord stimulation for failed back surgery syndrome: outcomes in a workers' compensation setting. Pain 2010;148:14-25.

† Conclusions from the original report:

Turner et al. (2010) "provided data on the short-term effectiveness of SCS compared with Pain Clinic and Usual Care treatments in FBSS patients with open workers' compensation claims in the State of Washington. In general, the cohort study found no differences in outcomes between patients in the SCS and two control groups.

- ***"Success" from a composite score:*** There was no difference between SCS, pain clinic (PC), or usual care (UC) groups at any follow-up up to 24 months in the percent of patients achieving the primary outcome composite measure of success (includes pain, function, and medication usage components).
- ***Pain relief:*** Significantly more patients in the SCS group achieved ≥ 50% leg pain relief by six months than those in the UC group, there was no difference between the SCS and PC group at the same follow-up; furthermore, no differences were identified between groups in the percentage of patients achieving leg pain relief of ≥ 50% or more at the 12- and 24-month follow-ups.
- ***Function:*** There were no significant differences in either the Roland-Morris Disability Questionnaire (RDQ) scores or ability to perform daily tasks between treatment groups in the prospective cohort study on workers' compensation patients.
- ***Health-related quality of life (HR-QoL):*** Reported no significant differences between treatment groups in SF-36 scores and work/disability status.
- ***Medication usage:*** Although significantly fewer patients in the SCS group used opioids on a less than daily basis than did those in the PC group at six months, no other significant differences between treatment groups were identified in the prospective cohort study on workers' compensation patients.

‡ Adjusted for baseline characteristics (cost in the year prior to enrollment, age, SF-36 mental health score, disability payments from another source, Roland-Morris Disability Questionnaire score, leg-pain intensity, duration of work time loss compensation, and legal representation)

§ NICE/NHS economic analysis included in original HTA; Simpson E, Duenas A, Holmes M, Papaioannou D, Chilcott J. Spinal cord stimulation for chronic pain of neuropathic or ischaemic origin: systematic review and economic evaluation. Health Technology Assessment 2009;13:1-179

** Kemler RCT included in original HTA; Kemler MA, Barendse GA, van Kleef M, et al. Spinal cord stimulation in patients with chronic reflex sympathetic dystrophy. N Engl J Med 2000;343:618-24.