



**INSTITUTE OF  
HEALTH ECONOMICS**  
ALBERTA CANADA

# **SPINAL CORD STIMULATION FOR NEUROPATHIC PAIN**

## **SUMMARY OF THE LITERATURE**

**Canadian Pain Society Special Interest Group on  
Neuropathic Pain**

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## **PREFACE**

During 2005 and 2006, the Canadian Pain Society Special Interest Group on Neuropathic Pain (NeP SIG) produced a clinical practice guideline on the pharmacological management of neuropathic pain. In 2007, the NeP SIG began developing a guideline on the use of other interventions for neuropathic pain, such as spinal cord stimulation, deep brain stimulation, nerve blocks (sympathetic blocks; nerve and nerve root blocks; trigger point blocks, epidural blocks, and other spinal injections); psychological treatments such as cognitive behavioural therapy, relaxation, biofeedback, meditation, hypnosis; and physical and occupational therapy modalities/interventions such as graded exposure to stimulation, mirror visual reprogramming, stretching, exercises, acupuncture, transcutaneous electrical nerve stimulation, transcranial magnetic stimulation, and multidisciplinary pain management programs. In 2007, a survey of NeP SIG members was undertaken to help prioritize this list of interventions. The results of the survey indicated that among the aggressive treatments used for neuropathic pain, the following four were considered high priority by the NeP SIG members:

- Epidural blocks.
- Nerve blocks.
- Intravenous infusions.
- Spinal cord stimulation.

In order to facilitate the development of the NeP SIG guideline on interventions for neuropathic pain, the Institute of Health Economics was recruited to assist in gathering and rating the quality of the available scientific literature on the four abovementioned interventions.

## **SCOPE OF THE PAPER**

This report provides a summary and critical appraisal of the available published evidence from the international medical literature regarding the use of epidural blocks, nerve blocks, intravenous infusions, and spinal cord stimulation for the treatment of neuropathic pain.

This literature summary was conducted according to a predefined methodology that was formulated in consultation with NeP SIG representatives. It does not represent a systematic review of the literature on this topic; thus, no firm conclusions are offered on the safety or effectiveness of the interventions described. In addition, the evidence was only summarized and no attempt was made to assess the veracity of the information contained within the included studies.

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## **METHODS**

### **Inclusion criteria**

#### ***Types of studies***

Systematic reviews (SRs), randomized controlled trials (RCTs), and clinical practice guidelines (CPGs) were included.

#### **Systematic reviews**

An article was deemed to be a SR if it met all of the following criteria as defined by Cook et al.:<sup>1</sup>

- 1) Focused clinical question.
- 2) Explicit search strategy.
- 3) Use of explicit, reproducible, and uniformly applied criteria for article selection.
- 4) Critical appraisal of the included studies.
- 5) Qualitative or quantitative data synthesis.

#### **Randomized and quasi-randomized controlled trials**

Randomized controlled trials were included. Trials using a quasi-random method of treatment allocation (quasi-randomized controlled trials), such as date of birth, day of the week, or medical record number, were also included.

#### **Clinical practice guidelines**

CPGs are most commonly defined as “systematically developed statements to assist practitioner and patient decisions about appropriate health care for specific clinical circumstances”.<sup>2</sup> For a CPG to be valid, the evidence supporting its recommendations must be cited.<sup>2,3</sup> Therefore, an article was deemed to be a CPG if it met all of the following criteria:

- 1) It contained the word ‘guideline’ or ‘recommendation’ in its title or introduction, or contained recommendations on managing patients with neuropathic pain in the form of advice or instructions.<sup>4</sup>
- 2) It was developed by at least two authors.
- 3) It was evidence-based.

CPGs that were not evidence-based, such as consensus statements that contained recommendations based only on expert opinion, were excluded.

Only CPGs formulated in countries with developed market economies were included since the health status, cultural norms, access to health care, and disease burden of individuals from countries with transitional or developing economies were likely to be too different from those of Canada to be clinically relevant. Countries deemed to have developed economies, as defined by the United Nations were as follows: Australia, Canada, Japan, New Zealand, the United States of America, and Europe (except for Albania, Bulgaria, Czech Republic, Hungary, Poland, Romania, Slovakia, Bosnia and Herzegovina, Croatia, Slovenia, the former Yugoslav Republic of

Macedonia, Yugoslavia, Estonia, Latvia, Lithuania, Belarus, the Republic of Moldova, the Russian Federation, and Ukraine).<sup>5</sup>

### ***Participants***

Data were collected on adult patients (18 years of age or older) with a peripheral or central neuropathic pain condition of any duration. Studies that referred to ‘patients’ or ‘adult patients’ without providing a specific age range were also included. However, any study that clearly included patients under the age of 18 years was excluded.

Patients with cancer pain were excluded unless they had a defined post-surgical pain syndrome with neuropathic contribution, such as post-mastectomy pain. Patients with visceral pain, migraine, headache, fibromyalgia, or ischemic pain were excluded.

### ***Index Intervention***

Any type of implantable spinal cord stimulator.

### ***Comparative intervention***

Any medical, mechanical, or surgical intervention designed to treat patients with neuropathic pain. Placebo and no treatment comparisons were also included. Studies that compared technical aspects or different modalities of spinal cord stimulation were excluded.

### ***Literature search strategy***

The medical literature was searched to identify relevant, publicly available SRs, RCTs, and CPGs published in English from January 1997 to May 2008 (see Appendix A for the search terms and databases used). Although the bibliographies of articles retrieved in hard copy form were not systematically searched for relevant references that may have been missed in the database searches (pearling), any additional relevant references accidentally uncovered during the examination of these full-text articles were retrieved.

### ***Literature selection process***

Study selection was conducted by one reviewer. Articles were excluded that, on the basis of their abstract, clearly did not meet the inclusion criteria. Copies of the full text of potentially eligible studies were retrieved. In some cases, when the full text of the article was retrieved, closer examination revealed that it did not meet the inclusion criteria. Consequently, these papers were excluded (Appendix B).

### ***Systematic reviews***

In cases where multiple SRs on a single topic were identified that were of the same quality and had identical comparators and patient populations, only the most recently published SR was included. In cases where a SR described a particular subgroup of neuropathic pain patients (e.g. postherpetic neuropathy, radiculopathy) or used different or additional comparators to those of the most recent SR, both SRs were included.

### ***Randomized and quasi-randomized controlled trials***

RCTs or quasi-RCTs that covered the same interventions and patient groups detailed in the included SRs and were published after the end date of the search strategy of the included SRs

were also included. When overlapping patient groups were reported in RCTs, only the paper quoting the most complete data set was used.

### ***Clinical practice guidelines***

In cases where multiple CPGs on a single topic were identified that were of the same quality and had identical comparators and patient populations, only the most recently published CPG was included. In cases where a CPG described a particular subgroup of neuropathic pain patients (e.g. postherpetic neuropathy, radiculopathy) or used different or additional comparators to those of the most recent CPG, both CPGs were included.

In cases where multiple CPGs on a single topic were identified that had identical comparators but were of differing quality, only the highest quality CPG was included if it was also the most recent. If the highest quality CPG was not the most recent, then both the highest quality CPG and the most current CPG, regardless of its quality, were included.

### **Assessment methods**

#### ***Study methodology appraisal***

The included studies were assessed with respect to various aspects of methodology and reporting using checklists specific for each particular study type (Appendices C, D, and E). The quality assessments were undertaken independently by two reviewers. The checklists were operationalized by constructing dictionaries that explained each criterion. The two reviewers discussed the dictionaries with respect to the interpretation of questions prior to assessing the studies. Critical appraisal results for all included studies are tabulated in Appendices C, D, and E.

#### **Systematic reviews**

The included SRs were assessed using a checklist developed in-house that was adapted from a number of sources (Appendix C).<sup>6-9</sup> This tool was chosen because it is more detailed and less subjective than other commonly used tools, such as the AMSTAR<sup>10</sup> and Oxman and Guyatt<sup>11</sup> checklists, and the reviewers were very experienced in its use. Any disagreements in scoring between the two reviewers that could not be resolved by discussion were referred to a third reviewer for mediation until consensus was reached.

The quality of SRs was assessed according to how well their methods excluded bias and confounding by examining: the search strategy used; how the data extraction, quality assessment of the included studies, and data analysis/synthesis were conducted; and whether the conclusions of the review match the results. Thus, the quality of the SR was rated numerically with respect to six quality subsections (grey boxes in checklist) as follows:

***Good*** – six criteria met, or five criteria met and one criterion ‘unclear’.

***Average*** – one criterion not met, or one criterion not met and one criterion ‘unclear’, or two criteria ‘unclear’.

***Poor*** – at least two criteria not met.

#### **Randomized controlled trials**

The included RCTs were assessed using the criteria list recommended in the method guidelines of the Cochrane Back Review Group for SRs<sup>12</sup> (Appendix D). This list has been used

in a number of SRs<sup>13-15</sup> in the field of chronic pain and includes all the criteria from the lists generated by Jadad et al.<sup>16</sup> and Verhagen et al.<sup>17</sup> It consists of internal and external validity criteria, as well as statistical criteria. The list was modified by removing items E (Was the care provider blinded?) and G (Was compliance acceptable?), since blinding of the care provider is generally not possible in SCS and compliance is not a relevant issue when SCS is the sole treatment. In addition, some instructions were reworded or supplemented with more detailed criteria descriptions from Downs and Black.<sup>18</sup> A simple nominal rating scale was used such that the studies were scored as positive (yes), negative (no), or unclear (don't know) for each quality criterion. Any disagreements in scoring between the two reviewers that could not be resolved by discussion were referred to a third reviewer for mediation until consensus was reached.

For descriptive purposes, the included RCTs were referred to as being good, moderate, or poor quality with respect to internal and external validity according to the total number of criteria met as follows:

- Internal validity (total number of criteria = 9) – good ( $\geq 7$  criteria met), moderate (between 4 and 6 criteria met), poor ( $< 4$  criteria met).
- External validity (total number of criteria = 6) – good ( $\geq 5$  criteria met), moderate (3 or 4 criteria met), poor ( $< 3$  criteria met).

### **Clinical practice guidelines**

The included CPGs were assessed using the Appraisal of Guidelines for Research and Evaluation (AGREE) instrument<sup>19</sup> (Appendix E). The AGREE instrument is an internationally developed, generic tool that is validated, transparent, and widely accepted, with satisfactory reliability for most domains. The instrument has 23 key items organized into six domains: scope and purpose (items 1-3); stakeholder involvement (items 4-7); rigor of development (items 8-14); clarity of presentation (items 15-18); applicability (items 19-21); and editorial independence (items 22-23).

The tool is accompanied by a detailed User Guide that explains how to score the 23 items. Each guideline is assessed using a 4-point scale (ranging from 4 = “strongly agree” to 1 = “strongly disagree”) to rate each of the 23 items. These scores are then combined for each of the six domains and converted into standardized domain scores according to the following formula:

$$\text{Standardized domain score (\%)} = \frac{\text{obtained score} - \text{minimum possible score}}{\text{maximum possible score} - \text{minimum possible score}} \times 100$$

The six domain scores are independent and cannot be combined into a single score. Instead, appraisers can provide an overall assessment of the guideline according to the following categories:

- Strongly recommended.
- Recommended (with provisos or alterations).
- Would not be recommended.
- Unsure.

Two modifications were made to the AGREE tool to reduce the ambiguity and subjectivity associated with item scoring, and to enable the differentiation of good from poor quality guidelines.

- 1) A detailed set of instructions, or dictionary, based on the AGREE guidance was constructed using logical operators (AND, OR, NOT) to quantify what constitutes a score of 4, 3, 2, or 1 for each of the 23 items.
- 2) Seven “essential” criteria were identified for categorizing guidelines as good, moderate, or poor quality.<sup>20</sup>
  - Item 8: Systematic search conducted
  - Item 10: Methods used to formulate recommendations described
  - Item 12: Link between recommendations and evidence
  - Item 13: External review by experts
  - Item 15: Specific, unambiguous recommendations
  - Item 22: Editorially independent from funder
  - Item 23: Conflicts of interest reported

The scores from the two reviewers were combined into an average quality score (maximum possible of 28 [7x4]), which was then rated as follows:

**Good** –score of 22 to 28;

**Average** –score of 15 to 21;

**Poor** –score 0 to 14.

### **Outcome measures and data extraction**

Study profile information, as well as relevant safety and efficacy data, was extracted by one reviewer using standardized data extraction forms developed *a priori*.

## SUMMARY OF THE LITERATURE

Thirty-eight studies were identified that potentially met the inclusion criteria. On closer examination of the full text article, 34 of these studies were excluded and the reasons documented (Appendix B). One SR and one CPG were included. Two RCTs that were published after the end date of the search strategy of the included SR and met the inclusion criteria were also included (Table 1). When overlapping patient groups were reported in the RCTs, only the paper quoting the most complete data set was used.

Study profiles of the included studies are summarized in Tables 2 to 4. The relevant safety and efficacy data extracted from each of the included studies are tabulated in Tables 5 to 7.

**Table 1: Summary of included studies**

Study	Year	Quality Rating	Pain Condition
<b>Systematic Reviews</b>			
Ontario Ministry of Health and Long-Term Care <sup>21</sup>	2005	Poor (3/6)	Failed back surgery syndrome Complex regional pain syndrome Types I and II Postherpetic neuralgia
<b>Randomized Controlled Trials</b>			
Kemler et al. <sup>22</sup>	2008	<i>Internal validity</i> Moderate (6/9) <i>External validity</i> Good (6/6)	Chronic regional pain syndrome type I Physical therapy (n=18) vs PT plus SCS (n=36)
Kumar et al. <sup>23</sup>	2007	<i>Internal validity</i> Good (9/9) <i>External validity</i> Good (6/6)	Failed back surgery syndrome Medical management (n=48) vs MM plus SCS (n=52)
<b>Clinical Practice Guidelines</b>			
Cruccu et al. <sup>24</sup>	2007	Average (21.5/28)	Neuropathic pain

## STUDY PROFILES – SYSTEMATIC REVIEWS

Table 2: Study profiles for *systematic reviews* on spinal cord stimulation for neuropathic pain

Systematic Review	Population	Selection Criteria/Outcomes	Methods
<p>Ontario Ministry of Health and Long-Term Care (2005)<sup>21</sup></p> <p><b>Objective:</b> To determine the effectiveness of spinal cord stimulation (SCS) for managing chronic, intractable neuropathic pain.</p> <p><b>Financial support:</b> Not reported. Prepared by the Medical Advisory Secretariat, Ontario Ministry of Health and Long-Term Care.</p> <p><b>Conflict of interest:</b> Not reported.</p>	<p><b>Total number:</b> n = not reported for health technology assessments; n = 104 for RCTs; n = 133 for case series studies.</p> <p><b>Age:</b> Adults.</p> <p><b>Included conditions:</b> - Neuropathic pain; - Failed back surgery syndrome with leg pain equal to or greater than low back pain; - Pain for at least 6 months and/or have failed conservative treatments.</p> <p><b>Excluded conditions:</b> Chronic mechanical back pain, ischemic limb or cardiac pain.</p>	<p><b>Intended comparators:</b> Conventional pharmacological, non-pharmacological or surgical therapies; self-controlled (case series studies).</p> <p><b>Study inclusion criteria:</b> Systematic reviews, randomized controlled trials (RCTs), prospective non-RCTs, before-and-after case series studies; publicly available health technology assessments.</p> <p><b>Study exclusion criteria:</b> Studies that: did not include a subjective measure of pain intensity; compared technical factors of SCS; had a mixed sample of pain conditions where the separate results for each pain type were not reported; or duplicated results of the same study sample reported previously.</p> <p><b>Outcomes measured:</b> <i>Primary:</i> pain relief. <i>Secondary:</i> functional status, quality of life, technical failures, and procedural complications.</p>	<p><b>Literature search:</b> <u>Time Period:</u> 2000 to January week 3, 2005. <u>Limits:</u> Human studies. Foreign language studies were included to determine bias in reviewing only English language reports. <u>Databases:</u> MEDLINE, EMBASE, Cochrane Database of systematic Reviews, Cochrane CENTRAL, INAHTA.</p> <p><b>Data extraction:</b> Methods not reported.</p> <p><b>Appraisal of study quality:</b> RCTs assessed with Jadad scale.<sup>16</sup> The quality of other study types was described narratively; a level of evidence table was used to categorize the RCTs and case series studies.</p> <p><b>Data analysis:</b> Semi-quantitative – number needed to treat calculated for some RCT outcomes.</p> <p><b>Conclusions supported by results:</b> Yes.</p>

## STUDY PROFILES – RANDOMIZED CONTROLLED TRIALS

Table 3: Study profiles for *randomized controlled trials* on spinal cord stimulation for neuropathic pain

Authors/Study Details	Intervention/Outcome Measures	Study Design/Execution
<p>Kemler et al. (2008)<sup>22</sup> The Netherlands <u>Study design:</u> Prospective randomized concurrently controlled trial. <u>Follow-up:</u> 1, 3, 6, 12, 24, 36, 48, and 60 months. <u>Study period:</u> March 1997 to July 1998. <u>Setting:</u> University hospital and medical centre. <u>Financial support:</u> Dutch Health Insurance Council.</p>	<p><b>Physical therapy (PT) (n=18)</b> A 6-month program of exercises involving a graded activity approach aimed to improve endurance, mobility, and function of the affected extremity. Continuation after 6 months was optional.</p> <p><b>PT plus spinal cord stimulation (SCS) (n=36)</b> All patients underwent a ≥7-day home screening trial after which those experiencing at least 50% reduction in pain during the last 4 days of testing or reporting “much improvement” (6 points) on a 7-point global perceived effect scale received an implantable SCS system. Patients not meeting these criteria continued with PT alone without a permanent SCS implant. <u>SCS system:</u> Itrel<sup>®</sup>3 system (Medtronic, Inc., Minneapolis, MN, USA). <u>Stimulation parameters:</u> Amplitude range of 0 to 10 V, pulse width of 210 µs, and rate of 85 Hz.</p> <p><b>PT &amp; SCS</b> <u>Outcome measures:</u> Pain intensity (visual analog scale); global perceived effect (ranging from 1 = worst to 7 = best ever); health-related quality of life (Nottingham Health Profile, Sickness Impact Profile-68, the EQ-5D, and the Self-Rating Depression Scale); technical and surgical complications.</p>	<p><u>Method of randomization:</u> Computer generated table of random numbers with stratification according to the location of disease (hand or foot). Ratio 2:1 for SCS:PT. <u>Time of randomization:</u> After baseline assessment. <u>Method of allocation concealment:</u> Randomization was assigned by independent investigator who contacted the patient by telephone. <u>Details of blinding:</u> Blinding not attempted. <u>Participation rate:</u> 85.5% (16/110). <u>Eligibility rate for study:</u> 42.6% (40/94). <u>Intention-to-treat analysis:</u> As-treated analysis since 4 PT patients who received SCS were excluded from analysis. <u>Crossovers:</u> Treatment crossovers were excluded from analysis. <u>Provider:</u> Not reported. <u>Assessor details:</u> Not reported. <u>Inclusion criteria:</u> Patients meeting the International Association for the Study of Pain criteria for chronic regional pain syndrome type I; age between 18 and 65 years; disease clinically restricted to ne extremity but affecting the whole hand or foot; disease duration of at least 6 months; failed previous standard therapy; a mean pain intensity of at least 5 cm (range 0 to 10) on a visual analog scale. <u>Exclusion criteria:</u> Presence of Raynaud disease; presence or history of neurological abnormalities unrelated to chronic regional pain syndrome type I; another condition affecting the function of diseased or contralateral extremities; blood clotting disturbances or anticoagulation drug therapy; presence of a cardiac pacemaker; a score of ≥200 on the psychological test Symptom Check List-90. <u>Conclusions supported by results:</u> Yes.</p>

**Table 3: Study profiles for randomized controlled trials on spinal cord stimulation for neuropathic pain (cont'd)**

Authors/Study Details	Intervention/Outcome Measures	Study Design/Execution
<p>Kumar et al. (2007)<sup>23</sup> Australia, Belgium, Canada, Israel, Italy, Spain, Switzerland, UK, USA</p> <p><u>Study design:</u> Multicentre, prospective randomized concurrently controlled trial.</p> <p><u>Follow-up:</u> 1, 3, 6, 9, and 12 months.</p> <p><u>Study period:</u> April 2003 to June 2005.</p> <p><u>Setting:</u> 12 centres worldwide; no further details provided.</p> <p><u>Financial support:</u> Medtronic, Inc.</p>	<p><b>Conventional medical management (CMM) (n=48)</b> Included oral medications (opioids, non-steroidal anti-inflammatory drugs, antidepressants, anticonvulsants/antiepileptics, and other analgesic therapies), nerve blocks, epidural corticosteroids, physical and psychological rehabilitative therapy, and/or chiropractic care. Invasive treatments such as spinal surgery or intrathecal drug delivery systems were excluded.</p> <p><b>CMM plus spinal cord stimulation (SCS) (n=52)</b> All patients underwent a screening trial after which those experiencing at least 80% overlap of their pain with stimulation-induced paresthesia and at least 50% leg pain relief received an implantable SCS system.</p> <p><u>SCS System:</u> Synergy™ or Irel®3 system (n=3) (Medtronic, Inc., Minneapolis, MN, USA).</p> <p><u>Stimulation Parameters (n=43):</u> Mean settings (standard deviation) were: amplitude of 3.7 V (2.0), pulse width of 350 µs (95.5), and rate of 49 Hz (16.4).</p> <p><b>CMM &amp; SCS</b> <u>Outcome Measures:</u> Pain intensity (visual analog scale); quality of life (Short-Form 36 questionnaire); functional capacity (Oswestry Disability Index); use of pain mediation and non-drug pain therapy; employment status; patient satisfaction with treatment; and adverse treatment-related events and complications.</p>	<p><u>Method of randomization:</u> Random computer-generated blocks of either 2 or 4 patients in a 1:1 ratio.</p> <p><u>Time of randomization:</u> After baseline assessment.</p> <p><u>Method of allocation concealment:</u> Randomization was electronically locked and could only be accessed after a patient entered the trial.</p> <p><u>Details of blinding:</u> Blinding not attempted since it's impossible to blind patients and difficult to blind investigators.</p> <p><u>Participation rate:</u> 74.1% (100/135). There was no statistically significant difference between participants and non-participants with respect to age or sex distribution.</p> <p><u>Eligibility rate for study:</u> 63.1% (135/214). Primary reason for exclusion was predominant back pain (n=51).</p> <p><u>Intention-to-treat analysis:</u> Intention-to-treat analysis for 6 month follow-up results; intention-to-treat and as-treated analysis for 12 month follow-up results.</p> <p><u>Crossovers:</u> After 6 months, patients failing to achieve adequate pain relief were permitted to crossover to the alternative treatment with physician approval.</p> <p><u>Provider:</u> Not reported.</p> <p><u>Assessor details:</u> Not blinded. No further details provided.</p> <p><u>Inclusion criteria:</u> Patients ≥18 years with neuropathic pain of radicular origin of an intensity ≥ 50 mm (range 0 to 100) on a visual analog scale for at least 6 months after a minimum of one anatomically successful surgery for a herniated disc.</p> <p><u>Exclusion criteria:</u> Another clinically significant or disabling chronic pain condition; inability to receive or operate the SCS system; history of a coagulation disorder, lupus erythematosus, diabetic neuropathy, rheumatoid arthritis, or ankylosing spondylitis; evidence of an active psychiatric disorder, another condition known to affect the perception of pain, or an inability to evaluate treatment outcome; life expectancy of &lt;1 year; existing or planned pregnancy.</p> <p><u>Conclusions supported by results:</u> Yes.</p>

## STUDY PROFILES – CLINICAL PRACTICE GUIDELINES

Table 4: Study profiles for *clinical practice guidelines* on spinal cord stimulation for neuropathic pain

Guideline	Target Population	Selection Criteria/Outcomes	Methods
<p>Cruccu et al. (2007)<sup>24</sup></p> <p><b>Objective:</b> To provide neurologists with evidence-based recommendations that may help to determine when a patient with neuropathic pain should try a neurostimulation procedure.</p> <p><b>Target users:</b> Neurologists.</p> <p><b>Financial support:</b> Not stated.</p> <p><b>Conflict of interest:</b> Five of the eight authors had affiliations with Medtronic, Inc.</p>	<p><b>Age:</b> Not stated.</p> <p><b>Included conditions:</b> Neuropathic pain.</p> <p><b>Excluded conditions:</b> Not stated.</p>	<p><b>Interventions:</b> Transcutaneous electrical nerve stimulation, peripheral nerve stimulation, nerve root stimulation, spinal cord stimulation, deep brain stimulation, epidural motor cortex stimulation, and repetitive transcranial magnetic stimulation.</p> <p><b>Study inclusion/exclusion criteria:</b> All studies designs were included except for case reports, case series studies of &lt;8 patients, and multiple-indication case series studies without disaggregated reported outcomes.</p>	<p><b>Literature search:</b> <u>Time period:</u> 1968 to May 2006. <u>Limits:</u> Not stated. <u>Databases:</u> MEDLINE, EMBASE, The Cochrane Library, pearling of reviews and textbooks.</p> <p><b>Appraisal of study quality:</b> The evidence was graded.</p> <p><b>Formulation of recommendations:</b> A task force of eight clinical experts reviewed the evidence and formulated the guidelines. Irreconcilable differences between group members were referred to a European Federation of Neurological Societies Scientific Committee for resolution.</p> <p><b>External review:</b> Peer review.</p> <p><b>Evidence linked to recommendations:</b> Yes.</p>

## SUMMARY OF RELEVANT DATA – SYSTEMATIC REVIEWS

Table 5: Summary of relevant data extracted from *systematic reviews* on spinal cord stimulation for neuropathic pain

Study/ Quality	Patients/ Pain Type	Comparators	Supporting Evidence*						Relevant Results/ Authors' Conclusions	
			SR/MA	NR	RCT	NRCS	CS	G		Other
<p>Ontario Ministry of Health and Long-Term Care (2005)<sup>21</sup></p> <p><b>Quality rating:</b> Poor (3/6)</p>	<p><b>Total number:</b> n = not reported for health technology assessments; n = 104 for RCTs; n = 133 for case series studies</p> <p><b>Conditions reviewed:</b> Failed back surgery syndrome (FBSS) Complex regional pain syndrome (CRPS) types I and II Postherpetic neuralgia</p>	<p><b>FBSS:</b> - reoperation</p> <p><b>Neuropathic pain:</b> - medical therapy - placebo</p> <p><b>CRPS type I:</b> - physiotherapy</p>	<p><b>6</b> 25-30</p>		<p><b>2</b> 31,32</p> <p><b>N.B.</b> These two studies are updated 2-year outcomes from studies included within those listed in the SR/MA column.</p>		<p><b>1</b> 33,34</p>			<p><b>Efficacy/effectiveness:</b> <i>SR evidence:</i> All 6 studies concluded that there is evidence (ranging in quality from very weak to moderate) to support the effectiveness of spinal cord stimulation (SCS) to manage pain in various neuropathic pain syndromes. Technical failures ranged from 1.6% to 42.8%. <i>RCT/CS evidence:</i> Level 2 (small RCT) evidence from two high quality studies indicates that SCS decreases pain and level 3a (pre-test/post-test case series study) evidence indicates that it improves functional status and quality of life in some people with neuropathic pain conditions. The most common technical failures related to problems with the lead (10.8%) or the implantable pulse generator (10.2%).</p> <p><b>Safety:</b> <i>SR evidence:</i> Infections ranged from 1.4% to 11.7%. <i>RCT/CS evidence:</i> The most common procedural complications were infection and dural puncture, each occurring at a rate of 1.2%. No treatment-related deaths were reported.</p> <hr/> <p><b>Authors' conclusions:</b> SCS may be considered for patients with chronic, neuropathic pain for whom standard pain treatments have failed and when there is no indication for surgical intervention to treat the underlying condition.</p>

CS - case series study; G - guideline; NR – non-systematic/narrative review; NRCS – non-randomized comparative study; RCT – randomized controlled trial; SR/MA – systematic review/meta-analysis

\*The integers listed in the Supporting Evidence columns represent the total number of discrete studies. Thus, when there are multiple publications for a single study, the integers are less than the number of references listed below them.

## SUMMARY OF RELEVANT DATA – RANDOMIZED CONTROLLED TRIALS

Table 6: Summary of relevant data extracted from *randomized controlled trials* on spinal cord stimulation for neuropathic pain

Study/Quality Rating	Interventions/Study Population	Relevant Results/Authors' Conclusions
<p>Kemler et al. (2008)<sup>22</sup>                      Prospective randomized concurrently controlled trial  <b>Quality rating:</b>  <i>Internal validity</i>                      Moderate (6/9)  <i>External validity</i>                      Good (6/6)</p>	<p><b>Physical therapy (PT); n=18</b>  <b>PT plus spinal cord stimulation (SCS); n=36</b>  <u>Patient diagnosis:</u> Chronic regional pain syndrome type I.  <u>Mean age:</u>                      PT: 35.0 years (standard deviation (SD) 8.0);                      SCS: 40.0 years (SD 12.0)  <u>Sex distribution:</u>                      PT: M/F = 3 (17%)/15 (83%);                      SCS: M/F = 14 (39%)/22 (61%)  <u>Pre-treatment mean visual analog scale (VAS) pain score (scale 0 to 10):</u>                      PT: 6.7 (SD 1.2); SCS: 7.1 (SD 1.5)  <u>Duration of pain:</u>                      PT: 34.0 months (SD 22.0); SCS: 40.0 months (SD 28.0)  <u>Patient co-morbidities:</u> Not stated.  <u>Pain location:</u>                      PT: Hand - 61%; Foot – 39%; <b>SCS:</b> Hand - 61%; Foot – 39%  <u>Previous treatment:</u> Not stated.                      There was no statistically significant difference between the two groups with respect to age, sex distribution, pain intensity, duration of disorder, location of pain, psychological distress, or health-related quality of life (P&gt;0.05).</p>	<p><b>SCS versus PT at 60 months' follow up:</b>                      PT (n=13), SCS (n=31; 22 with a permanent SCS implant)  <u>Lost to follow-up:</u> PT, 27.8% (5/18); SCS, 13.9% (5/36)  <u>Outcomes:</u>                      No statistically significant difference between the two groups with respect to changes in pain, perceived improvement, health-related quality of life, or psychological distress compared to baseline (P&gt;0.05).</p> <hr/> <p><b>Subgroup analysis: SCS (patients with permanent implant) versus PT at 60 months' follow up:</b>                      PT (n=13), SCS (n=20)  <u>Lost to follow-up:</u> PT, 27.8% (5/18); SCS, 8.3% (4/24)  <u>Outcomes:</u>                      No statistically significant difference between the two groups with respect to changes in pain, perceived improvement, health-related quality of life, or psychological distress compared to baseline (P&gt;0.05).                      More SCS patients (35.0%; 7/20) reported a 'much improved' global perceived effect compared to PT patients (15.4%; 2/13) (P=0.02).                      Of the SCS patients, 95.0% (19/20) would have the treatment again.  <u>Adverse events:</u>  <b>PT</b> (n=13): not reported.  <b>SCS</b> (n=24): reoperation (41.7%); permanent explantation (8.3%); pulse generator replacement (70.8%); lead repositioning (45.8%); pulse generator pocket revision (33.3%); lead replacement (25.0%).</p> <hr/> <p><b>Authors' conclusions</b>                      SCS does not produce a durable and statistically significant improvement in pain for patients with chronic regional pain syndrome type I, although patient satisfaction with SCS is high.</p>

**Table 6: Summary of relevant data extracted from *randomized controlled trials* on spinal cord stimulation for neuropathic pain (cont'd)**

Study/Quality Rating	Interventions/Study Population	Relevant Results/Authors' Conclusions
<p>Kumar et al. (2007)<sup>23</sup>                      Multicentre, prospective randomized concurrently controlled trial  <b>Quality score:</b>  <i>Internal validity</i> Good (9/9)  <i>External validity</i> Good (6/6)</p>	<p><b>Conventional medical management (CMM); n=48</b>  <b>CMM plus spinal cord stimulation (SCS); n=52</b>  <u>Patient diagnosis:</u> Failed back surgery syndrome with neuropathic pain of radicular origin.  <u>Mean age:</u>                      CMM: 52.0 yrs (standard deviation (SD) 10.7);                      SCS: 48.9 yrs (SD 10.0)  <u>Sex distribution:</u>                      CMM: M/F = 21 (43.8%)/27 (56.2%);                      SCS: M/F = 30 (57.7%)/22 (42.3%)  <u>Pre-treatment mean visual analog scale (VAS) score for leg pain (scale 0 to 10):</u>                      CMM: 73.4 (SD 14.0); SCS: 76.0 (SD 13.0)  <u>Pre-treatment mean VAS score for back pain (scale 0 to 10):</u>                      CMM: 44.8 (standard deviation (SD) 23.2); SCS: 54.5 (SD 24.3)  <u>Duration of pain:</u> At least 6 months  <u>Patient co-morbidities:</u> Not stated  <u>Patient details:</u>                      CMM: Currently employed - 21%; Unilateral leg pain – 67%; Bilateral leg pain – 33%;                      SCS: Currently employed - 23%; Unilateral leg pain – 63%; Bilateral leg pain – 37%  <u>Previous treatment (&gt;1 previous surgery):</u>                      CMM: 46%; SCS: 54%                      There was no statistically significant difference between the two groups with respect to age, sex distribution, time since last surgery, number of previous surgeries, employment status, history of legal action related to back pain, type of leg pain, and mean leg pain score. However, CMM patients had a slightly higher mean back pain score (P=0.03).</p>	<p><b>At 6 months' follow up:</b> CMM (n=44), SCS (n=50)  <u>Lost to follow-up:</u> CMM, 8.3% (4/48); SCS, 3.9% (2/52)  <u>Primary outcomes:</u> Leg pain relief ≥50%: CMM, 9%; SCS, 48%; (P&lt;0.001).  <u>Secondary outcomes:</u>                      Back pain mean VAS score (SD): CMM, 51.6 (26.7); SCS, 40.6 (24.9); (P=0.008)                      Leg pain mean VAS score (SD): CMM, 66.6 (24.0); SCS, 39.9 (26.3); (P&lt;0.0001)                      Oswestry Disability Index mean score (SD): CMM, 56.1 (17.9); SCS, 44.9 (18.8); (P&lt;0.001)                      Satisfied with pain relief: CMM, 18%; SCS, 66%                      SCS patients had greater health-related quality of life on 7/8 dimensions of the SF-36 (P≤0.02).                      No statistically significant difference between the two groups with respect to analgesic drug intake, non-drug therapy use, or rate of return to work (P&gt;0.01).</p> <hr/> <p><b>At 12 months' follow up:</b> CMM (n=41), SCS (n=47)  <u>Lost to follow-up:</u> CMM, 14.6% (7/48); SCS, 9.6% (5/52)  <u>Crossover to alternative treatment:</u> CMM, 58.3% (28/48); SCS, 9.6% (5/52)  <u>Primary outcome (leg pain relief ≥50%):</u>                      Per-treatment analysis: CMM, 18% (3/17); SCS, 48% (34/71); (P=0.03).                      Intention-to-treat analysis: CMM, 7%; SCS, 34%; (P=0.005).  <u>Adverse events:</u>  <b>CMM</b> (n=48): ≥1 drug adverse event (21%); ≥1 event of extra pain (4%).  <b>SCS</b> (n=52): ≥1 drug adverse event (4%); ≥1 event of extra pain (0%).  <b>SCS</b> (n=84): device-related complication (32%); electrode migration (10%); infection or wound breakdown (8%); loss of paresthesia (7%); surgery required to resolve event (24%).</p> <hr/> <p><b>Authors' conclusions</b>                      SCS improves pain relief, quality of life, functional capacity, and patient satisfaction, compared to CMM alone, in selected patients with neuropathic pain related to failed back surgery syndrome.</p>

## SUMMARY OF RELEVANT DATA – CLINICAL PRACTICE GUIDELINES

Table 7: Summary of relevant data extracted from *clinical practice guidelines* on spinal cord stimulation for neuropathic pain

Guideline/ Quality Rating	Synopsis of Recommendations	Supporting Evidence*						
		SR/MA	NR	RCT	NRCS	CS	G	Other
Cruccu et al. (2007) <sup>24</sup> (Europe)  <b>Quality rating:</b> Average (21.5/28)	SCS is efficacious in failed back surgery syndrome and chronic regional pain syndrome type I. Further comparative trials are warranted for SCS in other conditions.	<b>3</b> 25,29,35	<b>3</b> 36-38	<b>3</b> 23,32,39-41				

\*The integers listed in the Supporting Evidence columns represent the total number of discrete studies. Thus, when there are multiple publications for a single study, the integers are less than the number of references listed below them.

## APPENDIX A: SEARCH STRATEGY

The literature search was conducted by the IHE Research Librarian from May 5 to 12, 2008. Major electronic databases used included *The Cochrane Library*, the NHS Centre for Reviews and Dissemination (CRD Databases: NHS EED, HTA, DARE), PubMed, EMBASE, and AMED (Allied and Complementary Medicine). In addition, relevant library collections, web sites of practice guideline clearing houses, regulatory agencies, evidence-based resources, and HTA related agency resources were searched (Table A.1). Internet search engines were also used to locate grey literature.

Medical Subject Headings (MeSH) terms relevant to this topic include: Pain; Peripheral nervous system diseases; Neuralgia; Complex regional pain syndromes; Nerve Block; Infusions, Intravenous; Analgesia, Epidural.

**Table A.1: Databases and search terms used in the search strategy**

Database	Edition/Date Searched	Search Terms
<b>Databases</b>		
<i>The Cochrane Library</i> <a href="http://www.thecochranelibrary.com">http://www.thecochranelibrary.com</a>	May 5, 2008	(((neuropath* OR neurogenic) AND pain) OR neuralgia* OR "reflex system dystrophy" Or "reflex sympathetic dystrophy" OR "diabetic neuropathy" OR "peripheral neuropathy" OR radiculopath* or plexopath* or" complex regional pain syndrome" OR causalgia OR ("multiple sclerosis" and pain) OR sciatica OR (("nerve injury" OR "nerve injuries") and pain) OR syringomyelia OR "brachial plexus injury" OR "brachial plexus injuries" OR "phantom limb" OR amputation OR "post mastectomy" OR "post stroke" OR ("spinal cord" and pain) or (sacroiliac and pain)):ti,ab,kw  and ("nerve block" or "nerve blocks" or "nerve blockade" or "medial branch block" or "medial branch blocks" or "intravenous infusion" or "intravenous infusions" or "IV infusion" or "IV infusions" or "spinal nerve stimulation" or "spinal cord stimulation" OR "sympathetic block" or "sympathetic blocks" or "sympathetic blockade" or "epidural block" or "epidural blocks" or "epidural blockade" Or "epidural steroid injection" or tfesi or "epidural steroid injections" or "paravertebral block" or "paravertebral blocks" or "paravertebral injection" or "paravertebral injections" or "paraspinal block" or "paraspinal blocks" or "paraspinal injection" or "paraspinal injections" or "stellate ganglion block" or nonpharmacologic* or non-pharmacologic*):ti,ab, from 1997 to 2008
EMBASE –Ovid platform (Licensed resource)	May 5, 2008	See Note 1 for EMBASE search
MEDLINE/PubMed	May 5, 2008	See Note 2 for MEDLINE search  PubMed searched for in process citations. (search[tiab] OR medline[tiab] OR systematic review[tiab] OR metaanalys*[tiab] OR randomized[tiab] or clinical trial[ti]) AND (in process[sb] OR pubmednotmedline[sb] OR publisher[sb]) added to textword search

<p>Web of Science – ISI platform (Licensed resource)</p> <p>BIOSIS Previews – ISI platform (licensed resource)</p>	<p>May 5, 2008</p>	<p>neuropath* OR neurogenic OR neuralgia* OR “reflex system dystrophy” OR “reflex sympathetic dystrophy” OR “diabetic neuropathy” OR “peripheral neuropathy” OR radiculopath* OR plexopath* OR “complex regional pain syndrome” OR causalgia OR “multiple sclerosis” OR sciatica OR “nerve injury” OR “nerve injuries” OR syringomyelia OR “brachial plexus injury” OR “brachial plexus injuries” OR “phantom limb” OR amputation OR “post mastectomy” OR “post stroke” OR “spinal cord” OR sacroiliac</p> <p>AND pain</p> <p>AND “nerve block” or “nerve blocks” or “nerve blockade” or “medial branch block” or “medial branch blocks” or “intravenous infusion” or “intravenous infusions” or “IV infusion” or “IV infusions” or “spinal nerve stimulation” or “spinal cord stimulation” OR “sympathetic block” or “sympathetic blocks” or “sympathetic blockade” or “epidural block” or “epidural blocks” or “epidural blockade” Or “epidural steroid injection” or tfesi or “epidural steroid injections” or “paravertebral block” or “paravertebral blocks” or “paravertebral injection” or “paravertebral injections” or “paraspinal block” or “paraspinal blocks” or “paraspinal injection” or “paraspinal injections” or “stellate ganglion block” or nonpharmacologic* or non-pharmacologic*</p> <p>AND random* or "systematic review" or "practice guideline" or search* or "technology assessment" or "clinical trial" or double-blind* or meta-analys* or metaanalys*</p>
<p>CRD Databases (Results from DARE and HTA portions only)</p>	<p>May 5, 2008</p>	<p>neuropath* OR neurogenic OR neuralgia* OR “reflex system dystrophy” OR “reflex sympathetic dystrophy” OR “diabetic neuropathy” OR “peripheral neuropathy” OR radiculopath* OR plexopath* OR “complex regional pain syndrome” OR causalgia OR “multiple sclerosis” OR sciatica OR “nerve injury” OR “nerve injuries” OR syringomyelia OR “brachial plexus injury” OR “brachial plexus injuries” OR “phantom limb” OR amputation OR “post mastectomy” OR “post stroke” OR “spinal cord” OR sacroiliac</p> <p>AND pain</p> <p>AND “nerve block” or “nerve blocks” or “nerve blockade” or “medial branch block” or “medial branch blocks” or “intravenous infusion” or “intravenous infusions” or “IV infusion” or “IV infusions” or “spinal nerve stimulation” or “spinal cord stimulation” OR “sympathetic block” or “sympathetic blocks” or “sympathetic blockade” or “epidural block” or “epidural blocks” or “epidural blockade” Or “epidural steroid injection” or tfesi or “epidural steroid injections” or “paravertebral block” or “paravertebral blocks” or “paravertebral injection” or “paravertebral injections” or “paraspinal block” or “paraspinal blocks” or “paraspinal injection” or “paraspinal injections” or “stellate ganglion block” or nonpharmacologic* or non-pharmacologic*</p> <p>Year published 1997 – 2008 OR Published date 1997 - 2008</p>
<p>AMED</p>	<p>May 5, 2008</p>	<p>See Note 3 for AMED search</p>

CINAHL	May 5, 2008	<p>(MH "Pain+") or pain</p> <p>AND</p> <p>(MH "Peripheral Nervous System Diseases+") OR (MH "Facial Neuralgia") OR (MH "Trigeminal Neuralgia") OR (MH "Nervous System Diseases+") OR (MH "Reflex Sympathetic Dystrophy") or (MH "Complex Regional Pain Syndromes+") OR (MH "Radiculopathy") or (MH "Polyradiculopathy") or (MH "Polyradiculoneuritis") OR (MH "Multiple Sclerosis") OR (MH "Syringomyelia") OR (MH "Brachial Plexus Neuropathies+") OR (MH "Phantom Limb") or (MH "Phantom Pain") OR (MH "Amputation+") OR (MH "Somatosensory Disorders+") or neuralgia* or neuropath* or neurogenic or "reflex sympathetic dystrophy" or "complex regional pain syndrome" or radiculopath* or plexopath* or polyradiculopath* or causalgia or sciatica</p> <p>AND</p> <p>(MH "Nerve Block") OR (MH "Infusions, Intravenous") or (MH "Infusions, Intraspinal+") OR (MH "Central Nervous System Stimulants") OR (MH "Sympatholytics+") OR (MH "Analgesia, Epidural") or (MH "Infusions, Epidural") or (MH "Injections, Epidural+") OR (MH "Injections, Intraspinal") OR (MH "Ganglionic Blockers") OR "nerve block" or "nerve blocks" or "nerve blockade" or "sympathetic block" or "sympathetic blocks" or "sympathetic blockade" or "intravenous infusion" or "iv infusion" or "intravenous infusions" or "iv infusions" or "spinal nerve stimulation" or "spinal cord stimulation" or "epidural block" or "epidural blocks" or "epidural blockade" or "medial branch block" or "medial branch blocks" or "medical branch blockade" or "epidural steroid injection" or "epidural steroid injections" or tfesi or "paravertebral block" or "paravertebral blocks" or "paraspinal block" or "paraspinal blocks" or "paravertebral infusion" or "paravertebral infusions" or "paraspinal infusion" or "paraspinal infusions" or "ganglion block" or nonpharmacologic* or non-pharmacologic*</p> <p>AND</p> <p>(MH "Meta Analysis") OR (MH "Systematic Review") OR (MH "Practice Guidelines") OR (MH "Clinical Trials") or (MH "Double-Blind Studies") Or random* OR "systematic review" or "practice guideline" or search* or "technology assessment" or "clinical trial" or double-blind* or meta-analys* or metaanalys*</p>
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Theses Canada portal	May 7, 2008	Neuropathic; neuralgia; neuropathy; complex regional; reflex sympathetic; causalgia; radiculopathy; blockade; epidural; nerve block; nerve blocks; spinal cord stimulation Title keyword  Pain and nerve and treatment Any keyword
National Library for Health	May 7, 2008	Neuropathic pain; neuralgia; neuropathy; complex regional; reflex sympathetic; causalgia; radiculopathy; nerve block; nerve blockade; nerve blocks; epidural block(s,ade); spinal cord stimulation; iv infusion(s); intravenous infusions(s)
Proquest Dissertations and Theses	May 7, 2008	TITLE(neuropathic pain) TITLE(neuralgia or neuropathy or causalgia) AND (treat* or therap*) TITLE(complex regional) OR TITLE (reflex sympathetic) TITLE (nerve block or nerve blocks or nerve blockade) TITLE(epidural block or epidural blocks or epidural blockade) TITLE(iv infusion or iv infusions or intravenous infusion or intravenous infusions)
<b>Guidelines</b>		
AMA Clinical Practice Guidelines <a href="http://www.topalbertadors.org/TOP/CPG/CPGTopics.htm">http://www.topalbertadors.org/TOP/CPG/CPGTopics.htm</a>	May 7, 2008	Browsed list of guidelines
CMA Infobase <a href="http://mdm.ca/cpgsnew/cpgs/index.asp">http://mdm.ca/cpgsnew/cpgs/index.asp</a>	May 7, 2008	Neuropathic; neuropathy; neurogenic; neuralgia; pain; nerve; nerves; intravenous; block; stimulation; epidural
National Guideline Clearinghouse <a href="http://www.ngc.gov">http://www.ngc.gov</a>	May 7, 2008	"neuropathic pain"; "complex regional pain syndrome"; nerve block; nerve blocks; intravenous infusion; spinal nerve stimulation; spinal cord stimulation; sympathetic block; sympathetic blocks; epidural Clinical specialty; neurology
Guidelines International Network	May 7, 2008	Neuropathic pain; neuralgia; neuropathy; nerve block; nerve blockade; blockade; epidural; infusion; stimulation; complex regional; reflex; causalgia; radiculopathy; polyradiculopathy
New Zealand Guidelines Group <a href="http://www.nzgg.org.nz">http://www.nzgg.org.nz</a>	May 7, 2008	Browsed list of guidelines.
SIGN <a href="http://www.sign.ac.uk">http://www.sign.ac.uk</a>	May 7, 2008	Browsed list of guidelines.
<b>Clinical Trials</b>		
ClinicalTrials.gov (US) <a href="http://clinicaltrials.gov/">http://clinicaltrials.gov/</a>	May 7, 2008	Neuropathic pain and nerve block; Epidural block; Neuralgia pain block; Causalgia pain block Spinal cord stimulation Iv infusions pain; intravenous infusions pain Complex regional pain syndrome Reflex sympathetic dystrophy Radiculopathy
CenterWatch Clinical	May 7, 2008	Neuropathic pain

Trials Listing Service <a href="http://www.centerwatch.com/">http://www.centerwatch.com/</a>		Nerve block (s/ade) Epidural block (s/ade) Spinal cord stimulation Intravenous (IV) infusion pain CRPS Reflex sympathetic
metaRegister of Controlled Trials (mRCT) <a href="http://www.controlled-trials.com/mrct/">http://www.controlled-trials.com/mrct/</a>	May 12, 2008	Neuropathic pain and block Neuralgia Nerve block (s/ade) and pain Epidural block (s/ade) pain Epidural nerve pain Spinal cord stimulation Complex Regional pain syndrome Reflex sympathetic Iv infusion and pain; intravenous infusion and pain
<b>HTA resources</b>		
AETMIS <a href="http://www.aetmis.gouv.qc.ca">http://www.aetmis.gouv.qc.ca</a>	May 12, 2008	Neuropathic pain; neuralgia; causalgia; neuropathy; nerve; epidural; stimulation; pain syndrome; sympathetic; intravenous
CADTH <a href="http://www.cadth.ca">http://www.cadth.ca</a>	May 12, 2008	Neuropathic; neuralgia; causalgia; neuropathy; nerve; epidural; stimulation; pain syndrome; sympathetic; intravenous
Institute for Clinical and Evaluative Sciences (ICES), Ontario <a href="http://www.ices.on.ca/">http://www.ices.on.ca/</a>	May 12, 2008	Browsed list of reports
Health Technology Assessment Unit At McGill <a href="http://www.mcgill.ca/tau/">http://www.mcgill.ca/tau/</a>	May 12, 2008	Browsed list of reports
Medical Advisory Secretariat <a href="http://www.health.gov.on.ca/english/providers/program/mas/mas_mn.html">http://www.health.gov.on.ca/english/providers/program/mas/mas_mn.html</a>	May 12, 2008	Browsed list of analyses and recommendations
CCE <a href="http://www.med.monash.edu.au/healthservices/cce/">http://www.med.monash.edu.au/healthservices/cce/</a>	May 12, 2008	Browsed list of current evidence reviews
ASERNIP-S <a href="http://www.surgeons.org/asernip-s/">http://www.surgeons.org/asernip-s/</a>	May 12, 2008	Browsed list of publications
WorksafeBC <a href="http://www.worksafebc.com/health_care_providers/related_information/evidence_based_medicine/default.asp">http://www.worksafebc.com/health_care_providers/related_information/evidence_based_medicine/default.asp</a>	May 12, 2008	Browsed list of systematic reviews

NIHR Health Technology Assessment Programme <a href="http://www.ncchta.org">http://www.ncchta.org</a>	May 12, 2008	Browsed HTA research
NZHTA <a href="http://nzhta.chmeds.ac.nz/publications.htm">http://nzhta.chmeds.ac.nz/publications.htm</a>	May 12, 2008	Browsed list of publications
NICE (UK) <a href="http://www.nice.org.uk/">http://www.nice.org.uk/</a>	May 12, 2008	Neuropathic; neuralgia; causalgia; neuropathy; nerve; block; epidural; stimulation; pain; sympathetic; intravenous
MSAC <a href="http://www.msac.gov.au/">http://www.msac.gov.au/</a>	May 12, 2008	Browsed lists of current and completed assessments
National Horizon Scanning Centre <a href="http://www.pcpoh.bham.ac.uk/publichealth/horizon">http://www.pcpoh.bham.ac.uk/publichealth/horizon</a>	May 12, 2008	Browsed lists of publications and technology briefings
AHRQ <a href="http://www.ahrq.gov">http://www.ahrq.gov</a>	May 12, 2008	Browsed lists of technology assessments and evidence reports
California Technology Assessment Forum (CTAF) <a href="http://www.ctaf.org">http://www.ctaf.org</a>	May 12, 2008	Browsed list of assessments
Euroscan	May 12, 2008	Browsed list of technology reports

“\*” is a truncation character that retrieves all possible suffix variations of the root word e.g. surg\* retrieves surgery, surgical, surgeon, etc.

; separates search terms that were searched separately

### Note 1: EMBASE Search Strategy

1. pain.mp. or POSTOPERATIVE PAIN/ or exp PAIN/
2. exp Neuropathic pain/
3. 1 or 2
4. exp NEURALGIA/
5. exp Neuropathy/
6. (neuropath\$ or neurogenic or neuralgia\$.mp.
7. reflex sympathetic dystrophy.mp.
8. complex regional pain syndrome\$.mp.
9. exp Radiculopathy/
10. (radiculopath\$ or plexopath\$.mp.
11. exp Nervous System Injury/
12. post stroke.mp.
13. causalgia.mp.
14. Multiple Sclerosis/
15. exp Spinal Cord Disease/
16. sciatic nerve/
17. peripheral nerve/
18. peripheral nerve injur\$.mp.
19. brachial plexus/
20. (sciatica or ischialgia).mp.
21. exp spinal cord/
22. exp Nervous System Tumor/
23. exp Agnosia/

24. exp amputation/
25. post mastectomy.mp.
26. exp Somatosensory Disorder/
27. or/4-25
28. 3 and 27
29. (non-pharmacologic\$ adj2 (treatment\$ or intervention\$ or therap\$)).mp.
30. exp nerve block/
31. nerve block\$.mp.
32. medial branch block\$.mp.
33. intravenous drug administration/
34. ((intravenous or iv) adj1 infusion\$).mp.
35. spinal cord stimulation/
36. ((spinal cord or spinal nerve) adj1 stimulat\$).mp.
37. sympathetic blocking/
38. sympathetic block\$.mp.
39. exp epidural anesthesia/
40. epidural block\$.mp.
41. (epidural steroid injection\$ or tfesi).mp.
42. epidural drug administration/
43. ((paravertebral or paraspinal) adj1 (block\$ or injection\$)).mp.
44. stellate ganglion block\$.mp.
45. or/29-44
46. 28 and 45
47. meta-analysis.mp.
48. (medline or pubmed or search\$).mp.
49. systematic\$ review\$.mp.
50. (technology assessment\$ or hta).mp.
51. practice guideline.mp.
52. clinical pathway/
53. consensus development.mp. or consensus statement.ti.
54. or/47-53
55. 46 and 54
56. random\$.tw. or placebo\$.mp. or double-blind\$.tw. or trial.ti.
57. controlled clinical trial/ or randomized controlled trial/
58. 56 or 57
59. 46 and 58
60. 55 or 59
61. limit 60 to yr="1997 - 2008"

## **Note 2: MEDLINE Search Strategy**

1. pain.mp. or exp Pain/ or Pain, Postoperative/
2. neuropath\$.mp.
3. neurogenic.mp.
4. exp peripheral nervous system diseases/ or brachial plexus neuropathies/ or complex regional pain syndromes/ or diabetic neuropathies/ or neuralgia/ or sciatica/
5. Facial Neuralgia/
6. Trigeminal Neuralgia/
7. neuralgia\$.mp.
8. reflex sympathetic dystrophy.mp.
9. exp polyradiculopathy/
10. (radiculopath\$ or plexopath\$).mp.
11. complex regional pain syndromes/ or causalgia/ or reflex sympathetic dystrophy/
12. thalamic.mp.
13. post stroke.mp.
14. exp Multiple Sclerosis/
15. Syringomyelia/

16. Sciatic Nerve/ or Peripheral Nerves/
17. peripheral nerve injur\$.mp.
18. exp Brachial Plexus/ or brachial plexus injury pain syndrome.mp. or exp Brachial Plexus Neuropathies/
19. (sciatica or ischialgia).mp.
20. exp Spinal Cord/
21. exp Spinal Cord Diseases/
22. exp Nervous System Neoplasms/
23. Phantom Limb/
24. amputation/
25. post mastectomy.mp.
26. somatosensory disorders/ or hyperalgia/ or hyperesthesia/ or paresthesia/
27. (complex regional pain syndrome\$ or reflex sympathetic dystrophy\$ or causalgia).mp.
28. or/2-27
29. 1 and 28
30. (non-pharmacologic\$ adj2 (treatment\$ or intervention\$ or therap\$)).mp.
31. exp Nerve Block/
32. nerve block\$.mp.
33. Infusions, Intravenous/
34. ((intravenous or iv) adj1 infusion\$).mp.
35. Anesthetics, Local/
36. spinal nerve stimulat\$.mp.
37. spinal cord stimulat\$.mp.
38. sympathetic block\$.mp.
39. Analgesia, Epidural/
40. Injections, Epidural/
41. epidural block\$.mp.
42. medial branch block\$.mp.
43. (epidural steroid injection\$ or tfesi).mp.
44. ((paravertebral or paraspinal) adj1 (block\$ or injection\$)).mp.
45. stellate ganglion block\$.mp.
46. or/30-45
47. 29 and 46
48. meta-analysis.mp.pt.
49. (medline or pubmed or search\$).mp.
50. systematic\$ review\$.mp.
51. (technology assessment\$ or hta).mp.
52. practice guideline.mp.pt. or guideline.pt.
53. critical pathways/
54. consensus development conference.pt. or consensus statement.ti.
55. or/48-54
56. 47 and 55
57. Clinical trial.pt. or randomized.ab. or placebo.ab. or clinical trials/ or randomly.ab. or trial.ti.
58. 47 and 57
59. 56 or 58
60. limit 59 to yr="1997 - 2008"

### Note 3: AMED Search Strategy

1. pain.mp. or exp Pain/
2. (neuropath\$ or neurogenic or neuralgia\$).mp.
3. exp peripheral nervous system disease/
4. (reflex sympathetic dystrophy or complex regional pain syndrome\$).mp.
5. (radiculopath\$ or plexopath\$).mp.
6. causalgia.mp.
7. post stroke.mp.
8. thalamic.mp.
9. multiple sclerosis/
10. exp spinal cord disease/
11. exp spinal cord injuries/
12. exp peripheral nerves/
13. peripheral nerve injur\$.mp.
14. (sciatica or ischialgia).mp.
15. spinal cord/
16. exp nervous system neoplasms/
17. hyperalgesia/ or paresthesia/ or phantom limb/
18. amputation/
19. post mastectomy.mp.
20. or/2-19
21. 1 and 20
22. ((non-pharmacologic\$ or nonpharmacologic\$) adj2 (treatment\$ or intervention\$ or therap\$)).mp.
23. nerve block/
24. nerve block\$.mp.
25. medial branch block\$.mp.
26. ((intravenous or iv) adj1 infusion\$).mp.
27. ((spinal nerve or spinal cord) adj2 stimulat\$).mp.
28. sympathetic block\$.mp.
29. analgesia epidural/
30. epidural block\$.mp.
31. (epidural steroid injection\$ or tfesi).mp.
32. ((paravertebral or paraspinal) adj1 (block\$ or injection\$)).mp.
33. stellate ganglion block\$.mp.
34. or/22-33
35. meta-analys\$.mp. or search\$.tw. or review.pt. or systematic review.mp.
36. random\$.mp.
37. practice guidelines/ or practice guideline\$.mp.
38. or/35-37
39. 21 and 34 and 38
40. limit 39 to yr="1997 - 2008"

## APPENDIX B: EXCLUDED STUDIES

**Table B.1: Summary of excluded studies on *spinal cord stimulation* (listed in alphabetical order of first author)**

Study	Study Type	Reason for Exclusion
<b>Systematic reviews</b>		
Spinal cord stimulation for chronic pain of neuropathic or ischaemic origin. HTA Ref. No. 39295. Technology Assessment Report for NICE (Project). Available: <a href="https://www.nice.org.uk/guidance/index.jsp?action=byID&amp;o=11739">https://www.nice.org.uk/guidance/index.jsp?action=byID&amp;o=11739</a> .	Systematic review	Not available. Expected date of completion November 2008.
Agency for Healthcare Research and Quality. Management of chronic central neuropathic pain following traumatic spinal cord injury. Report No. 45. 2001. Available: <a href="http://www.ncbi.nlm.nih.gov/books/bv.fcgi?rid=hstat1.chapter.64890">http://www.ncbi.nlm.nih.gov/books/bv.fcgi?rid=hstat1.chapter.64890</a> .	Systematic review	Included studies on children/adolescents (>13 years of age).
Albazaz R. Complex Regional Pain Syndrome: A Review. <i>Annals of Vascular Surgery</i> 2008;22(2):297-306.	Quasi-systematic review	Included studies not critically appraised.
Cameron T. Safety and efficacy of spinal cord stimulation for the treatment of chronic pain: a 20-year literature review. <i>Journal of Neurosurgery</i> 2004;100(3 Suppl):254-67.	Systematic review	Included in Ontario Ministry of Health and Long-Term Care review (2005) <sup>21</sup> .
Coffey RJ, Lozano AM. Neurostimulation for chronic noncancer pain: an evaluation of the clinical evidence and recommendations for future trial designs. <i>Journal of Neurosurgery</i> 2006;105(2):175-89.	Systematic review	Included the same studies as Taylor et al. (2005) <sup>29</sup> .
Forouzanfar T, Koke AJ, van KM, Weber WE. Treatment of complex regional pain syndrome type I. <i>European Journal of Pain</i> 2002;6(2):105-22.	Systematic review	Does not include spinal cord stimulation.
Grabow TS, Tella PK, Raja SN. Spinal cord stimulation for complex regional pain syndrome: an evidence-based medicine review of the literature. <i>The Clinical Journal of Pain</i> 2003;19(6):371-83.	Systematic review	Included in Ontario Ministry of Health and Long-Term Care (2005) <sup>21</sup> .
Kemler MA. Complex regional pain syndrome type I. <i>Pain Reviews</i> 2001;8:35-45.	Quasi-systematic review	Included studies not critically appraised.
McQuay HJ, Moore RA, Eccleston C, Morley S, De C Williams AC. Systematic review of outpatient services for chronic pain control. <i>Health Technology Assessment</i> 1997;1(6):1-137. Available: <a href="http://www.ncchta.org/execsumm/summ106.htm">http://www.ncchta.org/execsumm/summ106.htm</a> .	Systematic review	Included a single review on spinal cord stimulation that was superseded by Taylor et al. (2005) <sup>29</sup> .
Middleton P, Simpson B, Maddern G. Spinal cord stimulation/neurostimulation: An accelerated systematic review. ASERNIP-S. 2003. Available: <a href="http://www.surgeons.org/AM/Template.cfm?Section=ASERNIP_S_Publications&amp;TEMPLATE=/CM/ContentDisplay.cfm&amp;CONTENTID=12868">http://www.surgeons.org/AM/Template.cfm?Section=ASERNIP_S_Publications&amp;TEMPLATE=/CM/ContentDisplay.cfm&amp;CONTENTID=12868</a> .	Systematic review	Included in Ontario Ministry of Health and Long-Term Care (2005) <sup>21</sup> .

North RB, Wetzel FT. Spinal cord stimulation for chronic pain of spinal origin: a valuable long-term solution. <i>Spine</i> 2002;27(22):2584-91.	Narrative review	Search strategy not described. Included studies not critically appraised.
Rushton DN. Electrical stimulation in the treatment of pain. <i>Disability and Rehabilitation</i> 2002;24(8):407-15.	Quasi-systematic review	Included studies not critically appraised.
Stocks RA, Williams CT. Spinal cord stimulation for chronic pain. STEER 2001;1(5). Available: <a href="http://www.wihrd.soton.ac.uk/projx/signpost/steers/STEE R_2001(5).pdf">http://www.wihrd.soton.ac.uk/projx/signpost/steers/STEE R_2001(5).pdf</a> .	Systematic review	Included a single review on spinal cord stimulation that was superseded by Taylor et al. (2005) <sup>29</sup> .
Taylor RS, Van Buyten J, Buchser E. Spinal cord stimulation for chronic back and leg pain and failed back surgery syndrome: a systematic review and analysis of prognostic factors. <i>Spine</i> 2005;30(1):152-60.	Systematic review	Included in Ontario Ministry of Health and Long-Term Care (2005) <sup>21</sup> .
Taylor RS, Van-Buyten JP, Buchser E. Spinal cord stimulation for complex regional pain syndrome: a systematic review of the clinical and cost-effectiveness literature and assessment of prognostic factors. <i>European Journal of Pain</i> 2006a;10(2):91-101.	Systematic review	Literature searches conducted up to January 1, 2002. Superseded by Ontario Ministry of Health and Long-Term Care (2005) <sup>21</sup> .
Taylor RS, Niv D, Raj PP. Exploration of the evidence. <i>Pain Practice</i> 2006b;6(1):10-21.	Quasi-systematic review	Included studies not critically appraised.
Taylor RS. Spinal cord stimulation in complex regional pain syndrome and refractory neuropathic back and leg pain/failed back surgery syndrome: results of a systematic review and meta-analysis. <i>Journal of Pain and Symptom Management</i> 2006c;31(4 Suppl 1):S13-S19.	Systematic review	Duplication of data from Taylor et al. (2005) <sup>29</sup> and Taylor et al. (2006a).
Turner JA, Loeser JD, Deyo RA, Sanders SB. Spinal cord stimulation for patients with failed back surgery syndrome or complex regional pain syndrome: a systematic review of effectiveness and complications. <i>Pain</i> 2004;108(1-2):137-47.	Systematic review	Included in Ontario Ministry of Health and Long-Term Care (2005) <sup>21</sup> .
Wetzel FT, Hassenbusch S, Oakley JC, Willis K.D, Simpson RK, Ross EL. Treatment of chronic pain in failed back surgery patients with spinal cord stimulation: a review of current literature and proposal for future investigation. <i>Neuromodulation</i> 3(2):59-74.	Quasi-systematic review	Included studies not critically appraised.
WCB Evidence Based Practice Group. Spinal cord stimulation: use in patients with complex regional pain syndrome. WorkSafe BC. 2003. Available: <a href="http://www.worksafebc.com/health_care_providers/Assets/PDF/spinal_cord_stimulatiion.pdf">http://www.worksafebc.com/health_care_providers/Assets/PDF/spinal_cord_stimulatiion.pdf</a> .	Systematic review	Included the same studies as Ontario Ministry of Health and Long-Term Care (2005) <sup>21</sup> .
<b>Randomized controlled trials</b>		
Kemler MA, de Vet HC, Barendse GA, FA, van Kleef M. Spinal cord stimulation for chronic reflex sympathetic dystrophy - five-year follow-up. <i>New England Journal of Medicine</i> 2006;354(22):2394-96.	Randomized controlled trial	Duplication of data from Kemler et al. (2008) <sup>22</sup> .

Kumar K. Spinal cord stimulation vs. conventional medical management: A prospective, randomized, controlled, multicenter study of patients with failed back surgery syndrome (PROCESS study). <i>Neuromodulation</i> 2005;8(4):213-18.	Randomized controlled trial	Methods for Kumar et al. (2007) <sup>23</sup> – no results reported.
<b>Guidelines</b>		
Airaksinen O, Brox JI, Cedraschi C, Hildebrandt J, Klaber-Moffett J, Kovacs F, et al. on behalf of the COST B13 Working Group on Guidelines for Chronic Low Back Pain. European guidelines for the management of chronic non-specific low back pain. 2004. Available: <a href="http://www.kovacs.org/Imágenes/EuropeanGuidelinesCHRONIC.LBP.pdf">http://www.kovacs.org/Imágenes/EuropeanGuidelinesCHRONIC.LBP.pdf</a> .	Guideline	Non-specific chronic low back pain only. Radicular pain not included.
Ambrosio F, Finco G, Mattia C, Mediati R, Paoletti F, Coluzzi F, et al. SIAARTI recommendations for chronic non-cancer pain. <i>Minerva Anestesiologica</i> 2006;72(11):859-80.	Guideline	Same interventions and patient groups as Cruccu et al. (2007) <sup>24</sup> , but guideline of lower quality and not as current.
American Society of Anesthesiologists. Practice guidelines for chronic pain management. A report by the American Society of Anesthesiologists Task Force on Pain Management, Chronic Pain Section. <i>Anesthesiology</i> 1997;86(4):995-1004.	Guideline	Same interventions and patient groups as Cruccu et al. (2007) <sup>24</sup> , but guideline of lower quality and not as current.
Boswell MV, Trescot AM, Datta S, Schultz DM, Hansen HC, Abdi S, et al. Interventional techniques: evidence-based practice guidelines in the management of chronic spinal pain. <i>Pain Physician</i> 2007;10(1):7-111.	Guideline	Same interventions and patient groups as Cruccu et al. (2007) <sup>24</sup> , but guideline of lower quality and not as current.
British Pain Society. <i>Spinal cord stimulation for pain: Information for patients</i> . London, United Kingdom: British Pain Society; 2005	Guideline	Same interventions and patient groups as Cruccu et al. (2007) <sup>24</sup> , but guideline of lower quality and not as current.
Gybels J, Erdine S, Maeyaert J, Meyerson B, Winkelmüller W, Augustinsson L, et al. Neuromodulation of pain. A consensus statement prepared in Brussels 16-18 January 1998 by the following task force of the European Federation of IASP Chapters (EFIC). <i>European Journal of Pain</i> 1998;2:203-9.	Guideline	Not evidence-based.
Hunter Integrated Pain Service. Pain matters: Procedural intervention guideline. Hunter Integrated Pain Service; 2005. Available: <a href="http://www.hnehealth.nsw.gov.au/__data/assets/pdf_file/0004/28165/Guideline_procedural_intervention.pdf">http://www.hnehealth.nsw.gov.au/__data/assets/pdf_file/0004/28165/Guideline_procedural_intervention.pdf</a> .	Guideline	Same interventions and patient groups as Cruccu et al. (2007) <sup>24</sup> , but guideline of lower quality and not as current.
Institute for Clinical Systems Improvement (ICSI). Assessment and management of chronic pain. Bloomington (MN): Institute for Clinical Systems Improvement (ICSI); 2007. Available: <a href="http://www.ngc.gov/summary/summary.aspx?doc_id=10724&amp;nbr=005586&amp;string=%22neuropathic+pain%22">http://www.ngc.gov/summary/summary.aspx?doc_id=10724&amp;nbr=005586&amp;string=%22neuropathic+pain%22</a> .	Guideline	Does not specifically address neuropathic pain.

Netherlands Society of Rehabilitation Specialists and the Netherlands Society of Anaesthesiologists. Guideline: Complex regional pain syndrome type I. 2006. Available: <a href="http://www.cbo.nl/product/richtlijnen/folder20021023121843/rl_crps_eng_07.pdf">http://www.cbo.nl/product/richtlijnen/folder20021023121843/rl_crps_eng_07.pdf</a> .	Guideline	Included studies on children.
New Zealand Accident Compensation Corporation. Spinal cord stimulation. 2005. Available: <a href="http://www.acc.co.nz/for-providers/interventional-pain-management/interventions/intervention-index/WCM1_033674">http://www.acc.co.nz/for-providers/interventional-pain-management/interventions/intervention-index/WCM1_033674</a> .	Guideline	Included studies on children/adolescents (>12 years of age).
Sanders SH, Harden RN, Vicente PJ. Evidence-based clinical practice guidelines for interdisciplinary rehabilitation of chronic non-malignant pain syndrome patients. <i>Pain Practice</i> 2005;5:303-15.	Guideline	Does not specifically address neuropathic pain.
Stanton-Hicks M, Baron R, Boas R, Gordh T, Harden N, Hendler N, et al. Complex Regional Pain Syndromes: guidelines for therapy. <i>Clinical Journal of Pain</i> 1998;14(2):155-66.	Consensus statement	Not an evidence-based guideline.

## **APPENDIX C: QUALITY ASSESSMENT CHECKLIST FOR SYSTEMATIC REVIEWS<sup>6-9</sup>**

### **Study Question**

The research question should be established a priori.

*Reported:*

The objectives of the review are clearly stated in the abstract, introduction, or methods.

*Partially reported:*

The objectives of the review are stated in:

- the abstract, introduction, or methods but are vague or unclear; or
- a section of the report other than the abstract, introduction, or methods.

*Not reported:*

The objectives are not stated in any section of the review.

### **Inclusion/Exclusion Criteria**

The participants, interventions, outcome measures, and types of studies considered for analysis should be established a priori.

*Reported:*

All four elements (participants, interventions, outcome measures, types of studies) are reported in the abstract, introduction, or methods section of the review.

*Partially reported:*

Only three of the four elements are reported in the abstract, introduction, or methods section.

*Not reported:*

Less than three of the four elements are reported in the abstract, introduction, or methods section; or

- The first mention of any of these elements occurs in the results section.

### **Search Strategy**

#### ***Electronic databases***

*Reported:*

At least one electronic database was searched and the names of the databases are provided.

*Partially reported:*

At least one electronic database was searched but the names are not provided.

*Not reported:*

Electronic databases were not searched or are not mentioned in the review.

**Quality subsection 1: At least MEDLINE and EMBASE**

*Yes:*

Both MEDLINE and EMBASE were searched.

*Unclear:*

It was unclear whether MEDLINE and EMBASE were searched because a complete list of all the electronic databases searched is not provided.

*No:*

The review stated that neither MEDLINE nor EMBASE was searched;

- Neither MEDLINE nor EMBASE is mentioned in the complete list of electronic databases searched; or
- Only one of the two the databases was searched.

**Other sources**

*Reported:*

At least one additional resource or method, other than searching electronic databases, was used to identify relevant literature (e.g. pearling or review of reference lists in retrieved articles, hand searching of journals).

*Partially reported:*

Other resource or methods were used but details are not provided.

*Not reported:*

The review did not use other resource or methods to identify relevant literature or does not mention it.

**Data Extraction**

**Data extraction method**

*Reported:*

The data extraction process is described.

*Partially reported:*

A data extraction process is mentioned but no details are provided.

*Not reported:*

A data extraction process was not used or described.

**Quality subsection 2: Standardized method**

*Yes:*

The data categories extracted are listed or the use of a standardized data extraction form is mentioned.

*Unclear:*

The review states that a standardized data extraction process was used but does not list the data categories extracted or mention the use of a standardized data extraction form.

*No:*

The data categories extracted are not listed or the use of a standardized data extraction form is not mentioned.

**Quality subsection 3: Independent data extraction by at least two reviewers**

*Yes:*

Data were extracted independently by at least two reviewers.

*Unclear:*

The number of reviewers who extracted data is not stated.

*No:*

Data were extracted by:

- only one reviewer; or
- one reviewer and checked by another.

**Quality Assessment**

**Criteria used to assess the validity of included studies**

*Reported:*

A quality assessment tool or checklist was used and details are provided (e.g. name or source).

*Partially reported:*

A quality assessment tool or checklist was used but no details are provided.

*Not reported:*

A quality assessment tool or checklist was not used or mentioned; or

- Studies were only categorized according to a level of evidence hierarchy.

**Quality subsection 4:****Independent quality assessment by at least two reviewers***Yes:*

The quality of the included studies was assessed independently by at least two reviewers.

*Unclear:*

The number of reviewers who appraised study quality is not stated.

*No:*

Studies were assessed by:

- only one reviewer; or
- one reviewer and checked by another.

**Inter-rater agreement***Reported:*

The review provides a statement of the degree of difference/equivalence between the reviewers or a statistical measure of inter-rater agreement.

*Partially reported:*

The review mentions that inter-rater agreement was measured but does not provide a statement of the degree of difference/equivalence or a statistical measure of inter-rater agreement.

*Not reported:*

The review does not provide any information on inter-rater agreement.

**Data Analysis/Synthesis**

Only ONE of the three methods for data analysis/synthesis can be assessed. Select the data analysis type according to the definitions below. Only score the quality subsection that pertains to the particular data analysis method used in the review.

*Qualitative review:*

A narrative summary of the study results with no statistical analysis or pooling of results.

**Quality subsection 5a:**

**Study quality used in analysis or discussion of study results**

*Yes:*

Results of the included studies are discussed or analyzed in terms of their quality.

*Unclear:*

- Study quality was assessed but is either not used at all or is only used to analyze some of the included studies.
- The review mentions selective inclusion of ‘quality’ studies, but without further assessment of their quality (e.g. only RCTs were included but the robustness of their execution was not assessed).

*No:*

- The results of the included studies are not discussed or analyzed in terms of their quality.
- Study quality was not assessed.

*Semi-quantitative review:*

Incorporates a statistical analysis of individual studies without pooling the results (e.g. relative risks calculated for individual study outcomes) or pooling of results using only descriptive statistics (e.g. median, mean, mode, frequency).

**Quality subsection 5b: Confidence interval/measures of dispersion reported**

*Yes:*

Confidence intervals or measures of dispersion (range, standard deviation, standard error of the mean) are reported for all relevant analyses.

*Unclear:*

- Confidence intervals or measures of dispersion are only reported for some of the relevant analyses.
- Confidence intervals are reported for all relevant analyses, but the level of confidence is not specified (e.g. unclear if 95% or 99% confidence intervals were calculated).
- Measures of dispersion are reported for all relevant analyses but the type is not specified (e.g. standard deviation or standard error).

*No:*

Confidence intervals or measures of dispersion are not reported.

*Meta-analysis:*

A pooled effect estimate is calculated for at least two studies. Reviews that contain a meta-analysis of some studies and a qualitative analysis of the remaining studies are considered a ‘meta-analysis’.

### **Quality subsection 5c: Precision of results reported**

*Yes:*

Confidence intervals are reported for all pooled effect estimates.

*Unclear:*

- Confidence intervals are reported for some but not all pooled effect estimates.
- Confidence intervals are reported for all pooled effect estimates but the level of confidence is not specified (e.g. unclear if 95% or 99% confidence intervals were calculated).

*No:*

Confidence intervals are not reported.

### **Quality subsection 5d: Test of homogeneity conducted**

*Yes:*

A statistical analysis of study heterogeneity is reported for all pooled studies.

*Unclear:*

- A statistical analysis of study heterogeneity is reported for some but not all pooled studies.
- A statistical analysis of study heterogeneity is reported for all pooled studies, but the type of model used is not specified (e.g. fixed-effect or random-effects).

*No:*

A statistical analysis of study heterogeneity was not conducted.

### **Test for publication bias**

*Reported:*

Publication bias was analysed or a reason provided for why it was not.

*Partially reported:*

- The review mentions analysing publication bias but does not present the results.
- The review states that publication bias was not analysed but does not explain why.

*Not reported:*

There was no mention of analysing publication bias.

### **Concluding Section**

#### **Potential methodological limitations**

*Reported:*

The methodological limitations or advantages of the review are described in a separate section or paragraph.

*Partially reported:*

The description of the methodological limitations or advantages of the review is cursory (e.g. single sentence or no separate paragraph or section).

*Not reported:*

There is no mention of the potential methodological limitations or advantages of the review.

### **Clinical application of results**

The clinical application of results is considered adequate if all of the following four elements are present in the concluding section (includes discussion) or statement of the review: treatment, treatment effect, patient group, and comparator.

*Reported:*

All four elements are present.

*Partially reported:*

Only three of the four elements are present.

*Not reported:*

Less than three of the four elements are present.

### **Incorporation of methodological quality**

The review should take into account the methodological quality of the included studies when formulating the conclusions.

*Reported:*

The methodological quality of the included studies is mentioned in the concluding section (includes discussion) or statement of the review.

*Partially reported:*

The study types, as designated by a level of evidence hierarchy category, are mentioned in the concluding section (includes discussion) or statement of the review, but not the quality of the studies.

*Not reported:*

The methodological quality of the included studies is not mentioned in the concluding section (includes discussion) or statement of the review.

#### **Quality subsection 6: Conclusions supported by results**

*Yes:*

The conclusions drawn by the authors of the review are supported by the evidence presented in the results section.

*Unclear:*

Some, but not all, of the conclusions drawn by the authors of the review are supported by the evidence presented in the results section.

*No:*

The conclusions drawn by the authors of the review are not supported by the evidence presented in the results section.

## Conflict of Interest and Funding

### Conflict of interest

*Reported:*

A statement of conflict of interest (if any) is provided.

*Partially reported:*

A conflict of interest is mentioned but details are not provided.

*Not reported:*

A statement of conflict of interest (if any) is not provided.

### Sources of funding

*Reported:*

- Funding sources are mentioned; or
- The review was developed without external funding (e.g. authors employed by a university or volunteered time to produce a Cochrane Review).

*Partially reported:*

External funding is mentioned but details are not provided.

*Not reported:*

Funding sources are not mentioned.

## Quality Rating

SRs were rated on how well their methods excluded bias and confounding by examining: the search strategy used; how the data extraction, quality assessment of the included studies, and data analysis/synthesis were conducted; and whether the conclusions of the review matched the results. The SRs were rated with respect to six essential quality criteria (grey boxes above) as follows:

**Good** – six criteria met, or five criteria met and one criterion ‘unclear’.

**Average** – one criterion not met, or one criterion not met and one criterion ‘unclear’, or two criteria ‘unclear’.

**Poor** – at least two criteria not met.

**N.B.** For a criterion to have been ‘met’, it must be scored as ‘yes’ (✓). For meta-analyses, the two applicable quality subsections (5c and 5d) are counted as a single quality criterion. Therefore, to meet the fifth quality criterion for meta-analyses both 5c and 5d must be scored as ‘yes’ (✓).

**Table C.1: Quality assessment results for included systematic reviews**

Review Characteristic		OHTAC (2005) <sup>21</sup>
Study question established a priori		●
Inclusion/exclusion criteria		●
Search strategy	Electronic databases	●
	<i>1. At least MEDLINE and EMBASE</i>	✓
	Other sources	●
Data extraction	Data extraction method	○
	<i>2. Standardized method</i>	X
	<i>3. Independent data extraction by at least two reviewers</i>	?
Quality assessment	Criteria used to assess the validity of included studies	●
	<i>4. Independent quality assessment by at least two reviewers</i>	?
	Inter-rater agreement for quality assessment	○
Data analysis/synthesis	Qualitative review	●
	<i>5a. Study quality used in analysis or discussion of study results</i>	✓
	Semi-quantitative review	N/A
	<i>5b. Confidence intervals or measures of dispersion reported</i>	
	Meta-analysis	N/A
	<i>5c. Precision of results reported</i>	
	<i>5d. Test of homogeneity conducted</i>	
Test for publication bias		○
Concluding section	Potential methodological limitations/advantages	○
	Clinical application of results	○
	Incorporation of methodological quality	●
	<i>6. Conclusions supported by results</i>	✓
Conflict/funding	Conflict of interest (if any)	○
	Sources of funding	○
Quality rating	Six criteria (search at least two databases; standardized data extraction; independent data extraction and quality rating by two reviewers; appropriate data synthesis; conclusions supported by results)	3/6 Poor

**Key for quality of reporting:**

Reported: ●; Partially reported: ◐; Not reported: ○; Not applicable: N/A

**Key for quality of review subsections (grey sections of table):**

Yes = ✓; Unclear = ?; No = X

## APPENDIX D: QUALITY ASSESSMENT CHECKLIST FOR RANDOMIZED CONTROLLED TRIALS

(Adapted from the list recommended in the method guidelines of the Cochrane Back Review Group,<sup>12</sup> with additional guidance derived from Downs and Black.<sup>18</sup>)

### Patient Selection

- A. *Were the eligibility criteria specified?*

Inclusion and/or exclusion criteria should be given.

- B. *Treatment allocation*

- 1) *Was a method of randomization performed?*

Studies stating that patients were randomized should be answered 'yes' except where the method of randomization would not ensure random allocation. Methods of allocation using date of birth, date of admission, hospital numbers, or alternation are not regarded as appropriate.

- 2) *Was the treatment allocation concealed?*

Assignment generated by an independent person not responsible for determining the eligibility of the patients.

- C. *Were the groups similar at baseline regarding the most important prognostic indicators?*

To receive a 'yes', groups must be similar at baseline regarding age, sex distribution, duration of pain, and at least one of the following: patient comorbidities, mobility, health-related quality of life, or pain intensity.

### Interventions

- D. *Were the index and control interventions explicitly described?*

The description should include (when applicable) type, modality, application technique, intensity, and duration as well as the number and frequency of sessions so that others can replicate the treatment. If any of the treatments are described by name only, with no further detail given, the question should be answered 'no'.

- E. *Were co-interventions avoided or comparable?*

Co-interventions should either be avoided in the trial design or comparable between the index and control groups.

- F. *Was the patient blinded to the intervention?*

For studies where the patients would have no way of knowing which intervention they received, this should be answered 'yes'. For studies that do not state whether blinding was attempted, the answer should be 'unclear'.

## Outcome Measurement

G. *Was the outcome assessor blinded to the intervention?*

For studies where the outcome assessor would have no way of knowing which intervention the patients received, this should be answered 'yes'. For studies that do not state whether blinding was attempted, the answer should be scored as 'unclear'.

H. *Were the outcome measures relevant?*

Outcome measures should be clearly described. Relevant measures for non-malignant chronic pain include changes in pain, mobility, and pain pressure threshold; generic functional status; global measure of improvement; and return to work.

I. *Were adverse effects described?*

Each event should be described and correctly attributed to the allocated treatment. If it was explicitly reported that no adverse events occurred then a 'yes' should be scored. When adverse events are described but not clearly attributed to a particular treatment, the answer should be scored as 'unclear'.

J. *Was the withdrawal/dropout rate described and acceptable?*

Patients included in the study but who did not complete the observation period or were not included in the analysis must be described. If the numbers of patients lost to follow-up were not reported, the question should be answered as 'unclear'. If the proportion lost to follow-up was too small ( $\leq 10\%$  in each treatment group for short-term follow-up and  $\leq 20\%$  for long-term follow-up) to affect the main findings, the question should be answered 'yes'. (**Note:** These percentages are arbitrary and are not supported by literature).

K. *Timing of follow-up measurements*

1) *Was a short-term follow-up measurement performed?*

Outcome assessment at the end of the intervention period.

2) *Was a long-term follow-up measurement performed?*

Outcome assessment  $>3$  months after randomization.

L. *Was the timing of the outcome assessment comparable in both groups?*

The timing of outcome assessment should be identical for all intervention groups and for all important outcome assessments. Where follow-up was the same for all study patients, the answer should be 'yes'. If the results were adjusted to account for different lengths of follow-up (for example by survival analysis), the answer should be 'yes'. Studies where differences in follow-up were ignored should be answered 'no'.

## Statistics

M. *Was the sample size for each group described?*

Simple outcome data (including denominators and numerators) should be reported for all major findings so that the reader can check the major analyses and conclusions.

N. *Did the analysis include an intention-to-treat analysis?*

All randomized patients are reported/analysed for the most important effect measurements (minus missing values) irrespective of non-compliance and co-interventions.

O. *Were point estimates and measures of variability presented for the primary outcome measures?*

Both point estimates and measures of variability should be presented separately for each important outcome. In non-normally distributed data the median and inter-quartile range should be reported. In normally distributed data the mean plus standard error, standard deviation, or confidence interval should be reported. If the distribution of the data is not described, it must be assumed that the estimates used were appropriate and the question should be answered 'yes'.

## Quality Rating

For descriptive purposes, the included RCTs were referred to as being good, moderate, or poor quality with respect to internal and external validity according to the total number of criteria met as follows:

- Internal validity (total number of criteria = 9) – good ( $\geq 7$  criteria met), moderate (between 4 and 6 criteria met), poor ( $< 4$  criteria met).
- External validity (total number of criteria = 6) – good ( $\geq 5$  criteria met), moderate (3 or 4 criteria met), poor ( $< 3$  criteria met).

**Table D.1: Quality assessment results for included randomized controlled trials**

Study Characteristic		Kemler et al. (2008) <sup>22</sup>	Kumar et al. (2007) <sup>23</sup>
<b>Patient Selection</b>	A. Were the eligibility criteria specified?	✓	✓
	B1. Was randomization performed adequately?	✓	✓
	B2. Was treatment allocation concealed?	✓	✓
	C. Were the groups similar at baseline?	✓	✓
<b>Interventions</b>	D. Were the index and control interventions explicitly described?	✓	✓
	E. Were co-interventions avoided or comparable?	?	✓
	F. Was the patient blinded to the intervention?	NA	NA
<b>Outcome measurement</b>	G. Was the outcome assessor blinded to the intervention?	NA	NA
	H. Were the outcome measures relevant?	✓	✓
	I. Were adverse events described?	✓	✓
	J. Was the withdrawal/dropout rate described and acceptable?	x	✓
	K1. Was a short-term follow-up measurement performed?	✓	✓
	K2. Was a long-term follow-up measurement performed?	✓	✓
	L. Was the timing of the outcome assessment comparable in both groups?	✓	✓
<b>Statistics</b>	M. Was the sample size for each group described?	✓	✓
	N. Did the analysis include an intention-to-treat analysis?	x	✓
	O. Were point estimates and measures of variability presented for the primary outcome measures?	✓	✓

Key: Yes = ✓; No = x; Unclear = ?; Not applicable or not possible because of the nature of the intervention = NA

Internal validity criteria: b, e, f, g, h, j, l, n; External validity criteria: a, c, d, i, k; Statistical criteria: m, o

## **APPENDIX E: QUALITY ASSESSMENT CHECKLIST FOR CLINICAL PRACTICE GUIDELINES**

(Adapted from The Agree Collaboration<sup>19</sup>)

### **Scope and Purpose (Items 1,2,3)**

#### ***Item 1 – Guideline objectives***

Information about the clinical condition, target population, and expected health benefit should be provided in the objectives statement.

- 4 – All three elements reported (condition, target population, health benefit).
- 3 – Two elements reported.
- 2 – Unclear or only one element reported.
- 1 – Objectives of the guideline are not provided.

#### ***Item 2 – Clinical question***

Information about the intervention and clinical condition should be provided.

- 4 – Two elements reported (intervention, clinical condition).
- 3 – One element reported.
- 2 – Unclear.
- 1 – Information about the clinical question is not provided.

#### ***Item 3 – Target population***

Information about the age (defined as “adults” or by an age range), comorbidity, and clinical description (if applicable) of the target population should be provided.

- 4 – All applicable elements reported (age, comorbidity, clinical description). In cases where at least one element is not applicable, the guideline is scored 4 only if all of the remaining applicable elements are present. For example, if comorbidity is not applicable, the guideline will only score 4 if age and clinical description are provided.
- 3 – One applicable element not reported.
- 2 – Unclear or two applicable elements not reported.
- 1 – Information about the target population is not provided.

### **Stakeholder Involvement**

#### ***Item 4 - Relevant professional groups***

Information about the composition of the guideline development group (GDG) and the discipline (job title, university department, etc.) and relevant expertise (particular area of skill, e.g. methodologist, occupational medicine) of its members should be provided.

- 4 – All three elements (composition of the entire GDG; discipline and expertise of all GDG members) are reported.

- 3 – Composition of the entire GDG is provided but two elements (discipline and relevant expertise) reported for only some of its members.
- 2 – Unclear or composition of the entire GDG is provided but only one element (discipline and relevant expertise) reported for all of its members.
- 1 – Information about the GDG is not provided or composition of the entire GDG is provided but one element (discipline or relevant expertise) reported only for some of its members.

***Item 5 - Patients' perspectives***

- 4 – Patient perspectives incorporated and methods reported.
- 3 – Patient perspectives discussed but methods not reported.
- 2 – Unclear.
- 1 – Patient perspectives not incorporated.

***Item 6 - Target users defined***

- 4 – Target users explicitly defined by specialty, e.g. general practitioners, neurologists, physiotherapists.
- 3 – Target users defined in broad terms, e.g. practitioners treating patients with chronic pain.
- 2 – Unclear.
- 1 – Target users not defined.

***Item 7 - Piloted among target users***

- 4 – Guideline piloted among target users and methods reported.
- 3 – Guideline piloted among target users but methods not reported.
- 2 – Unclear.
- 1 – Guideline not piloted among target users.

**Rigour of Development**

***Item 8 - Systematic methods used to search for evidence***

Information about the search terms used, sources consulted, and date limits of the literature searches should be provided.

- 4 – All three elements reported (search terms, sources, date limits).
- 3 – Two elements reported.
- 2 – Unclear or one element reported.
- 1 – Information about the methods used to search for evidence is not provided.

### **Item 9 - Selection criteria**

- 4 – Inclusion/exclusion criteria described and reasons for excluding (or including) evidence clearly stated.
- 3 – Inclusion/exclusion criteria described but reasons for excluding evidence (or including) are not stated.
- 2 – Unclear.
- 1 – Inclusion/exclusion criteria not stated.

### **Item 10 - Methods used to formulate recommendations**

Information on the methods used to formulate the recommendations, resolve disagreements, and reach final decisions should be provided.

- 4 – All three elements reported (formulation of recommendations, resolving disagreements, reaching final decisions).
- 3 – Two elements reported.
- 2 – Unclear or only one element reported.
- 1 – Information about the methods used to formulate the recommendations is not provided.

**N.B.** In cases where the guideline was written by a single author, the guideline is scored as follows:

- 4 – The methods used to formulate the recommendations are reported.
- 2 – Unclear.
- 1 – Information about the methods used to formulate the recommendations is not provided.

### **Item 11 - Consideration of benefits, side effects, and risks**

Information on the benefits, side effects, and risks of the recommendations should be provided.

- 4 – All applicable elements reported (benefits, side effects, risks). In cases where at least one element is not applicable, the guideline is scored 4 only if all of the remaining applicable elements are present. For example, if side effects are not applicable, the guideline will only score 4 if benefits and risks are provided.
- 3 – One applicable element not reported.
- 2 – Unclear or two applicable elements not reported.
- 1 – Information about the benefits, side effects, and risks not stated.

### **Item 12 - Link between recommendations and the supporting evidence**

- 4 – Each recommendation is explicitly linked to the references on which it is based.
- 3 – Only some of the recommendations are explicitly linked to the references on which they are based.

2 – Unclear.

1 – No explicit link between each recommendation and the references on which it is based.

**Item 13 - External review**

4 – Externally reviewed by independent clinical and methodological experts and methods reported.

3 – Externally reviewed and one of the following criteria met: methods reported, reviewers included clinical and methodological experts.

2 – Unclear or externally reviewed but none of the following criteria met: methods reported, reviewers included clinical and methodological experts.

1 – Not externally reviewed or no statement about external review.

**Item 14 - Procedure for updating the guideline**

4 – Statement about updating the guideline and methods reported.

3 – Statement about updating the guideline but methods not reported.

2 – Unclear.

1 – Guideline will not be updated or no statement about updating the guideline.

**Clarity and Presentation**

**Item 15 - Specific, unambiguous recommendations**

The recommendations were considered adequate if all of the following three elements were present: management or treatment, patient group, clinical situation.

4 – All three elements reported.

3 – Two elements reported.

2 – Unclear or one element reported.

1 – None of the elements reported.

**Item 16 - Different management options presented**

4 – Different management options were considered to be adequately presented if the comparators for each intervention were stated in the guideline. For example, massage therapy is more effective than relaxation therapy in patients with chronic low back pain.

3 – The comparators were stated for only some of the interventions.

2 – Unclear.

1 – The comparators for the interventions were not stated.

**Item 17 - Key recommendations identifiable**

- 4 – Key recommendations summarized and identifiable.
- 3 – Key recommendations reported but not summarized or highlighted for easy identification.
- 2 – Unclear.
- 1 – Key recommendations not identifiable.

**Item 18 - Additional support materials provided**

- 4 – Additional support materials provided.
- 3 – Additional support materials provided but not easily available e.g. published in a journal that is not open access.
- 2 – Unclear.
- 1 – Additional support materials not provided.

**Applicability**

**Item 19 - Organizational barriers discussed**

- 4 – Not applicable or organizational barriers discussed and required changes are outlined.
- 3 – Organizational barriers mentioned but required changes are not outlined.
- 2 – Unclear.
- 1 – Organizational barriers not discussed.

**Item 20 - Resource implications considered**

- 4 – Not applicable or resource implications discussed and the effects on resources are outlined.
- 3 – Resources implications mentioned but the effects on resources are not outlined (or are only outlined for some interventions).
- 2 – Unclear.
- 1 – Resource implications not discussed.

**Item 21 - Key review criteria presented**

- 4 – Key review criteria presented and specific thresholds provided.
- 3 – Key review criteria discussed but specific thresholds not provided.
- 2 – Unclear.
- 1 – Key review criteria not presented.

## Editorial Independence

### **Item 22 - Editorially independent from funding body**

- 4 – Developed without external funding or details of financial support provided plus an explicit statement that the funding body has not influenced the final recommendations.
- 3 – Details of financial support provided but no statement about the funding body's influence on guideline development.
- 2 – Unclear or no details about financial support.
- 1 – Funding body potentially influenced the final recommendations.

### **Item 23 - Conflicts of interest reported**

- 4 – Details of the affiliations and conflicts of interest (if any) of the development group are provided.
- 3 – Details of conflicts of interest (if any) are provided but without a list of the development group's affiliations.
- 2 – Unclear or a list of the development group's affiliations is provided but without details on conflicts of interest (if any).
- 1 – Details of the affiliations and conflicts of interest (if any) of the development group are not provided.

## Quality Rating

Guidelines were rated on how well their methods excluded bias by examining the search strategy used; how the recommendations were formulated and presented; whether the recommendations were directly linked to the evidence; the external review process; and whether conflicts of interest and funding sources were reported. The average quality rating score (maximum possible score is 28 (7 x 4)) for these criteria was derived by dividing the sum of the scores given by each reviewer by the number of reviewers. The guideline was then rated as follows (grey rows in Table E.1).

**Good** – average score of 22 to 28;

**Average** – average score of 15 to 21;

**Poor** – average score 0 to 14.

## Standardized Domain Scores

These scores for each of the six domains were combined and converted into standardized domain scores according to the following formula (Table E.2).

$$\text{Standardized domain score (\%)} = \frac{\text{obtained score} - \text{minimum possible score}}{\text{maximum possible score} - \text{minimum possible score}} \times 100$$

**Table E.1: AGREE tool quality assessment results for included clinical practice guidelines (two appraisers)**

Guideline Characteristic		Cruccu et al. (2007) <sup>24</sup>	
Scope/ purpose	1.Objectives	4	3
	2. Clinical question	4	3
	3. Target population	2	2
Stakeholder involvement	4. Relevant professional groups represented	2	2
	5. Patients' perspectives included	2	2
	6. Target users defined	4	4
	7. Piloted among target users	2	2
Rigour of development	8. Systematic search conducted	4	3
	9. Selection criteria described	3	3
	10. Methods used to formulate recommendations described	2	2
	11. Benefits, side effects, risks considered	4	4
	12. Link between recommendations and evidence	4	4
	13. External review by experts	2	2
	14. Updating procedure described	4	4
Clarity/ presentation	15. Specific, unambiguous recommendations	4	4
	16. Different management options presented	3	3
	17. Key recommendations easily identifiable	4	4
	18. Additional support materials provided	1	2
Applicability	19. Organizational barriers discussed	1	1
	20. Resource implications considered	1	1
	21. Key review criteria presented	1	1
Editorial independ- ence	22. Editorially independent from funder	2	2
	23. Conflicts of interest reported	4	4
Quality Rating	Seven criteria (systematic search, method of formulating recommendations, recommendations-evidence link, external review, clear recommendations, editorial independence, conflict of interest)	21.5 Average	

**Table E.2: AGREE tool standardized domain scores (%) for included clinical practice guidelines**

<b>AGREE Domain</b>	<b>Cruccu et al. (2007)<sup>24</sup></b>
Scope and purpose	67
Stakeholder involvement	50
Rigour of development	74
Clarity and presentation	71
Applicability	0
Editorial independence	67

## REFERENCES

1. Cook DJ, Mulrow CD, Haynes RB. Systematic reviews: Synthesis of best evidence for clinical decisions. *Annals of Internal Medicine* 1997;126(5):376-80.
2. Institute of Medicine. *Clinical Practice Guidelines: Directions for a New Program*. Field MJ, Lohr KN, editors. Washington, DC: National Academy Press; 1990. Available from: [http://www.nap.edu/catalog.php?record\\_id=1626](http://www.nap.edu/catalog.php?record_id=1626) (accessed September 10, 2008).
3. Wilson MC, Hayward RS, Tunis SR, Bass EB, Guyatt G. Users' guides to the Medical Literature. VIII. How to use clinical practice guidelines. B. what are the recommendations and will they help you in caring for your patients? The Evidence-Based Medicine Working Group. *Journal of the American Medical Association* 1995;274(20):1630-2.
4. Veldhuijzen W, Ram P, van der WT, Wassink M, Van D, V. Much variety and little evidence: a description of guidelines for doctor-patient communication. *Medical Education* 2007;41(2):138-45.
5. United Nations Public Administration Network. *List of Country Groupings and Sub-groupings for the Analytical Studies of the United Nations World Economic Survey and other UN Reports*. United Nations Public Administration Network; 1995.
6. Aggressive Research Intelligence Facility. ARIF Critical Appraisal Checklist. University of Birmingham 2008. Available from: <http://www.arif.bham.ac.uk/critical-appraisal-checklist.shtml> (accessed September 10, 2008).
7. Fishbain D, Cutler RB, Rosomoff HL, Rosomoff RS. What is the quality of the implemented meta-analytic procedures in chronic pain treatment meta-analyses? *Clinical Journal of Pain* 2000;16(1):73-85.
8. Greenhalgh T. How to read a paper: Papers that summarise other papers (systematic reviews and meta-analyses). *British Medical Journal* 1997;315(7109):672-5.
9. University of Alberta. Evidence Based Medicine Tool Kit. University of Alberta 2008. Available from: <http://www.med.ualberta.ca/ebm/main.htm> (accessed September 10, 2008).
10. Shea BJ, Grimshaw JM, Wells GA, Boers M, Andersson N, Hamel C, et al. Development of AMSTAR: a measurement tool to assess the methodological quality of systematic reviews. *BMC Medical Research Methodology* 2007;7(10).
11. Oxman AD, Guyatt GH. Validation of an index of the quality of review articles. *Journal of Clinical Epidemiology* 1991;44(11):1271-8.
12. van Tulder MW, Assendelft WJ, Koes BW, Bouter LM. Method guidelines for systematic reviews in the Cochrane Collaboration Back Review Group for spinal disorders. *Spine* 1997;22(20):2323-30.
13. Guzmán J, Esmail R, Karjalainen K, Malmivaara A, Irvin E, Bombardier C. Multidisciplinary bio-psycho-social rehabilitation for chronic low back pain. *Cochrane Database of Systematic Reviews* 2006, Issue 2. Art. No.: CD000963. DOI: 10.1002/14651858.CD000963.pub2.

14. Niemisto L, Kalso E, Malmivaara A, Seitsalo S, Hurri H. Radiofrequency denervation for neck and back pain. *Cochrane Database of Systematic Reviews* 2003, Issue 1. Art. No.: CD004058. DOI: 10.1002/14651858.CD004058.
15. Ostelo RW, van Tulder MW, Vlaeyen JW, Linton SJ, Morley SJ, Assendelft WJ. Behavioural treatment for chronic low back pain. *Cochrane Database of Systematic Reviews* 2005, Issue 1. Art. No.: CD002014. DOI: 10.1002/14651858.CD002014.pub2.
16. Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJM, Gavaghan DJ, et al. Assessing the quality of reports of randomized clinical trials: Is blinding necessary? *Controlled Clinical Trials* 1996;17(1):1-12.
17. Verhagen AP, de Vet HC, de Bie RA, Kessels AG, Boers M, Bouter LM, et al. The Delphi list: a criteria list for quality assessment of randomized clinical trials for conducting systematic reviews developed by Delphi consensus. *Journal of Clinical Epidemiology* 1998;51(12):1235-41.
18. Downs SH, Black N. The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions. *Journal of Epidemiology and Community Health* 1998;52(6):377-84.
19. The AGREE Collaboration. Appraisal of Guidelines for Research and Evaluation (AGREE) Instrument. The AGREE Collaboration 2001. Available from: <http://www.agreecollaboration.org/pdf/agreeinstrumentfinal.pdf> (accessed September 10, 2008).
20. Hayward RS, Wilson MC, Tunis SR, Bass EB, Guyatt G. Users' guides to the medical literature. VIII. How to use clinical practice guidelines. A. Are the recommendations valid? The Evidence-Based Medicine Working Group. *Journal of the American Medical Association* 1995;274(7):570-4.
21. Ontario Ministry of Health and Long-Term Care. Spinal cord stimulation for neuropathic pain, 2005. Available from: [http://www.health.gov.on.ca/english/providers/program/mas/tech/techlist\\_mn.html](http://www.health.gov.on.ca/english/providers/program/mas/tech/techlist_mn.html) (accessed September 10, 2008).
22. Kemler MA, de Vet HC, Barendse GA, van den Wildenberg FA, van KM. Effect of spinal cord stimulation for chronic complex regional pain syndrome Type I: five-year final follow-up of patients in a randomized controlled trial. *Journal of Neurosurgery* 2008;108(2):292-8.
23. Kumar K, Taylor RS, Jacques L, Eldabe S, Meglio M, Molet J, et al. Spinal cord stimulation versus conventional medical management for neuropathic pain: a multicentre randomised controlled trial in patients with failed back surgery syndrome. *Pain* 2007;132(1-2):179-88.
24. Cruccu G, Aziz TZ, Garcia-Larrea L, Hansson P, Jensen TS, Lefaucheur JP, et al. EFNS guidelines on neurostimulation therapy for neuropathic pain. *European Journal of Neurology* 2007;14(9):952-70.
25. Cameron T. Safety and efficacy of spinal cord stimulation for the treatment of chronic pain: a 20-year literature review. *Journal of Neurosurgery* 2004;100(3 Suppl):254-67.

26. Grabow TS, Tella PK, Raja SN. Spinal cord stimulation for complex regional pain syndrome: an evidence-based medicine review of the literature. *Clinical Journal of Pain* 2003;19(6):371-83.
27. Mailis GA, Furlan AD, Sandoval JA, Taylor R. Spinal cord stimulation for chronic pain. *Cochrane Database of Systematic Reviews* 2004, Issue 3. Art. No.: CD003783. DOI: 10.1002/14651858.CD003783.pub2.
28. Middleton P, Simpson B, Maddern G. Spinal cord stimulation/neurostimulation: an accelerated systematic review 2003. Available from: [http://www.surgeons.org/asernip-s/systematic\\_review/SCSaccelreview0603.pdf](http://www.surgeons.org/asernip-s/systematic_review/SCSaccelreview0603.pdf) (accessed September 10, 2008).
29. Taylor RS, Van Buyten J, Buchser E. Spinal cord stimulation for chronic back and leg pain and failed back surgery syndrome: a systematic review and analysis of prognostic factors. *Spine* 2005;30(1):152-60.
30. Turner JA, Loeser JD, Deyo RA, Sanders SB. Spinal cord stimulation for patients with failed back surgery syndrome or complex regional pain syndrome: a systematic review of effectiveness and complications. *Pain* 2004;108(1-2):137-47.
31. Kemler MA, de Vet HC, Barendse GA, van den Wildenberg FA, van KM. The effect of spinal cord stimulation in patients with chronic reflex sympathetic dystrophy: two years' follow-up of the randomized controlled trial. *Annals of Neurology* 2004;55(1):13-8.
32. North RB, Kidd DH, Farrokhi F, Piantadosi SA. Spinal cord stimulation versus repeated lumbosacral spine surgery for chronic pain: a randomized, controlled trial. *Neurosurgery* 2005;56(1):98-106.
33. Harke H, Gretenkort P, Ladleif HU, Koester P, Rahman S. Spinal cord stimulation in postherpetic neuralgia and in acute herpes zoster pain. *Anesthesia and Analgesia* 2002;94(3):694-700.
34. Spincemaille GH, Beersen N, Dekkers MA, Theuvenet PJ. Neuropathic limb pain and spinal cord stimulation: results of the Dutch prospective study. *Neuromodulation* 2004;7(3):184-92.
35. Taylor RS, Van-Buyten JP, Buchser E. Spinal cord stimulation for complex regional pain syndrome: a systematic review of the clinical and cost-effectiveness literature and assessment of prognostic factors. *European Journal of Pain* 2006;10(2):91-101.
36. Simpson BA. Spinal cord stimulation. *Current Review of Pain* 1994;1:199-230.
37. Simpson BA. *Spinal cord and brain stimulation*. In: Wall PD, Melzack R, editors. *Textbook of Pain*. 4th. London: Churchill Livingstone; 1999: p.1253-381.
38. Simpson BA, Meyerson BA, Linderoth B. *Spinal cord and brain stimulation*. In: McMahon SB, Koltzenburg M, editors. *Wall and Melzack's Textbook of Pain*. 5th. London: Elsevier Churchill Livingstone; 2006: p.563-82.
39. Kemler MA, de Vet HC, Barendse GA, FA, van Kleef M. Spinal cord stimulation for chronic reflex sympathetic dystrophy -- five-year follow-up. *New England Journal of Medicine* 2006;354(22):2394-6.

40. Kemler MA, de Vet HC, Barendse GA, FA, van Kleef M. Spinal cord stimulation for chronic reflex sympathetic dystrophy - five-year follow-up. *New England Journal of Medicine* 2006;354(22):2394-6.
41. Kumar K. Spinal cord stimulation vs. conventional medical management: A prospective, randomized, controlled, multicenter study of patients with failed back surgery syndrome (PROCESS study). *Neuromodulation* 2005;8(4):213-8.