Spinal cord stimulation for cancer-related pain in adults (Review)

Peng L, Min S, Zejun Z, Wei K, Bennett MI

THE COCHRANE COLLABORATION®

This is a reprint of a Cochrane review, prepared and maintained by The Cochrane Collaboration and published in *The Cochrane Library* 2015, Issue 6

http://www.thecochranelibrary.com

WILEY

TABLE OF CONTENTS

[Intervention Review]

Spinal cord stimulation for cancer-related pain in adults

Lihua Peng[1], Su Min[1], Zhou Zejun[1], Ke Wei[1], Michael I Bennett[2]

[1]The Department of Anaesthesia and Pain Medicine, The First Affiliated Hospital, Chongqing Medical University, Chongqing, China. [2]Leeds Institute of Health Sciences, University of Leeds, Leeds, UK

Contact address: Su Min, The Department of Anaesthesia and Pain Medicine, The First Affiliated Hospital, Chongqing Medical University, No 1 Youyi Road, Yuan-jia-gang, Yu-zhong District, Chongqing, 40016, China. ms89011068@163.com.

Editorial group: Cochrane Pain, Palliative and Supportive Care Group.
Publication status and date: New search for studies and content updated (no change to conclusions), published in Issue 6, 2015.
Review content assessed as up-to-date: 6 October 2014.

Citation: Peng L, Min S, Zejun Z, Wei K, Bennett MI. Spinal cord stimulation for cancer-related pain in adults. *Cochrane Database of Systematic Reviews* 2015, Issue 6. Art. No.: CD009389. DOI: 10.1002/14651858.CD009389.pub3.

ABSTRACT

Background

This is an update of a review first published in *The Cochrane Library* in Issue 3, 2013. Cancer-related pain places a heavy burden on public health with related high expenditure. Severe pain is associated with a decreased quality of life in patients with cancer. A significant proportion of patients with cancer-related pain are under-treated. There is a need for more effective control of cancer-related pain. Spinal cord stimulation (SCS) may have a role in pain management. The effectiveness and safety of SCS for patients with cancer-related pain is currently unknown.

Objectives

This systematic review evaluated the effectiveness of SCS for cancer-related pain compared with standard care using conventional analgesic medication. We also appraised risk and potential adverse events associated with the use of SCS.

Search methods

This is an update of a review first published in *The Cochrane Library* in Issue 3, 2013. The search strategy for the update was the same as in the original review. We searched the following bibliographic databases in order to identify relevant studies: the Cochrane Central Register of Controlled Trials (CENTRAL) in *The Cochrane Library*; MEDLINE; EMBASE; and CBM (Chinese Biomedical Database) in October 2014. We also handsearched relevant journals. There were no language restrictions.

Selection criteria

We planned to include randomised controlled trials (RCTs) that directly compared SCS with other interventions with regards to the effectiveness of pain management. We also planned to include cross-over trials that compared SCS with another treatment. We planned to identify non-randomised controlled trials but these would only be included if no RCTs could be found.

Data collection and analysis

The literature search for the update of this review found 121 potentially eligible articles. The initial search strategy yielded 430 articles. By scrutinising titles and abstracts, we found 412 articles irrelevant to the analytical purpose of this systematic review due to different scopes of diseases or different methods of intervention (intrathecal infusion system; oral medication) or aims other than pain control (spinal cord function monitoring, bladder function restoration or amelioration of organ metabolism). The remaining 18 trials were reviewed as full manuscripts. No RCTs were identified. Fourteen sporadic case reports and review articles were excluded and four before-and-after case series studies (92 participants) were included. Two review authors independently selected the studies to be included in the

review according to the prespecified eligibility criteria. A checklist for methodological quality of non-randomised controlled trials was used (STROBE checklist) and all review authors discussed and agreed on the inclusion of trials and the results of the quality assessment.

Main results

No new studies were identified for inclusion in this update of the review. Four before-and-after case series studies (a total of 92 participants) met our criteria for inclusion in the previous version of the review. All included trials adopted a visual analogue scale (VAS) to evaluate pain relief. Heterogeneity existed in terms of baseline characteristics, electrode and stimulator parameters, level of implantation and route of implantation; each trial reported data differently. In two trials, pain relief was achieved in 76% (48/63) of participants at the end of the follow-up period. In the third trial, pre-procedure VAS was 6 to 9 (mean 7.43); the one-month post-implant VAS was 2 to 4 (mean 3.07); the 12-month post-implant VAS was 1 to 3 (mean 2.67). In the fourth trial, the pre-procedure VAS was 6 to 9 (mean 7.07); 1 to 4 (mean 2.67) at one-month; 1 to 4 (mean 1.87) at 12 months. Analgesic use was largely reduced. The main adverse events were infection of sites of implantation, cerebrospinal fluid (CSF) leakage, pain at the sites of electrodes, dislodgement of the electrodes, and system failure; however, the incidence in participants with cancer could not be calculated. Since all trials were small, non-randomised controlled trials, they carried high or unclear risk of all types of bias.

Authors' conclusions

Since the first publication of this review, no new studies were identified. Current evidence is insufficient to establish the role of SCS in treating refractory cancer-related pain. Future randomised studies should focus on the implantation of SCS in participants with cancer-related pain.

PLAIN LANGUAGE SUMMARY

Spinal cord stimulation for cancer pain

People with cancer often experience pain. Cancer pain or cancer-related pain is one of the worst factors for these patients. This type of pain tends to get worse as the cancer progresses. Despite better analgesics (pain killers) and techniques, cancer pain is still a problem for many people.

Traditionally, cancer pain was controlled by drugs. When these drugs do not work, other ways of reducing pain can be used, such as neuromodulation (electrical stimulation of the nerves). Spinal cord stimulation is the most common method of neuromodulation.

Spinal cord stimulation (SCS) involves putting electrodes on the spinal cord to control pain. The electrodes deliver impulses that may reduce pain. The technique is reversible and minimally invasive. SCS appears to have very few side effects, e.g. tiredness, compared to drugs used for pain relief. This technique has been widely used in non-cancer patients, yet the role of SCS for cancer pain is still unclear.

In the original review, we intended to evaluate how well SCS worked for cancer pain, compared with standard care (e.g. drugs). We also planned to look at harm and side effects of the treatment. To update this review, in October 2014 we looked for clinical trials that used SCS to treat cancer pain. We found no randomised controlled trials and four before-and-after case series studies (a total of 92 participants with cancer). All studies were small and of low quality.

SCS participants used fewer drugs than standard treatment group. The main side effects were infection and pain at the sites of electrodes, cerebrospinal fluid (CSF) leakage, dislodged electrodes, and system failure. However, we could not tell which side effects occurred more frequently in cancer patients compared to non-cancer patients.

There is not enough good quality evidence to know whether SCS is better than drugs to relieve cancer pain. More trials comparing SCS with other ways of relieving pain are needed.

BACKGROUND

This is an update of the review titled 'Spinal cord stimulation for cancer-related pain in adults', first published in the *Cochrane Database of Systematic Reviews* in Issue 3, 2013.

Description of the condition

World-wide, cancer-related pain has increasingly become a heavy burden on public health with related high expenditure. It has been estimated that world-wide nearly seven million people suffer moderate-to-severe cancer-related pain each year caused directly by cancer or by cancer treatment. An epidemiological study revealed that some 15% of these patients fail to achieve acceptable pain relief with conventional management (Running 2011; Yakovlev 2008). Severe pain is associated with a decreased quality of life and unwanted life events such as depression, anxiety and even suicide. Conventional treatment is based on the World Health Organization (WHO) guidelines for cancer pain management which consists of a three-step ladder: (1) non-steroidal anti-inflammatory drugs (NSAIDs), aspirin, and acetaminophen for mild-to-moderate levels of cancer pain; (2) weak opioids for mild-to-moderate pain that does not respond to NSAIDs alone; and (3) strong opioids for moderate-to-severe levels of cancer pain (Schug 1990). Adjuvant medications, such as antiepileptics and tricyclic antidepressants, can also be added at any step of the ladder for optimal pain relief. Reduced pain intensity and standardised protocols have been used globally for improving cancer pain management. When this approach fails (10% of patients), interventional pain management has been proposed for this group with refractory pain (Miguel 2000).

Among all the diversified procedures of interventional management approaches for pain control, alternative strategies are needed such as (1) neuroaxial analgesia (spinal, epidural); (2) neurostimulation; (3) neurolysis (sympathetic blockades with phenol or alcohol); and (4) thermal neurolysis (radiofrequency) (Slavik 2004). The most commonly used forms of neuromodulation are (1) neurostimulation: the electric stimulation of peripheral nerves, the spinal cord (spinal cord stimulation (SCS)), and brain (deep brain stimulation); (2) intrathecal drug delivery system by means of programmed infusion pumps. To date, different techniques of neuromodulation are among the more frequently used types of interventional procedures in the treatment of non-cancer pain (Isagulian 2008).

Although the aetiology of cancer pain is not yet fully understood, altered peripheral nociception (the ability to feel pain) and central sensitisation involving the level of SCS have pivotal roles in its pathogenesis (Schmidt 2010). Within the cancer microenvironment, cancer and immune cells produce and secrete mediators that activate and sensitise primary afferent nociceptors. In addition, neuropathic mechanisms are also prevalent and cancer pain is often regarded as a mixed-pain mechanism (Ro 2005).

As our understanding of the peripheral and central mechanisms that underlie cancer pain improves, targeted analgesics for the patient with cancer will likely follow, especially in relation to the spinal cord (Boswell 2010; Christo 2008). Thus, when pharmacotherapy (such as opioids and potent COX-2 inhibitors) for severe and intractable cancer-related pain are ineffective, interventional management approaches have received considerable attention in an attempt to provide pain relief for patients with cancer pain. These offer important additional approaches to the WHO analgesic ladder to control cancer-related pain. Neurostimulation in particular has been recognised in non-cancer pain as having the potential for long-term effectiveness with minimal side effects observed clinically. Currently, the evidence that neurostimulation is effective for the long-term treatment of non-malignant painful conditions such as angina, limb ischaemia, and lower back pain has been established (Kemler 2010; Klomp 2009; North 2008; Taylor 2009). Since chronic cancer pain has some features in common in its pathogenesis with non-malignant pain, systematic reviews, sporadic case series and cohorts of observational studies have reported a marked reduction of pain intensity using this approach (Mailis-Gagnon 2004; Ubbink 2005; Yakovlev 2008).

SCS can provide long-term relief in managing patients with failed back surgery syndrome and the level of evidence recommendation is Level II-1 or II-2 (Michael 2009). SCS has also been recorded to be effective in reducing the chronic neuropathic pain of complex regional pain syndrome (CRPS) type I (Simpson 2009); this evidence has helped to establish the potential role of SCS in treating patients with cancer-related pain. However, the effectiveness and relative safety of SCS for cancer pain has not been adequately established (Engle 2013). Therefore, in this systematic review, we intended to provide scientific evidence as to the efficacy of SCS; the safety of patients receiving SCS; and to identify which patients are most likely to benefit.

Description of the intervention

SCS is achieved by placing electrodes in the epidural space on the dorsal surface of the spinal cord. The electrodes can be placed either by using an open procedure in which the dura is exposed (surgical laminotomy), or a closed procedure via epidural needles. The electrodes are connected to an impulse generator that is also inserted under the skin. The impulse generator is programmed using an external device to deliver impulses continuously or in preset patterns throughout a 24-hour period. The technique is reversible and minimally invasive (in contrast to nerve ablation) (Costantini 2005); and appears to result in no adverse effects such as sedation or lethargy, commonly associated with centrally-acting analgesic drugs.

How the intervention might work

The basic scientific background of SCS is based on the gate control theory of Melzack and Wall (Stephen 2005). It has been demonstrated in multiple studies that dorsal horn neuronal activity caused by peripheral noxious stimuli could be inhibited by concomitant stimulation of the dorsal columns. Various other mechanisms which may play a significant role in the mechanism of action of SCS include the suppressive effect of SCS on tactile allodynia (pain produced from a stimulus that would not normally produce pain), increased dorsal horn inhibitory action of gamma-aminobutyric acid (GABA), prevention or abolition of peripheral ischaemia, and effects on human brain activity (Stojanovic 2002). Thus, the use of SCS to treat cancer-related pain can be mechanism-based and tailored to the needs of the individual patient. Although opioids remain the mainstay of analgesia for cancer pain (IASP 2008), SCS can be used in addition to, or instead of, conventional approaches. The mixed-pain mechanisms that can result from cancer suggest that multi-modal approaches are likely to result in better outcomes for patients (Herr 2004).

Why it is important to do this review

Despite a few case series and expert recommendations of the potential significance of SCS for cancer-related pain, few cohort studies and fewer randomised controlled trials (RCTs) have been conducted to establish the efficacy of this approach in cancer pain. It is important to identify this in a systematic review so that it can help inform the need for further RCTs in this area and ultimately clinical practice.

OBJECTIVES

This systematic review evaluated the effectiveness of SCS for cancer-related pain compared with standard care using conventional analgesic medication. We also appraised risk and potential adverse events associated with the use of SCS.

METHODS

Criteria for considering studies for this review

Types of studies

For the purpose of generating high-quality evidence, we planned to include randomised controlled trials (RCTs) that directly compared spinal cord stimulation (SCS) with other interventions for pain management. We also intended to include cross-over trials comparing SCS with another treatment. Non-randomised controlled trials were included as no RCTs were identified.

Types of participants

Adult participants aged between 18 and 80 years old with cancer-related pain who were eligible for the implantation of SCS and treated accordingly with this intervention for cancer-related pain management.

Types of interventions

1. Participants receiving SCS versus participants receiving conventional medical treatments.
2. Participants receiving SCS plus conventional medical treatments versus participants receiving conventional medical treatments only.
3. Participants receiving SCS versus participants receiving physical therapies or complementary therapies.
4. Participants receiving SCS versus participants receiving other invasive interventions such as surgery or neuro-ablation therapies.

Types of outcome measures

Primary outcomes

Effectiveness of pain management:

- at least 50% reduction of pain (visual analogue score (VAS) as the primary parameter);
- health-related quality of life;
- physical and functional abilities;
- pain-related anxiety and depression.

Secondary outcomes

Adverse events related to SCS, e.g. rate of procedural complications (bleeding, infection, spinal cord compression etc), incidence of technical failures and withdrawal rate, incidence of treatment-related mortality.

Search methods for identification of studies

Electronic searches

For this update we searched the following bibliographic databases for relevant studies:

- the Cochrane Register of Controlled Trials (CENTRAL) in *The Cochrane Libary* (Issue 9, 2014);
- MEDLINE (July 2012 to 6 October 2014);
- EMBASE (July 2012 to 6 October 2014);
- CBM (Chinese Biomedical Database) (from July 2012 to 1 October 2014).

The search strategies used can be found in Appendix 1.

Searching other resources

We also searched the trials registry of the National Cancer Institute, the World Health Organization (WHO) International Clinical Trials Registry Platform (http://apps.who.int/trialsearch/) and clinicaltrials.gov supported by U.S. National Institutes of Health for eligible ongoing trials. We searched abstracts of international conferences related to cancer pain management using the term 'spinal cord stimulation'. We handsearched major international journals such as *Pain*, *The Clinical Journal of Pain*, *European Journal of Pain*, and conference articles of internationally renowned associations of pain such as the International Association for the Study of Pain (IASP), European Society of Regional Anesthesia & Pain Therapy (ESRA) and American Pain Society (APS) for preliminary reports of high-quality studies on a week-to-week basis. We checked reference lists of updated articles of importance. We also searched international conference proceedings and seminars for potential studies. There were no language restrictions.

Data collection and analysis

Selection of studies

In the updated and initial search, two review authors (Lihua Peng and Ke Wei) independently selected the studies to be included in the review according to the prespecified eligibility criteria. Disagreements were resolved by discussion. If this did not resolve the disagreement, we consulted a third review author (Michael I Bennett). We based decisions for inclusion or exclusion on the whole content of the studies if available.

Data extraction and management

One review author (Lihua Peng) extracted data and these were checked by a second review author (Su Min). Data entry into Review Manager (RevMan 2014) was also double-checked. We resolved disagreements concerning data extraction by reaching a consensus based on the inclusion criteria. Where we could not resolve disagreements, we consulted a third review author (Michael I Bennett).

We recorded the following data for each study:

- details of methodology including whether the study was randomised; and whether the methods of sequence generation, allocation sequence concealment, and blinding were reported;
- details of the participants including age, gender, and diagnosis before SCS;
- details of the experimental and control interventions including the intervention type, name, dosage, and schedules.

Assessment of risk of bias in included studies

Two authors (Ke Wei, Lihua Peng) independently assessed risk of bias for each study, using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011); and adapted from those used by the Cochrane Pregnancy and Childbirth Group, with any disagreements resolved by discussion. We completed a 'Risk of bias' table for each included study using the Risk of bias tool in RevMan (RevMan 2014) (Figure 1; Figure 2).

Figure 1. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

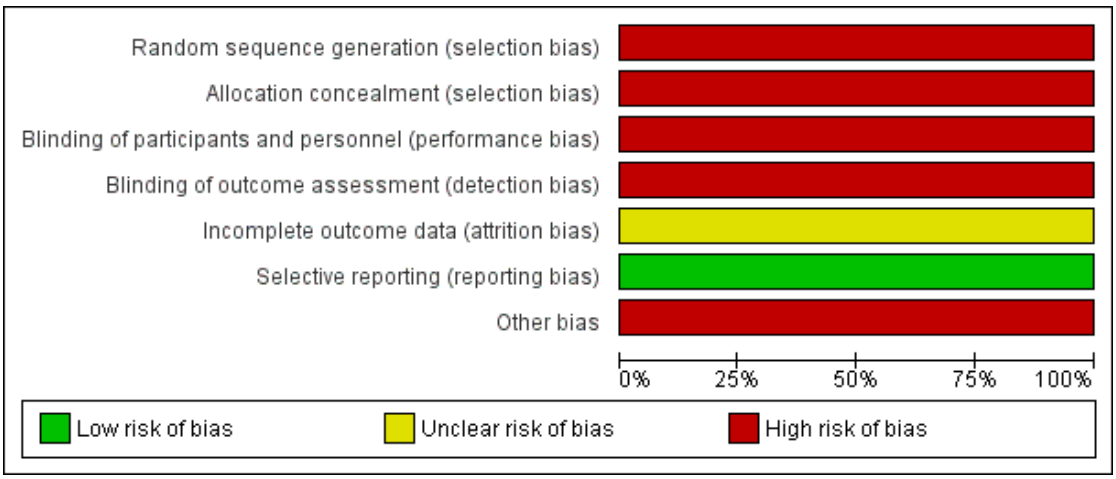
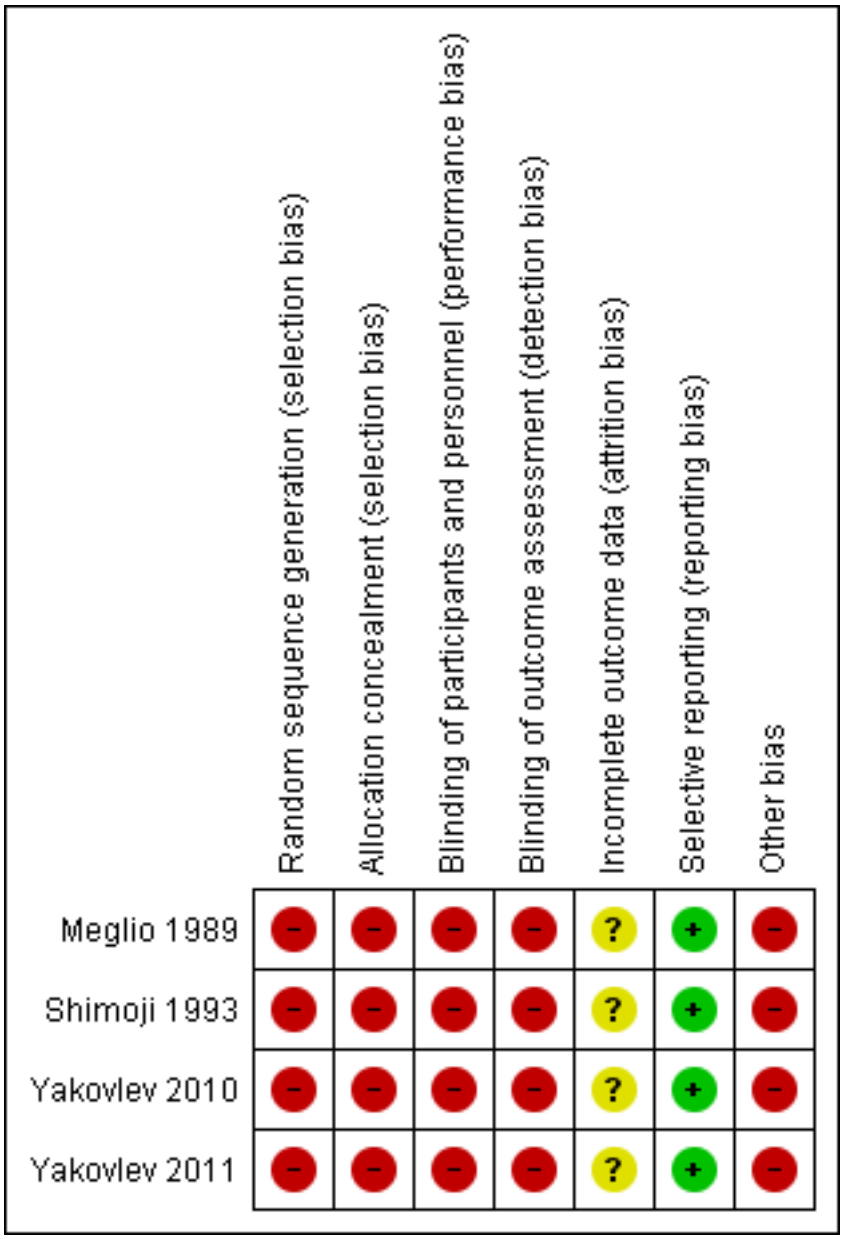


Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



We had planned to assess the following for each study:

- random sequence generation (checking for possible selection bias). We had planned to assess the method used to generate the allocation sequence as: low risk of bias (any truly random process, e.g. random number table; computer random number generator); and unclear risk of bias (method used to generate sequence not clearly stated). Studies using a non-random process (e.g. odd or even date of birth; hospital or clinic record number) would be excluded.
- allocation concealment (checking for possible selection bias). The method used to conceal allocation to interventions prior to assignment determines whether intervention allocation could have been foreseen in advance of, or during, recruitment; or changed after assignment. We had planned to assess the methods as: low risk of bias (e.g. telephone or central randomisation; consecutively numbered sealed opaque envelopes); unclear risk of bias (method not clearly stated). Studies that do not conceal allocation (e.g. open list) will be excluded.
- blinding of outcome assessment (checking for possible detection bias). We had planned to assess the methods used to blind study participants and outcome assessors from knowledge of which intervention a participant received. We had planned to assess the methods as: low risk of bias (study states that it was blinded and describes the method used to achieve blinding, e.g. identical tablets; matched in appearance and smell); unclear risk of bias (study states that it was blinded but does not provide an adequate description of how it was achieved). Studies that were not double-blind would be excluded.
- incomplete outcome data (checking for possible attrition bias due to the amount, nature and handling of incomplete outcome data). We had planned to assess the methods used to deal with incomplete data as: low risk (less than 10% of participants did not complete the study or used 'baseline observation carried forward' analysis or both); unclear risk of bias (used 'last observation carried forward' analysis); high risk of bias (used 'completer' analysis).
- Size of study (checking for possible biases confounded by small size). We had planned to assess studies as being at low risk of bias (equal to or greater than 200 participants per treatment arm); unclear risk of bias (50 to 199 participants per treatment arm); high risk of bias (fewer than 50 participants per treatment arm).

We had also planned to assess the quality of included studies using different aspects: adequate allocation concealment; scientific methods of randomisation and balanced enrolment of participants between different interventional arms; follow-up of adequate time; and inclusion of the intention-to-treat (ITT) principle during data analysis. As SCS is a minimally invasive yet prominent intervention against cancer pain, we assessed blinding of participants to genuine stimulation or sham stimulation along with conventional therapy. We indexed these as either adequate (independent pain physicians or investigators who assess the subjective outcome such as Visual Analogue Scale (VAS) score or quality of life (QoL)); or inadequate (not performed or similar).

However, as we only included non-randomised controlled trials in the initial research, we used STROBE (Strengthening the Reporting of Observational Studies in Epidemiology), a 22-item check list (see Table 1), to assess the overall quality of the studies.

Measures of treatment effect

In the original review, we planned to perform all analyses according to the ITT principle including all randomised participants. For dichotomous outcomes such as rate of adverse events, we planned to record percentages with 95% confidence intervals (CI). We intended to calculate the number needed to treat to benefit (NNTB) from the risk ratio (RR) or risk difference (RD) for RCTs. For continuous outcomes such as VAS scores, questionnaires or scores measuring quality of life, we used medians and standard errors (SEs) or interquartile ranges with CIs to summarise the value in each group. If different scales had been used to measure continuous data, we would have used standardised mean differences (SMD). For this update, we did not perform any meta-analysis or data synthesis; the results of original analysis were in line with current Cochrane methodological standards.

Unit of analysis issues

We planned to assess whether groups of individuals were randomised together to the same intervention, whether individuals undertook more than one intervention and whether multiple investigators observed the same outcome. For this update, we did not perform any meta-analysis or data synthesis; the results of original analysis were in line with current Cochrane methodological standards.

Dealing with missing data

We planned to contact the original investigators to request missing data whenever possible in person, by mail or by phone. If we had been unable to obtain missing data, we would have imputed the missing data using mean values. We planned to perform sensitivity analyses to assess how sensitive results were to reasonable changes in the assumptions that were made, and we would have addressed the potential impact of missing data on the findings of the review in the 'Discussion' section. We collected and reported dropout rates in the 'Risk of bias' table. We used available case analysis

for extracted data. If the total dropout rate had exceeded 20%, we planned to use available case analysis and perform subsequent sensitivity analysis to test the effects of missing data from dropout participants. If the dropout rate was less than 20%, we planned to perform ITT analysis.

Assessment of heterogeneity

For the original review, we had planned to use the Chi² test to assess statistical heterogeneity. If significant heterogeneity would be found, we planned to re-check that the data were correct and explore the reason for the heterogeneity. For this update, we did not perform any meta-analysis or data synthesis; the results of original analysis were in line with current Cochrane methodological standards.

Assessment of reporting biases

We performed comprehensive searches for studies that met the eligibility criteria, including unpublished studies and trial registries if possible, as authors with financial aid from pharmaceutical companies or authors of studies with negative outcomes tend to selectively report incomplete outcomes. We extracted all important outcomes of clinical relevance to attempt to eliminate this type of bias as far as possible.

Data synthesis

In the original study, for the outcome of pain relief, we used a random-effects to provide a descriptive analysis of extracted data and no statistical pooling was made (Analysis 1.1; Analysis 2.1). For this update, we did not perform any meta-analysis or data synthesis; the results of original analysis were in line with current Cochrane methodological standards.

Subgroup analysis and investigation of heterogeneity

In the original study, we planned to analyse the association between different kinds of stimulation apparatus and intervention effects. As sites of cancer-related pain (lower extremities, trunk or other sites) or different implantation systems may impact on the efficacy of SCS we would, if possible, have considered the above factors as parameters when performing subgroup analyses.

For this update, we did not perform any meta-analysis or data synthesis; the results of original analysis were in line with current Cochrane methodological standards.

Sensitivity analysis

If we had identified and included RCTs in the original study, we would have performed sensitivity analysis comparing studies that had or had not reported: allocation concealment, adequate blinding, or studies without full methodological detail (e.g. published as abstracts only). For included RCTs, we planned to include all studies at first, then eliminate one at a time those studies with moderate or poor quality or those only with abstracts to see if it altered the results. Finally, we planned to perform the analysis with data from studies of good methodological quality; thus, the sensitivity analysis would have been performed in a multiple-step way. Variation among included studies might cause the issue of heterogeneity. First, we planned to use the Chi² test to test the statistical significance of heterogeneity.

As only non-randomised trials were included, we analysed each trial in a descriptive way.

For this update, we did not perform any meta-analysis or data synthesis; the results of original analysis were in line with current Cochrane methodological standards.

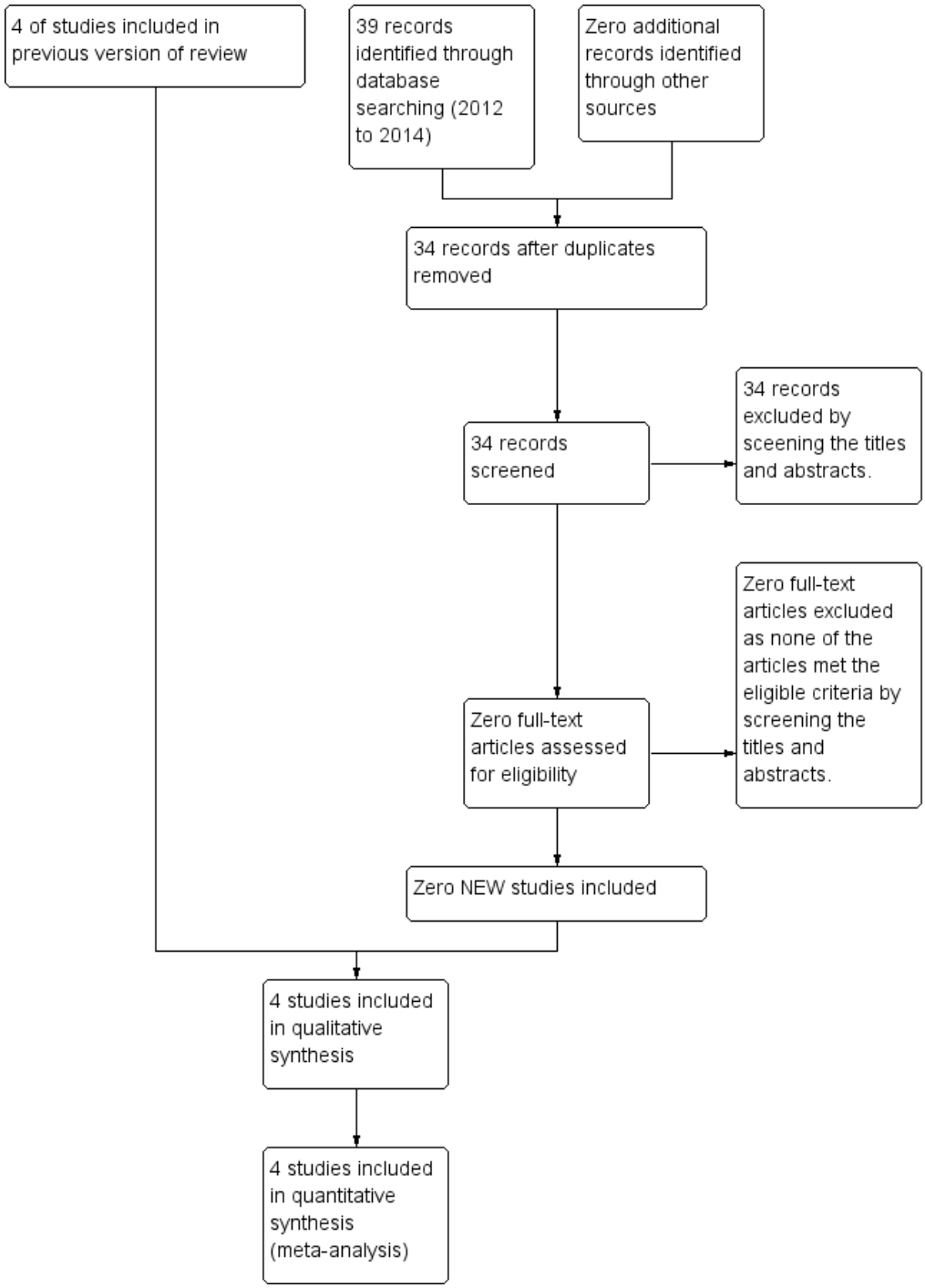
RESULTS

Description of studies

Results of the search

The initial search strategy yielded 430 articles. By scrutinising titles and abstracts, we excluded 412 articles due to different scopes of diseases or different methods of intervention (intrathecal infusion system; oral medication) or aims other than pain control (spinal cord function monitoring, bladder function restoration or amelioration of organ metabolism) in the original review. The remaining 18 trials were reviewed as full manuscripts. No randomised controlled trials (RCTs) were identified; 14 sporadic case reports were excluded and four uncontrolled longitudinal studies were included. No additional study was eligible for inclusion in this updated review. See the flowchart (Figure 3).

Figure 3. Study flow diagram.



Included studies

In the original review, comprehensive searching yielded 412 articles but there were no RCTs that met the inclusion criteria. One seemingly well-conducted RCT that reported on the use of transcutaneous spinal electro-analgesia was excluded because it did not meet the definition of spinal cord stimulation (SCS). After consultation with group editors and a group discussion, we modified our inclusion criteria to include non-randomised controlled trials for this review. By reading abstracts we identified 18 non-randomised controlled trials, and after scrutinising these 18 potentially relevant articles, 13 case reports of individual participants plus one review were also excluded. Four case series studies (Meglio 1989; Shimoji 1993; Yakovlev 2010; Yakovlev 2011) were included in the original review. We carried out quality assessment according to the STROBE statement which aims at assessing methodological quality of non-randomised controlled trials.

In the research for the update of this review, 39 additional articles were identified but, after scrutinising the title and abstract, none of these articles met the eligibility criteria of this review.

Four case series studies (92 participants with cancer) met our criteria for inclusion in the original review: please see the 'Characteristics of included studies' table.

Meglio 1989 retrospectively reported on 11 participants with cancer from a total of 109 participants who were diagnosed with six categories of diseases that were eligible for the implantation of SCS. The rest included participants with vasculopathic pain; lower back pain; paraplegic pain; deafferentation pain; and post-herpetic pain. A visual analogue scale (VAS) was used to assess the analgesic effect of the procedure. Participants with a 50% reduction of pain intensity were considered to be responders.

Shimoji 1993 reported a large survey of clinical outcomes using percutaneous, low-frequency SCS to alleviate pain caused by several types of diseases including cancer, post-herpetic neuralgia, spinal trauma, phantom limb pain etc. Visual analogue scales were used for the evaluation of pain. Percentage of pain relief, long-term efficacy and adverse events were also reported.

One author published two consecutive articles on treating participants with cancer-related pain with SCS. The first article reported on 14 participants who received spinal cord stimulator placement after surgical or radiological intervention against lung cancer (Yakovlev 2010). Significant pain relief was calculated as at least a 50% reduction of the VAS score. The follow-up duration was 12 months and the safety of the procedure was investigated. Yakovlev 2011 retrospectively analysed 15 participants with lower back pain after surgical resection or radiation therapy because of metastatic disease of adjacent organs. These two trials reported the percentage of opioid use before and after SCS implantation, pre-procedure, one month post-implant and 12 months post-implant using VAS.

Excluded studies

In the initial search, most papers recognised by our searches were individual case reports on spinal cord stimulation for cancer-related pain or experimental studies which did not contain clinical data. After obtaining full texts of potential eligible trials, 14 articles were excluded. Seven individual case reports of using spinal cord stimulation to treat cancer-related pain were ruled out because of limited clinical data obtained from the articles (Cata 2004; Eisenberg 2002; Hamid 2007; Lee 2009; Nouri 2011; Ting 2007; Tsubota 2009). Two further case reports were excluded: one included two participants (Yakovlev 2008); the other was an individual case report (Yakovlev 2009). Three retrospective case series focused on the effect of SCS on metabolism of, and blood flow to, cerebral cells; no information on pain control was provided (Clavo 2004; Clavo 2009; Robaina 2007). One review discussing the indications and outcomes of SCS was also excluded (Lee 2006). We also excluded one article that reported hardware failure of SCS in benign pain (Rainov 2007). In general, the scarcity of literature suggests a lack of high-quality clinical trials. Reasons for exclusion are listed in the 'Characteristics of excluded studies' table. No additional studies were excluded for this update.

Risk of bias in included studies

All included trials were non-randomised trials, so we used the STROBE 22-item checklist to evaluate the quality of observational studies (Vandenbroucke 2007). The CONSORT statement, aimed at evaluating allocation, blinding, incomplete outcome data and reporting bias, could not be used for non-randomised trials (Moher 2001) (Figure 1; Figure 2).

We used the STROBE checklist to assess the overall quality of each study; this checklist is specially designed for observational studies (see Table 1). All 22 items were rated as 'yes', 'no' or 'unclear': 'yes' means that the study was conducted and reported in accordance with the checklist; 'no' means that the study was not conducted as required by the checklist; 'unclear' means no information related to each item could be drawn from the article. Two review authors (Lihua Peng and Ke Wei) independently rated each article and disagreement was resolved by group discussion. Methodological quality was generally poor and lacked the components of 'prospective' trial design. Of all the 22 items, 5 to 10 items were considered fulfilled for all included trials (see Table 2). One of the common issues was the lack of statistical methods to examine or control possible confounding factors. For all included trials, the enrolment of participants lacked preset eligibility criteria; the reporting of primary outcome as pain relief generally lacked subgroup analysis or intervention interaction (analgesic use and implantation of spinal

cord stimulation); and all trials lacked a rational explanation of how the sampling sizes were decided. Therefore we concluded that all of the included trials were at high risk of bias.

Other potential sources of bias

None known.

Effects of interventions

Heterogeneity existed among all included trials and statistical pooling was not carried out.

Pain Relief

All included trials adopted visual analogue scales (VAS) to evaluate pain relief. In the earliest article, Meglio 1989 reported on 11 participants with cancer pain; three participants reported satisfactory analgesia (at least a 50% reduction of pain intensity) and received permanent implantation; the mean level of reduction of pain was 75% in these three participants. One participant lost the therapeutic effect after one month of implantation, the two remaining participants were reported to have experienced a 50% reduction of pain until death at 2½ and 5 months after implantation (baseline and post procedure VAS scores were not provided).

Shimoji 1993 retrospectively analysed a total of 454 participants receiving implantation of SCS for various conditions; subjective pain relief (at least 50% reduction of original VAS) was observed in 45 out of 52 participants with cancer-related pain. When the authors used a 2 x 2 Chi² test to examine the relationship of background diseases with pain relief, the number of participants who rated pain relief at more than 50% was significantly larger in participants with carcinoma/sarcoma than the overall effect (253/454); yet the study did not provide accurate scores of VAS in this group of participants and electrodes were withdrawn at the terminal stage in 49 cases of cancer-related pain. Analgesia use during SCS is also a parameter of clinical efficacy. In 454 participants, medication was stopped for 52 participants (11%); reduced analgesic use was observed in 263 participants (58%); 323 participants reported partial to complete pain relief (over 30% of pain reduction).

Yakovlev reported two consecutive before-and-after case series. The first study (Yakovlev 2010) enrolled 14 patients with intractable cancer-related chest pain. All participants received permanent implantation of an electrode at T3-T4-T5 level. Pain duration before implant was 9 to 23 months (median duration was 16 months). The rate of opioid use before implantation was 100% (14/14); and 29% (4/14) after the implant with a decreased dose. Mean value of pre-procedure VAS was 7.43 (standard deviation (SD) 0.94); one month post implant the VAS was 3.07 (SD 0.62); 12 months post implant VAS was 2.07 (SD 0.83).

The second study (Yakovlev 2011) reported on 15 participants with intractable cancer-related lower back pain receiving SCS; all participants had leads inserted at T11 to T12 or T12 to L1 level. Pain duration before implant was 14 to 26 months (median duration was 19 months). Rate of opioid use before implant was 100% (14/14) and 47% (7/15) after implant with a decreased dose. Mean values of pre-procedure VAS was 7.07 (SD 1.03); one month post implant VAS was 2.07 (SD 0.9); 12 months post-implant VAS was 1.87 (SD 0.83). Since no comparison could be made against other interventional groups, before-and-after comparisons of this outcome were reported and analysed in narrative forms (Analysis 1.1; Analysis 2.1).

None of the eligible trials reported the other outcomes of health-related quality of life, physical and functional abilities, or pain-related anxiety and depression.

Adverse events

Adverse events were reported in participants in two earlier studies with all diseases eligible for SCS (Meglio 1989; Shimoji 1993). Meglio 1989 revealed three cases of infection of implantation, four cases of aseptic meningitis, two cases of rejection of the electrode leads, three cases of cerebrospinal fluid (CSF) leakage, three cases of subcutaneous haematoma, two cases of pain at the electrode sites, three cases of dislodgement of the electrodes, and four cases of system failure. Other minor side effects included five cases of headache, five cases of asthenia, five cases of dizziness and six cases of muscle twitches/contractions in a total of 109 participants (including 11 participants with cancer-related pain). Shimoji 1993 reported 6 cases of CSF leakage, 27 cases of infection of implantation,19 cases of pain at the electrode sites, 22 cases of dislodgement of the electrodes and 8 cases of electrode dysfunction in a total of 454 participants (including 52 participants with cancer-related pain). In two other recent studies (Yakovlev 2010; Yakovlev 2011), no complications of SCS implantation were reported.

DISCUSSION

Summary of main results

Since the last version of this review, no new studies were found. In the four before-and-after case series studies included in this systematic review, clinical efficacy was reported as modest (Meglio 1989), to excellent (Shimoji 1993; Yakovlev 2010; Yakovlev 2011). Over 80% of participants reported at least a 50% reduction of pain intensity, more than 50% of participants reported decreased use of opioid medications. Major complications were infection of sites of implantation, CSF leakage, pain at the sites of electrodes, dislodgement of the electrodes and system failure although the incidence was very low. The follow-up period varied from one

week to more than one year. However, all these studies were at high risk of bias.

Overall completeness and applicability of evidence

In this systematic review, the lack of randomised controlled trials (RCTs) related to this topic left the question of effectiveness unanswered. Four case series including 92 participants were included for descriptive analysis. These four studies varied greatly in clinical setting, participant characteristics, electrode and stimulator parameters, level of implantation, route of implantation (subarachnoid cavity or epidural cavity) and methods of electrode implantation (laminectomy or percutaneous insertion). Meglio 1989 did not mention the types of cancer and sites of pain and three out 11 participants with cancer reported excellent pain relief after implantation. Shimoji 1993 reported outcomes of 52 participants with cancer-related pain in a cohort of 454 patients. Sites of pain included head and face, neck and upper extremities, trunk and lower extremities.Types of cancer and pre-procedure VAS scores were not provided. Adverse events were reported in participants, not only with cancer-related pain, but also with chronic pain of non-cancer origin. In the two later studies the author clarified types of cancer and sites of pain. One of these described 14 participants with lung cancer and intractable chest wall pain (Yakovlev 2010). In this study, pain relief at one-year follow-up was excellent without complication. In another study, 15 participants with cancer-related lower back pain from metastasis related to colon and anal cancer, and angiosarcoma of the sacrum were described (Yakovlev 2011). All participants reported significant pain relief (a reduction of over 50%) that was maintained for at least one year. A major limitation of the evidence base is that all included studies lacked preset eligibility of participants and comparison with control.

Quality of the evidence

Only non-controlled case series without interventional comparison were available. All studies had small numbers of participants with cancer and were poorly designed to reach a conclusion about the comparative efficacy of spinal cord stimulation (SCS) for cancer-related pain. Participant attrition, selective reporting and performance bias could have been factors influencing all of the included trials. Meglio 1989 was a retrospective analysis of SCS against chronic pain (cancer-related pain included) in a single institution without a power calculation. Shimoji 1993 did not perform a power calculation nor were the baseline characteristics reported. Yakovlev 2010 and Yakovlev 2011 provided baseline VAS scores and rate of opioid use; a before-and-after comparison was made. Lack of randomisation, allocation concealment or blinding introduced considerable risk of bias. Randomised controlled trials are still needed to clarify clinical efficacy of SCS in cancer-related pain. Optimal participant selection, time of implantation and approaches to minimise its side effects should be analysed.

Potential biases in the review process

All included studies did not comply with the CONSORT statement nor did they meet all essential criteria of the STROBE checklist. All included trials were before-and-after case series and no comparison with other interventions could be made. Furthermore, researchers are more likely to report 'positive outcomes' in a selected group of participants while leaving 'negative outcomes' overlooked. In summary, all trials carried with them a great risk of bias .

Agreements and disagreements with other studies or reviews

Our review focused on the efficacy and safety of SCS against cancer-related pain and no previous published systematic review was found. Spinal cord stimulation has been utilised for control of chronic cancer and non-cancer pain for nearly 40 years (Miles 1974; Sweet 1974), but the efficacy of SCS has only been established for chronic non-cancer pain, including failed back surgery syndrome, neuropathic pain, complex regional pain syndrome etc (Frey 2009; Grabow 2003; Simpson 2009; Taylor 2006). Neuromodulation has been given attention to alleviate cancer pain with encouraging outcomes (Hurlow 2012). Flagg 2012 recommended that cancer-related pain should be treated at an early stage with an algorithm integrating SCS. Although all included articles reported that participants with cancer-related pain may benefit from SCS, there is no evidence to support or refute the use of SCS in the treatment of pain in patients with cancer (Meglio 1989; Shimoji 1993; Yakovlev 2010; Yakovlev 2011). The bulk of the literature identified in this review were individual case reports with greater risk of bias, and which generally reported positive outcomes. Spinal cord stimulation should not be compared with 'sham stimulation' for ethical reasons in patients with cancer; however, the safety and efficacy of SCS should be compared with other means of pain control (oral medications; intrathecal drug delivery; transcutaneous electrostimulation) in patients with cancer.

AUTHORS' CONCLUSIONS

Implications for practice

No new relevant studies were identified since the original version of this review. Current evidence from small, low-quality trials is insufficient to establish the role of spinal cord stimulation (SCS) in treating refractory cancer-related pain in comparison with other

analgesic approaches. Evidence from non-randomised controlled trials is generally positive and is consistent with a stronger evidence base in non-cancer pain.

For people with cancer pain

The current evidence is insufficient to establish the role of spinal cord stimulation in treating cancer-related pain: this technique may be used after consulting with a clinician concerning its efficacy and safety.

For clinicians

The current evidence is insufficient to establish the role of spinal cord stimulation in treating cancer-related pain. The decision of clinicians to incorporate this technique into analgesic regimens should be based on the skills and experience of the clinicians, the preference of patients and best techniques available.

For policy makers

The current evidence is insufficient to establish the role of spinal cord stimulation in treating cancer-related pain; further studies are needed before this technique might be established as an essential method for pain management in cancer patients.

For funders

The priority of further funding should be given to randomised controlled trials comparing spinal cord stimulation with other analgesic methods.

Implications for research

General

Future research should focus on the implantation of SCS in patients with cancer-related pain at an early stage, and randomised controlled trials with larger samples are urgently needed to quantify the benefits and harms of this procedure, especially life-quality improvement and adverse events.

Design

Large, parallel randomised controlled trials, with at least 200 participants per arm, comparing spinal cord stimulation with other analgesic methods are urgently needed.

Measurement (endpoints)

Short-term and long-term analgesic efficacy and adverse events should be evaluated in future studies.

Other

Economic analysis of spinal cord stimulation for pain management in cancer patient could also be carried out in further research.

ACKNOWLEDGEMENTS

For the original review, we greatly thank the Cochrane Pain, Palliative and Supportive Care Review Group (PaPaS) editorial office for protocol editing.

For the updated review, we would also thank the PaPaS editorial office for guidance and help in updating this review.

Cochrane Review Group funding acknowledgement: The National Institute for Health Research (NIHR) is the largest single funder of the PaPaS. Disclaimer: the views and opinions expressed herein are those of the authors and do not necessarily reflect those of the NIHR, National Health Service (NHS) or the Department of Health.

No funding was used for this protocol or review.

REFERENCES

References to studies included in this review

Meglio 1989 *{published data only}*
Meglio M, Cioni B, Rossi GF. Spinal cord stimulation in management of chronic pain. A 9-year experience. *Journal of Neurosurgery* 1989;**70**(4):519–24.

Shimoji 1993 *{published data only}*
Shimoji K, Hokari T, Kano T, Tomita M, Kimura R, Watanabe S, et al. Management of intractable pain with percutaneous epidural spinal cord stimulation: differences in pain-relieving effects among diseases and sites of pain. *Anesthesia and Analgesia* 1993;**77**(1):110–6.

Yakovlev 2010 *{published data only}*
Yakovlev AE, Resch BE, Karasev SA. Treatment of cancer-related chest wall pain using spinal cord stimulation. *American Journal of Hospice and Palliative Medicine* 2010;**27**(8):552–6.

Yakovlev 2011 *{published data only}*
Yakovlev AE, Resch BE. Spinal cord stimulation for cancer-related low back pain. *American Journal of Hospice and Palliative Medicine* 2011;**29**(2):93–7.

References to studies excluded from this review

Cata 2004 *{published data only}*
Cata JP, Cordella JV, Burton AW, Hassenbusch SJ, Weng HR, Dougherty PM. Spinal cord stimulation relieves chemotherapy-induced pain: a clinical case report. *Journal of Pain Symptom Management* 2004;**27**(1):72–8.

Clavo 2004 *{published data only}*
Clavo B, Robaina F, Catalá L, Pérez JL, Lloret M, Caramés MA, et al. Effect of cervical spinal cord stimulation on regional blood flow and oxygenation in advanced head and neck tumours. *Annals of Oncology* 2004;**15**(5):802–7.

Clavo 2009 *{published data only}*
Clavo B, Robaina F, Montz R, Carames MA, Lloret M, Ponce P, et al. Modification of glucose metabolism in radiation-induced brain injury areas using cervical spinal cord stimulation. *Acta Neurochirurgica* 2009;**151**(11): 1419–25.

Eisenberg 2002 *{published data only}*
Eisenberg E, Brecker C. Lumbar spinal cord stimulation for cervical-originated central pain: a case report. *Pain* 2002; **100**(3):299–301.

Hamid 2007 *{published data only}*
Hamid B, Haider N. Spinal cord stimulator relieves neuropathic pain in a patient with radiation-induced transverse myelitis. *Pain Practice* 2007;**7**(4):345–7.

Lee 2006 *{published data only}*
Lee AW, Pilitsis JG. Spinal cord stimulation: indications and outcomes. *Neurosurgical Focus* 2006;**21**(6):E3.

Lee 2009 *{published data only}*
Lee MG, Choi SS, Lee MK, Kong MH, Lee IO, Oh HR. Thoracic spinal cord stimulation for neuropathic pain after spinal meningioma removal: a case report. *Clinical Journal of Pain* 2009;**25**(2):167–9.

Nouri 2011 *{published data only}*
Nouri KH, Brish EL. Spinal cord stimulation for testicular pain. *Pain Medicine* 2011;**12**(9):1435–8.

Rainov 2007 *{published data only}*
Rainov NG, Heidecke V. Hardware failures in spinal cord stimulation (SCS) for chronic benign pain of spinal origin. *Acta Neurochirurgica Supplement* 2007;**97**(Pt 1):101–4.

Robaina 2007 *{published data only}*
Robaina F, Clavo B. The role of spinal cord stimulation in the management of patients with brain tumors. *Acta Neurochirurgica Supplement* 2007;**97**(Pt 1):445–53.

Ting 2007 *{published data only}*
Ting JC, Fukshansky M, Burton AW. Treatment of refractory ischaemic pain from chemotherapy-induced Raynaud's syndrome with spinal cord stimulation. *Pain Practice* 2007;**7**(2):143–6.

Tsubota 2009 *{published data only}*
Tsubota S, Higaki N, Nagaro T. A case of neuropathic cancer pain in the lower extremities successfully treated with spinal cord stimulation. *Masui* 2009;**58**(11):1460–1.

Yakovlev 2008 *{published data only}*
Yakovlev AE, Ellia Y. Spinal cord stimulation as a treatment option for intractable neuropathic cancer pain. *Clinical Medicine & Research* 2008;**6**(3-4):103–6.

Yakovlev 2009 *{published data only}*
Yakovlev AE, Resch BE. Treatment of intractable abdominal pain patient with Bannayan-Riley-Ruvalcaba syndrome using spinal cord stimulation. *WMJ: official publication of the State Medical Society of Wisconsin* 2009;**108**(6):323–6.

Additional references

Boswell 2010
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. *Pain Physician* 2007;**10**(1):7–111.

Christo 2008
Christo PJ, Mazloomdoost D. Cancer pain and analgesia. Annals of the New York Academy of Sciences. 2008.

Costantini 2005
Costantini A. Spinal cord stimulation. *Minerva Anestesiology* 2005;**71**(7-8):471–4.

Engle 2013
Engle MP, Vinh BP, Harun N, Koyyalagunta D. Infectious complications related to intrathecal drug delivery system and spinal cord stimulator system implantations at a comprehensive cancer pain center. *Pain Physician* 2013;**16** (3):251–7. [PUBMED: 23703411]

Flagg 2012
Flagg A 2nd, McGreevy K, Williams K. Spinal cord stimulation in the treatment of cancer-related pain: "back to the origins". *Current Pain and Headache Reports* 2012;**16** (4):343–9. [PUBMED: 22610506]

Frey 2009
Frey ME, Manchikanti L, Benyamin RM, Schultz DM, Smith HS, Cohen SP. Spinal cord stimulation for patients with failed back surgery syndrome: a systematic review. *Pain Physician* 2009;**12**(2):379–97.

Grabow 2003
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.

Herr 2004
Herr K, Titler MG, Schilling ML, Marsh JL, Xie XJ, Ardery G, et al. Evidence-based assessment of acute pain in older adults: current nursing practices and perceived barriers. *Clinical Journal of Pain* 2004;**20**(5):331–40.

Higgins 2011
Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.

Hurlow 2012
Hurlow A, Bennett MI, Robb KA, Johnson MI, Simpson KH, Oxberry SG. Transcutaneous electric nerve stimulation (TENS) for cancer pain in adults. *Cochrane Database of Systematic Reviews* 2012, Issue 3. [DOI: 10.1002/14651858.CD006276.pub3]

IASP 2008
International Association for the Study of Pain (IASP). Opioid-induced hyperalgesia. Pain Clinical Updates of International Association for the Study of Pain. 2008; Vol. XVI, issue 2:1–4.

Isagulian 2008
Isagulian ED, Shabalov VA. Neuromodulation-controlled analgesia. Criteria for long efficiency. *Journal of Neurosurgical Problems* 2008;**2**:18–26.

Kemler 2010
Kemler MA, Raphael JH, Bentley A, Taylor RS. The cost-effectiveness of spinal cord stimulation for complex regional pain syndrome. *Value In Health* 2010;**13**(6):735–42.

Klomp 2009
Klomp HM, Steyerberg EW, Habbema JD, Van Urk H, ESES study group. What is the evidence on efficacy of spinal cord stimulation in (subgroups of) patients with critical limb ischemia. *Annals of Vascular Surgery* 2009;**23**(3):355–63.

Mailis-Gagnon 2004
Mailis-Gagnon A, Furlan AD, Sandoval JA, Taylor RS. Spinal cord stimulation for chronic pain. *Cochrane Database of Systematic Reviews* 2004, Issue 3. [DOI: 10.1002/14651858.CD003783.pub2]

Michael 2009
Michael EF, Laxmaiah M, Ramsin MB, David MS, Howard SS, Steven PC. Spinal cord stimulation for patients with failed back surgery syndrome: A systematic review. *Pain Physician* 2009;**12**:379–97.

Miguel 2000
Miguel R. Interventional treatment of cancer pain: the fourth step in the World Health Organization analgesic ladder?. *Cancer Control* 2000;**7**(2):149–56.

Miles 1974
Miles J, Lipton S, Hayward M, Bowsher D, Mumford J, Molony V. Pain relief by implanted electrical stimulators. *Lancet* 1974;**1**(7861):777–9.

Moher 2001
Moher D, Schulz KF, Altman DG. The CONSORT Statement: revised recommendations for improving the quality of reports of parallel-group randomised trials. *Lancet* 2001;**357**:1191–4.

North 2008
North RB, Shipley J, Taylor RS. Generating evidence on spinal cord stimulation for failed back surgery syndrome: not yet fully charged. *Clinical Journal of Pain* 2009;**24**(9):757–8.

Reeves 2011
Reeves BC, Deeks JJ, Higgins JPT, Wells GA. Chapter 13: Including non-randomised studies. In: Higgins JPT, Green S (editors). *Cochrane Handbook for Systematic Reviews of Interventions;Version 5.1.0*. The Cochrane Collaboration, 2011.

RevMan 2014
The Nordic Cochrane Centre, The Cochrane Collaboration. Review Manager (RevMan). 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014.

Ro 2005
Ro LS, Chang KH. Neuropathic pain: mechanisms and treatments. *Chang Gung Medical Journal* 2005;**28**(9):597–605.

Running 2011
Running A, Turnbeaugh E. Oncology pain and complementary therapy. *Clinical Journal of Oncology Nursing* 2011;**15**(4):374–9.

Schmidt 2010
Schmidt BL, Hamamoto DT, Simone DA, Wilcox GL. Mechanism of cancer pain. *Molecular Interventions* 2010;**10**(3):164–78.

Schug 1990
Schug SA, Zech D, Dorr U. Cancer pain management according to WHO analgesic guidelines. *Journal of Pain and Symptom Management* 1990;**5**:27–32.

Simpson 2009
Simpson EL, Duenas A, Holmes MW, Papaioannou D, Chilcott J. Spinal cord stimulation for chronic pain of neuropathic or ischaemic origin: systematic review and economic Evaluation. *Health Technology Assessment* 2009;**13**:number 17.

Slavik 2004
Slavik E, Ivanovic S. Cancer pain (neurosurgical management). *Acta Chirurgica Lugoslavica* 2004;**51**(4):15–23.

Stephen 2005
Stephen M, Martin K. *Wall and Melzack's Textbook of Pain*. Churchill Livingstone, 2005.

Stojanovic 2002
Stojanovic MP, Abdi S. Spinal cord stimulation. *Pain Physician* 2002 July;**5**(3):341.

Sweet 1974
Sweer WH, Wespic JG. Stimulation of the posterior columns of the spinal cord for pain control: indications, technique, and results. *Clinical Neurosurgery* 1974;**21**:278–310.

Taylor 2006
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.

Taylor 2009

Taylor RS, De Vries J, Buchser E, Dejongste MJ. Spinal cord stimulation in the treatment of refractory angina: systematic review and meta-analysis of randomised controlled trials. *Biomedcentral Cardiovascular Disorders* 2009;**7**:9–13.

Ubbink 2005

Ubbink DT, Vermeulen H. Spinal cord stimulation for non-reconstructable chronic critical leg ischaemia. *Cochrane Database of Systematic Reviews* 2005, Issue 3. [DOI: 10.1002/14651858.CD004001.pub2]

Vandenbroucke 2007

Vandenbroucke JP, von Elm E, Altman DG, Gøtzsche PC, Mulrow CD, Pocock SJ, et al. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE): explanation and elaboration.. *PLoS Medicine* 2007;**4**:e297.

* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Meglio 1989

Methods	Part of a retrospective study to analyse 109 patients with chronic pain who underwent spinal cord stimulation, clinical efficacy was analysed in relation to the aetiology of pain
Participants	From 1978 to 1986,109 participants were enrolled: 11 patients with cancer pain; 40 with vasculopathic pain; 19 with lower back pain; 15 with paraplegic pain; 9 with deafferentation pain; 10 with post-herpetic pain
Interventions	Percutaneous placement of the stimulator electrodes or positioned through a small laminectomy after a test period of 5 to 60 days, two kinds of stimulators were used: the first was a radiofrequency system; the second was programmable stimulators, which were programmed with a pulse width of 210 microseconds and a rate of 85 Hz, 64 seconds on, 1 to 4 minutes off, amplitude was at will to produce comfortable paraesthesia
Outcomes	Reduction of visual analogue scale as percentage of analgesia (0% denotes no effect, 100% denotes complete pain relief, a reduction of more than 50% of original pain was considered as responder); adverse events
Notes	None

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	High risk	No methods of randomisation were provided.
Allocation concealment (selection bias)	High risk	No methods of allocation concealment were provided.
Blinding of participants and personnel (performance bias) All outcomes	High risk	No method of blinding were provided.
Blinding of outcome assessment (detection bias) All outcomes	High risk	No methods of blinding were provided.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No information of patient dropout was provided.
Selective reporting (reporting bias)	Low risk	This trial reported both analgesic efficacy and adverse events

Meglio 1989 (*Continued*)

Other bias	High risk	Size of study: high risk of bias (< 50 participants per treatment arm). Retrospectively reported on 11 patients with cancer from a total of 109 patients who were diagnosed with six categories of diseases

Shimoji 1993

Methods	A survey of clinical results of using percutaneous epidural low-frequency spinal cord stimulation for chronic pain
Participants	Between 1970 and 1991, 454 patients with chronic pain received percutaneous epidural low-frequency spinal cord stimulation: 52 with carcinoma/sarcoma; 126 with post-herpetic neuralgia; 189 with causalgia; 12 with spinal trauma; 9 with SMON; 3 with tabes dorsalis; 8 with phantom pain; 14 with TAO/ASO; 9 with thalamic syndrome; 32 with other pain
Interventions	All patients received implantation of electrodes at sites of pain which connected to a stimulator that delivered saw-wave pulses (0.5ms in duration). The frequency of stimulation was adjustable by the patient at between 1.6 and 8.0 Hz, the intensity being 0.5V to 5.0V. The mode of stimulation was continuous in 9 patients with cancer or occasional (3 to 12 per day for 20 to 30 min) in 445 patients, depending on patients' complaints
Outcomes	Degree of pain relief as visual analogue scale, 50% of reduction was considered as pain relief; adverse events
Notes	None

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	High risk	No methods of randomization were provided.
Allocation concealment (selection bias)	High risk	No methods of allocation concealment were provided.
Blinding of participants and personnel (performance bias) All outcomes	High risk	No method of blinding were provided.
Blinding of outcome assessment (detection bias) All outcomes	High risk	No methods of blinding were provided.

Shimoji 1993 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No information of patient dropout was provided.
Selective reporting (reporting bias)	Low risk	This trial reported both analgesic efficacy and adverse events
Other bias	High risk	Size of study: high risk of bias (< 50 participants per treatment arm)

Yakovlev 2010

Methods	To retrospectively analyse the pain relief outcome of spinal cord stimulation in patients with cancer-related chest wall pain
Participants	From 2005 to 2008,14 patients diagnosed with lung cancer underwent thoracotomy or lung resection and postoperative radiation therapy, and complained of intractable chronic chest pain
Interventions	14 patients received percutaneous implantation of permanent leads and stimulators at T3,T4,T5 after a successful trial of at least 2 days; stimulators were programmed with a pulse width of 400 to 450 microseconds and a rate of 50 to 60 Hz,amplitude ranged from 1.5V to 2.3V
Outcomes	Rate of opioid use before and after treatment; pre-procedure, 1 month post implant and 12 months post implant visual analogue scale; complication
Notes	None

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	High risk	No methods of randomisation were provided.
Allocation concealment (selection bias)	High risk	No information of allocation concealment was provided.
Blinding of participants and personnel (performance bias) All outcomes	High risk	No information of blinding was provided.
Blinding of outcome assessment (detection bias) All outcomes	High risk	No information of blinding of outcome assessment was provided
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No information of patient dropout was provided.

Yakovlev 2010 (*Continued*)

Selective reporting (reporting bias)	Low risk	This trial reported both analgesic efficacy and adverse events
Other bias	High risk	Size of study: high risk of bias (< 50 participants per treatment arm)

Yakovlev 2011

Methods	To retrospectively analyse the pain relief of spinal cord stimulation for intractable cancer-related lower back pain
Participants	Between 2005 and 2009,15 patients underwent surgical resections and radiation therapy because of metastatic disease related to colon, anal cancer, angiosarcoma of the sacrum, and subsequently complained of intractable chronic low back pain
Interventions	15 patients received percutaneous implantation of permanent leads and stimulators at T11-12,T12/L1 after successful trial at least 2 days, stimulators were programmed with a pulse width of 390 to 480 microseconds and a rate of 40 to 60 Hz,amplitude ranged from 1.4V to 5.2V
Outcomes	Rate of opioid use before and after treatment; pre-procedure, 1 month post implant and 12 months post implant visual analogue scale; complications
Notes	None

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	High risk	No methods of randomisation were provided.
Allocation concealment (selection bias)	High risk	No information of allocation concealment was provided.
Blinding of participants and personnel (performance bias) All outcomes	High risk	No information of blinding was provided.
Blinding of outcome assessment (detection bias) All outcomes	High risk	No information of blinding was provided.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No information of patient dropout was provided.
Selective reporting (reporting bias)	Low risk	This trial reported both analgesic efficacy and adverse events

Yakovlev 2011 (*Continued*)

Other bias	High risk	Size of study: high risk of bias (< 50 participants per treatment arm)

ASO: arteriosclerosis obliterans
SMON: subacute myelo-optico-neuropathy
TAO: thromboangiitis obliterans

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Cata 2004	Individual case report.
Clavo 2004	Outcomes not related to the topic of systematic review.
Clavo 2009	Outcomes not related to the topic of systematic review.
Eisenberg 2002	Individual case report.
Hamid 2007	Individual case report.
Lee 2006	Review article of SCS.
Lee 2009	Individual case report.
Nouri 2011	Individual case report.
Rainov 2007	Outcomes not related to the topic of review.
Robaina 2007	Individual case report.
Ting 2007	Individual case report.
Tsubota 2009	Individual case report.
Yakovlev 2008	Case report including only 2 patients.
Yakovlev 2009	Individual case report.

SCS: spinal cord stimulation

DATA AND ANALYSES

Comparison 1. Pain Intensity after SCS implantation

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pain intensity---Visual Analogue Scale	2	58	Mean Difference (IV, Random, 95% CI)	4.38 [3.93, 4.83]

Comparison 2. Pain intensity---1 month after SCS versus 12 months after SCS

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pain Intensity---Visual Analogue Scale	2	58	Mean Difference (IV, Fixed, 95% CI)	0.91 [0.50, 1.32]

Analysis 1.1. Comparison 1 Pain Intensity after SCS implantation, Outcome 1 Pain intensity---Visual Analogue Scale.

Review: Spinal cord stimulation for cancer-related pain in adults

Comparison: 1 Pain Intensity after SCS implantation

Outcome: 1 Pain intensity—Visual Analogue Scale

Study or subgroup	before scs implantation N	Mean(SD)	after scs implantation N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Yakovlev 2010	14	7.43 (0.94)	14	3.07 (0.62)		57.9 %	4.36 [3.77, 4.95]
Yakovlev 2011	15	7.07 (1.03)	15	2.67 (0.9)		42.1 %	4.40 [3.71, 5.09]
Total (95% CI)	**29**		**29**			**100.0 %**	**4.38 [3.93, 4.83]**

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.01$, df = 1 (P = 0.93); $I^2 = 0.0\%$

Test for overall effect: Z = 19.11 (P < 0.00001)

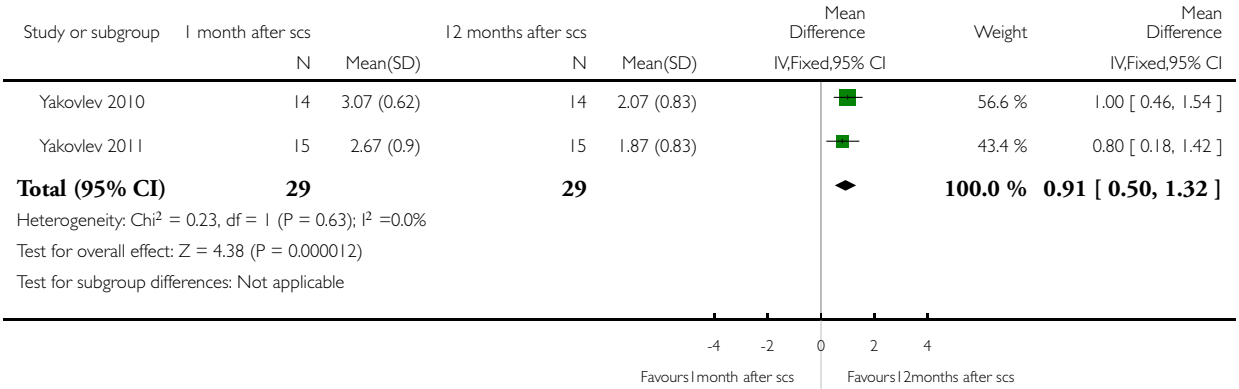
Test for subgroup differences: Not applicable

Analysis 2.1. Comparison 2 Pain intensity---1 month after SCS versus 12 months after SCS, Outcome 1 Pain Intensity---Visual Analogue Scale.

Review: Spinal cord stimulation for cancer-related pain in adults

Comparison: 2 Pain intensity—1 month after SCS versus 12 months after SCS

Outcome: 1 Pain Intensity—Visual Analogue Scale



ADDITIONAL TABLES

Table 1. STROBE checklist

Structure	Item	Recommendation
Title and abstract	1	Indicate the study's design with a commonly used term in the title or the abstract; provide in the abstract an informative and balanced summary of what was done and what was found
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported
Objectives	3	State specific objectives, including any prespecified hypotheses
Methods		
Study design	4	Present key elements of study design early in the paper.
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	6	Give the eligibility criteria, and the sources and methods of selection of participants

Table 1. STROBE checklist (*Continued*)

Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/ measurement	8	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias	9	Describe any efforts to address potential sources of bias.
Study size	10	Explain how the study size was arrived at.
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding. (b) Describe any methods used to examine subgroups and interactions. (c) Explain how missing data were addressed. (d) If applicable, describe analytical methods taking account of sampling strategy
Results		
Participants	13	(a) Report numbers of individuals at each stage of study-e.g. numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed. (b) Give reasons for non-participation at each stage. (c) Consider use of a flow diagram.
Descriptive data	14	(a) Give characteristics of study participants (e.g. demographic, clinical, social) and information on exposures and potential confounders. (b) Indicate number of participants with missing data for each variable of interest
Outcome data	15	Report numbers of outcome events or summary measures.
Main results	16	If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17	Report other analyses done-e.g. analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results	18	Summarise key results with reference to study objectives.
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias.
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence

Table 1. STROBE checklist (*Continued*)

Generalisability	21	Discuss the generalisability (external validity) of the study results
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

Table 2. Result of STOBE Checklist

Item No.	Meglio 1989	Shimoji 1993	Yakovlev 2010	Yakovlev 2011
1	Y	Y	Y	Y
2	N	Y	Y	Y
3	N	Y	Y	Y
4	N	N	N	N
5	N	N	Y	Y
6	N	N	N	N
7	N	N	N	N
8	N	N	N	Y
9	N	N	N	N
10	N	N	N	N
11	Y	Y	Y	Y
12	N	N	N	N
13	N	N	N	N
14	N	N	N	N
15	Y	Y	Y	Y
16	N	N	N	N
17	N	N	N	N
18	Y	Y	Y	Y
19	N	N	N	N

Table 2. Result of STOBE Checklist (*Continued*)

20	Y	Y	Y	Y
21	Y	Y	Y	Y
22	N	N	Y	Y

Y:Yes; N:No; U:Unlear

APPENDICES

Appendix 1. Search strategies

CENTRAL (*The Cochrane Library)*
MESH DESCRIPTOR Neoplasms EXPLODE ALL TREES
(cancer* or carcino* or tumour* or tumor* or neoplas* or malig*):TI,AB,KY
#1 OR #2
MESH DESCRIPTOR Pain EXPLODE ALL TREES
pain*:TI,AB,KY
#4 OR #5
MESH DESCRIPTOR Electric Stimulation Therapy EXPLODE ALL TREES
MESH DESCRIPTOR Spinal Cord EXPLODE ALL TREES
(spinal cord stimulation*):TI,AB,KY
SCS:TI,AB,KY
#7 OR #8 OR #9 OR #10
#3 AND #6 AND #11
11/07/2012 TO 30/10/2014:DL
#12 AND #13
MEDLINE (OVID)
1 (cancer$ or carcino$ or tumour$ or tumor$ or neoplas$ or malig$).tw.
2 exp Neoplasms/
3 1 or 2
4 exp pain/
5 pain$.tw.
6 4 or 5
7 exp Electric Stimulation Therapy/
8 exp Spinal Cord/
9 spinal cord stimulation$.tw.
10 scs.tw.
11 dorsal column stimulation.tw.
12 7 or 8 or 9 or 10 or 11
13 3 and 6 and 12
EMBASE (OVID)
1 (cancer$ or carcino$ or tumour$ or tumor$ or neoplas$ or malig$).tw.
2 exp Neoplasm/
3 1 or 2

4 exp pain/
5 pain$.tw.
6 4 or 5
7 exp Electrostimulation Therapy/
8 exp Spinal Cord/
9 spinal cord stimulation$.tw.
10 scs.tw.
11 dorsal column stimulation.tw.
12 7 or 8 or 9 or 10 or 11
13 3 and 6 and 12

CMB(Chinese Biomedical Database)

1 (肿瘤$ or 癌症$ or 新生物$ or 恶性$).tw.

2 exp 肿瘤/
3 1 or 2

4 exp 疼痛/

5 疼痛$.tw.
6 4 or 5

7 exp 电刺激/

8 exp 脊髓/

9 脊髓电刺激$.tw.

10 后索电刺激.tw.
11 7 or 8 or 9 or 10
12 3 and 6 and 11

WHAT'S NEW

Last assessed as up-to-date: 6 October 2014.

Date	Event	Description
6 February 2015	New citation required but conclusions have not changed	No new studies were identified for inclusion in this update and the conclusions remain unchanged accordingly. Risk of bias summary tables added
27 December 2014	New search has been performed	Search updated in October 2014.

CONTRIBUTIONS OF AUTHORS

Lihua Peng wrote the protocol draft, updated literature and wrote the updated review.

Michael Bennett modified the protocol and guided the data analysis in the original review.

Lihua Peng conceived the idea for this review and gave some suggestions on the protocol.

Su Min and Ke Wei did the search and extracted the data for the original review and the study selection of the updated review.

Ke Wei carried out the analysis for the full review.

DECLARATIONS OF INTEREST

Lihua Peng has no relevant conflicts of interest to declare.

Su Min has no relevant conflicts of interest to declare.

Zhou Zejun has no relevant conflicts of interest to declare.

Wei Ke has no relevant conflicts of interest to declare.

Michael I Bennett has no relevant conflicts of interest to declare.

SOURCES OF SUPPORT

Internal sources

- Department of Anaesthesia and Pain Medicine, Chongqing Medical University, China.

External sources

- Cochrane Pain, Palliative and Supportive Care Review Group, UK.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Where randomised trial evidence is desired but unlikely to be available, eligibility criteria defines that non-randomised trials would only be included where randomised trials are found not to be available and non-randomised trials will be appraised with commonly used checklists for methodological quality (Reeves 2011).

We intended to include randomised controlled trials (RCTs); however, we did not find any such trials. For the previous version of the review, after consultation with the Pain, Palliative and Supportive Care Review Group group editors and a group discussion, we modified our inclusion criteria to include non-randomised controlled trials for this review.

We added Cochrane 'Risk of bias' tool and summary tables in the updated version of this review.

INDEX TERMS

Medical Subject Headings (MeSH)

*Spinal Cord Stimulation; Analgesics, Opioid [administration & dosage]; Checklist; Neoplasms [*complications]; Pain [*etiology]; Pain Management [adverse effects; *methods]; Pain Measurement

MeSH check words

Adult; Humans