

Implantable pain therapy: Neurostimulation

Plain language summary

Treatments for persistent pain can involve many types of therapies such as medication, physiotherapy, and psychological therapy. In some patients these treatments may not work or cause unpleasant effects. For these patients neurostimulation can be an option. This is a therapy which directs electricity on to the nerves.

This requires surgery to put a device that makes the electricity under the skin (a neurostimulator). Connected to this are leads that are put on the nerves involved in the pain. The device is turned on and electricity is transmitted to the nerves involved in feeling pain. This may give pain relief by hiding the pain with a numbing or tickling feeling.

The most high quality, up-to-date research says:

- There is moderate evidence that spinal cord stimulation (SCS) relieves pain and improves function within 2 years in complex regional pain syndrome (CRPS).
- There is low evidence that spinal cord stimulation (SCS) relieves pain and improves function within 2 years in failed back surgery syndrome (FBSS).
- There is conflicting evidence that SCS improves quality of life.
- There is moderate evidence that occipital nerve stimulation is effective at reducing headaches and pain in patients with chronic migraine
- For all other types of neurostimulation there is insufficient evidence that it works.

There are also possible harms that can happen with neurostimulation. These include bleeding into the brain, nausea, headache or migraine and a small risk of death. Problems related to the device or the operation such as infection or mechanical problems can also occur. Sometimes another operation is needed to fix problems. This is known as a revision. Studies have found that revision operations have been needed in 12-38% of patients shortly after their first SCS operation.

Implantable Pain Therapies: Neurostimulation

Ornella Clavisi, Melissa Chee, Loyal Pattuwage, Anneliese Synnot

13 February 2015

Research report#: 115-0215-R04

A joint initiative of

This research report was prepared by:

Ornella Clavisi, Melissa Chee, Loyal Pattuwage, Anneliese Synnot: National Trauma Research Institute, Monash University.

For Transport Accident Commission and Victorian WorkCover Authority

This is an updated of a previous report (Donoghue 2011)

ISCRR is a joint initiative of the Victorian WorkCover Authority, the Transport Accident Commission and Monash University. The opinions, findings and conclusions expressed in this publication are those of the authors and not necessarily those of TAC, VWA or ISCRR.

Accompanying documents to this report

Title: *Implantable Pain Therapies: Neurostimulation*

- *Technical report (Report number: 115-0215-Z04)*
- *Plain language summary*

TABLE OF CONTENTS

TABLE OF CONTENTS	3
EVIDENCE REVIEW SUMMARY	4
BACKGROUND.....	10
QUESTIONS.....	12
METHODS.....	12
RESULTS	14
1. SPINAL CORD STIMULATION (SCS).....	15
2. PERIPHERAL NERVE STIMULATION (PNS)	31
3. OCCIPITAL NERVE STIMULATION (ONS).....	34
4. DEEP BRAIN STIMULATION (DBS).....	42
5. MOTOR CORTEX STIMULATION	46
6. SUBCUTANEOUS ELECTRICAL STIMULATION (SES)	50
DISCUSSION & CONCLUSION	51
DISCLAIMER.....	53
CONFLICT OF INTEREST	53
REFERENCES	54

EVIDENCE REVIEW SUMMARY

Implantable Pain Therapies: Neurostimulation

We searched for randomized controlled trials (RCTs) and systematic reviews (SRs) that evaluated the effect of neurostimulation for the treatment of persistent non-cancer pain. Overall we identified:

- 2 RCTs and 1 Health Technology Assessment (HTA) for spinal cord stimulation (SCS)
- 1 Evidence Based Guideline (EBG) for peripheral nerve stimulation (PNS)
- 4 RCTs for occipital nerve stimulation (ONS)
- 1 RCT for deep brain stimulation (DBS)
- 2 RCTs for motor cortex stimulation (MCS)

Key messages

Spinal cord stimulation (SCS)

There is moderate level evidence to validate the use of SCS in complex regional pain syndrome (CRPS) type I and low level evidence to validate the use of SCS in failed back surgery syndrome (FBSS). There is insufficient evidence to validate the use of burst SCS in patients with FBSS and high frequency SCS in patients with persistent low back pain.

Peripheral nerve stimulation (PNS)

No controlled trials to validate the use of PNS for neuropathic pain were identified.

Occipital nerve stimulation (ONS)

There is moderate level evidence to validate the use of ONS in chronic migraine.

Deep brain stimulation (DBS)

There is low-level evidence indicating that DBS is no more effective than sham in the treatment of severe refractory cluster headache.

Motor cortex stimulation (MCS)

There is low-level evidence indicating that MCS is no more effective than sham in the treatment of refractory peripheral neuropathic pain.

Subcutaneous electrical stimulation (SES)

No controlled trials addressing SES for persistent intractable pain were identified.

Purpose

The Transport Accident Commission (TAC) and the Victorian WorkCover Authority (VWA) requested a review of the evidence to determine whether neurostimulation is an effective

treatment compared to placebo in treatment of persistent non-cancer pain. This review sought to find the most up-to-date, high quality source of evidence to answer the following questions:

- In what conditions is neurostimulation indicated?
- What is the effectiveness of neurostimulation on persistent spinal pain in these conditions?
- What is the effect of neurostimulation on function (physical, psychological, social), quality of life, return to work, medication use and healthcare utilisation?
- In what patient groups/conditions is neurostimulation contraindicated?
- What are the risks associated with use of neurostimulation?
- What is the impact of training and/or experience of practitioners on patient outcomes?

Rationale

To ensure funding decisions made regarding the use of neurostimulation are evidence-based and in the best interests of injured Victorians.

New research relevant to neurostimulation is regularly being published. This review is important for VWA/TAC as it provides an independent, thorough search and quality assessment of the peer-reviewed literature in this area. This can then be used to support funding decisions regarding this treatment. The search can also be repeated in the future to incorporate new evidence as it arises.

Methods

Systematic review methods were used. A comprehensive search of Medline, Embase, the Cochrane Library, and All EBM was undertaken in April 2014 to identify relevant research. Reference lists of included studies were also scanned to identify relevant references.

Studies identified by the searches were independently screened for inclusion by two authors. In this review studies were only included if they were SRs, RCTs or CCTs that investigated the effects of neurostimulation compared with placebo (or other active treatments) in patients with persistent pain. Evidence that met the selection criteria was reviewed to identify the most up-to-date and comprehensive source of evidence, which was then critically appraised to determine whether it was of high quality.

Research findings and implications

In what conditions is neurostimulation indicated?

Neurostimulation is indicated for a small proportion of patients with non-cancer pain who do not experience sufficient pain relief or have intolerable side effects with conventional treatments such as: complex regional pain syndrome (Kemler 2000, Kemler 2004, Kemler 2008); failed back surgery syndrome (Kumar 2007, Kumar 2008, North 2005), chronic migraine (Saper 2011, Serra 2012, Silberstein 2012) and severe refractory cluster headache (Lipton 2009).

What is the effectiveness of neurostimulation on persistent pain and other patient relevant outcomes?

Spinal cord stimulation (SCS)

Conventional SCS vs Control

Three small RCTs have reported SCS to be superior to conventional therapies (conventional medical management, physical therapy or reoperation) in patients with persistent neuropathic pain at 6 months to 24 months with respect to pain, and perceived effect of treatment / patient satisfaction and disability. (Kemler 2000, Kemler 2004, Kemler 2008) (Kumar 2007, Kumar 2008) (North 2005) This effect however was not sustained long term (beyond 5 years).

Quality of life improvements with conventional SCS are unclear as one study reported a significant improvement with SCS (Kumar 2007) while another reported no difference between treatment arms (Kemler 2000).

Conventional SCS versus Burst SCS

Although one cross-over trial (De Ridder 2013) reported statistically significant improvements in pain with burst stimulation compared to standard tonic SCS and placebo, the results are uncertain as the risk of bias could not be assessed due to trial methodology not being adequately reported.

High Frequency SCS vs Sham

There is low level evidence indicating that there is no statistically significant improvement with high frequency SCS compared to sham at 12 weeks. (Perruchoud 2013). This study was underpowered to detect a significant result.

Peripheral nerve stimulation (PNS)

The evidence that is available is of low quality as it all came from case series, therefore insufficient to answer this question.

Occipital nerve stimulation (ONS)

Evidence from one RCT of moderate quality reported that significantly more ONS patients achieved $\geq 30\%$ reduction in pain compared to sham patients. (Silberstein 2012) In addition,

ONS patients had significantly less headache days; less migraine-related disability (MIDAS) and greater patient reported pain relief ($p=0.001$) (Silberstein 2012).

Two other RCTs reported no significant difference between ONS and sham. These results however, are uncertain due to methodological limitations, inadequate power and poor reporting of study methods (Lipton 2009, Saper 2010).

Deep brain stimulation (DBS)

Based on low level evidence, DBS is no more effective than sham for the treatment of refractory cluster headaches. (Fontaine 2012) Uncertainty regarding this estimate can be attributed to limitations with regards to study design including: imprecision of the estimate used to calculate sample size; delay between stimulation onset and therapeutic effect and suboptimal stimulation parameters.

Motor cortex stimulation (MCS)

Based on low level evidence, MCS is no more effective than sham for the treatment of refractory peripheral neuropathic pain. (Lefaucheur 2009, Nguyen 2008). The small size of the groups in both studies means that it is not possible to generalise the results. Adding to this complexity was a lack of reporting on several methodological parameters and an insufficient wash-out period between phases.

Subcutaneous electrical stimulation (SES)

No synthesized evidence or evidence from controlled trials was identified to answer this question.

In what patient groups/conditions is neurostimulation contraindicated?

This was not reported by any of the included studies

What are the risks associated with use of neurostimulation?

The risks identified for neurostimulation include:

Spinal cord stimulation (SCS)

Minor complications following SCS were relatively common though not life threatening. In Kemler (2004), 86% of the patients reported change in amplitude by bodily movements, 50% reported paraesthesia in other body parts, 45% reported pain or irritation from the pulse generator and 32% reported more pain in other body parts. Device related infection rate of 10% ($n=10$) was reported by Kumar (2008), while Kemler (2008) and North (2005) reported only one re-implantation due to an infection. In Kumar (2008), 24% of the patients encountered hardware related problems and 19% required surgical revisions. North (2005) reported 9% hardware revisions, and 13 of the 24 SCS patients (54%) in Kemler (2008) encountered 17 pulse generator replacements during the 5 years of follow up.

Peripheral nerve stimulation (PNS)

Reoperation after PNS was common (Cruccu 2007).

Occipital nerve stimulation (ONS)

The most common complication associated with ONS was lead migration (Serra 2012, (Silberstein 2012, Lipton 2009, Saper 2011). Other adverse events included persistent pain, and/or numbness at implantable pulse generator/lead site and site infection (Silberstein 2012).

No adverse events led to long-term complications or nerve damage.

Deep brain stimulation (DBS)

Three adverse events were reported in Fontaine (2010), in two patients (18% of total patient population). One subcutaneous infection happened three weeks after surgery. It completely resolved after hardware removal and antibiotic treatment. One patient experienced a preoperative loss of consciousness with hemiparesia shortly after test stimulation. Symptoms spontaneously resolved in two hours without sequelae. The same patient reported multiple severe micturition syncope associated with decrease of blood pressure in standing position during the open phase of the trial.

Motor cortex stimulation (MCS)

Both RCTs (Lefaucheur 2009, Nguyen 2008) did not report any adverse events associated with MCS.

Subcutaneous electrical stimulation (SES)

No evidence from controlled trials was identified to comment on the risks associated with SES.

What is the impact of training and/or experience of practitioners on patient outcomes?

The issue of training was not explored in any of the included studies.

Glossary of findings	
High quality*	Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality*	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate
Low quality*	Further research is very likely to have an important impact on our confidence in the estimate of effect and is like to change the estimate
Very low quality*	We are very uncertain about the estimate
Insufficient evidence	Little or no evidence exists to answer this question

Classifications are taken from GRADE Handbook (Schünemann 2013).

Report no: TBA

Date: 13 February 2015

ISCRR is a joint initiative of the Victorian WorkCover Authority, the Transport Accident Commission and Monash University. The opinions, findings and conclusions expressed in this publication are those of the authors and not necessarily those of Monash University or ISCRR or the TAC or VWA.

BACKGROUND

“Pain which persists for more than several months, or beyond the normal course of a disease or expected time of healing” is classified as persistent pain. It is clinically defined as measuring at least 50 mm on a 0-100 mm visual analogue scale (VAS) and lasting > 6 months in duration. Persistent pain can modify an individual’s physiological and psychological conditions leading to disabling changes in their quality of life (including general everyday activities, medication dependence and frequent absence from work).

Persistent pain is a difficult condition to cure and there are few known effective treatments. Conventional medical management (CMM) or first line therapy for persistent pain includes analgesic medications and physical therapies. However, patients may not experience complete pain relief with these treatments and side effects may occur. Some patients also try invasive interventions for pain relief that include surgery, nerve blocks, which can also be unsuccessful. A potential alternative treatment option for these patients is neurostimulation.

Neurostimulation is the electrical activation of nerves using electrodes and leads. A transmitter or implantable pulse generator (IPG) is placed under the skin, usually over the abdominal or chest regions. Leads are passed from the IPG to the nerves being stimulated. This requires surgery. The low voltage electricity to the nerves may block the sensation of pain. The IPG and leads can be removed by surgery if required. The following neurostimulation modalities will be the focus of this evidence report:

1. Spinal cord stimulation (SCS)
2. Peripheral nerve stimulation (PNS)
3. Occipital nerve stimulation (ONS)
4. Deep brain stimulation (DBS) (*intracranial*) and
5. Motor cortex stimulation (MCS) (*intracranial*)

1. Spinal cord stimulation (SCS)

Spinal cord stimulation (SCS) is a treatment used to mask areas of pain by making them feel numb or tingly (a phenomenon known as paraesthesia). This appears to block pain transmission. Individuals who are selected for SCS undergo trial stimulation or screening. This determines their suitability for permanent implantation of the device for long term treatment.

The SCS system consists of two components –

- a. A lead connected to an insulated plate electrode (multi-contact points), and
- b. An implantable pulse generator (IPG) or transmitter, which provides the electrical input to the electrode

Electrodes may be implanted percutaneously or following laminectomy. Once successfully implanted under general anaesthesia, the IPG is programmed (pulse width, frequency and amplitude) in the conscious patient.

2. Peripheral nerve stimulation (PNS)

Peripheral nerve stimulation (PNS) provides electrical stimulation to the peripheral nerves supplying areas of pain (i.e. nerves in the legs or arms). The electrode is implanted percutaneously along the course of peripheral nerves. A small electrical current is provided through an implantable pulse generator (IPG) inserted under the skin. (Stanton-Hicks 2009).

3. Occipital nerve stimulation (ONS)

Occipital nerve stimulation (ONS) involves bilateral stimulation of the occipital nerves which supplies the skin from the base of the skull to the vertex. The exact mechanism of action of ONS has not been established.

A trial period of a week or two is required for ONS in which temporary percutaneous electrodes are inserted before permanent implantation with one or more paddle electrodes (Weiner 2009).

4. Deep brain stimulation (DBS)

Deep brain stimulation (DBS) is a more invasive procedure than MCS, involving placement of electrodes into specific targeted anatomical sites of the brain (such as the sensory thalamus or periaqueductal grey matter, PAG) (NICE 2011). This alters the processing of the pain signal in the brain may provide pain relief for the patient. The common practice is to implant electrodes in multiple target areas involved in the pain response (PAG and the ventrocaudal thalamus).

Test stimulation is performed initially. Correct positioning of the electrodes is guided by magnetic resonance imaging (MRI) or computed topography (CT) imaging. If the test stimulation is successful, an IPG is implanted usually in the chest wall, and is programmed to deliver stimulation found to be successful in the trial (NICE 2011).

5. Motor cortex stimulation (MCS)

Motor cortex stimulation (MCS) involves placement of an electrode (usually quadripolar) via a craniotomy, epidurally or subdurally over the motor cortex of the brain. In the trial stimulation, the patient remains unconscious and areas of the motor cortex are stimulated to elicit a response. This response is monitored by electromyography (EMG) to ensure that the area of pain is being stimulated. Once this is established, a small electrical current is continued from the IPG which results in sub-threshold activation of muscles. The muscle stimulation can mask the pain.

The advantage of MCS over other types of neurostimulation is that no paresthesia (numbness or tingling) or sensory phenomena is experienced by patients, instead only a sense of pain relief (Levy 2010). In this case, placebo effects can be investigated in randomised clinical trials, giving higher quality evidence for the efficacy of MCS.

6. Subcutaneous electrical stimulation (SES)

Subcutaneous electrical stimulation (SES) involves subcutaneous implantation of electrodes at the centre of the painful region. It is also known as subcutaneous targeted

stimulation. The treatment aims to overlap areas of pain with paraesthesia. This may block pain signals to the patient's brain.

QUESTIONS

This review sought to find the most up-to-date, high quality source of evidence to answer the following questions:

1. In what conditions is neurostimulation indicated?
2. What is the effectiveness of neurostimulation on persistent spinal pain in these conditions?
3. What is the effect of neurostimulation on function (physical, psychological, social), quality of life, return to work, medication use and healthcare utilisation?
4. In what patient groups/conditions is neurostimulation contraindicated?
5. What are the risks associated with use of neurostimulation?
6. What is the impact of training and/or experience of practitioners on patient outcomes?

METHODS

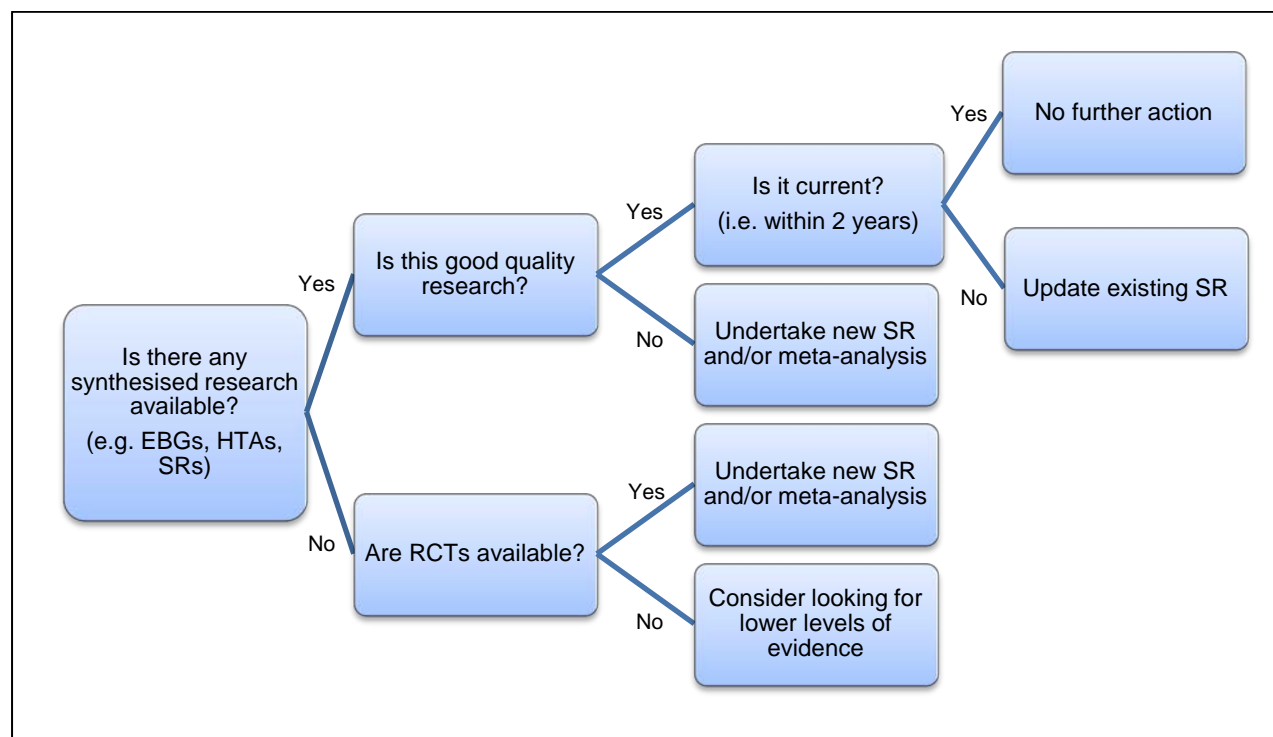
Methods are outlined briefly within this section. More detailed information about the methodology used to produce this report is available in Appendices 1 and 2 that are located in the Technical Report accompanying this document.

A comprehensive search of Medline, Embase, the Cochrane Library, All EBM, and CINAHL was undertaken in April 2014 to identify relevant synthesised research (i.e. evidence-based guidelines (EBGs), systematic reviews (SRs), health technology assessments (HTAs), randomised controlled trials (RCTs) and controlled clinical trials (CCTs). Reference lists of included studies were also scanned to identify relevant references.

Studies identified by the searches were screened for inclusion using specific selection criteria (see Appendix 2, Table A2.1). In this review, studies were only included if they were SRs, RCTs or CCTs that investigated the effects of neurostimulation compared with sham or active treatment in patients with persistent pain. Studies that met the selection criteria were reviewed to identify the most up-to-date and comprehensive source of evidence, which was then critically appraised to determine whether it was of high quality. Two reviewers conducted all screening and selection independently, results were compared and any discrepancies discussed and resolved.

The available evidence was mapped and the algorithm in Figure 1 was followed to determine the next steps necessary to answer the clinical questions.

Figure 1. Further action required to answer clinical questions



Data on characteristics of all included studies were extracted and summarised (see Appendix 4, Technical Report). The most recent, comprehensive, high quality EBG or systematic review for each stimulation modality was used to address the questions posed above.

RESULTS

We conducted an electronic database search in April 2014. The search yielded 1821 potentially relevant citations after duplicate citations were removed. After reviewing titles and abstracts, 132 full texts were reviewed. The inclusion and exclusion criteria were then applied and 53 publications were selected and categorized according to stimulation modality (see Table 1). The algorithm in Figure 1 was followed to determine the appropriate evidence to answer the clinical questions.

Table 1. Evidence map of identified studies by study-type including studies found on previous review of the literature and the most recent review.

Types of Neurostimulation	Synthesised Studies		Primary studies	Total
	EBGs	SRs & HTAs		
SCS	11	22	5	38
PNS	2	2	-	4
ONS	1	2	4	7
DBS	1	5	1	7
MCS	1	1	1	4
SES	-	-	-	0
TOTAL*	12	26	15	53

**column figures may not add up to column totals as some systematic reviews and primary studies (RCTs) evaluated more than one type of neurostimulation*

After application of the algorithm (Figure 1), the following evidence for each stimulation modality was identified for inclusion.

- Spinal cord stimulation: 1 health technology assessment and 2 cross-over trials
- Peripheral nerve stimulation: 1 evidence based guideline consisting of 3 case series
- Occipital nerve stimulation: 3 RCTs and 1 cross over RCT
- Deep brain stimulation: 1 cross-over RCT
- Motor cortex stimulation: 2 cross-over RCTs
- Subcutaneous electrical stimulation: no RCTs or controlled trials were identified

1. SPINAL CORD STIMULATION (SCS)

Evidence Identified

The most comprehensive, up to date source of synthesised evidence was a Health Technology Assessment (HTA) by Hashimoto (2010). We also identified two new crossover RCTs that met the inclusion criteria (Perruchoud 2013, De Ridder 2013). (Table 1.1) It should be noted that due to the heterogeneity of patient groups, methodology, comparators and outcome measures, studies were not combined.

Study Characteristics

Conventional SCS vs Control

An HTA which investigated the effectiveness and safety of SCS in refractory pain conditions included three studies (Hashimoto 2010); (1) a trial conducted in the Netherlands which included patients with complex regional pain syndrome (CRPS) type I (Kemler 2000, Kemler 2004, Kemler 2008), (2) a trial conducted in the UK that recruited patients with failed back surgery syndrome (FBSS) (Kumar 2007, Kumar 2008) and (3) a trial conducted in the US on patients with FBSS (North 2005). All three studies used standard spinal cord stimulation (SCS) as the intervention. Kumar et al used a mean amplitude of 3.7V, pulse width of 350 µsec and a rate of 49Hz. Kemler et al had the pulse generator activated (rate, 85Hz, pulse width 210 µsec) with the use of a console programmer. The patient could control the intensity of stimulation by adjusting the amplitude from 0-10V with the programmer. North (2005) did not report the parameters used for their SCS. Control interventions differed between studies with one using physical therapy (Kemler 2000, Kemler 2004, Kemler 2008); another using conventional medical management that included analgesic, anticonvulsant and anti-depressant therapy (Kumar 2007, Kumar 2008) and another used reoperation as the control group (North 2005).

Across these studies the following outcome measures were assessed; pain intensity and pain relief using a 10 point visual analogue scale (Kumar 2007, Kumar 2008), treatment success defined as at least 50% pain relief and patient satisfaction with treatment obtained by direct inquiry on the willingness to go through the procedure again for pain relief if needed (North 2005), health related quality of life using the Nottingham Health Profile and EQ-5D (Kemler 2008) and SF-36 (Kumar 2008), patients' satisfaction of the treatment and perceived effect using Global Perceived Effect score (Kemler 2000, Kemler 2004, Kemler 2008) or by direct inquiry (i.e. "Are you satisfied with the pain relief provided by your treatment?") (Kumar 2007, Kumar 2008). Kumar (2007) assessed disability status using Oswestry Disability Index. All RCTs reported adverse events and complications as reported in pages 18-19 of this report.

Conventional SCS versus Burst SCS

One cross over RCT compared burst SCS with standard SCS in patients with limb and back pain (the majority of which had FBSS) (De Ridder 2013). Fifteen patients underwent implantation of an electrode through laminectomy. Following a standard (tonic) programming

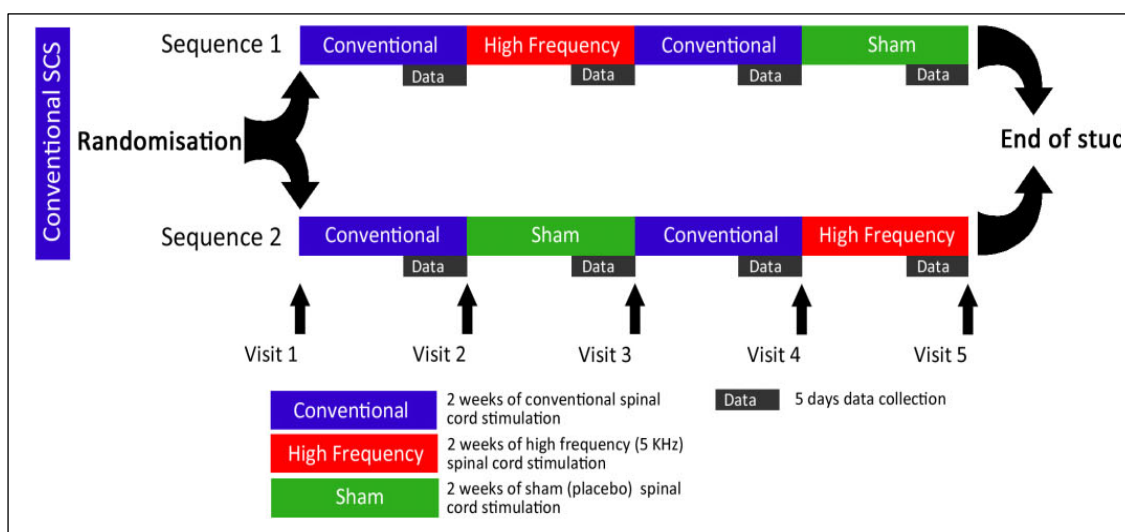
session, patients were randomly programmed to receive one week of tonic, one week of burst (5 spikes with 1ms pulse width and 1ms spike interval delivered at 500 times per sec (=500Hz spike mode), bursts of 5 spikes were applied 40 times per sec (=40 Hz burst mode)) and one week of placebo stimulation. This study assessed pain (using Visual Analogue Scale score) and attention to pain using pain vigilance and awareness questionnaire after 28 days.

High Frequency SCS versus Sham

One study compared high frequency SCS to sham (Perruchoud 2013). The patients included in this study had achieved stable pain relief with SCS for persistent low back pain radiating from both legs (aetiology not reported). This study was a cross over RCT, where patients were randomised to either high frequency SCS or sham (no stimulation). Patients randomized to receive high frequency SCS were programmed by the non-blinded investigator following four steps: 1) using no more than three active contacts, paresthesia covering as much as possible the area of pain is elicited with conventional stimulation; 2) while keeping the current amplitude below sensory threshold, the stimulation frequency is increased to 5000 Hz; 3) the current amplitude is progressively increased to the sensory threshold; and 4) the current amplitude is decreased again below threshold amplitude until the patient is unable to feel paresthesias regardless of the position. Pulse width is adjusted to 60 µsec under high frequency SCS.

At baseline (visit 1) all patients were started on conventional SCS for 2 weeks (see illustration below). After this period (visit 2) patients were then randomised to receive sham or high frequency SCS for another 2 weeks. At visit 3 there was a 2 week wash out period where all patients received conventional SCS. At visit 4 the patients were crossed over to receive either sham or high frequency SCS for 2 weeks. After this 2 week period patients were assessed for the final time (visit 5). At each visit data was collected and the results for high frequency SCS and sham were compared for the following outcomes; patient's global impression of change (PGIC), pain (visual analogue scale score), quality of life (EQ-5D), side effects of the procedure, overall medication use and the quality of the blinding (i.e. patients were asked to guess which group they were in at visits 3 and 5).

Illustration: Study design of Perruchoud (2013)



Risk of Bias

Conventional SCS vs Control

All three trials used computer generated random sequence to randomise patients to the SCS and to the control group. Two studies concealed the sequence from the investigators (Kumar 2007, North 2005), while (Kemler 2000) used a research assistant to assign participants to respective groups, concealed from the investigators. In order to minimise the risk of bias two studies used blinded outcome assessors that were not involved in the trial (Kemler 2000, North 2005). In another study, blinded trial investigators assessed the outcomes (Kumar 2007). Furthermore all trials assessed patient relevant outcomes and no selective outcome reporting was observed. (See Table 1.2.1)

Two trials (North 2005 and Kumar 2007) were sponsored by Medtronic, a manufacturer of SCS implants and another (Kemler 2000) was supported by a grant from the Dutch Health Insurance Council.

Conventional SCS versus Burst SCS

The intervention schedule used by De Ridder (2013) was not explicitly reported and the risk of bias assessment could not be completed. The patients were randomly programmed to receive tonic, burst and placebo stimulation modes for one week each, but the method of random sequence generation and allocation was not reported. The study did not report on any attempts to check whether the patients were able to guess the allocation (i.e. treatment they received). However the outcome assessor was blinded. It does not explicitly mention whether there had been an adequate washout period between interventions. (See Table 1.2.2)

Furthermore the first author of this trial (Dirk De Ridder) has obtained a patent for burst stimulation, which is declared in the study publication.

High Frequency SCS versus Sham

The single study that investigated high frequency SCS (Perruchoud 2013) used techniques to blind patients on allocation and used blinded outcome assessors. The patients were blinded by using a current leak, so the time taken to recharge the battery of the device was similar for the sham group and the high frequency SCS group. In addition the patients were unable to guess into which group they were allocated (See table 1.2.3).

Perruchoud (2013) was funded by Medtronic, a manufacturer of SCS implants, which may be a source of bias. In addition, the authors used 5kHz as the frequency for the intervention (high frequency), which is below the frequency used in current clinical practice (10kHz). The trial authors acknowledged the issue of using subthreshold level therapy as a study limitation and that delivering a potentially effective therapy at a suboptimal level could render the therapy ineffective.

Results

Conventional SCS vs Control

Pain

All three studies reported improvements in pain in the short term (12 weeks) compared to controls. North (2005) reported that 47% of patients receiving SCS had a $\geq 50\%$ reduction in pain and patient satisfaction in treatment compared to 12% in the reoperation group at six months ($p < 0.01$). After six months, Kemler (2000) reported mean pain decline of 2.4 (± 2.5) in visual analogue scale (VAS) for SCS patients compared to mean 0.2 (± 1.6) increase in the physical therapy patients ($p < 0.001$). At 6 months, Kumar (2007) reported that significantly more patients in the SCS group had $\geq 50\%$ reduction in leg pain (48% in SCS vs. 9% in Controls; OR: 9.23, 99% CI 1.99-42.84; $p < 0.001$).

The long term outcome results are uncertain in Kumar (2008) and in North (2005) due to patients moving from control to intervention arm during the trial period. In Kumar (2008), only 23% of patients remained in the control group by the end of 24 months compared to 92% in the SCS group. In this trial, 30 patients (62.5%) originally assigned to receive conventional medical management, ended up receiving SCS. In North (2005), 54% of the patients assigned to undergo reoperation crossed over to receive SCS and only 21% of patients originally assigned to the SCS group underwent reoperation after 2-3 years of treatment (it is not clear when they exactly crossed over). At 24 months Kemler (2004) reported a significant pain reduction mean 2.1 (± 2.8) in the SCS group compared to 0 (± 1.5) in controls ($p = 0.001$). After 5 years there was no difference in pain between the groups (mean 1.5 \pm 2.3 pain reduction in SCS compared to 0.9 \pm 2.8 reduction in VAS in controls ($p = 0.22$)). The five year analysis was conducted after excluding patients who crossed over to receive SCS from the control group ($n = 4$) and patients who were lost to follow up ($n = 5$).

Health Related Quality of Life

Kemler (2000) assessed health related quality of life (QoL) using a number of scales; the pain component of the Nottingham Health Profile, EQ-5D, Sickness Impact Profile-68 and the Self-Rating Depression Scale. There was no difference in health related Quality of Life (QoL) at 6 months (change 6% \pm 22% in SCS compared to 3% \pm 18% in the physical therapy group, $p = 0.58$). The results remained non-significant at 5 year follow up (mean change in EQ-5D: 16 \pm 25 for SCS compared to 19 \pm 46 for controls, $p = 0.80$ and mean change in Self-rating Depression scale: 0 \pm 9 for SCS compared to -3 \pm 11 for controls, $p = 0.47$).

Kumar (2007) used the SF-36 to assess health related QoL and reported significant improvement in the SCS group at 6 months in; physical function (38.1 \pm 23.0 vs. 21.8 \pm 16.2, $p < 0.001$), bodily function (33.0 \pm 20.9 vs. 19.5 \pm 12.9, $p < 0.001$) and general health (52.8 \pm 22.3 vs. 41.3 \pm 24.4, $p < 0.001$).

Patients' Assessment on Improvement

Kemler (2004) used the Global Perceived Effect (GPE) to measure patients' assessment/satisfaction with the intervention. The SCS group reported significant improvement at 6 months (GPE ≥ 6 ; 38.9% in SCS vs. 5.56% in controls, $p < 0.001$) and in 24

months (GPE ≥ 6 ; 43% in SCS vs. 6.0% in controls, $p < 0.001$). At 5 years, this effect was undetectable (GPE ≥ 6 ; 23.0% in SCS vs. 15% in controls, $p = 0.24$).

Kumar (2007) used a direct inquiry method to determine the patients' satisfaction with pain relief and their treatment. Significantly more patients in the SCS group were satisfied with pain relief compared to the control group (66% in SCS and 18% in controls, OR: 8.73; 99% CI 2.46-31.01, $p < 0.001$). This was also observed for treatment satisfaction (86% in SCS vs. 50% in controls; OR: 6.14, 95% CI 1.66-22.67, $p < 0.001$)).

Disability

Kumar (2007) reported less disability for the SCS group (mean 44.9 ± 18.8) compared to control group (mean 56.1 ± 17.9) after 6 months, using the Oswestry Disability Index (between group risk difference -11.2, 95% CI -21.2 to -1.3, $p < 0.001$).

Adverse Events

Spinal cord stimulation is associated with non-fatal, moderately high complication rates. Kemler (2008) reported a complication rate of 38% at 2 year follow up; 9 out of 24 SCS patients underwent reoperation for 21 complications. In five years 10 (24%) patients who were assigned to receive SCS underwent reoperation as a result of 29 complications due to the following reasons; "Pulse generators were replaced 4 times in 1 patient, 2 times in another, and once in 11 patients. Two patients underwent permanent explantation (removal), 2 patients were lost to follow-up, and 7 patients still had their first pulse generator at the final follow-up".

North (2005) reported that one SCS patient developed an infection at the receiver site after 6 months. The system was replaced without further complication. Three SCS patients (9% of permanent implants) underwent hardware revisions because of technical problems (electrode migration or malposition).

Kumar (2007) reported that 19 of 42 patients who underwent SCS (45%) experienced a total of 34 SCS related complications. The most frequent were electrode migration (14%), loss of therapeutic effect due to loss of or unpleasant paraesthesia (12%), pain at the implanted pulse generator incision site (12%), and infection or wound breakdown (10%).

Contraindications

Contraindications were not reported in any of the studies.

Effect of Training

Impact of training was not reported in the studies.

Conventional SCS versus Burst SCS

Pain

This crossover study (De Ridder 2013) included 15 patients. Burst stimulation reported the most mean improvement in general pain (55%), compared to tonic stimulation (30.9%) and placebo (10.9%; F value 7.44, $p<0.01$). Burst stimulation also reported the greatest mean improvement in limb pain (52.7% for SCS, 51.5% for tonic and 11.7% for placebo; F value 4.66, $p<0.05$) and back pain (51.3% for SCS, 30.3% for tonic and 18.9% for placebo; F value 6.20, $p<0.01$).

Adverse Events

Adverse events were not reported.

Contraindications

Contraindications were not reported.

Effect of Training

Impact of training was not reported.

High Frequency SCS versus Sham

Patient's Global Impression of Change (PGIC)

The overall proportion of patients responding (defined as reporting at least minimal improvement in PGIC scale compared to last visit) to high frequency (HF) SCS compared to sham was not significant (42.4% compared to 30.3% in sham). The difference in mean benefit between high frequency SCS compared to sham was 11.2% (95% CI -10.1%-32.5%, $p=0.30$). The mean benefit was calculated using the average of sequence 1 and sequence 2 (see below).

In sequence 1 (HF stimulation first), 9/17 (52.9%) HF stimulation patients reported at least minimal improvement compared to 2/17 (11.7%) to sham.

In sequence 2 (sham first), 5/16 (31.25%) HF stimulation patients reported at least minimal improvement compared to 8/16 (50.0%) to sham.

After period 1, similar proportion of patients responded to both treatments; 9/17 patients (52.9%) in HF stimulation compared to 8/16 patients (50.0%) in sham.

After period 2, 5/16 patients (31.3%) reported benefit in HF stimulation group compared to 2/17 patients (11.8%) in sham ($p=0.61$).

There was a statistically significant period effect; 17/33 of patients (51.5%) improved after period 1 but only 7/33 of patients (21.2%) improved at the end of period 2 irrespective of the treatment received (mean difference in proportions = 30.3%; 9-51%; $p=0.006$).

Pain

After adjusting for baseline pain there was no significant difference between high frequency SCS and sham, the difference (SCS minus sham) in visual analogue scale scores for pain was -0.09 (95% CI -0.68-0.86, $p=0.82$).

For Pain, there was a significant “period effect”: irrespective of treatment received, the mean VAS at visit 3 was 3.99 vs. 4.63 at visit 5; the difference (HF - sham) = -0.64 (95% CI, -1.41 to -0.14; $p = 0.11$).

Health Related Quality of Life

Quality of life was not significantly different between SCS and sham. Perruchoud (2013) used the EQ-5D to assess QoL and, adjusted for baseline values to compare high frequency SCS and sham, the difference (SCS minus sham) in EQ-5D scores for QoL was 0.017 (95% CI -0.101-0.135, $p=0.78$).

Adverse Events

One patient developed malaise and withdrew from the trial.

Contraindications

Contraindications were not reported.

Effect of Training

Impact of training was not reported.

Discussion

Conventional SCS vs Control

There is moderate evidence from one small randomized controlled trial (Kemler 2000) that SCS is superior to physical therapy in patients with complex regional pain syndrome (CPRS) type I and low level evidence from two small RCTs (Kumar 2007 and North 2005) that SCS is superior to conventional medical management or reoperation in patients with failed back surgery syndrome (FBSS) with respect to patient reported pain levels and perceived effect of treatment / patient satisfaction. In the only RCT that measured long term outcomes, the benefit of SCS decreased over time and was not significantly different compared to controls after 5 years (Kemler 2008).

The effect on quality of life outcomes is less clear, with one low quality RCT reporting substantial benefit of SCS compared with conventional medical management (CMM) at 6 months (Kumar 2007). A moderate quality RCT (Kemler 2000) found quality of life outcomes to be similar between SCS combined with physical therapy and physical therapy alone at 2 years. Similarly, function as measured by the Oswestry Disability Index score was better in the SCS group at 6 months versus CMM in one study (Kumar 2007). The ability to perform daily activities after 3 years was not different in a second (North 2005).

The issue of patients being un-blinded to treatment was a major limitation of these studies. In all three trials the comparator was an alternative treatment, not Sham SCS. Under these circumstances patients would have been aware as to which intervention they were allocated. Given this, there is the potential for a placebo effect to be attributed to the results. Particularly given that in the context of analgesic studies, it is quite plausible that patients and subjects have some degree of desire to avoid, terminate, or reduce ongoing pain (Price 2008). This issue is compounded in North (2005) and Kemler (2000) where patients had already failed the control therapy prior to entry into the trial with studies showing that patients who believed they belonged to the real treatment group were more likely to experience larger clinical improvement than those patients who believed they belonged to the control group (Bausell 2005).

In the two studies that compared conventional SCS with conventional medical management (Kumar 2004) or reoperation in FBSS patients (North 2005), there had been considerable cross over after six months questioning the validity of the analysis. For example, in Kumar (2008) more than 90% in the control group (randomised to conventional medical management) crossed over to receive SCS in two years, and in North (2005), 54% of the patients in the control group (randomised to reoperation) crossed over to receive SCS. North (2005) did not use intention to treat analysis and considered crossovers as study endpoints, but Kumar (2007) used a modified intention to treat analysis (i.e. crossovers are considered failures compared to usual intention to treat analysis in which the participants remain in the originally assigned group and analysed in that group) which can make the comparison challenging. Kemler (2004) excluded patients who received special implants from the intention to treat analysis.

Due to small sample sizes, unclear risk of bias and lack of high quality RCTs, the results should be interpreted with caution and should only be generalised to the patient groups recruited in the trials, such as FBSS and CRPS type I. More high quality RCTs are required to confirm the results of these studies. A multicentre, multinational randomized controlled trial (EVIDENCE study) assessing the effectiveness to patients and the cost-effectiveness of spinal cord stimulation in patients with FBSS has been terminated before completion due to slow enrolment. The results of this study would have been useful in assessing the effectiveness of conventional SCS (North 2011, ClinicalTrials.gov Identifier: NCT01036529 (2013))

Conventional SCS versus Burst SCS

De Ridder (2013) reported statistically significant improvement of pain by burst stimulation compared to standard tonic SCS and placebo. This evidence however is limited to one small crossover trial that included predominantly patients with FBSS who did not respond to opioids and anticonvulsants. The methodology used by De Ridder (2013) was not explicitly reported; therefore we were unable to adequately assess risk of bias. There was no information on how the randomisation process was conducted but outcomes were assessed by a blinded evaluator. No baseline and outcome information on VAS for pain was available for each intervention period (i.e. burst stimulation, tonic stimulation and no stimulation) and

information pertaining to crossover points and washout periods were also not available. Given the paucity of evidence, well conducted RCTs are needed to verify this result.

High Frequency SCS versus Sham

One crossover trial (Perruchoud 2013) investigated patients who were already using permanent SCS devices (aetiologies not provided) and compared high frequency SCS to sham. There is moderate level evidence indicating no statistically significant improvement in pain and patient's global impression of change following high frequency SCS, over sham. However this may be clinically significant as more than one in ten patients may benefit from the treatment. This study used techniques to conceal allocation, blinding both patients and outcome assessors.

The study used 5kHz as the frequency for the intervention (high frequency) and this is well below the standard frequency range (10kHz) that is being used in practice.

Table 1.1. Key information from most recent primary studies for SCS

Reference	Inclusion, exclusion criteria (for P.I.C.O)	Study design	Conclusion/recommendation	Direction of effects
Hashimoto (2010) Spinal Cord Stimulation	<p>This HTA included six papers from three RCTs that investigated the efficacy and effectiveness of SCS in persistent refractory pain conditions. These three trials contained 214 patients.</p> <p>Patient/population: One RCT (3 papers) included 54 patients with CRPS type I and followed up at 6, 24 and 60 months. The other RCT (2 papers) included 100 patients with FBSS and followed up at 6 and 12 months. The other study (1 paper) also contained 60 patients with FBSS and followed up for the mean of 2.9±1.1 years.</p> <p>Intervention: Spinal Cord Stimulation (SCS)</p> <p>Control: Sham procedure, conventional medical management, reoperation</p> <p>Outcomes assessed:</p> <ul style="list-style-type: none"> Pain intensity and relief Treatment success Health related quality of life Patient satisfaction and perceived effect Medication usage Complications 	HTA	There is evidence from a few small studies of low to moderate quality to demonstrate that SCS is effective in reducing pain in patients with CRPS type I and FBSS, in the short term. It is not clear how effective the treatment is long-term.	Positive
De Ridder (2013) Burst Spinal Cord Stimulation for Limb and Back Pain	<p>Patient/population: n=15. Consists mainly of patients with FBSS</p> <p>Intervention: Two types of SCS interventions</p> <p>Intervention 1: Tonic SCS (5 Hz stimulation at an amplitude that the patient finds bearable (+/- 1.5 mA))</p> <p>Intervention 2: Burst SCS (500 Hz burst at 5 Hz stimulation)</p> <p>Control: Sham (no stimulation, patient receive a sham stimulation (the implantable pulse generator is not running))</p>	Cross over trial	The effectiveness of the intervention is unable to be determined as the authors did not report on several important methodological parameters. Furthermore the study was underpowered to observe a significant result	Unclear

	Outcomes assessed: <ol style="list-style-type: none"> 1. Pain: back, limb, general and paraesthesia (visual analogue scale score-VAS) 2. Attention to pain: (pain vigilance and awareness questionnaire-PVAQ) 			
Perruchoud (2013) Analgesic Efficacy of High-Frequency Spinal Cord Stimulation: A Randomized Double-Blind Placebo-Controlled Study	Patient/population: N=33. Consists of patients with persistent low back pain radiating in one or both legs, treated with SCS Intervention: High frequency (HF) stimulation (5000 Hz) Control: Sham (no stimulation as the stimulator was switched off) Outcomes assessed: <ol style="list-style-type: none"> 1. Evaluation of treatment effect: Patient's Global Impression of Change (PGIC) 2. Pain: Visual Analogue Scale score (VAS) 3. Quality of life: EuroQoL (EQ-5D) 	Cross over trial	Moderate evidence showing HF SCS is no better than sham stimulation. This was a well conducted randomised two period- two sequence-two intervention study with low risk of bias.	No better than sham

Table 1.2.1 GRADE evidence profile for Kemler (2000), Kemler (2004) and Kemler (2008)

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Conventional Spinal Cord Stimulation	Sham	Relative (95% CI)	Absolute	
Change in pain scores (follow up: range 6 months; assessed with: Visual Analogue Scale)											
1	randomised trials	serious ¹	not serious	not serious	not serious	none	36	18	-	MD 2.6 lower (3.7 higher to 1.49 higher)	⊕⊕⊕○ MODERATE
Change in pain scores (follow up: range 24 months; assessed with: Visual Analogue Scale)											
1	randomised trials	serious ¹	not serious	not serious	not serious	none	35	16	-	MD 2.1 lower (3.28 higher to 0.91 higher)	⊕⊕⊕○ MODERATE
Change in pain scores (follow up: range 5 years; assessed with: Visual Analogue Scale)											
1	randomised trials	serious ^{1 2}	not serious	not serious	not serious	none	32	13	-	MD 0.07 lower (2.47 higher to 1.07 higher)	⊕⊕⊕○ MODERATE
Patient Related recovery (follow up: range 6 months; assessed with: Global Perceived Effect score)											
1	randomised trials	serious ¹	not serious	not serious	not serious	none	14/36 (38.9%)	1/18 (5.6%)	OR 10.82 (1.29 to 90.60)	333 more per 1000 (from 15 more to 786 more)	⊕⊕⊕○ MODERATE

Patient Related recovery (follow up: range 24 months; assessed with: Global Perceived Effect score)											
1	randomised trials	serious ¹	not serious	not serious	not serious	none	15/35 (42.9%)	1/18 (5.6%)	OR 12.75 (1.52 to 106.75)	373 more per 1000 (from 27 more to 807 more)	⊕⊕⊕○ MODERATE
Patient Related Recovery (follow up: range 5 years; assessed with: Global Perceived Effect score)											
1	randomised trials	serious ^{1 2}	not serious	not serious	not serious	none	7/31 (22.6%)	2/13 (15.4%)	OR 1.60 (0.29 to 9.01)	72 more per 1000 (from 104 fewer to 467 more)	⊕⊕⊕○ MODERATE

MD – mean difference, RR – relative risk

1. The blinding of participants, patients and outcome assessors were not clear and perhaps not done. For certain surgical interventions it may be difficult to blind the investigators and the patients, but it is still possible to use blinded outcome assessors. In this study, this information is not explicitly documented.
2. Comparatively high number of drop-outs and cross over from physical therapy to SCS

Table 1.2.2. GRADE evidence profile for Kumar (2007) and Kumar (2008)

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Conventional Spinal Cord Stimulation	Sham	Relative (95% CI)	Absolute	
Leg Pain relief >50% (follow up: range 6 months; assessed with: Visual Analogue Scale score)											
1	randomised trials	very serious ^{1 2}	not serious	not serious	not serious	none	24/50 (48.0%)	4/44 (9.1%)	OR 9.23 (2.87 to 29.68)	389 more per 1000 (from 132 more to 657 more)	⊕⊕⊕⊕ LOW
Disability (follow up: range 6 months; assessed with: Oswestry Disability Index)											
1	randomised trials	very serious ^{1 2}	not serious	not serious	not serious	none	50	44	-	MD 11.2 lower (21.2 higher to 1.3 higher)	⊕⊕⊕⊕ LOW
Patients satisfaction of pain relief (follow up: range 6 months)											
1	randomised trials	very serious ^{1 2}	not serious ²	not serious	not serious	none	33/50 (66.0%)	8/44 (18.2%)	OR 8.74 (3.33 to 22.91)	478 more per 1000 (from 243 more to 654 more)	⊕⊕⊕⊕ LOW

MD – mean difference, RR – relative risk

1. None of the patients, investigators and outcome assessors were blind to the intervention
2. Large number of controls crossed over to receive SCS after 6 months preventing meaningful intention to treat analysis

Table 1.2.3. GRADE evidence profile for North (2005)

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Spinal Cord Stimulation	Sham	Relative (95% CI)	Absolute	
Success of treatment (At least 50% pain relief satisfaction with treatment) (follow up: range 6 months)											
1	randomised trials	serious ^{1 2 3}	not serious	not serious	serious 4	none	9/24 (37.5%)	3/26 (11.5%)	OR 4.60 (1.07 to 19.80)	260 more per 1000 (from 7 more to 605 more)	⊕⊕⊕⊕ LOW

MD – mean difference, RR – relative risk

1. The patients who earlier had unsuccessful surgery went for the surgery again in the control group. This means they SCS is compared against an unsuccessful/harmful intervention for this group of patients
2. High drop-out rate
3. 15% patients did not participate after randomisation due to refusal by insurance
4. The definition of success and how it was measured (relevance of the method used to measure) is unclear

Table 1.2.4. GRADE evidence profile for Perruchoud (2013)

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Spinal Cord Stimulation	Sham	Relative (95% CI)	Absolute	
Responders to treatment (follow up: range 8 weeks; assessed with: Patient's Global Impression of Change scale (if reported minimal improvement at least))											
1	randomised trials	very serious ^{1 2}	not serious	not serious	not serious	none	14/33 (42.4%)	10/33 (30.3%)	OR 1.69 (0.61 to 4.67)	121 more per 1000 (from 93 fewer to 367 more)	⊕⊕⊕⊕ LOW
Pain (follow up: range 8 weeks; assessed with: Visual Analogue Scale score)											
1	randomised trials	very serious ^{1 2}	not serious	not serious	not serious	none			-	MD 0.09 lower (0.68 higher to 0.86 higher)	⊕⊕⊕⊕ LOW
Health Status (follow up: range 8 weeks; assessed with: EQ-5D)											
1	randomised trials	very serious ^{1 2}	not serious	not serious	not serious	none			-	MD 0.017 higher (0.101 higher to 0.135 higher)	⊕⊕⊕⊕ LOW

MD – mean difference, RR – relative risk

1. Adequacy of wash-out period is unclear
2. The frequency used for the intervention (high frequency) was 5kHz which is below the standard frequency of 10kHz that is used in practice. This sub-optimal frequency could have affected the outcome (i.e. pain relief).

2. PERIPHERAL NERVE STIMULATION (PNS)

Evidence Identified

The most comprehensive, up-to-date source of synthesised evidence was an EBG (Cruccu 2007) (Table 2.1).

Study Characteristics

Cruccu (2007) aimed to address the effectiveness of PNS for neuropathic pain. Although the authors did not specify any inclusion or exclusion criteria regarding specific types of neuropathic pain, their rigorous search strategy incorporated a comprehensive list of chronic pain conditions. Findings were limited to pain outcomes and there was no information provided regarding other important outcomes such as function, quality of life, return to work, or medication use.

Risk of bias

As the only evidence contained in the EBG is case series studies, the risk of bias of the evidence is very high.

Results

Effectiveness

Cruccu (2007) provided a summary of the evidence identified for PNS. Conditions listed for the six included studies were CRPS II, peripheral neuropathy, post-traumatic pain, radiculopathy, amputation and two studies involved various pain conditions (details of specific conditions not provided). Based on low level evidence (uncontrolled studies, case series) involving 202 participants, Cruccu (2007) reported an average success rate of 60% for PNS where 'responders' to treatment are those patients reporting pain relief greater than or equal to 50%. The guideline does not provide details of how pain was assessed in each of the primary studies or how the success rate from individual studies was determined.

Adverse Events

Risks were not specifically assessed by the studies, although reoperation had to be performed in some patients (actual numbers not reported).

Contraindications

Contraindications for PNS was not reported in the studies or discussed in the EBG.

Effect of Training

Impact of training was not reported in the studies or discussed in the EBG.

Discussion

Due to a lack of high quality, controlled primary studies, there is insufficient evidence to determine the effectiveness of PNS for the treatment of persistent pain. Further details of the study's characteristics can be found in the Technical Report, Table A 4.2.1.

The quality of the EBG in terms of the scope, purpose and rigorous methodology was moderate. Findings of the EBG were limited to pain outcomes; hence questions regarding function, quality of life and contraindicated use of PNS could not be answered.

As the included studies did not have adequate controls (low level evidence), we were unable to determine the effectiveness of PNS in the treatment of persistent pain.

Table 2.1. Key information from recent evidence based guideline for PNS

Reference	Inclusion, exclusion criteria (for P.I.C.O)	Study design	Conclusion/recommendation	Direction of effects
Cruccu (2007) EFNS guidelines on neurostimulation therapy for neuropathic pain.	Patient/population: n=202, six case series Conditions indicated for use: Pharmaco-resistant patients with CRPS II, peripheral neuropathy, post-traumatic pain, radiculopathy, amputation, or other pain conditions (not specified in the guideline). Intervention: Peripheral nerve stimulation Control: N/A (uncontrolled studies, case series) Outcomes assessed: Pain intensity and relief	EBG	None of the identified studies had an adequate control group, therefore unable to draw any conclusions for PNS recommendations. Of the few studies identified for PNS, most were old (1975-1999), suggesting this intervention is not increasing in popularity.	Insufficient evidence to determine

3. OCCIPITAL NERVE STIMULATION (ONS)

Evidence Identified

The most comprehensive, up-to-date sources of evidence identified are three RCTs (Silberstein 2012, Lipton 2009, Saper 2011) and one crossover RCT (Serra 2012). (Table 3.1)

Study Characteristics

Silberstein (2012) recruited a total of 157 patients with chronic migraine. Patients were first stratified by use of alternative treatments (such as acupuncture, herbal medications and massage) or non-alternative therapies and then randomised into either the Active or Control group in a 2:1 ratio (Active group n=105, Control group n=52). Patients in the Active group were programmed for appropriate stimulation and patients in the Control group were given a sham programmer that did not communicate with the implantable pulse generator. For the permanent implant, the patients had leads placed on either side of the midline caudally along the nerve or, more commonly, perpendicular to the course of the occipital nerves at the level of the craniocervical junction. Leads were placed either unilaterally or bilaterally depending on the pain distribution. No information regarding the pulse amplitude, rate or width were reported. The primary outcome for this study was mean daily Visual Analog Scale (VAS) measurements of average pain intensity recorded in a patient diary. A responder was defined as a patient with a reduction from baseline of 50% or greater together with no increase in average headache duration. The secondary outcomes included reduction in number of headache days, MIDS questionnaire and patient-reported headache pain relief. All variables were measured at 4 and 12 weeks post implant. Further details of the study's characteristics can be found in the Technical Report, Table A4.3.2.

In Serra (2012), 30 patients were recruited from the Pain Unit and the Headache Centre at Sacro Cuore Don Calabria Hospital in Negrar, Italy. They were randomised (1:1) into two arms – A (stimulation On) or B (stimulation Off). Parameter settings were variable in order to improve the effectiveness of stimulation in accordance with patients' specific needs. A bipolar configuration (one anode and one cathode) was usually used. The stimulation frequency was 50 Hz, the pulse width ranged between 330 µsec and 450 µsec while the stimulation amplitude could be modified to a maximum value of 10.5V. Patients randomised to Arm B (stimulation Off) could switch stimulation on if their headache attacks increased in severity or frequency by 30% or more. After 4 weeks, patients crossed over, except for Arm B patients who had already switched to stimulation on. Follow-up examinations were scheduled one, three, six and 12 months after implantation. Further details of the study's characteristics can be found in the Technical Report, Table A4.3.1.

The primary outcomes measured by this study included severity of attacks, assessed using a numeric rating scale (NRS-11). Secondary outcomes included headache-related disability and quality of life, assessed by Migraine Disability Assessment (MIDAS) and SF-36 respectively.

Saper (2010) is the same research team that conducted the study by Silberstein (2012). This was a feasibility study which recruited 75 patients with medically intractable chronic migraine (CM). In this study patients were randomised to three treatment arms 1) Adjustable stimulation group (AS) where patients were instructed to maintain the stimulator in the “on” position and to adjust the device to minimize pain (n=33); 2) ONS Pre-set group (PS) where the device was set at a stimulation setting for one minute each day during the blinded phase of the study (n=16); 3) Medical management group (MM), which underwent usual care (n=17); and 4) Ancillary group which met all entry criteria except response to occipital nerve block (ONB), which was an entry criterion for the study. Patients in the ancillary group were implanted and allowed to adjust the stimulation and were treated identically to the AS group. The product specifications of stimulation parameters for both models of implantable pulse generator were the same - pulse amplitude: 0–10.5V, pulse rate: 3–130 Hz and pulse width: 60–450 µsec. The primary outcomes of this study were: reduction in headache days per month; proportion of patients who achieved ≥ 50% reduction in headache days per month (responder rate); a 3-point or greater reduction in average overall pain intensity; disability and quality of life; and risks/complications. All variables were measured at 12 weeks.

Lipton (2009) was a multicentre study of 132 participants with refractory migraine who were randomised to receive bilateral active occipital nerve stimulation (250 µsec pulses, 60 Hz, 0–12.7 mA) for 12 weeks (n=63) or sham stimulation (10 µsec pulses, 2 Hz, < 1 mA, 1 sec on / 90 min off duty cycle) for 12 weeks (n=62). This was followed by an open phase where all patients received stimulation for an additional 10 months. All patients were assessed for pain relief (change from baseline in migraine days/month) and side effects/complications at 12 weeks for the trial phase and 12 months for the open phase (ClinicalTrials.gov Identifier: NCT00286078 2012).

Risk of Bias

Silberstein (2012) and Saper (2010) randomised patients using a computerized software program and allocated patients using sealed envelopes. Both investigators and patients were blinded to treatment and all patients were analysed using intention to treat analysis. Dropout rates were low in both studies with four patients from the stimulation group in Silberstein (2012) and six patients from Saper (2010) withdrawing (four from the AS group, one from the PS group and one from the Ancillary group). In Saper (2010) the treatment groups were similar with regards to demographic and baseline headache characteristics while in Silberstein (2012) patient groups were not similar with the mean number of headache days being significantly greater in the active group at baseline.

Lipton (2009) was a conference abstract with scant details regarding the research methods, thus a risk of bias assessment could not be performed.

Serra (2012) had several limitations in study design such as small number of patients (n=30) and the absence of a control group in the open phase. In addition, several methodological parameters such as method of randomisation, concealment of allocation and blinding of

patients and investigators was not reported. Thus, the quality of this was graded low as the overall risk of bias could not be assessed. See Table 3.2.1 for GRADE evidence profile.

Results

Effectiveness

Silberstein (2012), reported no significant difference in the percentage of responders ($\geq 50\%$ pain reduction from baseline), 18 patients in the Active group compared with seven in the Control group (17.1% vs 13.5%, 95% lower confidence bound (LCB) of -0.06; $p=0.55$). However, significantly more patients achieved $\geq 30\%$ reduction in pain in the ONS group compared to sham (95% LCB of 0.06; $p = 0.02$). This reduction is also a recognised clinically meaningful end point (Dworkin 2008, Silberstein 2008). There were also significant differences in the reduction of number of headache days (95% CI - 5.4 to -0.8; $p. 0.008$), migraine-related disability assessment (MIDAS) (95% CI -65.3 to -22.8; $p. 0.001$) and patient reported pain relief ($p=0.001$). (Table 3.2.2)

The results by Saper (2010) are in contrast to Silberstein (2012) which showed no significant improvement in the stimulation group compared to controls for the majority of outcome measures: changes in headache days, pain and duration, including reduction in headache days, overall pain intensity, peak pain intensity, headache free days, days with prolonged and severe headache and average headache duration. Because the number of subjects in the ancillary group was small, reliable comparisons could not be made.

Lipton (2009) reported no significant difference between stimulation and controls with regards to reduction in migraine days/month, (-5.5 vs.-3.9, $p = 0.29$). There was a trend towards a greater difference between treatment arms for those not overusing medication (-5.9 vs.-2.6) in comparison with the medication overuse subgroup (-5.0 vs.-4.8), although this was not significant.

In Serra (2012), ONS was effective compared to sham. The number of days with headache attacks was lower for the 'stimulation On' arm compared to 'stimulation OFF' (median 2.1 days, range: 1.2 – 3.3 vs 6.3 days, range: 3.6 – 7, $p<0.001$). This was also the observed for proportion of attacks per week (median 0.3, range: 0.2 - 0.5 stimulation On vs median 0.9, range: 0.5 – 1 stimulation Off, $p <0.001$) and severity of pain (median 5, range: 5 - 6 vs median 7.5, range: 7 - 8, $p<0.001$)

Data from the one-year follow-up open phase (where all patients received ONS) showed significant improvement in Migraine Disability Assessment (MIDAS) score when compared to baseline at each time point. Quality of life was significantly improved ($p<0.005$) and triptans and nonsteroidal anti-inflammatory drug also significantly decreased ($p< 0.001$).

Adverse Events

The most common adverse events was lead migration, which accounted for 4%-24% of all adverse events (Serra 2012, Silberstein 2012, Saper 2011)

Another common biological event was persistent pain, and/or numbness at IPG/lead site which accounted for 21.5% of all events (Silberstein 2012).

In Saper (2011) common hardware events was implant site infection 14%, increased migraine (9% of the AS group, 41% of the PS group and 24% of the MM). Adverse events related to medications were similar across treatment groups and ranged from 6% to 18%.

There was no evidence of adverse events leading to long term complications or potential nerve damage.

Lipton 2010 reported two-year aggregate safety data revealing infection, non-target area sensory symptoms, and implant site pain as the most-frequent device related adverse events.

Contraindications

Contraindications for ONS were not reported in the studies.

Effect of Training

The effect of training was not reported in the studies.

Discussion

There is moderate level evidence supporting the short term effectiveness (12 weeks) of ONS for migraine (Silberstein 2012), although there are some concerns regarding complications such as lead migration, site infection and increased migraine pain, and/or numbness at IPG/lead site. The main benefits were 30% reduction in pain scores and improved function (MIDAS).

This review identified three different RCT's from the same research group which were conflicted. The first Lipton (2009) was a multicentre RCT whose results have only been published as a poster abstract. The second Saper (2011) was a feasibility study and the third Silberstein (2012) was an effectiveness trial. Both Lipton (2009) and Saper (2011) found no significant difference between groups for reduction in migraine. While Silberstein (2012) observed significantly better pain outcomes for ONS, these differences could be explained in part by the fact that Saper (2011) was not specifically powered to observe a clinically significant difference, given that it was a feasibility study. Furthermore the study did not measure the same outcomes as Silberstein (2012) e.g. $\geq 30\%$ reduction in pain and MIDAS. With regards to Lipton (2009) only preliminary results and minimal study methods have been published so it is not possible to evaluate the risk of bias in this study. The completion date for this study is January 2015 (ClinicalTrials.gov Identifier: NCT00286078 2012), therefore there may be more evidence available in the near future to compare with the completed trials.

According to the results obtained by Serra (2012), ONS appeared to be an effective treatment for CM patients. However, this study had a relatively small number of patients (n=30), absence of a control group and insufficient information to assess the overall risk of bias.

Table 3.1. Key information from recent primary studies for ONS

Reference	Inclusion, exclusion criteria (for P.I.C.O)	Study design	Conclusion/recommendation	Direction of effects
Silberstein 2012 Safety and efficacy of peripheral nerve stimulation of the occipital nerves for the management of chronic migraine: Results from a randomized, multicenter, double-blinded, controlled study	Patient/population: n=157 Conditions indicated for use: Chronic migraine Intervention: Peripheral nerve stimulation (PNS) (parameters not reported) of the occipital nerves with a neurostimulation device, an implantable pulse generator (IPG) Control: Sham programmer that did not communicate with the IPG Outcomes assessed: The primary outcome was mean daily VAS measurements of average pain intensity recorded in a patient diary. Secondary outcomes included reduction in number of headache days (duration ≥4 hours with peak intensity reported as moderate or severe), MIDAS questionnaire, patient-reported headache pain relief (categorical and percentage) and adverse events.	RCT	There is moderate level evidence to support the use of ONS This RCT was well conducted and considered to have a low risk of bias (see Appendix 5 of the Technical Report for quality appraisal)	Positive
Serra 2012 Occipital nerve stimulation for chronic migraine: a randomized trial	Patient/population: n=30 Conditions indicated for use: Chronic migraine Intervention: Occipital nerves stimulation with internal neurostimulator (INS) (Stimulation On for 4 weeks) (frequency 50 Hz, pulse width ranged between 330 µsec and 450 µsec, stimulation amplitude could be modified to a maximum value of 10.5V) Control: INS Stimulation Off for 4 weeks, except when headache attacks increased in severity or frequency by 30% or more. Outcomes assessed: Migraine Disability Assessment (MIDAS) and SF-36 (19) questionnaires to assess headache-related disability and quality of life. Headache intensity was measured by means of the Numeric Rating Scale (NRS-11)	Cross over RCT	There is weak evidence to support the use of ONS The authors did not report on several methodological parameters (see Technical report, Table A5.3), hence unable to assess the quality of the study or the overall risk of bias.	Positive
Lipton (2009) PRISM study: occipital nerve stimulation for treatment of refractory migraine	Patient/population: n=132 (n=63 active stimulation, n=62 sham stimulation) Conditions indicated for use: Patients with treatment-refractory migraine Intervention: Bilateral active occipital nerve stimulation (250 µsec	RCT	“Active ONS did not produce statistically significant benefits in relation to sham stimulation on the primary endpoint. Heterogeneity in treatment response suggests that there may be a treatment responsive subgroup. Future studies should endeavour to identify and randomize patients likely to respond to	No better than sham

	<p>pulses, 60 Hz, 0–12.7 mA) for 12 weeks</p> <p>Comparator: Sham stimulation (10 mcirosec pulses, 2 Hz, < 1 mA, 1 sec on / 90 min off duty cycle) for 12 weeks, then conversion to active stimulation for another 10 months</p> <p>Outcomes assessed: Pain relief (change from baseline in migraine days/month), side effects/complications</p>		<p>stimulation, based in part on the absence of medication overuse and a favourable response to a trial of percutaneous treatment.” (pg 1)</p>	
<p>Saper (2010)</p> <p>Occipital nerve stimulation for the treatment of intractable chronic migraine: ONSTIM feasibility study.</p>	<p>Patient/population: n=75 (see Table A5.2 in the technical report for more information)</p> <p>Conditions indicated for use: Patients with medically intractable chronic migraine (CM)</p> <p>Intervention: ONS – Adjustable stimulation (AS) (pulse amplitude: 0–10.5V, ,pulse rate: 3–130 Hz, pulse width: 60–450 µsec) group was instructed to maintain the stimulator in the “on” position and to adjust the device to minimize pain</p> <p>Comparator: Preset stimulation group and medically managed control group</p> <p>Outcomes assessed:</p> <ul style="list-style-type: none"> • Reduction in headache days per months; • proportion of patients who achieved ≥ 50% reduction in headache days permonth (responder rate); • a 3-point or greater reduction in average overall pain intensity; • disability and QoL; • risks/complications 	RCT		No better than sham

Table 3.2.1 GRADE evidence profile for Serra (2012)

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Occipital nerve stimulation	Sham	Relative (95% CI)	Absolute	
Headache attacks (On-Off group) (follow-up 4 weeks; measured with: No. of days/week; Better indicated by lower values)											
1	randomised trials	very serious ^{1,2}	no serious inconsistency	no serious indirectness	serious ³	none	15	15	-	median 2.1 (range of 1.2 to 3.3)	⊕000 VERY LOW
Headache attacks (Off-On group) (follow-up 4 weeks; measured with: No. of days/week; Better indicated by lower values)											
1	randomised trials	very serious ^{1,2}	no serious inconsistency	no serious indirectness	serious ³	none	15	15	-	median 2.3 (range of 1.5 to 2.8)	⊕000 VERY LOW

¹ Several methodological parameters such as how was randomisation carried out, whether the allocation was concealed and whether the patients and investigators were blinded was not reported. Thus, the overall risk of bias could not be assessed.

² The patients were not blinded - they were allowed to switch the stimulation to On if they experienced 30% worsening in number and/or severity of headaches. This could potentially lead to high risk of performance bias.

³ Small sample size (n=30).

Table 3.2.2 GRADE evidence profile for Silberstein (2012)

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Occipital nerve stimulation	Sham	Relative (95% CI)	Absolute	
Visual analog scale (50% reduction in pain) (follow-up 12 weeks; assessed with: 0-10 point scale)											
1	randomised trials	no serious risk of bias	no serious inconsistency	serious ¹	serious ²	none	18/105 (17.1%)	7/52 (13.5%)	OR 1.33 (0.52 to 3.42)	37 more per 1000 (from 60 fewer to 213 more)	⊕⊕○○ LOW
Visual analog scale (30% reduction in pain) (follow-up 12 weeks; assessed with: 0-10 point scale)*											
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious ²	none	37/105 (35.2%)	9/52 (17.3%)	OR 2.6 (1.14 to 5.92)	179 more per 1000 (from 20 more to 380 more)	⊕⊕⊕○ MODERATE
Migraine disability assessment score (follow-up 12 weeks; Better indicated by lower values)											
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious ²	none	105	52	-	mean 64.6 lower (65.3 to 22.8 lower)	⊕⊕⊕○ MODERATE
Reduction in number of headache days (follow-up 12 weeks; Better indicated by lower values)											
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious ²	none	105	52	-	mean 6.1 lower (5.4 to 0.8 lower)	⊕⊕⊕○ MODERATE

¹ The author stated that though 50% reduction in pain was the acceptable standard at the point of designing the study, subsequent recommendations established a 30% reduction in pain as clinically meaningful. Thus, 50% reduction may not be as useful as a direct measurement anymore.

² Data from 1 relatively small study (n=157) only.

*Values estimated from figure 3 in (Silberstein 2012) using Web Plot Digitizer

4. DEEP BRAIN STIMULATION (DBS)

Evidence Identified

The most comprehensive, up-to-date source of evidence for DBS in persistent non-cancer pain was a crossover RCT (Fontaine 2010) (Table 4.1).

Study Characteristics

This was a prospective, crossover, double-blind, study. Eleven patients with severe refractory chronic cluster headache (CCH) were randomised to receive active or sham DBS stimulation over a 1-month period, followed by a 1-year open phase. Stimulation frequency and pulse duration were, respectively, 185 Hz and 60 μ sec. Voltage was individually adjusted according to side effects investigated by increasing voltage: 3 V by default or 80% of the threshold producing side effects. These stimulation parameters were kept constant during all along the randomised phase, but could be changed during the open phase. The primary outcome was frequency of weekly attacks and secondary outcomes were pain intensity, frequency of sumatriptan injections, emotional impact (Hospital Anxiety and Depression scale) and quality of life (SF12). Further details of the study's characteristics can be found in the Technical Report, Table A4.6.

Risk of Bias

This study was well designed with regards to a number of parameters including randomisation, blinding and intention to treat analysis. The study used a central randomisation procedure. Concealment of allocation was not reported. Blinding was adequately performed with neither the patients nor investigators able to identify their period allocation at the end of each cross over phase. All patients were accounted for in the analysis and there were no dropouts. However, there were a number of other limitations with regards to study design including: imprecision of the estimate used to calculate sample size; delay between stimulation onset and therapeutic effect and suboptimal stimulation parameters.

Results

Effectiveness

There was no significant difference in frequency of headache attacks between the DBS and sham periods. Furthermore there was no significant carry-over effect ($P = 0.855$) indicating that the effects of the first treatment period did not persist after the wash out. There was also no significant difference in patient satisfaction (0.853), emotional impact for anxiety (0.927) and depression (0.154), and quality of life physical scores (0.197) and mental scores (0.197) in both groups (On-Off and Off-On). In the open phase, only the outcome of anxiety significantly improved from baseline, all other outcomes remained non-significant (for more information refer to the Technical Report, Appendix 5).

Contraindications

Contraindications were not evaluated in this study

Adverse Events

Adverse events related to surgery included infection and neck pain. Adverse events related to test stimulation included complex oculomotor disturbances and loss of consciousness. Adverse events during the randomised phase of the study included mild hunger increases and decreases and mild libido decreases.

Impact of Training

Impact of training was not evaluated in the trial.

Discussion/ Conclusion

Based on low level evidence, DBS is not effective for refractory cluster headaches. The small sample size may have impacted on the precision of the effect as the sample size calculation was limited by the accuracy of the estimate for headache frequency. The estimated delay between stimulation onset and therapeutic effect of 1 month might have been too short to observe significant improvements; with evidence published after this study (Leone 2006) indicating a mean delay of 42 days was optimal. Finally, stimulation parameters were set by default using estimates from previous studies, instead of customising the parameters for each patient. This uncertainty was further compounded in the open phase of the study which did not show significant improvements from baseline in cluster headache attacks or quality of life, despite a longer therapeutic window (10 months) and optimisation of stimulation parameters (Table 4.2).

Table 4.1. Key information from most recent primary study for DBS

Reference	Inclusion, exclusion criteria (for P.I.C.O)	Study design	Conclusion/recommendation	Direction of effects
Fontaine (2010) Safety and efficacy of deep brain stimulation in refractory cluster headache: a randomized placebo-controlled double-blind trial followed by a 1-year open extension	Patient/population: n=11 Conditions indicated for use: Patients with severe refractory chronic cluster headache (CCH) Intervention: Deep Brain Stimulation ('on' for 1 month) at 185Hz and pulse duration of 60µsec. Control: Sham stimulation ('off' for 1 month) Outcomes assessed: <ul style="list-style-type: none"> • weekly attacks frequency (primary) • pain intensity (Likert scale) • sumatriptan injections, oxygen use (yes or no) • anxiety and depression levels (Hospital Anxiety Depression scale), quality of life (SF-12 scale), patient's satisfaction (Patient's Global Impression of Change) • blood pressure, heart rate, weight and body temperature • electrolyte balance and hormonal functions, and changes in thirst, appetite, libido, sleepwalking cycle and behaviour (AE) 	Crossover Randomised Controlled Trial	The results of this study are uncertain. The study had several limitations; small sample size, short delay between stimulation onset and therapeutic effect, and the stimulation parameters were set by default, hence non-optimal parameters may have been experienced by some patients.	No better than sham

Table 4.2 GRADE evidence profile for Fontaine (2010)

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Deep Brain Stimulation	Sham	Relative (95% CI)	Absolute	
Attacks/week (On-Off group) (follow-up 4 weeks; Better indicated by lower values)											
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious ^{1,2}	none	5	6	-	MD 0.2 higher (24 lower to 23.6 higher)	⊕⊕⊕⊕ LOW
Attacks/week (Off-On group) (follow-up 4 weeks; Better indicated by lower values)											
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious ^{1,2}	none	6	5	-	MD 2.7 lower (25.7 lower to 20.31 higher)	⊕⊕⊕⊕ LOW

¹ Small sample size (n=11).

² Possible non-optimal stimulation parameters.

5. MOTOR CORTEX STIMULATION

Evidence Identified

The most recent, highest levels of evidence for MCS were 2 crossover RCTs (Lefaucheur 2009, Nguyen 2008) (Table 5.1).

Study Characteristics

Lefaucheur (2009) was a small ($n=13$ for the randomised phase of the study) crossover trial carried out in France. After implantation, the stimulator was turned 'off' for about 3 weeks. At 1 month postoperative, the stimulator was switched 'on' for half the patients and remained 'off' for the other half of the patients. Initial stimulation settings were as follows: amplitude 2 V, pulse width 60 μ sec, rate 40 Hz, continuous mode. These parameters were readjusted during the study, with respect to clinical efficacy observed within the week after the time of programming. At 2 months postoperative, the 'on/off' condition of the stimulator was reversed. The stimulator was then switched 'on' in all cases after 3 months and open examinations were performed at 6, 9 and 12 months post-operation. Clinical assessments included visual analog scale (VAS), brief pain inventory, McGill Pain questionnaire, sickness impact profile and medication quantification scale. Further details of the study's characteristics can be found in the Technical Report, Table A4.7. (Table 5.2)

In Nguyen (2008), 10 patients underwent MCS implantation in two centres in France and Mexico. At the end of the second postoperative month, patients were randomly assigned into two groups. In the first group, the stimulator was switched 'Off' for two weeks and then was switched 'On' for the next two weeks. The opposite sequence was applied in the second group. The parameters of stimulation were initially set as follows: amplitude 2 V, rate 40 Hz, pulse width 60 μ sec, full-time mode. These parameters have been readjusted on empirical bases in some patients, with respect to the clinical effects observed within a few days after the time of programming. Pre- and postoperative assessment (until 1 year after surgery) was performed using visual analog scale (VAS), verbal scale, Wisconsin brief pain questionnaire, McGill questionnaire, McGill quality of life and medication quantification scale. Further details of the study's characteristics can be found in the Technical Report, Table A4.8. (Table 5.2)

Risk of Bias

The risk of bias in these studies is unclear as the authors of both RCTs did not report on the methods used for randomisation or if allocation concealment was performed

Results

Effectiveness

Both Lefaucheur (2009) and Nguyen (2008) reported that MCS did not significantly improve persistent neuropathic pain when compared with controls ($p>0.05$).

Out of all the functional outcomes measured, by Lefaucheur (2009) the only statistically significant difference observed between the intervention and control groups was the MPQ-R1

(27.4 'on stimulation' versus 33.6 'off-stimulation', $p=0.0166$). However, this was no longer significant after adjustment for multiple comparisons

In Nguyen (2008) although all values for the functional outcomes were lower in the ON-period than in the OFF-period, there were no statistically significant differences in any of the following outcome measures: quality of life (QoL) measures such as the Wisconsin Brief Pain Questionnaire (WBRQ), the McGill Pain Questionnaire-Rating Index (MPQ-PRI), and the Medication Quantification Scale (MQS). (ON vs. OFF: WBRQ - 36.0 vs. 53.0, MPQ-PRI - 33.9 vs. 60.1 and MQS - 20.3 vs. 26.3).

The results from the 2 studies could not be pooled due to differences between the studies in the length of time patients were stimulated, and outcome measures. Thus no meta-analysis was performed.

Adverse events

Adverse events were not reported or discussed in either of the studies

Contraindications

Contraindications were not evaluated in either of the studies.

Impact of Training

Impact of training was not evaluated in the trials.

Discussion

Based on low level evidence, MCS is not effective for the treatment of refractory peripheral neuropathic pain. Both RCTs used small patient groups ($n=13$ and $n=10$) and did not report if they used any power analysis to determine sufficient numbers for enrolment in the studies to detect a statistically significant effect. Also, Lefaucheur (2009) reported that the wash-out period between phases of the crossover study was not long enough to ensure that effects of the 'on' phase of stimulation did not carry over into the 'off' phase of stimulation. This is also true for the other study (Nguyen 2008) where the washout period was shorter.

The small size of the groups in both studies does not make it possible to generalise the results. Several methodological parameters were not reported by the authors of the studies.

Table 5.1. Key information from most recent primary study for MCS

Reference	Inclusion, exclusion criteria (for P.I.C.O)	Study design	Conclusion/recommendation	Direction of effects
Lefaucheur (2009) Motor cortex stimulation for the treatment of refractory peripheral neuropathic pain.	<p>Patient/population: n=13 (for the randomised phase of the study)</p> <p>Conditions indicated for use: Patients with persistent neuropathic pain of either peripheral or central origin</p> <p>Intervention: Motor cortex stimulation (stimulator 'on' for 1 month duration), amplitude 2 V, pulse width 60 µsec, rate 40 Hz, continuous mode</p> <p>Control: Sham stimulation (stimulator 'off' for 1 month duration)</p> <p>Outcomes assessed:</p> <ul style="list-style-type: none"> pain intensity and relief functional assessments (general activity, mood, walking ability, normal work, relations with other people, sleep and enjoyment of life) medication use 	Crossover Randomised Controlled Trial	<p>Based on low level evidence, MCS is not effective for refractory peripheral neuropathic pain</p> <p>This study had a complicated design of which the crossover RCT was only one component. The results from the crossover RCT were negative, however, small patient groups were used and the duration of the study may have been too short to see the true effect of the intervention.</p>	No better than sham
Nguyen (2008) Treatment of persistent neuropathic pain by motor cortex stimulation: results of a bicentric controlled crossover trial.	<p>Patient/population: n=10</p> <p>Conditions indicated for use: Patients with persistent neuropathic pain of either peripheral or central origin</p> <p>Intervention: Motor cortex stimulation for 2 weeks (ON period), amplitude 2 V, rate 40 Hz, pulse width 60 µsec, full-time mode</p> <p>Control: Sham stimulation for 2 weeks (OFF period)</p> <p>Outcomes assessed:</p> <ul style="list-style-type: none"> pain intensity and relief functional assessments (general activity, mood, walking ability, normal work, relations with other people, sleep and enjoyment of life) medication use 	Crossover Randomised Controlled Trial	<p>There were several limitations, including a small number of patients (n=10) and a short treatment duration. Due to the insufficient washout period and the above mentioned methodological shortcomings, it cannot be concluded that the observed effect is truly reflective of the intervention.</p>	No better than sham

Table 5.2 GRADE evidence profile for Lefaucheur (2009) and Nguyen (2008)

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Motor Cortex Stimulation	Sham	Relative (95% CI)	Absolute	
All outcomes (follow-up 12 months) (Lefaucheur (2009))											
1	randomised trials	serious	no serious inconsistency	no serious indirectness	very serious ^{1,2,3}	none	13	-	Insufficient data to calculate 95% CI for all outcomes	Insufficient data to calculate 95% CI for all outcomes	⊕○○○ VERY LOW
All outcomes (follow-up 12 months) (Nguyen (2008))											
1	randomised trials	serious ⁴	no serious inconsistency	no serious indirectness	very serious ^{2,3,5}	none	10	-	Insufficient data to calculate 95% CI for all outcomes	Insufficient data to calculate 95% CI for all outcomes	⊕○○○ VERY LOW

¹ Small sample size (n=13).

² Did not report if any power analysis was used to determine the sufficient numbers for enrolment in the studies to detect an effect.

³ Author reported that the wash-out period between phases of the crossover study was not long enough to ensure that effects of the 'on' phase of stimulation did not carry over into the 'off' phase of stimulation.

⁴ Several methodological parameters such as how was randomisation carried out and whether the allocation was concealed was not reported. Thus, the overall risk of bias could not be assessed.

⁵ Small sample size (n=10).

6. SUBCUTANEOUS ELECTRICAL STIMULATION (SES)

Evidence identified

The search did not identify any synthesised evidence or controlled trials for the use of subcutaneous electrical stimulation (SES) in the treatment of persistent, intractable pain.

In light of the apparent lack of synthesised research or controlled trials addressing SES for persistent pain, we are unable to report any findings regarding use of this intervention for the treatment of persistent pain.

DISCUSSION & CONCLUSION

1. Spinal cord stimulation (SCS)

Conventional SCS vs Control

The most comprehensive, current, high-quality piece of synthesised evidence was a HTA (Hashimoto 2010). This was a well conducted review with a low risk of bias. It provided varying levels of evidence on the effectiveness of SCS on pain, function and quality of life, as well as information about contraindications and risks.

This HTA found one moderate level RCT and two low level RCT which reported SCS to be superior to conventional therapies (conventional medical management, physical therapy or reoperation) in patients with persistent neuropathic pain at 6 months to 24 months with respect to pain, and perceived effect of treatment / patient satisfaction and disability. (Kemler 2000, Kemler 2004, Kemler 2008) (Kumar 2007, Kumar 2008) (North 2005). This effect however was not sustained beyond 5 years.

Quality of life improvements with conventional SCS are unclear, as one low level study reported a significant improvement with SCS (Kumar 2007) while another reported no difference between treatment arms (Kemler 2000).

Minor complications following SCS were relatively common though not life threatening and revisions due to side effects may go up to 38% of patients (Kemler 2004, Hashimoto 2010). Most common was electrode repositioning due to migration or changes in paraesthesia (Kemler 2008, Kumar 2007, North 2005). Hardware problems resulting in re-implantation or removal were also reported (Kumar 2007). Sometimes, the system may become ineffective in pain relief with time, requiring total removal. Infections and uncomfortable paraesthesia were also reported (Kumar 2007).

Overall due to small sample sizes, unclear risk of bias and lack of high quality RCTs, the results should be interpreted with caution and should only be generalised to patient groups recruited in the studies, patients with CRPS and FBSS.

Conventional SCS versus Burst SCS

There is insufficient evidence to assess the effectiveness of conventional SCS compared to Burst SCS. Only one small crossover trial of patients with FBSS was identified (De Ridder 2013,); and although this study reported statistically significant improvement in pain for burst SCS, these results cannot be confirmed as the study did not adequately report its research methods.

High Frequency SCS versus Sham

There is low level evidence indicating no significant improvements in limb and back pain with high frequency SCS compared to sham (Perruchoud 2013). Although the study was well conducted, it was underpowered and used a frequency level that can be considered sub-optimal for the intervention, which may explain why equivalence was observed. In order to

accurately assess the effect of high frequency SCS, further well conducted studies are required.

2. Peripheral nerve stimulation (PNS)

There is insufficient evidence to determine the effectiveness of PNS in the treatment of persistent pain. The most comprehensive, up-to-date source of evidence was an EBG on PNS (Cruccu 2007) . The quality of the EBG in terms of the scope, purpose and rigorous methodology was moderate. However the only evidence identified were case series studies without adequate controls, therefore we are unable to draw any conclusions on the effectiveness of PNS.

3. Occipital nerve stimulation (ONS)

There is moderate level evidence supporting the short term effectiveness (12 weeks) of ONS for chronic migraine (Silberstein 2012), although there are concerns regarding complications such as lead migration, site infection and increased migraine pain, and/or numbness at IPG/lead site. Although other RCT's were identified (Lipton 2009 and Saper 2011), from the same research team (Lipton 2009 and Saper 2011), which reported no significant effect for ONS, their results are uncertain given methodological limitations and lack of reporting study methods. More robust studies are required to confirm the results seen in Silberstein (2012). There are no studies of ONS in other pain conditions such as occipital neuralgia.

4. Deep brain stimulation (DBS) (intracranial)

There is low level evidence indicating that DBS is not effective for chronic cluster headache. The highest level of evidence was one small crossover RCT (Fontaine 2010) recruiting 11 patients, which had major methodological limitations. Issues regarding uncertainty in the sample size calculation, suboptimal therapeutic delay between stimulate on onset and therapeutic effect and lack of optimisation of stimulation parameters for patients, indicates that the results of this study are uncertain. Furthermore it is unclear whether DBS would be commonly used in practice given the advent of less invasive procedures such as occipital nerves stimulation (ONS), which has a better evidence profile.

5. Motor cortex stimulation (MCS)

There is low level evidence indicating that MCS is not effective for refractory peripheral neuropathic pain. The most recent evidence evaluating MCS were two separate RCTs which were conducted by the same clinical group (Lefaucheur 2009, Nguyen 2008). Both RCTs used small patient groups and had short study durations. Risk of adverse events is unknown, as both studies did not report any complications associated with MCS. As this type of stimulation is relatively new, it is envisaged that some risks would be apparent; hence further studies should investigate and confirm the findings of these RCTs. Both RCTs had a high risk of bias due to an insufficient washout period. Hence, the results of these studies are unlikely to be an accurate estimate of the real effect of MCS.

6. Subcutaneous electrical stimulation (SES)

No evidence was identified evaluating SES. Our search did not identify any synthesised evidence or controlled trials for the use of subcutaneous electrical stimulation (SES) in the

treatment of persistent, intractable pain. Therefore the effectiveness of SES in the treatment of persistent pain is unclear.

DISCLAIMER

The information in this report is a summary of that available and is primarily designed to give readers a starting point to consider currently available research evidence. Whilst appreciable care has been taken in the preparation of the materials included in this publication, the authors and the National Trauma Research Institute do not warrant the accuracy of this document and deny any representation, implied or expressed, concerning the efficacy, appropriateness or suitability of any treatment or product. In view of the possibility of human error or advances of medical knowledge the authors and the National Trauma Research Institute cannot and do not warrant that the information contained in these pages is in every aspect accurate or complete. Accordingly, they are not and will not be held responsible or liable for any errors or omissions that may be found in this publication. You are therefore encouraged to consult other sources in order to confirm the information contained in this publication and, in the event that medical treatment is required, to take professional expert advice from a legally qualified and appropriately experienced medical practitioner.

CONFLICT OF INTEREST

The TAC/VWA Evidence Service is provided by the National Trauma Research Institute. The NTRI does not accept funding from pharmaceutical or biotechnology companies or other commercial entities with potential vested interest in the outcomes of systematic reviews.

The TAC/VWA Health and Disability Strategy Group have engaged the NTRI for their objectivity and independence and recognise that any materials developed must be free of influence from parties with vested interests. The Evidence Service has full editorial control.

REFERENCES

1. Donoghue E, Piccenna L. Implantable Pain Therapies: Neurostimulation - Evidence Review. 2011;1-39.
2. Kemler MA, Barendse GA, van Kleef M, de Vet HC, Rijks CP, Furnee CA, van den Wildenberg FA. Spinal cord stimulation in patients with chronic reflex sympathetic dystrophy. *N Engl J Med*. 2000;343(9):618-24.
3. Kemler MA, De Vet HC, Barendse GA, Van Den Wildenberg FA, Van Kleef M. The effect of spinal cord stimulation in patients with chronic reflex sympathetic dystrophy: two years' follow-up of the randomized controlled trial. *Ann Neurol*. 2004;55(1):13-8.
4. Kemler MA, de Vet HC, Barendse GA, van den Wildenberg FA, van Kleef M. 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.
5. Kumar K, Taylor RS, Jacques L, Eldabe S, Meglio M, Molet J, Thomson S, O'Callaghan J, Eisenberg E, Milbouw G, Buchser E, Fortini G, Richardson J, North RB. 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.
6. Kumar K, Taylor RS, Jacques L, Eldabe S, Meglio M, Molet J, Thomson S, O'Callaghan J, Eisenberg E, Milbouw G, Buchser E, Fortini G, Richardson J, North RB. The effects of spinal cord stimulation in neuropathic pain are sustained: a 24-month follow-up of the prospective randomized controlled multicenter trial of the effectiveness of spinal cord stimulation. *Neurosurgery*. 2008;63(4):762-70; discussion 70.
7. 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; discussion -7.
8. Saper JR, Dodick DW, Silberstein SD, McCarville S, Sun M, Goadsby PJ, Investigators O. Occipital nerve stimulation for the treatment of intractable chronic migraine headache: ONSTIM feasibility study. *Cephalalgia : an international journal of headache*. 2011;31(3):271-85.
9. Serra G, Marchioretto F. Occipital nerve stimulation for chronic migraine: A randomized trial. *Pain Physician*. 2012;15(3):245-53.
10. Silberstein S, Dodick D, Saper J, Huh B, Reed K, Narouze S, Bacon D, Mogilner A, Banks J, Cady R, Black S, Slavin K, Goldstein J, Markley H, Deer T, Levy R, Mekhail N. Safety and efficacy of occipital nerve stimulation for the management of chronic migraine: Results from a prospective, multicenter, double-blinded, controlled study. *Neuromodulation*. 2012;15 (6):e9.
11. Lipton R, Goadsby P, Cady R, Aurora S, Grosberg B, Freitag F, Silberstein S, Whiten D, Jaaz K. PRISM study: occipital nerve stimulation for treatment-refractory migraine. *Cephalalgia*. 2009;29(Suppl. 1):30.
12. Kemler M, Barendse G, van Kleef M, de Vet H, Rijks C, Furnee C, van den Wildenberg F. Spinal cord stimulation in patients with chronic reflex sympathetic dystrophy. *N Engl J Med*. 2000;343(9):618-24.
13. Kemler M, De Vet H, Barendse G, Van Den Wildenberg F, Van Kleef M. The effect of spinal cord stimulation in patients with chronic reflex sympathetic dystrophy: two years' follow-up of the randomized controlled trial. *Ann Neurol*. 2004;55(1):13-8.
14. Kemler M, de Vet H, Barendse G, van den Wildenberg F, van Kleef M. 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. *J Neurosurg.* 2008;108(2):292-8.
15. Kumar K, Taylor R, Jacques L, Eldabe S, Meglio M, Molet J, Thomson S, O'Callaghan J, Eisenberg E, Milbouw G, Buchser E, Fortini G, Richardson J, North R. 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.
 16. Kumar K, Taylor R, Jacques L, Eldabe S, Meglio M, Molet J, Thomson S, O'Callaghan J, Eisenberg E, Milbouw G, Buchser E, Fortini G, Richardson J, North R. The effects of spinal cord stimulation in neuropathic pain are sustained: a 24-month follow-up of the prospective randomized controlled multicenter trial of the effectiveness of spinal cord stimulation. *Neurosurgery.* 2008;63(4):762-70; discussion 70.
 17. North R, Kidd D, Farrokhi F, Piantadosi S. Spinal cord stimulation versus repeated lumbosacral spine surgery for chronic pain: a randomized, controlled trial. *Neurosurgery.* 2005;56(1):98-106; discussion -7.
 18. Perruchoud C, Eldabe S, Batterham A, Madzinga G, Brookes M, Durrer A, Rosato M, Bovet N, West S, Bovy M, Rutschmann B, Gulve A, Garner F, Buchser E. Analgesic Efficacy of High-Frequency Spinal Cord Stimulation: A Randomized Double-Blind Placebo-Controlled Study. *Neuromodulation: Technology at the Neural Interface.* 2013;16(4):363-9.
 19. Lefaucheur JP, Drouot X, Cunin P, Bruckert R, Lepetit H, Creange A, Wolkenstein P, Maison P, Keravel Y, Nguyen JP. Motor cortex stimulation for the treatment of refractory peripheral neuropathic pain. *Brain.* 2009;132(Pt 6):1463-71.
 20. Nguyen JP, Velasco F, Brugieres P, Velasco M, Keravel Y, Boleaga B, Brito F, Lefaucheur JP. Treatment of chronic neuropathic pain by motor cortex stimulation: results of a bicentric controlled crossover trial. *Brain Stimulation.* 2008;1(2):89-96.
 21. Silberstein SD, Dodick DW, Saper J, Huh B, Slavin KV, Sharan A, Reed K, Narouze S, Mogilner A, Goldstein J, Trentman T, Vaisma J, Ordia J, Weber P, Deer T, Levy R, Diaz RL, Washburn SN, Mekhail N. Safety and efficacy of peripheral nerve stimulation of the occipital nerves for the management of chronic migraine: results from a randomized, multicenter, double-blinded, controlled study. *Cephalalgia.* 2012;32(16):1165-79.
 22. Lipton R, Goadsby P, Cady R, Aurora S, Grosberg B, Freitag F, Silberstein S, Whiten D, Jaax K. PRISM study: occipital nerve stimulation for treatment-refractory migraine. *Cephalalgia.* 2009;29(Suppl. 1):pge. 30 [presented at 14th Congress of the International Headache Society September 0 – 3, 2009 Philadelphia, PA].
 23. Saper J, Dodick D, Silberstein S, McCarville S, Sun M, Goadsby P. Occipital nerve stimulation for the treatment of intractable chronic migraine headache: ONSTIM feasibility study. *Cephalalgia.* 2011;31(3):271-85.
 24. Schünemann H, Brožek J, Guyatt G, Oxman A, editors. *GRADE handbook for grading quality of evidence and strength of recommendations.*
: The GRADE Working Group; 2013.
 25. Stanton-Hicks M. Peripheral nerve stimulation for pain peripheral neuralgia and complex regional pain syndrome. In: Krames ES PP, Rezai AR, , editor. *Neuromodulation: the textbook.* London: Academic Press; 2009. p. 397–407.
 26. Weiner R. Surgical placement of leads for occipital nerve stimulation. In: Krames ES PP, Rezai AR, , editor. *Neuromodulation: the textbook.* London: Academic Press; 2009. p. 1021-6.
 27. NICE. Deep brain stimulation for intractable trigeminal autonomic cephalalgias. *Interventional Procedure Guidelines 381.* London: NICE; 2011.

28. Levy R, Deer TR, Henderson J. Intracranial neurostimulation for pain control: a review. *Pain Physician*. 2010;13(2):157-65.
29. De Ridder D, Plazier M, Kamerling N, Menovsky T, Vanneste S. Burst spinal cord stimulation for limb and back pain. *World Neurosurgery*. 2013;80(5):642-9.e1.
30. Hashimoto R, Dettori J, Henrikson N, Kercher L. HTA Report: Spinal Cord Stimulation WA Health Technology Assessment: Spinal Cord Stimulation Final Report, Washington State Health Care Authority. 2010:164 pgs.
31. Price D, Finniss D, Benedetti F. A Comprehensive Review of the Placebo Effect: Recent Advances and Current Thought. *The Annual Review of Psychology*. 2008;59:565-90.
32. Bausell R, Lao L, Bergman S, Lee W, Berman B. Is acupuncture analgesia an expectancy effect? Preliminary evidence based on participants' perceived assignments in two placebo-controlled trials. *Evaluation & the Health Professions*. 2005;28:9-26.
33. North R, Kumar K, Wallace M, Henderson J, Shipley J, Hernandez J, Mekel-Bobrov N, Jaax K. Spinal cord stimulation versus re-operation in patients with failed back surgery syndrome: an international multicenter randomized controlled trial (EVIDENCE study). *Neuromodulation*. 2011;14(4):330-5; discussion 5-6.
34. ClinicalTrials.gov Identifier: NCT01036529. Spinal Cord Stimulation With Precision® System Versus Reoperation for Failed Back Surgery Syndrome (Evidence). ClinicalTrials.gov Identifier: NCT01036529 (2013);Responsible Party: Boston Scientific Corporation, Principal Investigator: Richard North(This study has been terminated due to continued slow enrollment).
35. ClinicalTrials.gov Identifier: NCT00286078. Treatment for Migraines With an Implantable Device. ClinicalTrials.gov Identifier: NCT00286078. 2012;Sponsor: Boston Scientific Corporation, Principal Investigator: Richard Lipton (The recruitment status of this study is unknown because the information has not been verified recently. Verified March 2012).
36. Dworkin R, Turk D, Wyrwich K, Beaton D, Cleeland C, Farrar J, Haythornthwaite J, Jensen M, Kerns R, Ader D, Brandenburg N, Burke L, Cella D, Chandler J, Cowan P, Dimitrova R, Dionne R, Hertz S, Jadad A, Katz N, Kehlet H, Kramer L, Manning D, McCormick C, McDermott M, McQuay H, Patel S, Porter L, Quessy S, Rappaport B, Rauschkolb C, Revicki D, Rothman M, Schmader K, Stacey B, Stauffer J, von Stein T, White R, Witter J, Zavisic S. Interpreting the clinical importance of treatment outcomes in chronic pain clinical trials: IMMPACT recommendations. *J Pain*. 2008;9(2):105-21.
37. Silberstein S, Tfelt-Hansen P, Dodick D, Limmroth V, Lipton R, Pascual J, Wang S. Guidelines for controlled trials of prophylactic treatment of chronic migraine in adults. *Cephalalgia*. 2008;28(5):484-95.
38. Fontaine D, Lazorthes Y, Mertens P, Blond S, Geraud G, Fabre N, Navez M, Lucas C, Dubois F, Gonfrier S, Paquis P, Lanteri-Minet M. Safety and efficacy of deep brain stimulation in refractory cluster headache: a randomized placebo-controlled double-blind trial followed by a 1-year open extension. *Journal of Headache & Pain*. 2010;11(1):23-31.
39. Leone M, Franzini A, Broggi G, Bussone G. Hypothalamic stimulation for intractable cluster headache: long-term experience. *Neurology*. 2006;67(1):150-2.
40. Cruccu G, Aziz T, Garcia-Larrea L, Hansson P, Jensen T, Lefaucheur J, Simpson B, Taylor R. EFNS guidelines on neurostimulation therapy for neuropathic pain. *European Journal of Neurology*. 2007;14(9):952-70.