Transport Accident Commission & WorkSafe Victoria

# Evidence Service

# Implantable pain therapies: 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 under the skin that makes electricity (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 within 5 years in persistent pain conditions, including complex regional pain syndrome (CRPS) and failed back surgery syndrome (FBSS).
- There is low level evidence that SCS improves function and quality of life in 5-10 years.
- 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.

| **Accompanying documents to this report** | |
|---|---|
| *Title* | *Report number* |
| Implantable pain therapies: Neurostimulation - Evidence Summary | 0611-002-R8.1 |
| Implantable pain therapies: Neurostimulation - Plain Language Summary | 0611-002-R8.2 |
| Implantable pain therapies: Neurostimulation - Technical Report | 0611-002-R8.3 |

A joint initiative of

# Implantable pain therapies: Neurostimulation

## Evidence summary

### Overview

This evidence review is an update of a previous review conducted in September 2008 (as requested by the Transport Accident Commission (TAC) and WorkSafe Victoria (WSV)).[1] Our findings are based on the most up-to-date, comprehensive, high-quality piece of evidence for each type of neurostimulation (see methods for details on the selection process).

This review examined the following types of neurostimulation:

- Spinal Cord Stimulation (SCS)
- Peripheral Nerve Stimulation (PNS)
- Subcutaneous Electrical Stimulation (SES)
- Motor Cortex Stimulation (MCS)
- Deep Brain Stimulation (DBS)
- Occipital Nerve Stimulation (ONS)

For SCS there is moderate evidence that SCS is effective in the short-term (<5years) for pain relief, and low level evidence supporting improvement in function and quality of life. In terms of harms and adverse events there is high level evidence to show that revision of the procedure is common. As in the previous report, our search did not identify any synthesised evidence or controlled trials for the effectiveness of subcutaneous electrical stimulation (SES) in chronic pain.

For all other types of neurostimulation there is currently insufficient evidence to determine effectiveness in pain relief, quality of life and functional outcomes in patients with persistent, non-cancer pain.

### Definition

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 receiver to the nerves being stimulated. The low voltage electricity blocks the sensation of pain. The receiver and leads can be removed by surgery if required. 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, neurostimulation may be an effective treatment option.

The following evidence review identified a total of forty-eight studies (twelve evidence-based guidelines - EBGs, three health technology assessments - HTAs, twenty three systematic reviews – SRs, seven randomised clinical trial – RCTs and three controlled clinical trials - CCTs) of neurostimulation for persistent pain that met the selection criteria. From this evidence the most comprehensive and up-to-date evidence was used for the review.

## General Comments

| | |
|---|---|
| SPINAL CORD STIMULATION (SCS): | A well conducted Health Technology (HTA) assessment with a low risk of bias was identified.[2] 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.<br>The HTA also provided information on indications for use and cost-effectiveness, however, this information is specific to the US and may not be generalisable to the Australian setting. |
| SUBCUTANEOUS ELECTRICAL STIMULATION (SES): | As in the previous report,[1] our search failed to identify any synthesised evidence or controlled trials to determine whether subcutaneous electrical stimulation (SES) is effective for the treatment of chronic, persistent non-cancer pain. |
| PERIPHERAL NERVE STIMULATION (PNS): | The most comprehensive, up-to-date, synthesised evidence for PNS was an EBG[3] that included three low level studies (case series).<br>The EBG was considered as being of moderate quality with regards to the scope, purpose and rigorous methodology. The overall risk of bias could not be determined due to insufficient information provided by the authors. |
| MOTOR CORTEX STIMULATION (MCS): | Two Randomised Controlled Trials[4, 5] (RCTs) were identified for motor cortex stimulation. These studies used parallel groups and a cross over design. Both RCT's had small study samples (n=13 and n=10). The quality of these studies could not be determined as the authors did not report on the methods used for randomization and allocation concealment. Furthermore, the washout period was not long enough (in particular reported in one study – 3 weeks) to negate the effect of the stimulation phase (duration of stimulation - 4 weeks). |
| DEEP BRAIN STIMULATION (DBS): | The most comprehensive, up-to-date, high level evidence for DBS was a crossover RCT.[6] This RCT had a moderate risk of bias due to a small sample size, short treatment duration and possible non-optimal stimulation parameters. Given these limitations this evidence may not accurately reflect the true effect of DBS in chronic pain.<br>There is insufficient evidence to determine the effectiveness of DBS for the treatment of chronic pain syndromes including chronic cluster headache. |
| OCCIPITAL NERVE STIMULATION (ONS): | The most comprehensive, high level evidence for ONS were two RCTs. Despite using different treatment protocols the results of both RCTs did not support the use of ONS. With regards to the study methodology one was a feasibility study and had small treatment groups[7]. The sample size was larger in the other study, although study quality could not be assessed, as specific methodological parameters were not reported.[8] In addition, the duration of both studies (3 months) was too short to assess long term effectiveness of ONS[7, 8].<br>There is insufficient evidence to determine the effectiveness of ONS for the treatment of chronic, persistent non-cancer pain. |

## In what clinical conditions is this intervention indicated for use?

In Australia, spinal cord stimulation, peripheral nerve stimulation and deep brain stimulation have been indicated and approved for use by the TGA[9, 10] and funded by the Medicare Benefits Scheme[11] for the

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|---|---|
| treatment of chronic, intractable neuropathic pain.<br>The conditions for which neurostimulation was used in the studies that form the basis of this report are outlined below. | |
| SPINAL CORD STIMULATION (SCS): | In a recent HTA[2], of the included studies one RCT investigated SCS compared with physical therapy in complex regional pain syndrome (CRPS) patients; two other high level RCTs investigated SCS in patients with failed back surgery syndrome (FBSS), and one prospective cohort study used FBSS patients. |
| SUBCUTANEOUS ELECTRICAL STIMULATION (SES): | As in the previous version of this report,[1] we did not identify any synthesised evidence or controlled trials to answer this question. |
| PERIPHERAL NERVE STIMULATION (PNS): | An EBG[3] included studies which investigated pharmacoresistant patients with conditions including complex regional pain syndrome (CRPS) II, peripheral neuropathy, post-traumatic pain, radiculopathy, amputation for the treatment of PNS. Another more recent EBG[12] also reported on studies with PNS in patients with complex regional pain syndrome (CRPS) I and II. |
| MOTOR CORTEX STIMULATION (MCS): | Two RCTs[4, 5] investigated patients with chronic neuropathic pain of either central or peripheral origin for use of MCS. |
| DEEP BRAIN STIMULATION (DBS): | One high level crossover RCT[6] included patients with severe refractory chronic cluster headache (CCH). |
| OCCIPITAL NERVE STIMULATION (ONS): | Two RCTs[7, 8] investigated ONS in patients with treatment-refractory chronic migraine. |
| **What is the efficacy and effectiveness of this intervention on persistent pain in these conditions?** | |
| SPINAL CORD STIMULATION (SCS): | In the **short term** (<5 years) - there is **moderate evidence** that **SCS is more effective** than conventional therapies in terms of **pain.**<br><br>In the **mid-term** (5 to <10 years) - there is **low evidence** that **SCS is no different** to physical therapy in terms of **pain, and perceived effect of treatment/patient satisfaction.**<br><br>There is **no evidence** available to assess **long-term efficacy** of SCS (>10 years) |
| SUBCUTANEOUS ELECTRICAL STIMULATION (SES): | As in the previous report,[1] we did not identify any synthesised evidence or controlled trials to answer this question. |
| PERIPHERAL NERVE STIMULATION (PNS): | There is **insufficient evidence** to answer this question. |
| MOTOR CORTEX STIMULATION (MCS): | There is **insufficient evidence** to answer this question. |
| DEEP BRAIN STIMULATION (DBS): | There is **insufficient evidence** to answer this question. |
| OCCIPITAL NERVE STIMULATION (ONS): | There is **insufficient evidence** to answer this question. |

| What is the effect of this intervention on function, quality of life, return to work, medication use and the healthcare system? | |
|---|---|
| SPINAL CORD STIMULATION (SCS): | In the **short-term** (<5 years) - there is **low level evidence** that **SCS is more effective** than comparators in terms of **function and quality of life**<br><br>In the **mid-term** (5 to <10 years) - there **is low evidence indicates that SCS is no different** to physical therapy in terms of **quality of life** |
| SUBCUTANEOUS ELECTRICAL STIMULATION (SES): | As in the previous report,[1] we did not identify any synthesised evidence or controlled trials to answer this question. |
| PERIPHERAL NERVE STIMULATION (PNS): | There is **insufficient evidence** to answer this question. |
| MOTOR CORTEX STIMULATION (MCS): | There is **insufficient evidence** to answer this question. |
| DEEP BRAIN STIMULATION (DBS): | There is **insufficient evidence** to answer this question. |
| OCCIPITAL NERVE STIMULATION (ONS): | There is **insufficient evidence** to answer this question. |
| **In what patient groups/conditions is use of this intervention contraindicated?** | |
| SPINAL CORD STIMULATION (SCS): | A recent HTA[2] reported the following contraindications for SCS -<br>"Patients should not receive permanent SCS therapy who:<br>• failed trial stimulation due to ineffective pain relief<br>• are poor surgical risks<br>• are pregnant<br>• are unable to operate the SCS system<br>• have cardiac pacemakers (unless specific precautions are taken regarding the mode and frequency of the device and not contraindicated for the particular device)<br>• have cardioverter defibrillators<br>• have active general infections<br>• have multiple illnesses<br>Additionally, SCS systems must be removed prior to diathermy or (depending on the device) exposure to any source of strong electromagnetic interference such as MRI (magnetic resonance imaging), therapeutic ultrasound, or defibrillation. Further, patients should turn the devices off prior to operating heavy machinery or power tools to avoid over-stimulation[26-28]„[2] |
| SUBCUTANEOUS ELECTRICAL STIMULATION (SES): | As in the previous report,[1] we did not identify any synthesised evidence or controlled trials to answer this question. |
| PERIPHERAL NERVE STIMULATION (PNS): | There is **insufficient evidence** to answer this question. |
| MOTOR CORTEX STIMULATION (MCS): | There is **insufficient evidence** to answer this question. |

| | |
|---|---|
| DEEP BRAIN STIMULATION (DBS): | There is **insufficient evidence** to answer this question. |
| OCCIPITAL NERVE STIMULATION (ONS): | There is **insufficient evidence** to answer this question. |

## What are the risks associated with use of this intervention?

| | |
|---|---|
| SPINAL CORD STIMULATION (SCS): | There is high level evidence (three RCTs) reporting that revision of SCS components was common. Overall short-term revision rates ranged from 12–38% of patients. Mid-term revision rates were 42% in one RCT.<br>Two RCTs reported that the rate of mortality due to SCS was low (0-1%).<br>Other possible SCS related side-effects include: infection, change in amplitude by bodily movements, paresthesia in other body parts, pain/irritation from the pulse generator, transient neurological defects, and severe wound-related pain at the stimulator implantation site, cerebrospinal fluid leak, and subcutaneous hematoma. |
| SUBCUTANEOUS ELECTRICAL STIMULATION (SES): | As in the previous version of this report,[1] we did not identify any synthesised evidence or controlled trials to answer this question. |
| PERIPHERAL NERVE STIMULATION (PNS): | One EBG[12] reported that "possible complications requiring reoperation are related to the surgical technique or PNS equipment design and include migration of the electrode in 33%, infection in 15% and the need for placement in an alternative location in 11% of patients ."[13] |
| MOTOR CORTEX STIMULATION (MCS): | In one EBG[3] harms associated with MCS included extradural hematoma, and hardware malfunction. Around 20% of MCS patients experienced one or more complications. |
| DEEP BRAIN STIMULATION (DBS): | A recent high level crossover RCT[6] reported infection, neck pain, mild hunger increases/decreases and mild libido decreases with DBS. |
| OCCIPITAL NERVE STIMULATION (ONS): | Risks associated with ONS included lead migration, infection, implant site pain, increased migraine, and nausea. [7, 8] |

| Glossary of Findings | |
|---|---|
| **Insufficient evidence** | Little or no evidence exists to answer this question |
| **High evidence*** | Strong evidence exists to answer this question.<br>i.e. several good quality studies exist and their findings all agree |
| **Moderate evidence*** | Evidence exists to answer this question, but it is less certain.<br>i.e. one or two studies of good quality exist, and their findings agree; or there are three or more good quality studies, but their findings do not agree |
| **Low evidence*** | Weak evidence exists to answer this question<br>i.e. one or two studies of good quality exist, but their findings do not agree; or there are three or more poor quality studies, but their findings agree |

*These classifications are taken from one of the included HTA[2]

Transport Accident Commission & WorkSafe Victoria

# Evidence Service

## Implantable pain therapies: Neurostimulation

## Evidence Review

## October 2011

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## BACKGROUND

Persistent or chronic pain can be defined as “pain which persists for more than several months, or beyond the normal course of a disease or expected time of healing”. 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.[14] Persistent pain can modify an individual’s physiological conditions and psychological

conditions leading to disabling changes in their quality of life (including general everyday activities, medication dependence and frequent absence from work).

Conventional medical management (CMM) or first line therapy for chronic pain includes strong analgesic medications and physical therapies. However, patients often do not experience complete pain relief with these treatments and frequently side effects occur. Some patients also try invasive interventions for pain relief that include fusion, decompression, ablation or nerve block, which sometimes fail. A potential alternative treatment option for these patients (which is reversible and non-pharmacological) is known as neurostimulation.

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

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

**1. Spinal cord stimulation (SCS)**

Spinal cord stimulation (SCS) is a treatment used to mask areas of pain associated with the spinal cord making them feel numb or tingly (a phenomenon known as paraesthesia). This results in blocked responses in the nervous system reducing pain transmission. Individuals who are selected for SCS have what is known as a 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 –

1. A lead connected to an insulated plate electrode (multi-contact points), and
2. 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. Subcutaneous electrical nerve stimulation (SENS) or subcutaneous targeted stimulation (STS)**

Subcutaneous electrical stimulation (SES) is a reversible pain therapy involving subcutaneous implantation of electrodes at the centre of the painful region. It is also known as subcutaneous targeted stimulation (STS).[15, 16] The treatment aims to overlap areas of the pain with paraesthesia (numbness or tingling) and provide pain relief to patients.

**3. Peripheral nerve stimulation (PNS)**

Peripheral nerve stimulation (PNS) provides pain relief through electrical stimulation to areas of pain associated with the peripheral nervous system (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. The system and procedure for PNS is similar to that described for SCS (section 1), although a trial period of one to two days is sufficient before permanent implantation.[17]

**4. 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, 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 sufficiently stimulated. Once this is established, a small electrical current is provided resulting in sub-threshold activation of muscles to 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.[18] In this case, placebo effects can be investigated in randomised clinical trials, giving higher empirical evidence for the efficacy of MCS.

**5. 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), rather than on top of the brain, using a stereotactic guide apparatus.[19] This alters the processing of the pain signal providing pain relief for the patient. Some patients experience specific pain syndromes, whilst others have combined pain syndromes (neuropathic and nociceptive pain in conjunction). 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 stimulation is successful, an IPG is implanted usually in the chest wall and is programmed to deliver the correct amount of pain relief the patient requires.[19]

### 6. Occipital nerve stimulation (ONS)

Occipital nerve stimulation (ONS) involves either bilateral stimulation of the occipital nerves or unilateral stimulation of the supraorbital nerve. ONS not only provides a direct activation of the peripheral nervous system to produce pain relief, it also provides secondary effects through the central nervous system. 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.[20]

## QUESTIONS

This Evidence Review sought to find the most up-to-date, high quality sources of evidence to answer the following questions regarding different types of neurostimulation for persistent pain due to work-related or traffic accident injuries:

- In what clinical conditions is this intervention indicated?
- What is the efficacy and effectiveness of this intervention on persistent pain in these conditions?
- What is the effect of this intervention on function (physical, psychological, social), quality of life, return to work, medication use and the healthcare system?
- In what patient groups/conditions is this intervention contraindicated?
- What are the risks associated with use of this intervention?

## METHODS

The current report is an update of a previous version requested by the Transport Accident Commission (TAC) and WorkSafe Victoria (WSV), conducted in September 2008.[1] Methods are outlined briefly below. More detailed information about the methodology used to produce this report is available in Appendices 1 and 2. All appendices are located in the Technical Report accompanying this document.

A comprehensive search of Medline, Embase and the Cochrane Library, was undertaken in June 2011 to identify relevant synthesised research (i.e. evidence-based guidelines (EBGs), systematic reviews (SRs), health technology assessments (HTAs)), and any relevant randomised controlled trials (RCTs) and controlled clinical trials (CCTs). A comprehensive search of the internet, relevant websites and electronic health databases was also undertaken (see Appendix 2, Tables A2.2-A2.4 for search details). 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). Synthesised evidence (EBGs, SRs and HTAs) 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. This process was repeated for additional sources of evidence, if necessary, until the most recent, comprehensive and high quality source of evidence was identified. Findings from the best available source of evidence were compared to other evidence sources for consistency of included references and findings.

The available synthesised evidence was mapped (see Table 2), and the algorithm in Table 1 was followed to determine the next steps necessary to answer the clinical questions.

**Table 1. Further action required to answer clinical questions**

| Is there any synthesised research available? (e.g. EBGs, HTAs, SRs) | | | | |
|---|---|---|---|---|
| Yes | | | No | |
| Is this good quality research? | | | Are RCTs available? | |
| Yes | | No | Yes | No |
| Is it current (within 2 years)? | | | | |
| Yes | No | | | |
| No further action | Update existing SR | Undertake new SR | Undertake new SR | Consider looking for lower levels of evidence |

Data on characteristics of all included studies were extracted and summarised (see Appendix 4).

## RESULTS

A search of electronic databases conducted in May 2008 and updated in June 2011 yielded 5,270 potentially relevant journal articles. After reviewing the title, abstract or full text, 3 HTAs,[21-23] 12 EBGs,[3, 12, 24-33] 23 SRs,[34-56] 7 RCTs,[4-7, 58-60] and 3 CCTs[61-63] were found that met our selection criteria (see Appendix 2, Table A2.1 for selection criteria). Several of the identified references[57, 64, 65] reported data from a single RCT.[58] Internet searches revealed one additional HTA,[2] and searches from identified studies yielded one additional RCT.[8] A list and summary of included studies can be found in Appendices 3 and 4, respectively.

For motor cortex stimulation, deep brain stimulation and occipital nerve stimulation the evidence based guidelines and systematic reviews were not included in the report as they were based on low level evidence and superseded by higher level primary studies.

**Table 2. Evidence map of included studies by study-type.**

| | Synthesised Studies | | Primary studies | TOTAL |
|---|---|---|---|---|
| Stimulation type | EBGs | SRs & HTAs | | |
| Spinal cord stimulation (SCS) | 11 | 22 | 4 | 37 |
| Subcutaneous Electrical Stimulation (SES) | - | - | - | 0 |
| Peripheral Nerve Stimulation (PNS) | 2 | 2 | - | 4 |
| Motor cortex stimulation (MCS) | 1 | 1 | 4 | 6 |
| Deep brain Stimulation (DBS) | 1 | 5 | 1 | 6 |
| Occipital Nerve Stimulation | 1 | 2 | 2 | 5 |
| TOTAL* | 12 | 26 | 11 | 49 |

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

Results are reported below by stimulation type.

# 1. SPINAL CORD STIMULATION (SCS)

## Evidence identified

The most high-quality, comprehensive, up-to-date source of synthesised research regarding SCS for chronic non-cancer pain was a HTA published in 2010 by the Washington State Health Care Authority.[2] Although other synthesised evidence was published in 2011 and 2010, this HTA had the most recent search date (February 2010), making it the most current. This study was quality appraised and found to be well conducted with a low risk of bias (see Appendix 5, Table A5.11). Key information from the HTA is presented below in Table 3.

**Table 3. Key information from the most recent, comprehensive, high quality Health Technology Assessment *(Hasimoto et al. 2010)* – SPINAL CORD STIMULATION**

| ***Hashimoto, R., et al., HTA Report: Spinal Cord Stimulation. 2010, Washington State Health Care Authority.: Olympia, WA.*** | |
|---|---|
| **Study design** | Health Technology Assessment (HTA) |
| **Scope** | **Patient/population:** adults with chronic neuropathic pain (a HTA of 3 RCTs, 4 prospective cohorts, 2 retrospective cohorts, 6 case series)<br>**Conditions indicated for use:** adults with chronic neuropathic pain due to conditions including (but not limited to) failed back surgery syndrome (FBSS), complex regional pain syndrome (CRPS), phantom limb or stump pain, central pain such as post-stroke pain, diabetic neuropathy, and post-herpetic neuralgia.<br>**Intervention:** spinal cord stimulation<br>**Outcomes assessed:** efficacy and effectiveness; safety; differential efficacy or safety issues in sub populations; cost implications and cost-effectiveness |
| **Efficacy and effectiveness of SCS for persistent pain** | **There is moderate level evidence that SCS is more effective than comparators in the short term (<5 years)**<br>"**Pain, perceived effect of treatment/patient satisfaction:** There is moderate evidence from three small randomized controlled trials that SCS is superior to conventional therapies (CMM, physical therapy or reoperation) in patients with chronic neuropathic pain during the first 2–3 years."<br>One RCT which measured outcomes for a longer period of time, found that "the benefit of SCS decreased over time and was not significantly different than controls for leg pain after 3 years of treatment."<br>**There is low level evidence that SCS is no different to physical therapy in the mid-term (5 - <10 years)**<br>"**Pain, quality of life, perceived effect of treatment:** There is low evidence from one small randomized controlled trial that SCS is no different from conventional therapy (physical therapy) in patients with chronic neuropathic pain 5-10 years following implant"<br>**There is no evidence available to assess long-term efficacy of SCS (>10 years).**<br>**There is no moderate or high evidence that SCS has differential efficacy or safety issues in sub populations (for more detailed information see** |

| | |
|---|---|
| | **accompanying technical report, Appendix 5.11).** |
| **Effect of SCS on function, quality of life, return to work, medication use and the healthcare system?** | **FUNCTION AND QUALITY OF LIFE**<br>**<u>There is low level evidence that SCS is more effective than comparators in the short term (<5 years)</u>**<br>"**Function, quality of life:** The effect on quality of life outcomes is less clear with one RCT reporting substantial benefit of SCS compared with CMM at 6 months follow-up, while another study found quality of life outcomes to be similar between SCS + physical therapy and physical therapy alone at 2 years follow-up. Similarly, function as measured by the Oswestry Disability Index score was better in the SCS group at 6 months versus CMM in one study but the ability to perform daily activities after 3 years was not different in a second study."<br>**<u>There is low level evidence that SCS is no different to physical therapy in the mid-term 5 - <10 years)</u>**<br>"**Pain, quality of life, perceived effect of treatment:** There is low evidence from one small randomized controlled trial that SCS is no different from conventional therapy (physical therapy) in patients with chronic neuropathic pain 5-10 years following implant with respect to pain, quality of life, and patient-reported global perceived effect."<br>**COST ANALYSIS**<br>"There is moderate evidence from three complete economic evaluations that in the short-term, SCS is associated with improved outcomes and increased costs compared with CMM and/or reoperation for the treatment of neuropathic pain. In the long-term, SCS appears to be dominant over the control treatments; however, only one study included in this assessment was conducted in a U.S. setting. More specifically, they found that there is some evidence that SCS is cost-effective at moderate (<$20,000) incremental cost effectiveness ratio (ICER) levels compared with CMM or reoperation, and that SCS cost-effectiveness increases and may be dominant over time compared with control treatments (i.e., CMM or reoperation) assuming device longevity of 4 years and at least a 30% pain threshold criteria."<br>The accuracy of this cost analysis is uncertain as the assumption of continued efficacy past 3 years is questionable from the only RCT reporting pain 5-10 years after implantation. Furthermore, it is unclear how this relates to an Australian setting as none of the studies were conducted in Australia. |
| **Which patient groups/ conditions is use of SCS contraindicated?** | "***Contraindications***[26-28]<br>Patients should not receive permanent SCS therapy who:<br>• failed trial stimulation due to ineffective pain relief<br>• are poor surgical risks<br>• are pregnant<br>• are unable to operate the SCS system<br>• have cardiac pacemakers (unless specific precautions are taken regarding |

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| | the mode and frequency of the device and not contraindicated for the particular device)<br>• have cardioverter defibrillators<br>• have active general infections<br>• have multiple illnesses<br>Additionally, SCS systems must be removed prior to diathermy or (depending on the device) exposure to any source of strong electromagnetic interference such as MRI (magnetic resonance imaging), therapeutic ultrasound, or defibrillation. Further, patients should turn the devices off prior to operating heavy machinery or power tools to avoid over-stimulation" |
| **Risks associated with use of SCS** | **<u>High level evidence (revision)</u>**<br>**There is high level evidence from three randomized controlled trials, one prospective comparative cohort study and six case series that revision of SCS components is not uncommon.** Overall short-term revision rates ranged from 12–38% of patients. Mid-term revision rates were 42% in one RCT and 60% in one case series. Reasons for revision include electrode repositioning or replacement, generator revision or replacement, revision of the connecting cable, and total removal and replacement of the system due to infection. There was no long-term data available.<br>**<u>High level evidence (mortality)</u>**<br>**There is high evidence that the rate of mortality due to SCS is low.** Among the four comparative studies, 2 deaths were reported in patients receiving SCS (2/139); one as a result of a cardiac event six months following SCS implantation, and the cause of the other was not reported. No deaths were recorded in the control groups during the same time period (0/179). Two additional deaths were identified in three case series with five year follow-up; one from a cerebrovascular accident in a patient implanted for cardiac ischemic pain, one as a result of suicide. No death was attributed to SCS; however one patient nearly died as a result of complications that arose following trial stimulation.<br>**<u>Moderate level evidence (other SCS-related side effects)</u>**<br>Side effects reported varied widely among studies and included infection, change in amplitude by bodily movements, paresthesia in other body parts, pain/irritation from the pulse generator, transient neurological defects, severe wound-related pain at the stimulator implantation site, cerebrospinal fluid leak, and subcutaneous hematoma. **The rate of side effects could not be determined from the papers reviewed**; however, one RCT reported that all patients experienced at least one side effect. |
| **Conclusion/Recommendation** | **SHORT TERM EFFECTIVENESS**<br>There is **moderate level evidence** that **SCS is more effective** than comparators in the short term (<5 years) in terms of: **pain, perceived effect of treatment/ patient satisfaction**, **function, and quality of life**.<br>**MID-TERM EFFECTIVENESS**<br>There is **low level evidence** that **SCS is no different** to physical therapy in the mid-term (5 - <10 years) in terms of: **Pain, quality of life, and perceived** |

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| | **effect of treatment**<br>**LONG-TERM EFFICACY**<br>There is **no evidence** available to assess long-term efficacy of SCS (>10 years) |
| **Recommendation category** | Positive for short-term effectiveness in terms of pain reduction. Insufficient and no evidence for the outcomes of function and quality of life in mid-term and long term, respectively. |
| **Quality assessment results** | Low risk of bias for the HTA.<br>One RCT had a high crossover rate from the reoperation group to the SCS group (54%, after six months), follow-up rate was only 75% contributing to possible attrition bias and bias in study design as the "study only compared SCS to reoperation, a treatment that had previously failed and is unlikely to improve outcomes in FBSS patients".<br>A prospective cohort study reported potential selection bias. "Patients in the SCS group tended to have more legal representation, longer duration of work time loss compensation, longer duration of leg pain and greater leg pain intensity compared with those in the pain clinic or usual care groups." |
| **Our comments/summary** | This is a well-conducted HTA with a low risk of bias.<br>The authors included studies related to some types of pain that would be excluded according to the selection criteria of our report (i.e. post-stroke pain), this may affect generalisability. |

## Findings

The most high-quality, comprehensive, up-to-date source of synthesised research was a well-conducted HTA with a low risk of bias.[2] The authors found:

Efficacy/Effectiveness

- **Moderate level evidence** of effectiveness of SCS (when compared to conventional therapies: CMM, physical therapy or reoperation) for outcomes measures of pain in the short-term (<5 years)
- **Low level evidence** of no difference in effectiveness for outcomes measures of pain between SCS and physical therapy in the mid-term (5 to <10 years)
- **No evidence** available to assess long term efficacy for outcomes measures of pain of SCS (>10 years).

Safety

- **High level evidence** that revision of SCS components is not uncommon
- **High level evidence** that mortality rates due to SCS are low
- The rate of side-effects could not be determined

## 2. SUBCUTANEOUS ELECTRICAL STIMULATION (SES)

### Evidence identified

As reported in the previous version of this report,[1] our search did not identify any synthesised evidence or controlled trials for the use of subcutaneous electrical stimulation (SES) in the treatment of chronic, intractable pain.

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

## 3. PERIPHERAL NERVE STIMULATION (PNS)

### Evidence identified

The most comprehensive, up-to-date source of synthesised evidence was an EBG[3] which was critically appraised in the previous report[1]. Although our update search identified a more recent EBG[12], it was excluded as there was insufficient information to assess its methodological quality and overall risk of bias.

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 chronic pain.

**Table 4. Key information from recent, comprehensive, high quality evidence based guideline *(Cruccu 2007)* – Peripheral Nerve Stimulation (PNS)**

| ***Cruccu G, Aziz TZ, Garcia-Larrea L, Hansson P, Jensen TS, Lefaucheur JP, et al. EFNS guidelines on neurostimulation therapy for neuropathic pain. Journal of Neurology. 2007;14: 952-70.*** | |
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| **Study design** | Evidence based guideline |
| **Scope** | **Patient/population:** n=202, six case series<br>**Conditions indicated for use:** Pharmacoresistant patients with CRPS II, peripheral neuropathy, post-traumatic pain, radiculopathy, amputation, or other pain conditions (not specified in the guideline).<br>**Intervention:** Peripheral nerve stimulation<br>**Comparator:** N/A (uncontrolled studies, case series)<br>**Outcomes assessed:**<br>• Pain intensity and relief |
| **Efficacy and effectiveness of PNS for persistent pain** | Based on low levels of evidence (case series) involving a total of 202 patients, Cruccu et al (2007) report an average success rate of 60% for PNS (success was defined as those patients reporting pain relief greater than or equal to 50%). The guideline did not provide details of how pain was |

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| | assessed in each of the primary studies or how the success rate from individual studies was determined. |
| **Effect of PNS on function, quality of life, return to work, medication use and the healthcare system?** | Not reported |
| **Which patient groups/ conditions is use of PNS contraindicated?** | Not reported |
| **Risks associated with use of PNS** | The summary of harms provided by Cruccu et al (2007) was based on the six studies identified for PNS. These studies reported that reoperation was performed in some patients. |
| **Conclusion/Recommendation** | Cruccu et al (2007) reported that none of the identified studies had an adequate control group and they were unable to draw any conclusions for PNS recommendations in the guideline. Of the few studies identified for PNS, they were old (between 1975-1999), suggesting this intervention is not increasing in popularity. |
| **Recommendation category** | Class IV (uncontrolled studies, case series, case reports, or expert opinion) for MCS. Class IV is considered insufficient evidence to determine recommendations. |
| **Quality assessment results** | Moderate |
| **Our comments/summary** | The guideline scored moderately well with regards to the scope, purpose and rigorous methodology employed. The outcome measures for pain in the included studies were not reported however, so consistency between the studies cannot be established (for more detailed information see accompanying technical report, Appendix 5.9). |

### Findings

Due to a lack of high quality, controlled primary studies, there is **insufficient evidence** to determine the effectiveness of peripheral nerve stimulation (PNS) for the treatment of persistent pain.

# 4. MOTOR CORTEX STIMULATION

## Evidence identified

The most recent, highest levels of evidence for MCS were 2 crossover RCTs[4, 5] and 1 CCT.[61] 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 real effect. Also, the authors of one RCT[4] 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 as its washout period was shorter.

The results from the two studies could not be pooled due to differences between the studies in the length of time patients were stimulated, and outcome measures.

The quality of the studies could not be determined as the authors of both RCTs did not report on the methods used for randomisation or if allocation concealment was performed. We conclude that there is insufficient evidence to determine the effectiveness of MCS for the treatment of chronic persistent pain.

**Table 5. Key information from recent, comprehensive, high quality primary study *(Lefaucheur 2009)* – Motor Cortex Stimulation (MCS)**

| ***Lefaucheur J-P, Drouot X, Cunin P, Bruckert R, Lepetit H, Creange A, et al. Motor cortex stimulation for the treatment of refractory peripheral neuropathic pain. Brain. 2009 Jun; 132(Pt 6):1463-71*** | |
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| **Study design** | Crossover Randomised Clinical Trial (RCT) |
| **Scope** | **Patient/population:** n=13 (for the randomised phase of the study)<br>**Conditions indicated for use:** Patients with chronic neuropathic pain of either peripheral or central origin<br>**Intervention:** Motor cortex stimulation (stimulator 'on' for 1 month duration)<br>**Comparator:** Sham stimulation (stimulator 'off' for 1 month duration)<br>**Outcomes assessed:**<br>• Pain intensity and relief<br>• Functional assessments (general activity, mood, walking ability, normal work, relations with other people, sleep and enjoyment of life)<br>• Medication use |
| **Efficacy and effectiveness of MCS for persistent pain** | The primary outcome assessed was pain intensity and pain relief, measured with a visual analogue scale (VAS). The VAS is a patient-reported outcome assessment where a result of 0 = no pain to 100 = highest imaginable pain. No significant difference was observed in the VAS between "on-stimulation" and "off-stimulation" conditions in the randomised period (p=0.92). |
| **Effect of MCS on function, quality of life, return to work, medication use and the healthcare system?** | The functional outcomes assessed included a ranking test assessing four major groups known as the McGill Pain Questionnaire (MPQ), the McGill Pain Questionnaire-Rating Index (MPQ-RI), the Sickness Impact Profile (SIP) used to assess quality of life (QoL) and the Medication Quantification Scale (MQS). |

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| | Out of all the functional outcomes measured, the only statistically significant difference observed between the intervention and control groups was the MPQ-RI (27.4 'on stimulation' versus 33.6 'off-stimulation', p=0.0166). However, after adjustment for statistical analysis was conducted, the significance was no longer apparent. |
| **Which patient groups/ conditions is use of MCS contraindicated?** | Not reported. |
| **Risks associated with use of MCS** | Not reported. |
| **Conclusion/Recommendation** | The results from the randomised period of the study did not reveal any significant difference in pain outcomes (VAS) assessed between the two groups – 'on stimulation' and 'off stimulation'. One of the functional outcomes assessed (MPQ-RI) showed a statistically significant difference between treatment groups, however due to the small patient numbers this result does not provide any evidence for an effect of MCS on function or quality of life. |
| **Recommendation category** | Negative |
| **Quality assessment results** | There was a high risk of bias. |
| **Our comments/summary** | This study had a complicated design of which the crossover RCT was only one component. The results from the crossover RCT were slightly 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.<br>Overall this study has a high risk of bias due to an insufficient wash-out period between phases of the cross-over RCT. The insufficient washout period combined with the small treatment groups mean we cannot have confidence that the results reflect the true effect of the intervention.<br>There is insufficient evidence to determine the effectiveness of MCS for the treatment of chronic neuropathic pain. |

**Table 6. Key information from recent, comprehensive, high quality primary study *(Nguyen 2008)* – Motor Cortex Stimulation (MCS)**

| ***Nguyen J-P, Velasco F, Brugieres P, Velasco M, Keravel Y, Boleaga B, et al. Treatment of chronic neuropathic pain by motor cortex stimulation: results of a bicentric controlled crossover trial. Brain Stimulation. 2008 Apr; 1(2):89-96.*** | |
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| **Study design** | Crossover Randomised Clinical Trial (RCT) |
| **Scope** | **Patient/population:** n=10<br>**Conditions indicated for use:** Patients with chronic neuropathic pain of either peripheral or central origin<br>**Intervention:** Motor cortex stimulation for 2 weeks (ON period)<br>**Comparator:** Sham stimulation for 2 weeks (OFF period)<br>**Outcomes assessed:**<br>• Pain intensity and relief<br>• Functional assessments (general activity, mood, walking ability, normal work, relations with other people, sleep and enjoyment of life)<br>• Medication use |
| **Efficacy and effectiveness of MCS for persistent pain** | There was no statistically significant difference in pain relief between the ON period and the OFF period as shown by VAS – mean (ON vs. OFF, 1st group): 53.5 vs. 78.0, versus (OFF vs. ON, 2nd group) 2.1 vs. 3.3. The visual analogue scale (VAS) is a patient-reported outcome where a score of 0 = no pain to 100 = highest imaginable pain. |
| **Effect of MCS on function, quality of life, return to work, medication use and the healthcare system?** | Several functional outcomes were assessed in the study. These included 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). 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 outcomes measures (ON vs. OFF: WBPQ - 36.0 vs. 53.0, MPQ-PRI - 33.9 vs. 60.1 and MQS - 20.3 vs. 26.3). |
| **Which patient groups/ conditions is use of MCS contraindicated?** | Not reported. |
| **Risks associated with use of MCS** | Not reported. |
| **Conclusion/Recommendation** | The authors' conclusions did not reflect the results of the study. There is insufficient evidence to conclude if MCS is effective for the treatment of chronic neuropathic pain of peripheral or central origin. |
| **Recommendation category** | Further evidence required. |
| **Quality assessment results** | The insufficient washout period means that the study has a high risk of bias. There was a lack of information provided on the methodology of the study. |
| **Our comments/summary** | Although the study was the first RCT to assess the effectiveness of MCS in chronic pain, 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, we |

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| | cannot conclude that the observed effect is truly reflective of the intervention. |

**Findings**

The most recent, highest levels of evidence for MCS were two primary RCTs[4, 5]. Both RCTs had complex study designs.

Both of the studies reported that MCS did not significantly improve chronic neuropathic pain when compared with controls.

The small size of the groups in both studies makes it impossible to generalise the results. Adding to this complexity was a lack of reporting on several methodological parameters by the authors of the studies. Furthermore the studies also had an insufficient wash-out period between phases.

There is **insufficient evidence** to determine if MCS is effective for the treatment of chronic neuropathic pain of central or peripheral origin.

## 5. DEEP BRAIN STIMULATION (DBS)

### Evidence identified

The most comprehensive, up-to-date source of evidence for DBS in chronic non-cancer pain was a high level, crossover RCT[6]. This crossover RCT was relatively well conducted in terms of the study design. However, the overall risk of bias was moderate, hence we cannot generalise the results of the study and make conclusions on whether DBS is effective for the treatment of chronic pain.

**Table 7. Key information from recent, comprehensive, high quality primary study *(Fontaine 2010)* – Deep Brain Stimulation (DBS)**

| ***Fontaine D, Lazorthes Y, Mertens P, Blond S, Geraud G, Fabre N, et al. 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 Feb; 11(1):23-31.*** | |
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| **Study design** | Crossover Randomised Clinical Trial (RCT) |
| **Scope** | **Patient/population:** n=11<br>**Conditions indicated for use:** Patients with severe refractory chronic cluster headache (CCH)<br>**Intervention:** Deep Brain Stimulation ('on' for 1 month)<br>**Comparator:** Sham stimulation ('off' for 1 month)<br>**Outcomes assessed:**<br>• Weekly attacks frequency (primary),<br>• Pain intensity (Likert scale),<br>• Sumatriptan injections, oxygen use (yes or no),<br>• Anxiety and depression levels (Hospital Anxiety Depression scale), quality of life (SF-12 scale), patient's satisfaction (Patient's Global Impression of Change)<br>• Blood pressure, heart rate, weight and body temperature<br>• Electrolyte balance and hormonal functions, and changes in thirst, appetite, libido, sleepwalking cycle and behaviour (AE) |
| **Efficacy and effectiveness of DBS for persistent pain** | "The weekly frequency of CH attacks did not significantly differ between the On and Off periods (Table 2). We did not detect any significant carry-over effect (P = 0.855) indicating that the effects of the first treatment period did not persist after the wash out. None of the secondary outcomes differed between stimulation and sham treatment." |
| **Effect of DBS on function, quality of life, return to work, medication use and the healthcare system?** | The authors reported that no significant differences were observed in any of the secondary outcomes, such as 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) (for more information refer to the Technical Report, Appendix 5). |
| **Which patient groups/ conditions is use of DBS contraindicated?** | Not reported |
| **Risks associated with use of DBS** | Adverse events related to surgery included infection and neck pain. Adverse |

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| | events related to test stimulation included complex occulomotor disturbances and loss of consciousness. Adverse events during the randomised phase of the study included mild hunger increases and decreases and mild libido decreases. |
| **Conclusion/Recommendation** | "Randomized phase findings of this study did not support the efficacy of DBS in refractory CCH." |
| **Recommendation category** | Further studies required |
| **Quality assessment results** | Moderate |
| **Our comments/summary** | Several biases in the study were reported including 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. |

### Findings

The most comprehensive high level evidence for DBS was a recent crossover RCT.[6]

Based on the results of this study, DBS did not significantly reduce pain or improve quality of life in severe refractory chronic cluster headache when compared with controls.

Although the study design was well thought out, several biases existed in the study including small sample size, short duration of treatment and possible non-optimal stimulation parameters. Hence, the results observed in the study may not accurately reflect the true effect of DBS.

Therefore, there is **insufficient evidence** available to determine the effect of deep brain stimulation (DBS) in the treatment of persistent pain including chronic cluster headache.

## 6. OCCIPITAL NERVE STIMULATION (ONS)

### Evidence identified

The most comprehensive, up-to-date sources of evidence identified for ONS in chronic non-cancer pain were 2 RCTs[7, 8]. Only one RCT[8] was of moderate quality with a low to moderate risk of bias. There was insufficient information provided for the second RCT to assess its quality and overall risk of bias.

**Table 8. Key information from a recent, comprehensive, high quality primary study *(Lipton 2009)* – Occipital Nerve Stimulation (ONS)**

| ***Lipton, R, Goadsby, P, Cady, R, Aurora, S, Grosberg, B, Freitag, F, Silberstein, S, Whiten, D and Jaax, K. PRISM study: occipital nerve stimulation for treatment-refractory migraine. Cephalalgia. 2009. 29 (Suppl. 1): 30.*** | |
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| **Study design** | Randomised controlled trial (RCT) |
| **Scope** | **Patient/population:** n=132 (n=63 active stimulation, n=62 sham stimulation)<br>**Conditions indicated for use:** Patients with treatment-refractory migraine<br>**Intervention:** Bilateral active occipital nerve stimulation for 12 weeks<br>**Comparator:** Sham stimulation for 12 weeks, then conversion to active stimulation for another 10 months<br>**Outcomes assessed:** Pain relief (change from baseline in migraine days/month), side effects/complications |
| **Efficacy and effectiveness of ONS for persistent pain** | "For the primary endpoint, reduction in migraine days/month, the difference across treatment arms was not significant (-5.5 vs.-3.9, p = 0.29). "<br>"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)." |
| **Effect of ONS on function, quality of life, return to work, medication use and the healthcare system?** | Not reported |
| **Which patient groups/ conditions is use of ONS contraindicated?** | Not reported |
| **Risks associated with use of ONS** | "Two-year aggregate safety data revealed infection, non-target area sensory symptoms, and implant site pain as the most-frequent device related adverse events." |
| **Conclusion/Recommendation** | "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 stimulation, based in part on the absence of medication overuse and a favourable response to a trial of percutaneous treatment." |
| **Recommendation category** | Neutral (no difference in effect between stimulation and sham stimulation groups) |
| **Quality assessment results** | There is insufficient information to assess the quality and risk of bias of the study. |

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| **Our comments/summary** | The authors did not report on the several methodological parameters (see technical report, Table A5.4 for a more detailed discussion), hence we were unable to assess the quality of the study or the overall risk of bias. This may have been due in part to the RCT being published as a program abstract only. We contacted the authors but received no response. It is important to note that the key prognostic variables for each group at baseline were not reported and no data is provided at 1 year of treatment as the authors reported. |

**Table 12. Key information from a recent, comprehensive, high quality primary study *(Saper 2011)* – Occipital Nerve Stimulation (ONS)**

| ***Saper, J, Dodick, D, Silberstein, S, McCarville, S, Sun, M, Goadsby, P, ONSTIM Investigators. Occipital nerve stimulation for the treatment of intractable chronic migraine headache: ONSTIM feasibility study. Cephalalgia. 2010. 31 (3):271-285.*** | |
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| **Study design** | Randomised controlled trial (RCT) |
| **Scope** | **Patient/population:** n=75 (see Table A5.2 in the technical report for more information)<br>**Conditions indicated for use:** Patients with medically intractable chronic migraine (CM)<br>**Intervention:** ONS – Adjustable stimulation (AS) group was instructed to maintain the stimulator in the ''on'' position and to adjust the device to minimize pain<br>**Comparator:** Preset stimulation group and medically managed control group<br>**Outcomes assessed:**<br>• Reduction in headache days per months;<br>• proportion of patients who achieved ≥ 50% reduction in headache days per month (responder rate);<br>• a 3-point or greater reduction in average overall pain intensity;<br>• disability and QoL;<br>• risks/complications |
| **Efficacy and effectiveness of ONS for persistent pain** | "For the majority of outcome measures (i.e. 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), the exploratory analyses showed no statistically significant improvement over baseline when comparing the AS group with the control groups (PS and MM), although a numerical advantage appeared to be associated with the AS group. Because the number of subjects in the ancillary group was small, reliable comparisons could not be made." |
| **Effect of ONS on function, quality of life, return to work, medication use and the healthcare system?** | The effect of ONS on functional outcomes and quality of life (QoL) was assessed using the well established and validated functional disability scale, the SF-36 test, subject satisfaction scores and change in medication use. Other measures included the Migraine Disability Assessment (MIDAS) and the Profile of Moods States (POMS) scores.<br>For most measures of disability and quality of life, no statistically significant |

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| | difference was observed with ONS in comparison to the control groups. This may have been attributable to the small number of patients in each of the treatment groups. The authors report that the difference may be more significant in further studies, however the present study is an exploratory one. |
| **Which patient groups/ conditions is use of ONS contraindicated?** | Not reported |
| **Risks associated with use of ONS** | "Three subjects experienced serious ADEs requiring hospitalization: implant site infection, lead migration and postoperative nausea. The most frequently reported ADE was lead migration, which occurred in 12 of 51 subjects (24%). There was no evidence of ADEs leading to long-term complications or potential nerve damage. There were no serious unanticipated ADEs reported or identified in this study."<br>"Nine percent of the AS group, 41% of the PS group and 24% of the MM group reported increased migraine. Adverse events related to medications were similar across treatment groups and ranged from 6% to 18% (Table 6)." |
| **Conclusion/Recommendation** | "On the basis of the current findings and in light of previously published work, we believe further investigational pursuit to evaluate the efficacy and safety of ONS for medically intractable CM is justified. Further study would be enhanced by improved stimulator design, implanting technique and lead design and by a well-targeted, carefully selected study population, more robust endpoints, longer trial duration and improved blinding techniques. Reliable conclusions regarding efficacy cannot be established on the basis of this study alone. Nonetheless, the results of this feasibility study offer promise and should prompt further study of ONS in medically intractable CM." |
| **Recommendation category** | Needs further evidence |
| **Quality assessment results** | Low to moderate risk of bias. |
| **Our comments/summary** | This study was well conducted with a low to moderate risk of bias. The results of the study were consistent with an earlier RCT performed by the same group revealing no statistically significant difference between treatment groups. Interestingly, the authors report that although no statistical difference was observed, there was "a numerical advantage associated with ONS". The small size of treatment groups and short duration of the study could have masked the true effect of the intervention. |

## Findings

The most comprehensive, up-to-date sources of evidence for ONS in the treatment of intractable, chronic headache and migraine conditions were two RCTs that were conducted by the same research group.

Both of the RCT's reported that ONS did not significantly reduce pain or improve functional outcomes when compared with controls.

The more recent RCT had smaller treatment groups (n=29 AS, n=16 PS and n=17 MM) in comparison to the earlier one (n = 63 stimulated, n=62 sham. The authors of both studies reported long-term follow-up of patients however the results were not provided,

Therefore, there is **insufficient evidence** to determine the effectiveness of occipital nerve stimulation (ONS) for the treatment of intractable, treatment refractory headache and migraine conditions.

## DISCUSSION & CONCLUSION

In assessing the effectiveness of neurostimulation in the treatment of chronic pain syndromes, several studies presented limitations for this report.[5, 8, 12, 38, 39, 66]

The first limitation pertains to the experimental or exploratory nature of some types of neurostimulation, such as subcutaneous electrical stimulation (SES), peripheral nerve stimulation (PNS) and occipital nerve stimulation (ONS). Until further comprehensive, well conducted high quality studies are performed to increase the evidence available for these types of neurostimulation, conclusions on their effectiveness for chronic pain cannot be made.

Another major limitation in this report was the inability to determine the quality of the included studies. Several authors did not provide sufficient information about important methodological aspects, essential in determining the overall quality of the study. Also, there was a lack of high quality primary studies assessing the effect of neurostimulation on function, quality of life, return to work, medication use and the use of the healthcare system.

Spinal cord stimulation had the most well developed evidence base, and was the only type of neurostimulation for which we could provide findings for all of the questions we sought to answer in this evidence review.

### SPINAL CORD STIMULATION (SCS)

The most comprehensive, current, high-quality piece of synthesised evidence identified was a HTA on SCS.[2] 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 moderate evidence that SCS is effective for pain relief and low evidence for an improvement in function and quality of life in the short term (<5 years), but there was insufficient evidence of effectiveness beyond this. In terms of safety, they found strong evidence that the need for revision of the procedure was common. Mortality rates due to SCS were low in the short term. The authors were unable to determine rates of SCS related side-effects, but noted that the following were possible: infection, change in amplitude by bodily movements, paresthesia in other body parts, pain/irritation from the pulse generator, transient neurological defects, severe wound-related pain at the stimulator implantation site, cerebrospinal fluid leak, and subcutaneous hematoma.
The HTA also provided information on indications for use of the healthcare system and cost effectiveness, but this information is specific to the US and may not be generalisable to the Australian setting.

We conclude that there is moderate evidence that SCS is effective for pain relief and low evidence for an improvement in function and improvement in quality of life in the short-term (<5years); there is strong evidence that revision of the procedure is common; and strong evidence that SCS related mortality rates are low.

## SUBCUTANEOUS ELECTRICAL STIMULATION (SES):

Similar to the previous version of this report, our search did not identify any synthesised evidence or controlled trials for the use of subcutaneous electrical stimulation (SES) in the treatment of chronic, intractable pain. Therefore the effectiveness of SES in the treatment of chronic pain is unclear.

## PERIPHERAL NERVE STIMULATION (PNS):

The most comprehensive, up-to-date source of evidence was an EBG[3] on PNS. The quality of the EBG in terms of the scope, purpose and rigorous methodology was moderate. The authors concluded that without adequate controls in the included studies (uncontrolled studies, case series) they were unable to draw any conclusions.

We conclude therefore that due to low level evidence (case series only), there is insufficient evidence to determine the effectiveness of PNS in the treatment of chronic pain.

## MOTOR CORTEX STIMULATION (MCS):

The most recent pieces of evidence for MCS were two RCTs[4, 5] which were conducted by the same clinical group but with modified methods. Both RCTs used small patient groups and had short study durations. Also of note is that both studies did not report any risks or 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 RCT findings.

Both RCTs[4] had a high risk of bias due to an insufficient washout period. Hence, the results of the study are unlikely to be an accurate estimate of the real effect of MCS. We therefore conclude that there is insufficient evidence to determine the effectiveness of MCS in the treatment of chronic pain of central or peripheral origin.

## DEEP BRAIN STIMULATION (DBS):

We concluded that there is insufficient evidence to determine the effectiveness and safety for DBS in the treatment of chronic pain syndromes and intractable trigeminal autonomic cephalalgias (TACs) such as chronic cluster headache.
Although the highest level of evidence was one relatively well conducted crossover RCT. The overall risk of bias was moderate due to small sample size, short treatment duration and possible non-optimal stimulation parameters for some patients. Hence we cannot generalise the results of the study and make conclusions on whether DBS is effective for the treatment of chronic pain.

## OCCIPITAL NERVE STIMULATION (ONS):

The most comprehensive, up-to-date sources of evidence for ONS were 2 RCTs.[7, 8, 66] Both RCTs found that there was no statistically significant difference between intervention and comparator groups at 3 months for the treatment of chronic migraine. The results of these studies should be taken with caution as the patient treatment groups were small and the duration of the study was short. Of the studies performed to date using ONS, it is thought that the maximal beneficial effects are often not experienced by patients until several months following implantation. [67] Further studies should consider this when designing their own studies.

We concluded that there is insufficient evidence for the effectiveness of ONS in treatment refractory migraine and headache conditions.

## 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/WSV 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/WSV Health Services Group has 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.

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Transport Accident Commission & WorkSafe Victoria

# Evidence Service

# Implantable Pain therapies: Neurostimulation

## Technical Report: Appendices 1-5

## October 2011

**Loretta Piccenna, Emma Donoghue**

| Accompanying documents to this report | |
|---|---|
| *Title* | *Report number* |
| Implantable pain therapies: Neurostimulation – Full Report | 0611-002-R8 |
| Implantable pain therapies: Neurostimulation - Evidence Summary | 0611-002-R8.1 |
| Implantable pain therapies: Neurostimulation - Plain Language Summary | 0611-002-R8.2 |

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## INTRODUCTION

This technical report is a companion document to "Implantable therapies: Neurostimulation - Evidence Review". It contains detailed information about the methods used in the development of the Evidence Review, summaries of the studies included in the review, and quality appraisal results for the most recent and/or most relevant included studies.

## CONTENTS

# APPENDIX 1: REVIEW PROCESS

A two-staged approach was undertaken.

## STAGE 1

### Identify evidence available for each intervention

• Run search in health databases, websites and on the internet, limit to EBGs, HTAs, SRs, RCTs and controlled clinical trials (CCTs)

• Apply inclusion and exclusion criteria

### Critically appraise synthesised research

• Start with most recent review, apply standard appraisal criteria

• If found to be of high quality, cross check to ensure references from all other synthesised research are included and check for consistency of findings

• If not high quality, appraise next most recent and repeat process

• If there are inconsistent findings across the existing reviews, investigate the possibility of synthesis of this information or whether a new systematic review is required

### Decide on actions for Stage 2

• Map available evidence (as per Table A1.1)

• Identify whether sufficient high level evidence exists to answer questions or identify what further action needs to be taken (see algorithm in Table A1.2).

## STAGE 2

Address further actions identified.

**Table A1.1. Map of available evidence**

| Categories of neurostimulation | Synthesised Studies | | Primary studies | TOTAL |
|---|---|---|---|---|
| | EBGs | SRs & HTAs | | |
| **Spinal Cord Stimulation (SCS)** | | | | |
| **Subcutaneous Electrical Stimulation (SES)** | | | | |
| **Peripheral Nerve Stimulation (PNS)** | | | | |
| **Motor Cortex Stimulation (MCS)** | | | | |
| **Deep Brain Stimulation (DBS)** | | | | |

**Table A1.2. Further action required to answer clinical questions**

<table>
<tr><td colspan="5">Is there any synthesised research available? (e.g. EBGs, HTAs, SRs)</td></tr>
<tr><td colspan="3">Yes</td><td colspan="2">No</td></tr>
<tr><td colspan="3">Is this good quality research?</td><td colspan="2">Are RCTs available?</td></tr>
<tr><td colspan="2">Yes</td><td>No</td><td>Yes</td><td>No</td></tr>
<tr><td colspan="2">Is it current (within 2 years)?</td><td rowspan="2"></td><td rowspan="2"></td><td rowspan="2"></td></tr>
<tr><td>Yes</td><td>No</td></tr>
<tr><td>No further action</td><td>Update existing SR</td><td>Undertake new SR</td><td>Undertake new SR</td><td>Consider looking for lower levels of evidence</td></tr>
</table>

# APPENDIX 2: METHODS

TAC/WSV staff assisted in the development of search terms and inclusion and exclusion.

## Inclusion and exclusion criteria

Inclusion and exclusion criteria were established *a priori* (Table A2.1). All references were screened by both reviewers independently to check for consistency of inclusion/exclusion decisions, and results were found to be 100% in agreement.

**Table A2.1 Inclusion and Exclusion criteria**

| | |
|---|---|
| **Patient/ population** | **Inclusion:** Any individual with persistent pain (chronic, persistent, refractory)<br>• All ages<br>• All genders |
| | **Exclusion:** Patients with –<br>• acute pain eg post-op,<br>• non-persistent pain i.e. dysmenorrhoea, gastroparesis<br>• vascular insufficiency, i.e. stroke,<br>• systemic inflammatory conditions, i.e. fibromyalgia, Postherpetic neuropathy, dystonia<br>• haematological conditions, i.e. diabetic neuropathy<br>• cancers<br>• vuval pain or chronic pelvic pain<br>• chronic pancreatitis |
| **Intervention/ indicator** | **Inclusion:** Implantable therapy –<br>• spinal cord stimulation,<br>• subcutaneous electrical stimulation,<br>• peripheral nerve stimulation,<br>• deep brain stimulation,<br>• motor cortex stimulation,<br>• occipital nerve stimulation |
| | **Exclusion:**<br>• sacral nerve stimulation<br>• vagus nerve stimulation<br>• gastric nerve stimulation<br>• phrenic nerve stimulation<br>• thalamic stimulation<br>• electro-stimulated graciloplasty<br>• percutaneous posterior tibial nerve stimulation |
| **Comparison/ control** | **Inclusion:**<br>• placebo,<br>• conventional medical management (standard treatment) or<br>• another implantable pain therapy |
| | **Exclusion:** Nil |
| **Outcomes** | **Inclusion:** Any (e.g. pain measures., physical function – mobility, disability, psychological – depression, social functioning/roles, activities of daily living , quality of life (QOL), return to work, medication use and healthcare utilisation) |

| | |
|---|---|
| | **Exclusion:** Nil |
| **Setting** | **Inclusion:** Any healthcare setting (e.g. acute, subacute, rehabilitation, community) |
| | **Exclusion:** Nil |
| **Study Design** | **Inclusion:** Evidence-based guidelines, systematic reviews, health technology assessments, randomised controlled trials and controlled clinical trials. |
| | **Exclusion:** Non-evidence-based guidelines (EBGs), non-systematic reviews (SRs), cohort studies, case-control studies, case series, editorials, letters or commentaries |
| **Publication details** | **Inclusion:** Studies in English and conducted on humans |
| | **Exclusion:** Studies in languages other than English and/or conducted on animals |
| **Time period** | **Inclusion:** Any publication date |
| | **Exclusion:** Nil |

## Searches undertaken

## Search methods

Searches were conducted in electronic health databases, relevant websites and the internet and were repeated from those performed in the initial 2008 evaluation.

### Search strategies in electronic databases

It is difficult to ensure a comprehensive, up-to-date systematic search given the vast number of analgesic drugs available, the variety of generic terms used in different countries and the change in brand names over time. Hence drug terms were not included, however all relevant studies should be identified by combining terms related to chronic pain with terms related to the applicable routes of administration for intrathecal infusions. No terms have been included for comparison or outcomes to enable a broader search.

### Internet searches to identify relevant websites

The reviewers were aware of websites of guideline clearinghouses, guideline developers, centres of evidence-based practice and Australian government health services known to contain evidence-based resources. Additional websites of specific relevance (e.g. accident compensation groups) were sought via an internet search using the Google 'Advanced Search' function. The term 'evidence' was combined with the terms 'accident', 'injury', 'trauma', 'road', 'transport', 'traffic', 'work', 'employment' and 'safety'.

Fourteen websites relevant to Implantable Pain Therapies were identified. These, and the 31 generic websites previously identified by the review team (9 professional organisations, 9 guideline services, 12 Australian government websites and 1 centre of evidence-based practice) were searched for relevant guidelines. The searches are outlined in detail in Table A2.4.

### Website searches to identify relevant EBGs

Websites were searched using any lists of guidelines, publications or other resources identified on the site and scanned for relevant documents for both neurostimulation and intrathecal infusion. Where an internal search engine was available websites were searched using appropriate search strings relating to pain and the method of drug delivery.

### Internet searches to identify relevant references

An internet search strategy was conducted using the Google 'Advanced Search' function. The search strings were limited to documents in English and were used to identify guidelines for both interventions

- pain AND (evidence OR guideline) AND (intrathecal OR intraspinal OR spinal OR subarachnoid OR subdural OR stimulation OR electrode OR implantable)
- pain AND (evidence OR systematic OR review) AND (intrathecal OR intraspinal OR spinal OR subarachnoid OR subdural OR stimulation OR electrode OR implantable)'

The searches are outlined in detail in Table A2.4.

The first 100 Google search results were screened and yielded no new studies. As Google search results are presented in order of relevance, we did not screen further.

### Searches of reference lists

The reference lists of EBGs and SRs were also checked to identify any other potentially relevant EBGs, SRs or CCTs that had not been identified in our electronic searches.

### Databases accessed

A highly sensitive search in all EBM Reviews (including the Cochrane library), Ovid Medline, CINAHL, and Embase as detailed below was undertaken for the review terms.

**Table A2.2 Databases accessed**

| Database | Period | Date searched | Hits |
|---|---|---|---|
| Medline (Ovid) | 1950-present | 11 May 2011 | 1068 |
| All EBM reviews (Ovid)* | Various | 11 May 2011 | 431 |
| CINAHL (Ovid) | 2008 - 2011 | 11 May 2011 | 315 |
| EMBASE | EMBASE 1996 to 2011 Week 20 | 11 May 2011 | 1742 |
| All Combined | | | 3556 |
| EndNote find duplicates | | | 623 |
| All Combined EndNote de-duplicated | | | 2933 |
| Manual find duplicates | | | 155 |
| Total de-duplicated all combined | | | 2778 |

*including The Cochrane Database of Systematic Reviews, DARE, CENTRAL, NHSEED, HTA and ACP Journal Club

**Table A2.3 Major medical database search strategies**

| | | | |
|---|---|---|---|
| 1 | pain | 25 | epidural |
| 2 | Pain/exp | 26 | brachial |
| 3 | 1 or 2 | 27 | plexus |
| 4 | persist* | 28 | 26 AND 27 |
| 5 | chronic | 29 | deep |

| | | | |
|---|---|---|---|
| 6 | long term | 30 | brain |
| 7 | long-term | 31 | 29 AND 30 |
| 8 | refractory | 32 | motor |
| 9 | intractable | 33 | 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 28 or 31 or 32 |
| 10 | 4 or 5 or 6 or 7 or 8 or 9 | 34 | 16 AND 33 |
| 11 | 3 AND 10 | 35 | 13 AND 34 |
| 12 | 'intractable pain'/de | 36 | cortex |
| 13 | 11 or 12 | 37 | 'nerve stimulation'/exp |
| 14 | 'electrostimulation'/de | 38 | 'neuromuscular electrical stimulation'/de |
| 15 | stimulat* | 39 | 'brain depth stimulation'/de |
| 16 | 14 or 15 | 40 | neurostimulat* |
| 17 | 'spinal cord'/exp | 41 | 36 or 37 or 38 or 39 or 40 |
| 18 | 'peripheral nerve'/de | 42 | 35 AND 41 |
| 19 | 'spinal nerve'/exp | 43 | [humans]/lim |
| 20 | 'motor cortex'/de | 44 | 42 AND 43 |
| 21 | neur* | 45 | [2008-2011]/py |
| 22 | nerv* | 46 | 44 AND 45 |
| 23 | spinal | | |
| 24 | dorsal | | |

* Search undertaken in Medline, adapted for use in other databases

**Table A2.4 Website searches to identify relevant EBGs**

| Search 1: Identification of relevant guidelines for intrathecal implantable therapies using specific guideline-related websites | | |
|---|---|---|
| **Guideline Services** | **Results** | **Search** |
| National Health and Medical Research Council (NHMRC) | Acute pain management: scientific evidence.2010<br>http://www.nhmrc.gov.au/publications/synopses/cp104syn.htm | Web page reviewed by: Health Guidelines |
| National Institute for Health and Clinical Excellence UK (NICE) | Spinal cord stimulation for chronic pain of neuropathic or ischaemic origin<br>http://guidance.nice.org.uk/TA159<br>Stereotactic radiosurgery for trigeminal neuralgia using the gamma knife<br>http://guidance.nice.org.uk/IPG85 | Web page reviewed by: published clinical guidelines, published interventional procedures<br>Additional search by terms: chronic pain, intrathecal infusion, neurostimulation |
| New Zealand Guideline Group (NZGG) | N/A | Web page reviewed by: Guidelines<br>Additional search by terms: pain, intrathecal infusion, neurostimulation |
| Scottish Intercollegiate Guidelines Network (SIGN) | N/A | Web page reviewed by: guidelines by subject<br>Additional search by terms: chronic pain, intrathecal infusion, neurostimulation |
| Joanna Briggs Institute | N/A | Web page reviewed by: chronic pain, intrathecal infusion, neurostimulation |
| Guidelines International Network | • EFNS guidelines on neurostimulation therapy for neuropathic pain. European Federation of Neurological Societies. NGC:005909 http://www.guideline.gov/content.aspx?id=11372<br>• Comprehensive evidence-based guidelines for interventional techniques in the management of chronic spinal pain. American Society of Interventional Pain Physicians. NGC:007428<br>• Spinal implants: DR8 pedicle screw system (Technology Review)<br>• Spinal cord stimulation for chronic pain of neuropathic or ischaemic origin (TA159)<br>• Khan kinetic treatment™ (KKT) (Technology Review)<br>• Lumbosacraal radiculair syndroom (M55)<br>• Epidurale Rückenmarkstimulation zur Therapie chronischer Schmerzen. S3-LL (DGAI/DGK/DGNC/DGN/DGSS) | Web page reviewed by: pain AND spinal, chronic pain, intrathecal, neurostimulation |

| | | |
|---|---|---|
| | • Durerea lombara joasa. Ghid pentru medicul de familie<br>• Percutaneous intradiscal laser ablation in the lumbar spine (IPG357)<br>• International guideline library update | |
| Guidelines Advisory Committee | N/A | Web page reviewed by: GAC Endorsed Guidelines |
| National Guideline Clearinghouse US (NGC) | Spinal cord stimulation for chronic pain of neuropathic or ischaemic origin. 2008 Oct. NGC:006752<br>National Institute for Health and Clinical Excellence (NICE) - National Government Agency [Non-U.S.].<br><br>Diagnosis and Treatment of Low Back Pain: A Joint Clinical Practice Guideline from the American College of Physicians and the American Pain Society. *What's New? What's Different?*<br><br>Best practices & practice guidelines. 2008. NGC:007125<br>International Chiropractors Association - Medical Specialty Society.<br><br>Chronic pain. 2008. NGC:007160 American College of Occupational and Environmental Medicine - Medical Specialty Society.<br><br>Pain (chronic). 2003 (revised 2008 May 19). NGC:006564<br>Work Loss Data Institute - Public For Profit Organization.<br><br>EFNS guidelines on neurostimulation therapy for neuropathic pain. 2007 Sep. NGC:005909<br>European Federation of Neurological Societies - Medical Specialty Society.<br><br>Diagnosis and treatment of degenerative lumbar spinal stenosis. 2002 (revised 2007 Jan). NGC:005896<br>North American Spine Society - Medical Specialty Society.<br><br>EFNS guidelines on pharmacological treatment of neuropathic pain. 2006 Nov. NGC:005495 | Searched by:<br>(1) pain AND (intrathecal* OR intra-thecal* OR intraspinal* OR intra-spinal* OR spinal* OR subarachnoid OR sub-arachnoid OR subdural* OR sub-dural*)<br>(2) pain AND (stimulation OR electrode OR implantable) |

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| | European Federation of Neurological Societies - Medical Specialty Society.<br>Practice guidelines for chronic pain management. An updated report by the American Society of Anesthesiologists Task Force on Chronic Pain Management and the American Society of Regional Anesthesia and Pain Medicine. 1997 Apr (revised 2010 Apr). NGC:007951<br>American Society of Anesthesiologists - Medical Specialty Society.<br>Assessment: efficacy of transcutaneous electric nerve stimulation in the treatment of pain in neurologic disorders (an evidence-based review). Report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. 2010 Jan. NGC:007678<br>American Academy of Neurology - Medical Specialty Society. | |
| TRIP Database<br>searched on 15/3/2011 – 144 results total 144<br><br>searched on 19/5/2008 – 1986 results total 89 | www.tripdatabase.com<br><br>Relevant publications downloaded to Endnote library | Searched by:<br>(1) pain AND (intrathecal* OR intra-thecal* OR intraspinal* OR intra-spinal* OR spinal* OR subarachnoid OR sub-arachnoid OR subdural* OR sub-dural*) Limited by: Guidelines) from:2008 to:2011<br>(2) pain AND (stimulation OR electrode OR implantable) Limited by: Guidelines from:2008 to:2011 |
| **Australian Government Websites containing Guidelines** | | |
| Australian Government Department of Health & Ageing | www.health.gov.au N/A | Scanned list of Topics for 'Pain' |
| Australian Institute of Health and Welfare | www.aihw.gov.au N/A | Web page reviewed by: Publications – searched within for guidelines uses Google to search |
| Health Insite | www.healthinsite.gov.au N/A | Web page reviewed by: Health topics – chronic pain – no guidelines locates SRs from the Cochrane Library |
| ACT Health | www.health.act.gov.au N/A | No EBGs |
| NSW Health | www.health.nsw.gov.au N/A | Only contains a small list of Paediatric Guidelines |
| NT Department of Health and Community Services | www.nt.gov.au/health N/A | No EBGs |

| | | |
|---|---|---|
| Queensland Health | www.health.qld.gov.au N/A | No EBGs |
| SA Department of Health and Human Services | www.health.sa.gov.au N/A | +guideline +pain |
| Tasmanian Department of Health and Human Services | www.dhhs.tas.gov.au N/A | guideline AND pain |
| Victorian Department of Human Services | www.dhs.vic.gov.au N/A | guideline AND pain |
| Victorian Government Health Information | www.health.vic.gov.au N/A | List of topics: Pain, Chronic Pain |
| WA Department of Health | www.health.wa.gov.au N/A | guideline AND intrathecal AND pain neurostimulation |
| ***Centres of Evidence Based Practice Websites*** | | |
| WA Centre for Evidence-based Nursing and Midwifery | http://wacebnm.curtin.edu.au N/A | Web page reviewed by: Resources – 'Reports, Guidelines and Article' (not relevant) |
| ***Other Accident Commissions*** | | |
| Transport Accident Commission | www.tac.vic.gov.au/ N/A | Search for Guidance, Guideline |
| Australian Transport Safety Bureau | http://www.atsb.gov.au/ N/A | Search for Guideline |
| Road Safety Victoria (TAC) | www.tacsafety.com.au/ | Search for Guideline |
| WorkSafe Victoria | http://www.workcover.vic.gov.au/<br>Evidence reviews<br>• Implantable Pain Therapy Policy<br>• Microsoft Word - Neurostimulation 20100430.doc | Search for intrathecal AND pain, neurostimulation<br>No Guidelines – in publications contains guidance materials but not evidence-based (included for interest) |
| Traffic Injury Research Foundation | http://www.trafficinjuryresearch.com/index.cfm | No Guidelines – contains traffic reports |
| Motor Accidents Authority NSW | http://www.maa.nsw.gov.au/ N/A | Intrathecal AND pain, neurostimulation |
| WorkSafe British Columbia | http://www.worksafebc.com/<br>• Intrathecal Fentanyl Use In Patients With Chronic Nonmalignant Pain<br>• Chronic Pain Treatments: What is the Evidence?<br>• The effectiveness of spinal cord stimulator in treating complex regional pain ... | Intrathecal AND pain, neurostimulation |
| Accident Compensation Corporation | http://www.acc.co.nz/index.htm | Intrathecal AND pain AND guideline |

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| | *ACC2404 Traumatic brain injury guidelines*<br>*Evidence tables: Infusion: Intrathecal Opioids*<br>*Considered Judgement Form: Intrathecal Infusion of Baclofen*<br>*Considered Judgement Form: Infusion - Intrathecal Baclofen*<br>*Evidence tables: Infusion: Intrathecal Baclofen*<br>*Evidence Based Review: Continuous Intrathecal Baclofen for Spasticity Management*<br>*Intrathecal baclofen*<br>*Evidence tables: Neuromodulation - Deep brain stimulation* | |
| Pain Treatment Topics | http://pain-topics.org/guidelines_reports/index.php<br>Pain Treatment Guidelines - Descriptions | (Intrathecal OR neurostimulation)Guideline |
| The George Institute | http://www.thegeorgeinstitute.org/iih/research/critical-care-&-trauma/critical-care-&-trauma_home.cfm<br>http://www.tac.vic.gov.au/upload/Neurostimulation - full report.pdf<br>http://www.tac.vic.gov.au/upload/Intrathecal infusion - full report.pdf | Intrathecal AND pain, neurostimulation |
| Injury Research and Prevention Unit | http://www.injuryresearch.bc.ca/ N/A | Intrathecal, neurostimulation |
| The Brain Trauma Foundation | http://tbiguidelines.org/glHome.aspx | Guidelines<br>- Inhospital Severe TBI Guidelines<br>- Surgical Management of TBI |
| Safer Roads | http://www.saferroads.org.uk/ | No Guidelines |
| Rail Accident Investigation Branch | http://www.raib.gov.uk/about_us/index.cfm | No Guidelines |
| Oslo Sports Trauma Research Centre | http://www.klokeavskade.no/en/ | No Guidelines |
| Oregon Evidence-Based Practice Centre | http://www.ohsu.edu/epc/pastProjects/index.htm N/A | Intrathecal pain, neurostimulation |
| Injury Prevention Network of Aotearoa New Zealand | http://www.ipnanz.org.nz/ N/A | Publications |
| Trauma Centre at Justice Resource Centre | http://www.traumacenter.org/ N/A | Publications |
| The DANA Foundation | http://www.dana.org/ N/A | Intrathecal pain Guideline, neurostimulation guideline |

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|---|---|---|
| European Association for Injury Prevention and Safety Promotion | http://www.eurosafe.eu.com/ N/A | Guideline AND pain |
| New Zealand Injury Prevention strategy | http://www.nzips.govt.nz/resources/publications.php N/A | Resources/ Publications/ |
| NHS Health at Work | http://www.nhsplus.nhs.uk/web/public/default.aspx?PageID=330 | TAC Guidelines only |
| Canadian Association of Road Safety Professionals | http://www.carsp.ca/index.php?0=page_content&1=59&2=134 N/A | Resources / Publications |

| **Search 2: Identification of relevant studies for intrathecal implantable therapies using Google** | |
|---|---|
| Find web pages that have **all these words** | pain AND (evidence OR guideline) AND (intrathecal OR intraspinal OR spinal OR subarachnoid OR subdural OR stimulation OR electrode OR implantable) |
| Limits | English, Past Year |
| Results 21/5/2008 completed search | About 2,410,000 results |

### Appraisal

Appraisal was undertaken in steps:

1. The most recent review (evidence-based guideline, systematic review or HTA) was assessed for quality using standard appraisal criteria.
2. If found to be of high quality, it was cross checked against the other available reviews to compare scope and consistency of findings.
3. If found not to be of high quality, the next most recent was appraised and the above process repeated.

### Quality

Evidence-based guidelines and systematic reviews were appraised using standard criteria by a single reviewer in consultation with colleagues as required. RCTs were also appraised using standard criteria by a single reviewer in consultation with colleagues as required. Details of quality appraisals are included in Appendix 5.

### Data Extraction

Data on characteristics of the studies were extracted and summarised.

### Consistency of findings

Where a current, good quality review was available, the findings were compared with those in the other available literature to identify any inconsistencies in the information provided.

## APPENDIX 3: LIST OF INCLUDED STUDIES


1. ACC. Interventional Pain Management (IPM) project.: Accident Compensation Commission; 2005 [updated 2005; cited 2008 May]; Available from: www.acc.co.nz
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# APPENDIX 4: SUMMARY OF INCLUDED STUDIES

**Table A4.1 summary of included studies**

| 1st author, year, title | Inclusion, Exclusion criteria ( for P.I.C.O) | Study design | Conclusion/Recommendation | Recommendation category | Other comments |
|---|---|---|---|---|---|
| **EVIDENCE BASED GUIDELINES (EBGs)** | | | | | |
| **SPINAL CORD STIMULATION (SCS)** | | | | | |
| **Van Eijs 2011**<br>*16. Complex Regional Pain Syndrome* | **POPULATION/CLINICAL INDICATION**<br>Patients with complex regional pain syndrome<br>**INTERVENTION**<br>Spinal cord stimulation + physical therapy<br>**COMPARATOR**<br>Physical therapy only<br>**OUTCOMES**<br>Reduction in pain | EBG | "Spinal cord stimulation is recommended if other treatments fail to improve pain and dysfunction (2 B+)." | Positive, when all else fails | *n.b. this EBG was also used as an included study for PNS* |
| **Van Boxem 2010**<br>11. Lumbosacral radicular pain | **POPULATION/CLINICAL INDICATION**<br>Patients with lumbosacral radicular pain (failed back surgery syndrome)<br>**INTERVENTION**<br>Spinal cord stimulation<br>**COMPARATOR**<br>Conventional treatment<br>**OUTCOMES**<br>**Effectiveness:** treatment of pain; patients satisfaction with treatment<br>**Safety:** Side effects or complications | EBG | "In patients with a therapy-resistant radicular pain in the context of a Failed Back Surgery Syndrome, spinal cord stimulation is recommended (2 A+). This treatment should be performed in specialized centers." | Positive with caveat | |
| **Van Zundert 2010**<br>4. Cervical radicular pain. | **POPULATION/CLINICAL INDICATION**<br>Patients with cervical radicular pain<br>**INTERVENTION**<br>Spinal cord stimulation<br>**COMPARATOR**<br>Not specified<br>**OUTCOMES**<br>Treatment of pain | EBG | No studies of spinal cord stimulation for cervical radicular pain were identified, however the authors recommendations were as follows:<br>"In selected patients with cervical radicular pain, refractory to other treatment options, spinal cord stimulation may be considered. This treatment should be performed in specialized centers, preferentially study related." | Positive as a last resort with caveats | No studies of spinal cord stimulation for cervical radicular pain were identified |

| 1st author, year, title | Inclusion, Exclusion criteria ( for P.I.C.O) | Study design | Conclusion/Recommendation | Recommendation category | Other comments |
|---|---|---|---|---|---|
| **Manchikanti 2009 p699**<br>Comprehensive evidence-based guidelines for interventional techniques in the management of chronic spinal pain | **POPULATION/CLINICAL INDICATION**<br>Patients with chronic spinal pain<br>**INTERVENTION**<br>Spinal cord stimulation<br>**COMPARATOR**<br>Conventional medical management, repeated lumbosacral surgery<br>**OUTCOMES:**<br>Effectiveness (pain reduction), cost effectiveness, safety and complications | EBG | ***"6.7.2 Cost Effectiveness***<br>Cost effectiveness of SCS has been performed in FBSS (995,996). Taylor et al (995) found that initial health care acquisition costs were offset by a reduction in post implant health care resource demands and costs. Mean 5-year costs were $29,123 in the intervention group compared to $38,029 in the control group for FBSS. Other investigators also showed similar findings illustrating cost effectiveness of spinal cord stimulation even though initial health care acquisition costs are higher than other treatments (996-999,1006).<br>***6.7.3 Safety and Complications***<br>The most common adverse event reported in the literature is lead migration followed by lead fracture and infection at the incision site of implantable pulse generator or in the surgical pocket (1000,1013,1014). Overall up to 34% of SCS patients may experience an adverse event (89).<br>***6.7.4 Indications***<br>While multiple indications are available, the indications in the United States are related to neuropathic pain of FBSS or CRPS.<br>***6.7.5 Level of Evidence***<br>The indicated evidence for SCS is Level II-1 or II-2 for long-term relief in managing patients with FBSS.<br>***6.7.6 Recommendations***<br>Based on Guyatt et al's (136) criteria, the recommendation is 1B or 1C/strong recommendation for clinical use on a long-term basis." | Positive for clinical use on a long-term basis | Information about this guideline is spread across Manchikanti 2009 p699, Manchikanti 2009 pE1, the NGC and personal communication<br>This guideline is part of a journal issue made up of a suite of pain management guidelines |
| **North 2007**<br>Practice parameters for the use of spinal cord stimulation in the treatment of chronic neuropathic pain | **POPULATION/CLINICAL INDICATION**<br>Neuropathic pain<br>**INTERVENTION**<br>Spinal cord stimulation | EBG | SCS is given a strong recommendation for successful treatment of Failed back surgery syndrome (FBSS) based on evidence that includes an RCT 29, and references to observational studies including 17 long-term follow-up studies (at least 24 months follow-up), 14 short-term follow-up studies, and three case studies that specifically focus on the use of SCS for patients with FBSS. North et al also references up to 40 additional observational studies (no RCTs) that include patients with FBSS (as well as other conditions) or low back/leg pain (not necessarily FBSS) where SCS has had a positive effect on outcomes.<br>A strong recommendation is also given by North et al for the use of SCS for CRPS types I and II 7. The recommendation is based on two separate RCTs involving CRPS I and references to observational studies including six long-term follow-up studies (at least 24 months follow-up), six short-term follow-up studies, and 11 case studies that specifically focus on the use of SCS for | Positive | *n.b. this summary information has been taken from the previous version of this report* |

| 1st author, year, title | Inclusion, Exclusion criteria ( for P.I.C.O) | Study design | Conclusion/Recommendation | Recommendation category | Other comments |
|---|---|---|---|---|---|
| | | | patients with CRPS. North et al also refers to 24 additional references to observational studies involving mixed populations (including CRPS) that support the use of SCS for this condition. | | |
| **Cruccu 2007**<br>EFNS guidelines on neurostimulation therapy for neuropathic pain | **POPULATION/CLINICAL INDICATION**<br>Neuropathic pain<br>**INTERVENTION**<br>Spinal cord stimulation | EBG | N/A | N/A | *n.b. this was an included study in the previous version of this report where summary information was not provided* |
| **Boswell 2007**<br>Interventional techniques: Evidence-based practice guidelines in the management of chronic spinal pain | **POPULATION/CLINICAL INDICATION**<br>Chronic spinal pain<br>**INTERVENTION**<br>Spinal cord stimulation | EBG | N/A | N/A | *n.b. this was an included study in the previous version of this report where summary information was not provided* |
| **Institute for Clinical Systems Improvement (ICSI) 2007**<br>Assessment and management of chronic pain | **POPULATION/CLINICAL INDICATION**<br>Chronic pain<br>**INTERVENTION**<br>Spinal cord stimulation | EBG | N/A | N/A | *n.b. this was an included study in the previous version of this report where summary information was not provided* |
| **Airaksinen 2006**<br>Chapter 4: European guidelines for the management of chronic nonspecific low back pain | **POPULATION/CLINICAL INDICATION**<br>Chronic low back pain<br>**INTERVENTION**<br>Spinal cord stimulation | EBG | N/A | N/A | *n.b. this was an included study in the previous version of this report where summary information was not provided* |
| **British Pain Society 2005**<br>Spinal cord stimulation for the management of pain: recommendations for best clinical practice | **POPULATION/CLINICAL INDICATION**<br>Chronic pain<br>**INTERVENTION**<br>Spinal cord stimulation | EBG | N/A | N/A | *n.b. this was an included study in the previous version of this report where summary information was not provided* |
| **Sanders 2005**<br>Evidence-based clinical practice guidelines for | **POPULATION/CLINICAL INDICATION**<br>Chronic pain<br>**INTERVENTION** | EBG | N/A | N/A | *n.b. this was an included study in the previous version of this report where summary* |

| 1st author, year, title | Inclusion, Exclusion criteria ( for P.I.C.O) | Study design | Conclusion/Recommendation | Recommendation category | Other comments |
|---|---|---|---|---|---|
| interdisciplinary rehabilitation of chronic nonmalignant pain syndrome patients | Spinal cord stimulation | | | | *information was not provided* |
| **PERIPHERAL NERVE STIMULATION (PNS)** | | | | | |
| **Cruccu 2007*** EFNS guidelines on neurostimulation therapy for neuropathic pain | **POPULATION/CLINICAL INDICATION** Patients with chronic neuropathic pain **INTERVENTION** Peripheral nerve stimulation **COMPARATOR** N/A – observational studies only **OUTCOMES:** Pain relief and side effects/complications | EBG | Cruccu et al (2007) report that none of the studies identified had an adequate control and they were unable to draw any conclusions for PNS recommendations in the guideline. Class IV (uncontrolled studies, case series, case reports, or expert opinion) for PNS. Class IV was considered insufficient evidence to determine recommendations. Of the few studies identified for PNS, they were old (between 1975-1999), suggesting this intervention is not increasing in popularity. | Insufficient evidence | Insufficient evidence to draw conclusions *n.b. this EBG was also used as an included study for MCS and DBS* |
| **Van Eijs 2011** 16. Complex Regional Pain Syndrome | **POPULATION/CLINICAL INDICATION** Patients with complex regional pain syndrome (formerly reflex sympathetic dystrophy) **INTERVENTION** Peripheral nerve stimulation **COMPARATOR** N/A – observational studies only **OUTCOMES:** Reduction in pain | EBG | "Peripheral nerve stimulation can be considered, preferentially in study conditions (2C+)*." *2C+ refers to "effectiveness only demonstrated in observational studies. Given that there is no conclusive evidence of the effect, benefits closely balanced with risk and burdens" | Positive but needs further evidence | Lack of reporting on the individual results of the included studies. Strengths and limitations of each of the studies were not reported Insufficient evidence to draw conclusions *n.b. this EBG was also used as an included study for SCS* |
| **MOTOR CORTEX STIMULATION (MCS)** | | | | | |
| **Cruccu 2007*** EFNS guidelines on neurostimulation therapy for neuropathic pain | **POPULATION/CLINICAL INDICATION** Patients with chronic neuropathic pain **INTERVENTION** Motor cortex stimulation **COMPARATOR** | EBG | "There is level C evidence (two convincing class III studies, 15–20 convergent class IV series) that MCS is useful in 50–60% of patients with CPSP and central or peripheral facial neuropathic pain, with small risk of medical complications. The evidence about any other condition remains insufficient." | Positive but needs further evidence | Insufficient evidence to draw conclusions *n.b. this EBG was also used as an included study for PNS and DBS* |

| 1st author, year, title | Inclusion, Exclusion criteria ( for P.I.C.O) | Study design | Conclusion/Recommendation | Recommendation category | Other comments |
|---|---|---|---|---|---|
| | N/A – observational studies only<br>**OUTCOMES:**<br>Pain relief and side effects/complications | | | | |
| **DEEP BRAIN STIMULATION (DBS)** | | | | | |
| **Cruccu 2007***<br>EFNS guidelines on neurostimulation therapy for neuropathic pain | **POPULATION/CLINICAL INDICATION**<br>Patients with chronic neuropathic pain conditions<br>**INTERVENTION**<br>Deep brain stimulation<br>**COMPARATOR**<br>N/A – observational studies only<br>**OUTCOMES:**<br>Pain relief and side effects/complications | EBG | **Low level evidence for DBS in the treatment of neuropathic pain.**<br>Class IV (uncontrolled studies, case series, case reports, or expert opinion) for DBS. Class IV was considered insufficient evidence to determine recommendations.<br>**Weak positive evidence for DBS in the treatment of peripheral neuropathic pain including facial pain and pain after amputation.**<br>The authors state that this is based on expert opinion (small case series, n<20) and requires confirmatory trials. | Insufficient evidence | Insufficient evidence to draw conclusions<br>*n.b. this EBG was also used as an included study for PNS and MCS* |
| **OCCIPITAL NERVE STIMULATION (ONS)** | | | | | |
| **Van Kleef 2009**<br>2. Cluster headache | **POPULATION/CLINICAL INDICATION**<br>Patients with chronic cluster headache (CH) refractory to all other treatments<br>**INTERVENTION**<br>Occipital nerve stimulation<br>**COMPARATOR**<br>N/A – observational studies only<br>**OUTCOMES:**<br>Pain relief and side effects/complications | EBG | "In patients with cluster headache refractory to all other treatments, occipital nerve stimulation may be considered, preferably within the context of a clinical study."<br>"The effectiveness of…occipital nerve stimulation is only evaluated in observational studies, resulting in a 2 C+ recommendation." | Positive but needs further evidence | No mention of adverse effects, whether there were none or if any existed in any studies, were reported for ONS.<br>Insufficient evidence to draw conclusions |
| **SYSTEMATIC REVIEWS (SRs)** | | | | | |
| **SPINAL CORD STIMULATION (SCS)** | | | | | |
| **Chou 2009**<br>Nonsurgical interventional therapies for low back pain: a review of the evidence for an American Pain Society clinical practice guideline | **POPULATION/CLINICAL INDICATION**<br>Patients with low back and radicular pain (FBSS with radiculopathy)<br>**INTERVENTION**<br>Spinal cord stimulation<br>**COMPARATOR**<br>Conventional medical management or reoperation | SR | "We found fair evidence that spinal cord stimulation is moderately effective for failed back surgery syndrome with persistent radiculopathy, though device-related complications are common."<br>"We found fair evidence from 2 trials that spinal cord stimulation is more effective than either repeat surgery[104] or continued conventional medical management[64] for failed back surgery syndrome with persistent radiculopathy. Unlike the other interventional therapies included in this review, spinal cord | positive | |

| 1st author, year, title | Inclusion, Exclusion criteria ( for P.I.C.O) | Study design | Conclusion/Recommendation | Recommendation category | Other comments |
|---|---|---|---|---|---|
| | **OUTCOMES**<br>Effectiveness/benefits | | stimulation involves the permanent placement of a device and is associated with a high rate of postimplant complications, though these events are usually not serious." | | |
| **Frey 2009**<br>Spinal cord stimulation for patients with failed back surgery syndrome: a systematic review | **POPULATION/CLINICAL INDICATION**<br>Patients with failed back surgery syndrome (FBSS)<br>**INTERVENTION**<br>Spinal cord stimulation<br>**COMPARATOR**<br>Conventional medical management or repeated lumbosacral spine surgery<br>**OUTCOMES**<br>pain relief (short-term relief ≤ one-year and long-term > one-year), improvement in functional status, psychological status, return to work, and reduction in opioid intake | SR | "Conclusion: This systematic review evaluating the effectiveness of SCS in relieving chronic intractable pain of failed back surgery syndrome indicated the evidence to be Level II-1 or II-2 for clinical use on a long-term basis."<br>"The results of this systematic review evaluating SCS in FBSS indicates a level of evidence of II-1 or II-2 with a 1B or 1C/strong recommendation for clinical use on a long-term basis." | Positive with warning of the risks | "The cost-effectiveness analysis in this review augers favorably for the use of SCS in patients with FBSS. However, more evidence is still needed to determine at which point in the treatment continuum SCS should be considered, who are the best candidates for this treatment, and to further refine the optimal stimulation parameters.<br>Also, complications are common |
| **Bala 2008**<br>Systematic review of the (cost-)effectiveness of spinal cord stimulation for people with failed back surgery syndrome | **POPULATION/CLINICAL INDICATION**<br>adult patients with chronic pain (lasting more than 6 months) owing to Failed Back Surgery Syndrome (FBSS)<br>**INTERVENTION**<br>Spinal cord stimulation<br>**COMPARATOR**<br>Not specified<br>**OUTCOMES**<br>Primary outcomes were: reduction of pain assessed with validated instruments, such as the McGill Pain Questionnaire or Visual Analog Scale (VAS).<br>Secondary outcomes were: quality of life (QoL), activities of daily living (ADL), functional status, depression, adverse events. | SR | "There is evidence from 2 small RCTs of moderate quality and 13 low-quality studies that SCS is effective in the treatment of FBSS in terms of pain reduction. The effect was consistent in all analyzed studies. Improvements were also reported for other outcomes. SCS treatment may be associated with some improvements in QoL, although the evidence comes from 6-month results of 1 RCT and from 3 low-quality studies. Low-quality studies also showed improvements in ADL or return to employment and in analgesic medication use, but this was not confirmed in the interim results of an RCT. Functional status was also shown to improve in 1 RCT and 3 low-quality studies. Patients were satisfied with SCS treatment in all studies assessing this outcome.<br>Three studies included in the economic evaluations section of this review offer the same conclusion that SCS is both more effective and less costly in the long-term. However, owing to the high costs associated with device implantation and maintenance there will be an initial incremental cost-effectiveness ratio that may, under some scenarios, put the ratio above commonly accepted levels of willingness to pay. The clinical data that informed all economic evaluations do have some limitations in terms of reliability, and the reliance on such a small number of studies in terms of policy changes will probably invoke justifiable uncertainty." | positive | |

| 1st author, year, title | Inclusion, Exclusion criteria ( for P.I.C.O) | Study design | Conclusion/Recommendation | Recommendation category | Other comments |
|---|---|---|---|---|---|
| **Albazaz 2008**<br>Complex Regional Pain Syndrome: A Review. | **POPULATION/CLINICAL INDICATION**<br>CRPS<br>**INTERVENTION**<br>Spinal cord stimulation | SR | N/A | N/A | *n.b. this was an included study in the previous version of this report where summary information was not provided* |
| **Bala 2006**<br>Systematic review of the (cost) effectiveness of Spinal Cord Stimulation for people with chronic pain | **POPULATION/CLINICAL INDICATION**<br>Chronic pain<br>**INTERVENTION**<br>Spinal cord stimulation | SR | N/A | N/A | *n.b. this was an included study in the previous version of this report where summary information was not provided* |
| **Accident Compensation Commission 2005**<br>Interventional Pain Management (IPM) project. | **POPULATION/CLINICAL INDICATION**<br>Chronic pain<br>**INTERVENTION**<br>Spinal cord stimulation | SR | N/A | N/A | *n.b. this was an included study in the previous version of this report where summary information was not provided* |
| **Coffey 2006**<br>Neurostimulation for chronic noncancer pain: An evaluation of the clinical evidence and recommendations for future trial designs. | **POPULATION/CLINICAL INDICATION**<br>Chronic pain<br>**INTERVENTION**<br>Spinal cord stimulation | SR | N/A | N/A | *n.b. this was an included study in the previous version of this report where summary information was not provided* |
| **Ontario Ministry of Health and Long-Term Care 2005**<br>Spinal cord stimulation for neuropathic pain. | **POPULATION/CLINICAL INDICATION**<br>Chronic pain<br>**INTERVENTION**<br>Spinal cord stimulation | SR | N/A | N/A | *n.b. this was an included study in the previous version of this report where summary information was not provided* |
| **Cameron 2004**<br>Safety and efficacy of spinal cord stimulation for the treatment of chronic pain: A 20-year literature review. | **POPULATION/CLINICAL INDICATION**<br>Chronic pain of the trunk and limbs<br>**INTERVENTION**<br>Spinal cord stimulation | SR | N/A | N/A | *n.b. this was an included study in the previous version of this report where summary information was not provided* |
| **Carter 2004** | **POPULATION/CLINICAL INDICATION** | SR | N/A | N/A | *n.b. this was an included* |

| 1st author, year, title | Inclusion, Exclusion criteria ( for P.I.C.O) | Study design | Conclusion/Recommendation | Recommendation category | Other comments |
|---|---|---|---|---|---|
| Spinal cord stimulation in chronic pain: A review of the evidence. | Chronic pain<br>**INTERVENTION**<br>Spinal cord stimulation | | | | *study in the previous version of this report where summary information was not provided* |
| **Mailis-Gagnon 2008**<br>Spinal cord stimulation for chronic pain | **POPULATION/CLINICAL INDICATION**<br>Chronic pain<br>**INTERVENTION**<br>Spinal cord stimulation | SR | N/A | N/A | *n.b. this was an included study in the previous version of this report where summary information was not provided* |
| **Turner 2004**<br>Spinal cord stimulation for patients with failed back surgery syndrome or complex regional pain syndrome: A systematic review of effectiveness and complications. | **POPULATION/CLINICAL INDICATION**<br>CRPS and FBSS<br>**INTERVENTION**<br>Spinal cord stimulation | SR | N/A | N/A | *n.b. this was an included study in the previous version of this report where summary information was not provided* |
| **Middleton 2003**<br>Spinal cord stimulation (neurostimulation): an accelerated systematic review | **POPULATION/CLINICAL INDICATION**<br>Chronic pain<br>**INTERVENTION**<br>Spinal cord stimulation | SR | N/A | N/A | *n.b. this was an included study in the previous version of this report where summary information was not provided* |
| **Taylor 2006**<br>Spinal Cord Stimulation in Complex Regional Pain Syndrome and Refractory Neuropathic Back and Leg Pain/Failed Back Surgery Syndrome: Results of a Systematic Review and Meta-Analysis. | **POPULATION/CLINICAL INDICATION**<br>CRPS and FBSS<br>**INTERVENTION**<br>Spinal cord stimulation | SR | N/A | N/A | *n.b. this was an included study in the previous version of this report where summary information was not provided* |
| **Workers Compensation Board Evidence-based Practice Group 2001**<br>Spinal cord stimulation: | **POPULATION/CLINICAL INDICATION**<br>CRPS<br>**INTERVENTION** | SR | N/A | N/A | *n.b. this was an included study in the previous version of this report where summary* |

| 1st author, year, title | Inclusion, Exclusion criteria ( for P.I.C.O) | Study design | Conclusion/Recommendation | Recommendation category | Other comments |
|---|---|---|---|---|---|
| use in patients with complex regional pain syndrome | Spinal cord stimulation | | | | *information was not provided* |
| **Grabow 2003**<br>Spinal cord stimulation for complex regional pain syndrome: an evidence-based medicine review of the literature | **POPULATION/CLINICAL INDICATION**<br>CRPS<br>**INTERVENTION**<br>Spinal cord stimulation | SR | N/A | N/A | *n.b. this was an included study in the previous version of this report where summary information was not provided* |
| **Stocks 2001**<br>Spinal cord stimulation for chronic pain. *STEER: Succinct and Timely Evaluated Evidence Reviews*. | **POPULATION/CLINICAL INDICATION**<br>Chronic low back pain<br>**INTERVENTION**<br>Spinal cord stimulation | SR | N/A | N/A | *n.b. this was an included study in the previous version of this report where summary information was not provided* |
| **Jadad 2001**<br>Management of chronic central neuropathic pain following traumatic spinal cord injury | **POPULATION/CLINICAL INDICATION**<br>Neuropathic pain<br>**INTERVENTION**<br>Spinal cord stimulation | SR | N/A | N/A | *n.b. this was an included study in the previous version of this report where summary information was not provided* |
| **McQuay 1997**<br>Systematic review of outpatient services for chronic pain control. | **POPULATION/CLINICAL INDICATION**<br>Chronic pain<br>**INTERVENTION**<br>Spinal cord stimulation | SR | N/A | N/A | *n.b. this was an included study in the previous version of this report where summary information was not provided* |
| **Turner 1995**<br>Spinal cord stimulation for chronic low back pain: A systematic literature synthesis. | **POPULATION/CLINICAL INDICATION**<br>Chronic low back pain<br>**INTERVENTION**<br>Spinal cord stimulation | SR | N/A | N/A | *n.b. this was an included study in the previous version of this report where summary information was not provided* |
| **PERIPHERAL NERVE STIMULATION (PNS)** | | | | | |

| 1st author, year, title | Inclusion, Exclusion criteria ( for P.I.C.O) | Study design | Conclusion/Recommendation | Recommendation category | Other comments |
|---|---|---|---|---|---|
| **Coffey 2006**<br>Neurostimulation for chronic noncancer pain: An evaluation of the clinical evidence and recommendations for future trial designs | **POPULATION/CLINICAL INDICATION**<br>Patients with chronic pain<br>**INTERVENTION**<br>Peripheral nerve stimulation | SR | N/A | N/A | *n.b. this SR was also used as an included study for MCS and DBS*<br>*Also, this was an included study in the previous version of this report where summary information was not provided* |
| **MOTOR CORTEX STIMULATION (MCS)** | | | | | |
| **Coffey 2006**<br>Neurostimulation for chronic noncancer pain: An evaluation of the clinical evidence and recommendations for future trial designs | **POPULATION/CLINICAL INDICATION**<br>Patients with chronic pain<br>**INTERVENTION**<br>Motor cortex stimulation | SR | An aggregate success rate of 59% (56 of 95 cases) for pain relief (with success defined as greater than 50% pain relief) | N/A | *n.b. this was an included study in the previous version of this report where summary information was not provided<br>**n.b. this SR was also used as an included study for PNS and DBS* |
| **DEEP BRAIN STIMULATION (DBS)** | | | | | |
| **National Institute for Health and Clinical Excellence 2010**<br>Interventional procedure overview of deep brain stimulation for refractory chronic pain syndromes (excluding headache) | **POPULATION/CLINICAL INDICATION**<br>Patients with chronic refractory pain syndromes (excluding headache), i.e. post-stroke pain, deafferentation pain and neuropathic pain<br>**INTERVENTION**<br>Deep brain stimulation<br>**COMPARATOR**<br>Motor cortex stimulation (for 2 post-stroke pain studies)<br>N/A – observational studies only<br>**OUTCOMES:**<br>Pain relief and side effects/complications | SR | Current evidence on the safety of deep brain stimulation (DBS) for refractory chronic pain syndromes (excluding headache) shows that there are serious but well-known risks. There is evidence that the procedure is efficacious in some patients who are refractory to other forms of pain control. Therefore this procedure may be used provided that normal arrangements are in place for clinical governance, consent and audit.<br><br>DBS should only be used in patients with refractory chronic pain syndromes that other treatments have failed to control. Patient selection should be carried out by a multidisciplinary team specialising in pain management. | Positive but needs further evidence | |

| 1st author, year, title | Inclusion, Exclusion criteria ( for P.I.C.O) | Study design | Conclusion/Recommendation | Recommendation category | Other comments |
|---|---|---|---|---|---|
| **National Institute for Health and Clinical Excellence 2010**<br>Interventional procedure overview of deep brain stimulation for intractable trigeminal autonomic cephalalgias | **POPULATION/CLINICAL INDICATION**<br>Patients with intractable trigeminal autonomic cephalalgias<br>**INTERVENTION**<br>Deep brain stimulation<br>**COMPARATOR**<br>Sham stimulation (1 cross-over RCT)<br>N/A – observational studies only<br>**OUTCOMES:**<br>Pain relief and side effects/complications | SR | Current evidence on the efficacy of deep brain stimulation (DBS) for intractable trigeminal autonomic cephalalgias (TACs) is limited and inconsistent, and the evidence on safety shows that there are serious but well-known side effects. Therefore this procedure should only be used with special arrangements for clinical governance, consent and audit or research.<br><br>Further research studies should clearly define patient selection and report the intensity and duration of stimulation, medication use and quality of life, in addition to documenting the effects on headache symptoms as clearly as possible. | Limited and inconsistent evidence | |
| **Coffey 2006**<br>Neurostimulation for chronic noncancer pain: An evaluation of the clinical evidence and recommendations for future trial designs | **POPULATION/CLINICAL INDICATION**<br>Patients with chronic pain<br>**INTERVENTION**<br>Deep brain stimulation | SR | N/A | N/A | *n.b. this was an included study in the previous version of this report where summary information was not provided<br><br>**n.b. this SR was also used as an included study for MCS and PNS* |
| **Bittar 2005**<br>Deep brain stimulation for pain relief: A meta-analysis | **POPULATION/CLINICAL INDICATION**<br>Patients with chronic pain<br>**INTERVENTION**<br>Deep brain stimulation | SR | DBS is more effective for nociceptive pain than for neuropathic pain (63% compared to 47% long-term success). In patients with neuropathic pain, higher rates of success were seen in patients with peripheral lesions such as phantom limb pain, radiculopathies, plexopathies, and neuropathies. | N/A | *n.b. this was an included study in the previous version of this report where summary information was not provided |
| **Jadad 2001**<br>Management of chronic central neuropathic pain following traumatic spinal cord injury | **POPULATION/CLINICAL INDICATION**<br>Patients with chronic neuropathic pain<br>**INTERVENTION**<br>Deep brain stimulation | SR | N/A | N/A | *n.b. this was an included study in the previous version of this report where summary information was not provided |
| **OCCIPITAL NERVE STIMULATION (DBS)** | | | | | |
| **Coffey 2006**<br>Neurostimulation for chronic noncancer pain: | **POPULATION/CLINICAL INDICATION**<br>Patients with chronic pain | SR | N/A | N/A | *n.b. this was an included study in the previous version of this report |

| 1st author, year, title | Inclusion, Exclusion criteria ( for P.I.C.O) | Study design | Conclusion/Recommendation | Recommendation category | Other comments |
|---|---|---|---|---|---|
| An evaluation of the clinical evidence and recommendations for future trial designs | **INTERVENTION**<br>Occipital nerve stimulation | | | | where summary information was not provided<br><br>**n.b. this SR was also used as an included study for PNS, MCS and DBS* |
| **Jasper 2008**<br>Implanted occipital nerve stimulators | **POPULATION/CLINICAL INDICATION**<br>Adult patients with frequent and intense headaches of > 6 months duration who had not adequately responded to conventional headache therapies<br>**INTERVENTION**<br>Occipital nerve stimulation<br>**COMPARATOR**<br>N/A<br>**OUTCOMES:**<br>Primary - pain relief<br>Secondary - functional measures were considered acceptable for inclusion: headache frequency, intensity, and duration; medication use; Morphine Dose Equivalents (MDE); number of doctor or ER visits; ratio of trial to permanent implantation; complications; the Neck Pain Disability Ques tionnaire (NPDQ); the Migraine Disability Assessment (MIDAS) scores; return to work; and Quality of Life. | SR | ONS is a useful tool in the treatment of chronic severe headaches with at least<br>Level IV (limited) evidence based on multiple positive studies. | Positive but needs further evidence | |
| **RANDOMISED CONTROLLED TRIALS** | | | | | |
| **SPINAL CORD STIMULATION (SCS)** | | | | | |
| **PROCESS TRIAL**<br>Eldabe 2010<br>Kumar 2008<br>Manca 2008<br>Kumar 2007 | **POPULATION/CLINICAL INDICATION**<br>Paitents with failed back surgery syndrome (FBSS)<br>**INTERVENTION**<br>Spinal cord stimulation (SCS) with conventional medical management (CMM)<br>**COMPARATOR**<br>CMM alone<br>**OUTCOMES**<br>Pain, quality of life, functional outcomes, medication use, patient | RCT | **Eldabe:** "The patients with FBSS selected for this study experienced levels of leg and back pain that had a major negative impact on both their function and HRQoL. The positive and sustained effects of SCS on these features underscore the importance of access to this treatment in this patient group. Nonetheless, despite the significant improvements gained through SCS, a notable proportion of FBSS patients continue to experience difficulties within some sub-categories of function and HRQoL. These remain important areas for future research to improve therapy for this refractory population. Compared with conventional medical management alone, patients also receiving | positive | We identified 4 papers reporting on this RCT |

| 1st author, year, title | Inclusion, Exclusion criteria ( for P.I.C.O) | Study design | Conclusion/Recommendation | Recommendation category | Other comments |
|---|---|---|---|---|---|
| | satisfaction, costs | | spinal cord stimulation (SCS) reported superior pain relief, function, and HRQoL at six months on overall and most sub-component scores. The majority of these improvements with SCS were sustained at 24 months. Nonetheless, 36–40% of patients experienced ongoing marked disability (standing, lifting) and HRQoL problems (pain/discomfort).**Conclusions:** Longer-term patient management and research must focus on these refractory FBSS patients with persisting poor function and HRQoL outcomes."<br><br>**Kumar 2008:** "At 24 months of SCS treatment, selected failed back surgery syndrome patients reported sustained pain relief, clinically important improvements in functional capacity and health-related quality of life, and satisfaction with treatment... In selected patients with FBSS, treatment with SCS results in pain relief that is sustained at 24 months and is associated with patient satisfaction and clinically important improvements in functional capacity and health-related quality of life."<br><br>**Manca:** "In conclusion, at 6-months observation and compared to CMM alone, SCS increases HRQoL in patients with chronic back and leg pain with a neuropathic component after one or multiple surgeries by 0.21 on the EQ-5D scale at additional mean healthcare cost of £11,373 (CAN$15,395; €9997) per patient…The addition of SCS to CMM in patients with neuropathic leg and back pain results in higher costs to health systems but also generates important improvements in patients' EQ-5D over the same period." | | |
| **North 2005**<br>Spinal cord stimulation versus repeated lumbosacral spine surgery for chronic pain: A randomized, controlled trial. | **POPULATION/CLINICAL INDICATION**<br>FBSS<br>**INTERVENTION**<br>Spinal cord stimulation | RCT | N/A | N/A | *n.b. this was an included study in the previous version of this report where summary information was not provided |
| **Kemler 2000**<br>Spinal cord stimulation in patients with chronic reflex sympathetic dystrophy | **POPULATION/CLINICAL INDICATION**<br>CRPS<br>**INTERVENTION**<br>Spinal cord stimulation | RCT | N/A | N/A | *n.b. this was an included study in the previous version of this report where summary information was not provided |

| 1st author, year, title | Inclusion, Exclusion criteria ( for P.I.C.O) | Study design | Conclusion/Recommendation | Recommendation category | Other comments |
|---|---|---|---|---|---|
| **MOTOR CORTEX STIMULATION (MCS)** | | | | | |
| **Lefaucheur 2009**<br>Motor cortex stimulation for the treatment of refractory peripheral neuropathic pain | **POPULATION/CLINICAL INDICATION**<br>Patients with chronic neuropathic pain of either peripheral or central origin<br>**INTERVENTION**<br>Motor cortex stimulation (stimulator 'on' for 1 month)<br>**COMPARATOR**<br>Sham stimulation (stimulator 'off' for 1 month)<br>**OUTCOMES:**<br>Pain relief and functional outcomes | RCT | "Although the results of the crossover trial were slightly negative, which may have been due to carry-over effects from the operative and immediate postoperative phases, observations made during the open trial were in favour of a real efficacy of MCS in peripheral neuropathic pain. Analgesic effects were obtained on the sensory-discriminative rather than on the affective aspect of pain. These results suggest that the indication of MCS might be extended to various types of refractory, chronic peripheral pain beyond trigeminal neuropathic pain." | Slightly negative | High risk of bias – Insufficient wash-out period between phases of the cross-over RCT could affect the results.<br>The small sample size and lack of information about characteristics of patients assigned to each group, randomisation and allocation concealment procedures mean it is not possible to determine if the groups were similar enough to be sure that any effects were due to the intervention and not pre-existing differences between groups. |
| **Nguyen 2008** | **POPULATION/CLINICAL INDICATION**<br>Patients with chronic neuropathic pain of either peripheral or central origin<br>**INTERVENTION**<br>Group 1: stimulator switched ''OFF'' for two weeks and then was switched ''ON'' for the next 2 weeks.<br>Group 2: stimulator switched ''ON'' for two weeks and then was switched ''OFF'' for the next 2 weeks.<br>**COMPARATOR**<br>Group 1: stimulator switched ''OFF'' for two weeks and then was switched ''ON'' for the next 2 weeks.<br>Group 2: stimulator switched ''ON'' for two weeks and then was switched ''OFF'' for the next 2 weeks.<br>**OUTCOMES:**<br>Pain relief, function and quality of life | RCT | "These results were in favor of real analgesic effects produced by MCS with no loss of benefit over time. The differential changes in MPQ subscores suggested that MCS relieved pain by acting predominantly on its affective aspect. The decrease in pain intensity was associated with improved daily living activities and quality of life and reduced consumption of analgesic medication."<br>"In conclusion, this controlled study showed that MCS was an effective method to improve various types of drug resistant chronic neuropathic pain, of either peripheral or central origin. These results need to be confirmed and extended in larger series of patients." | Positive but needs further evidence | A small number of patients were involved in the study and the authors do not state why they chose a cross-over design.<br>The method of randomisation and allocation concealment was not reported by the authors, which introduces selection bias into the results. Insufficient evidence to draw conclusions.<br>The duration of the study was too short to observe any long-term effects. |
| **DEEP BRAIN STIMULATION (DBS)** | | | | | |

| 1st author, year, title | Inclusion, Exclusion criteria ( for P.I.C.O) | Study design | Conclusion/Recommendation | Recommendation category | Other comments |
|---|---|---|---|---|---|
| **Fontaine 2010**<br>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 | **POPULATION/CLINICAL INDICATION**<br>Patients with severe refractory chronic cluster headache (CCH)<br>**INTERVENTION**<br>Active DBS for two 1 month periods<br>**COMPARATOR**<br>Sham stimulation for two 1 month periods<br>**OUTCOMES:**<br>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), blood pressure, heart rate, weight and body temperature. Electrolyte balance and hormonal functions, patient's satisfaction (Patient's Global Impression of Change), changes in thirst, appetite, libido, sleepwalking cycle and behaviour (AE) | RCT | "In the controlled phase of this study, we failed to demonstrate that DBS improved chronic CH when compared with sham stimulation. These findings contrasted with the results observed in the open phase of the study, which showed that more than 50% of the patients were improved over 50%, and that mean attack frequency and emotional impact were markedly decreased." | Further evidence required. | The overall risk of bias was moderate due to a small sample size, short duration of treatment and possible non-optimal stimulation parameters. |
| **OCCIPITAL NERVE STIMULATION (ONS)** | | | | | |
| **Lipton 2009**<br>PRISM study: occipital nerve stimulation for treatment-refractory migraine | **POPULATION/CLINICAL INDICATION**<br>Patients with treatment-refractory migraine<br>**INTERVENTION**<br>Bilateral active (250 lsec pulses, 60 Hz, 0–12.7 Ma) occipital nerve stimulation for 12 weeks<br>**COMPARATOR**<br>Sham (10 l sec pulses, 2 Hz, < 1 Ma, 1 sec on / 90 min off duty cycle) stimulation for 12 weeks, than conversion to active stimulation for another 10 months (follow-up for 52 weeks)<br>**OUTCOMES:**<br>Change from baseline in migraine days/month evaluated 12 weeks after implantation and adverse events. | 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 stimulation, based in part on the absence of medication overuse and a favourable response to a trial of percutaneous treatment." | Neutral (no difference in effect between interventions) but needs further evidence | The long-term effects of ONS on treatment refractory migraine cannot be assessed as the authors did not disclose the efficacy results for this time point.<br><br>Attrition rates at 52 weeks follow up were not reported |
| **Saper 2010**<br>Occipital nerve stimulation for the treatment of intractable chronic migraine headache | **POPULATION/CLINICAL INDICATION**<br>Patients with medically intractable chronic migraine (CM)<br>**INTERVENTION**<br>ONS – Adjustable stimulation (AS) group was instructed to maintain the stimulator in the ''on'' position and to adjust the device to minimize pain<br>**COMPARATOR** | RCT | "On the basis of the current findings and in light of previously published work, we believe further investigational pursuit to evaluate the efficacy and safety of ONS for medically intractable CM is justified. Further study would be enhanced by improved stimulator design, implanting technique and lead design and by a well-targeted, carefully selected study population, more robust endpoints, longer trial duration and improved blinding techniques. Reliable conclusions regarding efficacy cannot be established on the basis of this study alone. Nonetheless, the | Positive but needs further evidence | This study was a sponsored study by Medtronic, the company which produce neurostimulators.<br><br>This study was a feasibility study hence caution |

| 1st author, year, title | Inclusion, Exclusion criteria ( for P.I.C.O) | Study design | Conclusion/Recommendation | Recommendation category | Other comments |
|---|---|---|---|---|---|
| | Preset stimulation (n=17) and medically managed control (n=17) and ancillary group (n=8)<br>**OUTCOMES:**<br>• Reduction in headache days per months;<br>• proportion of patients who achieved ≥ 50% reduction in headache days per month (responder rate);<br>• a 3-point or greater reduction in average overall pain intensity;<br>• disability and QoL;<br>• risks/complications | | results of this feasibility study offer promise and should prompt further study of ONS in medically intractable CM." | | should be applied to the generalisability of the results. |
| **CONTROLLED TRIALS** | | | | | |
| **SPINAL CORD STIMULATION (SCS)** | | | | | |
| **Marchand 1991**<br>The effects of dorsal column stimulation on measures of clinical and experimental pain in man | **POPULATION/CLINICAL INDICATION**<br>Chronic pain<br>**INTERVENTION**<br>Spinal cord stimulation | CCT | N/A | N/A | *n.b. this was an included study in the previous version of this report where summary information was not provided |
| **MOTOR CORTEX STIMULATION (MCS)** | | | | | |
| **Ali 2011**<br>Differential Efficacy of Electric Motor Cortex Stimulation and Lesioning of the Dorsal Root Entry Zone for Continuous vs Paroxysmal Pain After Brachial Plexus Avulsion | **POPULATION/CLINICAL INDICATION**<br>Patients with intractable pain following brachial plexus avulsion (BPA)<br>**INTERVENTION**<br>Electric Motor Cortex Stimulation (EMCS) for an average duration of 47 months<br>**COMPARATOR**<br>DREZotomy and/or EMCS<br>**OUTCOMES:**<br>Pain intensity and relief | CCT | "EMCS was ineffective for paroxysmal pain but moderately effective for continuous pain. DREZotomy was highly effective for paroxysmal pain but moderately effective for continuous pain. It may be prudent to use EMCS for residual continuous pain after DREZotomy." | Positive for continuous pain but needs further evidence | Limitations of the study included small sample size (in particular for subgroup analysis) and a possible "carryover" effect for patients who underwent both DREZotomy and EMCS.<br>Insufficient evidence to draw conclusions |

| 1st author, year, title | Inclusion, Exclusion criteria ( for P.I.C.O) | Study design | Conclusion/Recommendation | Recommendation category | Other comments |
|---|---|---|---|---|---|
| **Velasco 2008**<br>Efficacy of motor cortex stimulation in the treatment of neuropathic pain: a randomised double-blind trial | **POPULATION/CLINICAL INDICATION**<br>Patients with neuropathic pain<br>**INTERVENTION**<br>Motor Cortex Stimulation | CCT | N/A | N/A | *n.b. this was an included study in the previous version of this report where summary information was not provided |

# APPENDIX 5: APPRAISAL TABLES

**Table A5.1 Critical appraisal table (*Cruccu European Journal of Neurology 2007)*, Peripheral nerve stimulation, Motor cortex stimulation and Deep brain stimulation**

| EFNS GUIDELINES ON NEUROSTIMULATION THERAPY FOR NEUROPATHIC PAIN (2007) | |
|---|---|
| **AUTHOR** | Cruccu, G., Aziz, T.Z., Garcia-Larrea, L., Hansson, P., Jensen, T.S., Lefaucheur, J-P., Simpson, B.A. and Taylor, R.S. |
| **PUBLISHER** | European Journal of Neurology 2007; 14: 952-970 |
| **FUNDER** | Not Documented |
| **LINK** | http://www.efns.org/index.php<br>http://www.blackwell-synergy.com/doi/abs/10.1111/j.1468-1331.2007.01916.x |
| **AIM** | To provide neurologists with evidence-based recommendations that may help to determine when a patient with neuropathic pain should try a neurostimulation procedure. |
| **CONTENTS** | Background and objectives, Search methods, Results, Peripheral stimulations (TENS, PNS and NRS), Spinal cord stimulation, Deep brain stimulation, Motor cortex stimulation, Repetitive transcranial magnetic stimulation, General comments, Declaration conflict of interest, Supplementary Materials, References. |

**QUALITY**

| AGREE Domain | Scores | | | Comments |
|---|---|---|---|---|
| | Reviewer 1 | Reviewer 2 | % | |
| Scope and purpose | 9/12 | 8/12 | 61 | The overall objective and patients to whom the guideline is meant to apply are clearly defined however the clinical questions covered are not documented. |
| Stakeholder involvement | 8/16 | 9/16 | 38 | The target audience is defined as clinical neurologists. It was unclear whether representation was sought from all relevant professional groups. It is unclear whether patients' views and preferences have been sought or whether the guideline was piloted. |
| Rigour of development | 23/28 | 23/28 | 76 | All aspects of the methodology scored highly however most of the methodology was present in supplementary material. |
| Clarity and presentation | 7/16 | 8/16 | 29 | The recommendations appear to be conclusions drawn from the evidence identified. Where there is a lack of evidence, the authors do not provide a consensus-based recommendation. Where evidence has been identified, the authors indicate whether this is positive, negative or inconclusive for each of the interventions and for different sources of neuropathic pain. The guideline is not supported with tools for application. |
| Applicability | 4/12 | 3/12 | 6 | Information concerning organisational barriers, cost implications and review criteria for each of the neurostimulation therapies addressed in this guideline is not documented. |
| Editorial independence | 6/8 | 6/8 | 67 | Editorial independence is unclear as the funding body is unknown. Five out of eight authors declared they had a consultant contract or had received honorariums from Medtronic (supplier of electrodes commonly used in neurostimulation procedures). |

| RELEVANCE | | | |
|---|---|---|---|
| Source | Europe | Settings | Rehabilitation/Long Term Care |
| Developers | Task Force members included representation from EFNS Panel on Neuropathic Pain, Vienna, Austria; Department of Neurological Sciences, La Sapienza University, Roma, Italy; Oxford Functional Neurosurgery, Department of Neurosurgery, Radcliffe Infirmary, Oxford, UK; INSERM 'Central integration of pain' (U879) Bron, University Lyon 1, France; Department of Neurosurgery, Pain Center, Karolinska University Hospital and Pain Section, Department of Molecular Medicine and Surgery, Karolinska Institutet, Stockholm, Sweden; Danish Pain Research Center, Aarhus University Hospital, Aarhus, Denmark; Department of Physiology, Henri Mondor Hospital, AP-HP, Créteil, France; Department of Neurosurgery, University Hospital of Wales, Heath Park, Cardiff, UK; and Peninsula Medical School, Universities of Exeter & Plymouth, UK | Target Audience | Neurologists |
| **METHODOLOGICAL QUALITY OF PRIMARY EVIDENCE** | | | |
| Level of evidence | Cruccu et al classified primary evidence according to the EFNS scheme of evidence for therapeutic interventions [35]. Primary evidence was classified as Class II Grade B (prospective matched-group cohort study, RCT with methodological limitations) for SCS and Class IV (uncontrolled studies, case series, case reports, or expert opinion) for PNS, MCS and DBS. Class IV was considered insufficient evidence to determine recommendations. | | |
| **SUMMARY** | | | |
| The guideline scored moderately well with regards to the scope, purpose and rigorous methodology employed. As the title suggests, this guideline is limited to assessing the available evidence for selected neurostimulation therapies rather than clinical questions regarding overall management of patients with neuropathic pain. It is not clear whether consumer input was sought during development of the guideline. Authors of the guideline do not provide consensus-based recommendations wherever evidence is lacking, resulting in limited clarity of the guideline. Applicability of the guideline is limited due to a lack of information regarding organisational factors, cost implications and review criteria that should be considered when utilising any of the neurostimulation therapies described. It is a potential conflict of interest that several of the authors have received financial support from one of the leading medical suppliers of these technologies however, this is more likely to have been a problem if the guideline had included consensus-based recommendations. | | | |

***N.B. – this guideline was appraised in the previous version of this report (Pitt V, Reid J, Garrubba M, Harris C. Implantable Pain Therapies: Neurostimulation - Evidence Review. 2008 September 2008:1-44).**

**Table A5.2 Critical appraisal table *(Fontaine J Headache Pain 2010)*, deep brain stimulation**

| **Study: Fontaine, D, Lazorthes, Mertens, P, Blond, S, Geraud, G, Fabre, N, Navez, Lucas, C, Dubois, F, Gonfrier, Paquis, P and 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 and Pain. 2010. 11:23-31.** |
|---|

| *Crossover Randomised Controlled trial* | |
|---|---|
| **Patient/population** | Patients with severe refractory chronic cluster headache (CCH) |
| **N** | 11 |
| **Setting** | Multicenter academic centres |
| **Intervention/indicator** | Deep brain stimulation |
| **Comparison/control** | Group 1: stimulator switched ‘‘On’’ for 1 month, followed by 1 week washout and then was switched ‘‘Off’’ for 1 month.<br>Group 2: stimulator switched ‘‘Off’’ for 1 month, followed by 1 week washout and then was switched ‘‘On’’ for 1 month. |
| **Outcomes** | • Weekly attacks frequency (primary)<br>• Pain intensity (Likert scale),<br>• Sumatriptan injections,<br>• Oxygen use (yes or no),<br>• Anxiety and depression levels (Hospital Anxiety Depression scale),<br>• Quality of life (SF-12 scale),<br>• Blood pressure, heart rate, weight and body temperature,<br>• Electrolyte balance and hormonal functions (thyroid hormones, TSH, ACTH, cortisol, SDHEA, insulin, prolactin, testosterone, estradiol, LH, FSH, GH and IGF-1),<br>• Patient’s satisfaction (Patient’s Global Impression of Change) and<br>• Changes in thirst, appetite, libido, sleepwalking cycle and behavior (AE) |
| **Inclusion Criteria** | • chronic CH according to ICHD-II criteria;<br>• disease duration over 3 years;<br>• resistance to pharmacological prophylactic treatment with adequate trials (verapamil up to 960 mg/day, lithium with plasma level from 0.6 to 1 mEq/l, association of both; in absence of adverse events);<br>• daily attacks;<br>• absence of substance abuse or dependence;<br>• age 18–65- year-old;<br>• normal findings on magnetic resonance imaging;<br>• no contraindications to surgery or anesthesia. |

| | |
|---|---|
| **Exclusion Criteria** | Not specified |

**Study Validity.**

| | | |
|---|---|---|
| **Is it clear that there are no conflicts of interest in the writing or funding of this study?** | Yes | "Study supported by grant from the Programme Hospitalier de Recherche Clinique and promoted by the Centre Hospitalier Universitaire de Nice. Stimulators have been purchased from Medtronic, which had no role in the study, but provided funds for the meetings of the investigators." |
| **Does the study have a clearly focused question?** | Yes | "We performed a prospective crossover, double-blind, multicenter study assessing the efficacy and safety of unilateral hypothalamic DBS in 11 patients with severe refractory CCH." |
| **Is a cross-over RCT the appropriate method to answer this question?** | Yes | |
| **Does the study have specified inclusion/exclusion criteria?** | Yes | "Patients with refractory chronic CH were enrolled in the study according to the following inclusion criteria: chronic CH according to ICHD-II criteria [2]; disease duration over 3 years; resistance to pharmacological prophylactic treat-ment with adequate trials (verapamil up to 960 mg/day, lithium with plasma level from 0.6 to 1 mEq/l, association of both; in absence of adverse events); daily attacks; absence of substance abuse or dependence; age 18–65-year-old; normal findings on magnetic resonance imaging; no contraindications to surgery or anesthesia." |
| **If there were specified inclusion/ exclusion criteria, were these appropriate?** | Yes | |
| **Did the study have an adequate method of randomisation?** | Yes | "We used a blocking scheme randomization and a central randomization procedure without stratification."<br>*(example of a low risk of bias)* |
| **Was allocation to intervention group concealed?** | Yes | "We used a blocking scheme randomization and a central randomization procedure without stratification." |
| **Were patients blind to intervention group?** | Yes | "Previous studies [9, 11, 12] demonstrated that posterior hypothalamic stimulation does not induce perceptible sensations, allowing double-blind trial as the patient is not able to identify the ''on'' or ''off'' condition."<br>"At the end of the randomized phase, patients and neurologists were not able to identify their period allocation, confirming the double-blind evaluation." |
| **Were investigators and care providers blind to** | Not reported | |

| | | |
|---|---|---|
| **intervention group?** | | |
| **Were outcome assessors blind to intervention group?** | Yes | "Clinical evaluation was performed by the neurologist blinded of the stimulation status. At each evaluation,<br>clinical data collected were: number of attacks during the last week (calculated from the individual patient's diary), mean attack intensity during the last week (according to Likert scale), number of subcutaneous sumatriptan administration during the last week (from the patient's diary), oxygen use (yes or no), anxiety and depression levels (Hospital Anxiety Depression scale), quality of life (SF-12 scale), supine and standing blood pressure, heart rate, weight and body temperature. Electrolyte balance and hormonal functions (thyroid hormones, TSH, ACTH, cortisol, SDHEA, insulin, prolactin, testosterone, estradiol, LH, FSH, GH and IGF-1) were evaluated at each evaluation. After surgery, evaluations additionally included: patient's satisfaction (Patient's Global Impression of Change) and changes in thirst, appetite, libido, sleep-walking cycle and behavior. Any new symptom or worsening of a preexisting symptom was classified as an adverse event. An adverse event was classified as serious in case of death, hospitalization, sequel or consideration as serious by the clinician." |
| **All outcomes were measured in a standard, valid and reliable way?** | Partial | "Review of the early DBS studies [9, 11] in CH, available when the present study has been designed, did not allow to find the mean and variability of our primary outcome, namely frequency of attacks per week, in this refractory CH patients candidates for surgery. **Due to absence of published data, this estimate was based on the characteristics of refractory chronic CH patients registered in the Nice University Hospital database.**"<br>"Patient impression of change was recorded using the PGIC which is a 7-point scale (1 extreme improvement; 2 significant improvement; 3 mild improvement; 4 no change; 5 mild worsening; 6 significant worsening; 7 extreme worsening). Emotional impact was assessed by the French version of the **widely used** Hospital Anxiety and Depression scale (HAD). The HAD involves seven anxiety items alternating with seven depression items. Anxiety and depression are defined by anxiety (HAD-A) and depression (HAD-D) scores superior to 7, respectively. The health-related quality of life was evaluated using the French version of the short-form 12 questionnaire (SF12) used to derive to summary scores, physical (SF12-PS) and mental (SF12-MS) component summaries. Lower numbers indicate greater disability" |
| **Were outcomes assessed objectively?** | Partial | |
| **Were outcomes assessed independently?** | Not reported | |
| **Were the groups similar at baseline with regards to key prognostic variables?** | Not reported | A table (page 27) on the prognostic variables at baseline is provided but the authors do not report if any differences were apparent qualitatively or quantitatively through statistical analysis. From qualitative perspective there appears to be a larger proportion of males than females (approx. 73%), some patients have experienced this condition (18-35 years) much longer than others (3-12 years) and attacks/wk varied too with 20-53 (n=3) vs. 7-14 (8). |
| **Aside from the experimental intervention, were the groups treated the same?** | Not reported | |
| **Were the outcomes measured appropriate?** | Partial | The primary outcome (no. of attacks/wk) was appropriate and most secondary outcomes were appropriate, except for two measures including no. of sumatriptan injections and oxygen use. The authors comment that "Some patients did not use attack treatment by sumatriptan and/or oxygen due to their lack of efficacy or side effects (such patients used opioids with weak efficacy)". Due to half of |

| | | |
|---|---|---|
| | | the study sample not using these treatments, it should not be used as a outcome measure to reflect what is observed for the whole sample. |
| **Was there sufficient duration of follow-up?** | Not reported | Is 1 year follow up sufficient?? |
| **Was there ≤20% drop out?** | Yes | "Twelve patients were included (May 2005–June 2007), 1 declined to participate, 11 were operated, 1 was explanted due to infection but re-implanted later, before the randomization. Consequently 11 patients completed the randomized phase and the open phase." |
| **Was this intervention suitable for a cross-over study?** | Yes | |
| **Was the washout period adequate?** | Yes | "We did not detect any significant carry-over effect (P = 0.855) indicating that the effects of the first treatment period did not persist after the wash out." |
| **Was the study sufficiently powered to detect any differences between the groups?** | Yes | "Power calculation was based on our estimate that at baseline mean weekly frequency of attacks would be 23.9 (SD 3.7). The study was designed to have an overall power of 90% to detect a 50% reduction of the primary endpoint during the stimulation period." |
| **If statistical analysis was undertaken, was this appropriate?** | Yes | "According to Jones and Kenward [17], three effects were tested: carry-over, periodand treatment effects. Type I error was fixed at 10% for the carry-over effect and 5% for the others. Non-parametric two-sided Wilcoxon rank-sum tests were used for the analysis, given the number of patients. The effect of treatment at 1 year compared to baseline was done with a Wilcoxon test for paired samples (two-sided, type I error rate = 5%) on primary and second outcomes. All the statistical analysis was performed using the SPSS version 11.0 program." |
| **Were all the subjects analysed in the groups to which they were randomly allocated (ie intention to treat analysis)?** | Yes | "All outcome measures were analyzed by intention to treat." |
| **Is the paper free of selective outcome reporting?** | Yes | |
| **Other** | | |
| **What is the overall risk of bias?** | Moderate | |

**Results.**

**Table 1** Characteristics of the 11 patients before implantation

| Center/ patient no. | Group | Sex | Age (years) | Disease duration (years) | Attack side | Onset clinical form | Attacks/ week | Pain intensity | Sumatriptan injection/ week | Oxygen use |
|---|---|---|---|---|---|---|---|---|---|---|
| C1/P1 | On/Off | M | 52 | 35 | Left | Episodic | 14 | 9 | 1 | No |
| C1/P2 | Off/On | M | 40 | 12 | Right | Chronic | 14 | 5 | 14 | No |
| C1/P3 | Off/On | M | 51 | 8 | Left | Episodic | 19 | 2 | 15 | No |
| C1/P4 | On/Off | M | 44 | 10 | Left | Chronic | 28 | 10 | 0 | No |
| C1/P5 | On/Off | M | 47 | 7 | Right | Chronic | 11 | 6 | 11 | No |
| C2/P1 | Off/On | M | 50 | 20 | Right | Episodic | 20 | 5 | 0 | No |
| C2/P2 | Off/On | F | 42 | 3 | Left | Chronic | 7 | 8 | 1 | Yes |
| C3/P1 | On/Off | F | 42 | 7 | Right | Episodic | 53 | 6.5 | 0 | Yes |
| C3/P2 | Off/On | M | 36 | 7 | Left | Chronic | 9 | 5 | 11 | No |
| C4/P1 | Off/On | M | 39 | 18 | Right | Episodic | 14 | 5 | 14 | No |
| C4/P2 | On/Off | F | 43 | 6 | Right | Chronic | 7 | 7 | 1 | Yes |
| Mean | | | 44.1 | 12.1 | | | 17.8 | 6.1 | 6.2 | |

Some patients did not use attack treatment by sumatriptan and/or oxygen due to their lack of efficacy or side effects (such patients used opioids with weak efficacy)

**Efficacy**

"At the end of the randomized phase, patients and neurologists were not able to identify their period allocation, confirming the double-blind evaluation. The weekly frequency of CH attacks did not significantly differ between the On and Off periods (Table 2). We did not detect any significant carry-over effect (P = 0.855) indicating that the effects of the first treatment period did not persist after the wash out. None of the secondary outcomes differed between stimulation and sham treatment. Stimulation voltages used during the randomized phase ranged from 1.0 to 2.8."

**Table 2** Changes in severity of cluster headache, emotional impact and quality of life during the randomized phase

| | Active stimulation followed by sham stimulation (On–Off group) ($n = 5$) Median [range] | | | Sham stimulation followed by active stimulation (Off–On group) ($n = 6$) Median [range] | | | Difference between active and sham stimulation in the On–Off group Mean [95% CI] | Difference between active and sham stimulation in the Off–On group Mean [95% CI] | *P* value (treatment effect) |
|---|---|---|---|---|---|---|---|---|---|
| | Baseline (week 8) | End of On period (week 12) | End of Off period (week 17) | Baseline (week 8) | End of Off period (week 12) | End of On period (week 17) | | | |
| Attacks/week | 11 [2–42] | 18 [1–55] | 6 [1–49] | 16 [7–25] | 14.5 [0–28] | 9 [6–21] | 0.2 [−24.0; 23.6] | −2.7 [−25.7; 20.31] | 0.927 |
| Sumatriptan (injection/week) | 7 [1–13] | 0 [0–18] | 1 [0–6] | 11.5 [1–29] | 12.5 [0–33] | 6.5 [0–25] | 2 [−9.0; 13] | −5.3 [−24.1; 13.5] | 0.349 |
| Pain intensity | 5.5 [4–9] | 5 [3–8] | 5.5 [3–8] | 6 [2–9] | 5.7 [0–10] | 4.5 [2–9] | 0 [−1.4; 1.4] | 0.3 [−9.5; 10] | 0.357 |
| PGIC | na | 2 [1–7] | 2 [1–6] | na | 2 [1–4] | 4 [1–7] | 0.8 [−20.1; 21.8] | 1.3 [−4.2; 6.8] | 0.853 |
| HAD-A | 8.8 [5–10] | 8 [3–12] | 6 [4–14] | 11.5 [6–15] | 8 [5–10] | 9 [6–15] | 0.2 [−23.6.1; 24.0] | −2.6 [−25.5; 20.3] | 0.927 |
| HAD-D | 8.5 [3–13] | 9 [4–13] | 1 [0–6] | 9.5 [1–13] | 4 [1–9] | 8 [1–16] | 1.3 [−22.4; 25.1] | 5.3 [−1.08; 11.7] | 0.154 |
| SF 12-MS | 33.1 [28.1–52.1] | 34.5 [31.6–56.2] | 30.3 [17.8–59.9] | 36.4 [27.5–53.3] | 48.9 [24.9–54.2] | 36.7 [16–52.9] | 5.8 [−12.8; 24.4] | −8.7 [−27.3; 9.9] | 0.197 |
| SF 12-PS | 29 [24.4–31.2] | 28.3 [27.2–29.0] | 33.8 [27.5–34.9] | 34.7 [32.2–46.5] | 37.9 [28.4–46.5] | 43.4 [28.1–51.5] | −3.9 [−13.1; 5.3] | 2.8 [−15.4; 21] | 0.197 |

All carryover and period effects were not significant. *P* values are for the between-group comparison of the difference between active and sham stimulation during the last week of each period (weeks 12 and 17). Severity of chronic CH has been assessed by weekly attack frequency, pain intensity (Liekert scale), and weekly sumatriptan injections. Patient impression of change was recorded using the PGIC which is a 7-point scale (*1* extreme improvement; *2* significant improvement; *3* mild improvement; *4* no change; *5* mild worsening; *6* significant worsening; *7* extreme worsening). Emotional impact was assessed by the French version of the widely used Hospital Anxiety and Depression scale (HAD). The HAD involves seven anxiety items alternating with seven depression items. Anxiety and depression are defined by anxiety (HAD-A) and depression (HAD-D) scores superior to 7, respectively. The health-related quality of life was evaluated using the French version of the short-form 12 questionnaire (SF12) used to derive to summary scores, physical (SF12-PS) and mental (SF12-MS) component summaries. Lower numbers indicate greater disability

**Adverse events**

"Three serious adverse events were reported during the study, in two patients. One subcutaneous infection, 3 weeks after surgery, completely resolved after hardware removal and antibiotic treatment. The patient was re-implanted 6 months later. One patient experienced a preoperative loss of consciousness with hemiparesia shortly after test stimulation. An immediate CT-scan was normal. Symptoms spontaneously resolved in 2 h without sequel."…. "Twenty-six non-serious adverse events (NSAE) were reported (Table 5). All of them were mild, and most of them were transient. Rates of NSAE were similar in both ''On'' and ''Off'' randomized periods."

**Table 5** Adverse events

| | |
|---|---|
| AE related to surgery | 2 |
| Superficial infection (hardware removal) (SAE) | 1 |
| Neck pain along the lead | 1 |
| Transient AE related to test stimulation | 5 |
| (Resolving after voltage reduction or contact change) | |
| Complex oculomotor disturbances[a] | 4 |
| Loss of consciousness with hemiparesia (SAE) | 1 |
| AE and changes during "On" period | 6 |
| Mild hunger increase | 3 |
| Mild hunger decrease | 1 |
| Mild libido decrease | 2 |
| AE and changes during "Off" period | 8 |
| Mild hunger increase | 2 |
| Mild hunger decrease | 1 |
| Mild thirst increase | 1 |
| Mild thirst decrease | 1 |
| Mild libido decrease | 1 |
| Increased testosterone level | 1 |
| Shorten menstrual cycle | 1 |

*SAE* serious adverse event

[a] Three patients reported a transient diplopia, one reported an impairment of gaze fixation without objective oculomotor paresis

**Author's Conclusions.**

"In the controlled phase of this study, we failed to demonstrate that DBS improved chronic CH when compared with sham stimulation. These findings contrasted with the results observed in the open phase of the study, which showed that more than 50% of the patients were improved over 50%, and that mean attack frequency and emotional impact were markedly decreased."

**Our Comments/Summary.**

The study design was appropriate to the intervention (DBS) as most neurostimulation studies are designed with a crossover period for ethical reasons on behalf of the patient. With the current RCT the authors report that “At the end of the randomized phase, patients and neurologists were not able to identify their period allocation, confirming the double-blind evaluation.” A longer duration of stimulation periods might then be feasible if patients cannot perceive the stimulation as is the case in most neurostimulation types (except MCS). The authors did not provide a summary of the results for each individual and did not report if any subgroup analysis was conducted to see if any effects existed based on specific groups or prognostic factors. We were unable to assess if investigators and caregivers were blind to the intervention groups or if the groups were similar in prognostic factors at baseline as the authors did not provide this information.

The overall risk of bias was moderate. The study involved a small number of patients (n=11), even though the authors randomly assigned patients to one of two groups – active stimulation then sham stimulation (On-Off) or sham stimulation then active stimulation (Off-On). “There was no significant difference in these characteristics between the two groups (On–Off and Off–On).” The Authors do acknowledge the small sample size “First, the small sample size could have lead to inconclusive results in the randomized phase. Due to the lack of published data concerning this sub-population of refractory chronic CH patients, sample size calculation was based on the estimation of characteristics of these CH patients, registered in our institution data-base. Considering that the variability of weekly attack frequency was higher in the included population (SD: 13.2) than the estimated one (SD: 3.7), the sample size calculation might be a posteriori not adequate.”

The wash out period may not have been adequate even though the authors reported that “we did not detect any significant carry-over effect (P = 0.855) indicating that the effects of the first treatment period did not persist after the wash out.” The wash out period was only 1 week. The authors comment that the delay between stimulation onset and therapeutic effect was documented in early publications before the RCT as <4 weeks, hence they designed the RCT with 1 month periods. A later publication alludes to the fact that the delay is actually longer, a mean of 42 days. With this information in mind, the wash out period would need to also be of this duration (good study practice) to make sure no carry over effect was apparent. This could be a reason for no significant different being found between the active and sham stimulation and therefore represents bias in the study results. However the evidence is from a case study so further high level studies should be conducted to eliminate the inconsistency.

The stimulation parameters were “set by default” by the clinician who performed the surgery and were “based on ones previously reported [9, 11].” The authors acknowledge that this may have had an effect on the result in the randomised phase of the study as some patients may have been receiving non-optimal stimulation.

The study was relatively well conducted in terms of the study design, however the moderate risk of bias means that further studies need to be conducted to confirm the results of the current study.

**Table A5.3 Critical appraisal table *(Lefaucheur Brain 2009)*, motor cortex stimulation**

| **Study: Lefaucheur J-P, Drouot X, Cunin P, Bruckert R, Lepetit H, Creange A, et al. Motor cortex stimulation for the treatment of refractory peripheral neuropathic pain. Brain. 2009 Jun;132(Pt 6):1463-71** | |
|---|---|
| ***Crossover Randomised Controlled trial*** | |
| **Patient/population** | "patients with drug-resistant pain secondary to peripheral nerve lesion" (refractory peripheral neuropathic pain), various pain origins: "trigeminal neuralgia (n = 4), brachial plexus lesion (n = 4), neurofibromatosis type-1 (n = 3), upper limb amputation (n = 2), herpes zoster ophthalmicus (n = 1), atypical orofacial pain secondary to dental extraction (n =1) and traumatic nerve trunk transaction in a lower limb (n = 1)" |
| **N** | patients enrolled (n=16), stimulator implanted (n=16), 1 month postoperative evaluation (n=15), randomised (n=13), completed the study randomised phase and open phase(n=12) |
| **Setting** | Hospital and community (patients at home) |
| **Intervention/indicator** | Motor cortex stimulation |
| **Comparison/control** | Stimulator switched on vs. stimulator switched off<br>Cross-over randomised controlled trial performed between 1 and 3 months postoperative, during which the stimulator was alternatively switched 'on' and 'off' for 1 month, followed by an open phase during which the stimulator was switched 'on' in all patients |
| **Outcomes** | **(0-100 VAS):** Self rated pain intensity<br>**Brief Pain Inventory (BPI) short form:** assesses "the degree to which pain interferes with seven different functions (general activity, mood, walking ability, normal work, relations with other people, sleep and enjoyment of life). Each item is rated on a 0–100 scale<br>**McGill Pain Questionnaire (MPQ):** which measures aspects of pain<br>**Sickness Impact Profile (SIP):** General health disturbance related to sickness<br>**Medication Quantification Scale (MQS):** Analgesic drug consumption<br>*See paper p1466 for further detail on outcome measurement*<br>"Regarding individual results at final examination, analgesic effects of MCS were classified into three categories...: good (VAS score reduction by 70–100%), satisfactory (reduction by 40–69%) and poor (reduction by <40%)." |
| **Inclusion Criteria** | "Patients were selected according to the following criteria: (i) age between 18 and 80; (ii) presence of unilateral or lateralized neuropathic pain due to peripheral nervous system lesion; (iii) chronic pain resistance for more than a year to at least three different types of analgesic medical treatments, including antiepileptics and antidepressants; (iv) average pain score ≥50 on a 0–100 visual analogue scale (VAS) over 7 days of self-assessment; and (v) informed consent signed before implant of the cortical stimulation lead." |
| **Exclusion Criteria** | "Patients presenting any of the following conditions were excluded: (i) pregnancy; (ii) malignant disease; (iii) history of epileptic seizures; (iv) thrombocytopaenia (550 000 platelets/mm3) or leukopaenia (52000 WBCs/mm3); (v) heart, renal or hepatic failure; (vi) psychotic disorder; or (vii) patient unable and/or unwilling to cooperate with study procedures or to comply with the required follow-up visits." |

| Study Validity. | | |
|---|---|---|
| **Is it clear that there are no conflicts of interest in the writing or funding of this study?** | Not reported | No statement about conflict of interest, but statement about funding<br>"Funding: Programme Hospitalier de Recherche Clinique (PHRC) 'STIMCORTEX'." |
| **Does the study have a clearly focused question?** | yes | "The present study is the first randomized controlled trial in which MCS efficacy—to treat peripheral neuropathic pain—is assessed." |
| **Is a cross-over RCT the appropriate method to answer this question?** | yes | MCS is an intervention with a temporary effect, and the population had a chronic condition (pain) |
| **Does the study have specified inclusion/exclusion criteria?** | yes | See above |
| **If there were specified inclusion/ exclusion criteria, were these appropriate?** | yes | |
| **Did the study have an adequate method of randomisation?** | Not reported | |
| **Was allocation to intervention group concealed?** | Not reported | |
| **Were patients blind to intervention group?** | Yes | "Double-blind examinations were performed at the end of each month (M2, M3) of the crossover trial. Neither the patient nor the clinical investigator could be aware of stimulator condition during this period, especially because no sensory percept or motor effect was resulting from active MCS." |
| **Were investigators and care providers blind to intervention group?** | Yes | "Double-blind examinations were performed at the end of each month (M2, M3) of the crossover trial. Neither the patient nor the clinical investigator could be aware of stimulator condition during this period, especially because no sensory percept or motor effect was resulting from active MCS." |
| **Were outcome assessors blind to intervention group?** | Yes | "Double-blind examinations were performed at the end of each month (M2, M3) of the crossover trial. Neither the patient nor the clinical investigator could be aware of stimulator condition during this period, especially because no sensory percept or motor effect was resulting from active MCS." |

| | | |
|---|---|---|
| **All outcomes were measured in a standard, valid and reliable way?** | Partial | Some measures reported as validated<br>"The patients were given a pain diary and asked to self-rate every day the mean pain intensity that they experienced on a 0–100 VAS (from 0 = no pain to 100 = highest imaginable pain). For analyses, the seven daily pain ratings preceding each visit were averaged.<br>Pain assessment was also carried out using the short form of the brief pain inventory (BPI), a tool initially designed for cancer patients (Cleeland and Ryan, 1994) and then validated for use in noncancer pain (Keller et al., 2004). The BPI provides information on the degree to which pain interferes with seven different functions (general activity, mood, walking ability, normal work, relations with other people, sleep and enjoyment of life). Interference was rated for each item on a 0–100 scale (0 = pain does not interfere to 100 = pain completely interferes), and the average value was taken for analysis.<br>Finally, pain was assessed by the McGill Pain Questionnaire (MPQ) (Melzack, 1975) in its validated translation into the French language. The MPQ consists of 20 descriptors that fall into four major groups: sensory (descriptors 1–10), affective (11–15), evaluative (16) and miscellaneous (17–20)...<br>General health disturbance related to sickness was quantified with the Sickness Impact Profile (SIP) (Bergner et al., 1981). This questionnaire consists of 136 items of 12 domains of daily functioning: ambulation, mobility, body care and movement, social interaction, alertness behaviour, emotional behaviour, communication, sleep and rest, eating, work, home management and recreation and pastimes. Only the total SIP score was taken into account.<br>Analgesic drug consumption was quantified using the Medication Quantification Scale (MQS) (Masters-Steedman et al., 1992). The MQS was developed as a tool for patients with chronic non-malignant pain...<br>Regarding individual results at final examination, analgesic effects of MCS were classified into three categories (Nguyen et al., 1999): good (VAS score reduction by 70–100%), satisfactory (reduction by 40–69%) and poor (reduction by<40%)" |
| **Were outcomes assessed objectively?** | No | Subjective self-report measures |
| **Were outcomes assessed independently?** | Yes | The scales used addressed different aspects of pain and QoL |
| **Were the groups similar at baseline with regards to key prognostic variables?** | Not reported | Demographic data given for all patients, but there was no indication of which group they were randomised to |
| **Aside from the experimental intervention, were the groups treated the same?** | Yes | All patients had the same care pre-randomisation when they had the stimulators implanted, by the time they were randomised and had their stimulator switched on or left off, they had been discharged from hospital so were not receiving care by the investigators, it is not clear if they were receiving other treatments outside the hospital through other health care providers |
| **Were the outcomes measured appropriate?** | Yes | |
| **Was there sufficient duration of follow-up?** | Yes | |
| **Was there ≤20% drop out?** | Yes | |

| | | |
|---|---|---|
| **Was this intervention suitable for a cross-over study?** | Yes | MCS is an intervention with a temporary effect |
| **Was the washout period adequate?** | No | "Although the stimulator was turned 'off' for about 3 weeks before the crossover period, carry-over effects could be expected because MCS applied for even a couple of days could induce long-lasting effects up to several weeks." |
| **Was the study sufficiently powered to detect any differences between the groups?** | Not reported | Unlikely to be sufficiently powered as this was a small study with only 16 patients enrolled and 13 randomised |
| **If statistical analysis was undertaken, was this appropriate?** | Yes | |
| **Were all the subjects analysed in the groups to which they were randomly allocated (ie intention to treat analysis)?** | Yes | |
| **Is the paper free of selective outcome reporting?** | Yes | |
| **Other** | | |
| **What is the overall risk of bias?** | High | Due to the insufficient wash-out period between phases of the cross-over RCT, the small sample size and the lack of information about characteristics of patients assigned to each group, and the randomisation and allocation concealment procedures, this study has a high risk of bias |

**Results.**

***N.B. The cross-over RCT was only part of a larger study reported in this paper. Only results relating to the randomised cross-over part of the study are reported here***

"Only 12 patients completed the study. Two patients (Patients 8 and 10) greatly improved after implantation and refused to accept the crossover trial and further evaluations. The stimulator was switched 'on' at M1. For both of them, we obtained the 7-day VAS pain ratings at 12 months postoperative: Patient 8 experienced 63% pain relief (mean VAS score decrease from 92 to 34); Patient 10 experienced 58% pain relief (mean VAS score decrease from 55 to 23). One patient (Patient 14) completed the crossover trial but refused to perform further evaluations due to the lack of efficacy of the procedure. She was still presenting maximal pain (VAS score of 100) 1 year after implantation. Finally, MCS was not activated in one patient (Patient 9). This patient accidentally fell in her hospital room the day after MCS electrode implantation. She broke one right rib, leading to the rupture of an emphysematous bulla that caused pneumothorax. She developed acute respiratory distress requiring drainage by a chest tube inserted into the pleural cavity and ventilation. After 1.5 months stay in intensive care unit, she was transferred to a rehabilitation unit and progressively improved, leading to almost complete clinical recovery. Five months after her accident, she was able to return home with only minor fluctuating dyspnoea. However, taking into account this complication, the spontaneous reduction in pain level during this episode and the age of the patient (80 years old), it was decided not to use the stimulator. This was the only serious adverse event. No haemorrhage, infection or neurological complications occurred in this series of patients."

...

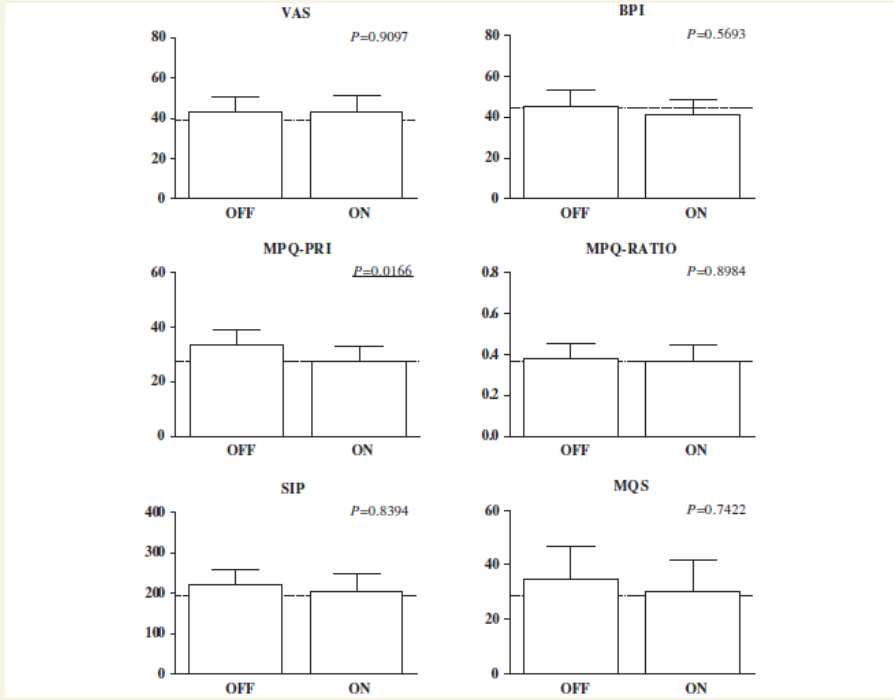



Figure 3 Clinical scores (mean, SEM) in 'on-stimulation' and 'off-stimulation' conditions during the crossover trial performed between 1 and 3 months postoperative. The dotted horizontal line corresponds to the mean value at 1 month postoperative before the crossover trial. *P* significance of the Wilcoxon matched-pairs signed-ranks test is presented in the upper right corner. VAS = visual analogue scale; BPI = brief pain inventory; MPQ-PRI, MPQ-ratio = McGill pain questionnaire—pain rating index, ratio between affective and sensory subscores; SIP = sickness impact profile; MQS = medication quantification scale.

"Regarding the randomized crossover trial, only MPQ-PRI differed between the two conditions of stimulation (27.4 'on-stimulation' versus 33.6 'off-stimulation', P = 0.0166, Wilcoxon test) (Fig. 3). However, this difference did not persist after adjustment for multiple comparisons. Although the MPQ-ratio did not vary with the condition, the MPQ sensory subscore tended to decrease when MCS was switched 'on' (14.3 'on-stimulation' versus 17.8 'off-stimulation', P = 0.01), whereas the MPQ affective subscore did not change (P = 0.30) (Fig. 4)...During the crossover trial, the mean MPQ-PRI decrease was 29% (individual results ranging from +60% to -100%). Seven of the 13 patients who completed the crossover trial showed MPQ-PRI reduction greater than 30% between 'on-stimulation' and 'off-stimulation' conditions. The stimulator was switched 'on' at M1 in three of these patients and at M2 in four. Pain was located at the face (n = 3), neck (n = 1), upper limb (n=1) or lower limb (n = 2). Among these seven patients, five showed good or satisfactory MCS efficacy at final examination compared to the preoperative baseline. Two patients who responded to MCS during the crossover trial remained poorly relieved at M12 (VAS score decreased by 10% and 31%). Conversely, two patients who did not respond to MCS during the crossover trial (MPQ-PRI reduced by 5% and 19%) were found to be greatly relieved at M12...MPQ-PRI reduction in 'on-stimulation' compared with 'off-stimulation' condition during the crossover period did not vary with pain location (29% facial pain versus 10% upper limb pain, P = 0.91) or the presence of sensori-motor deficit (14% sensori-motor deficit versus 43% no deficit, P = 0.45)...The reduction of MPQ-PRI in 'on-stimulation' condition during the crossover period did not correlate with age, pain duration before surgery, preoperative baseline or 1 month postoperative pain level (P = 0.48, 0.68, 0.65 and 0.17)."

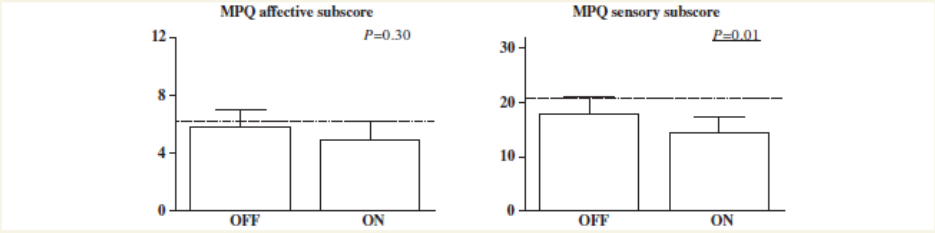



Figure 4 Affective and sensory subscores (mean, SEM) of the McGill pain questionnaire (MPQ) in 'on-stimulation' and 'off-stimulation' conditions during the crossover trial performed between 1 and 3 months postoperative. The dotted horizontal line corresponds to the mean value at 1 month postoperative before the crossover trial. *P* significance of the Wilcoxon matched-pairs signed-ranks test is presented in the upper right corner.

## Author's Conclusions.

"At final examination, the mean rate of pain relief on VAS scores was 48% (individual results ranging from 0% to 95%) and MCS efficacy was considered as good or satisfactory in 60% of the patients. Pain relief after 1 year tended to correlate with pain scores at 1 month postoperative, but not with age, pain duration or location, preoperative pain scores or sensory-motor status. **Although the results of the crossover trial were slightly negative, which may have been due to carry-over effects from the operative and immediate postoperative phases**, observations made during the open trial were in favour of a real efficacy

of MCS in peripheral neuropathic pain. Analgesic effects were obtained on the sensory-discriminative rather than on the affective aspect of pain. These results suggest that the indication of MCS might be extended to various types of refractory, chronic peripheral pain beyond trigeminal neuropathic pain."

**Our Comments/Summary.**

This study had a complicated design of which the crossover RCT was only one component. The results from the crossover RCT were slightly negative. However, this may have been due to an insufficient wash out period "Although the stimulator was turned 'off' for about 3 weeks before the crossover period, carry-over effects could be expected because MCS applied for even a couple of days could induce long-lasting effects up to several weeks. Given the carry-over effect, a ceiling effect might have occurred, therefore preventing further improvement in this population and thus explaining the lack of difference between the conditions in most of the clinical scores. This is an important limitation of this controlled study."

Overall this study has a high risk of bias. The insufficient wash-out period between phases of the cross-over RCT could affect the results, and the small sample size and lack of information about characteristics of patients assigned to each group and the randomisation and allocation concealment procedures mean that it is not possible to determine if the groups were similar enough to be sure that any effects were due to the intervention and not pre-existing differences between groups. Therefore, the results are inconclusive and should not be generalised.

**Table A5.4 Critical appraisal table *(Lipton Cephalalgia 2009)*, occipital nerve stimulation**

| **Study: Lipton, R, Goadsby, P, Cady, R, Aurora, S, Grosberg, B, Freitag, F, Silberstein, S, Whiten, D and Jaax, K. PRISM study: occipital nerve stimulation for treatment-refractory migraine. Cephalalgia. 2009. 29 (Suppl. 1): 30.** | |
|---|---|
| ***Randomised Controlled trial*** | |
| **Patient/population** | Patients with treatment-refractory migraine |
| **N** | 132 were implanted, 125 completed 12-week follow-up<br>Active stimulation arm (completed) – 63<br>Sham stimulation arm (completed) - 62 |
| **Setting** | Multi-centre medical clinics |
| **Intervention/indicator** | Bilateral active (250 lsec pulses, 60 Hz, 0–12.7 mA) occipital nerve stimulation for 12 weeks |
| **Comparison/control** | Sham (10 l sec pulses, 2 Hz, < 1 mA, 1 sec on / 90 min off duty cycle) stimulation for 12 weeks, than conversion to active stimulation for another 10 months (follow-up for 52 weeks) |
| **Outcomes** | "The primary endpoint, captured by daily electronic diary entries, was the change from baseline in migraine days/month evaluated 12 weeks after implantation."<br><br>Safety data (adverse events). |
| **Inclusion Criteria** | "This multi-center, double-blind, randomized controlled trial enrolled participants who (1) met the 2004 International Classification of Headache Disorders (ICHD-2) diagnostic criteria for migraine with aura, migraine without aura, and/or chronic migraine; (2) presented as drug-refractory (failed therapy with at least two acute and two preventive medications); and (3) had ≥ 6 days per month of long-duration (> 4 hours) migraine with moderate/severe pain (migraine day)" |
| **Exclusion Criteria** | Not specified |

| **Study Validity.** | | |
|---|---|---|
| **Is it clear that there are no conflicts of interest in the writing or funding of this study?** | Not reported | Two of the authors of the study are listed as being associated with Boston Scientific (Neuromodulation, Valencia, USA), but due to the format of the publication as an abstract from a Conference it is difficult to determine the contribution of theirs to the study. In the abstract they do not report any conflicts of interest or funding of the study. |
| **Does the study have a clearly focused question?** | Yes | "To investigate the safety and efficacy of occipital nerve stimulation (ONS) for the preventive treatment of refractory migraine." |
| **Is an RCT the appropriate method to answer this question?** | Yes | Previous to this RCT, no controlled studies were available to provide high quality evidence for the efficacy of ONS for the treatment of treatment-refractory migraine (van Kleef et al, 2009). This study is the first RCT available to provide information on the safety and efficacy of ONS for the treatment of refractory migraine.<br>It is a therapy which is being investigated and this requires a RCT (CCE handbook |

| | | |
|---|---|---|
| **Does the study have specified inclusion/exclusion criteria?** | Partial | See above. No exclusion criteria were reported for the study.<br><br>The study does report, "Of 179 patients screened for enrollment, 140 eligible subjects were randomized". The inclusion criteria would be established a priori for patients to be screened for enrollment. The authors do not report if the inclusion criteria was not adapted or added to during the study. |
| **If there were specified inclusion/ exclusion criteria, were these appropriate?** | Yes | |
| **Did the study have an adequate method of randomisation?** | Not reported | |
| **Was allocation to intervention group concealed?** | Not reported | |
| **Were patients blind to intervention group?** | Not reported | |
| **Were investigators and care providers blind to intervention group?** | Not reported | |
| **Were outcome assessors blind to intervention group?** | Not reported | |
| **All outcomes were measured in a standard, valid and reliable way?** | Yes | |
| **Were outcomes assessed objectively?** | No | "The primary endpoint, captured by **daily electronic diary entries**, was the change from baseline in migraine days/month evaluated 12 weeks after implantation."<br>Patients recorded most outcomes by daily electronic diary entries which may present a potential source of reporting bias. The safety outcomes were reported, but the way in which they were measured was not reported.<br>The authors reported that "diary follow-up continued for 52 weeks". The results were not reported for 52 weeks in relation to the primary endpoint (reduction of migraine days/month) or the attrition rate of patients relative to the ITT analysis. |
| **Were outcomes assessed independently?** | Not reported | |
| **Were the groups similar at baseline with regards to key prognostic variables?** | Not reported | |
| **Aside from the experimental intervention, were the groups treated the same?** | Not reported | |

| | | |
|---|---|---|
| **Were the outcomes measured appropriate?** | Yes | |
| **Was there sufficient duration of follow-up?** | Yes | Previous guidelines in the area of cluster headaches (van Kleef et al, 2009) have reported that "attacks in the chronic form occur for more than 1 year without remission periods". The follow up period in the study was 52 weeks, indicating a sufficient duration of follow-up, although the authors did not report these results. |
| **Was there ≤20% drop-out?** | Not reported | |
| **Was the study sufficiently powered to detect any differences between the groups?** | Not reported | Attrition rates after 12 weeks were also not reported. |
| **If statistical analysis was undertaken, was this appropriate?** | Partial | "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). In the active arm, a favourable response to the percutaneous treatment trial was moderately predictive of 12-week response (positive likelihood ratio = 2.0, 95% CI [1.4 2.9]; negative likelihood ratio = 0.21, CI [0.06 0.78])." |
| **Were all the subjects analysed in the groups to which they were randomly allocated (ie intention to treat analysis)?** | Yes | At 12 weeks the subjects were analysed as an ITT, but analysed results at 52 weeks were not reported.<br>The authors report "At 12 weeks, sham subjects were converted to active settings. Diary follow-up continued for 52 weeks." The attrition rate was not reported on however. |
| **Is the paper free of selective outcome reporting?** | No | |
| ***For cross-over studies only*** | | |
| **Was this intervention suitable for a cross-over study?** | Yes | |
| **Was the washout period adequate?** | Not reported | |
| **Other** | | |
| **What is the overall risk of bias?** | Insufficient information | |

**Results.**

**Efficacy**

"For the primary endpoint, reduction in migraine days/month, the difference across treatment arms was not significant (-5.5 vs.-3.9 days/month, P = 0.29)."

**Estimated 95% CI: -3.9 to 7.1*

Table 1.

| | *n* | Baseline days/month (mean ± SD) | Change at 12-weeks (mean ± SD) | *P*-value |
|---|---|---|---|---|
| Active | 63 | 20.2 ± 7.2 | -5.5 ± 8.7 | 0.29 |
| Sham | 62 | 19.2 ± 7.9 | -3.9 ± 8.2 | |

"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)."

"In the active arm, a favourable response to the percutaneous treatment trial was moderately predictive of 12-week response (positive likelihood ratio = 2.0, 95% CI [1.4 2.9]; negative likelihood ratio = 0.21, CI [0.06 0.78])."

**Safety**

"Two-year aggregate safety data revealed infection, non-target area sensory symptoms, and implant site pain as the most-frequent device related adverse events."

**Author's Conclusions.**

"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 stimulation, based in part on the absence of medication overuse and a favourable response to a trial of percutaneous treatment."

**Our Comments/Summary.**

This study was the first RCT to investigate the efficacy and safety of occipital nerve stimulation (ONS) for the preventive treatment of refractory migraine. The duration of the study was 12 weeks, prior to this treatment period all patients were involved in a (percutaneous) trial stimulation (according to their randomisation settings) to assess their predictive 12 week response to which a favourable response was observed in the active arm (see above). The results of the 12 week study were reported as not significant between the active and sham groups (p=0.29). This may not be indicative of the clinical significance.

The method of randomisation and allocation of patients to groups was not reported in the study. This could in part an effect on the results by way of selection bias, hence this should be noted when taking the results into account. Similarly, blinding of patients to the invention groups or blinding of investigators and outcome assessors was not reported, resulting in potential performance and detection bias. It therefore is possible that the results will be altered, affecting the authors' conclusions.

The key prognostic variables at baseline were not reported. Without this information it is difficult to observe if the treatment results are generalisable or if this had an effect on the heterogeneity in treatment response reported by the authors (conclusion only). Treatment of the groups was not reported either, hence it is not possible to establish if the intervention is responsible for the treatment effect or not. The duration of the study was reported as 12 weeks, it is difficult to establish if this is a sufficient period for efficacy of ONS to be assessed. In some studies, authors have reported a longer duration for stimulation to take effect (i.e. 6 months) (Schwedt et al, 2006).

The duration of follow up was reported as being 52 weeks. We cannot assess the long-term effects of ONS on treatment refractory migraine as the authors did not disclose the efficacy results for this time point. The authors did report the safety results after two years following ONS, but did not reveal the safety results at 12 weeks or at 52 weeks of follow up. Attrition rates at 52 weeks follow up were not reported, again not enabling a true indication of the treatment efficacy. Perhaps this could be interpreted as selective outcome reporting due to the 12 week results not being positive for ONS for refractory migraine.

Statistical analysis was undertaken to determine whether there was any significant difference in treatment effect between active and shame stimulation. The tests conducted and if they were established a priori were not reported.

**Table A5.5 Critical appraisal table *(Nguyen Brain Stimulation 2008)*, motor cortex stimulation**

| **Study: Nguyen J-P, Velasco F, Brugieres P, Velasco M, Keravel Y, Boleaga B, et al. Treatment of chronic neuropathic pain by motor cortex stimulation: results of a bicentric controlled crossover trial. Brain Stimulation. 2008 Apr;1(2):89-96.** | |
|---|---|
| ***Crossover Randomised Controlled trial*** | |
| **Patient/population** | Patients with chronic neuropathic pain of either peripheral or central origin |
| **N** | 10 patients |
| **Setting** | Hospital implantation with community follow-up |
| **Intervention/indicator** | Motor Cortex Stimulation (MCS) |
| **Comparison/control** | Group 1: stimulator switched ‘‘OFF’’ for two weeks and then was switched ‘‘ON’’ for the next 2 weeks.<br>Group 2: stimulator switched ‘‘ON’’ for two weeks and then was switched ‘‘OFF’’ for the next 2 weeks. |
| **Outcomes** | **(0-100 VAS)**: Self rated pain intensity<br>**6-point Verbal scale:** Self rated pain intensity<br>**Short version of the Wisconsin Brief Pain Questionnaire (WBPQ):** degree to which pain interferes with daily living activities<br>**McGill Pain Questionnaire (MPQ):** which measures aspects of pain<br>**modified McGill Quality of Life Scale (MQoL)**: Self rating of quality of life<br>**Medication Quantification Scale (MQS):** Analgesic drug consumption |
| **Inclusion Criteria** | “The inclusion criteria for the patients included the following: ages between 18 and 80 years, chronic neuropathic pain resistant for more than a year to at least three different types of analgesic medical treatments, and average pain level 60 or greater on a 0-100 visual analogue scale (VAS) over 7 days of self-assessments.” |
| **Exclusion Criteria** | “The exclusion criteria included the following: pregnancy, malignant disease, history of epileptic seizures, and unable to comply with study procedures and follow-up visits because of cognitive impairment.” |

| **Study Validity.** | | |
|---|---|---|
| **Is it clear that there are no conflicts of interest in the writing or funding of this study?** | Not reported | |
| **Does the study have a clearly focused question?** | Yes | “To compare MCS analgesic efficacy between ‘‘ON’’- and ‘‘OFF’’-stimulation conditions in a double-blinded crossover trial.” |
| **Is a cross-over RCT the appropriate method to answer this question?** | Yes | |

| | | |
|---|---|---|
| **Does the study have specified inclusion/exclusion criteria?** | Yes | |
| **If there were specified inclusion/ exclusion criteria, were these appropriate?** | Yes | |
| **Did the study have an adequate method of randomisation?** | Not reported | |
| **Was allocation to intervention group concealed?** | Not reported | |
| **Were patients blind to intervention group?** | Yes | "This procedure was double-blinded: neither the patient nor the clinical examiner was informed about the sequence."<br>"However, all patients and raters knew that the general design of the trial included 2 weeks ''ON'' and 2 weeks ''OFF'' in a randomized order." |
| **Were investigators and care providers blind to intervention group?** | Yes | "This procedure was double-blinded: neither the patient nor the clinical examiner was informed about the sequence."<br>"Clinical evaluation was conducted by a medical examiner, who was trained in the management of chronic pain and blinded for the parameters of stimulation." |
| **Were outcome assessors blind to intervention group?** | Yes | |
| **All outcomes were measured in a standard, valid and reliable way?** | Partial | |
| **Were outcomes assessed objectively?** | No | |
| **Were outcomes assessed independently?** | Not reported | |
| **Were the groups similar at baseline with regards to key prognostic variables?** | Not reported | |
| **Aside from the experimental intervention, were the groups treated the same?** | Not reported | |
| **Were the outcomes measured appropriate?** | Yes | |

| | | |
|---|---|---|
| **Was there sufficient duration of follow-up?** | Yes | "The evaluation of the patients, based on clinical scores, described later in this text, was performed 30 days before surgery (Pre) and then 30, 60, 75, and 90 days after surgery (M1, M2, M2.5, and M3). Long-term evaluation was performed at 6 and 12 months post operative (M6 and M12)."<br>The authors do not report if the stimulator was 'ON' or 'OFF' for the remainder of the 12 month follow-up or if the stimulators were removed. |
| **Was there ≤20% drop out?** | Yes | |
| **Was this intervention suitable for a cross-over study?** | Yes | |
| **Was the washout period adequate?** | No | |
| **Was the study sufficiently powered to detect any differences between the groups?** | Not reported | . |
| **If statistical analysis was undertaken, was this appropriate?** | Yes | |
| **Were all the subjects analysed in the groups to which they were randomly allocated (ie intention to treat analysis)?** | Not reported | |
| **Is the paper free of selective outcome reporting?** | Yes | |
| **Other** | | |
| **What is the overall risk of bias?** | Insufficient information | |

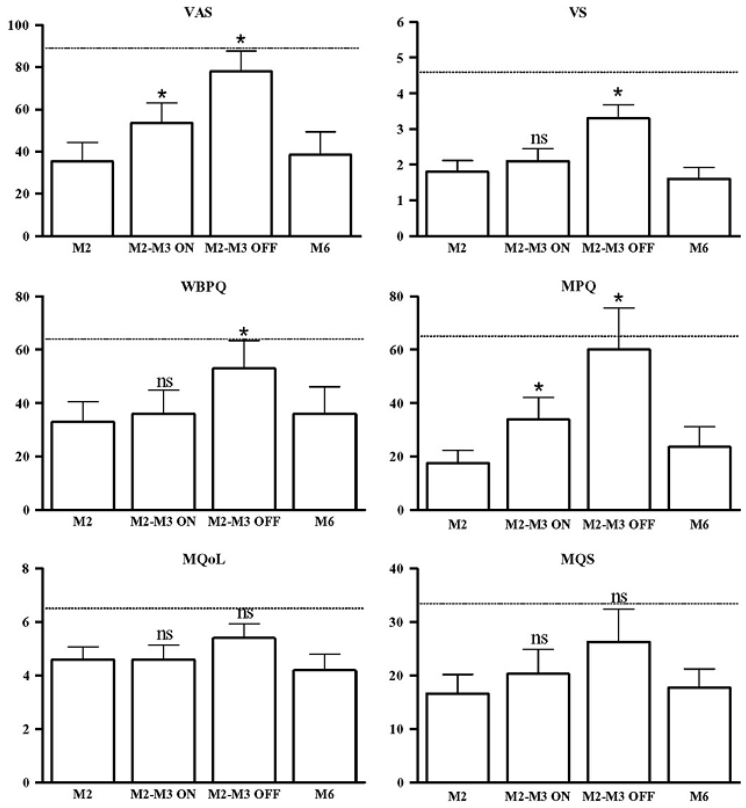
**Results.**

The following study investigated the effectiveness of motor cortex stimulation (MCS) in chronic neuropathic patients randomised to 2 weeks of 'ON' stimulation and 2 weeks of 'OFF' stimulation. The outcomes accessed included clinical scores for indications of pain and functional activities.

**Table 1** Clinical data

| Patient number | Sex | Age (y) | Origin of pain | Location of pain | Duration of pain (y) | Sensory disturbances in the painful zone |
|---|---|---|---|---|---|---|
| 1 | M | 70 | Stroke (hemorrhage) | Right hemibody | 5 | Hyperesthesia |
| 2 | F | 75 | Trigeminal neuropathy | Right hemiface | 5 | Allodynia |
| 3 | M | 57 | Stroke (ischemia) | Right hemibody | 5 | Hypoesthesia |
| 4 | M | 57 | Trigeminal neuropathy | Left hemiface | 6 | Hypoesthesia |
| 5 | F | 31 | Trigeminal neuropathy | Right hemiface | 3 | Hypoesthesia |
| 6 | F | 75 | Postherpetic neuralgia | Left intercostal T5-T6 | 4 | Allodynia |
| 7 | M | 68 | Postherpetic neuralgia | Right cervical C2-C3 | 4 | Hyperesthesia |
| 8 | M | 52 | Stroke (ischemia) | Left hemiface | 1 | Allodynia |
| 9 | M | 29 | CRPS | Left upper limb | 14 | Allodynia |
| 10 | F | 33 | CRPS | Left upper limb | 6 | Allodynia |

CRPS: complex regional pain syndrome.




The table above shows the prognostic values of all patients in the study.

*Overall*

"All patients completed the study without any adverse events. In particular, no seizure and no infection at the level of the implanted devices were observed. All clinical scores (VAS, VS, WBPQ, MPQ-PRI, MPQ-ratio, MQoL, and MQS) varied significantly in the follow- up (Friedman test, $P < .05$) (Figure 1). Post hoc analyses showed a significant decrease of all scores between preoperative evaluation and any post operative evaluation from 1-12 months after surgery (Dunn test, $P < .05$). In contrast, no significant differences were observed between 1-month and 1-year post operative assessments (Dunn test, $P > .05$).

"The following scores were lower in the ON-period than in the OFF-period (Wilcoxon test, $P < .05$): VAS (mean: 53.5 vs. 78.0), VS (2.1 vs. 3.3), WBPQ (36.0 vs. 53.0), and MPQ-PRI (33.9 vs. 60.1). The other scores did not change between the conditions ($P < .05$): MPQ –ratio (mean: 0.58 vs. 0.58), MQoL (4.6 vs. 5.4), and MQS (20.3 vs. 26.3)."

"The decrease in pain intensity provided by MCS was concomitant with an improvement in daily living activities and quality of life, as shown b y WBPQ and MQoL postoperative changes in the long term. Pain relief was also accompanied by a reduction in analgesic drug consumption, as shown by MQS evolution." (see figure on next page)

"Beyond the period of randomization, the initial improvement was restored in both groups. On average, clinical scores were found quite similar before (M1- M2) and after (M6- M12) the crossover trial. The efficacy of MCS was in the same range in the short-term (1 month) and the long-term (1 year) follow-up."

**Figure 2** Evolution of the clinical scores (mean, SEM) in a series of ten patients treated by chronic MCS, before, during, and after a period of randomized crossover trial. The stimulator was switched "ON" and "OFF," respectively, for 2 weeks from M2-M3 after surgery. The dotted horizontal line corresponds to mean preoperative baseline value for each score. Significance of the Wilcoxon test is presented above the M2-M3 ON-period bar for comparisons made between M2 and M2-M3 ON-period and above the M2-M3 OFF-period bar for comparisons made between M2-M3 ON-period and M2-M3 OFF-period. ns: Not significant ($P > .05$). *Significant ($P < .05$).

*Individual*

Six patients assessed their pain reduction following treatment (between preoperative and postoperative) as good (> 40% reduction) and four patients as poor (< 40% reduction).

"Postoperative evolution was similar for all scores in four patients (patients 7-10) but was more variable in the others. In patient 1, VAS and MQoL scores decrease d by 16-20%, MPQ, WBPQ and MQS scores decreased by 3 0-35%, and VS score decreased by 60%. In patient 2, all scores decrease by more than 50%, whereas the WB PQ score curiously remained constant. Patient 3 showed high VS and WBPQ scores reduction but only a little change in the MQS score. Patient 4 was totally relieved from pain but analgesic drug consumption was only reduced by 32%. Patients 5 and 6 did not experience any pain relief on VAS score and showed very heterogeneous changes regarding the other scores."

**Author's Conclusions.**

"These results were in favor of real analgesic effects produced by MCS with no loss of benefit over time. The differential changes in MPQ subscores suggested that MCS relieved pain by acting predominantly on its affective aspect. The decrease in pain intensity was associated with improved daily living activities and quality of life and reduced consumption of analgesic medication."

"In conclusion, this controlled study showed that MCS was an effective method to improve various types of drug resistant chronic neuropathic pain, of either peripheral or central origin. These results need to be confirmed and extended in larger series of patients."

**Our Comments/Summary.**

This study was the very first placebo-controlled studies to assess the effectiveness of motor cortex stimulation (MCS) in patients with chronic neuropathic pain (peripheral or central). Several limitations were noted in the study which does not allow a conclusion to be made about its methodological quality.

A small number of patients were involved in the study and the authors do not state why they chose a cross-over design. It can only be envisaged that the small number of patients enrolled in the study would lean more towards the cross-over design as patients can be used for both groups and as their own controls. The authors also did not report if they conducted any tests to assess if the power of the study was appropriate. This could affect the treatment effect observed.

The method of randomisation and allocation concealment was not reported by the authors, which introduces selection bias into the results. The authors did report that patients were blind to the intervention, although patients were aware of the study design having a sequence of either 2 weeks with the stimulator 'ON' followed by 2 weeks 'OFF' or the opposite. No information was revealed in relation to how blinding was maintained throughout the study. The authors did not report if the outcome assessors were blind to the intervention or not, introducing detection bias. Outcome assessment was not objectively performed, although pain studies are difficult to assess in this manner.

The duration of the study was too short to observe any long-term effects. The authors did comment that "The short duration of each period of the ON/OFF trial was related to an ethical issue (we were asked to limit the duration of the OFF-period). However, considering the present results and that a posteffect had been oft en observed with MCS, the duration of the randomized period should be prolonged to a least 1 month in future studies to better appraise the impact of MCS on various aspects of the chronic pain syndrome." The washout period for the study was not reported. This could represent a potential 'carry over' effect, hence the estimated treatment effect will be affected or biased. Follow-up was conducted at 6 and 12 months post-treatment, however the authors did not report whether the stimulators were removed or keep in.

One of the benefits of this type of stimulation (MCS) is that patients do not feel any subjective sensation when stimulation is switched 'ON', hence a double-blind trial is able to be conducted. The authors do

state “patients were not asked whether they were able to discern their devices were turned ‘‘OFF ’’ because the pain returned.” This would be useful as a control measure and to make sure the stimulation was correctly implanted or had no discernable complications.

Due to the lack of information provided on the methodology of the study, there is insufficient information to conclude the overall risk of bias and if the results obtained are true in clinical practice.

**Table A5.6 Critical appraisal table *(Saper Cephalalgia 2010)*, occipital nerve stimulation**

| | |
|---|---|
| **Study:** *Saper, J, Dodick, D, Silberstein, S, McCarville, S, Sun, M, Goadsby, P, ONSTIM Investigators. Occipital nerve stimulation for the treatment of intractable chronic migraine headache: ONSTIM feasibility study. Cephalalgia. 2010. 31 (3):271-285.* | |
| ***Randomised Controlled trial*** | |
| **Patient/population** | Patients with medically intractable chronic migraine (CM) |
| **N** | Total no. of patients enrolled - 75 |

| | Randomised at enrollment | Implanted | 3 months post-implant |
|---|---|---|---|
| Adjustable stimulation (AS) | 33 | 29 | 29 |
| Preset stimulation (PS) | 17 | 16 | 16 |
| Medically managed (MM) | 17 | 17 | 17 |
| Ancillary group (AG) | 8 | 6 | 5 |

| | |
|---|---|
| **Setting** | Headache Centre or Medical Clinic |
| **Intervention/indicator** | ONS – Adjustable stimulation (AS) group was instructed to maintain the stimulator in the ‘‘on’’ position and to adjust the device to minimize pain (n = 33) |
| **Comparison/control** | Preset stimulation (n=17) and medically managed control (n=17) and ancillary group (n=8)<br>*AG met all entry criteria except response to occipital nerve block. “A lack of response to ONB was defined as a failure to experience at least a 50% reduction in migraine pain within 24 hours of the injection of 3–5 ml of 0.5% bupivacaine into each greater occipital nerve distribution. Patients in the ancillary group were implanted and allowed to adjust the stimulation and were treated identically to the AS group.” |
| **Outcomes** | • Reduction in headache days per months;<br>• proportion of patients who achieved ≥ 50% reduction in headache days per month (responder rate);<br>• a 3-point or greater reduction in average overall pain intensity;<br>• disability and QoL;<br>• risks/complications |

| | |
|---|---|
| **Inclusion Criteria** | • Diagnosis of CM headache as defined by the 2004 IHS criteria:<br>  ○ Migraine headache occurring on 15 or more days/month for more than three months in absence of medication overuse.<br>  ○ Not attributed to another disorder.<br>• Headache pain defined by the following criteria:<br>  ○ During each of two consecutive periods of four consecutive weeks, a minimum of 15 days of CM headache with peak pain intensity ≥5 (on a 0–10 scale).<br>  ○ Subject may have headache of any intensity (0–10 scale) on days over 15 during each four-week period.<br>  ○ Headache pattern has been present for 12 months or longer.<br>  ○ Refractory, as determined by failure to respond or intolerance to an adequate trial of preventative medications from at least two different classes of drugs.<br>• Headache is characterized by:<br>  ○ Pain located between C3 level to vertex.<br>  ○ Any location between ears (i.e. occipital or suboccipital region within distribution of greater and/or lesser occipital nerves).<br>  ○ Pain may be unilateral or bilateral and may include pain in frontal, temporal or retro-orbital region or into neck/ shoulder location.<br>• Onset of migraine headache occurred before age 50 years.<br>• Current acute and prophylactic headache medication regimens have been stabilized for four weeks prior to preliminary enrollment visit.<br>• Response to a temporary, short-acting anesthetic block to the occipital distribution was positive.<br>• Subject is age 18 years or older and has signed informed consent form.<br>• Subject will be available for appropriate follow-up for the duration of study and is willing and able to maintain current medication regimens during enrollment process and through three-month follow-up visit.<br>• In physician's opinion, subject is willing and able to use electronic daily questionnaire equipment.<br>• Female subject of childbearing potential has negative pregnancy test at confirmation of enrollment visit, is not nursing and agrees to use adequate birth control methods for duration of study. |

| | |
|---|---|
| **Exclusion Criteria** | • In physician's opinion subject has health conditions or concerns that would render them unable to participate, would impact ability of subject to adequately assess incremental effects of ONS treatment, could possibly be aggravated by treatment or confound ability to interpret results (including, but not limited to, intractable epilepsy, active major depression, psychosis, somatoform disorder, severe personality disorder). Other conditions to be considered include cardiac arrhythmias, cognitive impairment and peripheral neuropathy.<br>• Previous destructive ganglionectomy, rhizotomy section or neurectomy procedure affecting C2/C3/occipital distribution.<br>• Subject is not candidate for or is not willing to undergo surgical implantation of neurostimulator system.<br>• Subject is deemed by investigator to have rebound headaches, and/or subject reports regular use on three or more days per week of acute medication that can cause rebound headaches.<br>• Subject has participated in:<br>  ○ Three clinical trials for headache, in last five years or<br>  ○ Previously terminated from this clinical trial or<br>  ○ Another neurological device or drug trial within last 90 days.<br>• Subject has other implanted electrical stimulation device(s) or any metallic implant or is expected to require an implant, including:<br>  ○ Cardiac demand pacemakers or defibrillators<br>  ○ Cochlear implant<br>  ○ CSF shunt<br>  ○ Aneurysm clip<br>  ○ Spinal cord stimulator<br>• Neurostimulation (implanted or external) for headache or other head or neck pain was received within last year.<br>• Significant psychological signs on examination and/or history, or has serious drug habituation or behavioral problems that in physician's judgment renders that person inappropriate for study.<br>• Unresolved legal issues related to their pain that is being assessed in this study.<br>• Failure to complete at least 23 out of 28 days, during two consecutive 28-day periods, of electronic daily questionnaire during enrollment process.<br>• Alternative therapy to treat headache pain (e.g. massage, biofeedback, bracing) is being used or will be used.<br>• MRI or diathermy may be required.<br>• Other medical or neurological conditions that would confound study. |

**Study Validity.**

| | | |
|---|---|---|
| **Is it clear that there are no conflicts of interest in the writing or funding of this study?** | No | "The authors thank Medtronic for technical assistance and CommGeniX (Tampa, FL, USA) for editorial support." |
| **Does the study have a clearly focused question?** | Yes | A feasibility study "to obtain preliminary safety and efficacy data for ONS treatment of CM." |
| **Is a RCT the appropriate method to answer this question?** | Yes | The question of the study involves the assessment of a intervention which is studies most appropriately with a RCT. Also, one other lower quality RCT was published (Lipton, R et al, 2009) and only case series and reports exist previous to this. Therefore, higher level and higher quality primary studies are needed to assess the effectiveness of ONS in chronic migraine patients. |
| **Does the study have specified inclusion/exclusion** | Yes | See above |

| | | |
|---|---|---|
| **criteria?** | | The authors did not report if the criteria were established a priori. |
| **If there were specified inclusion/ exclusion criteria, were these appropriate?** | Yes | |
| **Did the study have an adequate method of randomisation?** | Yes | "Subjects who met enrollment criteria were then randomized into one of three treatment groups, adjustable stimulation (AS), preset stimulation (PS) and medical management (MM), using a randomization ratio of 2:1:1, respectively."<br>"The randomization was not stratified for baseline characteristics. A central randomization process provided and managed by Medtronic Neuromodulation (Medtronic) assigned a unique randomization code to each subject. Initially, randomization revealed only whether a subject was assigned to ''medically managed'' or ''device implanted.'' |
| **Was allocation to intervention group concealed?** | No | "A sealed envelope with the complete randomization assignment (level of stimulation) was sent to implanter site personnel by Medtronic to be opened at the activation visit. Subjects were blinded to the anticipated value of adjustable stimulation over that of the preset stimulation. The sponsor's study personnel (Medtronic) were not blinded to the randomized treatment assignments for individual subjects." |
| **Were patients blind to intervention group?** | No | "To maintain blinding in the device-implanted group, a sealed envelope with the complete randomization assignment (level of stimulation) was sent to implanter site personnel by Medtronic to be opened at the activation visit. **Subjects were blinded to the anticipated value of adjustable stimulation over that of the preset stimulation**." This was not necessarily to the stimulation group itself. |
| **Were investigators and care providers blind to intervention group?** | Partial | "A neurologist (headache specialist) was first identified at each center as the principal investigator **except at two centers, where an implanter, usually an anesthesiologist, was first identified as the principal investigator**. All headache specialists were blinded to the subjects' group assignments and were responsible for establishing the diagnosis, optimizing subjects' medications and evaluating subjects' headaches at follow-up visits. **None of the implanters were blinded to the subjects' group assignments**, and all were responsible for follow-up with subjects on device implantation, device activation and programming." |
| **Were outcome assessors blind to intervention group?** | Not reported | |
| **All outcomes were measured in a standard, valid and reliable way?** | Yes | |
| **Were outcomes assessed objectively?** | Partial | "Data were collected using electronic diary for headache days, pain and duration measurements." The authors do not report if the patient maintained the diary. Follow-up visits to each centre were at one and three months post implantation. |
| **Were outcomes assessed independently?** | Yes | |
| **Were the groups similar at baseline with regards to key prognostic variables?** | Yes | Table 3 (page 278) |

| | | |
|---|---|---|
| **Aside from the experimental intervention, were the groups treated the same?** | Not reported | |
| **Were the outcomes measured appropriate?** | Yes | |
| **Was there sufficient duration of follow-up?** | Not reported | "The trial duration was short. A longer period of observation might reveal a different pattern of adverse events." |
| **Was there ≤20% drop-out?** | Yes | "Of the 75 subjects assigned to a treatment group, eight discontinued prior to the end of the three-month blinded phase of the study: four subjects withdrew consent prior to implant (two AS, one PS, 1 ancillary group); two subjects were intraoperative failures (one AS, one ancillary group); one AS subject was lost to follow-up prior to implant; one ancillary group subject discontinued after the one-month follow-up visit because of lack of efficacy. Of the 67 subjects who continued to the three-month blinded follow-up, one subject (AS) did not complete the EDQ between implant and three months; 66 subjects (28 AS, 16 PS, 17 MM, 5 ancillary group) completed the EDQ through the three-month follow-up period."<br>**Approximate 11-12% drop-out rate* |
| **Was the study sufficiently powered to detect any differences between the groups?** | Yes | "The sample size was chosen to gain experience with ONS therapy for the treatment of CM. In order to evaluate effectively the study design, a sample size of 24 subjects in the AS group and 12 subjects in each of the PS and MM groups was required. In keeping with the exploratory nature of the study, it was not powered for a single primary endpoint. However, according to the protocol, statistical analysis was performed to allow more critical consideration of the data in order to identify factors and nuances that might be helpful in further studies." |
| **If statistical analysis was undertaken, was this appropriate?** | Yes | "A per-protocol analysis, including all subjects who completed the electronic diary during the three-month blinded follow-up, was used to compare subjects."<br>A per-protocol analysis avoids dilution of the treatment effect, although this can introduce bias in the results.<br>"Pairwise comparisons between the AS group and each of the three other groups were not adjusted for multiple comparisons and are presented only as a guide to interpreting the study. We considered differences with $p < .05$ as potentially informative and these are nominally referred to as statistically significant throughout the paper, with actual p values not reported due to the exploratory nature of the analyses. Wilcoxon's rank sum tests were used to analyze headache days, pain intensity, disability and quality-of-life outcomes; these summary data are presented as mean ± standard deviation. Fisher's exact tests were used to analyse responder rate and subject satisfaction; these summary data are presented as frequency counts and percentages. For the safety objective of the study, descriptive summaries are presented. SAS software (version 9.1, SAS Institute, Cary, NC, USA) was used for all data analyses." |
| **Were all the subjects analysed in the groups to which they were randomly allocated (ie intention to treat analysis)?** | No | "A per-protocol analysis, including all subjects who completed the electronic diary during the three-month blinded follow-up, was used to compare subjects." |
| **Is the paper free of selective outcome reporting?** | Yes | |

| | | |
|---|---|---|
| **Other** | | |
| **What is the overall risk of bias?** | Low to Moderate | |

## Results.

**Table 3.** Patient demographics and characteristics

| | Treatment group | | | | |
|---|---|---|---|---|---|
| Patient baseline characteristics | Adjustable stimulation* (*N* = 28) | Preset stimulation (*N* = 16) | Medically managed (control) (*N* = 17) | Ancillary group (*N* = 5) | Total (*N* = 66) |
| Age (years, mean ± SD) | 41 ± 11.6 | 44 ± 10.0 | 44 ± 10.2 | 50 ± 6.4 | 43 ± 10.6 |
| Gender ratio (F/M) | 22/6 79%/21% | 13/3 81%/19% | 15/2 88%/12% | 3/2 60%/40% | 53/13 80%/20% |
| Headache history | | | | | |
| Duration of migraine (years migraine experienced prior to study entrance, mean ± SD) | 21 ± 12.4 | 22 ± 9.8 | 25 ± 13.7 | 18 ± 15.1 | 22 ± 12.3 |
| Disability scores (mean ± SD) | 4.0 ± 0.2 | 3.9 ± 0.3 | 4.0 ± 0.0 | 4.0 ± 0.0 | 4.0 ± 0.2 |
| Number of headache days per month (mean ± SD) | 22.4 ± 6.3 | 23.4 ± 5.1 | 23.7 ± 4.3 | 25.3 ± 5.0 | 23.2 ± 5.4 |

SD = standard deviation. F/M = female/male.
*Adjustable stimulation group: 29 subjects completed 3 months of treatment, but analysis includes only the 28 who completed 3 months assessment of headache information in the electronic daily questionnaire.

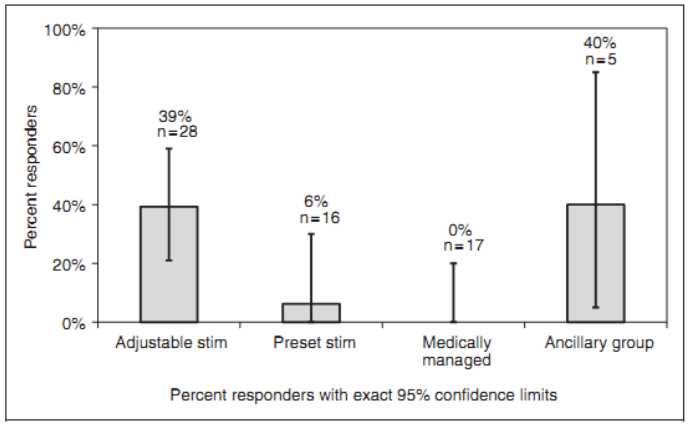
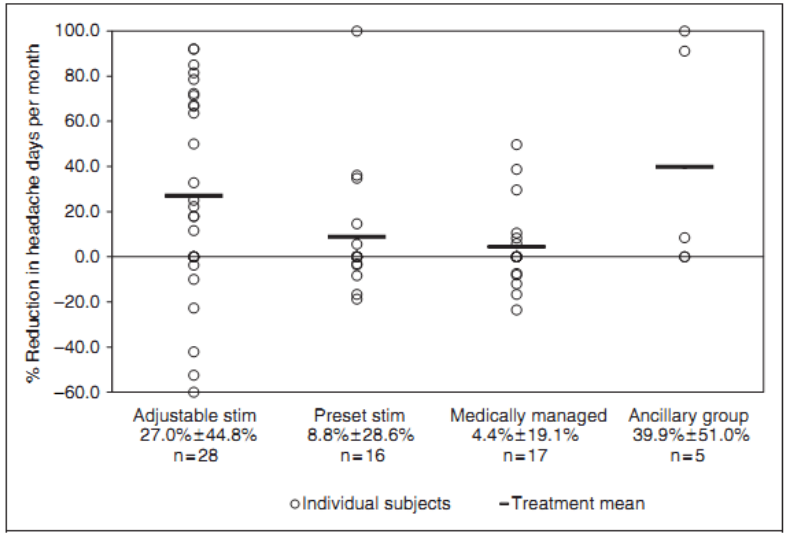
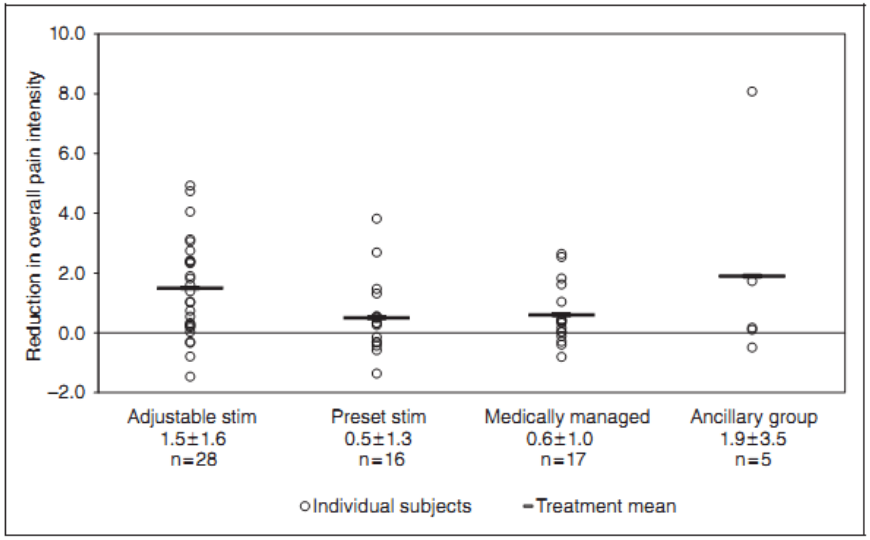



**Table 4.** Percentage change in number of headache days

| Treatment group | N | Mean ± SD | | |
|---|---|---|---|---|
| | | Baseline | 3 months | Percentage change from baseline |
| Adjustable stimulation | 28 | 22.4 ± 6.3 | 15.7 ± 10.0 | 27.0 ± 44.8 |
| Preset stimulation | 16 | 23.4 ± 5.1 | 21.9 ± 7.8 | 8.8 ± 28.6 |
| Medically managed | 17 | 23.7 ± 4.3 | 22.8 ± 6.3 | 4.4 ± 19.1 |
| Ancillary | 5 | 25.3 ± 5.0 | 16.3 ± 14.3 | 39.9 ± 51.0 |

SD = standard deviation.




**Quality of life and functional outcomes**

"Reductions in POMS scores from baseline to three months were as follows: 8.7 ±12.0 for AS, 1.6 ±10.1 for MM and 0.4 ±9.4 for PS. Sixty-six percent of subjects in the AS group and 25% of subjects in the MM group reported satisfaction with treatment at three months. Change from baseline in score on the functional disability scale was 0.3 ±0.5 for the AS group and 0.0 ±0.3 for the MM group. Change in acute

medication use was 1.6 ±7.6 in the AS group and -0.6 ±5.0 in the MM group. Change in MIDAS average grade was 0.4 ±0.8 for the AS group and 0.0 ±0.0 for the MM group, and change in MIDAS headache pain score was 1.3 ±1.8 for the AS group."

"The functional disability scale, MIDAS scores and SF-36, the exploratory analyses showed no significant improvement over base-line when comparing the AS group with the control groups (PS and/or MM)."

**Adverse device effects**

"Three subjects experienced serious ADEs requiring hospitalization: implant site infection, lead migration and postoperative nausea. The most frequently reported ADE was lead migration, which occurred in 12 of 51 subjects (24%). There was no evidence of ADEs leading to long-term complications or potential nerve damage. There were

no serious unanticipated ADEs reported or identified in this study."

**Non-device-related adverse events**

"Nine percent of the AS group, 41% of the PS group and 24% of the MM group reported increased migraine. Adverse events related to medications were similar across treatment groups and ranged from 6% to 18% (Table 6)."

**Author's Conclusions.**

"On the basis of the current findings and in light of previously published work, we believe further investigational pursuit to evaluate the efficacy and safety of ONS for medically intractable CM is justified. Further study would be enhanced by improved stimulator design, implanting technique and lead design and by a well-targeted, carefully selected study population, more robust endpoints, longer trial duration and improved blinding techniques. Reliable conclusions regarding efficacy cannot be established on the basis of this study alone. Nonetheless, the results of this feasibility study offer promise and should prompt further study of ONS in medically intractable CM."

**Our Comments/Summary.**

This study was a sponsored study by Medtronic, the company which produce neurostimulators. The authors report that "study personnel (Medtronic) **were not** blinded to the randomized treatment assignments for individual subjects" which could result in **selection bias**.

The study did have an adequate method of randomisation in which a central randomisation process occurred assigning a unique randomisation code to each subject. The authors did report that this process was only to reveal "whether a subject was assigned to 'medically managed' or 'device implanted'." It was not reported whether outcome assessors were blind to the intervention group or if the groups were treated the same. Hence it cannot be concluded if the intervention itself is responsible for the non-statistically significant difference observed in most of the outcomes (i.e. 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).

Analytically the authors did not adjust pairwise comparisons for multiple comparisons due to the "exploratory nature of the study". Therefore statistical differences assessed in the results were informative rather than established for this group of patients with this intervention. "The responder rate in the AS group was 39%, compared with 6% in the PS group and 0% in the MM group. The differences between the AS and the control groups were significant in exploratory analyses." Translation of these results into clinical practice should be applied with caution.

The authors did not report on how data for discontinued patients was assessed. Patients were enrolled into the trial even whilst taking migraine prophylactic medications and were allowed to continue with them without changing the medications and dosages. The authors of the study did not investigate if this may have had an impact on the results, although there may have been ethical issues preventing this.

The conclusions the authors make are justified, particularly due to the study being a feasibility study. Unfortunately as it is a feasibility study, the generalisabilty is low hence we cannot apply the results to clinical practice.

This study is well conducted with a low to moderate risk of bias.

**Table A5.7 Critical appraisal table *(NICE 2010a)*, deep brain stimulation**

| Study: *National Institute for Health and Clinical Excellence. Interventional procedure overview of deep brain stimulation for refractory chronic pain syndromes (excluding headache). June 2010. IP 802. pp. 1-43.* | |
|---|---|
| ***Systematic review*** | |
| **Patient/population** | Patients with chronic refractory pain syndromes (excluding headache) |
| **N** | 693 (3 non-randomised comparative studies, 1 meta-analysis of case-series and 5 case series)<br>**Please note all these studies may not have assessed our outcomes of interest.** |
| **Setting** | Not specified |
| **Intervention/indicator** | |

| Reference | Intervention |
|---|---|
| Katayama Y (2001) | Deep brain stimulation (n =12) in patients with post-stroke pain |
| Nandi D (2002) | Deep brain stimulation (n =4) in patients with post-stroke pain |
| Bittar R (2005) meta-analysis | Deep brain stimulation (n=424 cases from 6 case series) in patients with intractable pain with known origin |
| Levy R (1987) case series, included in Bittar | Deep brain stimulation (n=141 cases) in patients with severe, chronic, intractable pain |
| Hosobuchi Y (1986) case series, included in Bittar | Deep brain stimulation (n=122 cases) in patients with severe, chronic, intractable pain |
| Siegfried J (1987) case series | Deep brain stimulation (n=112 cases) in patients with chronic intractable deafferentation pain |
| Veloso F (1998) case series | Deep brain stimulation (n=64 cases) in patients with benign intractable chronic pain syndromes |
| Hamani C (2006) case series | Deep brain stimulation (n=21 cases) in patients with refractory chronic neuropathic pain |

**Comparison/control**

| Reference | Comparison |
|---|---|
| Katayama Y (2001) | Motor cortex stimulation (n=31) in patients with post-stroke pain |
| Nandi D (2002) | Motor cortex stimulation (n=6) in patients with post-stroke pain |

| | |
|---|---|
| **Outcomes** | Safety and efficacy |

| | |
|---|---|
| **Inclusion Criteria** | • Publication type – Clinical studies were included. Emphasis was placed on identifying good quality studies. Articles with abstracts containing information relevant to the safety and/or efficacy.<br>• Patients with chronic pain syndrome<br>• Intervention – Deep brain stimulation |
| **Exclusion Criteria** | • Publication type - Abstracts were excluded where no clinical outcomes were reported, or where the paper was a review, editorial, or a laboratory or animal study<br>• Articles not in English language, unless they were thought to add substantively to the English language evidence base. |

| **Study Validity.** | | |
|---|---|---|
| **Is it clear that there were no conflicts of interest in the writing or funding of this review?** | Not reported | |
| **Does the review have a clearly- focused question?** | Yes | "The National Institute for Health and Clinical Excellence (NICE) is examining Deep brain stimulation for refractory chronic pain syndromes (excluding headache) and will publish guidance on its safety and efficacy to the NHS in England, Wales, Scotland and Northern Ireland." |
| **Is a systematic review the appropriate method to answer the question?** | Yes | |
| **Does the review have specified inclusion/exclusion criteria?** | Yes | See above |
| **If there were specified inclusion/ exclusion criteria, were these appropriate??** | Yes | |
| **Does the review document a comprehensive search strategy?** | Partial | A wide, appropriate range of bibliographic databases were used ("Searches were conducted of the following databases, covering the period from their commencement to 23 November 2010: MEDLINE, PREMEDLINE, EMBASE, Cochrane Library and other databases. Trial registries and the Internet were also searched. No language restriction was applied to the searches (see appendix C for details of search strategy)."<br>The authors did not report if follow-up from reference lists was conducted. |
| **Were reviewers blind to authors, institutions and affiliations?** | Not reported | |
| **Were 2 or more independent reviewers used for:**<br>**1. application of inclusion criteria to assess eligibility of studies?** | Not reported | |

| | | |
|---|---|---|
| **2. extraction of data from study reports?** | Not reported | |
| **3. appraisal of study quality?** | Not reported | |
| **Were the strengths and limitations of included studies and potential impact on the results discussed?** | Partial | Limitations of the included studies were discussed (see Table 2 and page 21) briefly although how they impacted on the results was not discussed. |
| **Was the validity of included trials appraised using appropriate criteria?** | Not reported | |
| **Is there a summary of the results of individual studies?** | Yes | |
| **If meta-analyses were conducted, was it reasonable to do so?** | N/A | |
| **If meta-analyses were conducted, was it done appropriately?** | N/A | |
| **Other** | | |
| **What is the overall risk of bias?** | Insufficient information | |

**Results.**

*N.B. Outcomes were presented for each individual study and submitted to the Interventional Procedures Advisory Committee (IPAC) to formulate recommendations on the safety and efficacy of DBS for refractory chronic pain syndromes (excluding headache).*

**Efficacy**

A non-randomised comparative study of 43 patients with post-stroke pain reported a pain reduction greater than 60% in 25% (3/12) of patients treated with DBS and 48% (15/31) of patients treated with MCS (measured on a VAS [not described]; follow-up not reported)[1]

A non-randomised comparative study of 19 patients with phantom limb pain reported a pain reduction greater than 80% in 60% (6/10) of patients treated with DBS and 20% (1/5) of patients treated with MCS in follow-ups ranging from 2 to 18 years (measured on a VAS [not described]). Four additional patients were treated with both DBS and MCS; 1 responded better to MCS and 2 responded better to DBS (response of fourth patient not reported)[2]

A non-randomised comparative study of 10 patients with post-stroke pain reported a significant difference in pain reduction during the trial period in 3 of the 4 patients treated with DBS in one patients there was no significant difference (measured on McGill-Melzack pain scale, with high scores being worse; values ranged from 8.4 to 9 during 'off' periods and from 5 to 5.8 during 'on' periods, $p < 0.02$). Of those treated with MCS, 50% (3/6) had no pain relief, 1 had pain relief for 31 months before dying of unrelated causes, 1 had pain relief for 2 to 3 weeks before dying of unrelated causes 7 months later and 1 had complete pain relief lasting 2 to 3 weeks at the time of the report[3]

A meta-analysis of 6 case series, which included 424 patients treated with DBS for intractable pain, reported a significantly better success rate for patients with nociceptive pain compared with patients treated for deafferentation pain in follow-ups ranging from 1 month to 15 years (63% [129/204] vs 47% [103/220], $p < 0.01$, definition of success varied). The same study reported a significantly better success rate in those with peripheral deafferentation pain than those with central deafferentation pain in the same follow-up (51% [89/175] vs 31% [14/45], $p < 0.03$)[4]

A case series of 112 patients with chronic intractable deafferentation pain reported that 89 patients had significant pain reduction after the test stimulation, so they received a permanent subcutaneous receiver. 'Excellent' results were reported in 47% (42/89) of patients, and 32% (28/89) of patients were considered to be 'improved' in follow-ups ranging from 6 months to 6 years ('excellent' was defined as pain-free [0 on a 0 to 5 scale, with 5 indicating worst pain], analgesic-free, and recovery to normal daily activities; 'improved' patients were those that scored 1 to 2 on the same pain scale). The treatments for the remaining patients were considered failures (21% [19/89], with scores of 3 or 4 on the pain scale)[6]

A case series of 122 patients reported treatment success (defined as the patient being able to control their pain using the device with or without medication) in 77% (50/65) of patients with severe intractable pain of peripheral origin (follow-up not stated).

A case series of 21 patients with refractory chronic neuropathic pain reported an 'insertional effect' resulting in a 60–100% reduction in pain scores in 43% (9/21) of patients after insertion of the electrodes but before stimulation. This effect persisted without stimulation until recurrence occurred, at a median of 3 months, after which their electrodes were stimulated; 1 patient did not require stimulation because of a prolonged insertional effect[9]

In the same study, 62% (13/21) of all patients with a successful trial received an implanted pulse generator. Six patients were still benefiting at median 5-year follow-up: 5 from long-term stimulation and 1 with a prolonged insertional effect (all others did not benefit from the procedure so had the system removed)[9]

**Safety**

*Haemorrhage and death*

The case series of 141 patients with nociceptive or deafferentation pain reported intracranial haemorrhage in 4% (5/141) of patients; 1 patient died, 2 were left with significant deficits, and the deficit was completely resolved in 2 patients (time of occurrence not reported)[5]

The case series of 122 patients reported 2 deaths: 1 happened 9 weeks after ventricular haemorrhage from a massive coronary occlusion and the other happened after an intracerebral haemorrhage because of massive cerebral oedema and haematoma in the basal ganglia. Another patient had an intracerebral haemorrhage and 2 more had ventricular haemorrhage, but these patients recovered[8]

*Infection*

The case series of 141 patients with nociceptive or deafferentation pain reported infection in 12% (17/141) of patients (23 cases) either within 30 days of the procedure (n = 12) or thereafter (n = 10) (occurrence of 1 not reported, mostly superficial infection apart from 1 with meningitis); 1 patient was successfully treated with antibiotics alone, 2 with antibiotics and debridement, and 11 with antibiotics and electrode removal (other 3 patients not described)[5]

The case series of 122 patients reported ventriculitis in 1 patient, subgaleal infection in 4 patients and subdural empyema in 1 patient. The patient with ventriculitis and 3 of those with subgaleal infection were successfully treated with antibiotics but the remaining 2 patients required removal of the system hardware[8]

The case series of 21 patients reported that 1 patient had 2 consecutive infections requiring removal of parts of his DBS system (time of occurrence not reported) [9].

*Device-related complications*

The case series of 141 patients reported major safety events related to the device: erosion of hardware in 7% (10/141) of patients, leakage of current into soft tissues usually from electrical insulation fractures in 9% (12/141) of patients, electrode migration resulting in failure in 10% (14/141), and other hardware failure in 4% (6/141). In the patients with device erosion, 5 patients had the system removed and 5 had successful re-implantation without antibiotics. Electrode migration occurred only with early versions of the electrodes. 'Other hardware failure' was not described but was resolved with the replacement of specific components[5].

The same study reported foreign body reaction in 5% (7/141) of patients, requiring removal of the DBS system in 4 patients[5]

The case series of 122 patients reported erosion of the scalp overlying the connecter in 2 patients at 1 and 1.5 years, and electrode migration resulting in no pain relief in 2 patients (scalp erosion required plastic repair of scalp but sequelae not described for electrode migration)[8]

The case series of 21 patients reported that 1 patient had erosion in the region of the burr hole incision requiring removal of the system and another had iatrogenic electrode fracture when they were being reconnected to external cables for testing, requiring a procedure to replace the fractured electrodes with new ones (time of occurrence not reported)[9]

*Other*

The case series of 141 patients with nociceptive or deafferentation pain reported psychosis in 2% (3/141) of patients; 2 of these had a history of drug abuse[5]

The same study reported minor complications including headache (mostly transient) in 51% (72/141) of patients, diplopia caused by air/contrast ventriculography and PAG/PVG stimulation in 14% (20/141), nausea in 11% (15/141), vertical gaze palsies in 10% (14/141), blurred vision in 9% (13/141), hemi-or monoparesis in 9% (12/141), confusion in 8% (11/141), lethargy in 6% (9/141), dysphasia in 6% (8/141), and local pain in 5% (7/141) of patients. Events that occurred each in less than 5% of patients included horizontal nystagmus, persistent oscillopsia, seizures, urinary incontinence, cranial nerve palsies, ptosis, urinary retention, bronchospasm, hypesthesia, hallucinations, photophobia, memory loss, hypotension, facial pain, hypertension, shortness of breath, dysphoria, thrombophlebitis, and stimulation-induced sleep.

The case series of 122 patients reported permanent eye movement dysfunction in 3 patients that was thought to be caused by a particular placement of the tip of the electrode. This was considered to be avoided in future treated patients by moving the tip caudally[8]

The study of 64 patients treated with DBS for nociceptive or deafferentation pain reported that 25% (16/64) of patients had headache symptoms which occurred 1 to 2 months after the procedure in the majority of patients. Six of these patients reported headaches before implantation but the headaches were unchanged in 1 and significantly different in 5 (not clear if headaches were worse or better)[7]

The non-randomised study of 10 patients with post-stroke pain reported that 1 of the 4 patients treated with DBS developed a CSF leak when the electrode was being inserted into the PVG, so the electrode was not implanted. This patient had a haematoma over the pulse generator site (no more details provided)[3]

The case series of 21 patients reported that 1 patient had a seizure in the operating room during insertion of an electrode (no sequelae described) [9]

## Author's Conclusions.

1.1 Current evidence on the safety of deep brain stimulation (DBS) for refractory chronic pain syndromes (excluding headache) shows that there are serious but well-known risks. There is evidence that the procedure is efficacious in some patients who are refractory to other forms of pain control. Therefore this procedure may be used provided that normal arrangements are in place for clinical governance, consent and audit.

1.2 During the consent process patients should be informed that DBS may not control their chronic pain symptoms. They should be fully informed about the possible risks associated with this procedure including the small risk of death.

1.3 DBS should only be used in patients with refractory chronic pain syndromes that other treatments have failed to control. Patient selection should be carried out by a multidisciplinary team specialising in pain management.

## Our Comments/Summary.

It was not clear if there were any conflicts of interest in the writing of the overview. NICE consider the opinion of Specialist Advisors in the field, so it cannot be concluded with certainty that any reporting bias is absent. In addition, no information was provided as to whether two independent reviewers applied inclusion/exclusion criteria to the studies to assess their eligibility, the process of data extraction or a summary of the methodological process involved in appraising included studies. The criteria used for assessing the validity of the studies and if appropriate was not explicitly reported, although the authors did report study design, population, follow-up and other issues of the included studies. It was also not reported if reviewers were blind to authors, institutions and affiliations, which may influence the outcomes concluded and is a key indication of performance bias.

There is insufficient information provided on the methodological processes carried out to assess the quality of the study and the overall risk of bias.

**Table A5.8 Critical appraisal table *(NICE 2010b)*, deep brain stimulation**

| Study: *National Institute for Health and Clinical Excellence. Interventional procedure overview of deep brain stimulation for intractable trigeminal autonomic cephalalgias. June 2010. IP 895. pp. 1-27.* | |
|---|---|
| *Systematic review of RCTs (or other types of studies).)* | |
| **Patient/population** | Patients with intractable trigeminal autonomic cephalalgias |
| **N** | 45 patients (1 RCT and 4 case series)<br>**Please note all these studies may not have assessed our outcomes of interest.** |
| **Setting** | No specified |
| **Intervention/indicator** | **Reference** / **Intervention**<br>Fontaine D (2010) cross over RCT — Deep brain stimulation (n=5), patients with refractory chronic cluster headache<br>Broggi G (2007) case series — Deep brain stimulation (n=20), patients with refractory chronic cluster headache (16), SUNCT (1) and atypical facial pain (3)<br>Schoenen J (2005) case series — Deep brain stimulation (n=6), patients with refractory chronic cluster headache<br>Bartsch T (2008) case series — Deep brain stimulation (n=6), patients with refractory chronic cluster headache<br>Starr P (2007) case series — Deep brain stimulation (n=4), patients with refractory chronic cluster headache |
| **Comparison/control** | **Reference** / **Comparison**<br>Fontaine D (2010) — Sham stimulation (n=5), patients with refractory chronic cluster headache |
| **Outcomes** | Safety and/or efficacy |
| **Inclusion Criteria** | • Publication type – Clinical studies were included. Emphasis was placed on identifying good quality studies. Articles with abstracts containing information relevant to the safety and/or efficacy.<br>• Patients with intractable trigeminal autonomic cephalalgias<br>• Intervention – Deep brain stimulation |
| **Exclusion Criteria** | • Publication type - Abstracts were excluded where no clinical outcomes were reported, or where the paper was a review, editorial, or a laboratory or animal study<br>• Articles not in English language, unless they were thought to add substantively to the English language evidence base. |
| **Study Validity.** | |

| | | |
|---|---|---|
| **Is it clear that there were no conflicts of interest in the writing or funding of this review?** | Not reported | |
| **Does the review have a clearly- focused question?** | Yes | |
| **Is a systematic review the appropriate method to answer the question?** | Yes | |
| **Does the review have specified inclusion/exclusion criteria?** | Yes | See above |
| **If there were specified inclusion/ exclusion criteria, were these appropriate?** | Yes | |
| **Does the review document a comprehensive search strategy?** | Partial | A wide, appropriate range of bibliographic databases were used ("Searches were conducted of the following databases, covering the period from their commencement to 23 November 2010: MEDLINE, PREMEDLINE, EMBASE, Cochrane Library and other databases. Trial registries and the Internet were also searched. No language restriction was applied to the searches (see appendix C for details of search strategy)."<br>The authors did not report if follow-up from reference lists was conducted. |
| **Were reviewers blind to authors, institutions and affiliations?** | Not reported | |
| **Were 2 or more independent reviewers used for:**<br>**1. application of inclusion criteria to assess eligibility of studies?** | Not reported | About NICE interventional procedures from web, "NICE commissions an independent review body to carry out a systematic review when more information is needed before guidance can be developed on an interventional procedure. The review body consists of a consortium of the following organisations:<br>* School of Health and Related Research (ScHARR), University of Sheffield<br>* Institute of Applied Health Sciences, University of Aberdeen<br>* Sheffield Teaching Hospitals NHS Trust"<br>The information provided is not sufficient to know if 2 or more independent reviewers were used |
| **2. extraction of data from study reports?** | Partial | The information provided is not sufficient to know if 2 or more independent reviewers were used |
| **3. appraisal of study quality?** | Partial | The information provided is not sufficient to know if 2 or more independent reviewers were used |

| | | |
|---|---|---|
| **Were the strengths and limitations of included studies and potential impact on the results discussed?** | Partial | Limitations of the included studies were discussed (see Table 2 and page 5) briefly although how they impacted on the results was not discussed. |
| **Was the validity of included trials appraised using appropriate criteria?** | Not reported | |
| **Is there a summary of the results of individual studies?** | Yes | |
| **If meta-analyses were conducted, was it reasonable to do so?** | N/A | Rapid review of the literature – Interventional procedures group |
| **If meta-analyses were conducted, was it done appropriately?** | N/A | Rapid review of the literature – Interventional procedures group |
| **Other** | | |
| **What is the overall risk of bias?** | Insufficient information | |

**Results.**

**Efficacy**

*Effect on headache*

A crossover randomised study of 12 patients with chronic cluster headache (CH) reported that there was no significant difference between the periods when the device was switched 'on' and when it was switched 'off' in either the 'on then off' group or the 'off then on' group for a number of outcomes including frequency of attacks, pain intensity (measured on the Likert scale, which ranges from 1 to 7, with 7 indicating more pain), patient satisfaction (on Patients' Global Impression of Change 7-point scale, with 1 indicating best improvement) or emotional impact (measured on the Hospital Anxiety and Depression Scale [HAD])[1]

The study then included a 10-month open phase when all patients received DBS. At the end of the 10 months, the mean weekly attack frequency decreased by 48% from baseline (from 14 to 8 attacks per week; p = 0.08). A case series of 20 patients reported that all 16 patients treated for chronic cluster headache had pain relief at a mean follow-up of 23 months. Time to response occurred at a mean of 42 days (range 1 to 86 days) with mean 71% of pain-free days. The same study reported that 1 patient with short-lasting unilateral neuralgiform headache attacks and 3 patients with atypical facial pain had initial success after DBS but this failed to relieve pain in the longer term[2]

A case series of 6 patients with CH reported that, of the 4 who were successfully treated with the procedure, all improved in the 2 weeks after the operation. At a mean follow-up of 14.5 months, the clinical outcome was excellent for 3 patients (2 were pain-free and 1 had less than 3 attacks per month) but unsatisfactory in 1, who had transient remissions[3]

Another case series of 6 patients with CH reported that all patients had a decrease in attack frequency after the procedure. However, 4 were considered to have had a more profound response – a 90–100% decrease in attack frequency in the first few weeks and a reduction in the intensity of the remaining attacks from 10 at baseline to 1 or 4 at follow-up (measured on 10-point VAS, with 10 being worst pain). In 1

of these patients, attacks returned at 6 months and stimulation was aborted. At mean follow-up of 17 months, 3 patients were almost completely attack free, but the 2 with marginal transient effects did not have improvements despite adjustments in the stimulation parameters[4]

*Effect on anxiety and depression and quality of life*

The crossover RCT reported significantly reduced anxiety and depression scores measured on the HAD (7 anxiety items and 7 depression items with scores greater than 7 indicating anxiety and depression, respectively) in the 'open' phase only. Anxiety scores decreased from 13 to 7.5 ($p = 0.008$) and depression scores decreased from 10 to 4.5 ($p = 0.052$)[1]

A case series of 6 patients reported that 2 of the 4 patients who had a profound response to treatment had a tendency for improvement in quality of life after assessment as measured on the Short Form (36) health survey (SF-36), and normal postoperative values of 4 and 6 in the Hamilton depression scale (scores for SF-36 not reported and preoperative values in the Hamilton depression scale not reported; Hamilton depression scale is a 17-item scale, 0–54 with scores over 24 indicating severe depression)[4]

**Safety**

*Death*

In a case series of 6 patients with chronic CH, 1 patient died 3 days after the procedure from an intracerebral haemorrhage which developed along the lead tract a few hours after the procedure[3]

*Other*

The crossover RCT of 12 patients with chronic CH reported subcutaneous infection 3 weeks after surgery in 1 patient, which resolved after hardware removal and antibiotic treatment. Another patient lost consciousness with hemiparesis shortly after test stimulation but symptoms resolved spontaneously in 2 hours with no sequelae. However, during the open period, the same patient also had multiple severe micturition syncopes associated with a decrease in blood pressure in the standing position (no further details given)[1]

The case series of 4 patients reported a transient ischaemic attack 5 minutes after the test stimulation in 1 patient, which resolved without sequelae within 5 minutes. Authors hypothesised that a spasm causing the electrode tip to exit the floor of the third ventricle may have been induced from the test stimulation[5]

The RCT of 12 patients reported increased testosterone level (n = 1) and shortened menstrual cycle (n = 1) during the 'off' period. Mild increases or decreases in hunger, thirst and libido were reported in up to 8 patients during the 'on' and 'off' periods and the 'open' phase (there was no difference in rate of non-serious adverse events between the different phases)[1]

The case series of 20 patients reported 1 event each of deep infection requiring electrode removal (with complete recovery), cranial electrode migration requiring replacement after 1 year and mild, asymptomatic haemorrhage of the posterior wall of the third ventricle observed on routine postoperative CT, and transient difficulties in conjugate eye movements when the amplitude was increased (in the patient with SUNCT)[2]

One patient in the case series of 6 patients with CH reported panic sensation and had tachypnoea, tachycardia and moderate hypertension during the procedure. The operation was interrupted and the recording electrode was removed; the patient's parameters returned to normal[3]

## Author's Conclusions.

1.1 Current evidence on the efficacy of deep brain stimulation (DBS) for intractable trigeminal autonomic cephalalgias (TACs) is limited and inconsistent, and the evidence on safety shows that there are serious but well-known side effects. Therefore this procedure should only be used with special arrangements for clinical governance, consent and audit or research.

1.2 Clinicians wishing to undertake DBS for intractable TACs should take the following actions:

• Inform the clinical governance leads in their Trusts.

• Ensure that patients and their carers understand the uncertainty about the procedure's efficacy. They should be specifically informed that DBS may not control their headache symptoms and they should be fully informed about the possible risks associated with the procedure, including the small risk of death. Clinicians should provide them with clear written information. In addition, the use of NICE's information for patients ('Understanding NICE guidance') is recommended (available from www.nice.org.uk/guidance/IPG381publicinfo).

• Audit and review clinical outcomes of all patients having DBS for intractable TACs (see section 3.1).

1.3 Patient selection for DBS for intractable TACs should be carried out by a multidisciplinary team specialising in pain management.

1.4 Further research studies should clearly define patient selection and report the intensity and duration of stimulation, medication use and quality of life, in addition to documenting the effects on headache symptoms as clearly as possible.

**Our Comments/Summary.**

It was not clear if there were any conflicts of interest in the writing of the overview. NICE consider the opinion of Specialist Advisors in the field, so it cannot be concluded with certainty that any reporting bias is absent. In addition, no information was provided as to whether two independent reviewers applied inclusion/exclusion criteria to the studies to assess their eligibility, the process of data extraction or a summary of the methodological process involved in appraising included studies. The criteria used for assessing the validity of the studies and if appropriate was not explicitly reported, although the authors did report study design, population, follow-up and other issues of the included studies. It was also not reported if reviewers were blind to authors, institutions and affiliations, which may influence the outcomes concluded and is a key indication of performance bias.

There is insufficient information provided on the methodological processes carried out to assess the quality of the study and the overall risk of bias.

**Table A5.9 Critical appraisal table *(van Eijs Pain Practice 2011)*, peripheral nerve stimulation**

| Study: *van Eijs, F, Stanton-Hicks, M, Van Zundert, J, Faber, C, Lubenow, T, Mekhail, N, van Kleef, M and Huygen, F. 16. Complex Regional Pain Syndrome. Pain Practice. 2011. 11(1): 70-87.* | |
|---|---|
| *Evidence based guideline of observational studies for peripheral nerve stimulation (PNS).* | |
| **Patient/population** | Patients with complex regional pain syndrome (formerly reflex sympathetic dystrophy) |
| **N** | 115 patients (total)<br>*Individual studies –*<br>Hassenbusch, S et al, 1996 – 30 patients, Buschmann D and Oppel, P, 1999 – 47; Mobbs, R, Nair, S and Blum, P, 2007 – 38. |
| **Setting** | Not reported |
| **Intervention/indicator** | Peripheral nerve stimulation (PNS) |
| **Comparison/control** | N/A – observational studies only |
| **Outcomes** | Reduction in pain |
| **Inclusion Criteria** | Not reported |
| **Exclusion Criteria** | Not reported |

| Study Validity. | | |
|---|---|---|
| **Is it clear that there were no conflicts of interest in the writing or funding of this review?** | Yes | "The project is supported by a Dutch Government grant (BSIK03016)." |
| **Does the review have a clearly- focused question?** | Partial | This review on Complex Regional Pain Syndrome is part of the series "Evidence-Based Interventional Pain Medicine according to Clinical Diagnoses."<br>"In the EBM section of Pain Practice, a series of articles will be published over the next 2 years, which all aim at the professionalization of pain management, with special focus on the use of interventional pain management techniques under the appropriate circumstances." (van Kleef M, Mekhail, N and van Zundert, J, 2009, editorial) |
| **Is a systematic review the appropriate method to answer the question?** | Yes | As it is still a relatively experimental technique in this condition, mostly case series and reports are available to provide information on the effectiveness of PNS, hence it is appropriate for an EBG to answer this question. |

| | | |
|---|---|---|
| **Does the review have specified inclusion/exclusion criteria?** | Yes | The article itself did not contain explicit inclusion/exclusion criteria, however upon contacting the authors, they advised us with the following information –<br>"We want to draw your attention to the fact that the latest literature update was done in December 2009. Furthermore, because interventional pain management techniques have not all been assessed in randomized controlled trials, the criteria for withholding a publication were rather liberal. We mainly tried to avoid double publications.<br>The recommendation reflects:<br>1) The balance between effect and side effects/complication<br>2) The quality of the evidence (A, B, C or 0)<br>3) The outcome: positive, negative, or contradictory outcome."<br>"Only articles published in peer-reviewed journals are included." (van Kleef M, Mekhail, N and van Zundert, J, 2009, editorial) |
| **If there were specified inclusion/ exclusion criteria, were these appropriate?** | Yes | |
| **Does the review document a comprehensive search strategy?** | Partial | The article itself did not contain an explicit example of the search strategy, although upon contacting the authors they reported that "we searched PubMed with search strategy similar to the one below -<br>( "Cluster Headache/epidemiology"[Mesh] OR "Cluster Headache/etiology"[Mesh] OR "Cluster Headache/pathology"[Mesh] OR "Cluster Headache/physiopathology"[Mesh] OR "Cluster Headache/therapy"[Mesh] )<br>The full publications of the selected abstracts were retrieved and the reference list of those articles and important review articles were hand searched for additional information." |
| **Were reviewers blind to authors, institutions and affiliations?** | Not reported | |
| **Were 2 or more independent reviewers used for:**<br>**1. application of inclusion criteria to assess eligibility of studies?** | Partial | Upon contacting the authors with the following question, they responded with –<br>"A research associate selected all the abstracts that reported on: injection therapy, radiofrequency, pulsed radiofrequency and neuromodulation (neurostimulation)<br>The full publications of the selected abstracts were retrieved and the reference list of those articles and important review articles were hand searched for additional information." |
| **2. extraction of data from study reports?** | Yes | Upon contacting the authors it was confirmed that "Two independent reviewers (FvE and JVZ) assessed the studies, which included case reports, retrospective studies and prospective studies, they proposed an evidence rating based on the rating described in the publication (table 1)." |
| **3. appraisal of study quality?** | Yes | Upon contacting the authors it was confirmed that "Two independent reviewers (FvE and JVZ) assessed the studies, which included case reports, retrospective studies and prospective studies, they proposed an evidence rating based on the rating described in the publication (table 1)." |

| | | |
|---|---|---|
| **Were the strengths and limitations of included studies and potential impact on the results discussed?** | Not reported | |
| **Was the validity of included trials appraised using appropriate criteria?** | Not reported | |
| **Is there a summary of the results of individual studies?** | No | |
| **If meta-analyses were conducted, was it reasonable to do so?** | N/A | |
| **If meta-analyses were conducted, was it done appropriately?** | N/A | |
| **Other** | | |
| **What is the overall risk of bias?** | Insufficient information | |

**Results.**

**Efficacy of Peripheral Nerve Stimulation (PNS)**

"In a prospective case series, peripheral nerve stimulation (PNS) with surgically placed plate type electrodes connected with an implantable pulse generator reduced allodynic and spontaneous pain in 19 (63%) out of 30 implanted patients with CRPS and symptoms in the distribution of 1 major peripheral nerve.[80] In a retrospective study with 52 patients (48 CRPS-2 patients and 4 phantom limb patients), 47 patients were implanted after a positive trial stimulation. Of these patients, 43 (91%) had lasting excellent to good success with marked pain reduction and reduction of pain related disability.[81] In another retrospective study 41 PNS devices were implanted in 38 patients with pain in a peripheral nerve distribution. Over 60% of patients had significant improvement of their pain of more than 50% following implantation of the peripheral nerve stimulator.[82]

The technique can only be applied if the pain is in the distribution of a peripheral nerve and is thus less suitable for most CRPS-1 patients."

**Complications of Peripheral Nerve Stimulation (PNS)**

"Possible complications requiring reoperation are related to the surgical technique or PNS equipment design and include migration of the electrode in 33%, infection in 15% and the need for placement in an alternative location in 11% of patients."

**Table 6. Summary of Evidence for Interventional Pain Management of CRPS**

| Technique | Score |
|---|---|
| Intravenous regional block guanethidine | 2 A– |
| Ganglion stellatum (stellate ganglion) block | 2 B+ |
| Lumbar sympathetic block | 2 B+ |
| Plexus brachialis block | 2 C+ |
| Epidural infusion analgesia | 2 C+ |
| Spinal cord stimulation | 2 B+ |
| Peripheral nerve stimulation | 2 C+ |

**Author's Conclusions.**

"Peripheral nerve stimulation can be considered, preferentially in study conditions (2C+)."

2C+ refers to "effectiveness only demonstrated in observational studies. Given that there is no conclusive evidence of the effect, benefits closely balanced with risk and burdens"

**Our Comments/Summary.**

There was a lack of reporting on the individual results of the included studies. Also the strengths and limitations of each of the studies were not reported, particularly with relevance to the potential impact on the results.

The authors do not provide information how they assessed the quality of the included studies, they only refer us to a publication which explains how the grading and quality of evidence in clinical guidelines should be carried out (Guyatt, G et al, 2006). Due to this (insufficient information) we are unable to assess the methodological quality of the guidelines and hence what overall risk of bias exists.

**Table A5.10 Critical appraisal table *(van Kleef Pain Practice 2009)*, occipital nerve stimulation**

| Study: *van Kleef M, Lataster A, Narouze S, Mekhail N, Geurts JW, van Zundert J. 2. Cluster headache. Pain Practice. 2009; 9(6):435-42.* | |
|---|---|
| ***Evidence based guideline (including observational studies).*** | |
| **Patient/population** | Patients with CCH refractory to all other treatments |
| **N** | 1 SR, 4 case series |
| **Setting** | Not specified |
| **Intervention/indicator** | Occipital nerve stimulation (ONS) |
| **Comparison/control** | N/A |
| **Outcomes** | Pain relief (efficacy), side effects/complications |
| **Inclusion Criteria** | Not specified |
| **Exclusion Criteria** | Not specified |

| **Study Validity.** | | |
|---|---|---|
| **Is it clear that there were no conflicts of interest in the writing or funding of this review?** | Not reported | |
| **Does the review have a clearly- focused question?** | Partial | This review on cluster headache is part of the series "Evidence-Based Interventional Pain Medicine according to Clinical Diagnoses."<br>"In the EBM section of Pain Practice, a series of articles will be published over the next 2 years, which all aim at the professionalization of pain management, with special focus on the use of interventional pain management techniques under the appropriate circumstances." (van Kleef M, Mekhail, N and van Zundert, J, 2009, editorial) |
| **Is an EBG the appropriate method to answer the question?** | Yes | As it is still a relatively experimental technique in this condition, i.e. only two RCTs have been conducted in the last two years, mostly case series and reports exist previous to this, it is appropriate for an EBG to answer this question. |
| **Does the review have specified inclusion/exclusion criteria?** | Yes | The article itself did not contain explicit inclusion/exclusion criteria, however upon contacting the authors, they advised us with the following information –<br>"We want to draw your attention to the fact that the latest literature update was done in July 2009. Furthermore, because interventional pain management techniques have not all been assessed in randomized controlled trials, the criteria for withholding a publication were rather liberal. We mainly tried to avoid double publications.<br>The recommendation reflects: |

| | | |
|---|---|---|
| | | 1) The balance between effect and side effects/complication<br>2) The quality of the evidence (A, B, C or 0)<br>3) The outcome: positive, negative, or contradictory outcome."<br>"Only articles published in peer-reviewed journals are included." (van Kleef M, Mekhail, N and van Zundert, J, 2009, editorial) |
| **If there were specified inclusion/ exclusion criteria, were these appropriate?** | Yes | |
| **Does the review document a comprehensive search strategy?** | Partial | "We searched PubMed with the following search strategy<br>( "Cluster Headache/epidemiology"[Mesh] OR "Cluster Headache/etiology"[Mesh] OR "Cluster Headache/pathology"[Mesh] OR "Cluster Headache/physiopathology"[Mesh] OR "Cluster Headache/therapy"[Mesh] )" |
| **Were reviewers blind to authors, institutions and affiliations (of the included studies)?** | Not reported | |
| **Were 2 or more independent reviewers used for:**<br>**1. application of inclusion criteria to assess eligibility of studies?** | Partial | Upon contacting the authors with the following question, they responded with –<br>"A research associate selected all the abstracts that reported on: injection therapy, radiofrequency, pulsed radiofrequency and neuromodulation (neurostimulation)<br>The full publications of the selected abstracts were retrieved and the reference list of those articles and important review articles were hand searched for additional information." |
| **2. extraction of data from study reports?** | Yes | Upon contacting the authors it was confirmed that "Two independent reviewers (MvK and JVZ) assessed the studies, which included case reports, retrospective studies and prospective studies, they proposed an evidence rating based on the rating described in the publication (table 1)." |
| **3. appraisal of study quality?** | Yes | Upon contacting the authors it was confirmed that "Two independent reviewers (MvK and JVZ) assessed the studies, which included case reports, retrospective studies and prospective studies, they proposed an evidence rating based on the rating described in the publication (table 1)." |
| **Were the strengths and limitations of included studies and potential impact on the results discussed?** | Not reported | |
| **Was the validity of included trials appraised using appropriate criteria?** | Not reported | Upon contacting the author for greater detail on their search strategy, they provided us with information on how outcomes were assessed by the reviewers –<br>"Two independent reviewers (MvK and JVZ) assessed the studies, which included case reports, retrospective studies and prospective studies, they proposed an evidence rating based on the rating described in the publication (table 1).<br>Four physicians validated or adapted the proposed rating (MvK, JVZ, FH, JP). |

| | | |
|---|---|---|
| | | The recommendation reflects:<br>1) The balance between effect and side effects/complication<br>2) The quality of the evidence (A, B, C or 0)<br>3) The outcome: positive, negative, or contradictory outcome.” |
| **Is there a summary of the results of individual studies?** | No | |
| **If meta-analyses were conducted, was it reasonable to do so?** | N/A | |
| **If meta-analyses were conducted, was it done appropriately?** | N/A | |
| **Other** | | |
| **What is the overall risk of bias?** | Insufficient information | |

**Results.**

**Efficacy**

“ONS in patients with refractory cluster headache has been described in few case series.[18–21] One systemic review of ONS for chronic headache (including cluster headache) has been found.[22] This treatment appears to mainly decrease the intensity of the attacks. Noticeably, there is a relatively long (2 months or more) period of latency between the implantation of the electrode and a clinical effect.”

**Table 6. Summary of Interventional Pain Treatments**

| Technique | Score |
|---|---|
| Radiofrequency treatment of the pterygopalatine ganglion | 2 C+ |
| Occipital nerve stimulation | 2 C+ |

**Author’s Conclusions.**

“In patients with cluster headache refractory to all other treatments, occipital nerve stimulation may be considered, preferably within the context of a clinical study.”

“The effectiveness of…occipital nerve stimulation is only evaluated in observational studies, resulting in a 2 C+ recommendation.”

**Our Comments/Summary.**

There was a lack of reporting on the individual and summarised results of the studies for the section on occipital nerve stimulation (ONS). Only a description of the studies found and a broad statement about the efficacy was reported, "ONS in patients with refractory cluster headache has been described in few case series.[18–21] One systemic review of ONS for chronic headache (including cluster headache) has been found.[22] This treatment appears to mainly decrease the intensity of the attacks. Noticeably, there is a relatively long (2 months or more) period of latency between the implantation of the electrode and a clinical effect." The authors do not provide the data/information of how the studies were validated. Due to this we are unable to assess what overall risk of bias exists.

An earlier issue which includes an editorial on the "Evidence Based Interventional Pain Medicine" series explains "Incidence and severity of side effects and complications are also derived from three reviews that specifically address the complications of interventional pain relief techniques.[7,14,15]" No mention of adverse effects, whether there were none or if any existed in any studies, were reported for ONS, although a section on "Complications of Interventional Management" is present.

**Table A5.11 Critical appraisal table *(Hashimoto 2010)*, spinal cord stimulation**

| Study: *Hashimoto R, Dettori JR, Henrikson NB, Kercher L, Spectrum Research I. HTA Report: Spinal Cord Stimulation. Olympia, WA: Washington State Health Care Authority. 23 July 2010.* | |
|---|---|
| *Health Technology Assessment* | |
| **Patient/population** | "Studies of adults who underwent permanent implantation of spinal cord stimulation for the treatment of chronic neuropathic pain due to conditions including (but not limited to) failed back surgery syndrome (FBSS), complex regional pain syndrome (CRPS), phantom limb or stump pain, central pain such as post-stroke pain, diabetic neuropathy, and post- herpetic neuralgia. Diagnosis of neuropathic pain in at least 75% of patients was required for study inclusion." |
| **N** | 3 RCTs, 4 prospective cohorts, 2 retrospective cohorts, 6 case series |
| **Setting** | Not specified |
| **Intervention/indicator** | *E = Efficacy/effectiveness, S = safety, D = differential efficacy or safety in subpopulations* |

| Reference | Intervention |
|---|---|
| Kemler 2000, 2004, 2008 **RCT** *E,S* | SCS + physical therapy (PT) |
| Kumar 2007 (PROCESS trial) **RCT** *E,S* | SCS + conventional medical management (CMM) |
| North 2005 **RCT** *E,S* | SCS |
| Turner 2010 **prospective cohort** *E,S,D* | SCS |
| Burchiel 1995 **prospective cohort** *D* | SCS |
| Lamé 2009 **prospective cohort** *D* | SCS |
| Van Eijs 2010 **retrospective cohort** *D* | SCS |
| North 1991 **retrospective cohort** *D* | SCS |
| North 1996 **prospective cohort** *D* | SCS |
| Kay 2001 **case series** *S* | SCS |
| Kumar & Wilson 2007 **case series** *S* | SCS |
| Kumar & Toth 1998 **case series** *S* | SCS |
| Lanner 2007 **case series** *S* | SCS |
| North 1993 **case series** *S* | SCS |
| Sanchez-Ledesma 1989 **case series** *S* | SCS |

**Comparison/control**

| Reference | Comparison |
|---|---|
| Kemler 2000, 2004, 2008 **RCT** | PT alone (n = 18) |
| Kumar 2007 (PROCESS trial) **RCT** | CMM: (n = 48) |
| North 2005 **RCT** | Reoperation (n = 30) |
| Turner 2010 **prospective cohort** | Pain clinic (n = 39), Usual care (n = 68) |
| Burchiel 1995 **prospective cohort** *D* | Not specified |
| Lamé 2009 **prospective cohort** *D* | Not specified |
| Van Eijs 2010 **retrospective cohort** *D* | Not specified |
| North 1991 **prospective cohort** *D* | Not specified |
| North 1996 **prospective cohort** *D* | Not specified |

**Outcomes**

**efficacy and effectiveness; safety; differential efficacy or safety issues in sub populations; cost implications and cost-effectiveness**

**"**Key questions are developed by the Washington State Health Technology Assessment Program.

**When used in adult patients with chronic neuropathic pain who have failed alternative therapies:**

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

a. Short-term and long-term outcomes

b. Impact on pain, function, and quality of life

c. Other reported measures including: use of pain medications and opioids, return to work; intensity and duration of use

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

a. Adverse events type and frequency (mortality, major morbidity, other)

b. Revision and removal rates including loss of paresthesia (if not addressed in efficacy)

c. Infections

d. Lead migration

e. Technical malfunctions (e.g., early battery failure, broken leads)

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

a. Gender

b. Age

c. Psychological or psychosocial co-morbidities

d. Diagnosis or pain type

e. Other patient characteristics or evidence based patient selection criteria

f. Provider type, setting or other provider characteristics

| | |
|---|---|
| | g. Health care system type, including worker's compensation, Medicaid, state employees<br>**Key Question 4:** What is the evidence of cost implications and cost-effectiveness of spinal cord stimulators?<br>Including consideration of:<br>a. Costs (direct and indirect) in short term and over expected duration of use<br>b. Replacement"<br>***"1.3. Outcomes Assessed***<br>Because spinal cord stimulation is used as a treatment for chronic pain, the primary and most commonly reported outcome was pain relief. Typically, pain was reported by patients on a 0 to 10 cm VAS (visual analogue scale), with 0 cm indicating no pain and 10 cm indicating worst pain imaginable. Many studies report the percentage of patients that achieved 50% pain relief compared to baseline, while others reported the difference in pain intensity that occurred from treatment. Some studies reported the composite outcome of "success" as the primary outcome. Varying definitions were used, but "success" always included pain relief as one of its components; other components included patient satisfaction, function, and medication usage. Specific definitions are detailed in the results section as appropriate. Studies reported secondary outcomes that included patient satisfaction, global perceived effect (GPE), health-related quality of life outcome measures (EQ-5D, SF-36, Nottingham Health Profile, Self-Rating Depression Scale scores), function (Oswestry Disability Index, Roland-Morris Disability Questionnaire), and medication usage. Further details on the outcome measures used can be found in Table 4.**"** |
| **Inclusion Criteria** | "Included studies that evaluated permanently-implanted spinal cord stimulation devices. Studies with the following types of interventions were excluded: studies reporting only on temporarily placed spinal cord stimulation devices; transcutaneous electrical nerve stimulation; and neurostimulation involving other parts of the nervous system (such as deep brain or peripheral nerves)."<br>**Participants:** Adults with neuropathic pain (including, but not limited to: failed back surgery syndrome, complex regional pain syndrome, phantom limb or stump pain, central pain such as post-stroke pain, diabetic neuropathy and post-herpetic neuralgia)<br>**Intervention:** Spinal cord stimulation (permanently-implanted pulse generator systems and radiofrequency receiver systems)<br>**Comparators:** Medical and/or surgical treatment (appropriate to condition) that does not include SCS<br>**Outcomes:** Pain; Patient satisfaction; Global perceived effect (GPE); Health-related quality of life (HR-QoL); Function; Anxiety and depression; Medication use; Complications and adverse effects (e.g. procedural complications and technical failures)<br>**Study Design:** Comparative clinical studies (e.g. RCTs, cohort studies with concurrent controls) will be considered for questions 1-3 (question 3 is limited to studies with LoE of I or II)<br>Case series with at least 5 years follow-up for question 2<br>Formal cost-effectiveness analyses will be sought for question 4<br>**Publication:** Studies published in English in peer reviewed journals, published HTAs or publicly available FDA reports<br>Full formal cost-effectiveness economic analyses published in English in an HTA, or in a peer-reviewed journal published after those represented in previous HTAs. |

| | |
|---|---|
| **Exclusion Criteria** | **Participants:** Children, Patients with prior use of SCS, Patients who are pregnant<br>**Intervention:** Temporarily-implanted spinal cord stimulation; Neurostimulation that involved stimulation of other parts of the nervous system (e.g. peripheral nerves, deep brain); Transcutaneous electrical nerve stimulation<br>**Outcomes:** Non-clinical outcomes<br>**Study Design:** Case reports; Case series for questions 1 or 3 other than for context; Case series with < 5 years follow-up for question 2; Studies with LoE III or IV for question 3; Non-clinical studies; Studies with N < 10 patients total OR per group; Studies in which < 75% of patients have chronic neuropathic pain<br>**Publication:** Abstracts, editorials, letters, books; Studies without abstracts available online (by searching Pubmed, google, and the journal's website if available); Duplicate publications of the same study which do not report on different outcomes; Single reports from multicenter trials;<br>Studies reporting on the technical aspects spinal cord stimulation; White papers; Narrative reviews; Articles identified as preliminary reports when results are published in later versions; Other types of economic evaluations (ie., costing studies, cost-minimzation analyses, cost-utility analyses, cost-benefit analyses) |

**Study Validity.**

| | | |
|---|---|---|
| **Is it clear that there were no conflicts of interest in the writing or funding of this review?** | partial | The authors examine conflicts on interest in their included studies, but not their own<br>"This technology assessment report is based on research conducted by a contracted technology assessment center, with updates as contracted by the Washington State Health Care Authority. This report is an independent assessment of the technology question(s) described based on accepted methodological principles." |
| **Does the review have a clearly- focused question?** | Yes | |
| **Is an EBG the appropriate method to answer the question?** | Yes | |
| **Does the review have specified inclusion/exclusion criteria?** | Yes | See above |
| **If there were specified inclusion/ exclusion criteria, were these appropriate?** | Yes | |
| **Does the review document a comprehensive search strategy?** | Yes | |
| **Were reviewers blind to authors, institutions and affiliations (of the included studies)?** | Not reported | |
| **Were 2 or more independent reviewers used for:** | Yes | "We then screened all possible relevant articles using titles and abstracts in stage two. This was done by two individuals independently. Those articles that met a set of *a priori* retrieval criteria based on the criteria above were included. Any |

| | | |
|---|---|---|
| **4. application of inclusion criteria to assess eligibility of studies?** | | disagreement between screeners that were unresolved resulted in the article being included for the next stage. Stage three involved retrieval of the full text articles remaining. The final stage of the study selection algorithm consisted of the selection of those studies using a set of a priori inclusion criteria, again, by two independent investigators. Those articles selected form the evidence base for this report.*"* |
| **5. extraction of data from study reports?** | Not reported | |
| **6. appraisal of study quality?** | Not reported | |
| **Were the strengths and limitations of included studies and potential impact on the results discussed?** | Yes | |
| **Was the validity of included trials appraised using appropriate criteria?** | Yes | |
| **Is there a summary of the results of individual studies?** | Yes | |
| **If meta-analyses were conducted, was it reasonable to do so?** | N/A | |
| **If meta-analyses were conducted, was it done appropriately?** | N/A | |
| **Other** | | |
| **What is the overall risk of bias?** | Low | *Low - All of the criteria have been fulfilled or where criteria have not been fulfilled it is very unlikely the conclusions of the study would be affected.* |

**Results.**

**"Results**

For key question 1, we identified a total of three RCTs and one prospective cohort study. One RCT included only patients with complex regional pain syndrome (CRPS-I); two RCTs included only patients with failed back surgery syndrome (FBSS). The prospective cohort study was conducted specifically on patients with open Washington state workers' compensation claims. For key question 2, we identified six additional case series, all with mid-term follow-up. For key question 3, we identified four prospective and two retrospective cohort studies. We identified three cost-effectiveness analyses to address key question 4.

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

One RCT provided data on the short-term efficacy of SCS compared with physical therapy in complex regional pain syndrome (CRPS) patients. Two RCTs reported on the efficacy of SCS in patients with failed back surgery syndrome (FBSS): one RCT provided data on both the short- and mid-term efficacy of SCS and conventional medical management (CMM) compared with CMM alone, while another provided data on the short-term efficacy of SCS compared with lumbar reoperation. Heterogeneity between these studies prevented pooling of the data. In general, the RCTs reported significantly improved outcomes in the short-term for patients randomized to receive SCS than those randomized to the control groups; however, results were mixed at the mid-term follow-up in the one RCT reporting results after five years. One prospective cohort study provided data on the short-term effectiveness of SCS compared with Pain Clinic and Usual Care treatments in FBSS patients with open workers' compensation claims in the State of Washington. In general, the cohort study found no differences in outcomes between patients in the SCS and two control groups.

***"Success" from a composite score***

Efficacy: One RCT found that patients randomized to receive SCS had significantly improved "success" (a composite of pain relief and patient satisfaction) compared with those randomized to undergo lumbar reoperation at mean of 2.9 years follow-up. Effectiveness: The prospective cohort study on workers' compensation patients found no difference between SCS, pain clinic (PC), or usual care (UC) groups at any follow-up up to 24 months in the percent of patients achieving the primary outcome composite measure of success (includes pain, function, and medication usage components).

***Pain relief***

Efficacy: Patients randomized to receive SCS had significantly improved pain relief compared with those randomized to undergo control treatments in two RCTs with ≤ 2 year follow-up. One of these RCTs reported that the differences between groups in both the change in VAS scores (from baseline) and in mean VAS scores were no longer statistically significant by three to five years post-implantation.

Effectiveness: The prospective cohort study on workers' compensation patients reported that significantly more patients in the SCS group achieved ≥ 50% leg pain relief by six months than those in the UC group, there was no difference between the SCS and PC group at the same follow-up; furthermore, no differences were identified between groups in the percentage of patients achieving leg pain relief of ≥ 50% or more at the 12- and 24-month follow-ups.

***Function***

Efficacy: One RCT found that patients in the SCS group had significantly better Oswestry Disability Index scores than those in the CMM group at six months follow-up. Another RCT reported no significant differences between the SCS and reoperation groups in the neurological status or ability to perform daily activities a mean of 2.9 years follow-up, however, raw data were not provided.

Effectiveness: There were no significant differences in either the Roland-Morris Disability Questionnaire (RDQ) scores or ability to perform daily tasks between treatment groups in the prospective cohort study on workers' compensation patients.

***Health-related quality of life (HR-QoL)***

Efficacy: One RCT reported no difference in several QoL outcome measures between the SCS and physical therapy groups, including the mean percent change in quality of life at the 6- and 24- month follow-ups as well as the Nottingham Health Profile, EQ-5D (EuroQol-5D), and Self- Rating Depression Scale scores at five years. Another RCT reported that patients randomized to receive SCS had significantly better scores in seven of the eight SF-36 (Short-Form 36) outcome scales compared with those randomized to receive CMM at six months. The same RCT reported that the six-month EQ-5D utility scores were significantly better in the SCS compared with the CMM group. Further, no difference was found between groups in the rate of patients (not working at baseline) who had returned to work by six months.

Effectiveness: The prospective cohort study on workers' compensation patients reported no significant differences between treatment groups in SF-36 scores and work/disability status.

***Patient satisfaction and perceived effect***

Efficacy: One RCT reported that significantly more patients in the SCS group were satisfied with both their level of pain relief and with their treatment in general than those in the CMM group at six months follow-up. Another RCT incorporated patient satisfaction with pain relief into a composite outcome, "success", which was reported above. Another RCT reported global perceived effect (GPE) scores. Significantly more patients in the SCS group reported GPE of "much improved" or "best ever" at both the 6- and 24- month follow-ups compared with the physical therapy group; however the differences between groups were no longer statistically significant by five years.

***Medication usage***

Efficacy: One RCT reported no differences at six months between the SCS and CMM groups in the percentage of patients using opioids, non-steroidal anti-inflammatory medications, or antidepressants; however, significantly fewer SCS patients were taking anticonvulsants than those in the CMM group. There were no differences between the SCS and CMM groups in the percentage of patients using all reported non-drug therapies (eg., physical or psychological rehabilitation, acupuncture, or massage) except for TENS (transcutaneous electrical nerve stimulation), for which the rate of use was lower in SCS

compared with CMM patients. Another RCT found that significantly more patients in the SCS group were taking a stable or decreased dosage of opioids (versus baseline) than those in the reoperation group at a mean of 2.9 years follow-up.

Effectiveness: Although significantly fewer patients in the SCS group used opioids on a less than daily basis than did those in the PC group at six months, no other significant differences between treatment groups were identified in the prospective cohort study on workers' compensation patients.

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

Short-term (< 5 years) safety data were reported by three RCTs and one prospective cohort study; mid-term (5–10 years) safety data were reported by one RCT and six case series. No longterm safety data were available.

***Revision***

All three RCTs and the one cohort study reported short-term revision rates of SCS devices; one RCT and all six case series reported mid-term revision rates. However, each study reported the data differently, and not all studies reported an overall revision rate (the proportion of patients with one or more revision). Therefore, revision rates were difficult to pool. Reasons for revision included (but were not limited to): revision or replacement of electrodes/leads due to migration, improvement of paresthesia, defective electrodes, infection, fractured electrode, or hardware malfunction; revision or replacement of generators (or stimulators) due to painful pulse generator pockets, migration, battery depletion, defective generator, electrical leak, or failure; revision of the connecting cable/lead due to fracture, discomfort, or insulation damage; SCS systems were explanted (and often reimplanted) due to infection, recurrent rejection, discomfort, ineffective pain relief, new intolerable pain, defective transmitters, or seizures.

***Other SCS-related complications or side effects***

Complications or side effects ascribed to the SCS device were reported by two RCTs, one cohort study, and six case series; overall short-term rates ranged from 8–100% of patients. At two years follow-up, one RCT reported that side effects had occurred in 100% of available SCS patient; another RCT reported device-related complications not requiring revision in 14% of patients. Complications or side effects ascribed to the SCS system included: change in amplitude by bodily movements, paresthesia in other body parts, pain or irritation from pulse generator, disturbed urination, movements or cramps resulting from elevated amplitute, infection, loss of therapeutic effect, loss of parasthesia, or unpleasant paresthesia, subcutaneous hematoma, cerebrospinal fluid leak, dural puncture, or pain over SCS components.

***Complications not related to SCS***

Complications not related to SCS were reported by one RCT. Rates of new illness, injury, or condition and of worsening of the pre-existing condition were similar for both the SCS and the CMM group; however the percentage of patients that had experienced drug adverse events or extra pain events were 15 to 23% higher in the CMM group than in the SCS group at one year.

***Mortality***

Short-term mortality data were obtained from three RCTs and one prospective cohort study. Two deaths occurred in the SCS groups (2/139); one due to a sudden cardiac event at six months and another between six and twelve months for which the cause was not reported. No deaths occurred in any of the control groups (0/179). Mid-term mortality data were obtained from one RCT and three case-series. Two deaths occurred in SCS patients; one due to cerebrovascular accident in a patient being treated for angina, not neuropathic pain, and another due to suicide. No deaths were attributed to SCS; however one patient nearly died as a result of complications that arose following trial stimulation.

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

We identified six small prognostic studies (four prospective and two retrospective studies). In general, very little evidence was found that suggests that any of the factors evaluated were strongly associated with improved outcome following SCS. Prognostic factors evaluated included:

***Age***

Three studies evaluated whether age had an effect on pain relief in the first year following implantation. While one study reported that younger age was significantly associated with improved pain relief, two other studies found no association between patient age and pain relief. Furthermore, one prospective cohort study demonstrated that age was not correlated with SF-36 or GPE scores at nine months

***Sex***

Four studies evaluated the effect of patient sex on pain relief following SCS. Three studies found that sex was not predictive of pain relief in the first year, and one study reported that success at five years was significantly higher in females. This study also reported that females had significant improvements in a combination of everyday activities (ability to work, walk, climb stairs, sleep, have sex, drive, and eat), neurological function (strength, sensation, and bladder/bowel control), and medication use. One other study found no correlation between patient sex and SF-36 or GPE scores at nine months.

***Workers' compensation or other disability payments***

One study found no difference in the percentage of patients who achieved at least 50% pain relief at three months between those receiving workers' compensation or other disability payments than those not under such programs.

***Duration of pain***

Two studies evaluated and found no relationship between duration of chronic pain and pain relief in the first year following SCS implantation. One study reported that CRPS patients with a longer duration of chronic pain had significant improvements in quality of life at nine months as measured by two (of eight) domains of the SF-36 outcome measure by multivariate analysis; however, no association was found between pain duration and GPE scores.

***Pain intensity***

One study evaluated and found no association between the pain intensity at baseline and pain relief at one year.

***Time since first lumbar surgery***

One study found that the time since the first lumbar surgery was not associated with success or a composite score that included everyday activities, neurological function, and medication use at five years.

***Number of prior operations for pain***

Two studies evaluated and found no association between the number of previous operations for chronic pain and pain relief at three months or success at five years.

***Pain location***

Four studies evaluated and found no association between pain location and pain relief at followup, though each study compared different locations. One study reported no association between hand versus foot pain with nine-month SF-36 or GPE scores; another study found no difference in a combination of everyday activities, neurological function, and medication use between patients with axial versus radicular pain.

***Laterality of pain***

One study suggested that more SCS patients with unilateral pain achieved leg pain relief of at least 50% than did those patients with bilateral pain; similarly, more patients with unilateral pain had functional improvement (as measured by the RDQ) compared with those patients with bilateral pain.

***Allodynia or hyposthesia at baseline***

One retrospective study demonstrated that the absence of brush-evoked allodynia at baseline was significantly associated with success at one-year. In contrast, the presence of mechanical hypoesthesia at baseline was not correlated with success.

***McGill Pain Questionnaire***

Two studies evaluated the predictive effect of baseline McGill Pain Questionnaire scores with conflicting results. While one study found that higher McGill evaluative subscores were associated with improved pain relief, the other study found that none of the domains of the McGill Pain Questionnaire were predictive of success at five years.

***Minnesota Multiphasic Personality Inventory (MMPI)***

Two studies evaluated whether MMPI scores at baseline were associated with improved pain relief. One study found that lower scores for the depression subscale were significantly correlated with pain relief at three months, while the other study found no correlation between MMPI scores and pain relief at a mean of 3.5 years.

***SF-36 Mental Health Component***

One study found that SCS patients with baseline SF-36 Mental Health scores in the top third of patients had better pain relief and functional outcomes (as measured by the RDQ) compared with those patients with baseline scores in the lowest third.

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

We included three complete economic evaluations; two were published economic evaluations of SCS compared with other interventions for pain and one was included as part of the recent HTA conducted by NICE in the UK. We found that there is some evidence that SCS is cost-effective at moderate (<$20,000) incremental cost effectiveness ratio (ICER) levels compared with CMM or reoperation, and that SCS cost-effectiveness increases and may be dominant over time compared with control treatments (i.e., CMM or reoperation) assuming device longevity of 4 years and at least a 30% pain threshold criteria. However, the assumption of continued efficacy past 3 years is questionable from the only RCT reporting pain 5-10 years after implantation. Furthermore, only one study was conducted in a US setting.”

## Author’s Conclusions.

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

| SCS | Strength of evidence | Conclusions/Comments | Quality | Quantity | Consistency |
|---|---|---|---|---|---|
| **Efficacy** (Short-term: < 5 years) | **Moderate** | •**Pain, perceived effect of treatment/patient satisfaction:** There is moderate evidence from three small randomized controlled trials that SCS is superior to conventional therapies (CMM, physical therapy or reoperation) in patients with chronic neuropathic pain during the first 2–3 years with respect to patient reported outcomes of pain, and perceived effect of treatment/patient satisfaction. In the only RCT that measured outcomes for a longer period o time, the benefit of SCS decreased over time and was not significantly different than controls for leg pain after 3 years of treatment (see mid-term below). | + | - | + |
| | **Low** | •**Function, quality of life:** The effect on quality of life outcomes is less clear with one RCT reporting substantial benefit of SCS compared with CMM at 6 months follow-up, while another study found quality of life outcomes to be similar between SCS + physical therapy and physical therapy alone at 2 years follow-up. Similarly, function as measured by the Oswestry Disability Index score was better in the SCS group at 6 months versus CMM in one study but the ability to perform daily activities after 3 years was not different in a second study. | + | - | - |
| (Mid-term: 5 to < 10 years) | **Low** | •**Pain, quality of life, perceived effect of treatment:** There is low evidence from one small randomized controlled trial that SCS is no different from conventional therapy (physical therapy) in patients with chronic neuropathic pain 5-10 years following implant with respect to pain, quality of life, and patient-reported global perceived effect. | + | - | **NA** |
| (Long-term: ≥ 10 years) | **No evidence** | •There are no data available to assess long-term efficacy. | **none** | **none** | **none** |
| **Effectiveness** (Short-term: < 5 years) | **Low** | •**Composite of pain, function, and opioid use:** One prospective cohort study on workers’ compensation patients reported similar success on a composite score that includes pain, function and opioid use between SCS and either Pain Clinic or Usual Care treatment groups. There was a modest improvement in leg pain in the SCS group compared with the control groups at 6 months follow-up but this did not persist at the 12 month or 24 month evaluation. | + | - | NA |
| (Mid & Longterm: ≥ 5 years) | **No evidence** | •There are no data available to assess mid- or long-term effectiveness. | none | none | none |

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

| SCS | Strength of evidence | Conclusions/Comments | Quality | Quantity | Consistency |
|---|---|---|---|---|---|
| **Revision** | **High** | •There is high evidence from three randomized controlled trials, one prospective comparative cohort study and six case series that revision of SCS components is not uncommon. Overall short-term revision rates ranged from 12–38% of patients. Mid-term revision rates were 42% in one RCT and 60% in one case series. Reasons for revision include electrode repositioning or replacement, generator revision or replacement, revision of the connecting cable, and total removal and replacement of the system due to infection. There are no long-term data available. | + | + | + |
| **Other SCS-related side effects** | **Moderate** | •Side effects reported varied widely among studies and included infection, change in amplitude by bodily movements, paresthesia in other body parts, pain/irritation from the pulse generator, transient neurological defects, severe woundrelated pain at the stimulator implantation site, cerebrospinal fluid leak, and subcutaneous hematoma. The rate of side effects could not be determined from the papers reviewed; however, one RCT reported that all patients experienced at least one side effect. | + | + | - |
| **Mortality** | **High** | •There is high evidence that the rate of mortality due to SCS is low. Among the four comparative studies, 2 deaths were reported in patients receiving SCS (2/139); one as a result of a cardiac event six months following SCS implantation, and the cause of one was not reported. No deaths were recorded in the control groups during the same time period (0/179). Two additional deaths were identified in three case series with five year follow-up; one from a cerebrovascular accident in a patient implanted for cardiac ischemic pain, one as a result of suicide. No death was attributed to SCS; however one patient nearly died as a result of complications that arose following trial stimulation. | + | + | + |

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

**Summary: There is no moderate or high evidence that any of the factors evaluated were associated with improved outcome following SCS.** Factors evaluated: age, sex, workers' compensation or other disability payments, duration of pain, pain intensity, time since first lumbar surgery, number of prior surgeries for pain, pain location, laterality of pain, allodynia or hypoesthesia at baseline, McGill pain questionnaire, Minnesota Multiphasic Personality Inventory (MMPI), SF-36 Mental Health scores.

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

| SCS | Strength of evidence | Conclusions/Comments | Quality | Quantity | Consistency |
|---|---|---|---|---|---|
| **Cost-effectiveness** | **Moderate** | •There is moderate evidence from three complete economic evaluations that in the short-term, SCS is associated with improved outcomes and increased costs compared with CMM and/or reoperation for the treatment of neuropathic pain. In the long-term, SCS appears to be dominant over the control treatments; however, only one study included in this assessment was conducted in a U.S. setting. More specifically, we found that there is some evidence that SCS is cost-effective at moderate (<$20,000) incremental cost effectiveness ratio (ICER) levels compared with CMM or reoperation, and that SCS cost-effectiveness increases and may be dominant over time compared with control treatments (i.e., CMM or reoperation) assuming device longevity of 4 years and at least a 30% pain threshold criteria. However, the assumption of continued efficacy past 3 years is questionable from the only RCT reporting pain 5-10 years after implantation. Furthermore, only one study was conducted in a US setting. | + | - | + |

**Our Comments/Summary.**

This is a well-conducted HTA with a low risk of bias

The authors included studies related to some types of pain that would be excluded according to the selection criteria of our report (i.e. post-stroke pain), this may affect generalisability