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. 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). 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. 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]. 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

treatment of chronic, intractable neuropathic pain. 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.** 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.** 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** 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 - "Patients should not receive permanent SCS therapy who: • failed trial stimulation due to ineffective pain relief • are poor surgical risks • are pregnant • are unable to operate the SCS system • have cardiac pacemakers (unless specific precautions are taken regarding the mode and frequency of the device and not contraindicated for the particular device) • have cardioverter defibrillators • have active general infections • have multiple illnesses 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. Two RCTs reported that the rate of mortality due to SCS was low (0-1%). 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. 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. 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 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

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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) **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. **Intervention:** spinal cord stimulation **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)** "**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." 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." **There is low level evidence that SCS is no different to physical therapy in the mid-term (5 - <10 years)** "**Pain, quality of life, perceived effect of treatment:** There is low evidence from one small randomized controlled trial that SCS is no different from conventional therapy (physical therapy) in patients with chronic neuropathic pain 5-10 years following implant" **There is no evidence available to assess long-term efficacy of SCS (>10 years).** **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** **<u>There is low level evidence that SCS is more effective than comparators in the short term (<5 years)</u>** "**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." **<u>There is low level evidence that SCS is no different to physical therapy in the mid-term 5 - <10 years)</u>** "**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." **COST ANALYSIS** "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." 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] Patients should not receive permanent SCS therapy who: • failed trial stimulation due to ineffective pain relief • are poor surgical risks • are pregnant • are unable to operate the SCS system • have cardiac pacemakers (unless specific precautions are taken regarding

	the mode and frequency of the device and not contraindicated for the particular device) • have cardioverter defibrillators • have active general infections • have multiple illnesses 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	**High level evidence (revision)** **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. **High level evidence (mortality)** **There is high evidence that the rate of mortality due to SCS is low.** Among the four comparative studies, 2 deaths were reported in patients receiving 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. **Moderate level evidence (other SCS-related side effects)** Side effects reported varied widely among studies and included infection, change in amplitude by bodily movements, paresthesia in other body parts, pain/irritation from the pulse generator, transient neurological defects, severe wound-related pain at the stimulator implantation site, cerebrospinal fluid leak, and subcutaneous hematoma. **The rate of side effects could not be determined from the papers reviewed**; however, one RCT reported that all patients experienced at least one side effect.
Conclusion/Recommendation	**SHORT TERM EFFECTIVENESS** 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**. **MID-TERM EFFECTIVENESS** 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**

	effect of treatment **LONG-TERM EFFICACY** 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. 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". 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. 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.	
Study design	Evidence based guideline
Scope	**Patient/population:** n=202, six case series **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). **Intervention:** Peripheral nerve stimulation **Comparator:** N/A (uncontrolled studies, case series) **Outcomes assessed:** • 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

	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	
Study design	Crossover Randomised Clinical Trial (RCT)
Scope	**Patient/population:** n=13 (for the randomised phase of the study) **Conditions indicated for use:** Patients with chronic neuropathic pain of either peripheral or central origin **Intervention:** Motor cortex stimulation (stimulator 'on' for 1 month duration) **Comparator:** Sham stimulation (stimulator 'off' for 1 month duration) **Outcomes assessed:** • Pain intensity and relief • Functional assessments (general activity, mood, walking ability, normal work, relations with other people, sleep and enjoyment of life) • 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).

	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. 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. 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.	
Study design	Crossover Randomised Clinical Trial (RCT)
Scope	**Patient/population:** n=10 **Conditions indicated for use:** Patients with chronic neuropathic pain of either peripheral or central origin **Intervention:** Motor cortex stimulation for 2 weeks (ON period) **Comparator:** Sham stimulation for 2 weeks (OFF period) **Outcomes assessed:** • Pain intensity and relief • Functional assessments (general activity, mood, walking ability, normal work, relations with other people, sleep and enjoyment of life) • 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

	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.	
Study design	Crossover Randomised Clinical Trial (RCT)
Scope	**Patient/population:** n=11 **Conditions indicated for use:** Patients with severe refractory chronic cluster headache (CCH) **Intervention:** Deep Brain Stimulation ('on' for 1 month) **Comparator:** Sham stimulation ('off' for 1 month) **Outcomes assessed:** • Weekly attacks frequency (primary), • Pain intensity (Likert scale), • Sumatriptan injections, oxygen use (yes or no), • Anxiety and depression levels (Hospital Anxiety Depression scale), quality of life (SF-12 scale), patient's satisfaction (Patient's Global Impression of Change) • Blood pressure, heart rate, weight and body temperature • Electrolyte balance and hormonal functions, and changes in thirst, appetite, libido, sleepwalking cycle and behaviour (AE)
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

	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.	
Study design	Randomised controlled trial (RCT)
Scope	**Patient/population:** n=132 (n=63 active stimulation, n=62 sham stimulation) **Conditions indicated for use:** Patients with treatment-refractory migraine **Intervention:** Bilateral active occipital nerve stimulation for 12 weeks **Comparator:** Sham stimulation for 12 weeks, then conversion to active stimulation for another 10 months **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). " "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.

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.	
Study design	Randomised controlled trial (RCT)
Scope	**Patient/population:** n=75 (see Table A5.2 in the technical report for more information) **Conditions indicated for use:** Patients with medically intractable chronic migraine (CM) **Intervention:** ONS – Adjustable stimulation (AS) group was instructed to maintain the stimulator in the ‘‘on’’ position and to adjust the device to minimize pain **Comparator:** Preset stimulation group and medically managed control group **Outcomes assessed:** • Reduction in headache days per months; • proportion of patients who achieved ≥ 50% reduction in headache days per month (responder rate); • a 3-point or greater reduction in average overall pain intensity; • disability and QoL; • 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. For most measures of disability and quality of life, no statistically significant

	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." "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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