Systematic Reviews referred by the NICE Interventional Procedures Programme on behalf of the NICE Interventional Procedures Advisory Committee (IPAC)

Title	**Stimulation of peripheral nerves for the treatment of refractory pain (including peripheral nerve field stimulation)**
Produced by	Birmingham and Brunel Consortium
Home unit	School of Health & Population Sciences, University of Birmingham
Authors	Yen-Fu Chen, Research Fellow, University of Birmingham George Bramley, Research Fellow, University of Birmingham Gemma Unwin, Research Fellow, University of Birmingham Janine Dretzke, Research Fellow, University of Birmingham David Moore, Senior Lecturer, University of Birmingham Dalvina Hanu-Cernat, Consultant Anaesthetist and Pain Specialist, University Hospitals Birmingham NHS Foundation Trust Sue Bayliss, Information Specialist, University of Birmingham Carole Cummins, Senior Clinical Lecturer, University of Birmingham Richard Lilford, Professor of Clinical Epidemiology, University of Birmingham
Contribution of authors	YFC was the main reviewer and was involved in all the processes of the review; GB conducted study selection, data extraction and assessment of risk of bias for RCTs and case series; GU assessed the risk of bias for RCTs, checked data from case series and collated spontaneous reports of adverse events; JD and DM were involved in study selection and advised on review methodology; DH-C provided clinical advice and feedback on report drafts; SB carried out searches of electronic databases and the internet. CC and RL provided senior advice and support throughout the review process.
Correspondence to	Dr Yen-Fu Chen, School of Health and Population Sciences, University of Birmingham, Birmingham B15 2TT
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Declared interests of the authors
The authors declare no potential conflict of interests.

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The contents and opinions contained in this report are the responsibility of the Authors.

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1 DEFINITION OF TERMS AND LIST OF ABBREVIATIONS

1.1 Definition of terms

Chronic pain

Pain that persists for more than three months or that outlasts the healing process.

Dermatome

An area of skin that is mainly supplied by a single spinal nerve.

Hyperalgesia

An increased sensitivity to pain, which may be caused by damage to sensory receptors or peripheral nerves.

Nerve root

The initial segment of a nerve leaving the central nervous system.

Neuropathic pain

Pain initiated or caused by a primary lesion or dysfunction in the nervous system.

Nociceptive pain

Pain caused by stimulation of peripheral nerve fibres that respond only to stimuli approaching or exceeding harmful intensity.

Paraesthesia

An abnormal sensation (such as tingling, burning, pricking, or numbness) that is *not* unpleasant, whether spontaneous or evoked.

Radicular pain

Pain that is ‘radiated’ along the dermatome (sensory distribution) of a nerve due to inflammation or other irritation of the nerve root.

1.2 List of abbreviations

CE	Conformité Européenee
CI	Confidence Interval
EAC	External Assessment Centre
FDA	Food and Drug Administration (USA)
GCAE	General Conditioning and Aerobic Exercise
IASP	International Association for the Study of Pain
ICHD-II	International Classification of Headache Disorders, 2nd Edition
IMMPACT	Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials
MHRA	Medicines and Healthcare Products Regulatory Agency
MIDAS	Migraine Disability Assessment
NICE	National Institute for Health and Clinical Excellence
NSAID	Non-Steroidal Anti-Inflammatory Drug
ONS	Occipital Nerve Stimulation
PENS	Percutaneous Electrical Nerve Stimulation
PNFS	Peripheral Nerve Field Stimulation
PNS	Peripheral Nerve Stimulation
POMS	Profile of Mood States
RCT	Randomised Controlled Trials
SD	Standard Deviation
SF-36	The Short Form (36) Health Survey
SNS	Sacral Nerve Root Stimulation
TENS	Transcutaneous Electrical Nerve Stimulation
VAS	Visual Analogue Scale

2 EXECUTIVE SUMMARY

Background

Management of chronic refractory pain that does not respond to standard treatments, such as physical, psychological and/or pharmacological therapies, remains a major challenge. Electrical stimulation of peripheral nerves has emerged as a potentially attractive option for treating chronic refractory pain because the procedures involved are less invasive compared with stimulation of the central nervous system or other surgical procedures. Many different techniques of peripheral neurostimulation have been developed to treat different types of pain. A comprehensive review of relevant literature on the use of peripheral nerve stimulation for treating chronic pain will assist the NICE Interventional Procedures Programme to select suitable techniques for developing guidance and to monitor the development of this rapidly emerging field.

Objectives

The objectives of this assessment are:

(1) To carry out a comprehensive search of published and unpublished literature relevant to the review topic.

(2) To summarise the evidence available for different treatment/ condition combinations of chronic pain and headache disorders.

(3) To evaluate the strength and weakness of evidence on efficacy and safety related to each type of nerve stimulation procedure for each type of refractory pain using standard systematic review methodology. Three areas in which CE marked devices are available are described in particular detail. These are: occipital nerve stimulation (ONS) for chronic migraine, implanted peripheral nerve field stimulation (implanted PNFS) for chronic back pain, and percutaneous electrical nerve stimulation (PENS) for chronic peripheral neuropathic pain.

(4) To produce an evidence map that provides an overall summary of the quantity and quality of evidence for each type of nerve stimulation procedure and refractory pain.

The Review Question

This review aims to answer the following question:

(a) What evidence is available in the literature with regard to stimulation of peripheral nerves for treating refractory pain?

(b) What techniques have been used, and for what types of refractory pain?

(c) What is the best available evidence concerning the efficacy and safety of each of the techniques for each type of refractory pain?

The Scope

This review focuses on the use of invasive procedures to stimulate peripheral nerve(s) or an area of the body to treat chronic pain. Three main types of peripheral neurostimulation are covered:

(1) **Implanted peripheral nerve stimulation (implanted PNS)** refers to stimulation of specific named nerve(s) using implanted devices. The most common forms of implanted PNS include occipital nerve stimulation (ONS) and sacral nerve root stimulation (SNS).
(2) **Peripheral nerve field stimulation (PNFS)** refers to stimulation of a painful area without naming specific nerve(s) or dermatomes.
(3) **Percutaneous electrical nerve stimulation (PENS)** refers to stimulation of individual nerve(s) or dermatomes using needle probes.

Electroacupuncture, which is practised on the basis of a different concept, is not included in this review. Stimulation of the central nervous system (e.g. brain neurostimulation or spinal cord neurostimulation), muscles (neuromuscular stimulation) and non-invasive electrical stimulation (such as transcutaneous electrical nerve stimulation [TENS]) are also excluded.

Given the wide scope of this review, three areas in which CE marked devices are available are highlighted for detailed assessment:

(1) ONS for chronic migraine;
(2) Implanted PNFS for chronic back pain;
(3) PENS for chronic peripheral neuropathic pain.

The Methods

The protocol for this review was registered with PROSPERO – registration number CRD42012002633,[1] and the methodology for this review is set out in Section 5 of this report.

Inclusion criteria

Given the broad scope of this review study selection was carried out in two phases. In the first stage systematic reviews, randomised controlled trials (RCTs), case series and case reports that evaluated the use of any of the aforementioned peripheral neurostimulation techniques for the treatment of chronic pain were included. As a large number of studies were identified, systematic reviews, RCTs and case series that included ten or more patients and had been published after 1980 were retained for further assessment and development of an evidence matrix in the second stage of the review.

Search Strategy

Searches of major electronic databases were completed in March-April 2012, and the search of the FDA website for safety issues was conducted in August 2012.

Study selection, data extraction and quality assessment of selected studies

Two reviewers independently assessed each study for inclusion using standardised criteria based on title and abstract, extracted data using standardised data table and assessed the quality of RCT studies. We did not assess the quality of systematic reviews or case series as the former was primarily used to identify primary studies and the latter was used to provide additional information that is considered insufficient for making inference about relative effectiveness and safety due to lack of a control group.

Data analysis and presentation

Quantitative synthesis of data was limited by different outcome measurements being used across RCTs and insufficient reporting of data in published literature. Where data permitted, meta-analysis was carried out using random effects model. A panoramic meta-analysis, in which treatment effects of different stimulation techniques across different pain conditions were compared, was carried out for RCT evidence. An evidence matrix was developed to summarise the available evidence for different combinations of stimulation techniques and pain conditions. Study characteristics and findings were presented in detail in summary tables accompanied by narrative text for the three highlighted areas for which CE marked

[1] Can be accessed at: http://www.crd.york.ac.uk/prospero/

devices are available. An overview of efficacy evidence from RCTs and safety evidence from larger case series was also provided

The Results

Quantity and quality of evidence

Searches of electronic databases retrieved 6,212 unique records, from which 22 RCTs were selected for detailed assessment. In addition, six RCTs, that were either ongoing or had been completed but had no results available in the public domain, were identified. Sixty case series that included at least ten patients were also assessed to provide additional information on adverse events and technical issues related to devices.

Of the 22 RCTs with at least some results available, four investigated occipital nerve stimulation (ONS), two assessed peripheral nerve field stimulation (PNFS), and 16 evaluated percutaneous electrical nerve field stimulation (PENS). The painful conditions under investigation include chronic migraine (ONS, three RCTs), mixed types of headache (PENS, one RCT), fibromyalgia (ONS, one RCT), chronic low back pain (implanted PNFS, one RCT; PENS, nine RCTs), and one RCT each for chronic neck pain (PENS), diabetic neuropathic pain (PENS), sciatica (PENS), Category IIIB chronic non-bacterial prostatitis /chronic pelvic pain syndrome (PENS), osteoarthritis of the hip (PENS) and of the knee (temporary PNFS), and hyperalgesia associated with various neuropathic condition (PENS). It is worth highlighting that only seven of the 22 RCTs fall within the three highlighted areas for this review, indicating a mismatch between CE marked devices and published literature on relevant indications.

The risk of bias of the RCTs varied between studies, with detection (outcome assessment) bias due to difficulty in blinding patients and failure to use intention to treat analysis (i.e. including all randomised patients in the analysis) being the major threats for most studies. Effectiveness of blinding and/or patients' expectation of treatment effectiveness were assessed only in two RCTs.

Results of the benefits (efficacy) and risks (safety), relating to key outcomes

Three areas in which CE marked devices are available were selected for detailed assessment.

(1) ONS for chronic migraine (Section 6.2.1.1.1)

Efficacy

Key efficacy evidence was obtained from three industry-sponsored, multicentre RCTs (Lipton et al. 2009, Saper et al. 2011, Silberstein et al. 2011) that included a total of 364 patients. However, two of the larger RCTs (Lipton et al. [n=140] and Silberstein et al. [n=157]) have only been published as conference abstracts at present – abstracts are not normally considered during IP Programme guidance development, but these may be worth noting given their sample sizes and the limited evidence available from full text publications. The duration of follow-up was relatively short (three months) for the blinded period of all three RCTs. Long-term, open-label follow-ups of up to one to three years are ongoing. The Saper et al. study was judged to be at high risk of attrition and outcome reporting bias.

Significantly greater reduction in headache days (days with headache pain intensity ≥3) per month was observed in the ONS group (6.7 ± 10.0 days) compared with the sham stimulation group (1.5 ± 4.6 days, p=0.02 vs. ONS) and medical management group (1.0 ± 4.2 days, p=0.008 vs. ONS) at 3-month follow-up in the Saper et al. study. Patients in the ONS group also experienced a significantly greater reduction in overall pain intensity. The differences between the ONS group and the two control groups were not statistically significant for most of the other outcomes.

Of the two RCTs that have only been reported in conference abstracts, no significant difference between groups was found in the Lipton et al. study, but significant difference (p<.01) between groups in favour of ONS compared with sham control was observed for all assessments in the study by Silberstein et al.

Safety

Two of the RCTs and two larger case series provided information on safety. Lead migration and infections are common and contributed to some of the reported serious adverse events. In the ONSTIM study, lead migration/dislodgement occurred in 24% (12/51) of patients over three months and infection occurred in 14% (7/51) and 4% (2/51) of patients for implantation sites of leads/ extensions and neurostimulators respectively. Pain and discomfort at various

sites related to implantation procedure and implanted devices was also reported. No permanent nerve damage or unexpected serious adverse events were observed.

Discussion

At present, two of the three RCTs (Lipton et al. 2009 and Silberstein et al. 2011) have only been published as conference abstracts, limiting the available information for assessment of risk of bias and data synthesis. The only fully published RCT (Saper et al. 2011) had a relatively small sample size (n=67) and was considered to be of high risk with regard to attrition bias and outcome reporting bias. The lack of published information prevented pooling of results across studies, and potential biases introduced by difficulty in blinding patients, attrition and outcome reporting, mean that the effectiveness of ONS has not been proven beyond doubt, based on currently published evidence.

The inclusion criteria with regard to medication overuse and the use of/ response to trial stimulation or nerve block varied between studies. These may have also influenced the size of effects observed in each study.

(2) Implanted PNFS for chronic low back pain / failed back surgery syndrome (Section 6.2.2.1)

Efficacy

One RCT (Barolat et al. 2011, conference abstract, full-text publication pending) recruiting 30 patients, and two case series (Verrills et al. 2009 and Yakovlev et al. 2011), including a total of 31 patients, were found. The vast majority of patients included in these studies had failed back surgery syndrome.

The RCT reported in a conference abstract was a feasibility study with a randomised period of only 22 to 37 days in which patients were crossed over between four different modality of trial stimulation. It showed a similar proportion of patients achieving pain relief of greater than 50% for standard and low frequency PNFS (57% and 53% respectively). The proportion was lower in the sub-threshold stimulation (27%) and minimal stimulation (14%) group. Among the 23 patients who proceeded to permanent implantation, the response (of greater than 50% pain relief) was maintained in 67% of the patients at 52 weeks.

Two retrospective case series (Verrills et al. 2009a and Yakovlev et al. 2011) reported significant reduction in pain and reduced use of analgesics at varied follow-up between 3 to 12 months. Yakovlev et al. reported 100% (18/18) of patients having greater than 50% reduction in VAS pain at 12 months. Verrills et al. reported a reduction in VAS pain on the 0-10 scale from a mean score of 7.42 (SD 1.16) before PNFS to a mean score of 3.92 (SD 1.72) over a mean follow-up period of seven months ($p<0.05$).

Safety

Information on safety was not mentioned in the conference abstract of the RCT. One case series reported no adverse events or complications (Verrills et al. 2009). Another case series reported a case of post-operative infection requiring removal of the stimulation system, which was subsequently re-implanted. Two-thirds (12/18) of patients required re-programming and three patients required additional education regarding recharge device.

Discussion

Published evidence regarding PNFS for chronic low back pain/ failed back surgery syndrome was limited. Only one short-term feasibility RCT and two larger case series were identified.

(3) PENS for chronic peripheral neuropathic pain (Section 6.2.3.2)

Efficacy

Three crossover RCTs, with a total of 145 patients, were identified. The RCTs investigated sciatica (Ghoname et al. 1999), diabetic neuropathic pain (Hamza et al. 2000), and surface hyperalgesia associated with various types of neuropathic pain conditions (Raphael et al. 2011).

All three RCTs reported significantly greater reduction in pain and improvement in other outcomes for PENS compared with sham PENS. Ghoname and colleagues (n=64) reported significant reduction in pain (measured on VAS 0-10) compared to baseline in both PENS (from 7.2 to 4.1, $p<.05$) and TENS (from from 7.0 to 5.4, $p<.05$) groups but not in the sham PENS group (from 6.6 to 6.1, $p>.05$). The reduction in PENS group was significantly greater than both the TENS and sham PENS groups ($p<.01$). Hamza and colleagues (n=50) also reported significantly greater reduction in VAS pain in the PENS group compared with the sham-PENS group (from 6.2 to 2.5, and 6.4 to 6.3 respectively during the first period of the study, $p<.05$). In a further trial, Raphael and colleagues (n=31) reported significantly greater reduction in pain measured on the 0-10 numerical rating scale (median, 3.9 vs. 0.1, $p<.0001$) and greater increase in pressure pain threshold measured by pressure algometry (310 vs. 8, $p=.007$) for the PENS group compared with the sham PENS group.

Safety

Two of the RCTs reported no occurrence of adverse events and another did not mentioned adverse effects.

Discussion

The duration of treatment and follow-up was short in the three RCTs. There was a lack of data on longer-term efficacy and safety. There was a larger volume of RCT evidence for the use of PENS for non-neuropathic pain (evidence presented elsewhere in the report).

Carryover effect was an issue in two of the RCTs (Ghoname et al. 1999, Hamza et al. 2000), which had a short washout period before crossover. In addition, the effectiveness of blinding was not assessed. Data from the third trial (Raphael et al. 2011) showed that, compared to data from the first treatment period, the combined 2-period data over-estimated treatment effect when effective blinding of patients could not be maintained after crossover.

Only one study (Raphael et al. 2011) used a CE marked PENS system. No serious adverse events were reported in the three RCTs.

Issues for consideration by the Interventional Procedures Advisory Committee

Synthesis of results to inform the Committee's decision making

- A large volume of evidence within the broad scope of peripheral nerve stimulation for chronic pain was identified, including 22 RCTs, 60 case series with ≥10 patients, and more than 100 smaller case series and case reports. However, there is a mismatch between the volume of published evidence and the availability of CE marked devices. Only seven of the RCTs and four of the larger case series were directly relevant to the three highlighted areas chosen according to CE mark certification. Furthermore, three of the seven RCTs have only been published as conference abstracts, which are usually excluded from the Interventional Procedures committee's assessment for efficacy and are only considered when they report serious adverse events.
- Most studies were carried out in specialist centres in the USA, although international multicentre trials are emerging.
- The published literature showed predominant (but not always) positive results for the use of various techniques of peripheral neurostimulation compared with sham stimulation for a variety of chronic pain, including headache disorders. The major threat for the validity of these findings is the difficulty in effectively blinding the patients due to the sensation induced by electrical currency and the lack of assessment of patients' expectation of treatment effectiveness. Despite the inevitable contribution of a placebo/ study effect and possible bias associated with ineffective blinding in many of the RCTs, there are signs suggesting that treatment effects observed in some of the trials of peripheral neurostimulation went beyond the influence of placebo effect/ treatment

credibility. These include observation of better efficacy over comparators for which treatment credibility was expected to be similar, and reporting of effect duration longer than was likely to be expected of a placebo effect.

Suggested further research or data collection (if appropriate)

- Assessment of patients' expectation of treatment effectiveness at baseline and the effectiveness of blinding during treatment in double-blind RCTs, and the association between these and observed/reported treatment outcomes.
- Development of novel methods to overcome the difficulty in blinding patients in RCTs that involve electrical stimulation.
- RCTs of using peripheral neurostimulation to treat painful conditions that are particularly difficult to manage and for which early case series and care reports have shown promising results, such as painful bladder syndrome/ interstitial cystitis, complex regional pain syndrome, and injuries to the brachial plexus. Multicentre collaboration is essential to ensure recruitment of sufficient number of patients and wider generalisability of results.
- Development of new devices or surgical techniques that reduce the incidence of lead migration and infection. The effectiveness of these devices/ techniques should be evaluated in RCTs.
- Establishment of a registry of peripheral neurostimulation to allow prospective and systematic collection of data on long-term effectiveness, safety and device durability.
- Organisation of workshops to provide guidelines to optimise design and reporting of future studies in this area.

3 BACKGROUND

3.1 Indications

This review focuses on refractory pain, which refers to chronic pain (persisting for at least three months) that does not respond to standard treatments. There are several types of chronic pain, classified using different criteria, but the fundamental distribution is between nociceptive pain (associated with damage to tissues such as muscle, skin and bone) and neuropathic pain (caused by primary lesions or dysfunction in the nervous system). Chronic pain can sometimes be a hybrid of these types, being related to both tissue damage and subsequent neural dysfunction. This review aims to cover all refractory pain. More detailed classifications of pain are based upon the Classification of Chronic Pain by the International Association for the Study of Pain (IASP) (1994 and subsequent revisions)[1] and the International Classification of Headache Disorders by the International Headache Society.[2]

3.2 Current treatment

Choice of treatment for chronic refractory pain depends on the type, severity and cause of the pain. Current standard treatments include physical, psychological and/or pharmacological therapies. Neurostimulation of the brain, spinal cord or peripheral nerves has been introduced as a treatment option for patients whose condition is unresponsive to other forms of treatment.

3.3 What the procedure involves

Since the first publication of peripheral nerve stimulation in 1967,[3] many techniques that utilise electrical stimulation of nerves for the relief of pain have been developed. The terminology used in the literature regarding electrical stimulation of nervous systems is varied and potentially confusing. We follow the taxonomy recently proposed by Levy in which neurostimulation procedures are classified as brain, spinal or peripheral neurostimulation.[4] In this report we use peripheral neurostimulation as an umbrella term to cover all the invasive techniques involving peripheral nerves or areas innervated by them, and broadly classify the techniques into three major categories: implanted peripheral nerve stimulation (implanted PNS), peripheral nerve field stimulation (PNFS), and percutaneous electrical nerve stimulation (PENS). The procedure for each is described below.

Implanted peripheral nerve stimulation (implanted PNS) refers to stimulation of specific named nerve(s) using implanted devices. An implanted PNS system usually consists of

leads (electrodes) that are placed in subcutaneous areas near the targeted nerves, a pulse generator that is usually implanted in a pocket in a separate area of the body, and extension lead(s) (and sometime adapters) that connect the leads and the pulse generator.

The devices and the implantation techniques may vary according to the nerve(s) to be stimulated. Common types of implanted PNS include occipital nerve stimulation (ONS); stimulation of trigeminal and related nerves or ganglion; stimulation of various nerves in the upper and lower extremity; and sacral nerve root stimulation (SNS). Some techniques can be carried out under local anaesthesia (with or without mild sedation) while others may require general anaesthesia. Early work on implanted PNS (e.g. those carried out before the 1980s) used simple wires with cuff-type electrodes (which were wrapped around the exposed segment of nerves) or button-type electrodes, but these are no longer used in interventional pain management.[5] Instead, paddle-type (flat) electrodes (sometimes called surgical leads) or cylindrical electrodes (sometimes called percutaneous leads) are more commonly used. The former requires open surgical placement, whereas the latter can be inserted percutaneously through an introducer needle (Tuohy needle). Fluoroscopic guidance and intraoperative test stimulation can be used to help correct positioning of the electrodes, which are then sutured/ anchored to subcutaneous tissue. An extension lead is tunnelled under the skin to a specific site in the body (usually the anterior chest, abdominal region or buttock) where a pulse generator or radiofrequency receiver is secured in a subcutaneous pocket. The patient uses a remote control (or programmer) to electrically stimulate the nerve, resulting in paraesthesia. The stimulation can be intermittent or continuous, and the stimulation system can be turned off or removed if desired.

Before permanent implantation of a stimulation system, electrodes can be temporarily placed subcutaneously and connected to an external pulse generator for a trial stimulation that may last several days or weeks.

Peripheral nerve field stimulation (PNFS) refers to stimulation of a painful area without targeting specific nerve(s) or dermatomes. The majority of PNFS reported in the literature utilises implanted electrodes (implanted PNFS). The devices and procedures for implanted PNFS are very similar to those of implanted PNS. The main distinction is that it is a painful area, rather than a specific nerve (or nerves) that is identified and stimulated in PNFS. The wider coverage of an area means a larger number of leads (e.g. up to four compared to one or two in the implanted PNS) with broader contact areas may be required. This also means that stimulation from each lead can be programmed independently to suit the needs of the individual patient. However the larger number of leads also requires a higher power supply

from the impulse generator. Both chargeable and non-rechargeable generators are available.

In addition to the implanted PNFS described above, temporary PNFS was also reported in the literature where a particular device with microarrays of needle probes embedded within a patch-type electrode can be placed over the skin of a painful area.

Percutaneous electrical nerve stimulation (PENS) refers to stimulation of individual nerve(s) or dermatomes using needle probes. Various numbers of pairs of fine gauge needles are inserted into soft tissues near the targeted nerve(s) or in the dermatomes where pain occurs. The needles are connected to a low-voltage pulse generator and an electrical current is then applied to generate a sensation of paraesthesia without causing muscle contraction. The duration of treatment varies but each session typically lasts between 15 and 60 minutes.

In the medical literature the distinction between the three types of techniques (implanted PNS, PNFS and PENS) is not always clear. As the number of targeted nerves (and thus the area covered by the stimulation) increases, the boundary between PNS and PNFS becomes vague. PENS could be considered as a temporary form of either PNS or PNFS depending on what and how many nerves or dermatome areas are targeted. Readers are reminded that whilst an attempt has been made to use the terminology described above consistently in this report, these terms have often been used interchangeably and sometimes inconsistently in the literature. As a result, the terms used in this report do not necessarily reflect the terms used in the original publications of cited studies.

Implanted PNS, PNFS and PENS are developed on the basis of neurophysiology and are believed to provide pain relief by blocking local pain pathways and releasing endorphins. Electroacupuncture shares similarity with PENS in terms of the use of needles to deliver electrical stimulation underneath the skin. However, its practice is based on the regulation of ‘qi’ and stimulation of acupoints according to the theory of traditional Chinese medicine rather than stimulation of peripheral nerves. Given this fundamental difference electroacupuncture is not included in this review. Stimulation of the central nervous system (e.g. brain neurostimulation or spinal cord neurostimulation), muscles (neuromuscular stimulation) and non-invasive electrical stimulation (such as transcutaneous electrical nerve stimulation [TENS], which delivers high frequency, low intensity stimulation using surface electrodes,[6] and acupuncture-like TENS [low frequency, high-intensity stimulation]) are also excluded.

3.4 Other relevant guidance

Potentially relevant guidance issued by NICE include:

(1) Management of chronic pain and chronic conditions that cause pain:

- CG59 Osteoarthritis: The care and management of osteoarthritis in adults.
- CG88 Low back pain: Early management of persistent non-specific low back pain.
- CG96 Neuropathic pain: The pharmacological management of neuropathic pain in adults in non-specialist settings.
- CG126 Management of stable angina.

(2) Neurostimulation for chronic pain:

- TA159; Spinal cord stimulation for chronic pain of neuropathic or ischaemic origin.
- IPG381; Deep brain stimulation for intractable trigeminal autonomic cephalalgias.
- IPG382; Deep brain stimulation for refractory chronic pain syndromes (excluding headache).

(3) Neurostimulation for other conditions:

- IPG50; Vagus nerve stimulation for refractory epilepsy in children.
- IPG64; Sacral nerve stimulation for urge incontinence and urgency-frequency.
- IPG99; Sacral nerve stimulation for faecal incontinence.
- IPG278; Functional electrical stimulation for drop foot of central neurological origin.
- IPG307; Intramuscular diaphragm stimulation for ventilator-dependent chronic respiratory failure due to neurological disease.
- IPG330; Vagus nerve stimulation for treatment-resistant depression.
- IPG362; Percutaneous posterior tibial nerve stimulation for overactive bladder syndrome.
- IPG395; Percutaneous tibial nerve stimulation for faecal incontinence.

(4) Other interventional procedures for chronic pain:

- IPG12; Percutaneous vertebroplasty.
- IPG31; Endoscopic laser foraminoplasty.
- IPG83; Percutaneous intradiscal radiofrequency thermocoagulation for lower back pain.
- IPG173; Percutaneous disc decompression using coblation for lower back pain.
- IPG234; Laparoscopic uterine nerve ablation (LUNA) for chronic pelvic pain.
- IPG285; Ultrasound-guided regional nerve block.
- IPG311; Extracorporeal shockwave therapy for refractory plantar fasciitis.
- IPG321; Lateral (including extreme, extra and direct lateral) interbody fusion in the lumbar spine.
- IPG333; Therapeutic endoscopic division of epidural adhesions.
- IPG357; Percutaneous intradiscal laser ablation in the lumbar spine.
- IPG366; Non rigid stabilisation techniques for the treatment of low back pain.

In a guideline issued by the British Association for the Study of Headache in 2010,[7] the implantation of an occipital nerve stimulator was mentioned as one of the surgical options for the management of cluster headache under clinical investigation at specialist centres.

4 THE REVIEW QUESTION

The aim of the systematic review was to provide a comprehensive synthesis of evidence concerning the efficacy and safety of stimulation of peripheral nerves for the treatment of refractory pain, in order to inform the development of NICE Interventional Procedure (IP) guidance.

The specific objectives were:

(1) To carry out a comprehensive search of published and unpublished literature relevant to the review topic.

(2) To summarise the evidence available for different treatment/ condition combinations of chronic pain and headache disorders.

(3) To evaluate the strength and weakness of evidence on efficacy and safety related to each type of nerve stimulation procedure for each type of refractory pain, using standard systematic review methodology. Three areas in which CE marked devices are available are described in particular detail: occipital nerve stimulation (ONS) for chronic migraine, implanted peripheral nerve field stimulation (implanted PNFS) for chronic back pain, and percutaneous electrical nerve stimulation (PENS) for chronic peripheral neuropathic pain.

(4) To produce an evidence map that provides an overall summary of the quantity and quality of evidence for each type of nerve stimulation procedure and refractory pain.

These objectives can be translated into three main review questions:

(a) What evidence is available in the literature with regard to stimulation of peripheral nerves for treating refractory pain?

(b) What techniques have been used, and for what types of refractory pain?

(c) What is the best available evidence concerning the efficacy and safety of each of the techniques for each type of refractory pain?

5 METHODS

5.1 Identification of evidence

The protocol for this systematic review was registered with PROSPERO – registration number CRD42012002633.

Search methods

A scoping search was initially carried out to identify synthesised evidence (systematic reviews, health technology assessment reports, and evidence-based guidelines), which provided an idea of the volume of literature on the topic. Searches for primary studies were then conducted in order to capture as broad a range of studies as possible (randomised controlled trials [RCTs], non-randomised controlled studies, case series, and case reports). No study design filters were used. In addition, unpublished evidence, information from ongoing studies and from conference proceedings was sought.

Databases and search strategies

Databases outlined in NICE IP Programme methods guide (NICE 2007) were searched as follows:

- The Cochrane Library (Wiley), including the Cochrane Database of Systematic Reviews (CDSR) 2012 Issue 3 of 12, Database of Abstracts of Reviews of Effects (DARE) 2012 Issue 1 of 4, and Health Technology Assessment (HTA) database 2012 Issue 1 of 4.
- The Cochrane (Wiley) CENTRAL Register of Controlled Trials 2012 Issue 3 of 12, MEDLINE (Ovid) 1946 – March week 1 2012, MEDLINE In Process (Ovid) at 14 March 2012, EMBASE (Ovid) 1980 – 2012 week 10, and CINAHL (EBSCO) 1937 – 20 March 2012.
- The ZETOC (Mimas) database, and Conference Proceedings Citation Index (ISI Web of Knowledge) for conference proceedings up to 22 March 2012.
- Current Controlled Trials metaRegister, NIHR Clinical Research Network Portfolio, WHO International Clinical Trials Registry Platform (ICTRP), and ClinicalTrials.gov for ongoing studies at 21 March 2012.

Search strategies used are shown in Appendix 1.

Searches were restricted to human studies. No language or date limits were applied.

Additional searches

In addition to searches of electronic databases, reference lists of studies included in the review were checked to identify further papers.

A search of internet sites was also conducted on 21st March 2012, with a particular focus on the websites of the following organisations:

- National Institute for Health and Clinical Excellence (NICE);
- The Australian Safety and Efficacy Register of New Interventional Procedures (ASERNIP-S);
- Medicines and Healthcare products Regulatory Agency (MHRA);
- US Food and Drug Administration (FDA);
- Association of Anaesthetists of Great Britain and Ireland;
- British Society of Neurological Surgeons;
- British Pain Society;
- International Association for the Study of Pain (IASP);
- International Headache Society.

Manufacturers/ sponsors of devices used for peripheral nerve stimulation were identified from these additional searches and through contacts with clinical experts. Information on unpublished RCTs was sought from identified manufacturers/ investigators but no data was received.

The FDA database was rechecked for reports of adverse events on 14th August 2012.

5.2 Inclusion and exclusion of studies

Given the broad scope of the review, study selection was carried out as a two-stage process: the first stage aimed to identify all literature relevant to the intervention (peripheral nerve stimulation) and population (patients with chronic refractory pain) under consideration; the second stage aimed to select evidence that was most relevant (of highest internal validity and/ or clinical relevance) for more detailed assessment. The approach is consistent with the methods specified in NICE's guidance for the IP Programme.[8]

Records retrieved from searches of electronic databases were imported into a reference management program, which was able to filter out some duplicated records. Further duplicated records were deleted manually. The remaining records were independently screened by two reviewers using the inclusion/ exclusion criteria listed in Table 1.

Table 1 Selection criteria for the first stage of study selection

	Inclusion criteria	Exclusion criteria
Population	Patients with chronic pain.	Patients with acute pain; mixed population of acute and chronic pain where results could not be disaggregated.
Interventions	Any invasive techniques of stimulation of peripheral nerves.	Non-invasive techniques of electrical stimulation (e.g. TENS); stimulation of brain or spinal cord; neuromuscular stimulation; electroacupuncture.
Comparators	Any; also include studies with no comparator group.	N/A
Outcomes	Pain; other outcomes that could be influenced by pain; safety outcomes. These include: pain relief (immediate and long-term); time to pain relief; pain recurrence rates; time to pain recurrence; adverse events/ complications/ technical failures/ complications of procedure; quality of life.	Studies that focused on outcomes other than pain; studies which did not report any patient related outcomes.
Study design	Any study design that systematically synthesised or assessed patient outcomes, including systematic reviews*, RCTs, non-randomised controlled studies, uncontrolled before-and-after studies / case series, case reports.	Narrative reviews, commentaries, editorials and letters (unless including case reports or new data); economic evaluations and cost studies; in-vitro studies; animal studies.

** Defined as a review of literature in which a systematic search of electronic database(s) and an assessment of methodological quality or risk of bias of included studies were carried out*

Given the large number of potentially relevant studies identified, RCTs (irrespective of publication status) and published case series that included at least ten patients (referred to as larger case series in the rest of this report for brevity) were retained for evidence mapping and further assessment. Case series published before 1980, case series containing less than ten patients, case reports (except those specifically reporting adverse events), articles published in non-English languages (36 studies tagged), narrative reviews, and studies published only as conference abstracts (except those reporting an RCT) were tagged but were not reviewed further.

RCTs and case series retained in stage 1 were mapped to an evidence matrix (see section 5.5) showing different combinations of peripheral neurostimulation techniques and types of pain.

5.3 Quality assessment strategy

Quality assessment of RCT studies was carried out using Cochrane Collaboration's Risk of Bias tool.[9] Information regarding the effectiveness of blinding and patients' expectation of treatment were also noted where reported. Two additional items were assessed for crossover trials: (1) whether analysis was carried out using methods for paired data; and (2) whether carryover effect was assessed and/ or whether the duration of washout period was justified.[10] Quality assessment was carried out by a first reviewer (either YFC or GB) and all quality assessments were verified by a second reviewer (GU). Discrepancies were resolved through discussion.

Due to time constraints we were not able to assess the quality of case series. These studies were mainly used to provide information on adverse effects and technical issues related to devices and procedures. The lack of a control group allowing an estimate of relative effects is an inherent limitation that applies to all case series. Although we identified a large number of literature reviews, most of them did not state explicit search strategy. Even fewer assessed the risk of bias of included studies. On the other hand the scopes of some identified systematic reviews differed from this review (e.g. including deep brain stimulation, spinal cord stimulation, and/ or TENS) and it was difficult to integrate their findings into this review. We have therefore mainly used these reviews to identify primary studies that meet the inclusion criteria for this review.

5.4 Data abstraction strategy

Data abstraction was carried out for each RCT and case series where n ≥ 10 using standardised data tables (see Appendix 4 and Appendix 6 respectively). Data collected included features of study design and trial participants, techniques of nerve stimulation, funding sources, key effectiveness findings, and adverse events. YFC and GB carried out data extraction for each RCT using a standardised data table. RCTs were split between the two reviewers as first data extractors, and each then retrospectively quality assured the other by acting as the second data extractor. GB was first data extractor for case series and GU quality assured as second data extractor. Discrepancies were resolved through discussion.

5.5 Presentation of evidence

Given the diversity of stimulation techniques and painful conditions reported in the literature, we first constructed an evidence matrix to allow mapping of identified studies in stage 1 of the review and to guide the structure and presentation of the report. The development of the evidence matrix took into account the anatomy of the nervous system, established classifications of chronic pain and headache disorders, the link (known or postulated) between individual nerves and these painful conditions, and the techniques of peripheral neurostimulation that have been developed to treat these conditions. The matrix was developed and revised iteratively as the review proceeded. The final matrix is presented in Section 6.1. The matrix started with implanted PNS, using major targeted nerves listed as headings and associated types of pain as subheadings. The sections for PNFS and PENS follow. As these techniques usually targeted multiple nerves or a painful area without naming specific nerves, each of these two techniques were broadly divided into neuropathic pain and other chronic pain, followed by specific types of pain (and nerves stimulated where applicable). The separation of neuropathic pain from other types of pain was done to facilitate the development of NICE IP guidance (which takes into account CE mark certifications of available devices, some of which specify neuropathic pain) and also on the theoretical argument that neuropathic pain may be more likely to respond to peripheral neurostimulation.

Assessment of efficacy focused on evidence from RCTs. The characteristics of each RCT and its risk of bias were tabulated. Quantitative synthesis focused on pain and health-related quality of life, which were the most common outcome measures used in published studies. Analyses of additional outcomes, such as frequency of headaches, improvement in physical activity, and sleep quality were also performed where data permitted.

For continuous outcomes the mean difference between groups in change from baseline (or in the final score if baseline score was not available) was computed. Where the standard deviation (SD) for the change was not reported it was imputed using the SD of the baseline and final score assuming a correlation coefficient of 0.5.[11] Risk ratio was calculated for binary outcomes. Many of the included RCTs were crossover trials, for which, ideally, data from a paired analysis should be used. However, such data was rarely reported and so in the absence of paired data, we performed the analysis by comparing treatment effects for different treatment modalities (observed during different treatment periods) as if they were from parallel-group trials. This pragmatic approach was likely to result in confidence intervals being wider than they should have been, but may also have masked potentially important heterogeneity between studies.[12]

Where appropriate, meta-analysis was carried out using random effects modelling. Considering the above unit-of-analysis issue and the differences between studies in patient populations, stimulation techniques, comparators, outcome measures, duration of intervention and follow-up, and other study design features, quantitative pooling of data across studies may not be appropriate in many cases. Forest plots were mainly provided to facilitate visual inspection of results and illustrate heterogeneity between studies in such instances. Where provided, pooled estimates across different stimulation techniques should be considered exploratory, akin to the concept of a general hypothesis testing of the effectiveness of peripheral neurostimulation in a panoramic meta-analysis.

Given limited evidence on safety from RCTs, additional information on adverse events and technical issues were collected from large case series and summarised in tables. Reports of serious adverse events from MHRA and FDA were also highlighted.

6 RESULTS

6.1 Quantity and quality of research available

The process for literature search and study selection is summarised in Figure 1. Searches of electronic databases retrieved 6,212 unique records from which 22 RCTs were selected for detailed assessment. In addition, six RCTs, that were either ongoing or had been completed but with no results available in the public domain, were identified. Sixty case series that included at least ten patients were also assessed to provide additional information on adverse events and technical issues related to devices. The RCTs and case series were mapped to an evidence matrix, shown in Table 2.

Figure 1 Flow diagram for study selection process

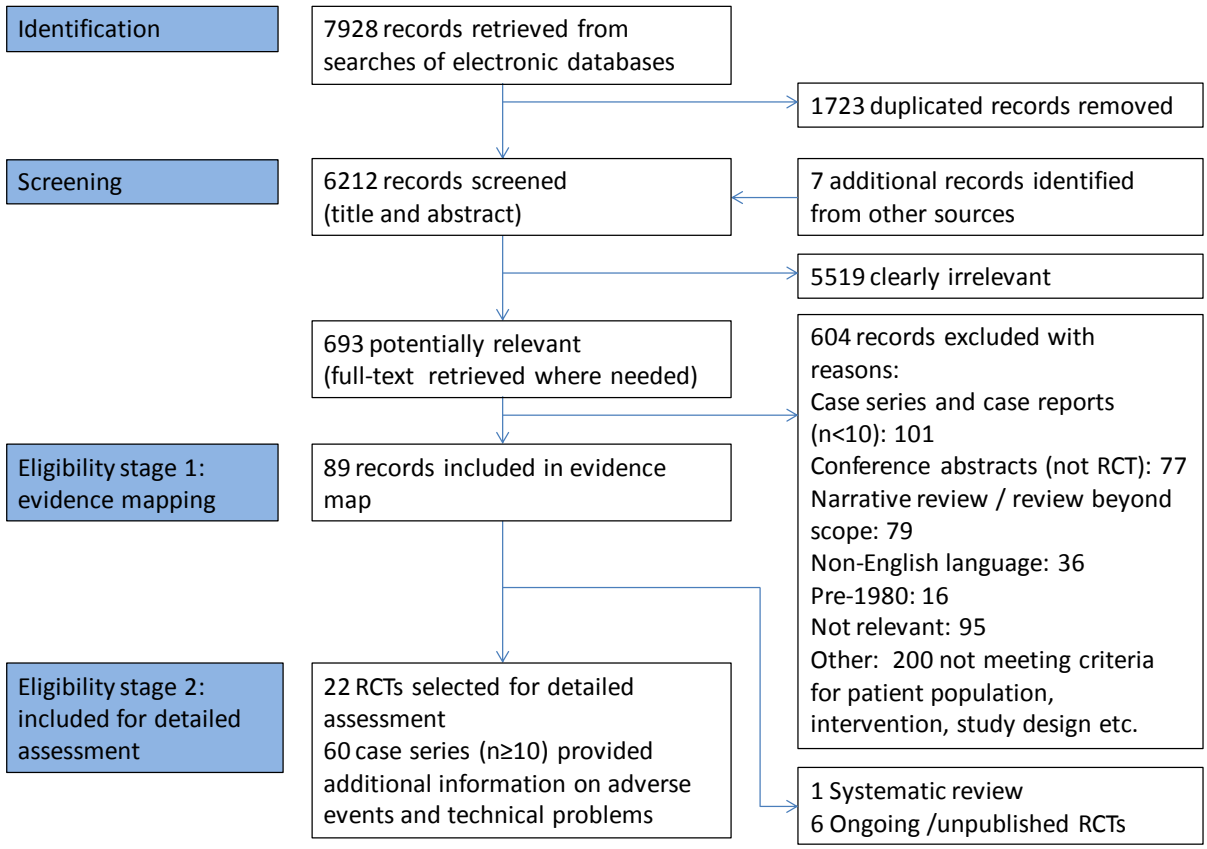


Table 2 Evidence matrix for peripheral neurostimulation

Implanted peripheral nerve stimulation (Implanted PNS)	No. of systematic reviews and RCTs	No. of case series (n≥10)
Occipital nerves	1 systematic review (& 1 rapid NICE review)	-
Chronic migraine / transformed migraine [Highlighted area 1 for this report]	6 RCTs (1 fully published, 2 published as abstracts only, 2 ongoing & 1 unpublished)	2
Cluster headache	1 ongoing RCT	4
Neuralgias, headaches and craniofacial pain associated with occipital nerves	-	6
Mixed types of headaches	-	4
Fibromyalgia	2 RCTs (1 abstract only, 1 publication pending)	1
Gasserian ganglion - trigeminal neuropathic pain and facial pain **Trigeminal nerves (nerve root)** - facial pain associated with trigeminal nerve injury **Supraorbital and/or infraorbital nerves** – neuralgia, craniofacial pain associated with trigeminal nerves/branches	- - -	5 1 2
Sphenopalatine ganglion – chronic migraine	1 ongoing RCT	1
Vagus nerve - migraine	-	1
Other nerves of the upper and lower extremity		
Complex regional pain syndrome (CRPS); pain in upper and lower extremity	-	5
Various nerves with injuries associated with surgical procedures, trauma or chemical assault	-	3
Sacral nerve (root)		
Painful bladder syndrome/interstitial cystitis	-	12
Chronic pelvic pain	-	3
Chronic anal pain	-	1
Peripheral nerve field stimulation (PNFS, implanted or temporary)		
Implanted PNFS		
10 Chronic low back pain / failed back surgery syndrome [Highlighted area 2 for this report]	1 RCT (abstract only)	2
Post surgery hip pain	-	1
Mixed types of pain	-	4
Temporary PNFS		
Osteoarthritis of the knee [temporary percutaneous stimulation]	1 RCT	-

Percutaneous electrical nerve stimulation (PENS, temporary stimulation using fine gauge needle)		
Headache disorders - Migraine, tension type headache, post-traumatic headache	1 RCT	-
Peripheral neuropathic pain [Highlighted area 3 for this report]		
Sciatica	1 RCT	-
Diabetic neuropathic pain	1 RCT	-
Surface hyperalgesia associated with various neuropathic pain	1 RCT	-
Other chronic pain		
Chronic neck pain	1 RCT	-
Chronic low back pain	9 RCTs	1
Osteoarthritis of the hip	1 RCT	-
Interstitial cystitis (posterior tibial nerve)	-	1
Chronic pelvic pain	-	2
Class IIIB chronic prostatitis/chronic pelvic pain (posterior tibial nerve)	1 RCT	

6.2 Summary of evidence for individual techniques

In this section we briefly summarise current level of evidence for each type of stimulation technique (implanted PNS, PNFS, PENS) based on the structure of the evidence matrix shown in Table 2 above. In order to support the development of guidance for the NICE IP Programme we provide more detail on three highlighted areas in which CE marked devices are available: ONS for chronic migraine, implanted PNFS for low back pain, and PENS for peripheral neuropathic pain.

6.2.1 Implanted peripheral nerve stimulation (implanted PNS: use of implantable devices to stimulate a specific nerve or nerves)

As shown in Table 3 on the next page, the main application of implanted PNS documented in the literature includes ONS, stimulation of trigeminal and related nerves/ganglion, stimulation of sphenopalatine ganglion, stimulation of vagus nerve, stimulation of nerves in the upper and lower extremity, stimulation of various nerves with injuries associated with surgical procedures, trauma or chemical assault, and sacral nerve (root) stimulation (SNS). CE marked devices are available for ONS for the treatment of chronic migraine and therefore this subsection is highlighted with more detailed information provided.

6.2.1.1 Occipital nerve stimulation (ONS)

ONS involves temporary or permanent placement of subcutaneous electrodes to stimulate peripheral nerves in the occipital region (the area innervated by spinal nerves C2 and C3). The main target nerve is the greater occipital nerve. The lesser occipital nerve and

supraorbital and infraorbital nerves (branches of trigeminal nerve) are also sometimes stimulated simultaneously.

One systematic review of ONS for headache disorders,[13] and a rapid literature review (IP699) conducted by NICE in 2008 [14] were identified. Their methodology and findings are summarised in Table 4. As both reviews were published before any RCTs investigating ONS became available, we mainly used findings from these reviews in our assessment of safety.

Table 3 Identified evidence for implanted peripheral nerve stimulation (implanted PNS)

Implanted peripheral nerve stimulation (Implanted PNS)	No. of systematic reviews and RCTs	No. of case series (n≥10)
Occipital nerves	1 systematic review (&1 rapid NICE review)	-
Chronic migraine / transformed migraine [Highlighted area 1 for this report]	6 RCTs (1 fully published, 2 published as abstracts only, 2 ongoing & 1 unpublished)	2
Cluster headache	1 ongoing RCT	4
Neuralgias, headaches and craniofacial pain associated with occipital nerves	-	6
Mixed types of headaches	-	4
Fibromyalgia	2 RCTs (1 abstract only, 1 publication pending)	1
Gasserian ganglion - trigeminal neuropathic pain and facial pain **Trigeminal nerves (nerve root)** - facial pain associated with trigeminal nerve injury **Supraorbital and/or infraorbital nerves –** neuralgia, craniofacial pain associated with trigeminal nerves/branches	- - -	5 1 2
Sphenopalatine ganglion – chronic migraine	1 ongoing RCT	1
Vagus nerve - migraine	-	1
Other nerves of the upper and lower extremity		
Complex regional pain syndrome (CRPS); pain in upper and lower extremity	-	5
Various nerves with injuries associated with surgical procedures, trauma or chemical assault	-	3
Sacral nerve (root)		
Painful bladder syndrome/interstitial cystitis	-	12
Chronic pelvic pain	-	3
Chronic anal pain	-	1

Table 4 Key features and findings of published systematic review and rapid review of occipital nerve stimulation

Jasper and Hayek 2008,[13] Implanted occipital nerve stimulators	
Scope	Occipital nerve stimulation for benign headache
Literature search	PubMed/MEDLINE and EMBASE 1966 – 2007. English language only.
Studies included	Included 4 observational prospective case series, 8 retrospective case series, 3 case reports, 3 narrative reports, and 3 technical reports. No RCTs were identified.
Assessment of risk of bias	The Agency for Healthcare Research and Quality criteria were used to provide a study quality score of up to 11. Most studies were rated between 7 to 9 (range 6 to 10).
Key efficacy findings	All included studies reported positive outcomes covering pain relief, reduced frequency, intensity and duration of headaches with reduced medication consumption. Treatment success was reported for 70% to 100% of patients. Reduction of pain is significant and rapid for transformed migraine and occipital headaches. Improvement may be less dramatic and may take several months to achieve for cluster headache.
Key safety findings	No long-term adverse events occurred. Short-term incidents included infection, lead displacement and battery depletion.
NICE 2008 (IP699 Overview),[14] Occipital nerve stimulation for intractable headache	
Scope	Occipital nerve stimulation for intractable headache
Literature search	MEDLINE, PREMEDLINE, EMBASE, Cochrane Library and other databases were searched up to March 2008. Trial registries and the Internet were also searched. No language restriction
Studies included	Included 8 case series of sample sizes between 8 and 20 and identified 2 ongoing trials.
Assessment of risk of bias	Not stated.
Key efficacy findings	Substantial reduction in pain (≥75% pain relief) was reported in 25% to 75% of patients. Headache frequency was decreased by 29% to 80% and headache intensity/severity reduced by 34% to 44%. Other reduction in pain measured using McGill Pain Questionnaire. Visual analogue scale was also reported. Patient satisfaction ranged from 88% to 100%.

Key safety findings	Electrode or lead migration was the most commonly reported adverse event. A few cases of infection and sepsis were reported, some of which required removal of the stimulation system with or without subsequent re-implantation. Removal of stimulation system due to severe pain at the implantable pulse generator site, unbearable paraesthesia, loss of stimulation effect, or significant improvement in pain was also reported.

ONS has been used for various types of headache disorders, including chronic/transformed migraine, cluster headache, and neuralgias, headaches and craniofacial pain associated with occipital nerves or areas innervated by them. In addition, ONS has also been investigated in patients with fibromyalgia. We present evidence for the treatment of chronic/transformed migraine in more detail below.

6.2.1.1.1 ONS for chronic/transformed migraine [Highlighted area 1 for this report]

Chronic migraine was defined in the International Classification of Headache Disorder 2nd edition (ICHD-II) as "migraine headache occurring on 15 or more days per month for more than 3 months in the absence of medication overuse". Transformed migraine refers to chronic migraine that developed from episodic migraine with increasing headache frequency but decreasing severity of migraine features. This term was proposed after the publication of an earlier version of ICHD (ICHD-I), but was not formally adopted in ICHD-II. Both chronic migraine and transformed migraine have been used in the literature, sometimes interchangeably, and with or without specific exclusion of migraine associated with medication overuse. We use the term 'chronic migraine' in the rest of this report for consistency, but use it to include chronic or transformed migraine in the various manifestations.

Efficacy

Three manufacturer-sponsored multicentre RCTs (Lipton et al. 2009, Saper et al. 2011, Silberstein et al. 2011),[15-17] that included a total of 364 patients, provided data on short-term efficacy. Only the Saper et al. study (n=67) has been published in full [16]; the other two trials have only been published as conference abstracts at the time of this report (Lipton et al. 2009, Silberstein et al. 2011),[15;17] although a manuscript for the trial by Silberstein et al. is being submitted for publication (personal communication, Professor Silberstein). In addition, two published case series, with a total of 35 patients, were also included. The characteristics and key findings of these studies are summarised in Table 5. Furthermore, three unpublished, single-centre RCTs (two ongoing, one completed but not yet published) recruiting approximately 30 patients each were also identified.[18-20]

All three multicentre RCTs included an initial blinded phase of 12 weeks, during which patients received active or sham stimulation according to randomised allocation. The blinded phase was followed by an open label phase of one to three years during which participants in the sham control group also switched to active stimulation (and thus there was no control group for longer-term follow-up). Sample sizes ranged from 67 to 157. The Saper et al. study also included a third arm of medication management group, which could be regarded as an open-label control group given that the patients were already refractory to medication management.[16] The Lipton et al. study and the study by Silberstein et al. were conducted in the USA.[15;17] The majority of study centres in the Saper et al. study were also located in the USA, but it also included a centre from the UK (which contributed 12 of the 66 patients analysed at three months).[16] Both case series were from the USA and shared common investigators. It was not clear whether any patients were included in both case series.

Trial stimulation was carried out in the Lipton et al. study, though a good response was not a criterion for inclusion in the trial.[15] Occipital nerve block was performed in the Saper et al. study prior to randomisation and a reduction of 50% in migraine pain was required for a patient to proceed to randomisation.[16] Eight of the patients who did not meet this response criterion were nevertheless included in an additional (not randomly allocated) 'ancillary group' and were implanted with a stimulator. For the study conducted by Silberstein and colleagues it was not clear whether trial stimulation or nerve block was performed prior to intervention or was part of the eligibility criteria.[17] The Lipton et al. study included both migraine with or without aura and chronic migraine, and included patients with or without medication overuse.[15] The Saper et al. study included only chronic migraine patients without medication overuse.[16] Baseline migraine days per month were similar for the studies by Lipton et al. and Saper et al. (23 vs. 20).[15;16] Details of patient classification and migraine frequency were not reported in the abstract by Silberstein et al.[17]

In the fully published Saper et al. study, patients and outcome assessors were blinded with regard to allocation between ONS and sham control, but allocation to the medication management group could not be blinded.[16] The Saper et al. study was judged to be at unclear or high risk for detection bias (patients in the active stimulation group received a programmer for controlling their stimulator, whereas patients in the sham control group did not; and the medication management group was not blinded); high risk for attrition bias (drop out 15% [5/33] in ONS group, 6% [1/17] in sham control group, and 0% in medication management group); and outcome reporting bias (numerical data for the sham control group

was not reported for Profile of Moods States, Migraine Disability Assessment [MIDAS], functional disability scale and SF-36, as difference was not statistically significant).[16]

Quality assessment of the other two RCTs (Lipton et al. 2009, Silberstein et al. 2011) was hampered by paucity of published information in the conference abstracts.[15;17] They were described as double-blind in the conference abstracts, but no further detail was provided.

Table 5 Characteristics and main findings of published and ongoing RCTs and published case series of ONS for chronic migraine

RCT				
Study & country	**Comparison & sample size**	**Patient selection and trial stimulation; baseline characteristics**	**Outcome measures and results**	**Comments**
Saper et al. 2011 [16] (ONSTIM study) Multicentre, USA, Canada and UK Single-blind 12 weeks, open label 3 years (ongoing) NCT00200109	ONS vs. sham stimulation vs. medication management (vs. ancillary - ONS in patients not responding to occipital nerve block) 110 screened 67 randomised (+ 8 assigned) 61 (+5) analysed	Required at least a 50% reduction in migraine pain with occipital nerve block; those who did not respond received ONS in a non-randomised 'Ancillary' group. Mean age: 43 Female: 80% Baseline migraine days per month: 20 ± 7.6	Reduction in headache days (in which overall headache pain intensity ≥3 out of 10) per month at 12 weeks: ONS (n=28) 27.0 ± 44.8% (6.7 ± 10.0 days) Sham (n=16) 8.8 ± 28.6% (1.5 ± 4.6 days) Medication (n=17) 4.4 ± 19.1% (1.0 ± 4.2 days) Ancillary (n=5) 39.9 ± 51.0% (9.1 ± 12.3 days) Responder rate (≥50% drop in headache days per month or a ≥3-point drop in pain intensity from baseline) at 12 weeks: ONS 39% (11/28), sham 6% (1/16), medication 0% (0/17), ancillary 40% (2/5)	Sponsored by Medtronic; high risk of detection bias, attrition bias and outcome reporting bias Also reported decrease in overall pain intensity, reduction in days with prolonged, severe headache per month, improvement in Profile of Moods States, functional disability, Migraine disability assessment (MIDAS) average grade, and SF-36
Lipton et al. 2009 [15] (PRISM study) Multicentre, USA Double-blind 12 week, open label 1 year **[Conference abstract only]**	ONS vs. sham stimulation 179 screened 140 randomised 132 implanted 125 analysed	Included migraine with and without aura, and chronic migraine. Trial stimulation was performed but a good response was not an inclusion criterion. Mean age: not reported Female: not reported Baseline migraine days per month: 23 ± 5.4	Change from baseline in migraine days per month at 12 weeks (mean ± SD): ONS (n=63): -5.5 ± 8.7. Sham (n=62): -3.9 ±8.2 p=0.29	Sponsored by Boston Scientific; not fully published - unable to assess risk of bias
Silberstein et al. 2011 [17] Multicentre, USA Double-blind 12 weeks, open label 1 year **[Conference abstract only – full publication pending]**	ONS vs. sham stimulation 157 randomised 153 analysed	Information not available	ONS vs. sham stimulation at 12 weeks Decrease in MIDAS headache days: 22.5 vs. 3.4 Improvement in total MIDAS scores: 64.6 vs. 20.4 Improvement in Pain and Distress Scale: 13.3 vs. 5.5 Decrease in VAS scores: 14.1 vs. 7.0, 30% reduction in VAS: 35.2% vs. 11.5% Reported improved QoL: 66.7% vs.17.2%	Sponsored by St. Jude Medical Neuromodulation; not fully published – unable to assess risk of bias
Goadsby 2011 [19] (PRISM UK study) Single centre, UK Double-blind 12 weeks, open label 1 year NCT00747812	ONS vs. sham stimulation 25 (estimated enrolment)	Information not available	Migraine frequency and severity Frequency of adverse events Medication use	Sponsored by Boston Scientific; **ongoing trial**
Gerardo 2011 [18] Single centre, Italy Open label, follow-up not reported NCT00407992	ONS vs. sham stimulation 34 (estimated enrolment)	Information not available	Number and the type of adverse events Reduction of headache frequency and intensity Reduction in drug intake Changes in QoL and interference in everyday activities	Sponsored by Ospedale Sacro Cuore - Don Calabria **Study completed but not published**

Caillon 2012 [21] (SENGO-CAM Study) Single centre, France Single-blind 14 days NCT01184222	ONS vs. sham stimulation 30 (estimated enrolment)	Migraine patients with medication overuse headache by non specific analgesics according to the ICHD-II diagnostic criteria who are admitted to hospital for medication withdrawal	Rate of headache-free patients, fourteen days after medication withdrawal Number of headache days during the 14 days withdrawal period Rescue medication used	Sponsored by Centre Hospitalier Universitaire de Nice ; **ongoing trial**

Case series

Study, country, sample size, follow-up	Patient selection & baseline characteristics	Outcome measures and results	Comments
Propeney & Aló 2003 [22] USA (Texas), single centre, n=25, mean follow-up 18 months	All 25 consecutive patients responded to temporary bilateral occipital nerve blockade. All patients completed a successful 5- to 7-day trial of outpatient stimulation (no patient failed). 76% (19/25) reported symptomatic medication overuse ≥ 6 months. Mean age 45 years (range 31-65), 88% female, median duration of transformed migraine 10 years	<table><tr><th>Outcome measure</th><th>Pre</th><th>post</th><th>p value</th></tr><tr><td>Headache frequency/90 days, mean (SD)</td><td>75.56 (26.81)</td><td>37.45 (7.49)</td><td>p<0.001</td></tr><tr><td>Headache severity (0-10), mean (SD)</td><td>9.32 (1.28)</td><td>5.72 (3.31)</td><td>p<0.001</td></tr><tr><td>MIDAS score, mean (SD)</td><td>121 (56)</td><td>15 (25.1)</td><td>p value not stated</td></tr><tr><td>Disability grade: I – no or little II – mild III – moderate IV - severe</td><td>100% grade IV</td><td>60% grade I 4% grade II 16% grade III 20% grade IV</td><td>p value not stated</td></tr></table> • Positive responder (≥50% improvement in frequency or severity of headache): 88% (22/25) • ≥75% pain relief: 80% (20/25), ≥50% pain relief: 20% (5/25) • Percentage reduction in MIDAS disability score, mean (SD): 88.7 (1.72)	Retrospective data collection via chart review and telephone interview. Cylindrical electrodes. 60% used stimulation intermittently and 40% used it continuously.
Oh et al. 2004 [23] USA (Pittsburgh and Houston), two centres, n=10, follow-up at 1 month and 6 months	10 patients with transformed migraine were consecutively implanted. The patients had failed ≥3 modes of conservative treatment (medication, physical therapy, blockade), had temporary complete or near complete (≥70%) relief of pain with occipital local anesthetic field block, with psychological screening revealing no major behavioral, drug habituation, or significant unresolved issues of secondary gain. All 10 patients obtained immediate paresthesia and pain relief of >50% during 'on the table' trial. Mean age 52 years (range 41-83), 100% female, median duration of symptom 12.5 years	Patients' subject rating of % reduction of pain : • At 1 month: 90% (9/10) had excellent pain relief (>90% pain relief), 10% (1/10) had good pain relief (75-90% pain relief) • At 6 months: 80% (8/10) had excellent pain relief, 20% (2/10) had good pain relief	Follow-up was obtained in the implanting physician's office or by phone interviews. Dual paddle style electrodes

Reduction in migraine days

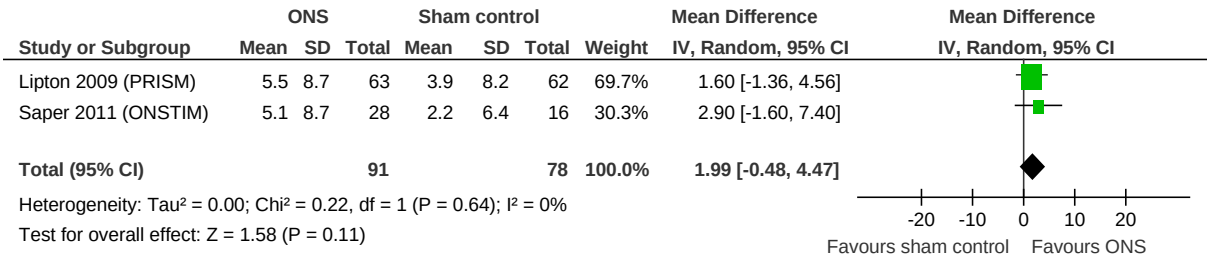
This outcome was measured and presented in various forms, with different definitions of migraine days (or headache days) adopted in different studies.

In the fully published Saper et al. study, greater reduction in headache days (days with headache pain intensity ≥3) per month was observed in the ONS group (6.7 ± 10.0 days or 27.0% ± 44.8%) compared with the sham stimulation group (1.5 ± 4.6 days or 8.8% ± 28.6%) and medical management group (1.0 ± 4.2 days or 4.4% ± 19.1%) at 3-month follow-up. The difference between ONS and the two control groups were statistically significant ([calculated by EAC] ONS vs. sham, mean difference 5.20 days, 95% CI 0.86 to 9.54, p=0.02; ONS vs. medical management, mean difference 5.70, 95% CI 1.49 to 9.91, p=0.008).[16]

Popeney and Aló reported in their uncontrolled case series that a reduction in headache frequency per 90 days from a baseline of 75.56 (SD 26.81) to 37.45 (SD 7.49) was observed over a mean follow-up of 18 months (p<0.001).[22]

Reduction in days with prolonged, moderate/severe headache was reported in both the studies by Lipton et al.[15] (migraine days, ≥4 hours of migraine with moderate/severe pain) and by Saper et al.[16] (days with prolonged, severe headache), but was not reported in the abstract by Silberstein and colleagues.[17] The pooled result from the two studies is shown in Figure 2. The pooled result, while favouring ONS compared to sham control (mean difference 1.99, 95%CI -0.48 to 4.47), was not statistically significant (p=0.11).

Figure 2 Mean reduction in the number of days with prolonged moderate/severe headache per months



The authors of the Lipton et al. study stated in their conference abstract that in a pre-specified subgroup analysis for this outcome, a trend in favour of patients without medication overuse (ONS vs. sham, reduction of 5.9 vs. 2.6 migraine days/month) was observed compared with patients with medication overuse (ONS vs. sham, reduction of 5.0 vs. 4.8

migraine days/month).[15] Results for a formal test of interaction for the difference between subgroups were not presented. Silberstein and colleagues (conference abstract) reported significantly greater decrease in MIDAS headache days (which took into account the impact on patient's life) at 3-month follow-up for the ONS group compared with sham control (22.5 vs. 3.4, p<0.01).[17]

Reduction in pain intensity

In the Saper et al. study, a greater reduction in overall intensity (0-10 scale) was observed in the ONS group (1.5 ± 1.6) compared with sham control (0.5 ± 1.3) and medical management (0.6 ± 1.0) at 3-month follow-up. The difference between the ONS group and the two control groups were statistically significant ([calculated by EAC] ONS vs. sham, mean difference 1.00, 95%CI 0.13 to 1.87, p=0.002; ONS vs. medical management, mean difference 0.90, 95% CI 0.14 to 1.66, p=0.02).[16] Silberstein and colleagues reported in their conference abstract a greater reduction in VAS pain (scale not stated) for ONS compared to sham control (14.1 vs. 7.0, p<0.01).[17] This outcome was not reported in the abstract for the study by Lipton et al.[15]

In a retrospective, uncontrolled case series, Popeney and Aló observed a significant reduction in headache severity (0-10 scale) from a baseline of 9.32 (SD 1.28) to 5.72 (SD 3.31) over a mean follow-up of 18 months (p<0.001).[22] In another retrospective, uncontrolled case series, Oh and colleagues reported that, at one month, 90% (9/10) of patients had excellent pain relief (>90% pain relief), while 10% (1/10) had good pain relief (75-90% pain relief). At six months, 80% (8/10) had excellent pain relief and 20% (2/10) had good pain relief. They stated that the pain relief was based on patient's subjective rating and was not measured using VAS.[23]

Responder rate

This outcome was reported in the Saper et al. study and was defined as ≥50% drop in headache days per month or a ≥3-point drop in pain intensity from baseline. At 3-month follow-up, responder rate was 39% (11/28) for ONS group, 6% (1/16) for sham control and 0% (0/17) for medical management. The authors stated that the difference between ONS and the two control groups was statistically significant (p value not given).[16] However, the difference just failed to reach statistical significance when the data was analysed according to intention to treat assuming patients who dropped out were non-responders ([calculated by the EAC] ONS vs. sham control, RR=5.67, 95%CI 0.80 to 40.30, p=0.08; ONS vs. medical management, RR=12.18, 95%CI 0.76 to 194.94, p=0.08).

Popeney and Aló reported a response rate (50% improvement in frequency or severity of headache) of 88% (22/25) in their uncontrolled case series.[22]

Lipton et al. (conference abstract) investigated potential predictors for treatment response. They reported that in the ONS arm, a favourable response to the percutaneous trial stimulation was moderately predictive of 12-week response (positive likelihood ratio = 2.0, 95% CI 1.4 to 2.9; negative likelihood ratio = 0.21, 95%CI 0.06 to 0.78).[15]

Other outcomes

The Saper et al. study was described as a feasibility study.[16] Several other outcomes such as Profile of Moods States, MIDAS and SF-36 were measured although no primary endpoint was pre-specified. Overall, while the results were favourable for the ONS group compared to the sham control and medication management groups the differences between groups were not statistically significant. The study also included a non-randomised 'ancillary' group that included patients who did not respond to occipital nerve block. Results suggested that these patients could still respond to ONS, but the number of patients (n=5) was too small to make any inference.

The published abstract of the trial by Silberstein et al. reported a significant difference between ONS and sham control for all assessments at 12 weeks ($p<0.01$) including quality of life (66.7% vs. 17.2%) (see Table 5 above).[17] Further information from this trial is expected to be published in the near future (personal communication).

Safety

Detailed information on both device-related and non-device related adverse events were reported in the paper published by Saper et al.[16]; whereas only limited information on safety was reported in the conference abstracts of the study by Lipton et al. and by Silberstein and colleagues.[15;17] In addition, safety data from two larger case series reported by Popeney and Aló,[22] and Oh et al. were also assessed.[23] Key findings from these studies are summarised in Table 6.

Serious adverse events

Three patients (6%) experienced serious adverse events requiring hospitalisation in the study by Saper et al.[16] These were related to implant site infection, lead migration and postoperative nausea. Silberstein and colleagues (conference abstract) reported a 1% rate of serious device- or procedure-related events, including one case of infection and one case of post-operative pain that required hospitalisation.[17]

Lead migration/ dislodgement

Lead migration/ dislodgement was common. It occurred in 24% (12/51) of patients over three months in Saper et al.'s RCT study,[16] but was not reported in the RCT studies by Lipton et al. or Silberstein et al.[15;17]. Popeney and Aló's retrospective case series of consecutive patients reported 36% (9/25) lead migration over a mean follow-up period of 18 months.[22] In another retrospective case series Oh and colleagues reported that all seven patients initially implanted with cylindrical leads had lead migration within the first six weeks. The patients were subsequently implanted with paddle leads with no further lead migration reported during follow-up.[23] Measures were instigated during the trial by Saper et al. to reduce lead migration. These included the use of circular coils when placing the lead extension to create strain-relief loops, and choosing the abdomen in preference of the buttock as the implant location for the neurostimulator where feasible. However, the impact of these measures was not reported.[16]

Problems with performance of programming and of the lead were also reported in the Saper et al. study.[16]

Intraoperative failure

Information on intraoperative failure was reported only in the Saper et al. trial, in which two out of 53 patients had inadequate paresthesia over the location of pain during intraoperative testing and did not proceed to device implantation.[16]

Infection

Infection at implant site for lead/extension tract and incision site complication was observed in the Saper et al. study in 14% (7/51) and 8% (4/51) of patients respectively.[16] The Lipton et al. study (conference abstract) referred to infections being the most frequent device related adverse event.[15] Infection rates were not reported in the Silberstein et al. conference abstract.[17] Popeney and Aló reported 4% (1/25) infection over a mean follow-up period of 18 months.[22] There were two infections in Oh and collegues' case series of ten patients.[23]

Table 6 Summary of key safety findings of ONS for chronic migraine

Study, design & no. of patients implanted	Duration of follow-up	Failed trial stimulation	Serious adverse events (SAEs)	Lead migration (lead type)	Infection	Removal of stimulation system	Other adverse events (AEs)	Comment
Saper et al. 2011 [16] (ONSTIM), RCT, n=51	3 months	2/53	3/51 (6%) with SAE requiring hospitalisation: implant site infection, lead migration and postoperative nausea	12/51 (24%) cylindrical	Infection at the site of: Lead/extension tract 7/51 (14%) Neurostimulator pocket 2/51 (4%) See also SAE	Not reported	36/51 reported a total of 56 AEs Product ineffective: programming 6/51 (12%), lead 2/51 (4%) Incision site complication 4/51 (8%) Pain/discomfort at various sites	Reported adoption of various measures to reduce lead migration during the trial
Lipton et al. 2011 [15] (PRISM), RCT, n=132	2 years	Not reported	Not reported	Not reported	Listed among 'most frequent device-related AE'	Not reported	Non-target area sensory symptoms Implant site pain	**Conference abstract only**
Silberstein et al. 2011, [17] RCT, n=157	3 months	Not reported	1% with procedure- or device-related SAE: infection (n=1) and expected post-operative pain that required hospitalization (n=1)	Not reported	Not reported (but see SAE)	Not reported	Not reported	**Conference abstract only**
Popeney & Aló 2003, [22] case series, n=25	18 months (mean)	0/25	Not reported	9[a]/25 (36%) cylindrical	1/25 (4%)	1/25 (same one due to infection)	Not reported	Consecutive patients, retrospective
Oh et al. 2004, [23] case series, n=10[b]	Varied (≥ 6 months)	0/10	Not reported	7/7 (100%) cylindrical; 0/10 paddle	2/10 (20%)	1/10 (due to infection)	Not reported	Consecutive patients, prospective

[a] 6 were traumatic migration (related to motor vehicle accident or fall etc) and 3 were spontaneous migration. All were successfully repositioned.

[b] This case series included 10 patients with transformed migraine and an additional 10 patients with occipital neuralgia. Results reported here are for the patients with transformed migraine unless otherwise specified.

Other adverse events

Other relatively common adverse events included pain and discomfort at various sites related to the procedure or implanted devices. Single case of rash, hematoma and stitch abscess was reported in the study by Saper et al.[16]

Long-term complications or potential nerve damage

Saper and colleagues stated that there was no evidence of adverse device effects leading to long-term complications or potential nerve damage and there were no serious unanticipated adverse device effects reported or identified in the first three months of their trial.[16]

Summary and discussion: ONS for chronic/transformed migraine

- Evidence on efficacy was obtained from three industry-sponsored, multicentre RCTs (Lipton et al. 2009, Saper et al. 2011, Silberstein et al. 2011),[15-17] including a total of 364 patients, and two case series covering a total of 35 patients.
- Two of the three RCTs (Lipton et al. 2011 and Silberstein et al. 2011),[15;17] including a total of 297 patients, have only been published as conference abstracts at the time of this report, limiting the available information for assessment of risk of bias and data synthesis. The risk of bias for the fully published study by Saper et al. (n=67) was considered high with regard to attrition bias and outcome reporting bias.[16] Assessment of success of blinding, or patients' expected effectiveness of treatment, was not mentioned in any of the trials.
- The duration of follow-up was relatively short (three months) for the blinded period of the RCTs. Long-term open-label follow-up of between one to three years are ongoing. Duration of follow-up varied in the case series and was up to 18 months.
- The majority of studies were carried out in the USA. Only a single centre from the UK was included in one of the RCTs.
- The inclusion criteria with regard to medication overuse and the use of/response to trial stimulation or nerve block varied between studies.
- Significantly greater reduction in headache days (days with headache pain intensity $\geq$3) per month was observed in the ONS group (6.7 $\pm$ 10.0 days) compared with the sham stimulation group (1.5 $\pm$ 4.6 days, p=0.02 vs. ONS) and medical management group (1.0 $\pm$ 4.2 days, p=0.008 vs. ONS) at 3-month follow-up of the study by Saper et al.[16] Patients in the ONS group also experienced a significantly greater reduction in overall intensity (1.5 $\pm$ 1.6 on a 0-10 scale) compared with sham control (0.5 $\pm$ 1.3, p=0.002 vs. ONS) and medical management (0.6 $\pm$ 1.0, p=0.02 vs. ONS). The differences between the ONS group and the two control groups (sham stimulation and medication

management) were not statistically significant for responder rates when analysed by intention to treat (p=0.08) and for most of the other outcomes including Migraine Disability Assessment (MIDAS) and SF-36.

- Of the two RCTs that have been reported only in conference abstracts, no significant difference between groups was found for reduction in days with prolonged, moderate or severe headache per month in the Lipton et al. trial (ONS 5.5 $\pm$ 8.7 vs. sham 3.9 $\pm$ 8.2, p=0.29).[15] By contrast, Silberstein and colleagues reported significant difference (p<0.01) between groups in favour of ONS compared to sham control for all assessment including VAS pain, MIDAS headache days and total scores, Zung Pain and Distress Scale, and quality of life.[17]
- The trial by Silberstein and colleagues is expected to be published as a peer-reviewed article in the near future. Additionally, two ongoing RCTs (including a single centre UK study) and one unpublished study may provide further information.
- Lead migration and infections are common and contributed to some of the reported serious adverse events. Lead migration occurred in 24% (12/51) of patients over three months in the study by Saper et al.[16] and 36% (9/25) reported by Popeney and Aló.[22] The type of lead appears to determine the prevalence of migration with all seven cylindrical leads migrating in Oh et al. case series and none of the paddle lead placements.[23] Infection occurred at implantation sites in 14% (7/51) and 4% (2/51) of patients for leads/extensions and neurostimulators respectively over three months in the Saper et al. study.[16] Oh et al. reported a higher infection rate of 20% (2/10),[23] and Popeney and Aló a lower infection rate of 4% (1/25).[22] Pain and discomfort at various sites related to implantation procedure and implanted devices was also reported by the study by Saper et al.[16] No permanent nerve damage or unexpected serious adverse events were observed.
- Methods for reducing lead migration including the use of strain-relief loops, choosing the abdomen in preference of the buttock as the implant location for the neurostimulator, and the use of a paddle lead instead of a cylindrical lead have been suggested.
- Findings from a subgroup analysis of the Lipton et al. study suggested that ONS may be more effective in patients without medication overuse compared to those with medication overuse. Data from the trial also suggested that a positive response to trial stimulation may be predictive of subsequent treatment success.[15] On the other hand, data from the Saper et al. study indicated that patients who did not respond to occipital nerve block may still respond to ONS.[16] These preliminary findings require further validation.

6.2.1.1.2 ONS for cluster headache

One ongoing international RCT,[24] and four larger case series [25-28] were identified. We have no information beyond the protocol for RCT reported in a conference abstract. The findings from the four case series are reported in Table 14. In the absence of RCT evidence, it is not possible to present here findings on the efficacy of ONS for cluster headaches.

Replacement of batteries, leads and electrodes

Burns et al.[29] reported that 6/14 patients required battery replacements and 4/14 new electrodes or leads.

Request for removal

Fontaine et al.[26] reported that 1/14 patients requested removal of device after six months as they experienced no improvement.

Lead Migration

The prevalence of lead migration ranged from none, reported by Fontaine et al.[26] (average follow-up of 14.6 months) and Müeller et al.[28] (12 months), to 1/15 cases by Magis et al.[27] (36.8 months), to 4/14 reported by Burns et al.[29] (17.5 months).

Infections

All three studies reported incidents of infections ranging from less than 10% (1/13 cases) infection rate over an average follow up period of 14.6 months,[26] to 25% over a 36.8 month follow up period (3/12).[27] Müeller et al. reported a 10% infection rate (1/10) over 12 months average follow up period: this local infection led to explantation of the generator and externalisation of the electrodes until the infection healed before implanting another generator in a different location.[28]

Discomfort

Discomfort was reported in three of the four case series. Burns et al. reported neck stiffness and painful overstimulation.[29] Fontaine et al. reported a single case of unpleasant paresthesia (1/14);[26] and Magis et al. reported two cases of unbearable paresthesia (2/15), discomfort from the battery (2/15), and connecting wire discomfort (2/15).[27] Müeller et al. reported patients who had requested generators to be located in the abdomen experiencing painful pressure when lifting or carrying heavy objects.[28]

Pressure ulcer

Müeller et al. reported one case of pressure ulcer (2nd degree, superficially located, no super infection) at the operation site.[28]

Scar formation

Müeller et al. reported one case where they needed to re-operate because of scar formation around the thoracic connector, which was causing discomfort.[28]

6.2.1.1.3 ONS for neuralgias, headaches and craniofacial pain associated with occipital nerves

Six larger case series were identified.[23;30-34]

6.2.1.1.4 ONS for mixed types of headaches

Four larger case series were identified.[35-38]

6.2.1.1.5 ONS for fibromyalgia

Contrary to headache disorders, fibromyalgia may not be an obvious indication for ONS. The interest in the use of ONS for pain relief in patients with fibromyalgia arose from early incidental observations that patients with fibromyalgia associated headache who were treated with ONS appeared to have experienced pain relief beyond the headache.

Two RCTs and one larger case series were identified. Both RCTs were conducted in the same centre in Belgium. One was published as a conference abstract and the other has not yet been published, though its publication is expected in the near future (personal communication, Dr Plazier). The results published in the conference abstract are summarised in the data table in Appendix 4 for Plazier et al. 2011.[39] This crossover RCT (n=15) compared standard/ supra-threshold stimulation with sub-threshold stimulation and minimal stimulation. Improvement in outcomes measured by the Fibromyalgia Impact Questionnaire was observed in all three groups (indicating a significant placebo effect), but the improvement was greater in the standard/ supra-threshold stimulation compared with sub-threshold and minimal stimulation.

6.2.1.2 Implanted PNS of trigeminal and related nerves/ganglion

Eight larger case series were identified.[40-47]

6.2.1.3 Implanted PNS – stimulation of sphenopalatine ganglion

We identified one ongoing RCT for treating patients with chronic or high frequency, high disability migraine (due for completion in 2015), and one larger case series.[48]

6.2.1.4 Implanted PNS – stimulation of vagus nerve

One larger case series was identified, in which patients who suffered from migraine and were also treated with vagus nerve stimulation for seizure were studied.[49]

6.2.1.5 Implanted PNS of nerves in the upper and lower extremity

Five larger case series were identified.[50-54]

6.2.1.6 Implanted PNS of various nerves with injuries associated with surgical procedures, trauma or chemical assault

Three larger case series were identified.[55-57]

6.2.1.7 Sacral nerve (root) stimulation (SNS)

Sixteen larger case series were identified.[58-70] The majority (12) of these reported the use of SNS for treating painful bladder syndrome/interstitial cystitis (some of which also covered chronic pelvic pain); two for chronic pelvic pain; and one for chronic anal pain. There is some overlap between this literature and the application of SNS for other urological conditions for which NICE Interventional Procedures guidance has been issued.

6.2.2 Peripheral nerve field stimulation (PNFS, electrical stimulation of a painful area using implanted devices [implanted PNFS] or temporary percutaneous stimulation [temporary PNFS])

Evidence identified for the use of PNFS for chronic pain is shown in Table 7. The vast majority involves PNFS using implanted devices. The main area of application is chronic low back pain and failed back surgery syndrome, which was investigated in one RCT (Barolat et al.,[71] published only as a conference abstract at the time of this report) and two larger case series totalling 32 patients (Verrills et al., Yakovlev et al. 2011).[72,73] CE marked devices are available for this indication, and therefore the subsection is highlighted with detailed information provided. One additional case series of 12 patients with implanted PNFS focused on post-surgical hip pain (Yakolev et al.)[74] and four further case series totalling 252 patients reported the use of implanted device for mixed types of pain (Verrills et al.; Sator-Katzenschlager et al.; Verrills; Falco et al.).[75-78] Some of the techniques used in the latter four case series would have been classified as implanted PNS (e.g. ONS and implanted PNS of trigeminal and related nerves) and are covered in earlier sections of this report. One pilot RCT investigated a device for a single session temporary PNFS for osteoarthritis of the knee (Kang et al.).[79] The device has FDA approval but is not CE marked.

Table 7 Identified evidence for implanted and temporary peripheral nerve field stimulation (implanted PNFS and temporary PNFS)

Peripheral nerve field stimulation (PNFS, implanted or temporary)	No. of RCTs	No. of case series (n≥10)
Implanted PNFS		
Chronic low back pain / failed back surgery syndrome [Highlighted area 2 for this report]	1 RCT (abstract only – publication pending)	2
Post surgery hip pain	-	1
Mixed types of pain	-	4
Temporary PNFS		
Osteoarthritis of the knee [temporary percutaneous stimulation]	1 RCT	-

6.2.2.1 Implanted PNFS for chronic low back pain and failed back surgery syndrome [Highlighted area 2 for this report]

Only one not fully published RCT (Barolat et al.)[71] and two larger case series (Verrills et al.; Yakovlev et al)[73;73] were available for inclusion in our analysis. The characteristics and key efficacy findings of these studies are summarised in Table 8, and key safety findings in Table 9. The RCT (n=30) was a feasibility study and has so far only been published as a conference abstract. A full-text manuscript has been submitted for publication (personal communication, Professor Barolat). The trial adopted a crossover design which compared standard PNFS with low frequency PNFS, sub-threshold PNFS, and minimal stimulation during a trial period of 22 to 37 days. It was described that 'patients rotated through the four arms during this period in 4 to 8 days intervals', and thus it was not clear whether there was any washout period between each of the stimulation modalities. Patients who had a 50% reduction in pain at the end of the trial period proceeded to permanent implantation of the stimulation system and were followed up for 52 weeks. The randomised controlled phase therefore only covered the trial stimulation period. We were unable to properly assess the risk of bias for this RCT due to insufficient information. The two case series (Verrills et al.; Yakovlev et al)[72;73] were retrospective but included consecutive patients (who proceeded to permanent implantation of PNFS). Follow-up data for the case series by Verrills and colleagues was collected by questionnaire with a 93% (13/14) response rate.[72] All patients in the RCT by Barolat et al.,[71] (Prof Barolat, personal communication) and in the case series by Yakovlev et al.,[73] and 11 of the 13 patients in the Verrills et al. case series [72] had had surgical procedures for their back pain without resolution of symptoms and thus could be considered as having failed back surgery syndrome.

Efficacy

Pain Relief

The proportion of participants with ≥ 50% pain relief after completing each stimulation modality in the trial stimulation phase of the RCT (conference abstract) were 14% (4/29) for minimal stimulation, 27% (8/30) for sub-threshold stimulation, 57% (17/30) for low frequency stimulation, and 53% (16/30) for standard stimulation. Among those who proceeded to permanent implantation, 67% (15/23) reported having ≥ 50% pain relief and the same proportion classified their pain relief as 'excellent' or 'good' at 52 weeks.[71]

Given the limited evidence from RCTs it is necessary to draw on evidence from two case series. The first case series (Yakovlev et al.)[73] of 18 patients, reported 100% of patients having greater than 50% reduction in VAS pain at 12 months. The second case series

(Verrills et al.)[72] of 13 patients, conducted with questionnaire survey with mean follow-up of 7 months, reported a reduction in VAS pain on the 0-10 scale from a mean score of 7.42 (SD 1.16) before PNFS to a mean score of 3.92 (SD 1.72) at follow-up ($p<0.05$). Pain relief was rated as excellent (improvement ≥75%) in 15% (2/13) of patients, good (improvement 50-74%) in 38% (5/13), fair (improvement 25-49%) in 38% (5/13), and poor (improvement <24%) in 8% (1/13).

Reduced use of analgesics

Yakovlev et al. reported 89% (16/18) of patients having decreased or stopped analgesic use.[73] In the case series by Verrills et al.it was reported that 54% (7/13) of patients reduced analgesic usage.[72]

Satisfaction with treatment

Similarly, Verrills et al. reported that 77% (9/13) of patients being satisfied or very satisfied with treatment (see Table 8).[72]

Operational effectiveness of device

Yakovlev et al. reported in their case series that two-thirds (12/18) of patients required re-programming within the first six weeks and three patients required additional education regarding recharge device.[73]

Table 8 Characteristics and main efficacy findings of published RCT and case series (n≥10) of implanted PNFS for chronic low back pain and failed back surgery syndrome

Study, country, follow-up and funding source	Sample size and comparison (where applicable)	Patient selection and trial stimulation; baseline characteristics	Outcome measures and results	Comments
Barolat et al. 2011 [71] USA Crossover RCT during a trial period of 22 to 37 days Sponsored by St. Jude Medical	n=30; PNFS standard stimulation vs. low frequency stimulation vs. sub-threshold stimulation vs. minimal stimulation; patients 'rotated through 1 of 4 stimulation modes in 4 to 8 day interval'.	Trial stimulation formed the randomised phase of the study. Implantation of stimulator was carried out after the trial period for patients with ≥50% reduction in pain at the end of the randomised phase. Chronic intractable back pain. All patients had lumbar spine surgery (personal communication, Prof Barolat). Information on baseline characteristics not available.	≥50% pain relief during trial stimulation: Minimal stimulation (n = 29) 13.8% Sub-threshold stimulation (n = 30) 26.7% Low frequency stimulation (n = 30) 56.7% Standard stimulation (n = 30) 53.4% ≥50% pain relief with implanted device at week 52 (n=23): 66.7%	**Conference abstract only (full-text publication pending) –** unable to appropriately assess risk of bias 52-week open-label follow-up for implanted stimulation
Verrills et al. 2009 [72] Australia Retrospective case series of consecutive patients Follow-up: 7 months (range 3 to 12)	No comparator group. 14 patients surveyed. 13 responded	Trial stimulation: stated that 'about 55% of clinic patients respond positively' to trial stimulation and progressed to permanent implantation. 11/13 patients met diagnostic criteria of failed back surgery syndrome. Mean age 61 years (range 42 to 80). 54% female. Mean duration of pain: not reported. Baseline VAS pain: 7.42 ± 1.16	Mean improvement in VAS pain: 3.77 ± 1.65 or 50.1% ± 21.8% Decreased analgesic use: 54% (7/13) Satisfaction with treatment: Completely satisfactory 8% (1/13), Very satisfied 15% (2/13) Satisfied 54% (7/13) Not completely satisfied 15% (2/13) Unsatisfied 8% (1/13)	Also reported results by subgroups – mean reduction in VAS pain Age > 60: 4.38 ± 1.53 Age 60: 2.8 ± 1.48 p>0.05
Yakovlev et al. 2011 [73] USA Retrospective case series, consecutive patients Follow-up: 12 months	n=18	Trial stimulation: 2 days. The case series included only patients who proceeded to permanent implantation. Patients with chronic low back pain associated with post-laminectomy syndrome. Mean age 62 years (range 45 to 81), 39% female. Mean duration of pain: 22 months. Baseline VAS pain: 7.44	At 12 months: >50% reduction in VAS pain: 100% (18/18) Decreased or discontinued use of pain medications: 89% (16/18)	22% (4/18) had previously had spinal cord stimulation which lost efficacy over time. Suggested a delay of two weeks to activate PNFS to avoid making patients confused between surgical site pain and low back pain

Table 9 Safety findings of published RCT and case series (n≥10) of implanted PNFS for chronic low back pain and failed back surgery syndrome

Study, design & no. of patients implanted	Duration of follow-up	Failed trial stimulation	Serious adverse events (SAEs)	Lead migration (lead type)	Infection	Removal of stimulation system	Other adverse events (AEs) or technical issues	Comment
Barolat et al. 2011 [71] n=23	1 year	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Conference abstract only; publication pending
Verrills et al. 2009 [72] n=13	Mean 7 months (range 3 to 12)	Only patients responding to trial implanted and included in this study	None reported	None reported; 1 x 8-contact electrode, cylindrical	None reported	None reported	Stated 'no adverse events or complications were reported.	Follow-up using questionnaire.
Yakovlev et al. 2011 [73] n=18	Mean 12 months	Not reported	Not reported	None reported; 4 x 4-contact electrode, cylindrical	Post-operative wound infection: 1/18 (6%)	1*/18 (6%)	12 patients had reprogramming of PNFS in the first 6 weeks 3 needed additional teaching sessions on the use of recharging devices	4 patients used both PNFS and spinal cord stimulation

*The same patient who had post operative wound infection. Re-implantation of the system was carried out successfully 12 weeks after explanation

.

Safety

Adverse events and safety were not mentioned in the conference abstract of Barolat and colleagues RCT,[71] and only limited information was reported in the two case series.[72;73] The first case series (Verrills et al.) was a follow-up conducted by questionnaire survey on patients who had received an implant in the previous year (minimum follow up period being 3 months) and reported no adverse events or complications.[72]

Infection

The second case series (Yakovlev et al.) reported a case of post-operative infection (1/18) requiring removal of the stimulation system, which was subsequently re-implanted.[73]

Summary and discussion - Implanted PNFS for chronic low back pain and failed back surgery syndrome

- The evidence on use of implanted PNFS for chronic lower back pain and failed back surgery syndrome is currently limited.
- One not fully published RCT (Barolat et al.,conference abstract, full-text publication pending) recruiting 30 patients,[71] and two case series (Verrills et al.; Yakovlev et al.) [72,73] including a total of 31 patients were included.
- We were unable to properly assess the risk of bias of the RCT due to insufficient information reported in the conference abstract. The RCT was a feasibility study with a randomised period of only 22 to 37 days in which patients were crossed over between four different modalities of trial stimulation.
- Results from the RCT showed a similar proportion of patients achieving pain relief of greater than 50% for standard and low frequency PNFS (57% and 53% respectively). The proportion was lower in the sub-threshold stimulation (27%) and minimal stimulation (14%) group. Among the 23 patients who proceeded to permanent implantation, the response (of greater than 50% pain relief) was maintained in 67% of the patients at one year.
- Two retrospective case series reported significant reduction in pain and reduced use of analgesics at varied follow-up between 3 to 12 months.
- There is limited information on safety. It was not mentioned in the conference abstract of the RCT and only one of the two case series identified reported that there were no adverse events or complications.[72] Another case series described a case of post-operative infection requiring removal of the stimulation system, which was subsequently re-implanted.

- Yakovlev et al. has reported during a one year follow-up that two-thirds (12/18) of patients required re-programming and three required additional education regarding the use of the recharging device.[73]
- The vast majority of patients included in the studies of implanted PNFS had failed back surgery syndrome. The pain in these patients was more difficult to manage compared to the patients with chronic low back pain included in the studies of PENS (section 6.2.3.3.2).

6.2.2.2 Implanted PNFS for post surgery hip pain

One larger case series was identified.[74]

6.2.2.3 Implanted PNFS for mixed types of pain

Four larger case series were identified.[75-78] These case series have included chronic pain of various nature in different areas of the body. Stimulation carried out in areas innervated by occipital nerves and trigeminal nerves, which is classified as implanted PNS and covered in sections 6.2.1.1 and 6.2.1.2 of the report, was also included in some of the papers.

6.2.2.4 Temporary PNFS for osteoarthritis of the knee

One pilot, single-blind RCT (Kang et al.) evaluated temporary PNFS using a stimulation device (not CE marked) with arrays of 1,014 micro-needles embedded within a patch-type electrode in 63 patients with osteoarthritis of the knee.[79]

Pain reduction

Reduction in pain was measured immediately and up to 48 hours after a single 30-minute active or sham stimulation session. A statistical significant greater reduction in pain intensity was observed in the active PNFS group compared to the sham group immediately after the stimulation session ($p=0.361$), but the difference become smaller and non-significant 48 hours after treatment ($p=0.1789$).

Medication use

There were statistically significant difference in the use of medication one week after treatment with 54% (19/35) of active PNFS reporting a decrease compared with 0% (0/28) of the sham ($p<0.0001$).

Further information from this study can be found in the data table for Kang et al. (2007)[79] in Appendix 4.

6.2.3 Percutaneous electrical nerve stimulation (PENS, temporary electrical stimulation of nerves or dermatomes using fine gauge needles)

PENS has been used for treating a wide variety of chronic pain, such as various types of headache disorders, chronic peripheral neuropathic pain (including sciatica and diabetic neuropathic pain), chronic neck and back pain, osteoarthritis of the hip, interstitial cystitis, and chronic pelvic pain (see Table 10). In contrast with other types of technique, for which only a few RCTs have been reported, a large number (16) of RCTs were identified. For this technique CE marked PENS devices are available for chronic peripheral neuropathic pain, and therefore this subsection is highlighted with detailed information provided. Evidence from RCTs of other indications will be covered in an overview of best available evidence across techniques in section 6.3 . Further details of individual RCT can also be found in data tables in Appendix 4.

Table 10 Identified evidence for percutaneous electrical nerve stimulation (PENS)

Percutaneous electrical nerve stimulation (PENS, temporary stimulation using fine gauge needle)	**Systematic reviews and RCTs**	**Case series (n≥10)**
Headache disorders - Migraine, tension type headache, post-traumatic headache	1 RCT	-
Peripheral neuropathic pain [Highlighted area 3 for this report]		
Sciatica	1 RCT	-
Diabetic neuropathic pain	1 RCT	-
Surface hyperalgesia associated with various neuropathic pain	1 RCT	-
Other chronic pain		
Chronic neck pain	1 RCT	-
Chronic low back pain	9 RCTs	1
Osteoarthritis of the hip	1 RCT	-
Interstitial cystitis (posterior tibial nerve)	-	1
Chronic pelvic pain	-	2
Class IIIB chronic prostatitis/chronic pelvic pain (posterior tibial nerve)	1 RCT	-

6.2.3.1 PENS for headache disorders

The effectiveness of PENS was evaluated in a single centre, crossover RCT (Ahmed et al.) in patients with various types of headache including chronic migraine (n=12), tension type

headache (n=13), and post-traumatic headache (n=5).[80] PENS was found to be more effective than a 'needles only' control in reducing headache frequency (number of headaches per week, p <0.05) and pain (VAS scores, p<0 .05), improving physical activity (VAS, p<0.05) and sleep quality (SF-36). Further details can be found in the data table for Ahmed et al. (2000)[80] in Appendix 4.

6.2.3.2 PENS for peripheral neuropathic pain [Highlighted area 3 for this report]

Types of neuropathic pain

Three RCTs investigated PENS (Ghoname et al.; Hamza et al.; Raphael et al.) for chronic peripheral neuropathic pain were identified and included in the analysis.[81-83] These RCTs assessed the effectiveness of PENS on sciatica (Ghoname et al.)[80], diabetic neuropathic pain (Hamza et al.),[82] and surface hyperalgesia associated with various types of neuropathic pain conditions (Raphael et al.).[83] The characteristics and key efficacy findings of each study are summarised in Table 11.

Design of RCTs

All three RCTs were crossover trials with a sham control group. The trial by Ghoname and colleagues also included a TENS arm.[81] The number and length of treatment sessions varied across the RCTs. In the studies by Ghoname et al.[81] and Hamza et al.,[82] the treatment sessions were of 30 minutes duration, three times per week for three weeks in the trials; whereas in the study by Raphael et al.[83] the treatment comprised of a single 25-minute session. Age profiles also varied across the three RCTS with mean age of the patients being 43 in the study by Ghoname et al.[81] and around 55 in the other two RCTs.[82,83] Similarly, there were differences in pain at baseline ranging from 6.3 (mean, VAS, Hamza et al.),[82] to 7.5 (median, numerical rating scale, Raphael et al.).[83]

Assessment of bias

Two of the RCTs were conducted in the same centre in Dallas, USA and they adopted similar study design and reporting styles, which did not provide sufficient information to assess risk of bias in some domains.[81-82] For example, the method for generation of the random sequence was not given and no details were provided on allocation concealment and attrition. Although outcome assessors were blinded, all outcome measures were self-reported by patients and it was difficult to blind patients to paresthesia induced by electrical stimulation, particularly after crossover. The researchers made no assessment of the effectiveness of blinding. We therefore rated the risk of detection bias as unclear before crossover and as high after crossover. The other study by Raphael and colleagues was

conducted in two centres in the West Midlands, UK.[83] The risk of bias was low for all risk of bias domains, except for the same issue of blinding patients in a crossover trial. The authors in this study reported that blinding was effective for the first treatment session, but all patients knew whether they received active or sham stimulation after crossover due to differences in sensation. They therefore also presented results for the first treatment session before crossover.

Efficacy

The key efficacy findings from these three studies are shown in Table 11 and further details of each study can be found in the data tables for Ghoname et al. (1999),[81] Hamza et al. (2000),[82] and Rapheal et al. (2000) [83] in Appendix 4.

Pain relief

Ghoname and colleagues compared PENS with sham PENS and TENS in patients with pain due to sciatica in a crossover RCT (n=64).[81] Significant reduction in pain (measured on VAS 0-10) compared to baseline was observed in both PENS (from 7.2 to 4.1, $p<0.05$) and TENS (from from 7.0 to 5.4, $p<.05$) groups, but not in the sham PENS group (from 6.6 to 6.1, $p>0.05$). The reduction in the PENS group was significantly greater than those observed in the TENS and sham-PENS groups ($p<0.01$). The researchers also observed a cumulative treatment effect in the PENS group over the 3-week treatment period. Given the short washout period (one week), a carryover effect was likely in this study after crossover, but results were not reported separately for each study period.

From the same research centre, Hamza and colleagues compared PENS with sham PENS in another crossover RCT in patients with diabetic neuropathic pain in the lower extremity.[82] They also observed a cumulative effect in the PENS group (but not in the sham group). For example, VAS pain scores in the PENS group were 6.2, 3.6, 3.3 and 2.5 for baseline and at the end of weeks 1, 2 and 3 respectively. As a result of the short washout period (one week), patients who were initially treated with PENS had significantly better baseline scores (i.e. lower pain intensity) before starting sham PENS at the beginning of the second treatment period, compared with the baseline scores of those who received sham PENS during the first treatment period. Consequently, when data from both treatment periods (pre- and post-crossover) were combined, the pre-treatment scores for PENS was significantly worse compared to the pre-treatment scores for sham PENS (for example, baseline VAS pain 6.2 for PENS vs. 5.2 for sham PENS). In other words, there was imbalance in baseline scores between PENS and sham PENS when data from the two treatment periods were combined

due to carryover effect. We therefore present data from the first treatment period (i.e. before crossover) for this study in the following text.
Hamza and colleagues reported significantly greater reduction in pain (measured on VAS 0-10) in the PENS group (from 6.2 to 2.5) compared with the sham-PENS group (from 6.4 to 6.3) during the first period of the study ($p<0.05$).[82]

In a crossover RCT (n=31) conducted in the UK, Raphael and colleagues compared a single session PENS versus sham PENS for the treatment of surface hyperalgesia associated with various types of neuropathic pain, including surgical scar pain (n=7), chronic low back pain (n=5), occipital neuralgia (n=4), pain following total knee replacement surgery (n=3), post-traumatic neuropathic pain (n=3), post-inflammatory neuropathic pain (n=3), and stump pain (n=2), and one patient each for complex regional pain syndrome, chronic pelvic pain and post-herpetic neuralgia.[83] Given the issue described earlier regarding inability to blind patients after crossover, only data from the first treatment period is presented here. Raphael and colleagues reported significant greater reduction in pain measured on the 0-10 numerical rating scale (median, 3.9 vs. 0.1, $p<0.0001$) and greater increase in pressure pain threshold measured by pressure algometry (310 vs. 8, $p=0.007$) for the PENS group compared to the sham PENS group.

Physical activity
This outcome was reported in two of the RCTs (Ghoname et al. and Hamza et al.).[81,82]
Ghoname and colleagues reported significant improvement from baseline in physical activity (measured on a 0-10 VAS scale, 0=best) in both the PENS group (from 6.4 to 4.0, $p<.05$) and the TENS group (from 5.8 to 4.5, $p<.05$) but not in the sham PENS group (from 6.0 to 5.5, $p>.05$) in patients with sciatica. The improvement in the PENS group was significantly greater than those observed in the TENS and sham PENS groups ($p<.01$).[81] Hamza and colleagues also reported significantly greater improvement (measured on a 0-10 scale, 0=worst) in the PENS group (from 5.2 to 7.9, $p<.05$ vs. baseline) compared with the sham PENS group (from 5.3 to 6.0, $p>.05$ vs. baseline) in the first period of their trial among patients with diabetic neuropathic pain (PENS vs. sham PENS, $p<.05$).[82]

Quality of life (SF-36)
Ghoname et al. reported in their RCT of sciatica patients that statistically significant improvement in SF-36 physical and mental component scores was observed in all three groups (PENS, TENS and sham PENS) post-intervention, but the most significant improvements were observed in the PENS group. The physical and mental component score increased from 26.7 ± 7.6 and 39.5 ± 5.2 respectively at baseline, to 35.3 ± 8.2 and 44.2

±6.4 in the PENS group (p<.001), 29.6 ± 7.4 and 42.1 ± 6.0 in the TENS group (p<0.05), and 28.4 ± 6.7 and 41.7 ± 6.2 in the sham PENS group (p<0.05).[81] Hamza et al. also reported improvements in physical and mental components of the SF-36 in patients with diabetic neuropathy for both PENS and sham PENS, and similarly the improvement was greater for PENS (p<0.05).[82] PENS scores increased from pre-study score of 31.2 ±7.3 to 36.8 ± 11.6 for the physical component (p<0.01) and from 41 ± 5.8 to 43.9 ± 5.6 (p<0.01) for the mental component. Whereas in the sham PENS the physical component score improved to 32.4 ± 7.5 (p<0.05) and the mental component to 42 ±5.5 (p<0.05).[82] In both studies the post-intervention scores for PENS groups were still below normal population score of 50.

Use of analgesics

Ghoname et al. reported 50% (±19) reduction over a three week period in daily use of analgesics with PENS treatment compared to TENS (29% ±17) and Sham PENS (8% ±13) (p value not reported). There was significant difference in use from after day one on baseline for PENS (2.5 pills per day falling to 1.5 pills per day).[81] Hamza et al. also observed significantly greater reduction in analgesic use in the PENS group (49% ± 19) compared with sham PENS group (14% ± 10). [82]

Sleep

Ghoname and colleagues reported significant improvement from baseline in quality of sleep (measured on a 0-10 VAS scale, 0=best) in both the PENS group (from 5.5 to 3.1, p<0.05) and the TENS group (from 5.0 to 4.0, p<0.05) but not in the sham PENS group (from 5.2 to 4.9, p>0.05). The improvement in the PENS group was significantly greater than those observed in the TENS and sham PENS groups (p<0.01).[81] In another trial, Hamza et al. also report greater improvements in quality of sleep (measured on VAS 0-10, 0= worst) in PENS than sham (p<0.05). In the first period of their trial (before crossover), the VAS score changed from 5.8 to 8.3 (p<0.05) in the PENS group; and from 6.0 to 6.6 (p>0.05) in the sham PENS group.[82]

Wellbeing

Hamza et al. also reported on changes in Profile of Mood Status (POMS) scores from baseline at completion of the study (data from both study periods combined). They observed that there was significant improvement from baseline in both PENS and sham PENS groups for all POMS measures except the vigor-activity subscale (p value not given). They stated that the improvement was greater (p<0.05) for PEN compared with sham PENS for all POMS measures. However, in their data table, significant difference was indicated only for

three of the seven subscales, these being fatigue-inertia (reduction from 56.1 ± 6.6 to 43.3 ± 7.1 for PENS compared to sham 51.4 ± 7.1, p<.01), confusion-bewilderment (53.5 ± 7.4 to 44.4±6.3 compared to 50.2 ± 8.3, p<0.01) and total mood disturbance (71.3±32.1 to 29.5±27.6 compared to 57.8±34.4, p<0.01). The post-treatment scores for the other four subscales were: tension-anxiety (reduction from 54.6 ± 7.4 to 44.1 ±5.6 for PENS compared to sham 50.4 ± 7.1), depression-dejection (reduction from 58.6 ± 9.4 to 47.5 ±7.2 for PENS compared to sham 56.1 ± 10.8), anger-hostility (reduction from 62.9 ± 12.2 to 51.1 ±9.1 for PENS compared to sham 59.3 ± 12.1) and vigour-activity (reduction from 53.1 ± 6.1 to 50.9 ±12.4 for PENS compared to sham 50.6 ± 7.7).[82]

Satisfaction with treatment

Ghoname et al. reported that the majority of patients (73%) rated PENS as the most desirable treatment modality compared to TENS (21%) and sham PENS (6%).[81]

Issues in interpreting study's findings

The observed treatment effects for PENS and TENS appeared to be cumulative over the course of the three week treatment period, and thus a carryover effect was likely in two of the studies (Ghoname et al.; Hamza et al.),[81;82] given the short washout period (one week) between treatment modalities. However, results were not reported separately for the two treatment periods in Ghoname et al.[81] In addition, the effectiveness of blinding was not assessed in the above two studies, and the blinding was clearly unsuccessful after crossover in Raphael et al.[83]

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Table 11 Characteristics and main efficacy findings of published RCT of PENS for peripheral neuropathic pain

Study, country, duration of follow-up and funding source	Comparison & sample size	Patient selection criteria and baseline characteristics	Outcome measures and results	Comments
Ghoname et al. 1999 [81] Single centre, USA (Dallas), follow-up: post treatment Funding source not stated. Two of the authors subsequently incorporated a company to produce PENS device.[83]	PENS vs. sham PENS vs. TENS, n=64 30 mins per session, 3 times per week for 3 weeks with 1-week washout between treatment modalities	Patients with typical radicular pain (sciatica) due to radiologically confirmed lumbar disc herniation. Mean age 43 years (range not reported), 53% female, mean duration of pain 21 months, baseline VAS pain 7.2 (for PENS group)	Mean scores 24 hrs before the 1st session / after the last session , VAS (0 best, 10 worst) PENS pre: Degree of pain 7.2 (1.8); Level of activity 6.4 (2.1); Quality of sleep 5.5 (1.9) PENS post: 4.1 (1.4); 4.0 (1.7); 3.1 (1.9) Sham pre: 6.6 (1.9); 6.0 (1.9); 5.2 (2.1) Sham post: 6.1 (1.9); 5.5 (2.1); 4.9 (1.9) TENS pre: 7.0 (1.9); 5.8 (1.7); 5.0 (2.0) TENS post: 5.4 (1.9); 4.5 (1.7); 4.0 (2.0) SF-36, mean score 24 hours after last session PENS: Physical component summary 35.3 (8.2); Mental component summary 44.2 (6.4) Sham PENS: 28.4 (6.7); 41.7 (6.2) TENS: 29.6 (7.4); 42.1 (6.0)	Also reported significant reduction in oral analgesic use in PENS and TENS groups but not in sham control. Compared to pre-treatment values (24h before each treatment modality) PENS was associated with 50% (±19) reduction over 3 week c.f. TENS (29% ±17) and Sham PENS (8% ±13) Overall patient evaluation of relative effectiveness after undergone all treatment modalities indicated PENS was the therapy preferred by the highest proportion of patients. Risk of bias was unclear for most of the assessed domains. Risk of detection bias was high given the crossover design. Carryout effect was likely.

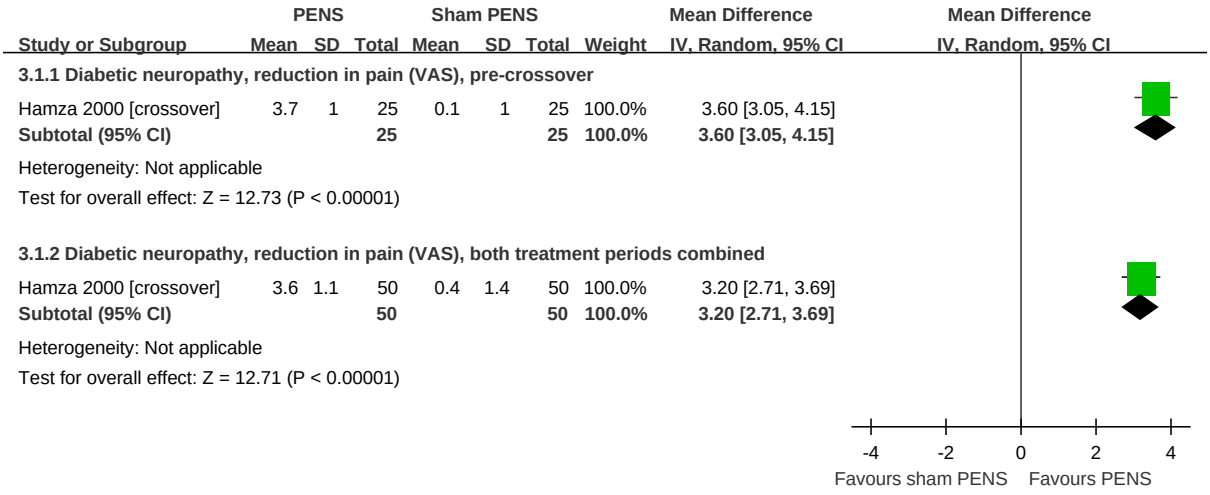
Hamza et al. 2000 [82] Single centre, USA (Dallas), follow-up: post treatment Funded by Ambulatory Anaesthesia Research Foundation and Egyptian Consulate. Two of the authors subsequently incorporated a company to produce PENS device.[83]	PENS (of tibial and deep perineal erve) vs. Sham PENS, n=50 30 mins per session, 3 times per week for 3 weeks with 1-week washout between PENS and sham PENS	Patients with type 2 diabetes and peripheral neuropathic pain > 6 months invovling the lower extremities Mean age 55 years (range 34 to 71), 56% female, mean duration of symptomatic neuropathy 18 months, baseline VAS pain 6.3	Mean scores 24 hrs before the 1st session / after the last session, VAS (lower value for pain and higher value for level of activity and quality of sleep indicates improvement): Degree of pain / Level of activity / Quality of sleep PENS pre 6.2 (1.3) / 4.8 (1.2) / 5.7 (1.3) PENS post wk 1 3.8 (1.2) / 6.5 (0.8) / 7.5 (1.2) PENS post wk 3 2.6 (0.9) / 7.8 (1.1) / 8.6 (1.0) Sham pre 5.2 (1.6) / 5.9 (1.3) / 6.8 (1.5) Sham post wk 1 4.6 (1.5) / 6.4 (1.1) / 7.3 (1.3) Sham post wk 3 4.8 (1.2) / 6.3 (1.2) / 7.1 (1.2) SF-36, mean score 24 hrs before the 1st session / 36 hrs after the last session Physical component summary / Mental component summary Baseline 31.2 (7.3) / 41.0 (5.8) PENS 36.8 (6.7) / 43.9 (5.6) Sham PENS 32.4 (7.5) / 42.0 (5.5)	Also reported similar results in the Beck Depression Inventory (n=46), Profile of Mood Status (n=44) and use of analgesics. Risk of bias was unclear for most of the assessed domains. Risk of detection bias was unclear before crossover and was high after crossover. Carryover effect was evident.
Raphael et al. 2011 [83] 2 centres, UK (West Midlands), follow-up 1 week post treatment Sponsored by the Higher Education Funding Council for England. Previously received research funding unrelated to this RCT from Algotec Ltd.	PENS vs. sham PENS n=31, one-off treatment of 25 minutes duration, with 4 weeks washout period before crossover	Adult patients with localised surface hyperalgesia from various chronic neuropathic pain conditions, had pain months and refractory to previous medical treatments Mean age 56 years, 58% female, mean duration of pain 8 years, median pain (numerical rating scale) 7.5	Pain intensity numerical rating scale (0-10), median Baseline / 1 wk post-treatment PENS 7.5 ± 1 / 0.5 ± NR Sham PENS 7.5 ± 1 / 7.5 ± 1 Pressure pain threshold, mean (gm) Baseline / 1 wk post-treatment PENS 202 ± 137 / 626 ± 228 Sham PENS 202 ± 134 / 206 ± 133 <u>Analysis of data from first treatment period only</u> Pain intensity numerical rating scale (0-10), median, reduction from baseline PENS 3.9 ± 3.2 Sham PENS 0.1 ± 0.4 p<0.0001 Pressure pain threshold, change from baseline PENS 310 ± 267 Sham PENS 8 ± 4 p=0.007	Overall PENS was found to be significantly more effective than sham PENS in reducing pressure pain (p<.0001) and pressure pain (p<.001). Low risk of bias for all Cochrane risk of bias domains. Reported that blinding was effective during the first treatment but all patients could tell whether they received active or sham therapy during the second treatment (after crossover).

Hamza et al. presented data for the first treatment period only (before crossover; this can be treated as data from a parallel-group study) and for the two treatment periods combined.[82] This allowed an assessment of the impact of the carryover effect and potential ineffective blinding of patients after crossover. Figure 3 shows that results from both datasets were similar, but the combined 2-period data slightly under-estimated the between-group difference in pain reduction and over-estimated the improvement in physical activity and sleep quality compared to the data from the first treatment period only.

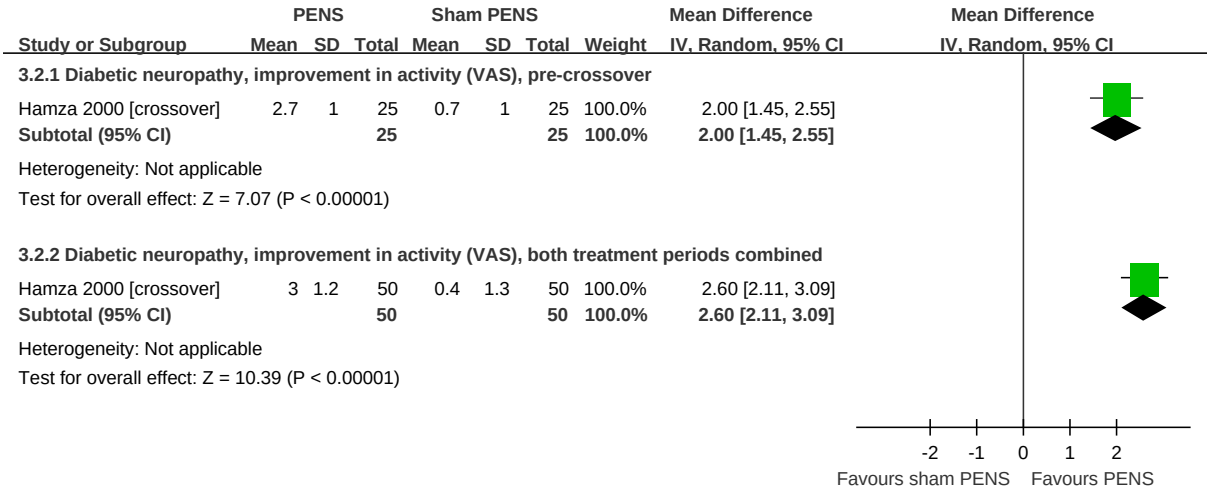
In the study by Raphael et al., given the single-session treatment and the longer washout period (four weeks) between treatments, carryover effect was not observed.[83] However, the authors assessed the effectiveness of blinding and found that patients were essentially unblinded during the second treatment (after crossover) as they could tell the difference from the first treatment they had received due to difference in sensation. The authors therefore presented data from the first treatment period only. The results still showed significant difference between-group in favour of PENS, but the effect size was much smaller compared to the combined 2-period data (see Table 11 and data table in Appendix 4).

Figure 3 Comparison of results between pre-crossover data and combined data from both treatment periods in the crossover trial of diabetic neuropathic pain by Hamza and colleagues.[82]

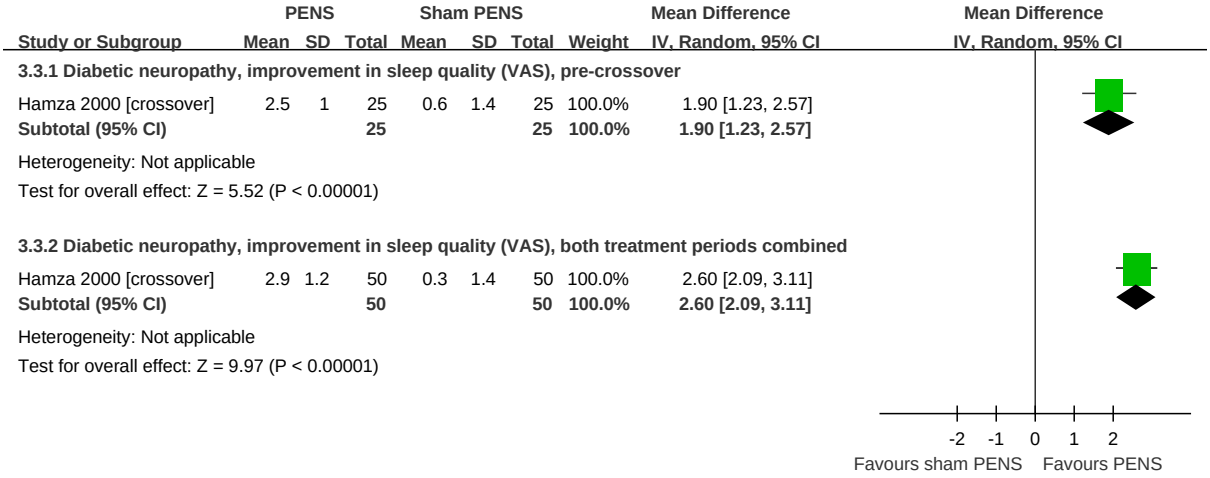
Reduction in pain (VAS 0-10)



Improvement in physical activity (VAS 0-10)



Improvement in quality of sleep (VAS 0-10)



Safety

Adverse effects were not mentioned in the study by Ghoname et al.[81] Both Hamza et al. and Raphael et al.stated that no adverse events were reported.[82;83]

Summary and discussion – PENS for chronic peripheral neuropathic pain

- Three crossover RCTs including a total of 145 patients were included in our analysis. The RCTs investigated different types of chronic peripheral neuropathic pain, including sciatica (Ghoname et al.),[80] diabetic neuropathic pain (Hamza et al.),[82] and surface hyperalgesia associated with various types of neuropathic pain conditions (Raphael et al. 2011).[83]
- Two of the RCTs were conducted in the same centre in the USA (Ghoname et al.; Hamza et al.),[81;82] and one was conducted in the West Midlands in the UK (Raphael et al. 2011).[83]
- The two US studies were judged to be at unclear risk for most of the bias domains. In addition there was carryover effect due to the short washout period. The UK study had low risk of bias for all the bias domains except blinding of patients for the second treatment period (after crossover), which was an issue for all three RCTs.
- All three RCTs reported significantly greater reduction in pain and improvement in other outcomes for PENS compared with sham PENS. The study by Ghoname and colleagues also showed that PENS was more effective than TENS in patients with sciatica.[81]
- Two of the studies (Hamza et al.; Raphael et al.)[82;83] reported data from the first treatment period separately. Data from Raphael et al. showed that, compared with data from first treatment period, the combined 2-period data over-estimated treatment effect

when effective blinding of patients could not be maintained after crossover.[83] This was also observed for two of the outcomes (physical activity and sleep quality), but not for reduction in pain in the trial by Hamza et al. in which both carryover effect and potential ineffective blinding could have influenced the results.[82]

- Acupuncture needles were used in the two USA studies, whereas a CE marked PENS system was used in the UK study. Therefore, there were differences in the devices used (e.g. the length of needles and stimulation frequency generated). In addition, data was collected at different timeframes (immediately after treatment to 72 hours after treatment for the USA studies, and one week after treatment for the UK study). It is not clear whether and by how much these differences could have impacted on the results observed.
- The duration of treatment and follow-up was short in the three RCTs. There is a lack of data on longer-term efficacy and safety.
- While no adverse effect was reported for PENS in the short-term, general safety precautions regarding the use of needles and electrical appliances for therapeutic purpose shall still apply.

6.2.3.3 PENS for other chronic pain

Twelve RCTs [84-95] and three larger case series [96-98] investigated the use of PENS for various chronic pain that is not generally considered neuropathic. The available evidence for each type of pain is briefly described below. Further details for the RCTs can be found in data-tables for individual studies in Appendix 4. An overview of findings from RCTs will also be provided in section 6.3.

6.2.3.3.1 PENS for chronic neck pain

One single centre crossover RCT conducted in the USA (Dallas) compared PENS in the painful area (local PENS) with PENS in a remote area (remote PENS) and 'needles only' in patients with non-radiating neck pain secondary to cervical disk disease (White et al.).[85] Local PENS (stimulating the dermatomes around the neck) was found to be significantly more effective compared to remote PENS (stimulating the dermatomes around the low back) and needles only.

6.2.3.3.2 PENS for chronic low back pain

Nine RCTs [84;86-93] and one larger case series [96] were identified. CE marked PENS devices currently do not cover the indication of chronic low back pain. However, given the large

volume of RCT evidence, detailed information is also provided in this section on the advice of the NICE technical team.

Design of RCTs

The nine RCTs included four crossover RCTs,[84;86-88] from the centre in Dallas and five parallel-group RCTs,[89-93] two of which where from a centre in Pittsburgh (both focused on older adults aged ≥65 years),[89;90] and one of each was from Spain,[91] Turkey,[92] and Japan.[93] The findings for these nine RCTs are presented in Table 12.

Efficacy

Overall results by comparators

All studies which included a sham PENS group reported that PENS was significantly more effective than sham PENS except in one study by Weiner and colleagues in which no significant difference was found between PENS and sham PENS.[89] PENS was found to be more effective compared with TENS in two studies (Topuz et al.; Yokoyama et al.),[92;93] and of similar efficacy compared with dry needling of trigger points in another study (Pérez-Palomares et al.).[91] One study found that PENS was more effective than exercise therapy (Ghoname et al.),[84] whereas another found no significant difference between PENS and exercise therapy (Weiner et al.).[89]

Pain relief

In their crossover trial Ghoname et al. reported PENS resulted in significantly greater improvement in VAS pain scores (6.3 ±1.5 to 3.4±1.4) over the study period than sham PENS (5.7±1.8 to 5.5 ±1.9), TENS (6.2±1.7 to 5.6±1.7) and exercise (6.5±1.4 to 6.4±1.9) ($p<.02$).[84] In the same year Ghoname et al. reported that a frequency of 15/30Hz resulted in a greater reduction in degree of pain (58% of patients) compared to sham (7%), 4Hz (41%) and 100Hz (49%) ($p<0.05$).[86] In their crossover trial, Hamza et al. reported 30 and 45 minutes stimulation produced similarly significant reductions in VAS pain score pre-first and post first treatment (6.4±1.9 to 3.9±1.8 and 6.3±1.9 to 3.8±1.8 respectively, $p<.01$) and pre- and post-sixth and final treatment (4.5±1.5 to 1.5±1.4 and 4.6±1.5 to 1.5±1.4, $p<.01$).[87] Whereas stimulation of duration of15 minutes required more sessions to achieve a statistically significant reduction in VAS pain scores. Therefore, Hamza et al. concluded that 30 minutes sessions are more optimal.

Topuz et al. reported greater reductions in the use of PENS over a two week period (3.61±1.98) than conventional TENS (2.80±2.00), low frequency TENS (2.60±1.40) and placebo TENS (-0.16±1.11) ($p<0.05$).[92]

Weiner et al. examined whether PENS might be complementary to physical therapy for older people.[90] Their study involved a three month follow up and good quality statistical analysis in which they used MANOVA (multiple analysis of variance) to assess group, time and interaction effects. They found significant group effects (physical therapy with PENS superior to physical therapy with sham ($p<0.02$)), time effects (improvement over time ($p<0.002$)), and interaction effects (differences in improvement over time between the two groups ($p<0.004$)) for pain intensity (see Table 12). In a later study Weiner et al. directly compared PENS against sham PENS (which provided five minutes of electrical stimulation through one pair of needles in each treatment session), sham PENS combined with general conditioning and aerobic exercise (GCAE) and PENS combined with GCAE.[89] Significant reduction in pain was observed in all four groups and no significant differences were observed between the groups over a period of six months.

A study by White et al. described the relative effectiveness of different montages (arrangement of electrodes) and found the 2nd montage to be more effective than other arrangements in improving VAS scores (significantly better than 3rd and 4th montage arrangements at $p<0.05$).[88]
Pérez-Palomares et al. found no significant difference between PENS and dry needling of trigger points.[91]

Physical activity
Ghoname et al. reported 51% (31/60) of patients reported improved physical activity for PENS compared to 4% (2/60) for Sham PENS, 8% (5/60) for TENS and 0% (0/60) for exercise modalities in their crossover trial.[84] Ghoname et al. reported that a frequency of 15/30Hz resulted in a greater increase in physical activity (65% of patients) compared to sham (6%), 4Hz (41%) and 100Hz (50%) ($p<.05$).[86] Whilst Hamza et al. found stimulation of 15, 30 and 45 minute sessions resulted in increased physical activity after a block of six treatments over two weeks from base (mean percentage improvement 28% ($p<.05$), 52% ($p<.01$)and 50% ($p<.1$)).[87]

Pérez-Palomares et al. found no significant difference between PENS and dry needling.[91]

Quality of life

Ghoname et al. reported differences in change between 4.66 and 5.82 for PENS compared to other treatment modalities for the physical component of SF36 and more modest differences of 1.7 to 1.84 for the mental component.[83] Topuz et al. found that PENS produced better improvements in SF-36 scores than conventional and low intensity TENS ($p<0.05$).[92]

Pérez-Palomares et al. (2010) found no significant difference between PENS and dry needling.[91]

Use of analgesics

Ghoname et al. reported significantly greater reduction in usage of oral non-opioid analgesics (pill per day) compared to sham PENS, TENS and exercise ($p<0.03$).[84] Ghoname et al. reported that a frequency of 15/30Hz resulted in a greater reduction in use of analgesics (48% of patients) compared to sham (5%), 4Hz (35%) and 100Hz (33%) (n.s.).[86]

Sleep

Ghoname et al. reported significantly greater improvement in sleep measured by VAS than other modalities ($p<0.02$).[83] Ghoname et al. reported that a frequency of 15/30Hz resulted in a greater improvement in sleep VAS scores (65% of patients) compared to sham (6%), 4Hz (48%) and 100Hz (50%) ($p<0.05$).[86]

Pérez-Palomares et al. (2010) found no significant difference between PENS and dry needling.[91]

Satisfaction with treatment

In the crossover trial by Ghoname et al. 91% (55/60) of patients reported PENS to be their preferred treatment modality compared to 6% (4/60) Sham PENS, 7% (4/60) TENS and 0% (0/60) exercise.[84]

Safety

None of the RCTs reported adverse events. Seroussi et al. reported a case series of 39 patients of which eight withdraw prior to responded screen.[96] One patient was excluded due to their leg pain being greater than their lower back pain, and three because they believed their back pain worsened and two felt soreness they attributed to electrode placement (the remaining two were unable to attend appointments) (See

Table 16).

Table 12 Characteristics and main efficacy findings of published RCTs of PENS for chronic low back pain

Study, country, duration of follow-up and funding source	Comparison & sample size	Patient selection criteria and baseline characteristics	Outcome measures and results	Comments
Ghoname et al. 1999 [84] Single centre USA (Dallas) Follow-up immediately after each treatment session and 24-72 hours after the last treatment session for each modality. Supported by Ambulatory Anesthesia Research Foundation of Dallas, Egyptian Cultural and Educational Bureau (Washington DC). Two of the authors subsequently incorporated a company 'PENS Inc' to produce FDA approvable PENS devices.	PENS vs. sham PENS vs. TENS vs. exercise therapy, n=60 Cross-over 4 x 3 weeks with 1- week washout in between	Low back pain secondary to degenerative disk disease **Mean age**: 43 years (±1.9y). **Sex**: 52% female. **Mean duration of pain**: Not stated. Baseline VAS pain 6.3 (for PENS group)	VAS pain (0-10), 48 hr before 1st and 24 hr after last (9th) treatment session. Pre-treatment / Post-treatment PENS 6.3 (1.5) / 3.4 (1.4)* Sham PENS 5.7 (1.8) / 5.5 (1.9) TENS 6.2 (1.7) / 5.6 (1.9) Exercise 6.5 (1.4) / 6.4 (1.9) *Significantly different from Sham PENS, TENS and exercise (p<0.02). SF-36, difference between treatment modalities in change from baseline at 24 hrs after last treatment session. Physical component / Mental component PENS vs. sham PENS 4.97 (2.99) / 1.84 (3.56) PENS vs. TENS 4.66 (2.85) / 1.70 (4.19) PENS vs. exercise 5.82 (2.93) / 1.84 (3.56) Overall patient evaluation of relative effectiveness after receiving all four treatment modalities. PENS / Sham PENS / TENS / Exercise Most desirable modality 55 (91%) / 1 (2%) / 4 (7%) / 0 (0%) Improved physical activity 31 (51%) / 2 (4%) / 5 (8%) / 0 (0%) Improved sense of wellbeing 46 (76%) / 7 (12%) / 10 (16%) / 6 (10%) Preferred pain therapy 55 (91%) / 1 (2%) / 4 (7%) / 0 (0%) Willing to pay extra for therapy 49 (81%) / 4 (6%) / 5 (9%) / 2 (4%)	Also reported that PENS produced significantly greater improvement in level of activity and quality of sleep (VAS) (p<0.02) and greater decrease in the usage of oral non-opioid analgesics (pills/day) (p<0.03) compared to sham PENS, TENS and exercise. **Adverse events:** Not stated.

<table>
<tr>
<td>Ghoname et al. 1999 [86]

Single centre
USA (Dallas)

Follow-up: 5-10 minutes after each treatment session and 72 hours after the final treatment session for each stimulus frequency.

Conflict of interest: Not stated.</td>
<td>PENS comparing 4 different stimulation frequencies (100 Hz, 15/30 Hz, 4 Hz, 0 Hz [sham]), n=68

Crossover 4 x 2 weeks with 1-week washout in between</td>
<td>Low back pain secondary to degenerative lumbar disk disease

Mean age: 46 years (±21y).

Sex: 56% female.

Mean duration of pain: Not stated</td>
<td>VAS pain (0-10), pre/5-10 mins post treatment.
<table>
<tr><th></th><th>Pre</th><th>Post</th></tr>
<tr><td>100 Hz 1st session</td><td>5.7 (1.6)</td><td>2.7 (1.5)</td></tr>
<tr><td>100 Hz 6th session</td><td>4.5 (1.5)</td><td>1.2 (1.5)</td></tr>
<tr><td>15/30 Hz 1st session</td><td>6.0 (1.7)</td><td>2.5 (1.3)</td></tr>
<tr><td>15/30 Hz 6th session</td><td>4.0 (1.4)</td><td>1.1 (1.4)</td></tr>
<tr><td>4 Hz 1st session</td><td>6.4 (1.6)</td><td>2.3 (1.2)</td></tr>
<tr><td>4 Hz 6th session</td><td>4.7 (1.6)</td><td>1.2 (1.2)</td></tr>
<tr><td>Sham 1st session</td><td>5.8 (1.5)</td><td>5.6 (1.8)</td></tr>
<tr><td>Sham 6th session</td><td>5.7 (1.7)</td><td>5.5 (1.8)</td></tr>
</table>
% improvement from baseline after last (6th) treatment session, measured by VAS (0-10) except analgesic usage.
<table>
<tr><th></th><th>Degree of pain*</th><th>Physical activity*</th><th>Sleep quality*</th><th>↓ in analgesic usage</th></tr>
<tr><td>100Hz</td><td>49%</td><td>50%</td><td>39%</td><td>33%</td></tr>
<tr><td>15/30Hz</td><td>58%**</td><td>65%**</td><td>60%**</td><td>48%</td></tr>
<tr><td>4Hz</td><td>41%</td><td>48%</td><td>43%</td><td>35%</td></tr>
<tr><td>Sham</td><td>7%</td><td>6%</td><td>4%</td><td>5%*</td></tr>
</table>
*Values estimated from figures.
**Significantly higher than the other three treatment modalities (p<0.05).

SF-36, mean change from baseline after last (6th) session.
<table>
<tr><th></th><th>Physical component summary</th><th>Mental component summary</th></tr>
<tr><td>100Hz</td><td>7.1</td><td>3.1</td></tr>
<tr><td>15/30 Hz</td><td>7.3</td><td>3.2</td></tr>
<tr><td>4Hz</td><td>7.0</td><td>2.8</td></tr>
<tr><td>Sham</td><td>Not reported*</td><td></td></tr>
</table>
*Stated ‘did not show any significant improvement’.</td>
<td>Other outcome measures: Overall patient evaluation of relative effectiveness after undergone four stimulus frequencies indicated 15/30Hz was the therapy preferred by the highest proportion of patients.

Adverse events:
Not stated.</td>
</tr>
</table>

Hamza et al. 1999 [87] Single centre USA (Dallas) **Follow-up:** 5-10 mins after each session, and after last session. **Conflict of interest:** Funded by Forest Park Institute, Egyptian Cultural and Education Bureau, Ambulatory Anaesthesia Research Foundation of Dallas**.**	PENS comparing 4 different stimulation duration (45, 30, 15, 0 minutes, n=72 Crossover - 4 x 2 weeks . three session per week with 1-week washout in between	Low back pain secondary to degenerative lumbar disk disease **Mean age**: 47 years (±18 years). **Sex:** 55% female. **Mean duration of pain**: 38 months.	Comparison of acute for each stimulation interval: Mean VAS pain score immediately before and after treatment (5-10 mins after treatment). VAS Pain Scores (mean ±SD) — Pre 1st Treatment — Post 1st Treatment — Pre 6th (final) Treatment — Post 6th Treatment Sham (0 min) — 6.2 ±1.9 — 5.8 ±1.7 — 6.0 ±1.6 — 5.4 ±1.9 15 min — 6.8 ±1.7 — 5.9 ±1.9 — 3.8 ±1.9 — 2.0 ±1.7* 30 min — 6.4 ±1.9 — 3.9 ±1.8** — 4.5 ±2.1 — 1.6 ±1.8 ** 45 min — 6.3 ±1.9 — 3.8 ±1.8** — 4.6 ±1.5 — 1.5 ±1.4 ** * p<.05; **p<.01 Mean % improvement from baseline (24h before 1st treatment) and end of 2 weeks (estimated from figures) and reduction in oral non-opioid medication. Pain — Physical activity — Sleep — Analgesic medication (pills per day) Sham (0 min) — 10 — 8 — 6 — 8 ±11% 15 min — 22* — 28* — 24* — 21 ±13%* 30 min — 46**† — 52**† — 45**† — 38 ±16%** 45 min — 41**† — 50**† — 40**† — 35 ±17%**† *Significantly different from sham (p<0.05) ** (p<0.01) †Significantly different from 15 mins (p<0.05) SF-36, mean change from baseline after last (6th) session Physical component — Mental component Sham (0 min) — not reported 15 min — 5.4* — 2.1* 30 min — 7.4** — 3.1** 45 min — 7.1** — 2.9** *p<0.01 vs. sham; **p<0.001 vs. sham	**Adverse events:** Not stated.

Pérez-Palomares et al. 2010 [91] Single centre Spain Follow up 3 weeks	PENS vs. dry needling of trigger points for 3 weeks, n=122	Low back pain ≥4 months **Mean age**: 45.85 years (±14.4). **Sex**: 75 % female. **Mean duration of pain**: Not stated.	Change from baseline for VAS scores at end of treatment (3 weeks): PENS median (SD) / Dry needling median (SD) Pain: 2.38 (2.27) / 2.35 (2.58) >40% reduction in VAS pain: n=28 (53.85%) / n=24 (46.15%) Sleep quality: 1.72 (2.67) / 1.85 (2.66) Number of patients included in analysis was not reported. Change from baseline for Oswestry Disability Index at end of treatment (3 weeks): PENS median (SD) / Dry needling median (SD) Personal care: 0.38 (0.97) / 0.34 (0.82) Lifting weight: 0.59 (1.42) / 0.06 (0.96) Walking: 0.17 (0.98) / 0.15 (0.57) Sitting: 0.21 (0.89) / 0.33 (1.05) Standing: 0.25 (0.84) / 0.41 (0.82) Social life: 0.72 (1.10) / 0.72 (3.03) Also measured change from baseline for algometry readings in right and left deep paraspinal muscles, right and left quadrates lumborum muscles, and right and left gluteus medius muscles. No significant differences were found between PENS and dry needling.	**Adverse events:** Not stated. Only mentioned post-treatment soreness 'could justify the higher rates of abandonment' in the dry needling treatment.
Topuz et al. 2004 [91]2 Single centre Turkey **Follow-up:** None. **Conflict of interest:** None stated	PENS vs. conventional TENS vs. low frequency TENS vs. sham TENS for 2 weeks, n=60	Low back pain ≥ 3 months **Study population:** Chronic lower back **n=** 55 (60). **Mean age:** 44.1 years (±12.21). **Sex:** 74.5% female. **Mean duration of pain:** 17.4 ± 11.72m	Reduction in VAS pain (0-10) at 2 weeks Current pain / Activity pain PENS: 3.61 ± 1.98 / 4.07 ± 1.75 C-TENS: 2.80 ± 2.00 / 2.50 ± 1.45 Low-TENS: 2.60 ± 1.40 / 2.15 ± 1.18 Placebo TENS: -0.16 ± 1.11 / 0.16 ± 0.83 Also measured functional disability measured by Low Back Pain Outcome Scale (LBPOS) and Oswestry Disability Index (ODI), and SF-36. PENS, C-TENS and Low TENS were significantly more effective than placebo TENS in respect to current pain, activity pain, Low Back Pain Outcome Scale, Oswestry Disability Index and SF36 ($p<.05$). PENS produced better improvements in activity pain and SF36 scores than C-TENS and low-TENS ($p<.05$).	**Adverse events:** None stated

Weiner et al. 2003 [90] Single centre USA (Pittsburgh) **Mean age**: 73.8 years **Sex:** 53% female. **Mean duration of pain:** 13.6 years	PENS vs. sham PENS (concurrent physical therapy in both groups) for 6 weeks, n=34	Older people with chronic low back pain	Primary outcome measures. MANOVA (p value) Pre / Post / 3 month follow up / Group effect / Time Effect / Inter-action effect Pain intensity — .02 / .002 / .004 McGill Pain Questionnaire — .04 / .005 / .009 PENS 13.06 (±1.31) / 6.66 (±0.87) / 6.19 (±0.88) Sham 12.24 (±1.69) / 12.47 (±2.04) / 11.82 (±1.90) MPI Pain Severity — .003 / .012 / .025 PENS 3.21 (±0.25) / 2.00 (±0.20) / 2.16 (±0.30) Sham 3.28 (±0.28) / 3.22 (±0.23) / 3.10 (±0.16) Pain related disability — .29 / .028 / .012 Roland disability scale — .26 / .042 / .034 PENS 12.63 (±1.13) / 7.81 (±1.02) / 9.25 (±1.08) Sham 11.24 (±1.47) / 11.06 (±1.17) / 12.18 (±1.21) MPI Interference Scale — .27 / <.001 / .036 PENS 3.52 (±0.37) / 2.44 (±0.33) / 2.61 (±0.26) Sham 3.30 (±0.37) / 3.10 (±0.40) / 2.97 (±0.37) PENS +PT significant reduction in pain intensity from pre to post treatment (p<.001) but Sham did not (p=.94) and pain related disability (p=.002 cf p=.81).	**Adverse events** Not stated.

Weiner et al. 2008 [89] Single Centre USA (Pittsburgh) **Follow-up:** Six months **Conflict of interest:** Second author has received funding from Eli Lily & Co. Research. Funded by National Centre for Complementary and Alternative Medicines, the National Institute on Aging, NIH and Pepper Older American Independence Centre.	PENS vs. sham PENS vs. general conditioning and aerobic exercise (GCAE) vs. sham PENS + GCAE for 6 weeks, n=200	Older people with chronic low back pain **Mean age**: 73.90 years **Sex:** 57 % female.	MPQ total (pain intensity)	Baseline	Post intervention Change on baseline	6 months follow up Change on baseline	This paper reports other outcomes: Generic Depression Scale, Chronic Pain Self-Efficacy Scale, the Catastrophrizing Scale of Cognitive Strategies Questionnaire, Fear-Avoidance Beliefs Questionnaire, pain medication, and physical function tests (usual pace gait speed, chair rise time, stair climb time) and reports these in a number of formats. **Adverse events:** 'In our experience, minor bruising and pain flares occur in less than 5% of patients and significant side effects are absent'.
			PENS	13.4 ±8.5	10 {-2.9 ±9.2 [.04]} [85]	9.7 {-3.4 ±7.4 [.47]}	
			PENS + GCAE	12.2 ±3.3	8.2 {-4.1 ±8.2 [.56]}	8.7 {-3.8 ±8.9 [.51]}	
			Control PENS	10.7 ±6.2	8.3 {-2.3 ±6.3 [.31]}	7.7 {-3.3 ±7.4 [.45]}	
			Control PENS + GCAE	12.0 ± 8.0	8.5 {-3.1 ±7.9 [.42]}	8.3 {-3.1 ±7.1 [.41]}	
			Roland (pain disability)				
			PENS	10.5 ±4.1	-2.6 ±4.5	-2.1 ±4.2	
			PENS + GCAE	10.2 ±3.8	-2.6 ±4.6	-2.1 ±4.3	
			Control PENS	10.5 ±5.2	-2.7 ±3.8	3.0 ±4.7	
			Control PENS + GCAE	11.0 ±5.4	-3.0 ±4.7	-2.8 ±5.3	
			Pittsburgh sleep score				
			PENS	13.4±8.5	-0.02±2.0	-0.4±2.7	
			PENS + GCAE	12.2±6.6	0.02±2.3	0.1±2.7	
			Control PENS	10.7±6.2	0.0±2.7	-0.4±2.6	
			Control PENS + GCAE	12.0±8.0	-0.7±2.3	-0.6±2.9	
			SF36 -PC				
			PENS	60.4±28.7	-1.1±20.7	-5.8±21.0	
			PENS + GCAE	51.0±27.4	3.9±25.8	4.4±23.5	
			Control PENS	56.3±26	5.9±23.8	5.1±24.7	
			Control PENS + GCAE	46.6±28.1	6.9±22.7	8.5±27.4	
			SF36-MC				
			PENS	88.8±14.3	1.5±12.0	-1.8±15.5	
			PENS + GCAE	90.5±10.3	-0.3±11.4	-0.2±13.7	
			Control PENS	90.9±9.7	-0.1±10.8	1.2±11.3	
			Control PENS + GCAE	85.9±18.6	2.8±13.7	1.5±13.9	

<table>
<tr>
<td>White et al. 2001 [88]
Single centre
USA (Dallas)

Follow-up: 5-10 minutes after each treatment (24 hours after the last session of each montage for SF-36).
Conflict of interest: Funded in part by the White Mountain Institute.</td>
<td>PENS comparing 4 different ‘montage patterns, n=72’

Cross over - 4 x 2 weeks with 1-week washout in between</td>
<td>Low back pain of > 6 month duration

Mean age: Not stated (range 21 to 76 years).
Sex: 57% female.
Mean duration of pain: Not stated.</td>
<td>VAS pain (0-10), 5-10 mins pre/post treatment.
<table>
<tr><th></th><th>Pre</th><th>Post</th></tr>
<tr><td>Montage 1, 1st session</td><td>6.0 (1.6)</td><td>3.8 (1.7)</td></tr>
<tr><td>Montage 1, 6th session</td><td>4.4 (1.6)</td><td>1.4 (1.3)</td></tr>
<tr><td>Montage 2, 1st session</td><td>6.1 (1.7)</td><td>3.2 (1.5)</td></tr>
<tr><td>Montage 2, 6th session</td><td>3.8 (1.4)</td><td>1.2 (1.7)</td></tr>
<tr><td>Montage 3, 1st session</td><td>5.5 (1.9)</td><td>3.9 (1.8)</td></tr>
<tr><td>Montage 3, 6th session</td><td>4.5 (1.5)</td><td>1.6 (1.5)</td></tr>
<tr><td>Montage 4, 1st session</td><td>5.5 (1.9)</td><td>4.1 (1.8)</td></tr>
<tr><td>Montage 4, 6th session</td><td>4.6 (1.5)</td><td>1.5 (1.4)</td></tr>
</table>
VAS pain (0-10), 24 hr before 1st and after last treatment
<table>
<tr><th></th><th>Pre-treatment</th><th>Post-treatment</th></tr>
<tr><td>Montage 1</td><td>6.0 (1.6)</td><td>3.2 (1.2)</td></tr>
<tr><td>Montage 2</td><td>6.1 (1.7)</td><td>2.2 (1.3)</td></tr>
<tr><td>Montage 3</td><td>6.1 (1.6)</td><td>3.5 (1.5)</td></tr>
<tr><td>Montage 4</td><td>6.2 (1.7)</td><td>3.6 (1.5)</td></tr>
</table>
Percentage change from baseline at the end of each montage
<table>
<tr><th>VAS (0-10)</th><th>Degree of pain</th><th>Level of activity</th><th>Quality of sleep</th><th>Usage of oral analgesic</th></tr>
<tr><td>Montage 1</td><td>47%</td><td>42%</td><td>30%</td><td>-43% (23%)</td></tr>
<tr><td>Montage 2</td><td>64%</td><td>51%</td><td>46%</td><td>-47% (21%)</td></tr>
<tr><td>Montage 3</td><td>43%</td><td>37%</td><td>28%</td><td>-27% (23%)</td></tr>
<tr><td>Montage 4</td><td>42%</td><td>35%</td><td>29%</td><td>-23% (23%)</td></tr>
</table>
SF-36, 24 hours after last session, mean change from baseline
<table>
<tr><th></th><th>Physical component summary</th><th>Mental component summary</th></tr>
<tr><td>Montage 1</td><td>7.1</td><td>2.9</td></tr>
<tr><td>Montage 2</td><td>7.6</td><td>3.2</td></tr>
<tr><td>Montage 3</td><td>5.9</td><td>1.9</td></tr>
<tr><td>Montage 4</td><td>5.7</td><td>1.8</td></tr>
</table>
All post-treatment scores were significantly different from pre-treatment scores ($p<0.05$ or 0.01). Montage 2 was more effective than the other montages for overall percentage change at the end of treatment for VAS pain, level of activity ($p<0.05$ vs. montages 3 and 4) and quality of sleep ($p<0.05$ vs. montages 1, 3 and 4). For SF-36 physical and mental component summary scores and oral analgesic usage, the change from baseline for montages 1 and 2 were significantly greater than montages 3 and 4 ($p<0.05$).</td>
<td>Adverse events
Not stated.</td>
</tr>
</table>

Yokoyama et al. 2004 [93] Single centre Japan **Follow-up:** 2 months (study 16weeks). **Conflict of interest:** Not stated.	PENS only vs. PENS followed by TENS vs. TENS only for 8 weeks, n=60	Low back pain ≥ 6 months **Mean age:** 59 years (N/A). **Sex:** 57% female. **Mean duration of pain:** not stated	Peak pain VAS (0-100) score at: PENS (n=18): 4 wks 37 ± 10; 8 wks 32 ± 11; 16 wks 49 ± 13 PENS→TENS (n=17): 4 wks 36 ± 13; 8 wks 44 ± 12; 16 wks 55 ± 12* TENS only (n=18): 4 wks 52 ± 12*; 8 wks 48 ± 11; 16 wks 56 ± 12* *Estimated from graph During treatment PENS group VAS scores decreased significantly with baseline scores (2 wks p<.05; 4wks p<.01; 8wks p<.01) and 1 month significantly lower (p<.01), but returned to pre-treatment levels at 2 months (week 16). Peak pain level was significantly lower during treatment for PENS than TENS only group and 1 month follow up (2 weeks p<.05, 4 weeks p<.01, 8 weeks p<.01 and 12 weeks p<.01). In PENS→TENS there were also significant decrease in peak pain over 8 week treatment period compared to baseline but not at 1 month follow-up (12 weeks).	Also measured were physical impairment and daily intake of NSAIDs. Results consistent with pain outcomes measures and suggest PENS more effective than TENS and that the effects of PENS gradually wane after treatment stops

Summary and discussion – PENS for chronic low back pain

- Nine RCTs including 748 patients were included in our analysis.
- The RCTS varied significantly in focus from testing the effectiveness of different montages, stimulation frequency and length of sessions to assessing efficacy when combined with other therapies (physical therapy or exercise), direct comparison with TENS and sham treatments.
- There is reasonable evidence on the efficacy of PENS in reducing pain as measured by VAS and other indices across the nine RCTs.
- In addition to reduction of chronic lower back, there is some evidence that PENS positively affects secondary outcomes such as improved quality of sleep, physical activity and quality of life.
- While the RCTs do not report adverse effects there is only limited evidence on safety from one identified case series.

6.2.3.3.3 PENS for osteoarthritis of the hip

One double-blind, parallel-group RCT conducted in Sheffield found significant placebo effect in the sham PENS group, but no significant difference between PENS and sham PENS in patients with osteoarthritis of the hip awaiting join replacement (Cottingham et al.).[94]

6.2.3.3.4 PENS of posterior tibial nerves for urological and pelvic pain

One RCT and three larger case series were found. A parallel-group RCT (Kabay et al.) was conducted in patients with category IIIB chronic prostatits/ chronic pelvic pain.[94] Blinding was not mentioned. The study showed that PENS was more effective than sham PENS in reducing pain and improving symptoms and urgency. One of the case series investigated PENS in patients with interstitial cystitis (Zhao et al.),[97] and two evaluated PENS in chronic pelvic pain (Kim et al.; van Blaken et al.).[98;99] This technique of peripheral neurostimulation is also known as posterior tibial nerve stimulation, which has been covered by NICE Interventional Procedures guidance IPG362 ‘Percutaneous posterior tibial nerve stimulation for overactive bladder syndrome’ and IPG395 ‘Percutaneous tibial nerve stimulation for faecal incontinence’.

6.3 Overview of best available evidence across stimulation techniques

Having outlined the body of evidence in the field of peripheral neurostimulation for chronic pain and described in detail the three areas in which CE marked devices are currently available, we provide a panoramic overview of best available evidence in this section,[100] highlighting the strength and weakness of evidence and methodological issues in the published literature.

6.3.1 Characteristics and quality of RCTs

The characteristics of the 22 included RCTs (four of which are published as conference abstracts only) and six additional ongoing/unpublished RCTs are shown in Table 13, sorted by stimulation techniques (ONS, PNFS and PENS) and types of pain. Of the 22 RCTs from which at least some results are available, four investigated ONS (three of which were published only as conference abstracts), two assessed PNFS (one as conference abstract) and 16 evaluated PENS. The painful conditions under investigation include chronic migraine (ONS, three RCTs), mixed types of headache (PENS, one RCT), fibromyalgia (ONS, one RCT), chronic low back pain (PENS, nine RCTs), and one RCT each for chronic neck pain (PENS), chronic back pain (PNFS), diabetic neuropathic pain (PENS), sciatica (PENS), Category IIIB chronic non-bacterial prostatitis /chronic pelvic pain syndrome (PENS), osteoarthritis of the hip (PENS) and of the knee (PNFS), and hyperalgesia associated with various neuropathic condition (PENS).

The majority (15/22) of the RCTs were conducted in the USA. Most were single centre studies (16/22) although multicentre, international trials have started emerging. Half (11/22) adopted a crossover design. Sample sizes ranged from 15 to 200, with four trials recruiting more than 100 patients. Duration of treatment and follow-up for the randomised controlled periods was short, with a 12-week follow-up for the ONS migraine studies and shorter treatment and follow-up for most of the studies of other painful conditions. Two PENS studies had a 6-month follow-up. Longer-term, uncontrolled open-label follow-up was planned for a few recent trials.

Some form of sham control was used in the majority (19/22) of trials. Other comparators included TENS, dry needling of trigger points, exercise, and medication management. Six studies compared different stimulation parameters (e.g. stimulation frequency, duration, location and montage). Diverse outcome measures were used (see Appendix 2).

Table 13 Characteristics of identified RCTs (results not yet available for the shaded studies which are either unpublished or ongoing)

Study	Type of pain	Country	Centre	Comparison	Design	Blinding	Sample size	Duration of treatment	Follow up	Status
Implanted PNS - occiptial nerve stimulation (ONS)										
Lipton et al. 2009 [15] (PRISM study)	Migraine	USA	Multicentre	ONS vs. sham	Parallel group	Double-blind (12 weeks) then open label	140	12 weeks then 1 year	3 months (2-year follow-up for safety)	Conference abstract only
Saper et al. 2011 [16] (ONSTIM study)	Migraine	USA, Canada, UK	Multicentre	ONS vs. sham vs. medication management	Parallel group	Double-blind (3 months) then open label	75	3 months then until 3 years	1 & 3 months and 3 years (ongoing)	3-month results published
Silberstein et al. 2011 [17]	Migraine	USA	Multicentre	ONS vs. sham	Parallel group	Double-blind (12 weeks) then open label	157	12 weeks then until 1 year	1 year	Conference abstract only; publication pending
Gerardo 2011 [18] NCT00407992	Migraine	Italy	Single centre	ONS vs. sham	Crossover	Open label	34	Not reported	Not reported.	Completed but not yet published
Goadsby 2011 [19] (PRISM UK study) NCT00747812	Migraine	UK (London)	Single centre	ONS vs. sham	Crossover	Double-blind	25	12 weeks then 4 weeks then until 1 year	1 year	Ongoing
Caillon 2012 [21] SENGO-CAM Study) NCT01184222	Headache associated with medication overuse	France	Single centre	ONS vs. sham	Parallel group	Single blind (participants)	30*	14 days	14 days	Ongoing
Wilbrink 2011 [24] (ICON study) NCT01151631	Cluster headache	International	Multicentre	ONS 100% vs. ONS 30%	Parallel group	Double-blind (6 months) then open label	144*	6 months then until 1 year	1 year	Ongoing
De Ridder and Plazier 2009 [101]NCT00917176	Fibromyalgia	Belgium	Single centre	ONS sub-threshold vs. sham	Crossover	Double-blind	Not reported	Not reported	10 weeks	Completed; publication pending
Plazier et al. 2011 [38]; Diaz 2011 [20] NCT01298609	Fibromyalgia	Belgium	Single centre	ONS vs. sham vs. sub-threshold	Crossover	Double-blind	15 (40*)	3 x 2 weeks then permanent	6 week & 6 months	6-week results (n=15) published as conference abstract

Study	Type of pain	Country	Centre	Comparison	Design	Blinding	Sample size	Duration of treatment	Follow up	Status
Implanted PNS - sphenopalatine ganglion stimulation										
Jensen 2012 [102]	Chronic or high frequency, high disability migraine	Belgium, Denmark, Spain	Multicentre	Implanted PNS vs. sham PNS	Parallel group	Single blind (patient)	30	14 to 22 weeks	14 to 22 weeks	Ongoing
Peripheral nerve field stimulation (PNFS)										
Barolat et al. 2011 [71]	Chronic intractable pain of the back	USA	Unclear	PNFS trial stimulation (standard vs. low frequency vs. subthreshold vs. minimal)	Crossover	Not described	30	4 x 4-8 days	22 to 37 days (randomised phase, trial stimulation); 1 year (implanted, without control group)	Conference abstract only
Kang et al. 2007 [79]	Osteoarthritis of the knee	USA (Chicago)	Single centre	PNFS (temporary) vs. sham	Parallel group	Single-blind (patient)	70	Single session	6, 24, 48 hrs and 1 week after treatment	Published
Percutaneous electrical nerve stimulation (PENS)										
Ahmed et al. 2000 [80]	Tension-type headache, migraine, or post-traumatic headache symptoms	USA (Dallas)	Single centre	PENS vs. sham PENS	.Crossover	Single-blind (assessor)	30	2 x 2 weeks with 1- week washout in between	5-10 mins after each session	Published
White et al. 2000 [85]	Chronic non-radiating neck pain secondary to cervical disk disease	USA (Dallas)	Single centre	Local PENS vs. remote PENS vs. needles only	Crossover	Single-blind (assessor)	68	3 x 3 weeks with 1-week washout in between	5-10 mins after each session and 24 hrs after last session	Published
Ghoname et al. 1999 [84]	Low back pain secondary to degenerative disk disease	USA (Dallas)	Single centre	PENS vs. sham PENS vs. TENS vs. exercise therapy	Crossover	Single-blind (assessor)	60	4 x 3 weeks with 1- week washout in between	5-10 mins after each session and 24-72 hrs after last session	Published
Ghoname et al. 1999 [86]	Low back pain secondary to degenerative lumbar disk disease	USA (Dallas)	Single centre	PENS comparing 4 different stimulation frequencies (100 Hz, 15/30 Hz, 4 Hz, 0 Hz [sham])	Crossover	Single-blind (assessor)	68	4 x 2 weeks with 1-week washout in between	5-10 mins after each session and 72 hrs after last session	Published

Study	Type of pain	Country	Centre	Comparison	Design	Blinding	Sample size	Duration of treatment	Follow up	Status
Hamza et al. 1999 [82]	Low back pain secondary to degenerative lumbar disk disease	USA (Dallas)	Single centre	PENS comparing 4 different stimulation duration (45, 30, 15, 0 minutes)	Crossover	Single-blind (assessor)	75	4 x 2 weeks with 1-week washout in between	5-10 mins after each session, and after last session	Published
Percutaneous electrical nerve stimulation (PENS) - continued										
White et al. 2001 [88]	Low back pain of > 6 month duration	USA (Dallas)	Single centre	PENS comparing 4 different 'montage patterns'	Crossover	Single-blind (assessor)	72	4 x 2 weeks with 1-week washout in between	5-10 mins after each session and 24 hrs after last session	Published
Weiner et al. 2003 [89]	Older people with chronic low back pain	USA (Pittsburgh)	Single centre	PENS vs. sham PENS (concurrent physical therapy in both groups)	Parallel group	Double-blind	34	6 weeks	Within 1 week and then 3 months after completion of intervention	Published
Topuz et al. 2004 [90]	Low back pain ≥ 3 months	Turkey	Single centre	PENS vs. conventional TENS vs. low frequency TENS vs. sham TENS	Parallel group	Single-blind (participant)	60	2 weeks	2 weeks	Published
Yokoyama et al. 2004 [93]	Low back pain ≥ 6 months	Japan	Single centre	PENS only vs. PENS followed by TENS vs. TENS only	Parallel group	Open-label	60	8 weeks	16 weeks	Published
Weiner et al. 2008 [89]	Older people with chronic low back pain	USA (Pittsburgh)	Single centre	PENS vs. sham PENS vs. general conditioning and aerobic exercise (GCAE) vs. sham PENS + GCAE	Parallel group, factorial design	Double-blind	200	6 weeks	6 weeks and 6 months	Published
Pérez-Palomares et al. 2010 [91]	Low back pain ≥4 months	Spain	4 centres	PENS vs. dry needling of trigger points	Parallel group	Single-blind (assessor)	122	3 weeks	3 weeks	Published

Study	Type of pain	Country	Centre	Comparison	Design	Blinding	Sample size	Duration of treatment	Follow up	Status
Ghoname et al. 1999 [81]	Sciatica due to lumbar disc herniation	USA (Dallas)	Single centre	PENS vs. Sham PENS vs. TENS	Crossover	Single-blind (assessor)	64	3 x 3 weeks with 1-week washout in between	Immediately after each session and 24-72 hrs after last session	Published
Cottingham et al. 1985 [94]	Osteoarthritis of the hip	UK (Sheffield)	Single centre	PENS (radial, median and saphenous nerves) vs. sham PENS	Parallel group	Double-blind	35	2 weeks	Post treatment and 1, 3 and 6 months	Published
Percutaneous electrical nerve stimulation (PENS) - continued										
Hamza et al. 2000 [82]	Diabetic neuropathic pain	USA (Dallas)	Single centre	PENS vs. sham PENS	Crossover	Single-blind (assessor)	50	2 x 3 weeks with 1-week washout in between	Post each week of treatment and 24-48 hrs after last session	Published
Kabay et al. 2009 [95]	Category IIIB chronic non-bacterial prostatitis /chronic pelvic pain syndrome	Turkey (Kutahya)	Single centre	PENS (posterior tibial nerve) vs. sham PENS	Parallel group	Not described	89	12 weeks	12 weeks	Published
Raphael et al. 2011 [83]	Patients with surface hyperalgesia from various chronic pain conditions	UK (Birmingham)	2 centres	PENS vs. sham PENS	Crossover	Double-blind	30	2 x single session with 4-week washout in between	1 week after treatment	Published

*Estimated enrolment

The results of quality assessment of the 22 RCTs are summarised in Appendix 3. Generation of random sequences and/or allocation concealment were not clearly reported in the majority of studies. Both items were considered adequate in only three studies. Although 17 studies included a sham control group, the effectiveness of blinding and patients' expectation of treatment effectiveness was assessed in only two studies. These assessments are particularly important in studies in which no electrical currency was applied to the sham control, as it is likely that study participants were able to distinguish it from the active treatment due to lack of sensation of paraesthesia. Blinding of investigators treating the patients was not possible. Blinding of outcome assessors was reported in many studies although this may have limited impact as most of the measured outcomes were patient-reported. Attrition was generally low, but was not reported in the series of trials of PENS conducted in Dallas, USA. With two exceptions, intention to treat analysis was not used and patients who dropped out were excluded from analysis. However, the number of dropouts was generally small. Risk of outcome reporting bias was considered high only in the study by Saper and colleagues.[16] We were unable to properly assess the quality of the four RCTs which have only been published as conference abstracts.

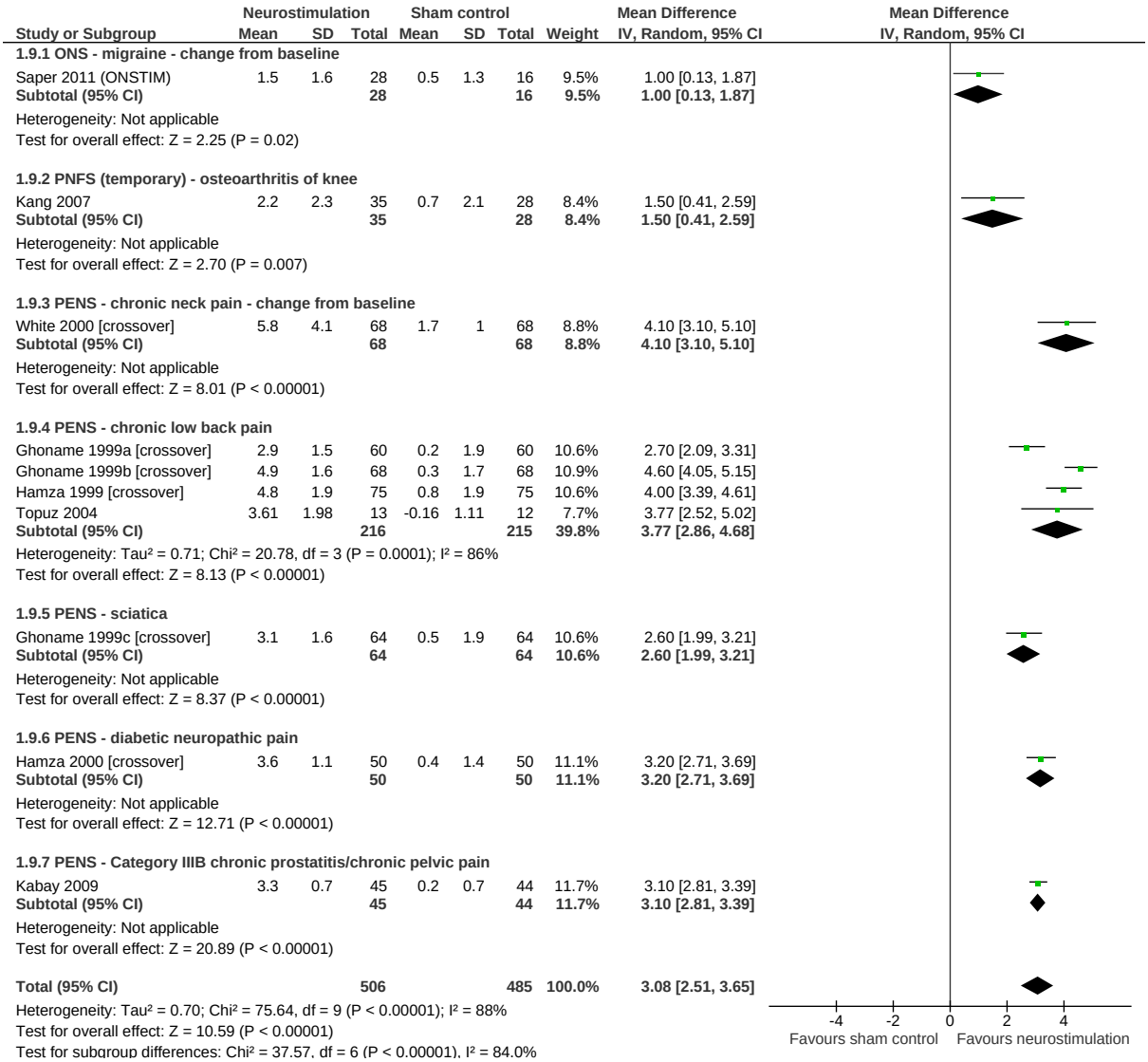
6.3.2 Effectiveness of neurostimulation versus sham control

6.3.2.1 Reduction in pain

Whilst outcomes related to pain were reported in most studies (except for a few trials of migraine and fibromyalgia published as conference abstracts, see Appendix 2) different measurement tools have been used. It is therefore worth emphasising that data amenable for quantitative synthesis and shown in figures below only represented approximately half of the trials. Figure 4 shows the reduction in pain measured in 0-10 VAS scale, which was the most commonly used tool. Significantly greater reduction in pain was observed in all ten trials reporting the outcome. The reduction reported in the ONS trial for migraine and the PNFS trial for osteoarthritis appeared smaller than the other eight trials of PENS for various pain conditions. Seven of the eight PENS trials were conducted in the same centre at Dallas, USA. Significant reduction in pain compared to sham control was also observed in other studies using different scales such as Pain and Distress scale,[17] McGill Pain Questionnaire,[90] numerical rating scale,[83] (all PENS studies) and >50% pain relief (PNFS).[71] There were, however, two exceptions. One was an RCT (n=31) of two week PENS treatment for patients with osteoarthritis of the hip awaiting joint replacement, in which no significant difference in VAS score of worse pain was observed at the two week and six month follow-ups (3.4 vs. 2.4, 7.5 vs. 7.5 for PENS and sham group, respectively).[94] The other was an RCT (n=200) of PENS for chronic low back pain in older adults. The trial

adopted a factorial design comparing six week interventions of PENS, sham PENS, PENS with therapeutic exercise and sham PENS with therapeutic exercise. There was significant reduction in pain and improvement in self-reported disability in all four groups, with no significant difference between the groups (e.g. reduction in average pain in the past week measured on pain thermometer, 0.7 vs. 0.6 at six weeks and 0.5 vs. 0.6 at six months for PENS vs. sham PENS, respectively) except for fear avoidance beliefs, which were significantly fewer in the two groups with therapeutic exercise. The use of oral analgesics in the neurostimulation groups (where reported) was significantly reduced compared to the sham control group in the trials where significant pain reduction was observed, but was reduced to a similar extent between groups in the trial in which no difference in pain reduction was observed.[94]

Figure 4 Panoramic synthesis of reduction in pain measured in visual analogue scale (VAS)



6.3.2.2 Improvement in other outcomes

The results for outcomes in other domains including physical functioning, emotional functioning, sleep quality and health-related quality of life are generally consistent with the pain outcomes. Further details of key findings of each RCT can be found in data tables in Appendix 4, and results of further quantitative analysis are shown in Appendix 5.

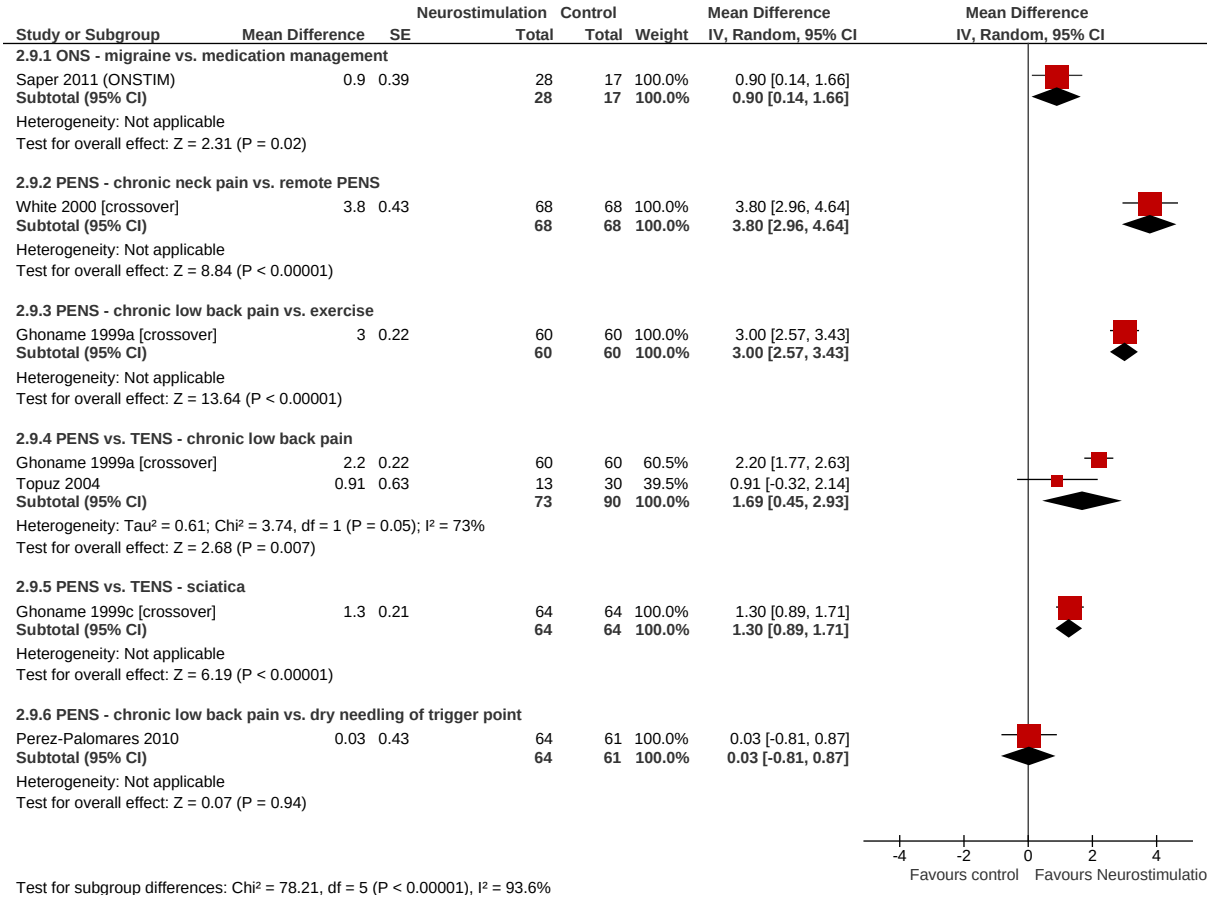
6.3.3 Effectiveness of neurostimulation versus other comparators

In addition to sham control, neurostimulation techniques were also compared with other comparators. These included comparison of ONS with medication management in patients with migraine, and PENS compared with exercise therapy, TENS and dry needling of trigger points. The results for pain reduction are shown in Figure 5. ONS was shown to be significantly more effective than medication management in chronic refractory migraine and PENS was more effective than TENS. PENS was superior to exercise in one trial but was equivalent to exercise therapy in another study.

Stimulation parameters were systematically explored in a series of RCTs of PENS by the team based in Dallas, USA. They concluded that:

- an alternating frequency of 15/30 Hz (effective for 58%) was more effective than either 4 Hz (41%) or 100 Hz (49%) of patients [86];
- a stimulation duration of 30 minutes was more effective than 15 minutes and equally as effective as 45 minutes (both 30 and 45 minutes sessions resulted in statistically significant reduction in VAS pain score (0-10) in the first session and this was durable over the six sessions (3 sessions per week for 2 weeks) whereas statistically significant reduction in VAS scores took longer emerge for 15 minutes sessions) [87];
- a montage that provided stimulation along the involved nerve roots at the dermatomal levels corresponding to the patients' pain symptoms was more effective than other montages.[88]

Figure 5 Reduction in pain for various neurostimulation techniques compared to comparators other than sham control.



6.4 Safety Results

6.4.1 Evidence from RCTs

Of the 22 RCTs, 12 did not mention any adverse event.[38;80;81;84;86-88;90;92;93;95;103] Most of the other RCTs either described minor adverse events, such as tingling or slight pain in the needling site, or stated that no adverse event occurred. Adverse events were reported in three RCTs of ONS for migraine. Lipton et al.[15] (conference abstract only) reported that infection, non-target area sensory symptoms and implant site pain were the most-frequent device related adverse events. Saper et al.[16] described device-related events including intraoperative failures 4% (2/53), serious adverse events requiring hospitalisation 6% (3/51), implant site infection, lead migration 24% (12/51), and postoperative nausea. They stated that there was “no evidence of adverse events leading to long-term complications or potential nerve damage”. Silberstein et al.[17] reported a 1% rate of serious device or procedure-related events, including one case of infection and one case of expected post-operative pain that required hospitalization.

Of the reminding seven RCTS three specifically stated there were no serious adverse events,[82;83;85] but four mentioned minor adverse events, including tingling,[79;94] drowsiness,[104] skin rash,[79] minor bruising,[89] and pain flair.[104;1045]

6.4.2 Evidence from large case series

Sixty case series with ≥ 10 patients were assessed. The results for ONS, PNFS and PENS are shown in Table 14 to

Table 16. Additional data for other implanted PNS techniques is listed in Appendix 6. Overall, serious adverse events were uncommon. Lead migration occurred fairly frequently. Infection and device malfunction have also been reported

.

Table 14 Reported adverse events and other technical/safety issues in case series of occipital nerve stimulation

Author	Follow-up	Failed trial (1st stage)	Implanted	Lead migration	Lead type	Lead malfunction or disconnect	Infection	Requested removal	Allergy	Safety issues as reported	Device / notes
Transformed migraine											
Popeney and Aló, 2003 [22]	Mean 18.3m	0/25	25	9/25	C	0/25	1/25	0/25	0/25		Pisces Quad Plus/Synergy
Oh et al. 2004 [23]	8m-5y	0/20	20	7/20	P	0/20	2/20	1/20	0/20	1 battery depletion after 3 years	Mixed population: 10 transformed migraine and 10 occipital neuralgia
Cluster headache											
Burns et al. 2009 [29]	Median 17.5m (4-35m)		14	4						'Adverse events of concern were lead migration and battery depletion'. 6 required battery replacement due to depletion 4 required new electrodes/leads. 'Muscle recruitment, neck stiffness, skin discomfort, superficial infections and painful overstimulation were also seen.'	Quad electrodes and IPG, Medtronic
Fontaine et al. 2011 [26]	Mean 14.6m		13 (14 – 1 moved region)		P & C		1*	1*		1 wound issue without infection 1 perceived the stimulation induced infection paresthesia as unpleasant *Removed after 6 m as patient did not improve. Infection occurred in the same patient.	Resume electrode (4), Quad (4), Medtronic Lamitrode 44 St Jude ANS (5)
Magis et al. 2011 [27]	Mean 36.82m (11-64m)		15	1	P		3/12			2 Unbearable paresthesia 1 Dsyesthesias in the ear 2 Battery discomfort 2 Connecting wire discomfort 1 Muscle contraction 1Diffuse headache on tilting head	Medtronics 3587A Resume II paddle, Medtronic 7425 Itrel 3 internal battery; when battery went flat Medtronic Synergy or Restore stimulator.

Author	Follow-up	Failed trial (1st stage)	Implanted	Lead migration	Lead type	Lead malfunction or disconnect	Infection	Requested removal	Allergy	Safety issues as reported	Device / notes
Müeller et al. 2011 [28]	Mean 12m (3-8)	0	10 (2/8)		C		1/10			1 local infection leading to explantation of generator and externalisation of electrodes until infection healed, and before implanting another generator in a different location. Dislocation of electrode. 1 re-operated because of scar formation around thoracic connector which caused discomfort Patients opting for generator to located in abdomen experienced painful pressure when lifting or carrying heavy objects Those opting for gluteal location reported foreign body feeling when sitting for prolonged periods. 1 developed a pressure ulcer (2nd degree, superficially located, no super infection) at operation site. 3 required modification of polarity.	Not clear as researchers 'advise' the use of 4 pole electrodes with large distance between electrode poles (e.g. Pisces Quad Plus, Medtronic) or 8 pole (e.g. Octrode, ANS St Jude).

Table 14 (cont.)

Author	Follow-up	Failed trial (1st stage)	Implanted	Lead migration	Lead type	Lead malfunction or disconnect	Infection	Requested removal	Allergy	Safety issues as reported	Device / notes
Neuralgia and headache and craniofacial pain associated with occipital nerve											
Weiner & Reed 1999 [30]	N/R		13	1/13	C	1/13	1/13	0/13			
Oh et al. 2004 [23]	8m-5y	0	20	7/20	P	0/20	2/20	1/20	0/20	2 infections (1 required removal and replacement) 1 reported worsened pain elsewhere and requested explant 1 allergic and developed severe pain at generator site, leading to explant 7 experienced lead migration due to anchor dislodgement (replaced with dual paddle style electrode without further dislodgement)	Peripheral paddle style electrode (Resume II/Resume TL, Medtronic) Itrel III/Synergy IPG, Medtronic
Slavin et al. 2006 [32]	Mean 22m (5-32m)	4/14	10 (7/3)	1 (x2)/14	C	0/10	1/10	1/10	0/10	1 infection leading to partial explant 1 request for removal as patient experiencing tightness and spasms in neck and right side of bidy (same person who experienced lead migration) Battery depletion at last follow-up 2 explanted or partially explanted	Quad PICES, Medtronic or Quatrode, Advanced Neuromodulation Systems
Melvin 2007 [34]	12w	3/14	11(9/2)	1/11	C	1	0				Awaiting paper
Slavin et al. 2006 [31]	Mean 35m (1-77m)	8/30	22/30	1/22	C	1/22	1/22			5/22 removals due to: Improvement in pain intensity & stopped using stimulator 6m prior (2) Initial benefit lost (2) Infection (1) Infection: 0/22 post operative period; 1/22 infection developed in generator pack 2years later Also reported but comprised in above: 1 skin erosion over electrode tip 1 infection between electrode and extention cable 1 migration of electrode	Note: mixed type of stimulation Supraobital (7) Infraobital (6) Occipital (21) 1+nerve (19) E.g. Quad, Octad Plus or Quad Compact, Medtronic; Quattrode, Octrode or Axxess, Advanced Neuromodulation Systems; Linear, Advanced Bionics

Table 14 (cont.)

Author	Follow-up	Failed trial (1st stage)	Implanted	Lead migration	Lead type	Lead malfunction or disconnect	Infection	Requested removal	Allergy	Safety issues as reported	Device / notes
Vadivelu et al. 2011 [33]	11-51m	5	13	2/13	?		1/13			1 lead tip erosion 1 discomfort at generator site requiring revision	Eight contact leads, Medtronic or St Jude. Note: specific population: refractory occipital headache in Chiari malformation
Mixed types of headaches											
Franzini et al. 2009 [36]	Mean 1y		17	0	C	0	0			None of the patients experienced lead migration, breakage of wires or system failure; there were no cases of infections or subcutaneous hematomas in our series	Pisces Quad 1 occipital neuralgia 14 cluster 2 transformed migraine Kinetra & Solertra IPGs
Schwedt et al. 2007 [35]	3y	0/15	15	8/15	C	0/15	0/15	0/15	0/15	Proportion of patients with lead migration increased with longer follow-up: 33% at 6 months, 60% at 1 & 2 years, 100% at 3 years. Also reported at 3 years: 42% battery died, 13% neck stiffness, 7% battery site pain, 7% contact dermatitis, 7% lead site pain, 7% myofascial incision site pain, 7% implantable pulse generator revision.	Note: mixed type of headache: 3 Cluster 4 Hermicrania 4 Continua 8 Migraine 2 Post traumatic
Falowski et al. 2010 [37]	Mean 21m (2 to 60m)		28	7 patients (13 revisions)	P		5			3 lead migration secondary to trauma 2 battery migration 4 infections P) antibiotics 1 Infection IV antibiotics 6 lack of efficacy 1 lead malfunction 1 battery malfunction 4 battery end o f life	ANS (n=16) Medtronic (n=8) ABS (n=4)

Table 14 (cont.)

Author	Follow-up	Failed trial (1st stage)	Implanted	Lead migration	Lead type	Lead malfunction or disconnect	Infection	Requested removal	Allergy	Safety issues as reported	Device / notes
Paemeleire et al. 2010 [38]	1m		44	2/44	C	9/44 lead fracture 3/44 connection problems	2 /44			14/44 had 18 revisions	Custom made curve needle (Medtronic Inc)
Fibromyalgia											
Thimineur & De Ridder 2007 [107]	6m	0	12 (9/3)		C					Not reported	Quatrode lead, ANS Medical

Table 15 Reported adverse events and other technical/safety issues in case series of peripheral nerve field stimulation (PNFS, implanted device)

Study	Condition	Follow-up	Failed trial (1st stage)	Implanted	Lead migration	Lead type	Lead malfunction / disconnection	Infection	Requested removal	Allergy	Safety issue as reported	Device
Chronic low back pain / failed back surgery syndrome and post surgical pain												
Verrills et al. 2009 [72]	Chronic lower back and failed back surgery syndrome	7m (3-12m)	11	14		C					'No adverse events of complications were reported' (p.71).	8 contact electrode (Octrode) lead (Advanced Neuromodulation system, Plano TX, USA)
Yakovlev et al. 2011 [73]	Chronic lower back pain with post laminectomy syndrome	12m		18		C		1 post-operative			12 had reprogramming of PNFS in first 6 weeks	Quadripolar leads, Titan Anchors (Medtronic) rechargeable Restore Ultra or non-rechargeable Prime Advanced generator
Yakovlev et al. 2010 [74]	Post surgery hip pain	12m		12	0	C	0	0	0	0	'No complications reported during trial, permanent implantation or post operative period.'	8-electrode standard Octad Leads, Medtronic
Mixed types of pain												
Verrrills et al. 2009 [75]	Mixed types of pain:13 LBP 5 Occipital 2 thorax 2 abdominal 1 elbow	Mean 7.6m (3-19m)	0	23		C					8 had reprogramming in first 6 weeks 2 removed implants before trial: 1 due to infection 1 due to unsatisfactory pain relief	Octrode and Genesisd IPG, Advanced Neuromodulation Systems
Sator-Katzenschlaer et al. 2010 [76]	Indications for STS (n=93): 29 low back 37 failed back surgery 15 cervical neck pain 12 post herpetic neuralgia		8/119	111	14/111		6/111	7/111			Complications after surgical procedure 27%	Majority Medtronic Others Advanced Neuromodulation Systems
Verrills et al. 2011 [77]	100 occipital/ craniofacial	8.1m (1-		100	2	C		1			14 reported 16 AEs 1 lead infection (1y post	Octrode leads (St Jude, Medical

	44 lumbosacral 8 thoracic 5 groin/pelvis 3 abdominal pain	23m)									implant minor trauma over occipital lead area) 7 hardware erosions 2 hardware migrations 3 leads too superficial 1 lead too tight 2 hardware failure Total of 5 explants (3 conditions resolved, 3 lack of efficacy)	Neuromodulation, Boston Scientific) 14G angiocath, (Becton Dickinson) IPG
Falco et al. 2009 [78]	Non-appendicular regional pain associated with 'wide variety of chronic pain disorders' 3 neuropathic pain 5 nociceptive pain 10 mixed pain	3m (5w-6m)	2/28	18	3	C					Lead migrations leading to burning sensation in 1 andsever painful electrical sensation in another.	Octrode leads and wide spaced quad leads (St Judes)

*C: cylindrical (percutaneous) type; P: paddle type

Table 16 Reported adverse events and other technical/safety issues in case series of percutaneous electrical nerve stimulation (PENS, temporary needle probes)

Study	Condition	Nerve/ Approach	Follow-up	Sample size	Infection	Allergy	Safety issue as reported	Device
Zhao et al. 2004 [97]	Intractable interstitial cystitis	Posterior tibial nerve	10 weeks	14		1	One patient 'with an allergy background' stopped the treatment due to recurrence of voiding frequency and pain. 'Rare complications with the procedure, including minor bleeding immediately after removing the needle or a temporary painful feeling at the insertion site. Some patients had slight tenderness at the insertion site and next examination.'	Device not named
Kim et al. 2007 [98]	Chronic pelvic pain	Posterior tibial nerve	12 weeks	15			'Rare complications with procedure including a temporary painful feeling at insertion site.'	Device not named
Van Blaken et al. 2003 [98]	Chronic pelvic pain	Tibial nerve	12 week	33			No discussion of side effects / complications 20 no improvement on VAS 6 ≥25% and ≤50% 7 ≥50%	34guage steel needle, stick on electrode n on arch of foot both connected to stimulator (Urgent Pc, CystoMedix)
Zhao et al. 2008 [65]	Interstitial cystitis	Posterior tibial nerve	5 weeks	18			'All patients completed the 10 sessions with no complications' 'Rare complications occurred with procedure.' Minor bleeding immediately following removal of needles. Slight tenderness at insertion site	
Seroussi et al. 2003 [96]	Chronic lower back pain Severe axial LBP	Low back region	4-20 weeks	39			3 patients believed their back pain worsened 2 felt soreness they attributed to an electrode placement 2 unable to attend appointments "No other complications or significant side-effects of electrode placement or electrical stimulation were reported during this trial."	Vertis Neuroscience computerized instrumentation system

6.4.3 Safety alerts and spontaneous reports of adverse events

Two safety alerts were identified.[108;109] They highlighted procedures which should be considered as a contraindication for patients with implanted neurostimulation devices, namely diathermy therapy and magnetic resonance imaging (see Table 17 below).

Table 17 Safety alerts related to devices for peripheral neurostimulation

Medtronic [107]	16 May 2001	Use of diathermy on patients with any implanted neurostimulation device can cause heating at the tissue/stimulation electrode interface, which under certain circumstances can result in permanent tissue or nerve damage.
FDA [108]	10 May 2005	Several cases of serious injuries, possibly caused by heating of the electrodes at the end of the leadwires, were reported when patients with implanted neurological stimulators underwent magnetic resonance imaging (MRI). Although the reports involved deep brain stimulators and vagus nerve stimulators, similar injuries could occur with peripheral nerve stimulators.

Searches of the FDA Manufacturer and User Facility Device Experience database (MAUDE) under the category of implanted peripheral neurostimulation devices identified 83 voluntary reports of adverse events. The classification of devices was not well defined and some of the retrieved reports actually involved other types of neurostimulation such as spinal cord stimulation. The majority of the cases consisted of erosion and malfunction of the devices (including fractures and disconnections), hardware migration, infection, and inefficacy or loss of effects requiring repositioning. A notable report described a revision surgery leading to no feeling in upper/lower extremities and the patient was admitted to intensive care unit.

7 DISCUSSION

7.1 Summary of principal findings on efficacy and safety

7.1.1 Overview of the literature

This systematic review identified a large volume of published evidence, reflecting the recent surge of interest in the use of peripheral neurostimulation for treating chronic refractory pain. We included twenty-two RCTs for detailed assessment, supplemented the evidence with 60 case series of no less than 10 patients, and identified many more smaller case series and case reports in this field. We identified six ongoing RCTs, including a large international trial of ONS for cluster headache.

We developed an evidence matrix, grouped the techniques into three broad categories of implanted PNS, PNFS and PENS. Identified RCTs and larger case series were mapped according to the matrix.

Although we identified 22 RCTs, only seven of them match the specific technique-condition of CE marked devices. There is therefore a mismatch between the published literature and the specific evidence that could be used for developing guidance. This is compounded by the lack of full publication and incomplete reporting of some directly relevant RCTs. The pending publication of results from some of the RCTs is likely to have major impact in the area of ONS for chronic migraine.

Taken in the round, the evidence in the broad area of peripheral nerve stimulation for chronic pain is encouraging and suggests that peripheral neurostimulation may be effective at least for some types of painful condition. However the evidence is not entirely convincing due to methodological challenges and it is crucial that good quality evidence continues to be accrued from high quality RCTs and prospective long-term observations. Serious adverse effects are uncommon but data on long-term safety is still scant.

7.1.2 Summary of principal findings for individual pairs of stimulation techniques and condition

This review covers a very broad scope of using invasive techniques to stimulate peripheral nerves or painful areas for chronic pain. Following the comprehensive of published literature and mapping of evidence, three areas in which CE marked devices are available were selected for detailed assessment.

ONS for chronic migraine

Currently the evidence on the efficacy of ONS for chronic/transformed migraine is limited to three industry sponsored RCTs (of which two are only published as conference abstracts) and two case series provide further information on safety. While all three RCTS report reduction in number of headache days only study reports a statistical significant reduction. Lead migration and infections are common. Lead migration occurred in 24% (12/51) of patients over three months in the study by Saper et al.,[16] and 36% (9/25) reported by Popeney and Aló.[22] The type of lead appears to determine the prevalence of migration with all seven cylindrical leads migrating in Oh et al. case series and none of the paddle lead placements.[23] Infection occurred at implantation sites in 14% (7/51) and 4% (2/51) of patients for leads/extensions and neurostimulators respectively over three months in the study by Saper et al.[16] Oh et al. reported a higher infection rate of 20% (2/10),[23] and Popeney and Aló reported a lower infection rate of 4% (1/25).[22] Pain and discomfort at various sites related to implantation procedure and implanted devices was also reported by the Saper et al. study.[16] No permanent nerve damage or unexpected serious adverse events were observed. Further information can be found at Section 6.2.1.1.1.

Implanted PNFS for chronic low back pain / failed back surgery syndrome

The evidence on use of implanted PNFS for chronic lower back pain and failed back surgery syndrome is currently very limited. Our searches identified one RCT (Barolat et al. conference abstract, full-text publication pending) recruiting 30 patients,[71] and two case series (Verrills et al.; Yakovlev et al.)[72;73] with 31 patients in total were included. Results from the RCT showed a similar proportion of patients achieving pain relief of greater than 50% for standard and low frequency PNFS (57% and 53% respectively). The proportion was lower in the sub-threshold stimulation (27%) and minimal stimulation (14%) group. Among the 23 patients who proceeded to permanent implantation, the response (of greater than 50% pain relief) maintained in 67% of the patients at one year. Two retrospective case series reported significant reduction in pain and reduced use of analgesics at varied follow-up between 3 to 12 months. There is limited information on safety, which was not mentioned in the conference abstract of the RCT and one of the two case series identified reported that there were no adverse events or complications.[72] The other case series described a case of post-operative infection requiring removal of the stimulation system, which was subsequently re-implanted. Further information can be found at Section 6.2.2.1.

PENS for chronic peripheral neuropathic pain

Again the evidence is limited to three crossover RCTs including a total of 145 patients were included in our analysis. The RCTs investigated different types of chronic peripheral

neuropathic pain, including sciatica (Ghoname et al.),[81] diabetic neuropathic pain (Hamza et al.)[81] and surface hyperalgesia associated with various types of neuropathic pain conditions (Raphael et al.).[83] Two studies were judged to be at unclear risk for most of the bias domains. In addition there was carryover effect due to the short washout period. The third study had low risk of bias for all the bias domains except blinding of patients for the second treatment period (after crossover), which was an issue for all three RCTs. All three RCTs reported significantly greater reduction in pain and improvement in other outcomes for PENS compared with sham PENS. The study by Ghoname and colleagues also showed that PENS was more effective than TENS in patients with sciatica.[81] The duration of treatment and follow-up was short in the three RCTs. There is a lack of data on longer-term efficacy and safety. While no adverse effect was reported for PENS in the short-term, general safety precautions regarding the use of needles and electrical appliances for therapeutic purpose shall still apply. Further information can be found at Section 6.2.3.2

7.2 Strengths and limitations of the assessment

The strength of this assessment includes:

- Comprehensive search of electronic databases and ongoing trials and duplicated sifting of retrieved records.
- Wide coverage of stimulation techniques and chronic painful conditions.
- Development of an evidence matrix, which can serve as a framework for summarising and mentoring evidence in this field.
- Consistent use terms.
- Detailed assessment of methodology of RCTs.
- Quantitative synthesis of RCT data, supplemented by additional data from larger case series.

However the strength with which conclusions can be drawn is limited by the availability of evidence and the methodological quality of the available evidence:

- Although several RCTs were included in this assessment, the duration of treatment was generally short, ranging from a single session to a maximum of 12 weeks. The studies with duration of treatment shorter than a month are better regarded as ‘proof-of-concept’ studies than clinical effectiveness studies considering the chronic nature of pain.

- In the considerable majority of the RCTs, patients treated with peripheral neurostimulation experienced significantly greater reduction in pain and improvement in other outcomes compared to those treated with sham control. This promising evidence must be interpreted with caution. The vast majority of the RCTs were single-centre studies conducted in specialist centres. Whilst most studies did attempt to blind the patients and/or the outcome assessors, the effectiveness of blinding particularly for the patients was questionable in many cases. This is important as pain is a very subjective outcome. The presence or absence of paraesthesia caused by electrical stimulation is likely to have considerably reduced the effectiveness of blinding.

- About half of the 22 RCTs adopted a crossover design, which may not be a suitable design considering the cumulative effect observed during multiple stimulation session (and thus possible carryover effect after crossover if washout period is not sufficiently long). In addition, the aforementioned issue highlighted that effective blinding of patients is unlikely to be achieved in crossover trials.

In addition to the limitation related to the evidence base, this review also several limitations:

- Given the broad scope for this review and the large number of records that were retrieved from the literature search, we cannot rule out the possibility that a small number of relevant studies may have been missed.

- Diverse outcome measures were used in different studies, which hampered quantitative synthesis of evidence across studies.

- We have not assessed the cost-effectiveness of peripheral neurostimulation as it is beyond the remit of the Interventions Procedures Programme.

7.3 Outstanding question

- The extent to which the observed treatment effects in RCTs were due to placebo effect and/or differences in expected treatment effectiveness.

- The optimal criteria for predicting and selecting patients who could benefit from peripheral neurostimulation.

- More evidence is needed for the long-term effectiveness and safety of different techniques of peripheral neurostimulation.

- For ONS for chronic migraine, whether the treatment is less effective in patients with medication overuse.

- The overall benefit and risk of harm of cylindrical (percutaneous) leads versus paddle (surgical) leads in ONS needs to be determined.

- The role of trial stimulation and nerve block in predicting long-term treatment success of implanted PNS remains to be clarified.

7.4 Suggestions for further research

- Assessment of patients' expectation of treatment effectiveness and preference at baseline and the effectiveness of blinding during treatment in double-blind RCTs, and the association between these and observed/reported treatment outcomes.[109;110].

- Development of novel methods to overcome the difficulty in blinding patients in RCTs that involve electrical stimulation.[111]

- RCTs of using peripheral neurostimulation to treat painful conditions that are particularly difficult to manage and for which early case series and care reports have shown promising results, such as painful bladder syndrome/interstitial cystitis, complex regional pain syndrome and injuries to the brachial plexus. Multicentre collaboration is essential to ensure recruitment of sufficient number of patients and wider generalisability of results.

- The design of future RCTs should take into account published guidance for trials of chronic pain (such as those produced by IMMPACT)[112] and headache disorders,[113] and their reporting of results should follow the CONSORT statement to facilitate assessment and synthesis of the evidence.

- Development of new devices or surgical techniques that reduce the incidence of lead migration and infection. The effectiveness of these devices/techniques should be evaluated in RCTs.

- Establishment of a registry of peripheral neurostimulation to allow prospective and systematic collection of data on long-term effectiveness, safety and device durability.

8 ISSUES FOR CONSIDERATION BY THE COMMITTEE

- Only one of the three RCTs of ONS for migraine has been published as a full paper (Saper et al.)[16] and the other two have only been published as conference abstracts (Lipton et al.; Silberstein et al.).[15;17] The results of the latter are expected to be published in the near future. The only RCT for implanted PNFS is also expected to be published soon.

- The vast majority of studies were carried out in the USA. Currently the number of centres with expertise in techniques of peripheral neurostimulation may be relatively small in the UK, although the techniques share some similarity with spinal cord stimulation (for PNS and PNFS) and electroacupuncture (for PENS), both of which are practised in the UK.

- Given the advance in devices and techniques related to peripheral neurostimulation, findings from case series conducted prior to 1990s, such as those which used cuff-type electrodes, may not represent the effectiveness and safety of contemporary practice. Improvement in devices and techniques may also have occurred gradually over time in recent years, although a systematic evaluation of incremental benefit for specific advance in devices and techniques seems to be lacking.

- There is some mismatch between current level of evidence and availability of CE marked devices. PNS and PNFS can be carried out using devices (leads/electrodes and pulse generators) that were originally designed for spinal cord stimulation, and indeed this has been the case for many of the studies reported in the literature[5]. For PENS, disposable acupuncture needles rather than needles specifically manufactured for peripheral neurostimulation have been used in most of the studies included in this review. As a result, whilst the quantity (and to a less extent quality) of the literature broadly reflects clinical needs in this area, the availability of CE marked devices and evidence generated directly from their use does not. The possibility of off-label use of devices designed for spinal cord stimulation and the hurdle for obtaining CE mark (and FDA approval) have not provided much incentive for manufacturers to specifically tailor the devices for peripheral neurostimulation and to conduct good quality RCTs for the new devices. This has been blamed for lack of high quality evidence in this area.[5]

- The use of devices designed for spinal cord stimulation for peripheral neurostimulation also means that the performance and durability of the peripheral

neurostimulation may not be optimal due to the different anatomical structure and different level of mobility of the body part in which the devices are implanted. Consequently, there may be room for improvement for the efficacy, safety and durability of peripheral neurostimulation if tailor-designed devices become available.

- Despite the almost inevitable contribution of placebo/trial/Hawthorne effects and possible over-estimation of treatment effect due to difficulties in blinding patients in many of the RCTs, there are signs suggesting that treatment effects observed in some of the trials of peripheral neurostimulation went beyond the influence of placebo effect/treatment credibility. Differential effects were observed between treatment groups in RCTs in which patients' expectation of treatment effectiveness was not expected to differ, for example, when different montages or stimulation frequencies (beyond 0 Hz) were compared. PENS was also found to be more effective than TENS in patient population who had not been exposed to either treatments and thus was likely to have similar expectation of treatment effectiveness.[93] In addition, significant difference was observed for objectively measured outcome, such as pressure pain threshold (PPT), measured by pressure algometry in a double-blind study.[83] Furthermore, the duration of effect reported in some case series seemed to go beyond what would be expected of a placebo response, and there were reports of sudden loss of efficacy subsequently confirmed to be due to lead migration or depletion of battery, with restoration of efficacy after these problems were corrected. Findings from studies conducted using functional magnetic resonance imaging, while not reviewed in this report, could provide further evidence.

- Patients who are considered for peripheral neurostimulation are likely to have exhausted other non-invasive treatment modalities for the control of refractory pain, which can be debilitating and severely impact their quality of life. It could be argued that if peripheral neurostimulation were able to provide significant reduction in pain and improvement in physical and emotional function and quality of life that is sustained over a long period of time with acceptable adverse effect profiles, the question with regard to whether or how much placebo effect contributes to the observed treatment effect is less relevant.

- The possibility of organising a workshop to provide guidelines to optimise the design and reporting of future studies in this area could be considered.

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10 APPENDICES

Appendix 1: Literature Search Strategies

Search strategies - Systematic Reviews

Database: Ovid MEDLINE(Ovid) 1946 to March Week 1 2012

Search Strategy:

1 (stimulat$ adj peripheral nerve).mp.

2 ((peripheral or percutaneous or subcutaneous or epicranial or epifacial or infraorbital or occipital or sacral or suboccipital or supraorbital or trigeminal or medial plantar) adj (nerve stimulat$ or neuromodulation or neurostimulat$)).mp

3 ((occipital or sacral or suboccipital or supraorbital or trigeminal or percutaneous or subcutaneous or large fibre or subcutaneous target or conditioning electric$ or epifacial electric$ or sensory nerve or selective nerve root) adj stimulat$).mp.

4 electroacupuncture.mp. or exp Electroacupuncture/

5 exp Electric Stimulation Therapy/

6 exp Peripheral Nervous System/

7 5 and 6

8 1 or 2 or 3 or 4 or 7

9 pain.mp. or exp Pain/

10 headache$.mp. or exp Headache/

11 migraine$.mp. or exp Migraine Disorders/

12 failed back surgery syndrome.mp. or exp Failed Back Surgery Syndrome/

13 FBSS.mp.

14 exp Complex Regional Pain Syndromes/ or complex regional pain.mp.

15 CRPS.mp.

16 causalgia.mp. or exp Causalgia/

17 reflex sympathetic dystrophy.mp. or exp Reflex Sympathetic Dystrophy/

18 angina.mp. or exp Angina Pectoris/

19 exp Neuralgia/ or neuralgia.mp.

20 sciatica.mp. or exp Sciatica/

21 neuropathy.mp.

22 hemicrania.mp.

23 SUNCT Syndrome/ or SUNCT.mp.

24 or/9-23

25 8 and 24

26 limit 25 to humans

27 limit 26 to "reviews (maximizes specificity)"

Databases: Cochrane Library (Wiley) Cochrane Database of Systematic Reviews (CDSR) Issue 3 of 12 Database of Reviews of Effects (DARE) Issue 1 of 4 Health Technology Assessment (HTA) Database Issue 1 of 4

Search strategy:

#1 stimulat* next peripheral next nerve

#2 peripheral next nerve next field

#3 (peripheral or percutaneous or subcutaneous or epicranial or epifacial or infraorbital or occipital or sacral or suboccipital or supraorbital or trigeminal or plantar)

#4 (nerve next stimulat*) or neuromodulation or neurostimulat*

#5 (#3 AND #4)

#6 (occipital or sacral or suboccipital or supraorbital or trigeminal or percutaneous or subcutaneous) next stimulat*

#7 subcutaneous next target next stimulat*

#8 conditioning next electric* next stimulat*

#9 epifacial next electric* next stimulat*

#10 sensory next nerve next stimulat*

#11 selective next nerve next root

#12 electroacupuncture

#13 MeSH descriptor Electroacupuncture explode all trees

#14 MeSH descriptor Electric Stimulation Therapy explode all trees

#15 MeSH descriptor Peripheral Nervous System explode all trees

#16 (#14 AND #15)

#17 (#1 OR #2 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #16)

#18 pain or headache* or migraine* or FBSS or CRPS or causalgia or angina or neuralgia or sciatica or neuropathy or hemicrania or SUNCT

#19 failed next back next surgery

#20 complex next regional next pain

#21 reflex next sympathetic next dystrophy

#22 MeSH descriptor Pain explode all trees

#23 MeSH descriptor Headache explode all trees

#24 MeSH descriptor Migraine Disorders explode all trees

#25 MeSH descriptor Failed Back Surgery Syndrome explode all trees

#26 MeSH descriptor Complex Regional Pain Syndromes explode all trees

#27 MeSH descriptor Angina Pectoris explode all trees

#28 MeSH descriptor Neuralgia explode all trees

#29 MeSH descriptor SUNCT Syndrome explode all trees

#30 (#18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29)

#31 (#17 AND #30)

Search strategies - All studies.

Database: Ovid MEDLINE(Ovid) 1946 to March Week 1 2012

Search Strategy:

1 (stimulat$ adj peripheral nerve).mp.
2 peripheral nerve field.mp.
3 ((peripheral or percutaneous or subcutaneous or epicranial or epifacial or infraorbital or occipital or sacral or suboccipital or supraorbital or trigeminal or medial plantar) adj (nerve stimulat$ or neuromodulation or neurostimulat$)).mp.
4 ((occipital or sacral or suboccipital or supraorbital or trigeminal or percutaneous or subcutaneous or large fibre or subcutaneous target or conditioning electric$ or epifacial electric$ or sensory nerve or selective nerve root) adj stimulat$).mp
5 electroacupuncture.mp. or exp Electroacupuncture/
6 exp Electric Stimulation Therapy/
7 exp Peripheral Nervous System/
8 6 and 7
9 1 or 2 or 3 or 4 or 5 or 8
10 pain.mp. or exp Pain/
11 headache$.mp. or exp Headache/
12 migraine$.mp. or exp Migraine Disorders/
13 failed back surgery syndrome.mp. or exp Failed Back Surgery Syndrome/
14 FBSS.mp.
15 exp Complex Regional Pain Syndromes/ or complex regional pain.mp.
16 CRPS.mp.
17 causalgia.mp. or exp Causalgia/
18 reflex sympathetic dystrophy.mp. or exp Reflex Sympathetic Dystrophy/
19 angina.mp. or exp Angina Pectoris/
20 exp Neuralgia/ or neuralgia.mp.
21 sciatica.mp. or exp Sciatica/
22 neuropathy.mp.
23 hemicrania.mp.
24 SUNCT Syndrome/ or SUNCT.mp.
25 or/10-24
26 9 and 25
27 limit 26 to humans

Database: Ovid MEDLINE(Ovid) In-Process & Other Non-Indexed Citations March 14, 2012

Search Strategy:

1 (stimulat$ adj peripheral nerve).mp.

2 ((peripheral or percutaneous or subcutaneous or epicranial or epifacial or infraorbital or occipital or sacral or suboccipital or supraorbital or trigeminal or medial plantar) adj (nerve stimulat$ or neuromodulation or neurostimulat$)).mp.

3 ((occipital or sacral or suboccipital or supraorbital or trigeminal or percutaneous or subcutaneous or large fibre or subcutaneous target or conditioning electric$ or epifacial electric$ or sensory nerve or selective nerve root) adj stimulat$).mp.

4 electroacupuncture.mp.

5 pain.mp.

6 headache$.mp.

7 migraine$.mp.

8 failed back surgery syndrome.mp.

9 FBSS.mp.

10 exp Complex Regional Pain Syndromes/ or complex regional pain.mp.

11 CRPS.mp.

12 causalgia.mp.

13 reflex sympathetic dystrophy.mp.

14 angina.mp.

15 neuralgia.mp.

16 sciatica.mp.

17 neuropathy.mp.

18 hemicrania.mp.

19 SUNCT.mp.

20 or/5-19

21 or/1-4

22 20 and 21

Database: EMBASE (Ovid) 1980 to 2012 Week 10

Search Strategy:

1 (stimulat$ adj peripheral nerve).mp.

2 ((peripheral or percutaneous or subcutaneous or epicranial or epifacial or infraorbital or occipital or sacral or suboccipital or supraorbital or trigeminal or medial plantar) adj (nerve stimulat$ or neuromodulation or neurostimulat$)).mp.

3 ((occipital or sacral or suboccipital or supraorbital or trigeminal or percutaneous or subcutaneous or large fibre or subcutaneous target or conditioning electric$ or epifacial electric$ or sensory nerve or selective nerve root) adj stimulat$).mp.

4 peripheral nerve field.mp.

5 electroacupuncture.mp. or exp electroacupuncture/

6 exp electrostimulation therapy/
7 exp peripheral nervous system/
8 6 and 7
9 1 or 2 or 3 or 4 or 5 or 8
10 exp pain/ or pain.mp.
11 headache$.mp. or exp headache/
12 migraine$.mp. or exp migraine/
13 failed back surgery syndrome.mp. or exp failed back surgery syndrome/
14 FBSS.mp. or exp failed back surgery syndrome/
15 exp complex regional pain syndrome/ or complex regional pain.mp.
16 causalgia.mp. or exp causalgia/
17 reflex sympathetic dystrophy.mp.
18 angina.mp. or exp angina pectoris/
19 exp neuralgia/ or neuralgia.mp.
20 sciatica.mp. or exp ischialgia/
21 neuropathy.mp. or exp neuropathy/
22 hemicrania.mp.
23 SUNCT syndrome.mp. or exp SUNCT syndrome/
24 or/10-23
25 9 and 24
26 limit 25 to human

Databases: Cochrane Library (Wiley) Cochrane CENTRAL Register of Controlled Trials Issue 3 of 12
Search strategy:
#1 stimulat* next peripheral next nerve
#2 peripheral next nerve next field
#3 (peripheral or percutaneous or subcutaneous or epicranial or epifacial or infraorbital or occipital or sacral or suboccipital or supraorbital or trigeminal or plantar)
#4 (nerve next stimulat*) or neuromodulation or neurostimulat*
#5 (#3 AND #4)
#6 (occipital or sacral or suboccipital or supraorbital or trigeminal or percutaneous or subcutaneous) next stimulat*
#7 subcutaneous next target next stimulat*
#8 conditioning next electric* next stimulat*
#9 epifacial next electric* next stimulat*
#10 sensory next nerve next stimulat*
#11 selective next nerve next root
#12 electroacupuncture
#13 MeSH descriptor Electroacupuncture explode all trees
#14 MeSH descriptor Electric Stimulation Therapy explode all trees

#15 MeSH descriptor Peripheral Nervous System explode all trees
#16 (#14 AND #15)
#17 (#1 OR #2 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #16)
#18 pain or headache* or migraine* or FBSS or CRPS or causalgia or angina or neuralgia or sciatica or neuropathy or hemicrania or SUNCT
#19 failed next back next surgery
#20 complex next regional next pain
#21 reflex next sympathetic next dystrophy
#22 MeSH descriptor Pain explode all trees
#23 MeSH descriptor Headache explode all trees
#24 MeSH descriptor Migraine Disorders explode all trees
#25 MeSH descriptor Failed Back Surgery Syndrome explode all trees
#26 MeSH descriptor Complex Regional Pain Syndromes explode all trees
#27 MeSH descriptor Angina Pectoris explode all trees
#28 MeSH descriptor Neuralgia explode all trees
#29 MeSH descriptor SUNCT Syndrome explode all trees
#30 (#18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29)
#31 (#17 AND #30)

Database: CINAHL (EBSCO) 1937 – 20 March 2012
Search strategy:
S1 TX peripheral nerve stimulat*
S2 TX (peripheral or percutaneous or subcutaneous or epicranial or epifacial or infraorbital or occipital or sacral or suboccipital or supraorbital or trigeminal or plantar) and (nerve next stimulat*) or neuromodulation or neurostimulat*
S3 TX (occipital or sacral or suboccipital or supraorbital or trigeminal or percutaneous or subcutaneous) and stimulat*
S4 TX subcutaneous target stimulat*
S5 conditioning electric*

S6 epifacial electric* stimulat*
S7 sensory nerve stimulat*
S8 selective nerve root
S9 electroacupuncture
S10 S1 or S2 or S3 or S4 or S5 or S6 or S7 or S8 or S9
S11 (MH "Peripheral Nervous System+")
S13 S11 and S12
S14 S10 or S13

S15 TX pain or headache* or migraine* or FBSS or CRPS or causalgia or angina or neuralgia or sciatica or neuropathy or hemicrania or SUNCT

S16 TX failed back surgery syndrome

S17 TX Complex regional pain syndrome

S18 TX Reflex sympathetic dystrophy

S19 (MH "Failed Back Surgery Syndrome")

S20 (MH "Complex Regional Pain Syndromes+")

S21 (MH "Angina Pectoris+")

S22 (MH "Neuralgia+")

S23 S15 or S16 or S17 or S18 or S19 or S20 or S21 or S22

S24 S14 and S23

Appendix 2 Outcome measures used in RCTs

Study	Pain		Analgesic use / drug intake	Headaches	Function	Quality of Sleep	Depression	Satisfaction with treatment	Quality of life	Other	Adverse effects
	VAS	Others									
Occipital nerve stimulation (ONS) - unpublished or ongoing studies with no results available are shaded											
Lipton et al. 2009 [15] (PRISM study)	No	No	No	Migraine days (days with moderate/severe headache ≥4hrs)	No	No	No	No	No	No	Yes
Saper et al. 2011 [16] (ONSTIM study)	Yes (pain intensity)	MIDAS headache pain score	Acute medication use	Headache days, days with prolonged and severe headache, headache duration, rate of responders	Functional disability scale, MIDAS	No	No	Yes	SF-36	Profile of Moods States	Yes
Silberstein et al. 2011 [17]	Yes	Zung Pain and Distress scale	No	MIDAS headache days	MIDAS	No	No	Yes	Yes (not specified)	No	Yes
Gerardo et al. 2011 [18] NCT00407992	No	No	Yes	Headache frequency and intensity	No	No	No	No	Yes (not specified)	No	Yes
Goadsby et al. 2011 [19] (PRISM UK study) NCT00747812	No	No	Medication use	Migraine frequency and severity, headache frequency	No	No	No	No	No	No	Yes

Caillon et al. 2012 [21] SENGO-CAM Study) NCT01184222	No	No	Rescue medication used	Headache free patients, headache days, maximum intensity and duration of rebound headache	No	No	No	No	No	Withdrawal facility perceived by patient	No
Wilbrink et al. 2011 [24](ICON study) NCT01151631	No	No	Use of acute attack medication	Mean attack frequency, mean attack intensity, rate of responders, responder identification	No	No	No	Yes	No	Economic evaluation, anticipated group randomisation, awareness of paraesthesias	Yes
De Ridder and Plazier 2009 [101] NCT00917176	Yes	Pain catastrophizing scale, pain vigilance and awareness questionnaire	No	No	No	No	No	No	No	Scores on Fatigue and Mood	No
Plazier et al. 2011 [39] NCT01298609	No	No	No	No	No	No	No	No	No	Fibromyalgia Impact Questionnaire	No
Implanted PNS – sphenopalatine ganglion stimulation											
Jensen 2012 [102]	Unclear	Pain relief at 1 hour, pain freedom at 1 hour	Prophylactic and acute medication use	Migraine pain days, headache frequency, migraine associated symptom relief, MIDAS	MIDAS	No	No	Global patient evaluation	SF-36v2	No	Yes
Peripheral nerve filed stimulation (PNFS)											
Barolat et al. 2011 [71]	Unclear	Greater than 50% pain relief	No	No	No	No	No	No	No	No	No

Kang et al. 2007 [78]	Yes	WOMAC pain	No	No	WOMAC physical function	No	No	No	No	WOMAC stiffness	Yes
Percutaneous electrical nerve stimulation (PENS)											
Ahmed et al. 2000 [80]	Yes	No	Oral analgesic usage	Number of headaches per week	Physical activity (VAS)	VAS	No	No	SF-36	No	No
White et al. 2000 [85]	Yes	No	Oral analgesic usage	No	Physical activity (VAS)	VAS	No	No	SF-36	No	Yes
Ghoname et al. 1999 [86]	Yes	No	Oral analgesic usage	No	Physical activity (VAS)	VAS	No	Patients' overall assessment of relative effectiveness	SF-36	No	No
Ghoname et al. 1999 [87]	Yes	No	Oral analgesic usage	No	Physical activity (VAS)	VAS	No	Patients' overall assessment of relative effectiveness	SF-36	No	No
Hamza et al. 1999 [87]	Yes	No	Oral analgesic usage	No	Physical activity (VAS)	VAS	No	No	SF-36	No	No
White et al. 2001 [88]	Yes	No	Oral analgesic usage	No	Physical activity (VAS)	VAS	No	No	SF-36	No	No

Weiner et al. 2003 [90]	No	McGill Pain Questionnaire, Pain Severity scale of the Multidimensional Pain Inventory (MPI)	No	No	Roland and Morris Back Pain Disability Questionnaire, Pain Interference Scale of MPI, physical performance (timed chair rise, functional reach, gait speed, static and isoinertial lifting)	Pittsburgh Sleep Quality Index	Geriatric Depression Scale	No	No	Life Control Scale of MPI, Folstein Mini-Mental State Examination (MMSE), Trail Making Test Part B, Hopkins Verbal Learning Test	No
Topuz et al. 2004 [92]	Yes (current and activity pain)	No	No	No	Low Back Pain Outcome Scale, Oswestry Disability Index	No	No	No	SF-36	No	No
Yokoyama et al. 2004 [93]	Yes (peak pain)	No	Intake of NSAIDs	No	Physical impairment	No	No	No	No	No	No

Weiner et al. 2008 [89]	No	Pain thermometer, McGill Pain Questionnaire	No	No	Roland and Morris Questionnaire, pain subscale of Functional Status Index, Physical Activity Scale for the Elderly, gait speed over 25 feet, timed repetitive chair rise, timed stair climbing	Pittsburgh Sleep Quality Index	Geriatric Depression Scale	Global rating of improvement by physicians and the participants	SF-36	Chronic Pain Self-Efficacy Scale, Catastrophizing Scale of the Cognitive Strategies Questionnaire, Fear-Avoidance Beliefs Questionnaire, self-rated health, treatment credibility	Yes
Pérez-Palomares et al. 2010 [91]	Yes	Pain tolerance measured by algomemter on selected trigger points	No	No	Oswestry Disability Index	VAS	No	No	No	No	No
Ghoname et al. 1999 [81]	Yes	No	Oral analgesic usage	No	Physical activity (VAS)	VAS	No	No	SF-36	No	No
Cottingham et al. 1985 [94]	Yes	Pain relief (5 categories)	Analgesic intake	No	Mobility (5 categories)	No	No	No	No	No	Yes
Hamza et al. 2000 [87]	Yes	No	Oral analgesic usage	No	Physical activity (VAS)	VAS	Beck Depression Inventory	Patients' overall assessment of relative effectiveness	SF-36	Profile of Mood Status	Yes
Kabay et al. 2009 [95]	Yes	National Institute of Health Chronic Prostatitis Symptom Index, (NIH-CPSI) pain domain	No	No	No	No	No	No	NIH-CPSI quality of life domain	Urgency (VAS), NIH-CPSI micturition domain, NIH-CPSI total score	No

Raphael et al. 2011 [83]	No	Numerical rating scale, pressure pain threshold	No	No	No	No	No	No	No	No	Yes

Appendix 3 Quality assessment

		Occipital nerve stimulation			
		Lipton 2009	**Saper 2011**	**Silberstein 2011**	**Plazier 2011**
Bias domain	**Source of bias**				
Selection bias	Random sequence generation	Unclear	Unclear	Unclear	Unclear
	Allocation concealment	Low	Low risk	Low	Unclear
Performance bias	Blinding of participants	Unclear	Unclear	Unclear	High
	Blinding of study personnel	Low	Low	Low	Unclear
Detection bias	Blinding of outcome assessment: patient reported outcomes	Unclear	Unclear	Unclear	High
	Blinding of outcome assessment: investigator assessed outcomes (adverse events)	Low	Unclear	Low	Unclear
Attrition bias	Incomplete outcome data	Unclear	High	Low	Unclear
Reporting bias	Selective reporting	Unclear	High	Unclear	Unclear
Other bias	Any other important concerns about bias not covered in the other domains above	Based on conference abstract with very limited information	-	Based on conference abstract with very limited information	Unclear
	Measurement of effectiveness of blinding and/or patients' expectation of treatment effectiveness	Unclear	No	Unclear	Unclear
Crossover design	Analysis of paired data	Not applicable	Not applicable	Not applicable	Unclear
	Assessment of carryover effects and/or justification of washout period	Not applicable	Not applicable	Not applicable	Unclear

		Ahmed 2000	Barolat 2011	Cottingham 1985	Ghoname 1999a
Bias domain	**Source of bias**	Unclear	Unclear	Unclear	Low
Selection bias	Random sequence generation	Unclear	Unclear	Unclear	Unclear
	Allocation concealment	High	High	Unclear	High
Performance bias	Blinding of participants	High	High	High	High
	Blinding of study personnel	High	High	Unclear	High
	Blinding of outcome assessment: patient reported outcomes	Unclear	Unclear	Low	Low
	Blinding of outcome assessment: investigator assessed outcomes (adverse events)	Unclear	High/Unclear	Unclear	Unclear
Attrition bias	Incomplete outcome data	Low	Unclear	Low	Unclear
Reporting bias	Selective reporting	Unclear	Unclear	Low	Unclear
Other bias	Any other important concerns about bias not covered in the other domains above	No	No	No	No
	Measurement of effectiveness of blinding and/or patients' expectation of treatment effectiveness	Yes	Unclear	N/A	Yes
Crossover design	Analysis of paired data	No	No	N/A	No
	Assessment of carryover effects and/or justification of washout period	Unclear	Unclear	Unclear	Low

		Ghoname 1999b	Ghoname 1999c	Hamza 1999	Hamza 2000
Bias domain	**Source of bias**	Unclear	Unclear	Unclear	Unclear
Selection bias	Random sequence generation	Unclear	Unclear	Unclear	Unclear
	Allocation concealment	High	High	High	High
Performance bias	Blinding of participants	High	High	High	High
	Blinding of study personnel	High	High	High	High
	Blinding of outcome assessment: patient reported outcomes	Low	Low	Low	Low
	Blinding of outcome assessment: investigator assessed outcomes (adverse events)	Unclear	Unclear	Unclear	Unclear
Attrition bias	Incomplete outcome data	Low	Low	Low	Low
Reporting bias	Selective reporting	Low	Unclear	Low	Low
Other bias	Any other important concerns about bias not covered in the other domains above	No	Not done	No	No
	Measurement of effectiveness of blinding and/or patients' expectation of treatment effectiveness	Yes	Yes	Yes	Yes
Crossover design	Analysis of paired data	No	No	No	Yes
	Assessment of carryover effects and/or justification of washout period	Unclear	Unclear	Unclear	Unclear

		Kabay 2009	Kang 2007	Pérez-Palomare 2010	Raphael 2004
Bias domain	**Source of bias**	Unclear	Unclear	Low	Low
Selection bias	Random sequence generation	Unclear	Unclear	Low	Low
	Allocation concealment	High	Low	High	High
Performance bias	Blinding of participants	High	High	High	Low
	Blinding of study personnel	High	Low	High	High
	Blinding of outcome assessment: patient reported outcomes	High	High	Low	Low
	Blinding of outcome assessment: investigator assessed outcomes (adverse events)	Unclear	High	High	Low
Attrition bias	Incomplete outcome data	Low	Low	Low	Low
Reporting bias	Selective reporting	High	Low	Low	Low
Other bias	Any other important concerns about bias not covered in the other domains above	No	No	No	Yes
	Measurement of effectiveness of blinding and/or patients' expectation of treatment effectiveness	N/A	N/A	N/A	Yes
Crossover design	Analysis of paired data	N/A	N/A	N/A	No
	Assessment of carryover effects and/or justification of washout period	Unclear	Unclear	Low	Low

		Topuz 2004	Weiner 2003	Weiner 2008	White 2000
Bias domain	**Source of bias**	Low	Low	Low	Unclear
Selection bias	Random sequence generation	Low	Low	Low	Unclear
	Allocation concealment	Low	Unclear	Unclear	High
Performance bias	Blinding of participants	High	High	Unclear-High	High
	Blinding of study personnel	Low	Unclear	Unclear	High
	Blinding of outcome assessment: patient reported outcomes	High	Low	Low	Low
	Blinding of outcome assessment: investigator assessed outcomes (adverse events)	Unclear	Low	Low	Unclear
Attrition bias	Incomplete outcome data	Low	Low	Low	Low
Reporting bias	Selective reporting	Unclear	Low	Low	Unclear
Other bias	Any other important concerns about bias not covered in the other domains above	Unclear	No	Yes	No
	Measurement of effectiveness of blinding and/or patients' expectation of treatment effectiveness	N/A	N/A	N/A	Yes
Crossover design	Analysis of paired data	N/A	N/A	N/A	No
	Assessment of carryover effects and/or justification of washout period	Low	Low	Low	Unclear

Appendix 4 Data tables for each of the 22 RCTs listed by procedure, condition and alphabetically according to first author/year.

Occipital Nerve Stimulation – migraine

<table>
<tr><th>Study details</th><th>Key efficacy findings</th><th>Key safety findings</th><th>Comments</th></tr>
<tr>
<td>Lipton et al. (2009) [15]
Study type: Multicentre, double-blind RCT.
Country: USA.
Study period: Not stated.
Study population: Patients with refractory migraine.
n=179 screened, 140 randomised, 132 implanted, 125 completed 12-week followed-up.
Mean age: Not stated.
Sex: Not stated.
Duration of Pain: Not stated.
Inclusion criteria: ICHD-II criteria for migraine with or without aura, and/or chronic migraine; drug-refractory (failed therapy with at least two acute and two preventive medications); had ≥ 6 days per month of long-duration (≥ 4 hours) migraine with moderate to severe pain (migraine day).
Technique: Implanted bilateral ONS vs. sham stimulation for 12 weeks, with 5-10 days of percutaneous trial stimulation prior to implantation.
Follow-up: Double-blind 12 weeks, open label 52 weeks, safety 2 years.
Conflict of interest: Sponsored by Boston Scientific.</td>
<td>Number of migraine days (≥4 hrs with moderate/severe pain) per month.
<table>
<tr><th></th><th>Baseline mean (SD)</th><th>Change from baseline at 3 months* mean (SD)</th></tr>
<tr><td>Active (n=63)</td><td>20.2 (7.2)</td><td>-5.5 (8.7)</td></tr>
<tr><td>Sham (n=62)</td><td>19.2 (7.9)</td><td>-3.9 (8.2)</td></tr>
</table>
*p=0.29

Pre-specified subgroup analysis, number of migraine days/month:
<table>
<tr><th></th><th>Medication overuse (mean)</th><th>No medication overuse (mean)</th></tr>
<tr><td>Active</td><td>-5.0</td><td>-5.9</td></tr>
<tr><td>Sham</td><td>-4.8</td><td>-2.6</td></tr>
</table>
N and SD not reported.
Test for interaction not reported.

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 to 2.9; negative likelihood ratio = 0.21, 0.06 to 0.78).</td>
<td>Adverse events: Infection, non-target area sensory symptoms, and implant site pain were the most-frequent device related adverse events.</td>
<td>Conference abstract only

Study authors' overall conclusion: Active ONS did not produce statistically significant benefits in relations to sham stimulation on the number of migraine days per month. Heterogeneity in treatment response suggests that there may be a treatment responsive subgroup.
Other outcome measures: not stated
Risk of bias: See Appendix 3
Stimulation devices and parameters: Bilateral active (250μs pulses, 60Hz, 0-12.7mA) versus sham (10μs pulses, 2Hz, < 1mA, 1s on/90min off duty cycle) stimulation for 12 weeks post-implantation of an ONS device.</td>
</tr>
</table>

<table>
<tr><th>Study details</th><th>Key efficacy findings</th><th>Key safety findings</th><th>Comments</th></tr>
<tr>
<td>Saper et al. (2011) [16]

Study type: Parallel group, sham-controlled RCT.

Country: USA (7 centres), Canada (1 centre), UK (1 centre).

Study period: 2004-2007.

Study population: Chronic migraine according to ICHD-II.

n=67 randomised, 66 analysed (75 assigned).

Mean age: 43 years (range not provided).

Sex: 80% female.

Mean duration of pain: 22 years.

Inclusion criteria: Headaches occurring on ≥15 days per months for > 3 months; pain involving the occipital or suboccipital region; pain refractory to preventive medications.

Technique*: AS (adjustable stimulation, n=28),
PS (pre-set stimulation, n=16),
MM (Medically managed, n=17),
AN (ancillary, n=5).

Follow-up: One & three months (up to 36 months of open-label follow-up ongoing).

Conflict of interest: Sponsored by Medtronic.</td>
<td>No primary endpoint was pre-specified but multiple outcomes were measured.
Results at 3 months:
Reduction in headache days (in which overall headache pain intensity ≥3) per month:
<table>
<tr><td>AS</td><td>27.0 ± 44.8% (6.7±10.0 days)</td></tr>
<tr><td>PS</td><td>8.8 ± 28.6% (1.5±4.6 days)</td></tr>
<tr><td>MM</td><td>4.4 ± 19.1% (1.0±4.2 days)</td></tr>
<tr><td>Ancillary</td><td>39.9 ± 51.0% (9.1±12.3 days)</td></tr>
</table>
Decrease in overall pain intensity (0-10):
<table>
<tr><td>AS</td><td>1.5 ± 1.6</td></tr>
<tr><td>PS</td><td>0.5 ± 1.3</td></tr>
<tr><td>MM</td><td>0.6 ± 1.0</td></tr>
<tr><td>Ancillary</td><td>1.9 ± 3.5</td></tr>
</table>
Responder rate (≥50% drop in headache days per month or a ≥3-point drop in pain intensity from baseline):
<table>
<tr><td>AS</td><td>39% (11/28)</td></tr>
<tr><td>PS</td><td>6% (1/16)</td></tr>
<tr><td>MM</td><td>0% (0/17)</td></tr>
<tr><td>Ancillary</td><td>40% (2/5)</td></tr>
</table>
% reduction in days with prolonged, severe headache per month:
<table>
<tr><td>AS</td><td>24.4 ± 43.6% (5.1±8.7 days)</td></tr>
<tr><td>PS</td><td>10.3 ± 34.0% (2.2±6.4days)</td></tr>
<tr><td>MM</td><td>-1.2 ± 38.9% (0.8±5.6 days)</td></tr>
<tr><td>Ancillary</td><td>33.5 ± 43.2% (7.7±11.7 days)</td></tr>
</table>
SF-36 mental health domain:
<table>
<tr><td>AS</td><td>5.5 ± 9.7</td></tr>
<tr><td>MM</td><td>-1.5 ± 6.3</td></tr>
</table>
</td>
<td>Adverse events:
Adverse device-related events.

Intra operative failures 4% (2/53).

Serious adverse events requiring hospitalisation 6% (3/51): implant site infection, lead migration, postoperative nausea.

Lead migration: 24% (12/51).

Reported ‘no evidence of adverse events leading to long-term complications or potential nerve damage’.</td>
<td>Study authors’ overall conclusion: The results of this feasibility study offer promise and should prompt further controlled studies of ONS in chronic migraine.

Other outcome measures: Also included Profile of Moods States (POMS), functional disability scale, migraine disability assessment (MIDAS), acute medication use and satisfaction with treatment. Except for responder rate, differences between groups were not statistically significant for the majority of outcomes.

Risk of bias See Appendix 3.

Stimulation device and parameters: Medtronic Synergy and Synergy Versitrel implantable pulse generators, Pisces Quad and Pisces Quad-Compact leads, clinician and patients programmers and other tool kits. Pulse amplitude: 0-10.5V, pulse rate 3-130Hz, pulse width 60-450µs.

*Additional notes: AS was the intervention group. PS was the sham control in which patients were implanted with a stimulator which was set to be on for one minute per day. MM was a comparator group in which no implantation took place. All patients in these three groups had at least a 50% reduction in migraine pain with occipital nerve block using 0.5% bupivacaine injection prior to randomisation. A further ‘ancillary’ group included patients who had a lack of response to the occipital nerve block. Treatment for this group was identical to AS group but allocation was not random.</td>
</tr>
</table>

<table>
<tr><th>Study details</th><th>Key efficacy findings</th><th>Key safety findings</th><th>Comments</th></tr>
<tr>
<td>Silberstein et al. (2011) [17]
Study type: Parallel group, double-blind, sham controlled RCT.
Country: USA (multicentre).
Study period: Not stated.
Study population: Patients with chronic migraine.
n= 157 randomised, 153 completed 12-week assessment.
Mean age: Not stated.
Sex: Not stated.
Mean duration of pain: Not stated.
Inclusion criteria: Not stated.
Technique: ONS vs. control.
Follow-up: Double-blind 12 weeks, open label 24, 48, 52 weeks.
Conflict of interest: Sponsored by St. Jude Medical Neuromodulation.</td>
<td>MIDAS, Zung Pain and Distress Scale (PAD), VAS, quality of life (QoL), satisfaction.
<table>
<tr><th></th><th>ONS</th><th>Control</th></tr>
<tr><td>Decrease in MIDAS headache days*</td><td>22.5</td><td>3.4</td></tr>
<tr><td>Improvement in total MIDAS scores*</td><td>64.6</td><td>20.4</td></tr>
<tr><td>Improvement in PAD scores*</td><td>13.3</td><td>5.5</td></tr>
<tr><td>Decrease in VAS scores*</td><td>14.1</td><td>7.0</td></tr>
<tr><td>30% reduction in VAS</td><td>35.2%</td><td>11.5%</td></tr>
<tr><td>Improved QoL</td><td>66.7%</td><td>17.2%</td></tr>
<tr><td>Satisfied with therapy</td><td>51.4%</td><td>19.2%</td></tr>
</table>
Significant differences for all assessments (p< 0.01)

*Numbers were taken directly from the abstract. They are likely to be percentages rather than absolute values.</td>
<td>Adverse events
Rate of serious device- or procedure-related events was 1.0%, including one case of infection and one case of expected post-operative pain that required hospitalization.</td>
<td>Conference abstract only – limited information available.
Study authors' overall conclusion: Results provide evidence to support safety and effectiveness of ONS for the management of headache pain and disability associated with chronic migraine.
Other outcome measures: Not stated
Risk of bias: See Appendix 3.
Stimulation device and parameters: A neurostimulation system (St. Jude Medical Neuromodulation).</td>
</tr>
</table>

Occipital Nerve Stimulation – Fibromyalgia

<table>
<tr><th>Study details</th><th>Key efficacy findings</th><th>Key safety findings</th><th>Comments</th></tr>
<tr>
<td>Plazier et al (2011) [101]
Study type: Cross-over.
Country: Belgium.
Study period: Not stated.
Study population: Patients with Fibromyalgia.
n= 15 (1 dropped out).
Mean age: Not stated.
Sex: Not stated.
Inclusion criteria: Not stated.
Technique: Patients implanted with temporary leads by occipital nerve and randomised to receive wither minimal stimulation (MiS) or sub threshold Stimulation (SuS) for first two weeks then crossover for two weeks. At four weeks all received Suprathreshold/Standard stimulation (StS) for two weeks.
Follow-up: Not stated
Conflict of interest: Paid consultants of device manufacturers St Jude Medical Neuromodulation Division.</td>
<td>Fibromyalgia Impact questionnaire (FIQ) completed at baseline, 2, 4 and 6 weeks.

14/15 completed trial
<table>
<tr><th></th><th>FIQ score</th></tr>
<tr><td>Baseline</td><td>67.5 ±15.0</td></tr>
<tr><td>MiS</td><td>53.8 ±19.5</td></tr>
<tr><td>SuS</td><td>56.0 ±20.5</td></tr>
<tr><td>StS</td><td>38.6 ±19.7</td></tr>
</table>
The maximum possible score is 100. The average FM patient scores about 50, severely afflicted patients are usually 70 plus.</td>
<td>Adverse events:
Not stated.</td>
<td>Taken from structured conference abstract

Study authors' overall conclusion: Treatment was safe and effective when compared to minimal stimulation controls.
Significant placebo effect was observed (similar reduction by MiS and SuS) but much greater reduction with StS.
Other outcome measures: Not stated
Risk of bias: See Appendix 3
Stimulation device and parameter:
Eon Neurostimulation System (St Jude Medical.</td>
</tr>
</table>

Implanted Peripheral Nerve Stimulation – Chronic lower back

<table>
<tr><th>Study details</th><th>Key efficacy findings</th><th>Key safety findings</th><th>Comments</th></tr>
<tr>
<td>Barolat et al. (2011) [71]
Study type: Two-phase randomised cross-over.
Country: USA (Denver).
Study period: Not stated.
Study population: Localised lower back pain.
n= 30
Mean age: Not stated.
Sex: Not stated.
Mean duration of pain: not stated
Inclusion criteria: Not stated.
Technique: Phase 1 involved patients rotating through four arms (minimal, sub threshold. Low frequency, standard stimulation) over a period lasting between 22 to 37 days in 4-8 day intervals. If experienced ≥50% reduction in pain proceeded to Phase 2, which begin with permanent implantation (Eon IPG, Octrode or Quattrode leads) and lasted 52 weeks.
Follow-up: Not stated.
Conflict of interest: Researcher team included paid consultants of device manufacturer St Jude Medical Neuromodulation Division.</td>
<td>Phase 1
<table>
<tr><th></th><th>≥50% pain relief</th></tr>
<tr><td>Minimal</td><td>4/29</td></tr>
<tr><td>Sub threshold</td><td>8/30</td></tr>
<tr><td>Low</td><td>17/30</td></tr>
<tr><td>Standard</td><td>16/30</td></tr>
</table>
23 went onto Phase 2 of which 16/23 reported ≥50% pain relief at 52 weeks and 16/23 classified as ‘excellent’ or ‘good’.</td>
<td>Adverse events:
Not stated.</td>
<td>Taken from structured conference abstract.
Study authors’ overall conclusion: PNFS appears to be a promising treatment for back pain.
Other outcome measures: Cannot assess from abstract
Risk of bias: See Appendix 3
Stimulation device and parameter: Eon IPG; Octrode and Quattrode leads, St Jude Medical Neuromodulation Division, Plano, TX.</td>
</tr>
</table>

Temporary Peripheral Nerve Stimulation – Osteoarthritis of the Knee

<table>
<tr><th>Study details</th><th>Key efficacy findings</th><th>Key safety findings</th><th>Comments</th></tr>
<tr>
<td>Kang et al. (2007) [79]
Study type: Single blinded sham randomized pilot study.
Country: USA.
Study period: March to December 2005.
Study population: Knee osteoarthritis.
n= 63 (70, 7 lost to follow up).
Mean age: 56.6 years (28-83).
Sex: 71% female.
Inclusion criteria: Aged between 18-85, diagnosis of osteoarthritis with a VAS ≥30mm.
Technique: For all patients the active percutaneous electrode was positioned on their site of maximum knee pain while feed electrode was placed directly across the joint line (medial and lateral or anterior and posterior). Treatment for groups was 30mins. Live instructed to tell examiner when achieved highest possible tolerable intensity – assessed at 5, 10, 15 minutes from initiation. Sham told would not experience the normal pins and needles sensation associated with electrical stimulation.
Follow-up: One week.
Conflict of interest: Not stated.</td>
<td>Reduction in VAS pain 0-10, SD not reported.
<table>
<tr><th></th><th>Immediately after</th><th>At 48 hours</th></tr>
<tr><td>Live (n=35)</td><td>2.1</td><td>0.80</td></tr>
<tr><td>Sham (n=28)</td><td>1.15</td><td>0.10</td></tr>
</table>
p=0.0361 (immediate) and 0.1789 (at 48 hours)

Also measured:

Pain control: significantly better for live at 48hrs for live (p=.039), 35% live reported well under or complete control c.f. 7% sham (68% of Sham poor or no control c.f. 32% live).
Satisfaction with treatment significant higher for live (p=.0128 immediately; p=.0459 at 6h; p=.0287 at 24h and p=.0007 at 48h. Satisfaction level did not exceed 50% at any measurement point.
Western Ontario and McMaster Osteoarthritis Index (WOMAC). Greater change in live compared to sham in pain (4,1 p=.1483; stiffness 1,0 p=0.296;function 12,2 p=0.0539).
Medication use at 1 week post treatment.

<table>
<tr><th></th><th>Increased</th><th>Same</th><th>Decreased</th></tr>
<tr><td>Live</td><td>1 (4%)</td><td>15 (43%)</td><td>19 (54%)</td></tr>
<tr><td>Sham</td><td>3 (11%)</td><td>25 (89%)</td><td>0 (0%)</td></tr>
</table>
Significant at p<.0001</td>
<td>Adverse events:
No serious adverse effects reported in either group.
One patient reported mild erythematous maculopapular rash, which resolved itself in 24hrs.
Three (one sham) reported mild tingling that resolved within 6 hours.</td>
<td>Study authors' overall conclusion: Study demonstrated safety and comfort with no serious adverse events and efficacy of device.
Other outcome measures: None
Risk of bias See Appendix 3.
Stimulation device and parameter: Biowave deep tissue neuromodulation pain therapy device (Deepwave). 1.5 inch diameter percutaneous electrode array embedded within a 2.5 inch diameter round carbon /silver electrode (Unipatch. Wabash, Minn). The electrode placed opposite the pain site was classic 2404 4x2 self-adhesive electrode (Unipatch).

Study limitations noted by authors include sample size, daily variation in knee pain based on time of day ad activity.</td>
</tr>
</table>

Percutaneous electrical nerve stimulation (PENS, temporary needle probes) – headache disorders

<table>
<tr><th>Study details</th><th>Key efficacy findings</th><th>Key safety findings</th><th>Comments</th></tr>
<tr>
<td>Ahmed et al. (2000)[80]

Study type: Sham-controlled, crossover RCT.

Country: USA (Dallas).

Study period: Not stated.

Study population: Patients with tension-type headache (n=13), chronic migraine (n=12), or post-traumatic headache (n=5) of at least 6 months duration.

n=30

Mean age: 39 years (range 24 to 56).

Sex: 60% female.

Mean duration of pain: Tension-type headache or post-traumatic headache –4 years
Migraine – 11 years.

Inclusion criteria: Severe headache ≥ 4 times per week, managed with oral non-opioid analgesics for ≥6 months. Cluster headache was excluded.

Technique: PENS vs. ‘needles only’ for 30 minutes, three times per week for two weeks. Ten needle probes were placed in the soft tissue to a depth of 1-3cm in the back of the neck (C2, C5, C7 and T4) and scalp, and connected to five pairs of positive and negative leads. PENS was administered at an alternating frequency of 15Hz and 30Hz.

Follow-up: 5-10 minutes after each treatment session.

Conflict of interest: No.</td>
<td>Pain, 10-cm VAS: 0 (best) to 10 (worst)
<table><tr><th></th><th>Tension-type headache</th><th>Migraine</th><th>Post-traumatic headache</th></tr><tr><td>Baseline</td><td>7.1 ± 1.0</td><td>7.6 ± 1.1</td><td>7.3 ± 1.0</td></tr><tr><td>Post-PENS</td><td>3.1 ± 0.7*</td><td>3.0 ± 0.7*</td><td>3.1 ± 0.6*</td></tr><tr><td>Post-needles only</td><td>6.3 ± 0.9</td><td>6.5 ± 0.9</td><td>5.7 ± 0.9</td></tr></table>*p<0.05 vs. baseline and p<0.05 vs. post needles only.

Number of headaches per week
<table><tr><th></th><th>Tension-type headache</th><th>Migraine</th><th>Post-traumatic headache</th></tr><tr><td>Baseline</td><td>6 ± 2</td><td>6 ± 1</td><td>6 ± 3</td></tr><tr><td>Post-PENS</td><td>3 ± 1*</td><td>3 ± 2*</td><td>4 ± 2</td></tr><tr><td>Post-needles only</td><td>6 ± 2</td><td>6 ± 2</td><td>6 ± 3</td></tr></table>*p<0.05 vs. baseline.

Physical activity, 10-cm VAS: 0 (best) to 10 (worst)
<table><tr><th></th><th>Tension-type headache</th><th>Migraine</th><th>Post-traumatic headache</th></tr><tr><td>Baseline</td><td>6.4 ± 0.9</td><td>5.8 ± 1.0</td><td>6.0 ± 0.8</td></tr><tr><td>Post-PENS</td><td>3.0 ± 0.7*</td><td>2.8 ± 0.7*</td><td>3.0± 0.6*</td></tr><tr><td>Post-needles only</td><td>5.8 ± 0.9</td><td>5.1 ± 0.9</td><td>5.3 ± 1.0</td></tr></table>*p<0.05 vs. baseline and p<0.05 vs. post needles only.
Also reported significant improvement in sleep quality and physical and mental component scores of the SF-36 for PENS compared with needles only.</td>
<td>Adverse events:
Not stated.</td>
<td>Study authors’ overall conclusion:
PENS appears to be a useful complementary therapy to analgesic and anti migraine drugs for the short-term management of headaches.

Other outcome measures: SF36

Risk of bias: See Appendix 3

Stimulation device and parameter:

Ten 32-gauge (0.2mm), 15mm long stainless steel needle probes (ITO, Tokyo, Japan) connected to five pairs of positive and negative leads. PENS was administered at an alternating frequency of 15Hz and 30Hz.</td>
</tr>
</table>

Percutaneous electrical nerve stimulation (PENS, temporary needle probes) – Peripheral Neuropathic Pain

<table>
<tr><th>Study details</th><th>Key efficacy findings</th><th>Key safety findings</th><th>Comments</th></tr>
<tr>
<td>Ghoname et al. (1999) [81]

Study type: Crossover RCT.

Country: USA (Dallas).

Study period: Not stated.

Study population: Patients with typical radicular pain (sciatica) due to radiologically confirmed lumbar disc herniation.

n=64

Mean age: 43 years (range not reported).

Sex: 53% female.

Mean duration of pain: 21 months (range 6 to 28).

Inclusion criteria: Patients > 18 years with a history of sciatica (constant or intermittent pain in one leg radiating below the knee, a positive straight-leg raising test, evidence of nerve-root compression at the L5-S1 level confirmed by radiologic testing) that had been maintained at a stable level with non-opioid analgesics for ≥6 weeks.

Technique: Placement of acupuncture-like needle probes into the soft tissue and/or muscle in the symptomatic leg to a depth of 2-4cm. Each session lasted 30 minutes, 3 times per week for 3 weeks with 1-week washout between modalities.

Follow-up: Immediately after each treatment session and 72 hours after the last treatment session.

Conflict of interest: Not stated.</td>
<td>Mean scores 24 hrs before the 1st session / after the last session.
<table>
<tr><th>VAS (0 best -10 worst)</th><th>Degree of pain</th><th>Level of activity</th><th>Quality of sleep</th></tr>
<tr><td>PENS pre</td><td>7.2 (1.8)</td><td>6.4 (2.1)</td><td>5.5 (1.9)</td></tr>
<tr><td>PENS post</td><td>4.1 (1.4)</td><td>4.0 (1.7)</td><td>3.1 (1.9)</td></tr>
<tr><td>Sham PENS pre</td><td>6.6 (1.9)</td><td>6.0 (1.9)</td><td>5.2 (2.1)</td></tr>
<tr><td>Sham PENS post</td><td>6.1 (1.9)</td><td>5.5 (2.1)</td><td>4.9 (1.9)</td></tr>
<tr><td>TENS pre</td><td>7.0 (1.9)</td><td>5.8 (1.7)</td><td>5.0 (2.0)</td></tr>
<tr><td>TENS post</td><td>5.4 (1.9)</td><td>4.5 (1.7)</td><td>4.0 (2.0)</td></tr>
</table>
% reduction from baseline in pain and oral analgesic usage 24hrs after the last treatment session.
<table>
<tr><th></th><th>Pain (VAS 0-10)</th><th>Oral analgesic usage</th></tr>
<tr><td>PENS</td><td>42% (18%)</td><td>50% (19%)</td></tr>
<tr><td>Sham PENS</td><td>8% (11%)</td><td>8% (13%)</td></tr>
<tr><td>TENS</td><td>23% (16%)</td><td>29% (17%)</td></tr>
</table>
SF-36, mean score 24 hours after last session.
<table>
<tr><th></th><th>Physical component summary</th><th>Mental component summary</th></tr>
<tr><td>PENS</td><td>35.3 (8.2)</td><td>44.2 (6.4)</td></tr>
<tr><td>Sham PENS</td><td>28.4 (6.7)</td><td>41.7 (6.2)</td></tr>
<tr><td>TENS</td><td>29.6 (7.4)</td><td>42.1 (6.0)</td></tr>
</table>
</td>
<td>Adverse events:
Not stated.</td>
<td>Study authors' overall conclusion: PENS was more effective than TENS when administered at a frequency of 4Hz.

Other outcome measures: Overall patient evaluation of relative effectiveness after undergone all treatment modalities indicated PENS was the therapy preferred by the highest proportion of patients.

Risk of bias: See Appendix 3.

Stimulation device and parameter: Ten 32-gauge stainless steel acupuncture-like needle probes connected to five bipolar leads from a low-output electrical generator and stimulated at 4Hz. The intensity was adjusted to produce the highest tolerable electrical 'tapping' sensation without muscle contractions. Maximum amplitude 250µA with a unipolar square-wave pattern and a pulse width of 0.1s. The electrical current was DC and the duty cycle was continuous. The sham PENS was placed identically to the above but with no electrical stimulation applied. The TENS utilised four 2.5 cm cutaneous electrode pads (SnapEase®, Empi, St. Paul, Minnesota) in a standardised dermatomal pattern. Stimulation was given at a frequency of 4Hz with pulse duration of 0.1s.</td>
</tr>
</table>

<table>
<tr><th>Study details</th><th>Key efficacy findings</th><th>Key safety findings</th><th>Comments</th></tr>
<tr>
<td>Hamza et al. (2000) [82]
(Tibial and deep perineal nerve).
Study type: Sham controlled investigator blinded crossover RCT.
Country: USA.
Study period: Not stated.
Study population: Adults with Type 2 diabetes with peripheral pain >6 months involving lower extremities.
n= 50
Mean age: 55 years (range 34 to 71).
Sex: 56% female.
Inclusion criteria: Referred from diabetes clinic with diagnosis of peripheral neuropathy confirmed by an abnormal nerve conduction study. Patients reported burning pain with paresthesia in both legs. Neurological examination revealed sensory abnormalities in both lower extremities.
Technique: PENS (needles with stimulation and sham (needles only). Thirty minutes of active or sham electrical stimulation three times a week for three weeks. One week washout before cross-over.
Follow-up: After treatment.
Conflict of interest: funded by Ambulatory Anaesthesia Research Foundation and Egyptian Consulate.</td>
<td>
<table>
<tr><td></td><td colspan="3">Before crossover, n=25 for each of the treatments</td><td colspan="3">Data from the two treatment periods (pre- and post-crossover) combined, n=50 for both treatments</td></tr>
<tr><td></td><td>Baseline</td><td>Week 1</td><td>Week 3</td><td>Baseline</td><td>Week 1</td><td>Week 3</td></tr>
<tr><td colspan="7">VAS Pain (cm) ↓ = improvement</td></tr>
<tr><td>Sham</td><td>6.4 ±0.9</td><td>5.9 ±1.1</td><td>6.3 ±1.1</td><td>6.2 ±1.3</td><td>3.8 ±1.2</td><td>2.6 ±0.9</td></tr>
<tr><td>Active</td><td>6.2 ±1.0</td><td>3.6 ±1.2</td><td>2.5 ±0.9</td><td>5.2 ±1.6</td><td>4.6 ±1.5</td><td>4.8 ±1.2</td></tr>
<tr><td colspan="7">VAS Activity (cm) ↑ = improvement</td></tr>
<tr><td>Sham</td><td>5.3 ±0.9</td><td>5.7 ±1.0</td><td>6.0 ±1.1</td><td>4.8 ±1.2</td><td>6.5 ±0.8</td><td>7.8 ±1.1</td></tr>
<tr><td>Active</td><td>5.2 ±1.0</td><td>6.4 ±0.8</td><td>7.9 ±1.0</td><td>5.9 ±1.3</td><td>6.4 ±1.1</td><td>6.3 ±1.2</td></tr>
<tr><td colspan="7">VAS Sleep (cm) ↑ = improvement</td></tr>
<tr><td>Sham</td><td>6.0 ±1.5</td><td>6.9 ±1.2</td><td>6.6 ±1.3</td><td>5.7 ±1.3</td><td>7.5 ±1.2</td><td>8.6 ±1.0</td></tr>
<tr><td>Active</td><td>5.8 ±1.3</td><td>7.5 ±0.9</td><td>8.3 ±0.7</td><td>6.8 ±1.5</td><td>7.3 ±1.3</td><td>7.1 ±1.2</td></tr>
<tr><td colspan="7">Oral analgesics (pills/day)</td></tr>
<tr><td>Sham</td><td>3.1 ±1.1</td><td>2.8 ±0.9</td><td>2.9 ±0.8</td><td>N/R</td><td></td><td></td></tr>
<tr><td>Active</td><td>3.3 ±1.3</td><td>2.2 ±0.9</td><td>1.3 ±0.6</td><td></td><td></td><td></td></tr>
</table>
All active significant improvement to baseline at p<.05. (Also reported weeks 2 data).

Study reported significant improvement in level of depression as measured on Becks Depression Inventory for both Sham and Active and this improvement was significantly greater for active. (Not clear whether measurement used was taken before crossover or end study).
</td>
<td>Adverse events: Stated ‘No side effects reported with either therapeutic modality’.</td>
<td>Study authors’ overall conclusion: PENS is useful in treating diabetic neuropathic pain. In addition to decreasing extremity pain PENS improves physical activity, sense of wellbeing and quality of sleep while reducing the need for oral nonopioid analgesic medication.
Other outcome measures: none
Risk of bias: See Appendix 3.
Stimulation device and parameter: Ten 32-gauge (0.2mm) stainless steel acupuncture-like needle probes (ITO, Tokyo) to depth of 1-3cm into soft issue and/or muscle in leg and foot bilaterally at:
• Right and left medial (lower border medial tibial condyle and 3” above malleolus close to tibia (leads 1 and 2));
• Right and left lateral (1” below tuberosity of tibia on anterior edge of tibialis anterior and posterior between lateral malleolus and tendo-calcaneus (leads 3 and 4));
• Fifth lead linking between 1st and 2nd toe proximal to web.
Needle probes connected to five bipolar leads connected to a low output generator. Probes stimulated at alternating frequencies of 15Hz and 30Hz every 3s for active and 0Hz for sham. Generator produced a maximum of 25mA electrical stimulation with biphasic square wave pattern with pulse of 0.5ms in</td>
</tr>
</table>

	There were similar improvements in Profile of Mood Status. SF36 pre-study scores were 31.2±7.3 for PCS and 41±5.8 for MCS. Both Sham and Active resulted in statistically significant improvements. PENS PCS increased to 36.8 ±11.6 and MCS to 43.9 ±5.6 ($p<.01$) c.f. normal population score of 50. Sham PCS increased to 32.4 ±7.5 and MCS to 42 ±5.5 ($p<.05$).		continuous duty cycle. Intensity at highest tolerable level without producing muscle contractions.

<table>
<tr><th>Study details</th><th>Key efficacy findings</th><th>Key safety findings</th><th>Comments</th></tr>
<tr>
<td>Raphael et al. (2011)[81]

Study type: Crossover RCT.

Country: UK (Birmingham).

Study period: Not stated.

Study population: Adult patients with various types of neuropathic pain, with surface hyperalgesia, and refractory to previous medical treatment.

n=31 (one dropped out after first treatment).

Mean age: 55.8 years (23-84).

Sex: 58 % female.

Mean duration of pain: 8.1 years (range 1-35).

Inclusion criteria: Adult patients with various chronic pain conditions who had pain >6 months, with a localised area of hyperalgesia on the body surface, and had not obtained pain relief with previous medical treatments.

Technique: One percutaneous probe was passed into the area of primary pain identified and mapped prior to treatment.

Follow-up: One week post treatment (with a 4-week washout period between treatments).

Conflict of interest: Sponsored by the Higher Education Funding Council for England. Previously received research funding unrelated to this RCT from Algotec Ltd.</td>
<td>Pain intensity VAS (0-10), median
<table>
<tr><th></th><th>Baseline</th><th>1 wk post-treatment</th></tr>
<tr><td>PENS</td><td>7.5 ± 1</td><td>0.5 ± NR</td></tr>
<tr><td>Sham PENS</td><td>7.5 ± 1</td><td>7.5 ± 1</td></tr>
</table>
Pressure pain threshold, mean (gm, measured with the von Frey aesthesiometer)
<table>
<tr><th></th><th>Baseline</th><th>1 wk post-treatment</th></tr>
<tr><td>PENS</td><td>202 ± 137</td><td>626 ± 228</td></tr>
<tr><td>Sham PENS</td><td>202 ± 134</td><td>206 ± 133</td></tr>
</table>
<u>Analysis of data from first treatment period only</u>
Pain intensity VAS (0-10), median
<table>
<tr><th></th><th>Reduction from baseline</th></tr>
<tr><td>PENS</td><td>3.9 ± 3.2</td></tr>
<tr><td>Sham PENS</td><td>0.1 ± 0.4</td></tr>
</table>
p<0.0001

Pressure pain threshold
<table>
<tr><th></th><th>Change from baseline</th></tr>
<tr><td>PENS</td><td>310 ± 267</td></tr>
<tr><td>Sham PENS</td><td>8 ± 4</td></tr>
</table>
p=0.007</td>
<td>Adverse events:
Stated ‘no adverse events were reported’.</td>
<td>Study authors’ overall conclusion: PENS therapy appears to be effective in providing short-term pain relief in chronic pain conditions. Studies with larger sample sizes and longer follow-up are recommended.
Patients’ conditions included: surgical scar pain (n=7), occipital neuralgia (n=4), past-traumatic neuropathic pain (n=3), stump pain (n=2), inflammatory neuropathic pain (n=3), chronic low back pain (n=5), complex regional pain syndrome (n=1), pain following total knee replacement surgery (n=3), chronic cervical pain (n=1), and post-herpetic neuralgia (n=2).

Other outcome measures: None

Risk of bias: See Appendix 3.

Stimulation device and parameters: Electrical stimulation was provided via conduction cables to the probe and to an earth plate on another non-painful skin site (NeuroStimulator, Algotec Ltd). Electrical currents with frequencies automatically alternating between 2-100Hz, at a rate of every 3s, were provided for a total duration of 25 mins. Wires were not connected to the PENS device but taped to the working surface (i.e. with no power supply) for the sham control.</td>
</tr>
</table>

Percutaneous electrical nerve stimulation (PENS, temporary needle probes) – Chronic neck pain

<table>
<tr><th>Study details</th><th>Key efficacy findings</th><th>Key safety findings</th><th>Comments</th></tr>
<tr>
<td>White et al. (2000) [84]

Study type: Crossover RCT.

Country: USA (Dallas).

Study period: Not stated.

Study population: Patients with non-radiating neck pain.

n=68.

Mean age: 52 years (range 27 to 80).

Sex: 54% female.

Mean duration of pain: 43 months.

Inclusion criteria: Patients with chronic non-radiating neck pain, radiologically confirmed cervical disk disease, a stable level of pain ≥3 months before enrolling and no previous experience with electroanalgesic therapies.

Technique: Placement of ten acupuncture needle probes to a depth of 2-4cm into the soft tissues and/or paraspinous muscles in the cervical region according to the dermatomal distribution of the neck pain (for ‘local stimulation’ and ‘needle only’) or in the low back region (for ‘remote stimulation’). Stimulation was carried out three times per week for three consecutive weeks for each of the three modalities, with one-week washout period between the modalities.

Follow-up: 5-10 minutes after each treatment session and 24 hours after each modality.

Conflict of interest: Sponsored in part by the Forest Park institute, the Ambulatory Anesthesia Research Foundation and the White Mountain institute.</td>
<td>VAS pain (0-10), 5-10 mins pre/post treatment.*
<table>
<tr><th></th><th>Pre</th><th>Post</th></tr>
<tr><td>Local PENS, 1st session</td><td>6.8 (4.1)</td><td>2.1 (4.1)</td></tr>
<tr><td>Local PENS, 9th session</td><td>4.0 (4.1)</td><td>1.0 (4.1)</td></tr>
<tr><td>Remote PENS, 1st session</td><td>6.6 (1.6)</td><td>6.1 (1.6)</td></tr>
<tr><td>Remote PENS, 9th session</td><td>5.9 (1.6)</td><td>4.8 (1.6)</td></tr>
<tr><td>Needles only, 1st session</td><td>6.2 (1.2)</td><td>5.9 (0.8)</td></tr>
<tr><td>Needles only, 9th session</td><td>5.6 (0.8)</td><td>4.5 (0.8)</td></tr>
</table>
*Values estimated from figures.

VAS (0-10), % improvement from baseline (pre-1st session) 24 hrs after last (9th) treatment session.
<table>
<tr><th></th><th>Degree of pain*</th><th>Level of activity*</th><th>Quality of sleep*</th><th>Reduction in analgesic usage</th></tr>
<tr><td>Local PENS</td><td>38%</td><td>41%</td><td>34%</td><td>37% (18%)</td></tr>
<tr><td>Remote PENS</td><td>13%</td><td>16%</td><td>10%</td><td>9% (13%)</td></tr>
<tr><td>Needles only</td><td>9%</td><td>11%</td><td>7%</td><td>6% (15%)</td></tr>
</table>
*Values estimated from figures.

SF-36, 24 hours after last session, mean change from baseline.
<table>
<tr><th></th><th>Physical component summary</th><th>Mental component summary</th></tr>
<tr><td>Local PENS</td><td>7.9</td><td>3.6</td></tr>
<tr><td>Remote PENS</td><td>3.7</td><td>1.9</td></tr>
<tr><td>Needles only</td><td>3.4</td><td>1.7</td></tr>
</table>
</td>
<td>Adverse events:
Stated ‘there were no observed cutaneous reactions, hematomas, or inflammatory changes at any of the needle insertion sites after the treatment sessions’.</td>
<td>Study authors’ overall conclusion: Local PENS was more effective compared to remote PENS and needles only.

Other outcome measures: None

Risk of bias: See Appendix 3.

Stimulation device and parameters: Ten 32-gauge stainless steel acupuncture needle probes (ITO, Tokyo) connected to five bipolar leads from an investigational low-output electrical generator. Stimulation lasted 30 minutes per session, at an alternating frequency of 15Hz and 30Hz (15/30Hz). Maximal amplitude 37mA, with an asymmetric biphasic waveform pattern, a pulse width of 0.7ms, and a continuous duty cycle. Intensity was adjusted to produce a gentle tapping sensation without muscle contraction.</td>
</tr>
</table>

Percutaneous electrical nerve stimulation (PENS, temporary needle probes) – Chronic lower back pain

<table>
<tr><th>Study details</th><th>Key efficacy findings</th><th>Key safety findings</th><th>Comments</th></tr>
<tr>
<td>Ghoname et al. (1999a)[84]
Study type: Crossover RCT.
Country: USA (Dallas).
Study period: March to December 1997.
Study population: patients with chronic low back pain secondary to radiologically confirmed degenerative disk disease.
n=60
Mean age: 43 years (±1.9y).
Sex: 52% female.
Mean duration of pain: Not stated.
Inclusion criteria: Age > 18 years with a history of lower back pain that had been maintained at a stable level with oral non-opioid analgesics ≥3 months.
Technique: Placement of acupuncture-like needle probes into the soft tissue and/or muscle in the lower back region to 2-4 cm depth according to the dermatomal distribution of the pain.
Treatment was administered for 30 minutes three times a week for three weeks; compared to sham PENS, TENS and low back exercise.
Follow-up: Immediately after each treatment session and 24-72 hours after the last treatment session for each modality.
Conflict of interest: Supported by Ambulatory Anesthesia Research</td>
<td>VAS pain (0-10), 48 hr before 1st and 24 hr after last (9th) treatment session.
<table>
<tr><th></th><th>Pre-treatment</th><th>Post-treatment</th></tr>
<tr><td>PENS</td><td>6.3 (1.5)</td><td>3.4 (1.4)*</td></tr>
<tr><td>Sham PENS</td><td>5.7 (1.8)</td><td>5.5 (1.9)</td></tr>
<tr><td>TENS</td><td>6.2 (1.7)</td><td>5.6 (1.9)</td></tr>
<tr><td>Exercise</td><td>6.5 (1.4)</td><td>6.4 (1.9)</td></tr>
</table>
*Significantly different from Sham PENS, TENS and exercise (p<0.02).

SF-36, difference between treatment modalities in change from baseline at 24 hrs after last treatment session.
<table>
<tr><th></th><th>Physical component summary</th><th>Mental component summary</th></tr>
<tr><td>PENS vs. sham PENS</td><td>4.97 (2.99)</td><td>1.84 (3.56)</td></tr>
<tr><td>PENS vs. TENS</td><td>4.66 (2.85)</td><td>1.70 (4.19)</td></tr>
<tr><td>PENS vs. exercise</td><td>5.82 (2.93)</td><td>1.84 (3.56)</td></tr>
</table>
Overall patient evaluation of relative effectiveness after receiving all four treatment modalities.
<table>
<tr><th></th><th>PENS</th><th>Sham PENS</th><th>TENS</th><th>Exercise</th></tr>
<tr><td>Most desirable modality</td><td>55 (91%)</td><td>1 (2%)</td><td>4 (7%)</td><td>0 (0%)</td></tr>
<tr><td>Improved physical activity</td><td>31 (51%)</td><td>2 (4%)</td><td>5 (8%)</td><td>0 (0%)</td></tr>
<tr><td>Improved sense of wellbeing</td><td>46 (76%)</td><td>7 (12%)</td><td>10 (16%)</td><td>6 (10%)</td></tr>
<tr><td>Preferred pain therapy</td><td>55 (91%)</td><td>1 (2%)</td><td>4 (7%)</td><td>0 (0%)</td></tr>
<tr><td>Willing to pay extra for therapy</td><td>49 (81%)</td><td>4 (6%)</td><td>5 (9%)</td><td>2 (4%)</td></tr>
</table>
</td>
<td>Adverse events:
Not stated.</td>
<td>Study authors' overall conclusion: PENS was more effective than sham PENS, TENS and exercise. Cumulative effects of PENS were observed.
Other outcome measures: PENS produced significantly greater improvement in level of activity and quality of sleep (VAS) (p<0.02) and greater decrease in the usage of oral non-opioid analgesics (pills/day) (p<0.03) compared to sham PENS, TENS and exercise.
Risk of bias: See Appendix 3.
Stimulation device and parameter: Ten 32-gauge stainless steel acupuncture-like needle probes connected to five bipolar leads (with each lead connected to one positive and one negative probe) from an investigational low output (<25mA) electrical generators, which produced a unipolar square-wave pattern of electrical stimulation at a frequency of 4Hz with a pulse width of 0.5ms. The intensity of the electrical stimulation was adjusted to produce the maximum tolerable 'tapping' sensation without muscle contractions. Sham PENS was identical except no electrical currency was applied. The TENS therapy utilised four medium-sized cutaneous electrode pads (SnapEase, Empi, St Paul, Minn). Stimulation was given at a frequency of 4Hz with a pulse duration of 0.1ms.</td>
</tr>
</table>

Foundation of Dallas, Egyptian Cultural and Educational Bureau (Washington DC). Two of the authors subsequently incorporated a company 'PENS Inc' to produce FDA approvable PENS devices.			

<table>
<tr><th>Study details</th><th>Key efficacy findings</th><th>Key safety findings</th><th>Comments</th></tr>
<tr>
<td>Ghoname et al. (1999b) [86]

Study type: Crossover RCT.

Country: USA (Dallas).

Study period: Not stated.

Study population: Patients with low back pain associated with radiologically confirmed degenerative lumbar disc disease. n=68

Mean age: 46 years (±21y).

Sex: 56% female.

Mean duration of pain: Not stated.

Inclusion criteria: A history of lower back pain that remained unchanged on a stable oral non-opioid analgesic regimen for ≥ 3 months before enrolling. Sciatica was excluded.

Technique: Placement of acupuncture-like needle probes into the soft tissue and/or muscle in the low back region to a depth of 2-4 cm according to the dermatomal distribution of the pain. Crossed over between four stimulus frequencies: 0Hz (sham), 4Hz, alternating 15Hz and 30Hz (15/30 Hz) and 100Hz. Stimulation lasted 30 minutes per session, 3 times per week for 2 consecutive weeks for each stimulus frequency.

Follow-up: 5-10 minutes after each treatment session and 72 hours after the final treatment session for each stimulus frequency.

Conflict of interest: Not stated.</td>
<td>VAS pain (0-10), pre/5-10 mins post treatment.
<table>
<tr><th></th><th>Pre</th><th>Post</th></tr>
<tr><td>100 Hz 1st session</td><td>5.7 (1.6)</td><td>2.7 (1.5)</td></tr>
<tr><td>100 Hz 6th session</td><td>4.5 (1.5)</td><td>1.2 (1.5)</td></tr>
<tr><td>15/30 Hz 1st session</td><td>6.0 (1.7)</td><td>2.5 (1.3)</td></tr>
<tr><td>15/30 Hz 6th session</td><td>4.0 (1.4)</td><td>1.1 (1.4)</td></tr>
<tr><td>4 Hz 1st session</td><td>6.4 (1.6)</td><td>2.3 (1.2)</td></tr>
<tr><td>4 Hz 6th session</td><td>4.7 (1.6)</td><td>1.2 (1.2)</td></tr>
<tr><td>Sham 1st session</td><td>5.8 (1.5)</td><td>5.6 (1.8)</td></tr>
<tr><td>Sham 6th session</td><td>5.7 (1.7)</td><td>5.5 (1.8)</td></tr>
</table>
% improvement from baseline after last (6th) treatment session, measured by VAS (0-10) except analgesic usage.
<table>
<tr><th></th><th>Degree of pain*</th><th>Physical activity*</th><th>Sleep quality*</th><th>↓ in analgesic usage</th></tr>
<tr><td>100Hz</td><td>49%</td><td>50%</td><td>39%</td><td>33%</td></tr>
<tr><td>15/30Hz</td><td>58%**</td><td>65%**</td><td>60%**</td><td>48%</td></tr>
<tr><td>4Hz</td><td>41%</td><td>48%</td><td>43%</td><td>35%</td></tr>
<tr><td>Sham</td><td>7%</td><td>6%</td><td>4%</td><td>5%*</td></tr>
</table>
*Values estimated from figures.
**Significantly higher than the other three treatment modalities (p<0.05).

SF-36, mean change from baseline after last (6th) session.
<table>
<tr><th></th><th>Physical component summary</th><th>Mental component summary</th></tr>
<tr><td>100Hz</td><td>7.1</td><td>3.1</td></tr>
<tr><td>15/30 Hz</td><td>7.3</td><td>3.2</td></tr>
<tr><td>4Hz</td><td>7.0</td><td>2.8</td></tr>
<tr><td>Sham</td><td colspan="2">Not reported*</td></tr>
</table>
*Stated ‘did not show any significant improvement’.</td>
<td>Adverse events:
Not stated.</td>
<td>Study authors’ overall conclusion: Frequency of electrical stimulation is an important determinant of the analgesic response to PENS therapy. Alternating stimulation at 15Hz and 30Hz frequencies was more effective than either 4Hz or 100Hz.

Other outcome measures: Overall patient evaluation of relative effectiveness after undergone four stimulus frequencies indicated 15/30Hz was the therapy preferred by the highest proportion of patients.

Risk of bias: See Appendix 3.

Stimulation device and parameter: Ten 32-gauge (0.2 mm) stainless steel acupuncture-like needle probes (ITO, Tokyo, Japan) connected to five bipolar leads (with each lead connected to one positive and one negative probe) from an investigational low-output electrical generator. Maximal amplitude 25mA, with a unipolar square-wave pattern and a pulse with of 0.5ms. The electrical current was DC and the duty cycle was continuous. The intensity was adjusted to produce the highest tolerable electrical sensation without muscle contractions (except for the sham treatments).</td>
</tr>
</table>

<table>
<tr><th>Study details</th><th>Key efficacy findings</th><th>Key safety findings</th><th>Comments</th></tr>
<tr>
<td>Hamza et al. (1999) [87]

Study type: Sham-control crossover RCT.

Country: USA (Dallas).

Study period: Not stated.

Study population: Lower back pain (LBP) secondary to radiologically confirmed degenerative lumber disk disease. 42% undergone previous back surgery. n= 75

Mean age: 47 years (±18 years).

Sex: 55% female.

Mean duration of pain: 38 months.

Inclusion criteria: LBP related to degenerative lumbar disk disease with a pain level unchanged over ≥3 months.

Technique: Comparison of four durations of stimulation (0 (Sham), 15, 30 and 45 mins). Patients exposed to all stimulation intervals in random sequence over 11 week study period and told that each treatment session would last 60 mins with varying level of electrical stimulation (no sensation or light tapping). Three treatments per week for two weeks, followed by one week washout. Ten needle probes were inserted into soft tissue or muscle to depth of 2-4cm in lower back according to dermatomal (or sclerotomal) distribution of pain for 60 minutes (L1 to LT5, S2 to S3) and connected by five bi-polar probes (see fig1 of the paper) to low outputs generator and stimulated for 0, 15, 30, or 45 minutes</td>
<td>Comparison of acute for each stimulation interval: Mean VAS pain score immediately before and after treatment (5-10 mins after treatment).
<table>
<tr><th>VAS Pain Scores (mean ±SD)</th><th>Pre 1st Treatment</th><th>Post 1st Treatment</th><th>Pre 6th (final) Treatment</th><th>Post 6th Treatment</th></tr>
<tr><td>Sham (0 min)</td><td>6.2 ±1.9</td><td>5.8 ±1.7</td><td>6.0 ±1.6</td><td>5.4 ±1.9</td></tr>
<tr><td>15 min</td><td>6.8 ±1.7</td><td>5.9 ±1.9</td><td>3.8 ±1.9</td><td>2.0 ±1.7*</td></tr>
<tr><td>30 min</td><td>6.4 ±1.9</td><td>3.9 ±1.8 **</td><td>4.5 ±2.1</td><td>1.6 ±1.8 **</td></tr>
<tr><td>45 min</td><td>6.3 ±1.9</td><td>3.8 ±1.8 **</td><td>4.6 ±1.5</td><td>1.5 ±1.4 **</td></tr>
</table>
* p<.05; **p<.01

Mean % improvement from baseline (24h before 1st treatment) and end of 2 weeks (estimated from figures) and reduction in oral non-opioid medication.
<table>
<tr><th></th><th>Pain</th><th>Physical activity</th><th>Sleep</th><th>Analgesic medication (pills per day)</th></tr>
<tr><td>Sham (0 min)</td><td>10</td><td>8</td><td>6</td><td>8 ±11%</td></tr>
<tr><td>15 min</td><td>22*</td><td>28*</td><td>24*</td><td>21 ±13%*</td></tr>
<tr><td>30 min</td><td>46**†</td><td>52**†</td><td>45**†</td><td>38 ±16%**</td></tr>
<tr><td>45 min</td><td>41**†</td><td>50**†</td><td>40**†</td><td>35 ±17%**†</td></tr>
</table>
*Significantly different from sham (p<0.05) ** (p<0.01)
†Significantly different from 15 mins (p<0.05)</td>
<td>Adverse events:
Not stated.</td>
<td>Study authors' overall conclusion: Duration of electrical stimulation influences degree of pain relief and improvement in function over two week treatment period. Thirty minutes may be optimal as there were no additional benefits from longer stimulation. The researchers note the study is open to bias due to inability to blind and placebo effect.

Other outcome measures: none

Risk of bias: See Appendix 3

Stimulation device and parameter: Ten 32-guage stainless steel acupuncture needle probes (ITO, Tokyo) connected by five polar leads to low-output electrical generator (make and model not given). Alternating frequency of 15 and 30Hz, maximum amplitude 25mA, unipolar wave pattern and pulse width 0.5ms. Direct current and duty cycle continuous.</td>
</tr>
</table>

<table>
<tr>
<td>at alternating frequency of 15 and 30Hz. Intensity adjusted until tolerable tapping sensation with muscle contractions.

Follow-up: None.

Conflict of interest: Funded by Forest Park Institute, Egyptian Cultural and Education Bureau, Ambulatory Anaesthesia Research Foundation of Dallas.</td>
<td>SF-36, mean change from baseline after last (6th) session
<table>
<tr><th></th><th>Physical component summary</th><th>Mental component summary</th></tr>
<tr><td>Sham (0 min)</td><td colspan="2">not reported</td></tr>
<tr><td>15 min</td><td>5.4*</td><td>2.1*</td></tr>
<tr><td>30 min</td><td>7.4**</td><td>3.1**</td></tr>
<tr><td>45 min</td><td>7.1**</td><td>2.9**</td></tr>
</table>
*p<0.01 vs. sham; **p<0.001 vs. sham</td>
<td></td>
<td></td>
</tr>
</table>

<table>
<tr><th>Study details</th><th>Key efficacy findings</th><th>Key safety findings</th><th>Comments</th></tr>
<tr>
<td>Hamza et al. (2000) [82]
(Tibial and deep perineal nerve).
Study type: Sham controlled investigator blinded crossover RCT.
Country: USA.
Study period: Not stated.
Study population: Adults with Type 2 diabetes with peripheral pain >6 months involving lower extremities.
n= 50
Mean age: 55 years (range 34 to 71).
Sex: 56% female.
Inclusion criteria: Referred from diabetes clinic with diagnosis of peripheral neuropathy confirmed by an abnormal nerve conduction study. Patients reported burning pain with paresthesia in both legs. Neurological examination revealed sensory abnormalities in both lower extremities.
Technique: PENS (needles with stimulation and sham (needles only). Thirty minutes of active or sham electrical stimulation three times a week for three weeks. One week washout before cross-over.
Follow-up: After treatment.
Conflict of interest: funded by Ambulatory Anaesthesia Research Foundation and Egyptian Consulate.</td>
<td>
<table>
<tr><td></td><td colspan="3">Before crossover, n=25 for each of the treatments</td><td colspan="3">Data from the two treatment periods (pre- and post-crossover) combined, n=50 for both treatments</td></tr>
<tr><td></td><td>Baseline</td><td>Week 1</td><td>Week 3</td><td>Baseline</td><td>Week 1</td><td>Week 3</td></tr>
<tr><td colspan="7">VAS Pain (cm) ↓ = improvement</td></tr>
<tr><td>Sham</td><td>6.4 ±0.9</td><td>5.9 ±1.1</td><td>6.3 ±1.1</td><td>6.2 ±1.3</td><td>3.8 ±1.2</td><td>2.6 ±0.9</td></tr>
<tr><td>Active</td><td>6.2 ±1.0</td><td>3.6 ±1.2</td><td>2.5 ±0.9</td><td>5.2 ±1.6</td><td>4.6 ±1.5</td><td>4.8 ±1.2</td></tr>
<tr><td colspan="7">VAS Activity (cm) ↑ = improvement</td></tr>
<tr><td>Sham</td><td>5.3 ±0.9</td><td>5.7 ±1.0</td><td>6.0 ±1.1</td><td>4.8 ±1.2</td><td>6.5 ±0.8</td><td>7.8 ±1.1</td></tr>
<tr><td>Active</td><td>5.2 ±1.0</td><td>6.4 ±0.8</td><td>7.9 ±1.0</td><td>5.9 ±1.3</td><td>6.4 ±1.1</td><td>6.3 ±1.2</td></tr>
<tr><td colspan="7">VAS Sleep (cm) ↑ = improvement</td></tr>
<tr><td>Sham</td><td>6.0 ±1.5</td><td>6.9 ±1.2</td><td>6.6 ±1.3</td><td>5.7 ±1.3</td><td>7.5 ±1.2</td><td>8.6 ±1.0</td></tr>
<tr><td>Active</td><td>5.8 ±1.3</td><td>7.5 ±0.9</td><td>8.3 ±0.7</td><td>6.8 ±1.5</td><td>7.3 ±1.3</td><td>7.1 ±1.2</td></tr>
<tr><td colspan="7">Oral analgesics (pills/day)</td></tr>
<tr><td>Sham</td><td>3.1 ±1.1</td><td>2.8 ±0.9</td><td>2.9 ±0.8</td><td>N/R</td><td></td><td></td></tr>
<tr><td>Active</td><td>3.3 ±1.3</td><td>2.2 ±0.9</td><td>1.3 ±0.6</td><td></td><td></td><td></td></tr>
</table>
All active significant improvement to baseline at p<.05. (Also reported weeks 2 data).

Study reported significant improvement in level of depression as measured on Becks Depression Inventory for both Sham and Active and this improvement was significantly greater for active. (Not clear whether measurement used was taken before crossover or end study).
</td>
<td>Adverse events: Stated ‘No side effects reported with either therapeutic modality’.</td>
<td>Study authors’ overall conclusion: PENS is useful in treating diabetic neuropathic pain. In addition to decreasing extremity pain PENS improves physical activity, sense of wellbeing and quality of sleep while reducing the need for oral nonopioid analgesic medication.
Other outcome measures: none
Risk of bias: See Appendix 3.
Stimulation device and parameter: Ten 32-gauge (0.2mm) stainless steel acupuncture-like needle probes (ITO, Tokyo) to depth of 1-3cm into soft issue and/or muscle in leg and foot bilaterally at:
• Right and left medial (lower border medial tibial condyle and 3” above malleolus close to tibia (leads 1 and 2));
• Right and left lateral (1” below tuberosity of tibia on anterior edge of tibialis anterior and posterior between lateral malleolus and tendo-calcaneus (leads 3 and 4));
• Fifth lead linking between 1st and 2nd toe proximal to web.
Needle probes connected to five bipolar leads connected to a low output generator. Probes stimulated at alternating frequencies of 15Hz and 30Hz every 3s for active and 0Hz for sham. Generator produced a maximum of 25mA electrical stimulation with biphasic square wave pattern with pulse of 0.5ms in</td>
</tr>
</table>

	There were similar improvements in Profile of Mood Status. SF36 pre-study scores were 31.2±7.3 for PCS and 41±5.8 for MCS. Both Sham and Active resulted in statistically significant improvements. PENS PCS increased to 36.8 ±11.6 and MCS to 43.9 ±5.6 ($p<.01$) c.f. normal population score of 50. Sham PCS increased to 32.4 ±7.5 and MCS to 42 ±5.5 ($p<.05$).		continuous duty cycle. Intensity at highest tolerable level without producing muscle contractions.

<table>
<tr><th>Study details</th><th>Key efficacy findings</th><th>Key safety findings</th><th>Comments</th></tr>
<tr>
<td>Pérez-Palomares et al. (2010)[91]
Study type: Parallel group RCT.
Country: Spain.
Study period: July 2004 and 2005.
Study population: Patients with chronic low back pain, referred to physiotherapy by primary care physician.
n=122 (but stated n=67 for PENS and n=68 for dry needling; 10 patients dropped out).
Mean age: 45.85 years (±14.4).
Sex: 75 % female.
Mean duration of pain: Not stated.
Inclusion criteria: Patients > 18 years with chronic low back pain ≥4 months (or shorter if recurrent), had modest or little improvement on NSAIDs and/or analgesics. Excluded fibromyalgia, suspected or diagnosed structural lesions in the lumbar column, concomitant non-pharmacological treatments.
Technique: PENS - eight acupuncture needles introduced at a depth of 2-2.5 cm, positioned at the level from L2 to L5. 30 minutes per session, three times a week for three weeks. Dry needling: using fast-in and fast-out Hong’s technique on trigger points diagnosed during initial assessment. Once per week for three weeks.
Follow-up: none
Conflict of interest: None</td>
<td>Change from baseline for VAS scores at end of treatment (3 weeks):
<table>
<tr><th></th><th>PENS median (SD)</th><th>Dry needling median (SD)</th></tr>
<tr><td>Pain</td><td>2.38 (2.27)</td><td>2.35 (2.58)</td></tr>
<tr><td>>40% reduction in VAS pain</td><td>n=28 (53.85%)</td><td>n=24 (46.15%)</td></tr>
<tr><td>Sleep quality</td><td>1.72 (2.67)</td><td>1.85 (2.66)</td></tr>
</table>
Number of patients included in analysis was not reported.

Change from baseline for Oswestry Disability Index at end of treatment (3 weeks):
<table>
<tr><th></th><th>PENS median (SD)</th><th>Dry needling median (SD)</th></tr>
<tr><td>Personal care</td><td>0.38 (0.97)</td><td>0.34 (0.82)</td></tr>
<tr><td>Lifting weight</td><td>0.59 (1.42)</td><td>0.06 (0.96)</td></tr>
<tr><td>Walking</td><td>0.17 (0.98)</td><td>0.15 (0.57)</td></tr>
<tr><td>Sitting</td><td>0.21 (0.89)</td><td>0.33 (1.05)</td></tr>
<tr><td>Standing</td><td>0.25 (0.84)</td><td>0.41 (0.82)</td></tr>
<tr><td>Social life</td><td>0.72 (1.10)</td><td>0.72 (3.03)</td></tr>
</table>
Also measured change from baseline for algometry readings in right and left deep paraspinal muscles, right and left quadrates lumborum muscles, and right and left gluteus medius muscles. No significant differences were found between PENS and dry needling.</td>
<td>Adverse events: Not stated. Only mentioned post-treatment soreness ‘could justify the higher rates of abandonment’ in the dry needling treatment.</td>
<td>Study authors’ overall conclusion: Effectiveness of dry needling is comparable to that of PENS.
Other outcome measures: none
Risk of bias: See Appendix 3.
Stimulation device and parameters: PENS - low frequency (4Hz) electric current was applied through eight 0.3 x 25 mm acupuncture needles using a portable device normally used in primary care facilities [Carin TNS 190 portable]. Duration of impulse 0.3ms. Dry needling: needles with plastic guide tubes, measuring 0.3 x 40 mm, with application of vapocoolant spray.</td>
</tr>
</table>

<table>
<tr><th>Study details</th><th>Key efficacy findings</th><th>Key safety findings</th><th>Comments</th></tr>
<tr>
<td>Topuz et al. (2004) [91]
Study type: RCT.
Country: Turkey.
Study period: Not stated.
Study population: Chronic lower back
n= 55 (60).
Mean age: 44.1 years (±12.21).
Sex: 74.5% female.
Mean duration of pain: 17.4 ± 11.72m
Inclusion criteria: Patients with lower back pain ≥ 3 months seen in an outpatient clinic of a Physical Medicine and Rehabilitation Department.
Technique: TENS – symmetric, bi-phasic rectangular pulses with 100µs duration. Four medium sized (2x2cm) carbon impregnated rubber cutaneous electrodes bilaterally placed over most painful lumbar region. Conventional TENs group received high frequency (80Hz) and current intensity increased to patients reported paraesthesia. Low intensity (4Hz) with maximum tolerated amplitude without muscle contraction. In Placebo TENs group electrodes placed in same position with no stimulation applied through electrodes. PENS group received low frequency stimulation (4Hz) and currency intensity was increased to produce a ‘tapping sensation’. Modalities were administered for 20 minutes, five times per week, for two weeks.
Follow-up: None.
Conflict of interest: None stated</td>
<td>Reduction in VAS pain (0-10) at 2 weeks
<table>
<tr><th></th><th>Current pain</th><th>Activity pain</th></tr>
<tr><td>PENS</td><td>3.61 ± 1.98</td><td>4.07 ± 1.75</td></tr>
<tr><td>C-TENS</td><td>2.80 ± 2.00</td><td>2.50 ± 1.45</td></tr>
<tr><td>Low-TENS</td><td>2.60 ± 1.40</td><td>2.15 ± 1.18</td></tr>
<tr><td>Placebo TENS</td><td>-0.16 ± 1.11</td><td>0.16 ± 0.83</td></tr>
</table>
Also measured functional disability measured by Low Back Pain Outcome Scale (LBPOS) and Oswestry Disability Index (ODI), and SF-36.

PENS, C-TENS and Low TENS were significantly more effective than placebo TENS in respect to current pain, activity pain, Low Back Pain Outcome Scale, Oswestry Disability Index and SF36 (p<.05).

PENS produced better improvements in activity pain and SF36 scores than C-TENS and low-TENS (p<.05).</td>
<td>Adverse events:
None stated</td>
<td>Study authors’ overall conclusion: Evidence of short-term effectiveness of C-TENS, low-TENs and PENS on pain, functional disability and quality of life in patients with chronic LBP. PENS is more effective in TENS in providing early relief of activity pain and some components of health quality.
Other outcome measures: none
Risk of bias: See Appendix 3.
Stimulation device and parameter: TENs was performed with Trio 300units (ITO Corp. Japan) that generates symmetric, bi-phasic rectangular pulses with 100µs duration. Four medium sized (2x2cm) carbon impregnated rubber cutaneous electrodes bilaterally placed over most painful lumbar region.
C-TENS received hi-frequency (80Hz) stimulation and Low-TENS 4Hz frequency.
PENS was performed using IC 4107 units (ITO Corp. Japan) that generate unipolar square waves pulses 4Hz for 100µs duration through four 32-gauge stainless steel needles placed symmetrically to a depth of 2-4cm in standard dermatomal pattern over the most painful lumbar region.</td>
</tr>
</table>

<table>
<tr><th>Study details</th><th>Key efficacy findings</th><th>Key safety findings</th><th>Comments</th></tr>
<tr>
<td>Weiner et al. (2003) [90]

Study type: Parallel group, sham-controlled RCT.

Country: USA (Pittsburgh).

Study period: Not stated.

Study population: Community-dwelling older adults with chronic lower back pain.

n= 34.

Mean age: 73.8 years

Sex: 53% female.

Mean duration of pain: 13.6 years

Inclusion criteria: Aged 65+ with CLBP of at least moderate intensity occurring almost every day for previous three months. Recruited by newspaper advertisement (105). Screened first by telephone (54) and then by history and physical examination (46/50 screened). 12 declined. Detailed exclusion criteria.

Technique: PENS administered according to approach described by Ghoname et al (1999a). Needle insertion and stimulation appropriate dermatomal, myotomal and sclerotomal levels using modified Craig-PENS protocol progressing from 2Hz to 200Hz depending on patient response over the treatment period. Twice a week for six weeks each session lasting 30 minutes. Sham needles were applied in the same way as PENS group with no electrical stimulation. Patients in both groups received physical therapy (PT) and therapist was masked to subject</td>
<td>Primary outcome measures.
<table>
<tr><td></td><td></td><td></td><td></td><td colspan="3">MANOVA (p value)</td></tr>
<tr><td></td><td>Pre</td><td>Post</td><td>3 month follow up</td><td>Group effect</td><td>Time Effect</td><td>Inter-action effect</td></tr>
<tr><td colspan="4">Pain intensity</td><td>.02</td><td>.002</td><td>.004</td></tr>
<tr><td colspan="4">McGill Pain Questionnaire</td><td>.04</td><td>.005</td><td>.009</td></tr>
<tr><td>PENS +PT</td><td>13.06 ±1.31</td><td>6.66 ±0.87</td><td>6.19 ±0.88</td><td></td><td></td><td></td></tr>
<tr><td>Sham +PT</td><td>12.24 ±1.69</td><td>12.47 ±2.04</td><td>11.82 ±1.90</td><td></td><td></td><td></td></tr>
<tr><td colspan="4">MPI Pain Severity</td><td>.003</td><td>.012</td><td>.025</td></tr>
<tr><td>PENS +PT</td><td>3.21 ±0.25</td><td>2.00 ±0.20</td><td>2.16 ±0.30</td><td></td><td></td><td></td></tr>
<tr><td>Sham +PT</td><td>3.28 ±0.28</td><td>3.22 ±0.23</td><td>3.10 ±0.16</td><td></td><td></td><td></td></tr>
<tr><td colspan="4">Pain related disability</td><td>.29</td><td>.028</td><td>.012</td></tr>
<tr><td colspan="4">Roland disability scale</td><td>.26</td><td>.042</td><td>.034</td></tr>
<tr><td>PENS +PT</td><td>12.63 ±1.13</td><td>7.81 ±1.02</td><td>9.25 ±1.08</td><td></td><td></td><td></td></tr>
<tr><td>Sham +PT</td><td>11.24 ±1.47</td><td>11.06 ±1.17</td><td>12.18 ±1.21</td><td></td><td></td><td></td></tr>
<tr><td colspan="4">MPI Interference Scale</td><td>.27</td><td><.001</td><td>.036</td></tr>
<tr><td>PENS +PT</td><td>3.52 ±0.37</td><td>2.44 ±0.33</td><td>2.61 ±0.26</td><td></td><td></td><td></td></tr>
<tr><td>Sham +PT</td><td>3.30 ±0.37</td><td>3.10 ±0.40</td><td>2.97 ±0.37</td><td></td><td></td><td></td></tr>
</table>
PENS +PT significant reduction in pain intensity from pre to post treatment (p<.001) but Sham did not (p=.94) and pain related disability (p=.002 cf p=.81).</td>
<td>Adverse events
Not stated.</td>
<td>Study authors' overall conclusion: PENS is promising treatment with sustained effects on primary (pain intensity and disability) and some secondary outcomes (psychosocial and two tests of physical performance time chair and lifting endurance).

Researchers note that:
Possible ceiling effect on functional reach and sleep; static lifting may be unaffected because short duration of PT;
Possible Placebo effect but maintain persistence of effect across multiple measures makes this less likely;
PENS may be complement to home element of PT resulting in a combined effect.
Other outcome measures: None

Risk of bias: Not possible to truly mask randomisation of groups.

Stimulation device and parameter: Make and model of device used not provided.

Note: Some measures of outcomes specific to older adult population.</td>
</tr>
</table>

randomisation. Treatment session goals mutually agreed between patient and therapist.

Follow-up: Three months.

Conflict of interest: Funded by USPHS Research Grant and NIH.

Secondary Outcome measures

				MANOVA (p value)		
	Pre	Post	3 month follow up	Group effect	Time Effect	Inter-action effect
Physical performance						
Chair rise, seconds				.30	.81	.029
PENS +PT	3.69 ±0.13	3.12 ±0.17	3.19 ±0.18			
Sham +PT	3.42 ±0.38	3.77 ±0.21	3.75 ±0.27			
Gait speed, seconds				.07	.003	.88
PENS +PT	17.60 ±0.82	16.34 ±0.70	16.45 ±0.81			
Sham +PT	15.51 ±0.80	14.45 ±0.67	14.35 ±0.79			
No. Dynamic lifts				.12	.10	.034
PENS +PT	34.00 ±4.51	47.13 ±2.12	47.00 ±1.67			
Sham +PT	34.58 ±4.98	34.17 ±5.22	30.80 ±5.11			
Psychosocial factors				.60	.023	.041
Geriatric depression scale				.75	.11	.024
PENS +PT	6.81 ±1.73	3.44 ±0.90	4.11 ±0.87			
Sham +PT	5.00 ±1.09	5.50 ±1.22	5.41 ±1.37			
Sleep index				.31	.052	.29
PENS +PT	5.38 ±1.15	3.56 ±063	5.19 ±0.85			
Sham +PT	6.59 ±0.87	5.35 ±0.88	5.59 ±0.86			

	MPI Life Control Scale				0.039	0.027	0.016	
	PENS +PT	4.22 ±0.21	5.10 ±0.13	5.08 ±0.14				
	Sham +PT	4.32 ±0.28	4.23 ±0.21	4.34 ±0.27				
	Other measures: Functional reach, static lifting strength, cognitive function (Hopkins Verbal learning and Trail Marking B Test). Significant group by time interaction for chair rise with PENs +PT showing a significant pre- to post treatment (p=.011), which was maintained from post to follow-up (p=.62), but sham showed no significant changes over time (p=.41). Significant changes were found for gait speed for both PENS+PT (p=.045) and Sham + PT (p=.032).							

<table>
<tr><th>Study details</th><th>Key efficacy findings</th><th>Key safety findings</th><th>Comments</th></tr>
<tr>
<td>Weiner et al. (2008) [89]

Study type: Four arms, parallel-group, sham controlled RCT (with factorial design).

Country: USA (Pittsburgh).

Study period: not stated

Study population: Older adults aged ≥ 65 with chronic lower back pain.

n= 200 – 50 assigned each to:
(a) Lumbar PENS only;
(b) PENS + general conditioning and aerobic exercise (GCAE);
(c) Control PENS (intensity and short duration unlikely to have affect);
(d) Control PENS + GCAE.

Mean age: 73.90 years

Sex: 57 % female.

Median duration of pain: (a) 10y; (b) 9y; (c) 7y and (d) 5y.

Inclusion criteria: Aged 65, English speaking, LBP everyday or almost every day of least moderate intensity for more than 3 months.

Technique: PENS and control PENS were administered according to Craig et al technique (frequency increased from 2Hz as treatment sessions progress to 200Hz depending on response at previous session), using 32 gauge 40mm needles inserted c.15mm into subcutaneous fascia placed at levels corresponding to T-12, L3, L5 and S2 and motor point for piriformis</td>
<td>
<table>
<tr><th>MPQ total (pain intensity)</th><th>Baseline</th><th>Post intervention Change on baseline</th><th>6 months follow up Change on baseline</th></tr>
<tr><td>PENS</td><td>13.4 ±8.5</td><td>10 {-2.9 ±9.2 [.04]}</td><td>9.7 {-3.4 ±7.4 [.47]}</td></tr>
<tr><td>PENS + GCAE</td><td>12.2 ±3.3</td><td>8.2 {-4.1 ±8.2 [.56]}</td><td>8.7 {-3.8 ±8.9 [.51]}</td></tr>
<tr><td>Control PENS</td><td>10.7 ±6.2</td><td>8.3 {-2.3 ±6.3 [.31]}</td><td>7.7 {-3.3 ±7.4 [.45]}</td></tr>
<tr><td>Control PENS + GCAE</td><td>12.0 ± 8.0</td><td>8.5 {-3.1 ±7.9 [.42]}</td><td>8.3 {-3.1 ±7.1 [.41]}</td></tr>
<tr><td colspan="4">Roland (pain disability)</td></tr>
<tr><td>PENS</td><td>10.5 ±4.1</td><td>-2.6 ±4.5</td><td>-2.1 ±4.2</td></tr>
<tr><td>PENS + GCAE</td><td>10.2 ±3.8</td><td>-2.6 ±4.6</td><td>-2.1 ±4.3</td></tr>
<tr><td>Control PENS</td><td>10.5 ±5.2</td><td>-2.7 ±3.8</td><td>3.0 ±4.7</td></tr>
<tr><td>Control PENS + GCAE</td><td>11.0 ±5.4</td><td>-3.0 ±4.7</td><td>-2.8 ±5.3</td></tr>
<tr><td colspan="4">Average pain past week (pain thermometer)</td></tr>
<tr><td>PENS</td><td>2.5±0.9</td><td>-0.7 ±1.1</td><td>-0.5±1.1</td></tr>
<tr><td>PENS + GCAE</td><td>2.4±0.8</td><td>-0.7 ±0.9</td><td>-0.6±1.1</td></tr>
<tr><td>Control PENS</td><td>2.3±0.8</td><td>-0.6 ±0.7</td><td>-0.6±0.8</td></tr>
<tr><td>Control PENS + GCAE</td><td>2.4±0.9</td><td>-0.6±1.2</td><td>-0.58±1</td></tr>
<tr><td colspan="4">Strongest pain past week</td></tr>
<tr><td>PENS</td><td>3.3±1.0</td><td>-0.7 ±1.3</td><td>-0.4±1.4</td></tr>
<tr><td>PENS + GCAE</td><td>3.3±0.9</td><td>-0.7±1.4</td><td>-0.8±1.4</td></tr>
<tr><td>Control PENS</td><td>3.0±0.8</td><td>-0.6 ±1.1</td><td>-0.6±1.1</td></tr>
<tr><td>Control PENS + GCAE</td><td>3.1±0.8</td><td>-0.5 ±1.1</td><td>-0.6±1.2</td></tr>
<tr><td colspan="4">Pittsburgh sleep score</td></tr>
<tr><td>PENS</td><td>13.4±8.5</td><td>-0.02±2.0</td><td>-0.4±2.7</td></tr>
</table>
</td>
<td>Adverse events:
'In our experience, minor bruising and pain flares occur in less than 5% of patients and significant side effects are absent'.</td>
<td>See Weiner 2003 study which looked at PENS as supplement to physical therapy whereas this study looks at PENS with and without general conditioning and aerobic exercise.

Study authors' overall conclusion: 'Results indicate that six weeks of twice daily PENS, whether delivered using electrical stimulation for 30 or 5 min, affords sustained pain reduction for six months and is associates with no side effects.' Findings contrast with authors' previous study where control PENS who also received a flexibility and conditioning programme combined with education experienced no improvement in pain or physical function, either immediately following the completion of the intervention or at 3 month follow up.

Study limitations mentioned by researchers include: (1) one third had previously been exposed to acupuncture which may have influenced expectations; (2) participants were relatively frail and the lack of response to GCAE may be due to inadequate intensity. (3) findings may not be generalisable to more robust older adults.

Other outcome measures: This paper reports other outcomes: Generic Depression Scale, Chronic Pain Self-Efficacy Scale, the Catastrophrizing</td>
</tr>
</table>

<table>
<tr>
<td>muscles. A crossed in and out montage was used in the vent that participant pain was unilateral. Electrical stimulation was applied for 30 mins twice a week for six weeks using Pantheon Research electro-stimulator. The frequency used determined by previous treatment session. Control PENS frequency of 100Hz (as individuals quickly accommodate to higher frequencies) for all 12 treatments for five minutes before stimulator is turned off to avoid delivery of potentially therapeutic micro current.

Follow-up: Six months

Conflict of interest: Second author has received funding from Eli Lily & Co. Research. Funded by National Centre for Complementary and Alternative Medicines, the National Institute on Aging, NIH and Pepper Older American Independence Centre.</td>
<td>
<table>
<tr><td>PENS + GCAE</td><td>12.2±6.6</td><td>0.02±2.3</td><td>0.1±2.7</td></tr>
<tr><td>Control PENS</td><td>10.7±6.2</td><td>0.0±2.7</td><td>-0.4±2.6</td></tr>
<tr><td>Control PENS + GCAE</td><td>12.0±8.0</td><td>-0.7±2.3</td><td>-0.6±2.9</td></tr>
<tr><td colspan="4">SF36 -PC</td></tr>
<tr><td>PENS</td><td>60.4±28.7</td><td>-1.1±20.7</td><td>-5.8±21.0</td></tr>
<tr><td>PENS + GCAE</td><td>51.0±27.4</td><td>3.9±25.8</td><td>4.4±23.5</td></tr>
<tr><td>Control PENS</td><td>56.3±26</td><td>5.9±23.8</td><td>5.1±24.7</td></tr>
<tr><td>Control PENS + GCAE</td><td>46.6±28.1</td><td>6.9±22.7</td><td>8.5±27.4</td></tr>
<tr><td colspan="4">SF36-MC</td></tr>
<tr><td>PENS</td><td>88.8±14.3</td><td>1.5±12.0</td><td>-1.8±15.5</td></tr>
<tr><td>PENS + GCAE</td><td>90.5±10.3</td><td>-0.3±11.4</td><td>-0.2±13.7</td></tr>
<tr><td>Control PENS</td><td>90.9±9.7</td><td>-0.1±10.8</td><td>1.2±11.3</td></tr>
<tr><td>Control PENS + GCAE</td><td>85.9±18.6</td><td>2.8±13.7</td><td>1.5±13.9</td></tr>
</table>
</td>
<td></td>
<td>Scale of Cognitive Strategies Questionnaire, Fear-Avoidance Beliefs Questionnaire, pain medication, and physical function tests (usual pace gait speed, chair rise time, stair climb time) and reports these in a number of formats.

Risk of bias: See Appendix 3

Stimulation device and parameter:

All PENS and controlled PENS administered by acupuncturist to mask randomisation assignment and staff collecting data were blinded.</td>
</tr>
</table>

<table>
<tr><th>Study details</th><th>Key efficacy findings</th><th>Key safety findings</th><th>Comments</th></tr>
<tr>
<td>
White et al. (2001) [88]
Study type: Crossover RCT.
Country: USA (Dallas).
Study period: Not stated.
Study population: Patients with low back pain of > 6 months duration.
n= 72.
Mean age: Not stated (range 21 to 76 years).
Sex: 57% female.
Mean duration of pain: Not stated.
Inclusion criteria: Age >18 years, radiologically confirmed degenerative lumbar spine disease, with a stable level of low back pain and analgesic usage for ≥ 3 months.
Technique: PENS using ten acupuncture needles placed into the soft tissue and/or muscle in the low back region to a depth of 2-4 cm. Each session lasted 30 minutes and was given three times per week for two consecutive weeks for each montage (pattern and location of placing electrodes). All patients received four different montages over 11 weeks (two weeks for each montage with one week washout between different montages).
Follow-up: 5-10 minutes after each treatment (24 hours after the last session of each montage for SF-36).
Conflict of interest: Funded in part by the White Mountain Institute.
</td>
<td>
VAS pain (0-10), 5-10 mins pre/post treatment.
<table>
<tr><th></th><th>Pre</th><th>Post</th></tr>
<tr><td>Montage 1, 1st session</td><td>6.0 (1.6)</td><td>3.8 (1.7)</td></tr>
<tr><td>Montage 1, 6th session</td><td>4.4 (1.6)</td><td>1.4 (1.3)</td></tr>
<tr><td>Montage 2, 1st session</td><td>6.1 (1.7)</td><td>3.2 (1.5)</td></tr>
<tr><td>Montage 2, 6th session</td><td>3.8 (1.4)</td><td>1.2 (1.7)</td></tr>
<tr><td>Montage 3, 1st session</td><td>5.5 (1.9)</td><td>3.9 (1.8)</td></tr>
<tr><td>Montage 3, 6th session</td><td>4.5 (1.5)</td><td>1.6 (1.5)</td></tr>
<tr><td>Montage 4, 1st session</td><td>5.5 (1.9)</td><td>4.1 (1.8)</td></tr>
<tr><td>Montage 4, 6th session</td><td>4.6 (1.5)</td><td>1.5 (1.4)</td></tr>
</table>
VAS pain (0-10), 24 hr before 1st and after last treatment
<table>
<tr><th></th><th>Pre-treatment</th><th>Post-treatment</th></tr>
<tr><td>Montage 1</td><td>6.0 (1.6)</td><td>3.2 (1.2)</td></tr>
<tr><td>Montage 2</td><td>6.1 (1.7)</td><td>2.2 (1.3)</td></tr>
<tr><td>Montage 3</td><td>6.1 (1.6)</td><td>3.5 (1.5)</td></tr>
<tr><td>Montage 4</td><td>6.2 (1.7)</td><td>3.6 (1.5)</td></tr>
</table>
Percentage change from baseline at the end of each montage
<table>
<tr><th>VAS (0-10)</th><th>Degree of pain</th><th>Level of activity</th><th>Quality of sleep</th><th>Usage of oral analgesic</th></tr>
<tr><td>Montage 1</td><td>47%</td><td>42%</td><td>30%</td><td>-43% (23%)</td></tr>
<tr><td>Montage 2</td><td>64%</td><td>51%</td><td>46%</td><td>-47% (21%)</td></tr>
<tr><td>Montage 3</td><td>43%</td><td>37%</td><td>28%</td><td>-27% (23%)</td></tr>
<tr><td>Montage 4</td><td>42%</td><td>35%</td><td>29%</td><td>-23% (23%)</td></tr>
</table>
SF-36, 24 hours after last session, mean change from baseline
<table>
<tr><th></th><th>Physical component summary</th><th>Mental component summary</th></tr>
<tr><td>Montage 1</td><td>7.1</td><td>2.9</td></tr>
<tr><td>Montage 2</td><td>7.6</td><td>3.2</td></tr>
<tr><td>Montage 3</td><td>5.9</td><td>1.9</td></tr>
<tr><td>Montage 4</td><td>5.7</td><td>1.8</td></tr>
</table>
</td>
<td>
Adverse events
Not stated.
*Additional notes for key efficacy findings: All post-treatment scores were significantly different from pre-treatment scores (p<0.05 or 0.01). Montage 2 was more effective than the other montages for overall percentage change at the end of treatment for VAS pain, level of activity (p<0.05 vs. montages 3 and 4) and quality of sleep (p<0.05 vs. montages 1, 3 and 4). For SF-36 physical and mental component summary scores and oral analgesic usage, the change from baseline for montages 1 and 2 were significantly greater than montages 3 and 4 (p<0.05).
</td>
<td>
Study authors' overall conclusion: Montage 2, which stimulated locations along the involved nerve roots at corresponding to the patients' pain symptoms, was the most effective montage. Montage 1 (used in earlier trials [Ghoname et al. 1999a [82], Ghoname et al. 1999b [85] and White et al. 2000 [83]] conducted by this research team) was also effective. Cumulative effects were observed over each two-week treatment period.
Other outcome measures: none
Risk of bias: See Appendix 3.
Stimulation device and parameter: Ten 32-gauge stainless steel acupuncture needles connected to five bipolar leads with a low-output battery-powered generator. Maximal amplitude 37mA, with an asymmetric biphasic waveform pattern, a pulse width of 0.7ms, and a continuous duty cycle. Intensity was adjusted to produce the maximal tolerable 'tapping' sensation without eliciting muscle contractions.
</td>
</tr>
</table>

<table>
<tr><th>Study details</th><th>Key efficacy findings</th><th>Key safety findings</th><th>Comments</th></tr>
<tr>
<td>Yokoyama et al. (2004) [92]
Study type: RCT
A – PENS for 8 weeks;
B – PENS for 4 weeks then TENS for 4 weeks;
C – TENS for 8 weeks (control group).
Country: Japan (Okayama City).
Study period: Not stated.
Study population: Patients with chronic lower back pain.
n = 53 (60 enrolled).
Mean age: 59 years (N/A).
Sex: 57% female.
Mean duration of pain: not stated
Inclusion criteria: LBP ≥ 6m and reported peak pain intensity ≥ 40 on VAS. Pain intensity maintained at stable level using NSAIDs for ≥3m and not previously received PENS.
Technique: Subjects underwent two weeks pre-observation. Twice weekly for eight weeks. PENs involved placement of 10 32-guage (0.2mm) stainless steel acupuncture needles probes at depth of 2-4cm according to dermatomal distribution of pain and connected to five bi-polar leads and stimulated for 20mins at 4/30Hz. TENS consisted of placing four medium sized cutaneous electrode pads in standardized dermatomal pattern which were stimulated at 4/30Hz for 20mins.
Follow-up: 2 months (study 16weeks).
Conflict of interest: Not stated.</td>
<td>Peak pain VAS (0-100) score at:
<table>
<tr><th></th><th>4 wks</th><th>8 wks</th><th>16 wks</th></tr>
<tr><td>PENS (n=18)</td><td>37 ± 10</td><td>32 ± 11</td><td>49 ± 13</td></tr>
<tr><td>PENS→TENS (n=17)</td><td>36 ± 13</td><td>44 ± 12</td><td>55 ± 12*</td></tr>
<tr><td>TENS only (n=18)</td><td>52 ± 12*</td><td>48 ± 11</td><td>56 ± 12*</td></tr>
</table>
*Estimated from graph

During treatment PENS group VAS scores decreased significantly with baseline scores (2 wks p<.05; 4wks p<.01; 8wks p<.01) and 1 month significantly lower (p<.01), but returned to pre-treatment levels at 2 months (week 16). Peak pain level was significantly lower during treatment for PENS than TENS only group and 1 month follow up (2 weeks p<.05, 4 weeks p<.01, 8 weeks p<.01 and 12 weeks p<.01). In PENS→TENS there were also significant decrease in peak pain over 8 week treatment period compared to baseline but not at 1 month follow-up (12 weeks).</td>
<td>Adverse events:
Not stated.</td>
<td>Study authors' overall conclusion: PENS therapy is more effective than TENS in treating chronic lower back pain. Given that effects are not sustained at 2 months, treatment needs to be continued to maintain analgesia. Authors discuss possible mechanisms for a ceiling effect in PENS treatment of chronic pain as well as cumulative effects.
Other outcome measures: Also measured were physical impairment and daily intake of NSAIDs. Results consistent with pain outcomes measures and suggest PENS more effective than TENS and that the effects of PENS gradually wane after treatment stops.
Risk of bias: See Appendix 3
Stimulation device and parameter: PENs involved placement of ten 32-guage (0.2mm) stainless steel acupuncture needles probes at depth of 2-4cm according to dermatomal distribution of pain and connected to five bi-polar leads and stimulated for 20mins at 4/30Hz. TENS consisted of placing four medium sized cutaneous electrode pads in standardized dermatomal pattern which were stimulated at 4/30Hz for 20mins</td>
</tr>
</table>

Percutaneous electrical nerve stimulation (PENS, temporary needle probes) – Osteoarthritis of the hip

<table>
<tr><th>Study details</th><th>Key efficacy findings</th><th>Key safety findings</th><th>Comments</th></tr>
<tr>
<td>Cottingham et al. (1985) [94]
Study type: Parallel group RCT.
Country: UK (Sheffield).
Study period: Not stated.
Study population: Patients with osteoarthritis of the hip awaiting joint replacement.
n=35 (31 included in analysis)
Mean age: 59.3 years (29-72).
Sex: 48% female.
Inclusion criteria: patients with osteoarthritis of the hip diagnosed by an orthopaedic surgeon.
Technique: PENS of the radial, median and saphenous nerves using eight needles placed bilaterally in various parts of arms and legs. Stimulation lasted one hour per session and was administered for ten consecutive week days. Patients in the control group received the same intervention except that no electrical current was delivered during the sessions.
Follow-up: 6 months.
Conflict of interest: Not stated.</td>
<td>VAS, worse pain (0-10), median*
<table>
<tr><th></th><th>Baseline</th><th>2 wks</th><th>6 mo</th></tr>
<tr><td>PENS (n=16)</td><td>7.1</td><td>3.4</td><td>7.5</td></tr>
<tr><td>Sham (n=15)</td><td>6.8</td><td>2.4</td><td>7.5</td></tr>
</table>
At least some pain relief*
<table>
<tr><th></th><th>2 wks</th><th>6 mo</th></tr>
<tr><td>PENS (n=16)</td><td>47%</td><td>9%</td></tr>
<tr><td>Sham (n=15)</td><td>60%</td><td>19%</td></tr>
</table>
Taking less analgesic medications*
<table>
<tr><th></th><th>2 wks</th><th>6 mo</th></tr>
<tr><td>PENS (n=16)</td><td>58%</td><td>15%</td></tr>
<tr><td>Sham (n=15)</td><td>61%</td><td>17%</td></tr>
</table>
*Estimated from figures.</td>
<td>Adverse events:
Side effects included tingling and slight pain at the site of needle insertion, and a feeling of drowsiness immediately after treatment, reported by up to one third of patients and distributed evenly between groups. All side effects ceased following the first two weeks of the study.</td>
<td>Study authors' overall conclusion: PENS and sham PENS provided comparable analgesia, which may be explained by a placebo response.
Other outcome measures: Also measured mobility and use of analgesics.
Risk of bias: See Appendix 3.
Stimulation device and parameters: Eight 26-gauge needles were connected to an RDG Tiger Pulse nerve stimulator, which provided a rectangular wave current of 220 µA to each pair of needles. The current was pulsed at 20Hz (pulse width 100 µsec). No current was delivered for the control group.</td>
</tr>
</table>

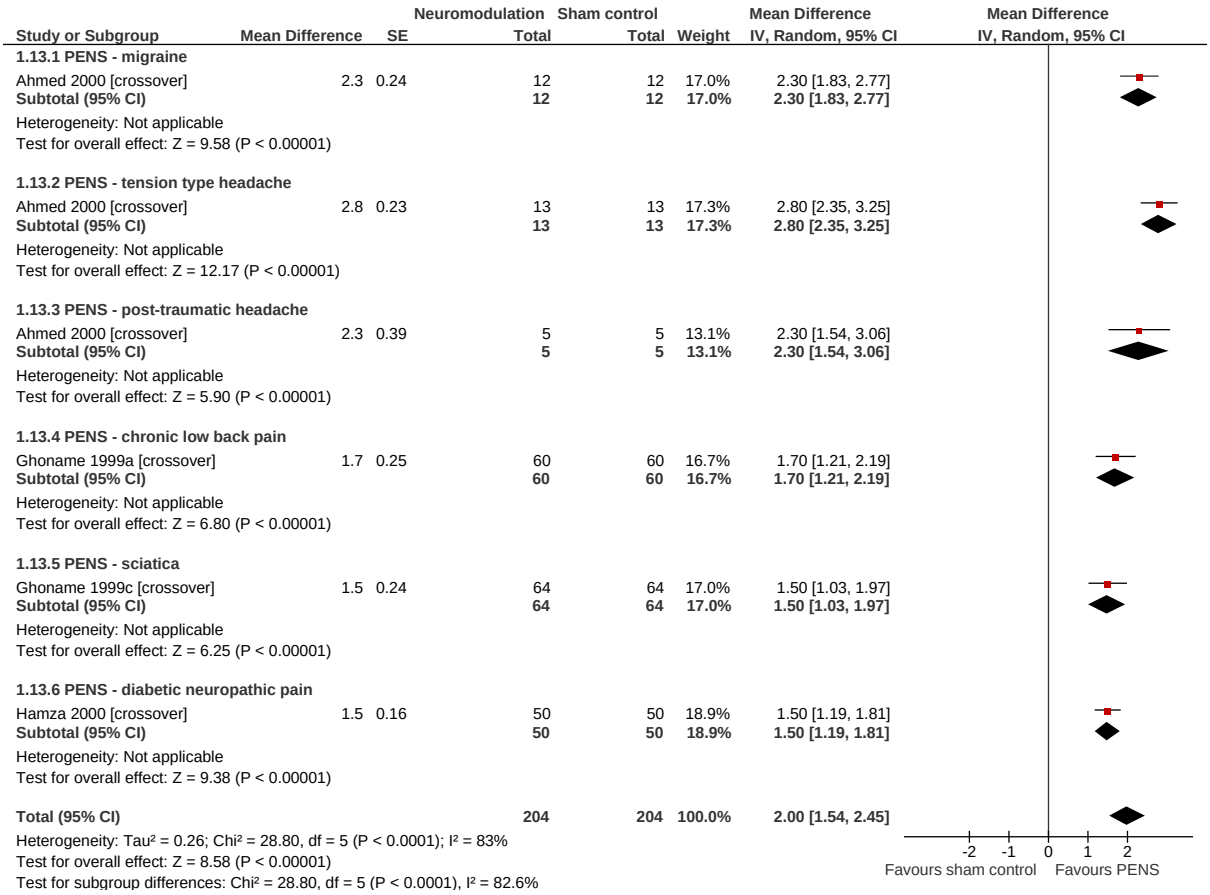
Percutaneous electrical nerve stimulation (PENS, temporary needle probes) – Chronic Pelvic Pain

<table>
<tr><th>Study details</th><th>Key efficacy findings</th><th>Key safety findings</th><th>Comments</th></tr>
<tr>
<td>
Kabay et al. (2008) [95]
Posterior Tibial Nerve Stimulation (PTNS).
Study type: Sham RCT.
Country: Turkey.
Study period: May 2006 to March 2008.
Study population: Therapy resistant pelvic pain.
n= 89
Mean age: 38 years (24-54).
Sex: Not stated.
Inclusion criteria: Pain in the bladder, groin, genitals or lower abdomen and/or perineal or perianal pain without any obvious abnormities on examination or priors surgical intervention. Analgesics were stopped two weeks prior to Posterior Tibial Nerve Stimulation (PTNS) and Sham. Physiotherapy or electrotherapy restricted for at least three months prior to PTNS.
Technique: PTNS unilaterally applied with 26-gauge stainless disposable concentric steel needles inserted in 5cm cephalad from medial malleolus and posterior to the edge of the tibia and ground neutral electrode placed on the same leg near the arch of the foot connected to the stimulator. Stimulation was applied unilaterally with charge compensated 200µs pulses of 20Hz. Intensity level just set below threshold for contraction. The stimulation amplitude was set at the maximum tolerable level according to the subject usually 1.5 times threshold for evoking planter flexion of the toes and or toe fanning (range 1-10mA). Twelve weeks of outpatient treatment sessions, each lasting 30mins. Sham not described.
Follow-up: Outcomes measured at end of 12 week treatment period.
Conflict of interest: Not declared.
</td>
<td>
Objective success defined as 50% decrease in mean VAS and NIH-CPSI scores. A decrease between 25-50% considered a partial success. All patients were responsive with 18 (40%) objective response and 27 (60%) partial response on VAS at 12 weeks. 30 (66.6%) objective and 15 (33.3%) partial response on NIH-CPSI for PTNS.

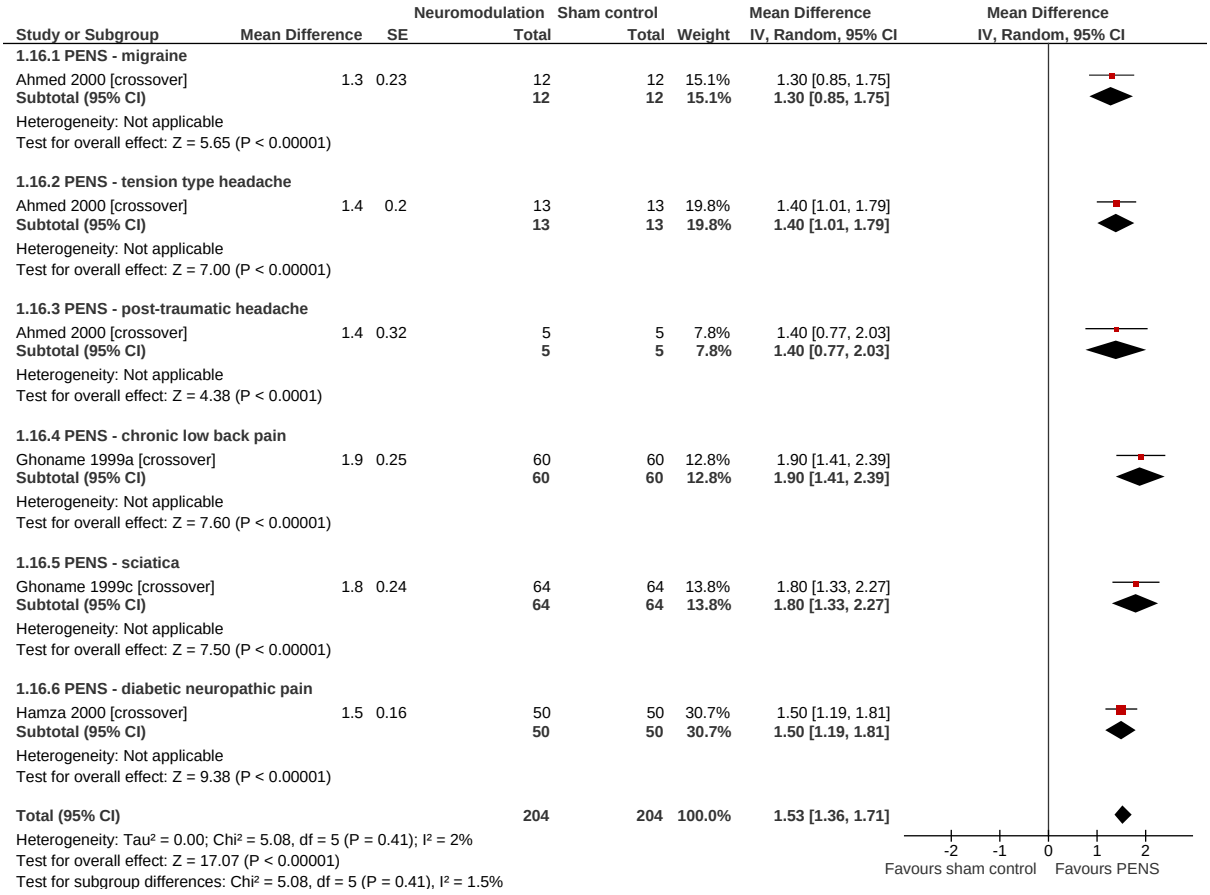
VAS pain (0-10).
<table>
<tr><th></th><th>Baseline</th><th>12 weeks</th></tr>
<tr><td>PTNS</td><td>7.6 ± 0.8</td><td>4.3 ± 0.6</td></tr>
<tr><td>Sham</td><td>7.4 ± 0.9</td><td>7.2 ± 0.4</td></tr>
</table>
NIH-CPSI total (0-43).
<table>
<tr><th></th><th>Baseline</th><th>12 weeks</th></tr>
<tr><td>PTNS</td><td>23.6 ±6.3</td><td>10.2 ±3.6</td></tr>
<tr><td>Sham</td><td>22.8±5.4</td><td>21.4 ±4.6</td></tr>
</table>
Changes significant in PTNS.
</td>
<td>
Adverse events:
Not stated.
</td>
<td>
Study authors' overall conclusion: PTNS treatment for 12 weeks significantly improves VAS for pain and NIH-CPSI scores for chronic prostatitis and chronic pelvic pain patients. PTNS may be considered as an alternative treatment for some refractory pain patients.
Other outcome measures: none
Risk of bias: See Appendix 3.
Stimulation device and parameter: Medtronic disposable 26-gauge stainless steel concentric needles, ground neutral electrode and Medtronic Keypoint Net electrical stimulator. 200µs pulses at 20Hz.
</td>
</tr>
</table>

Appendix 5 Further quantitative analysis

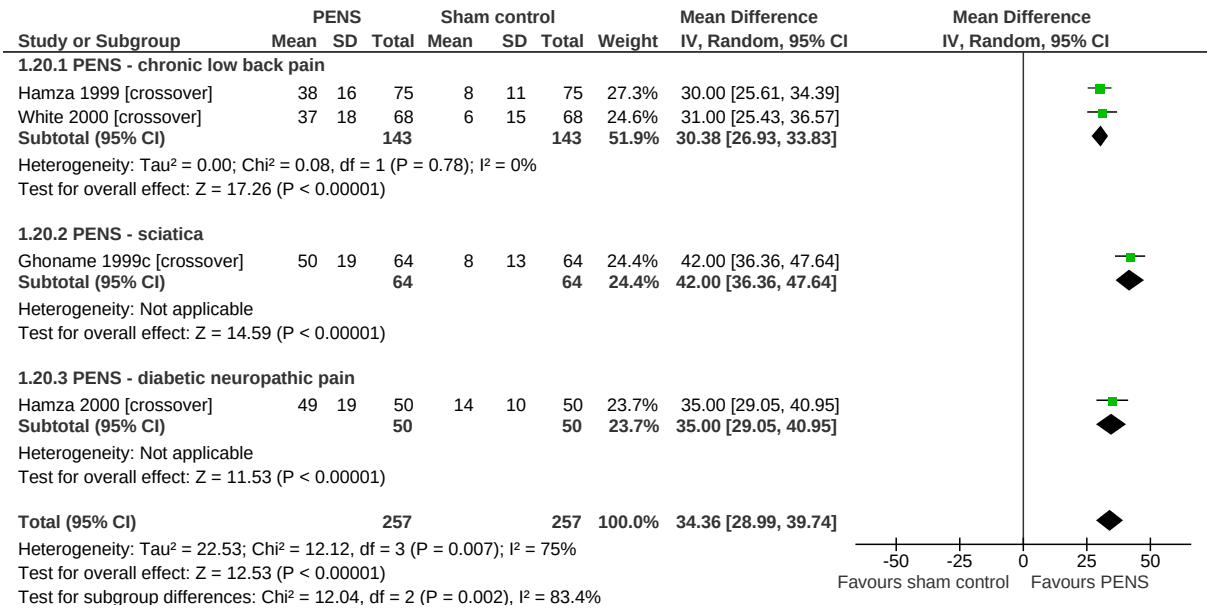
Neurostimulation vs. sham, improvement in physical activity (VAS, 0-10)
(Data available only from RCTs of PENS)



Neurostimulation vs. sham, improvement in sleep quality (VAS, 0-10)
(Data available only from RCTs of PENS)



Neurostimulation vs. sham, percentage reduction in the use of oral analgesics
(Data available only from RCTs of PENS)



Appendix 6 Additional tables for safety issues reported in large case series of PNS

Reported adverse events and other technical/safety issues in case series of peripheral nerve stimulation of trigeminal related nerves/ganglion

Author	Condition	Follow-up	Failed trial (1st stage)	Implanted (F/M)	Lead migration	Lead type	Lead malfunction or disconnect	Infection	Requested removal	Allergy	Safety issues as reported	Device/ notes
Stimulation of gassarian gangion												
Meyerson 1986 [40]	Trigeminal neuropathy	Mean 4y (1 to 7y)		14 (10/4)	2	?	Yes, 2+				'No serious surgical complications.' 1 patient slight ptosis and weakness of abducens nerve 1 moderate facial palsy (symptoms disappeared within a month) 2 replantations: failure to produce paresthesia due electrode being dislodged 2 electrodes exchanged after a year, after which stimulation became effective again. 'Multiple equipment failures' in early cases using prototype electrode. Several patients needed electrode to be changed because insulation on wire leads broke.	Gasserian electrode assembly

Author	Condition	Follow-up	Failed trial (1st stage)	Implanted (F/M)	Lead migration	Lead type	Lead malfunction or disconnect	Infection	Requested removal	Allergy	Safety issues as reported	Device/ notes
Machado 2007 [41]	Trigeminal neuropathic pain	12m	2/10	8	1	C?					First six months: 2 explanted due to loss of efficiency: 1 due to lead migration and 1 as patient never ha a good response. 'No other direct procedural complications.'	Quadripolar electrode, Medtronic, model 3387 used in trial, model 7482 for permanent implant. Medtronic Itrel 3 IPG
Taub 1997 [43]	Facial pain of various causes 22 peripheral damage to trigeminal nerve 7 central neural damage 4 postherpetic damage 1 unclassified	Median 22.5m (successful cases only)	15/34	19	2 (prior to adoption of anchoring to maxilla)	C	1	7			1 ipsilateral brain abscess 6m after removal of infected electrode (resolved with antibiotics) 1 reoccurring infections 3 further sensory loss in face possibly due to injury to trigeminal root ganglion or divisions during stage 1 and 2 2 developed transient diplopia from injury to 4th or 6th cranial nerve during transcutaneous insertion procedure 2 reported stimulation made their pain worse 10 revisions: 5 required repositioning of electrodes because of inadequate coverage of painful area by paresthesia 2 migration 2 replacement or repositioning of stimulator 1 repairs of disconnect. Infection rate was higher when stimulating electrode left in from stage 1 (6/14) than new electrodes in stage 2 (1/5) (p>0.05).	Covers period 1982 to 1995. Technique changed over period. Electrodes used over period included Medtronic, Pisces Sigma or Meyerson. IPG usually Medtronic (model X-trel) in recent cases.

Lazorthes 1987 [44]	Atypical facial neuralgia	2y (18-32m)	16/21	5 (4/1)		C	3				Permanently implanted patients only Neurological complications: 1 temporary paralysis of facial nerve 1 vertigo and tinnitus Technical complications: 1 inadequate stimulation so electrode replaced 2 displacement and replacement 1 replacement of electrode 2 change of stimluator	Pisces electrode (Medtronic) 4 patients Quad (Medtronic) 1 patient Multistim (Neuromed)
Waidhauser 1994 [42]	Trigeminal neuralgia		68/149	81								Itrel Medtronic IPG
Stimulation of trigeminal nerves (nerve root)												
Young 1995 [45]	Facial pain	24m (12-45m)		23 (17/6)	1	C		0	0		'No serious complications.' 8 discontinued between 1 and 18m after implantation due to ineffective pain control. 1 displaced electrode. 3 repositioning. 'No instances of electrode breakage, infection, or delayed lead displacement were encountered'.	Quintatrigeminal electrode , Medtronic
Stimulation of supraorbital and/or infraorbital nerves												
Johnson 2004 [46]	Trigeminal neuropathic pain (facial trauma/ Herpes zoster infection)	26.6m ±4.7m	1	10 (3/7)		C					Complication rate requiring reoperation was 30% (n=30) 2 wound breakdown developed over connector requiring surgical revision 1 required lead to be lengthened due to discomfort when turning head.	Pisces Quad stimulating electrode (model 3487A, Medtronic) Itrel Pulse Generator (model 7425, Medtronic) Permanent IPG: Itrel 3, Medtronic (Model 7423)
Amin 2008 [47]	Supraobital neuralgia		6	10(6,4)	3 required revisions	C		2			Skin erosion Infection levels high (20%)	Pisces Quad or Octade Lead

											due to retroangular connector and extension leads. Discussion on relative infection rates –VNS (7%) and GG (40%)	

Reported adverse events and other technical/safety issues in case series of peripheral nerve stimulation of vagus nerve and Sphenopalatine Ganglion

Author	Condition	Nerve/approach	Follow-up	Failed trial	Implanted (F/M)	Lead migration	Lead type	Lead fx or disconnect	Infection	Requested removed	Allergy	Complications	Device
Lenaerts (2008) (questionnaire follow up study) [49]	migraine	Vagus	Mean 17m (4-36m)		34 identified, 10 participated (5,5)							Complications and side effects not reported	
Tepper 2009 [48]	migraine	Sphenopalatine Ganglion	<1h		11 (10/1)		C					'No AE occurred during study'	Medtronic 3057temporary lead; Medtronic model 3625 or 3628 generator

Reported adverse events and other technical/safety issues in case series of PNS of nerves of the upper and lower extremity

Author	Condition	Follow-up	Nerve /Approach	Failed trial (1st stage)	Implanted (F/M)	Lead migration	Lead type	Lead malfunction or disconnect	Infection	Requested removal	Allergy	Safety issues as reported	Device
Hassenbursch 1996 [50]	Severe reflex sympathetic dystrophy (RSD)	2-4y	Median (7) Ulnar (10) Radial (1) Common peroneal (5) Posterior tibial (7)	2	30 (21/7)		P		0			8 required revisions of electrode, 2 extension wire, 2 generator and 3 removal of generator	Resume, Medtronic; permanent IPG Itrel II Medtronic
Ischizuka 2007 [51]	Complex regional pain syndrome type (CRPS) II	5d to 24m+	PNS		11 (6/5)	4	P		3			4 migration 3 infection 2 required revision due to suboptimal original placement Authors conclude that 'although infection is attributable to clinical technique, most complications requiring repeat surgery (9/27) were due to equipment design.'	Awaiting paper

Nashold 1982 [52]	Pain in upper and lower extremity		Median (11) Ulnar (6) Median and radial (1) Median and ulnar (1)		35 (8/27)		?			2		Nerve Ischemia (1)	Covers implantations between 1970 and 1977. Query relevance as technology has progressed.
Novak 2000 [53]	Peripheral Nerve injury	21m ±15m	Ulnar (10) Median (1), Radial (1) Posterior tibial (5)		17 (10/7)		?		1			2 nerve stimulators were removed: 1 33m after implantation because of local discomfort at battery site and no longer had pain in ulnar nerve distribution, 1 removed because of infection.	Medtronic (device numbers not provided)
Schon 2001 [54]	Lower extremity nerve pain and chronic peripheral	29.3m (13 - 61m)	Stimulated 1-4 nerves involving: tibial, sural, saaphenous,		62 (31/27) (Also reports		?		6	2 requested removal & opted for amputation		Of 62 patients, 29 required revisions during 5 year study period: 21/29 lead	Figures on patient population are not

	neuralgia		superficial peroneal, deep peroneal, femoral.		on 58 vein wrapping)							replacements (of which 10 required another nerve to be stimulated; 8 pulse generator for battery depletion; 2 new pulse generators) Average battery life 2.7y but one patient required new device every 3 to 4m) 4/29 postoperative infections within 6m 2/29 late infection (one at 1.5y, the other 3y) 4/6 infections resolved by intravenous infections and had subsequent re implantation with satisfactory results. 1/6 had history of Osteomyelitis & requested amputation. The	consistent. Medtronic (device numbers not provided)

												other was initially satisfied with pain relief for 1.3y decided to undergo transtibial amputation 2m prior to onset of late infection	

Reported adverse events and other technical/safety issues in case series of PNS of various nerves with injuries associated with surgical procedures, trauma or chemical assault

Author	Condition	Follow-up	Nerve /Approach	Failed trial (1st stage)	Implanted	Lead migration	Lead type	Lead malfunction or disconnect	Infection	Requested removal	Allergy	Safety issues as reported	Device
Eisenberg 2004 [55]	'peripheral nerve injuries'	3-16y	PNS		46(26/20)							Complications occurred in 5 patients: 2 with wound infection at receiver implantation site, 1 with skin necrosis over receiver implantation site, 2 with electrode migrations (all reimplanted/repositioned successfully)	
Mobbs 2007 [56]	Chronic pain	31m (9-89m)	PNS	4	38 (19/19)	8	P	1	2	1		6 required removal (2 due to infection, 3 inadequate pain relief, 1 requested removal as no longer needed).	Modified Resume electrodes (Medtronic) Medtronic IPG

												A single lead replaced after fracture (following a fall from a tree) 2 battery generators replaced, 2 generator/lead combinations repositioned, and 1 electrode repositioned 8 lead migrations.	
Law 1980 [57]	Chronic Pain		PNS		22 (7/15)		?		1	1		8 revisions to reposition electrode cuff on same nerve or a different nerve 2 correct difficulties in joint mobility due inadequate length of electrode wire 1 repositioning of unused male electrode connector 2 replacements of failed equipment 6 to remove stimulating device (4 no pain relief, 1 cosmetic, 1 infection)	August 1971 and July 1978. All but 2 neuropathic . Devices not named

Reported adverse events and other technical/safety issues in case series of sacral nerve (root) stimulation

Author	Condition	Follow-up	Nerve /Approach	Failed trial (1st stage)	Implanted	Lead migration	Lead type	Lead malfunction or disconnect	Infection	Requested removal	Allergy	Safety issues as reported	Device
Maher et al 2001 [58]	Interstitial cystitis	Not clear	Sacral (S3)	0/15	11 (11/0)	'some'	C?	0	0	0	0	'No complications recorded in the trial period.' 'Some women had problems with lead migration in the later part of the evaluation period.'	Medtronic (n=6)
Comiter 2003 [59]	Interstitial cystitis	14m (2 to 28m)	Sacral (S3)	8/25	17(16/1)	0	C	0	0	0	0	'There were no complications associated with either test stimulation or permanent implantation.'	Quadriplor lead and InterStim IPG, Medtronic
Peters & Konstandt 2004 [61]	Interstitial cystitis	15.4m (7.4-23.1m)	Sacral		21 (17/4)		C					Study focused on narcotic use. Does not report complications.	InterStim, Medtronic
Zabihi et al 2008 [43]	Interstitial cystitis, painful bladder syndrome and chronic pelvic pain (CPP)	Mean 15m (6-32m)	Sacral (bilateral, S2-S4)	/307	30 (21/9)		C		4			5/23 explanted (4 failures, 1 infection)	Quadripolar tined lead (Medtronic); Synergy-Versitrel IPG (Medtronic)
Al-Zahrani 2011 [66]	Lower urinary tract dysfunction Bladder pain syndrome (BPS) (n=78)	Median 50.7m (12 to 157m) 46 BPS followed up (44/2)	Sacral		96 (88/8) 78 BPS (70/8)		C					Explanation rate for BPS 28.3% Revision rate for BPS 50% Most common reason for revision was poor response (24) then local pain from IPG device (7), painful stimulation (5) and radiation of	InterStim, Medtronic

												pain towards leg (5) (not broken down by condition)	

Author	Condition	Follow-up	Nerve /Approach	Failed trial (1st stage)	Implanted	Lead migration	Lead type	Lead malfunction or disconnect	Infection	Request removal	Allergy	Safety issues as reported	Device
Peters et al 2003 [62]	Refectory interstitial cystitis	Mean 5.6m	Sacral	Traditional test: 15/21 Staged test: 1/16	26 Traditional: test: 11/21 Staged test: 15/16		C		0			Overall reoperation rate: 11.5% (3/26): 3 required reoperation (2 lead readjustment due to discomfort and 1 new generator pack) No infections or explantations occurred.	Quadripolar lead, InterStim, Medtronic
Steinb3rg 2007 [62]	Interstitial cystitis	14.1m (8-18m)	Sacral (bilateral, S3)	.	15(15/0)		C					Not reported	InterStim, Medtronic
Gajewski and Al-Zahrani 2010 [67]	Bladder pain syndrome	Median 61.5m (12-132m)	Sacral	34/78	46 (44/2)		?		0	4		Removal (explant rate 28%) poor outcome (9, not defined) Painful stimulation (3) Radiation of pain to leg (1) Revisions (revision rate 50%) Poor outcome (12) Painful stimulation (3) Box pain (6) Radiation of pain to leg (3)	Quadriplor lead, Interstim IPG
Ghazwani 2011 [68]	Bladder pain syndrome	Mean 71.5 ±9.3m 60-84m	Sacral (unilateral, S3)	10/21	11 (11/0)		C					2 IPG had to be changed end of battery life 3 pain at site of implantation (2 managed by changing sides, 1 by adjusting stimulation parameters). No complications led to explant.	FTined leads (model 3889-28cm) and InterStim, Medtronic

Marinkovic 2011 [69]	Interstitial cystitis	86m (=/- 9.8m)	Sacral	4/34	30 (30/0)	5	C		None reported			27% reoperation rate which researchers attribute to relatively young physically active patients. 5 lead migrations secondary to falls and automobile trauma 3 IPG erosions secondary to trauma	Tined lead with larger lead #1 (model 3093) InterStim IPG (model 3023), Medtronic

Author	Condition	Follow-up	Nerve /Approach	Failed trial (1st stage)	Implanted	Lead migration	Lead type	Lead malfunction or disconnect	Infection	Requested removal	Allergy	Safety issues as reported	Device
Abejon 2010 [114]	7 Gastrointestinal dysfunctions 2 Pain 11 Chronic Pelvic Pain	12 m	Sacral (bilateral, S3)	?	20(17/3) 11 (10/1) CCP		C					Not reported	Two tined lead electrodes (Medtronic)
Seigel 2001 [115]	Chronic pelvic pain	Median 19m 6 to 74m	Sacral (S3, n=8; S4, n=8)		10 (9/1)	2	C		1	3		27 AE in 10 patients. 6 Wound complications 4 Pain location change 4 IPG site pain 3 Return to baseline pain 2 Urinary tract infection 2 Permanent explantation 2 Revision of IPG/Lead 2 Electrical shock sensation 1 Worse pain relief 1 Infection with implant No serious device complications Reoperation rate 50%	InterStim, Medtronic

Author	Condition	Follow-up	Nerve /Approach	Failed trial (1st stage)	Implanted	Lead migration	Lead type	Lead malfunction or disconnect	Infection	Requested removal	Allergy	Safety issues as reported	Device
Falletto 2009 [116]	Chronic idiopathic anal pain	Mean 15m (3-80m)	Sacral	12/27 (plus 3 refused permanent implant)	12 (10/2)		C		1			'No major complications were recorded.' 1 Infection at site of neurostimulator 1 Device removed after 24m due failure 1 Stimulator moved from gluteal to abdominal site due to pain	Until 2001, evaluation involved temporary implantation of one mono polar lead (Medtronic InterStim model 3057) connected to external stimulator (Medtronic Screener model 3625). After 2001 first stage evaluation involved self-blocking tin lead (Medtronic InterStim model 3889) Permanent SNS comprises quadripolar lead (Medtronic InterStim 3080) connected to Medtronic InterStim 3889).
Vaarala et al 2011 [70]	Urgency frequency syndrome (45/105) Urinary retention (22/54) Painful bladder/ Interstitial cystitis (7/21)	Mean 41m (0-143m)	Sacral (S3 or S4)	106/180	74 (43/31)		C		2			Revision required in 15: 9 loss of response 2 pain in implant area/malfunction 2 malfunction 2 infection	Later procedures Quadripolar permanent tined lead device (InterStim, Medtronic)

Author	Condition	Follow-up	Nerve Approach	Failed trial (1st stage)	Implanted	Lead migration	Lead type	Lead malfunction or disconnect	Infection	Requested removal	Allergy	Safety issues as reported	Device/ notes
Everaert et al (2001) [117]	(Unexplained) pelvic pain syndromes	32 (+/- 12) weeks	Sacral nerve stimulation	10	11	1	C	-	1	-	-	2 failures, considered as false positive percutaneous nerve evaluation tests, occurring immediately after insertion of the implant (pp. 13) 1 explant due to infection of the prosthesis 1 revision following electrode migration (in a patient who received an earlier type of electrode without a fixed anchor) 2 patients had their frequency increased to 21Hz to avoid loss in battery lifetime.	Medtronic quadripolar electrode and pulse generator Unilateral quadripolar electrode (S3 root) M/F for all those trialled at first stage: 10/16

Appendix 7 Evidence Matrix

Evidence matrix for peripheral neurostimulation. Numbers shown in brackets are sample sizes, and where applicable , no. analysed/no. randomised or no. tested/no. implanted

Peripheral nerve stimulation (PNS, implanted device)	Systematic review and RCT	Case series (n≥10)
Occipital nerves	Jasper 2008 [systematic review] [13]	
Chronic migraine	Lipton 2009 (140)[a] [15] (abstract only) Saper 2011 (75) [16] Silberstein 2011 (153/157) [17] (abstract only – publication pending) Gerardo 2011 (34) [18] (Unpublished) Goadsby 2011 (25) [19] (Ongoing)	-
Transformed migraine	Caillon 2012 (30) [21] (Ongoing) -	Popeney 2003 (25) [22] Oh 2004 (10) [23]
Cluster headache	Wilbrink 2011 (144) [24] (Ongoing)	Burns 2009 (14) [29] Fontaine 2011 (13) [26] Magis 2011 (15) [110] Muller 2011 (10) [111]
Neuralgias Occipital neuralgia C2-mediated occipital headaches Neuropathic craniofacial pain Refractory occipital headache in Chiari malformation		Weiner 1999 (13) {2270) Oh 2004 (10) [23] Slavin 2006b (14) [32] Melvin 2007 (14) [34] Slavin 2006a (13)[e] [31] Vadivelu 2011 (13/18) [33]
Mixed types of headaches	-	Schwedt 2007 (15) [35] Franzini 2009 (17) [36] Falowski 2010 (28) [37] Paemeleire 2010 (26) [38]
Fibromyalgia	Plazier 2011 (15) [39] (abstract only – publication pending) De Ridder 2009 (n=?) [101] (unpublished - publication pending)	Thimineur 2007 (12) [106]
Gasserian ganglion Trigeminal neuropathy Trigeminal neuropathic pain Atypical trigeminal neuralgia Facial pain of various cause Atypical facial neuralgia **Trigeminal nerves (nerve root)** Facial pain associated with trigeminal nerve injury **Supraorbital and/or infraorbital nerves** Trigeminal neuralgia Supraorbital neuralgia Neuropathic craniofacial pain	- - -	 Meyerson 1986 (14) [40] Machado 2007 (10) [41] Waidhauser 1994 (81) [42] Taub 1997 (34) [43] Lazorthes 1987 (5/21) [44] Young 1995 (23) [45] Johnson 2004 (10) [46] Amin 2008 (10/16) [47]
Sphenopalatine ganglion – chronic migraine	Jensen 2012 (ongoing) CM7	Tepper 2009 (11) [48]
Vagus nerve - migraine	-	Lenaerts 2008 (10) [49]
Branchial plexus		
Other nerves of the upper and lower extremity		
Complex regional pain syndrome (CRPS) CRPS type II Pain in upper and lower extremity		Hassenbusch 1996 (32) [50] Ishizuka 2007 (11) [51] Nashold 1982 (35) [52] Novak 2000 (17) [53]

Pain in lower extremity		Schon 2001 (62) [54]
Various nerves with injuries associated with surgical procedures, trauma or chemical assault		Eisenberg 2004 (46/154) [55] Mobbs 2007 (38) [56]
Mixed post traumatic neuropathy		Law 1980 (22) [57]
Sacral nerve (root)		
Painful bladder syndrome/interstitial cystitis		Maher 2001 (15) [58] Comiter 2003 (17/25) [59] Peters 2003 (26) [61] Peters 2004 (21) [62] Steinberg 2007 (15) [63] Zabihi 2008 (23/30)[b] [64] Zhao 2008 (18) [65] Al-Zahrani 2011 (46)[c] [66] Gajewski 2011 (78) [67] Ghazwani 2011 (21) [68] Marinkovic 2011 (34) [69] Vaarala 2011 (74) [70]
Chronic pelvic pain		Everaet 2001 (11) [117] Siegel 2001 (10) [115] Abejón 2010 (20) [114]
Chronic anal pain		Falletto 2009 (12) [116]
Other mixed types of pain		Erickson 1975 (13/32) [118] Picaza 1975 (23) [119] Campbell 1976 (33) [120] Picaza 1977 (37) [121]
Implanted peripheral nerve field stimulation (Implanted PNFS)		
Chronic low back pain / failed back surgery syndrome	Barolat 2011 (30) [71] (abstract only)	Verrills 2009a (14) [72]
Post-laminectomy syndrome		Yakovlev 2011 (18) [73]
Post surgery hip pain		Yakovlev 2010 (12) [74]
Mixed types of pain		Verrills 2009b (23) [75] Sator-Katzenschlager 2010 (111) [76] Verrills 2011 (100) [77]
Non-appendicular regional pain		Falco 2009 (18) [78]
Temporary peripheral nerve field stimulation (temporary PNFS)		
Osteoarthritis of the knee [temporary stimulation]	Kang 2007 (63/70) [79]	
Percutaneous electrical nerve stimulation (PENS, temporary needle probes)		
Headache disorders		
Migraine	Ahmed 2000 (12)[d] [80]	
Tension type headache	Ahmed 2000 (13)[d] [80]	
Post-traumatic headache	Ahmed 2000 (5)[d] [80]	
Peripheral neuropathic pain		
Sciatica	Ghoname 1999c (64) [81]	
Diabetic neuropathic pain	Hamza 2000 (50) [82]	
Surface hyperalgesia associated with various neuropathic pain	Raphael 2011 (30) [83]	
Other chronic pain		
Chronic neck pain	White 2000 (68) [85]	
Chronic low back pain	Ghoname 1999a (60) [84] Ghoname 1999b (68) [86] Hamza 1999 (75) [87] White 2001 (72) [88] Weiner 2003 (34) [90] Topuz 2004 (60) [92] Yokoyama 2004 (60) [93] Weiner 2008 (200) [89]	Seroussi 2003 (36) [95]

	Pérez-Palomares 2010 (122) [91]	
Osteoarthritis of the hip	Cottingham 1985 (35) [94]	
Interstitial cystitis (posterior tibial nerve)		Zhao 2004 (14) [97]
Chronic pelvic pain (posterior tibial nerve)		Kim 2007 (15) [98] van Blaken 2003 (33) [99]
Class IIIB chronic prostatitis/chronic pelvic pain (posterior tibial nerve)	Kabay 2009 (89) [95]	

[e] The case series included both ONS (n=13) and PNS of infraorbital nerve (n=3) and supraorbital nerve (n=4), and combined ONS and PNS (n=2).
[b] Included mixed population of interstitial cystitis, painful bladder syndrome and chronic pelvic pain.
[c] The case series included additionally 50 patients with urgency urinary incontinence or idiopathic urinary retention.
[d] This RCT included different types of headaches
[a] Including both migraine with and without aura, and chronic migraine

Appendix 8 Lists of excluded studies with rationale

List of identified case series and case reports with less than 10 patients

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