2017

Transcutaneous electrical nerve stimulation (TENS) for neuropathic pain in adults

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This article was originally published as:

Original article available here:
https://dx.doi.org/10.1002/14651858.CD011976.pub2

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Transcutaneous electrical nerve stimulation (TENS) for neuropathic pain in adults (Review)

Gibson W, Wand BM, O’Connell NE


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Transcutaneous electrical nerve stimulation (TENS) for neuropathic pain in adults (Review)  
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Transcutaneous electrical nerve stimulation (TENS) for neuropathic pain in adults

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Editorial group: Cochrane Pain, Palliative and Supportive Care Group.


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ABSTRACT

Background

Neuropathic pain, which is due to nerve disease or damage, represents a significant burden on people and society. It can be particularly unpleasant and achieving adequate symptom control can be difficult. Non-pharmacological methods of treatment are often employed by people with neuropathic pain and may include transcutaneous electrical nerve stimulation (TENS). This review supersedes one Cochrane Review ‘Transcutaneous electrical nerve stimulation (TENS) for chronic pain’ (Nnoaham 2014) and one withdrawn protocol ‘Transcutaneous electrical nerve stimulation (TENS) for neuropathic pain in adults’ (Claydon 2014). This review replaces the original protocol for neuropathic pain that was withdrawn.

Objectives

To determine the analgesic effectiveness of TENS versus placebo (sham) TENS, TENS versus usual care, TENS versus no treatment and TENS in addition to usual care versus usual care alone in the management of neuropathic pain in adults.

Search methods

We searched CENTRAL, MEDLINE, Embase, PsycINFO, AMED, CINAHL, Web of Science, PEDro, LILACS (up to September 2016) and various clinical trials registries. We also searched bibliographies of included studies for further relevant studies.

Selection criteria

We included randomised controlled trials where TENS was evaluated in the treatment of central or peripheral neuropathic pain. We included studies if they investigated the following: TENS versus placebo (sham) TENS, TENS versus usual care, TENS versus no treatment and TENS in addition to usual care versus usual care alone in the management of neuropathic pain in adults.

Data collection and analysis

Two review authors independently screened all database search results and identified papers requiring full-text assessment. Subsequently, two review authors independently applied inclusion/exclusion criteria to these studies. The same review authors then independently extracted data, assessed for risk of bias using the Cochrane standard tool and rated the quality of evidence using GRADE.
Main results

We included 15 studies with 724 participants. We found a range of treatment protocols in terms of duration of care, TENS application times and intensity of application. Briefly, duration of care ranged from four days through to three months. Similarly, we found variation of TENS application times; from 15 minutes up to hourly sessions applied four times daily. We typically found intensity of TENS set to comfortable perceptible tingling with very few studies titrating the dose to maintain this perception. Of the comparisons, we had planned to explore, we were only able to undertake a quantitative synthesis for TENS versus sham TENS. Insufficient data and large diversity in the control conditions prevented us from undertaking a quantitative synthesis for the remaining comparisons.

For TENS compared to sham TENS, five studies were suitable for pooled analysis. We described the remainder of the studies in narrative form. Overall, we judged 11 studies at high risk of bias, and four at unclear risk. Due to the small number of eligible studies, the high levels of risk of bias across the studies and small sample sizes, we rated the quality of the evidence as very low for the pooled analysis and very low individual GRADE rating of outcomes from single studies. For the individual studies discussed in narrative form, the methodological limitations, quality of reporting and heterogeneous nature of interventions compared did not allow for reliable overall estimates of the effect of TENS.

Five studies (across various neuropathic conditions) were suitable for pooled analysis of TENS versus sham TENS investigating change in pain intensity using a visual analogue scale. We found a mean postintervention difference in effect size favouring TENS of -1.58 (95% confidence interval (CI) -2.08 to -1.09, P < 0.00001, n = 207, six comparisons from five studies) (very low quality evidence). There was no significant heterogeneity in this analysis. While this exceeded our prespecified minimally important difference for pain outcomes, we assessed the quality of evidence as very low meaning we have very little confidence in this effect estimate and the true effect is likely to be substantially different from that reported in this review. Only one study of these five investigated health related quality of life as an outcome meaning we were unable to report on this outcome in this comparison. Similarly, we were unable to report on global impression of change or changes in analgesic use in this pooled analysis.

Ten small studies compared TENS to some form of usual care. However, there was great diversity in what constituted usual care, precluding pooling of data. Most of these studies found either no difference in pain outcomes between TENS versus other active treatments or favoured the comparator intervention (very low quality evidence). We were unable to report on other primary and secondary outcomes in these single trials (health-related quality of life, global impression of change and changes in analgesic use).

Of the 15 included studies, three reported adverse events which were minor and limited to ‘skin irritation’ at or around the site of electrode placement (very low quality evidence). Three studies reported no adverse events while the remainder did not report any detail with regard adverse events.

Authors’ conclusions

In this review, we reported on the comparison between TENS and sham TENS. The quality of the evidence was very low meaning we were unable to confidently state whether TENS is effective for pain control in people with neuropathic pain. The very low quality of evidence means we have very limited confidence in the effect estimate reported; the true effect is likely to be substantially different. We make recommendations with respect to future TENS study designs which may meaningfully reduce the uncertainty relating to the effectiveness of this treatment modality.

**PLAIN LANGUAGE SUMMARY**

**Transcutaneous electrical nerve stimulation (TENS) for neuropathic pain**

**Bottom line**

For adults with neuropathic pain, it is impossible to confidently state whether TENS is effective in relieving pain when compared to sham TENS.

**Background**

Neuropathic pain is pain due to injury or disease to nerves and can be difficult to treat effectively. It may occur following direct nerve injury or develop due to problems like diabetes, shingles and carpal tunnel syndrome. TENS is a common treatment for a range of pain conditions. It involves using a small battery operated unit to apply low level electrical currents through electrodes attached to the skin. This is suggested to relieve pain.
Review question

Does TENS improve pain intensity and health related quality of life in adults with neuropathic pain?

Study characteristics

We reviewed all eligible clinical trials comparing TENS to 'fake' TENS (known as 'sham'), usual care or no treatment, or comparing TENS plus usual care versus usual care alone, for neuropathic pain in adults. As of September 2016, we found 15 studies eligible for inclusion. Of these 15 studies, we were able to combine results from five studies to investigate the effect of TENS compared to sham TENS for treatment of pain. The studies involved a range of neuropathic pain problems (e.g. people with spinal cord injury, back pain with nerve involvement, complications associated with diabetes, etc.). We found the quality of the studies overall to be low.

Key findings

We were unable to confidently state whether TENS is effective in relieving pain compared to sham TENS in people with neuropathic pain. This is due to the very low quality of the evidence, which means we have very limited confidence in this result and that future studies are likely to change this result. Lack of reported data meant we were unable to draw any conclusion on the effect of TENS treatment on health related quality of life, pain relieving medicine use or people's impression of how TENS changed their condition.

We described the results of 10 further studies comparing TENS against other types of treatment. These 10 studies were quite varied and so we could not combine them and analyse them together. This, together with the very low quality of these 10 studies, meant we were unable to judge pain relief, health related quality of life, pain medication use or impression of change.

In three of the 15 studies, some people using TENS experienced skin irritation under the electrode pads. Three studies reported no problems and the remaining studies did not provide any details on side effects. Based on this, it is not realistic to comment on side effects associated with TENS use.
### Summary of Findings for the Main Comparison

**TENS versus sham TENS for neuropathic pain in adults**

**Patient or population:** adults with neuropathic pain  
**Settings:** secondary care  
**Intervention/comparison:** TENS vs sham TENS  
**Outcome:** changes in pain intensity (VAS)

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Effect estimate (95% CI)</th>
<th>No of participants (studies)</th>
<th>Quality of the evidence (GRADE)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain intensity changes (VAS 0-10)</td>
<td>Favoured TENS. Mean difference -1.58 (95% CI -2.08 to -1.09)</td>
<td>207 (5)</td>
<td>★★★★★ Very low(^a)</td>
<td>Downgraded 3 levels due to multiple sources of potential bias, small number and size of studies.</td>
</tr>
<tr>
<td>Changes in health related quality of life</td>
<td>No data</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Changes in participant global impression of change</td>
<td>No data</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Change in analgesic medication use</td>
<td>Not estimable</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Incidence/nature of adverse events</td>
<td>Not estimable</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

CI: confidence interval; TENS: transcutaneous electrical nerve stimulation; VAS: visual analogue scale.

**GRADE Working Group grades of evidence**

- **High quality:** we are very confident that the true effect lies close to that of the estimate of the effect.
- **Moderate quality:** we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of effect, but there is a possibility that it is substantially different.
- **Low quality:** our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
- **Very low quality:** we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

\(^a\)Downgraded twice for limitations of studies and once for imprecision.

### Background

**Description of the condition**

Neuropathic pain is defined as “pain caused by a lesion or disease of the somatosensory system” and represents a significant source of...
chronic pain and loss of function at both an individual and societal level (Jensen 2011). Approximately 20% of adults in the USA and 27% in the EU report chronic pain (Kennedy 2014; Leadley 2012). Within this, it is estimated that 20% of people with chronic pain will have neuropathic pain characteristics, translating to an approximate prevalence of 6% to 7% in the general population (Bouhassira 2008). This is confirmed by one systematic review that estimated a population prevalence for neuropathic pain of 6.9% to 10% (van Hecke 2014). Neuropathic pain is often rated as particularly intense and distressing and can have a significant negative impact on activities of daily living and quality of life (Leadley 2014; McDermott 2006; Moore 2014).

Neuropathic pain may be classified as peripheral or central in origin depending on the site of lesion or disease. Peripheral neuropathic pain results from injury or disease of the peripheral nerves and includes conditions such as post-traumatic nerve injury, diabetic peripheral neuropathy (or painful diabetic neuropathy (PDN)) and postherpetic neuralgia (PHN). Central neuropathic pain results from injury or disease affecting the central nervous system (spinal cord, brainstem or brain) and includes central poststroke pain, postspinal cord injury pain and pain related to multiple sclerosis. Regardless of the causal condition or classification there are common features associated with neuropathic pain. Typically, neuropathic pain is associated with positive features such as spontaneous pain, hyperalgesia (excessive pain to a painful stimulus) and allodynia (pain evoked by a normally non-painful stimulus), as well as negative features such as sensory loss, weakness and hypoaesthesia (reduced sense of touch or sensation) (Baron 2010; Vranken 2012). For patients, this translates to pain being caused by innocuous stimuli such as light touch or gentle movement, increased pain in response to noxious stimuli, and reduced sensory and motor function (Baron 2010; Maier 2010; Vranken 2012). Additionally, pain may be perceived in the absence of provoking stimuli (Baron 2010; Baron 2012).

The mechanisms underpinning this persistent pain state are complex. It is most likely that a mix of peripheral and central mechanisms are responsible for ongoing pain perception. Following a lesion or disease in a peripheral somatosensory structure (e.g. peripheral nerve), inflammatory mediators are released that causes sensitisation of nociceptors (nerve receptors that respond to tissue damaging stimuli or threat of damage) resulting in lowered stimulation thresholds and enhanced activity in these receptors (Cohen 2014). Damage to neural structures (at both peripheral nerve and central nervous system levels) can result in longer term changes to their structure and function (Black 2008; Levinson 2012), resulting in abnormal or excessive activity in areas of damaged neural tissue that is thought to lead to ongoing and often severe and intractable pain (Cohen 2014). These changes may also be accompanied by a decreased capacity of the body’s natural pain modulation mechanisms (known as endogenous analgesia), further compounding the pain perceived (Baron 2010). These multiple, integrated pain mechanisms result in neuropathic pain being particularly difficult to treat and ongoing pain with limited response to treatment is common. First line management of neuropathic pain is primarily pharmacological (Dworkin 2013; O’Connor 2009); however, it is also common for management to include non-pharmacological treatments such as psychological or physical interventions including transcutaneous electrical nerve stimulation (TENS). Standard TENS units are portable, widely available, easily self-administered and are a popular adjunct therapy for people with chronic neuropathic pain (Johnson 2011).

Description of the intervention

TENS is the therapeutic application of transcutaneous (over the skin) electrical stimulation and is primarily used for pain control in a wide range of acute and chronic pain conditions (APTA 2001). TENS units typically use adhesive electrodes applied to the skin surface to apply pulsed electrical stimulation that can be modified in terms of frequency (stimulation rate), intensity and duration (Johnson 2011). TENS application is commonly described as being in either high or low frequency modes. Low frequency TENS is consistently defined as being 10 Hz or less (Bjordal 2003; Moran 2011; Sabino 2008), while high frequency TENS typically appears to be described as ranging up to 50 Hz or 100 Hz and above (Moran 2011; Santos 2013; Sluka 2003; Sluka 2005). Low frequency TENS is often used at higher intensities eliciting motor contraction, while high frequency TENS has traditionally been used at lower intensities (Walsh 2009). Modulated TENS applies stimulation across a range of frequencies and may help ameliorate development of tolerance to TENS (Sluka 2013).

Intensity appears to be a critical factor in optimising TENS efficacy and increasingly it is thought that regardless of frequency of application, the intensity needs to produce a strong, non-painful sensation that ideally is titrated during treatment to maintain the intensity level (Bjordal 2003; Moran 2011; Sluka 2013). To account for the suggested importance of this, it was proposed that this review would undertake a subgroup analysis based on intensity: strong and titrated versus all other application of intensities. Placement of electrodes may influence response, although this issue is somewhat ambiguous with local, related spinal segment and contralateral electrode placement demonstrating an effect in both animal and human studies (Brown 2007; Chesterton 2003; Dailey 2013; Sabino 2008; Somers 2009). Timing of outcome measurement requires consideration when analysing TENS studies as theory predicts that the TENS analgesia induced should peak during or immediately after use (Sluka 2013).

How the intervention might work

TENS induced analgesia is thought to be multifactorial and encompasses likely peripheral, spinal and supraspinal mechanisms. In one animal study, the increased mechanical sensitivity caused

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by peripheral injection of serotonin (a substance naturally produced following injury/inflammation) was decreased by application of TENS (Santos 2013). Importantly, it was demonstrated that this analgesia was partly mediated by peripheral mechanisms as preinjection of a peripheral opioid receptor blocker decreased the analgesia produced, implying the TENS effect was mediated via activation of these peripheral receptors (Santos 2013). A spinal effect for electrical stimulation was initially demonstrated by Wall 1967, and was suggested to work via the ‘pain-gate’ mechanism proposed in 1965 (Melzack 1965). The pain gate theory proposes that large diameter (Aβ) afferent fibres (carrying sensations such as vibration, touch, etc.) inhibit nociceptive activity in the dorsal horn of the spinal cord, with a resultant decrease in pain perception (Melzack 1965). TENS application and its stimulation of peripheral neural structures is a source of considerable large diameter afferent activity and this is therefore a plausible means of TENS induced analgesia. TENS is also thought to have additional spinal segmental effects; decreased inflammation-induced dorsal horn neuron sensitisation (Sabino 2008), altered levels of neurotransmitters such as gamma-aminobutyric acid (GABA) and glycin, which are thought to be involved in inhibition of nociceptive traffic (Maeda 2007; Somers 2009), and modulation of the activity of the cells that provide support/surround neurons (glial cells) in the spinal cord (Matsuo 2014), have all been suggested as means by which TENS may produce analgesia at a spinal segmental level.

Further, it appears that TENS may have an effect on endogenous analgesia. Descending activity relayed via the midbrain periaqueductal grey (PAG) and the rostral ventral medulla (RVM) in the brainstem may have inhibitory effects at the segmental level (Gebhart 2004). This PAG-RVM relayed segmental inhibition is mediated in part via opioidergic pathways (Calvino 2006; Gebhart 2004). TENS induced analgesia has been shown to be reversible with preinjection of opioid receptor blockers in both the PAG and RVM in rats with experimentally induced peripheral inflammation implying that this may be an operational pathway by which TENS contributes to analgesia (DeSantana 2009; Kalra 2001). This descending mechanism may also exist in humans with pain. An enhanced conditioned pain modulation (descending modulation) response has been observed in people with fibromyalgia during active TENS application compared to no TENS or placebo TENS (Dailey 2013). The descending modulation of pain is apparently not related to frequency of TENS stimulation employed (DeSantana 2009), rather it is the intensity of stimulation that appears to be critical in TENS analgesia (Moran 2011; Sluka 2013). Low frequency and high frequency TENS effects have been shown to be mediated via μ- and δ-opioid receptor classes, respectively, and as such low frequency TENS effects may be limited in people using opioids for pain relief as they primarily act via μ-opioid receptor pathways (Leonard 2010; Leonard 2011; Sluka 2013). Given that pharmacological management of neuropathic pain may involve opioid medication, it is possible this may impact upon low frequency TENS efficacy if used concurrently. Therefore, this review proposes a subgroup analysis of low versus high frequency TENS application to investigate this further.

These descending inhibitory mechanisms have also been implicated in placebo analgesia (the phenomena of improvements in pain that follow the delivery of an inert treatment) (Eippert 2009); therefore, it is possible that the suggested mechanisms of TENS induced analgesia described above may not necessarily represent specific effects of electrical stimulation but could possibly result purely from the therapeutic ritual of providing a TENS unit.

**Sham credibility issues in studies of transcutaneous electrical nerve stimulation**

One issue regarding the credibility of sham conditions specifically for TENS studies is whether the sham condition that is employed controls adequately for all aspects of the treatment experience. Various types of sham TENS have been proposed including deactivated units that are identical in appearance but deliver no actual stimulation to devices where an initial brief period of stimulation at the start of use is delivered and then faded out (Rakel 2010). To try to enhance blinding in these paradigms, the information given to participants is often limited regarding what they should feel when the device is switched on. However, it is clear that there are substantial threats to the credibility of these shams when compared to active stimulation that elicits strong sensations. Given that the effectiveness of TENS is widely thought to be related to the intensity of the stimulus, a true sham that establishes robust blinding of participants is not achievable (Sluka 2013). This represents a risk of bias to all sham controlled trials of TENS.

**Why it is important to do this review**

TENS is a widely used and readily available adjunct therapy for people with chronic pain and has the benefit of having an apparently low risk profile. This review supersedes one Cochrane Review: ‘Transcutaneous electrical nerve stimulation (TENS) for chronic pain’ (Nnoaham 2014 (withdrawn)); and one withdrawn protocol ‘Transcutaneous electrical nerve stimulation (TENS) for neuropathic pain in adults’ (Claydon 2014 (withdrawn)). The original review for chronic pain was split into two titles, one on neuropathic pain and one on fibromyalgia (Johnson 2016). This review replaces the original protocol for neuropathic pain that was withdrawn. There are a number of systematic reviews of the effect of TENS across various painful conditions (e.g. labour pain, rheumatoid arthritis, phantom limb pain and chronic low back pain) (Brosseau 2003; Khadilkar 2008; Dowswell 2009; Johnson 2010; Johnson 2015). There are no consistent findings and most reviews comment on the lack of good quality trials and consequent difficulty in estimating effect sizes. However, there is no previous
Cochrane Review examining the effect of TENS on neuropathic pain.

**OBJECTIVES**

To determine the analgesic effectiveness of TENS versus placebo (sham) TENS, TENS versus usual care, TENS versus no treatment and TENS in addition to usual care versus usual care alone in the management of neuropathic pain in adults.

**METHODS**

**Criteria for considering studies for this review**

**Types of studies**

We included randomised controlled trials (RCTs) or quasi-randomised trials (including cross-over designs) of TENS applied as treatment for central or peripheral neuropathic pain of any aetiology in adults. We excluded non-randomised studies, case reports/series, studies of experimental pain, clinical observations and systematic reviews. We assessed studies for inclusion regardless of their publication status. We excluded studies designed to test the immediate effects of a single treatment only with follow-up less than 24 hours. For non-English language papers, we sourced translators through Cochrane Pain, Palliative and Supportive Care Review Group as well as personal networks where available.

**Types of participants**

We included participants aged 18 years or over identified as having pain of neuropathic origin from a wide range of conditions, including, but not limited to:

- cancer-related neuropathy;
- HIV neuropathy;
- painful diabetic neuropathy (PDN);
- phantom limb pain;
- postherpetic neuralgia (PHN);
- postoperative or traumatic neuropathic pain;
- spinal cord injury;
- poststroke pain;
- trigeminal neuralgia.

We excluded studies that included participants with a mix of neuropathic and non-neuropathic pain where it was impossible to extract data for the neuropathic pain participants independently. We excluded studies that included participants with complex regional pain syndrome (Type I or II) or fibromyalgia as these studies are considered in separate Cochrane Reviews (Johnson 2016; Smart 2016).

**Types of interventions**

We included all standard modes of TENS, regardless of the device manufacturer, in which the TENS condition delivered a clearly perceptible sensation. Given that self-use and portability are key clinical features of TENS, we excluded non-portable electrical stimulation devices such as interferential therapy (IFT). We included any parameters of treatment that evoked a perceptible sensation, and any frequency or duration of treatment or surface electrode configuration. We excluded studies delivering intensities of TENS that were subperceptual or barely perceptual due to the risk of suboptimal treatment. We excluded studies where current was delivered percutaneously (e.g. electroacupuncture, percutaneous electrical nerve stimulation (PENS), neuroreflexotherapy) and where the effect of TENS could not be separated from the effects of other treatments (i.e. comparison interventions standardised between groups). The comparisons of interest were TENS versus placebo (sham) TENS, TENS versus usual care, TENS versus no treatment and TENS in addition to usual care versus usual care alone.

**Types of outcome measures**

We included studies with pain intensity as the primary or secondary outcome.

**Primary outcomes**

- Changes in pain intensity as measured using a visual analogue scale (VAS), numerical rating scale (NRS), verbal rating scale or Likert scale.
- Changes in health related quality of life (HRQoL) using any validated tool (e.g. 36-item Short Form (SF-36), six-item Short Form (SF-6), EuroQol).

**Secondary outcomes**

- Changes in participant global impression of change (PGIC) scales.
- Change in analgesic medication use.
- Incidence/nature of adverse events.

**Search methods for identification of studies**

**Electronic searches**

We searched the following electronic databases using a combination of controlled vocabulary, medical subject headings (MeSH) and free-text terms to identify published articles.
There were no language restrictions. The search strategies used can be found in Appendix 1.

Searching other resources

We searched the metaRegister of controlled trials (mRCT) (www.controlled-trials.com/mRCT), ClinicalTrials.gov (www.clinicaltrials.gov), and the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) (apps.who.int/trialsearch/) for ongoing trials. In addition, we checked the reference lists of reviews and retrieved articles for additional studies. We also sought relevant expert input in an attempt to elicit further contribution regarding novel studies.

Unpublished data

To minimise the prospect of publication bias, we undertook a further search of the following:
- OpenGrey (System for Information on Grey Literature in Europe);
- Dissertation abstracts (ProQuest);
- National Research Register Archive;
- Health Services Research Projects in Progress;
- Pan African Clinical Trials Registry;
- EU Clinical Trials Register.

Data collection and analysis

Selection of studies

Two review authors (WG and BMW) independently assessed the titles and abstracts of potential studies identified by the search strategy for their eligibility. If the eligibility of a study was unclear from the title and abstract, we assessed the full paper. We excluded studies that did not match the inclusion criteria (see Criteria for considering studies for this review). We resolved disagreements between review authors regarding a study’s inclusion by discussion. A third review author (NEO) was available to assess relevant studies if resolution and agreement could not be reached. This option was not required. We did not anonymise studies prior to assessment. A PRISMA study flow diagram documents the screening process (Figure 1) (Liberati 2009), as recommended in Part 2, Section 11.2.1 of the Cochrane Handbook for Systematic Reviews of Interventions (Schünemann 2011).
Figure 1. Study flow diagram.

4081 records identified through database searching

4 additional records identified through other sources

2930 records after all duplicates removed

2930 records screened

2281 records excluded

31 full-text articles excluded:
- participants not definitive neuropathic presentation (n = 9);
- ineligible outcome measures (n = 10);
- not a standard TENS unit (as protocol definition) (n = 2);
- not a randomised controlled trial or follow-up < 24 hours (n = 9);
- treatment parameters not specified (sub-perceptual as protocol) (n = 1).

Awaiting classification (n = 3).

46 full-text records assessed for eligibility.
3 studies for further assessment

15 studies included

10 studies included in qualitative synthesis

5 studies included in quantitative synthesis (meta-analysis)
Data extraction and management

Two review authors (WG and BMW) independently extracted data from all included studies using a standardised, piloted data extraction form. We resolved any discrepancies/disagreement by consensus. A third review author (NEO) was available for arbitration if consensus was not achieved. This option was not required. We extracted the following data from each study included in the review:

- country of origin;
- study design;
- study population (including diagnosis, diagnostic criteria used, symptom duration, age, gender);
- concomitant treatments that may affect outcome (medication, procedures, etc.);
- sample size, active and control/comparator groups;
- intervention(s) (including type, parameters (e.g. frequency, intensity, duration, electrode position, setting and professional discipline of the clinician delivering the therapy);
- type of placebo/comparator intervention;
- outcomes (primary and secondary) and time points assessed (only for the comparisons of interest to this review);
- adverse events;
- industry sponsorship;
- author conflict of interest statements.

Assessment of risk of bias in included studies

Two review authors (WG and BMW) independently assessed risk of bias for each study, using the criteria outlined in the Cochrane Handbook for Systematic Reviews of Interventions and adapted from those used by the Cochrane Pregnancy and Childbirth Group, with any disagreements resolved by discussion (Higgins 2011). In cases where consensus was not reached, a third review author (NEO) was available for arbitration. This option was not required. For each study of parallel design, we assessed the following.

- **Random sequence generation** (selection bias). We assessed the method used to generate allocation sequence as:
  - low risk of bias (any truly random process, e.g. random number table; computer random number generator);
  - unclear risk of bias (method used to generate sequence not clearly stated);
  - high risk of bias (studies using a non-random process, e.g. odd or even date of birth; hospital or clinic record number).

- **Allocation concealment** (checking for possible selection bias). We assessed the method used to conceal allocation to group assignment as:
  - low risk of bias (e.g. telephone or central randomisation; consecutively numbered sealed opaque envelopes);
  - unclear risk of bias (method not clearly stated);
  - high risk of bias (studies that did not conceal allocation e.g. open list).

- **Blinding of study participants** (checking for possible performance and detection bias). We assessed the methods used to blind participants and personnel (care providers) as follows:
  - low risk of bias (participants/personnel blinded to allocated intervention; and unlikely that blinding broken);
  - unclear risk of bias (insufficient information to permit judgement of low/high risk of bias);
  - high risk of bias (participants/personnel not blinded to allocated intervention, two interventions clearly identifiable to personnel as experimental and control OR participants/personnel blinded to allocated intervention but it is likely that blinding may have been broken).

- **Blinding of outcome assessor** (detection bias). We assessed the methods used to blind outcome assessors as:
  - low risk of bias (outcome assessor (including ‘participants’ with respect to self-report outcomes) blinded to participants’ allocated interventions and unlikely that blinding broken);
  - unclear risk of bias (insufficient information to permit judgement of low/high risk of bias);
  - high risk of bias (outcome assessor (including ‘participants’ with respect to self-report outcomes) unblinded to participants’ allocated interventions OR outcome assessor blinded to allocated intervention but likely that blinding may have been broken).

- **Incomplete outcome data** (attrition bias). We assessed attrition bias by considering if participant dropout rate was appropriately described and acceptable:
  - low risk of bias (less than 20% dropout and appeared to be missing at random. Numbers given per group and reasons for dropout described);
  - unclear risk of bias (if less than 20% but reasons not described and numbers per group not given. Unclear that data were missing at random);
  - high risk of bias (if over 20% even if imputed appropriately).

- **Incomplete outcome data** (participant exclusion). We assessed whether participants were analysed in the group to which they were allocated as:
  - low risk of bias (if analysed data in group to which originally assigned with appropriately imputed data or as an available-case analysis);
  - unclear risk of bias (insufficient information provided to determine if analysis was per protocol or intention to treat);
  - high risk of bias (if per-protocol analysis used. Where
available data were not analysed or participant data were included in group they were not originally assigned to).

- **Selective reporting** (reporting bias). We assessed whether studies were free of the suggestion of reporting bias as:
  - low risk of bias (study protocol available and all prespecified outcomes of interest adequately reported; study protocol not available but all expected outcomes of interest adequately reported; all primary outcomes numerically reported with point estimates and measures of variance for all time points);
  - unclear risk of bias (inadequate information to allow judgement of a study to be classified as 'low risk' or 'high risk');
  - high risk of bias (incomplete reporting of prespecified outcomes; one or more primary outcomes was reported using measurements, analysis methods or subsets of data that were not prespecified; one or more reported primary outcomes were not prespecified; one or more outcomes of interest reported incompletely and cannot be entered into a meta-analysis; results for a key outcome expected to have been reported excluded).

- **Size of study** (checking for possible biases confounded by small sample size). We assessed studies as:
  - low risk of bias (200 participants or more per treatment arm);
  - unclear risk of bias (50 to 199 participants per treatment arm);
  - high risk of bias (fewer than 50 participants per treatment arm).

- **Other sources of bias**. We also assessed other risk factors such as whether trials were stopped early, differences between groups at baseline, differences between groups in timing of outcome assessment, insufficient control of cointerventions and author source of funding declarations.

**Measures of treatment effect**

We analysed primary outcomes and presented this on a continuous scale as mean difference (MD) with 95% confidence intervals (CI). Where data were available, we planned to present outcomes in a dichotomised format. For dichotomised data (responder analyses), we planned to consider analyses based upon a 30% or greater reduction in pain to represent a moderately important benefit, and a 50% or greater reduction in pain intensity to represent a substantially important benefit as suggested by the IMMPACT guidelines (Dworkin 2008). Where possible, we planned to present risk ratio (RR) and risk difference (RD) with 95% CIs for dichotomised outcome measures. We planned to calculate the number needed to treat for an additional beneficial outcome (NNTB) as an absolute measure of treatment effect. However, these data were not available in the included studies. For HRQoL data, we preplanned a minimally important clinical difference to be greater than 10% of the scale employed (Furlan 2009), however we were unable to report on HRQoL.

The IMMPACT thresholds are based on estimates of the degree of

**Unit of analysis issues**

In cross-over studies, we planned to use first period data only whenever possible (Higgins 2011). Where this was not reported, we undertook analysis as if the treatment periods were parallel and highlighted the potential bias this may have introduced. All included studies randomised at the level of the individual participant.

**Dealing with missing data**

Where insufficient data were presented to enter into an otherwise viable meta-analysis, we contacted the study authors. Two included studies did not present data in a format suitable for data extraction. One study author replied with further data (Buchmuller 2012). We were unable to contact the authors of one further study (Prabhakar 2011).
Assessment of heterogeneity

We planned to combine studies that examined similar conditions. However, given the limited number of studies, we pooled data from studies in different neuropathic pain conditions but have considered whether diagnostic group appears to be a source of important heterogeneity. We evaluated the included studies for clinical homogeneity regarding study population, treatment procedure, control intervention, timing of follow-up and outcome measurement. We did not combine studies that compared TENS to usual care with studies that compared TENS to sham/placebo in the same analysis. We formally explored heterogeneity using the Chi² test to investigate the statistical significance of any heterogeneity, and the I² statistic to estimate the amount of heterogeneity. Where significant heterogeneity (P < 0.1) was present, we planned to explore subgroup analyses. Preplanned comparisons are described in Subgroup analysis and investigation of heterogeneity.

Assessment of reporting biases

We planned to consider the possible influence of publication/small study biases on review findings. The influence of small study biases were, in part, addressed by the risk of bias criterion ‘study size.’ We planned to use funnel plots to visually explore the likelihood of reporting biases when there were at least 10 studies in a meta-analysis and included studies differ in size. For continuous outcomes, we planned to use Egger’s test to detect possible small study bias and, for dichotomised outcomes, we planned to test for the possible influence of publication bias on each outcome by estimating the number of participants in studies with zero effect required to change the NNTB to an unacceptably high level (defined as a NNTB of 10), as outlined by Moore 2008. Given the small number of studies in the meta-analysis and that the remaining studies investigated different TENS comparisons, we did not undertake the above processes.

Data synthesis

We extracted data and classified them according to outcome and duration of follow-up (during-use effects; short term: zero to less than two weeks postintervention; mid-term: two to seven weeks postintervention; and long term: eight or more weeks postintervention). Where adequate data existed, we used a random-effects model to meta-analyse outcome data from suitably homogeneous studies using Review Manager 5 (RevMan 2014). For the pooled analysis, pain intensity data was extracted as 0-10 VAS rating scale except one study which used a 0-100 VAS scale (Barbarisi 2010). For this study, we converted the results to a 0-10 scale by dividing the measure by 10. The pooled effect sizes for changes in pain intensity were presented as MDs. We planned to pool data for adverse events across conditions though adequate data were not available to do so. We considered meta-analysis appropriate for only one comparison (TENS versus sham TENS). This decision reflects the clinical diversity across the included studies, particularly in relation to the control condition. We described the remaining studies as a narrative synthesis. We used the GRADE system to summarise the quality of the body of evidence for key comparisons (Guyatt 2008).

• Limitations of studies: downgraded once if greater than 25% of participants were from studies at high risk of bias across any key ‘Risk of bias’ criteria.
• Inconsistency: downgraded once if heterogeneity was statistically significant and I² ≥ 40% or when reported treatment effects were in opposition directions.
• Indirectness: downgraded once if greater than 50% of the participants were outside the target group.
• Imprecision: downgraded once if fewer than 400 participants for continuous data and fewer than 300 events for dichotomous data (Guyatt 2011).
• Publication bias: downgrade once where there was direct evidence of publication bias.

We considered single studies both inconsistent and imprecise (unless sample size was greater than 400 participants for continuous data and greater than 300 events for dichotomous data). Two review authors (WG and BW) made these judgements independently and we resolved disagreements by discussion. A third review author (NEO) was available if agreement could not be reached. This option was not required.

The GRADE system uses the following criteria for assigning grade of evidence:

• high: we are very confident that the true effect lies close to that of the estimate of the effect;
• moderate: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of effect, but there is a possibility that it is substantially different;
• low: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect;
• very low: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

We included a ‘Summary of findings’ table to present the main findings for the comparison ‘TENS versus sham TENS’ in a transparent and simple tabular format. In particular, we included key information concerning the quality of evidence, the magnitude of effect of the intervention examined and the sum of available data on the outcome(s). Due to clinical heterogeneity and lack of studies, we were unable to compare TENS versus usual care, TENS versus no treatment or TENS in addition to usual care versus usual care alone, therefore we did not present ‘Summary of findings’ tables for these comparisons.

Subgroup analysis and investigation of heterogeneity
We planned subgroup analysis in the following domains:
- type of neuropathic pain: central neuropathic pain (pain due to identifiable pathology of the central nervous system (e.g. stroke, spinal cord injury) or peripheral neuropathic pain (pain resulting from pathology of the nerve root or peripheral nerves);
- type of neuropathic condition (as feasible from included studies);
- stimulation parameters: intensity (subgroup studies in which intensity was titrated to a strong sensation versus studies in which intensity was not titrated);
- stimulation parameters: frequency (low frequency TENS 10 Hz or less versus high frequency TENS 100 Hz or greater).

We did not undertake these analyses due to insufficient number of included studies and for the pooled analysis clinical homogeneity.

Sensitivity analysis
We undertook a sensitivity analysis on risk of bias (investigating the effect of including/excluding studies at high risk of bias from the analysis) and the choice of meta-analysis model (investigating the impact of applying a fixed-effect instead of a random-effects model) for the comparison TENS versus sham TENS. We described all other studies narratively.

RESULTS

Description of studies
For a detailed description of all studies see Characteristics of included studies and Characteristics of excluded studies table.

Results of the search
The literature search was conducted in September 2016 and found 4081 records. We removed duplicates and were left with 2330 study records. Two review authors (BW and WG) then independently reviewed titles and abstracts of all study records against inclusion and exclusion criteria. These independent selections were compared and consensus reached over study inclusion/assessment of full text papers. We selected 46 records for further investigation in full-text format and from this agreed on 15 papers to include in the review (Barbarisi 2010; Bi 2015; Buchmuller 2012; Casale 2013; Celik 2013; Gerson 1977; Ghoname 1999; Koca 2014; Nabi 2015; α zkul 2015; Prabhakar 2011; Rutgers 1988; Serry 2015; Tilak 2016; Vitalii 2014). One review author (BW) translated and conducted inclusion/exclusion criteria for two papers with the help of a native German speaker (Heidenreich 1988; Lehmkuhl 1978); a volunteer identified through Cochrane Task Exchange translated another study, which two review authors (BW and WG) assessed for inclusion/exclusion (Pourmomeny 2009). See Figure 1 for a summary of the screening process.

Included studies
A detailed description of all studies included in this review is provided in the Characteristics of included studies table, and detailed descriptions of participants and TENS treatment parameters in individual studies (where reported) can be found in Table 1. We included 15 studies and extracted data from 14 of these. One study did not provide useable data (Rutgers 1988). We contacted two study authors with respect to clarifications around published data. On request, Barbarisi 2010 provided detail on post-treatment VAS pain intensity score variance; Buchmuller 2012 provided clarification on the process of subgrouping of participants into a neuropathic pain group and data on VAS pain intensity for this group. Nabi 2015 provided methodological information with respect to outcome assessment timeframe postintervention. We contacted two study authors regarding clarification of published data but received no response (Prabhakar 2011; Serry 2015). Lack of up to date contact information meant one study author could not be contacted (Rutgers 1988).
A detailed narrative description of all included studies can be found in Appendix 2.

Design
All studies included in the review were RCTs. Of these, we considered five were appropriate to pool data for the comparison of TENS versus sham (Barbarisi 2010; Bi 2015; Buchmuller 2012; Celik 2013; Vitalii 2014). Each of these five were two arm parallel designs with TENS versus sham TENS. The remaining 10 studies were RCTs with two parallel intervention arms (Casale 2013; Gerson 1977; Nabi 2015; Rutgers 1988; Tilak 2016), three parallel intervention arms (Koca 2014; Prabhakar 2011), or were randomised cross-over designs with either two (α zkul 2015), or three sequenced interventions (Ghoname 1999).

Participants
The 15 studies included 728 participants at intake. Seven of the included studies did not have a formal mechanism employed to classify/diagnose participants (Barbarisi 2010; Bi 2015; Gerson 1977; Prabhakar 2011; Rutgers 1988; Serry 2015; Tilak 2016). Two studies employed confirmatory nerve conduction studies (Casale 2013; Koca 2014), two used the Leeds Assessment of Neuropathic Symptoms and Signs (LANSS) scale (Celik 2013; Vitalii 2014), and one study used the Douleur Neuropathique 4 (DN4) questionnaire (α zkul 2015). Three studies classified participants by clinical assessment (Buchmuller 2012; Ghoname 1999; Nabi 2015). Within participants, neuropathic pain was associated with spinal cord injury in four studies (Bi 2015; Celik 2013; α zkul 2015; Vitalii 2014), PHN in three studies (Barbarisi 2010; Gerson...
Effects of TENS for neuropathic pain in adults (Review)

Outcomes

All five studies used in the pooled analysis assessed pain intensity immediately postintervention and are all therefore classified as assessing short-term outcome. Four of the five studies reported VAS using a 0-10 scale while one study used a 0-100 scale (Barbarisi 2010). In the pooled analysis, outcome assessment occurred immediately postintervention period which varied in length from 10 days (Celik 2013; Vitalii 2014) to four weeks (Barbarisi 2010) to three months (Bi 2015; Buchmuller 2012).

The majority of studies included in the narrative synthesis assessed pain intensity on a 0-10 VAS scale immediately postintervention, (Casale 2013; Ghoname 1999; Ṣzkul 2015; Prabhakar 2011; Serry 2015; Tilak 2016). Within this group, the length of intervention varied in duration from four days (Tilak 2016) to two weeks (Ṣzkul 2015), three weeks (Casale 2013; Ghoname 1999; Prabhakar 2011), and eight weeks (Serry 2015). One study assessed pain intensity at three weeks' postintervention therefore reporting mid-term effects (Koca 2014), and one study reported pain intensity at one week, one month and three months' postintervention covering short, mid and long term outcome effects (Nabi 2015).

Only one study assessed during use effects, with pain intensity (0-100 VAS scale) reported at week eight of an overall 10 week intervention protocol (Gerson 1977). Lastly, one study reported assessment of pain intensity using a 10 point stepwise scale at six weeks, nine weeks and six months; however, no useable data were presented (Rutgers 1988).

Two studies collected data on HRQoL (Buchmuller 2012; Ghoname 1999). However, we were unable to use these data. No studies reported on PGIC. Three studies monitored/reported on medication use; however, we were unable to analyse the data further. Lastly, three studies reported on minor skin irritation as adverse events (Buchmuller 2012; Koca 2014; Nabi 2015). Further detail regarding these outcomes is supplied in the Effects of interventions section.

Excluded studies

A list of the 31 excluded studies and reasons for exclusion is provided in the Characteristics of excluded studies table. In summary, reasons for exclusion were as follows: not definitive neuropathic pain participants (nine studies); not an RCT or follow-up less than 24 hours postrandomisation (nine studies); composite outcome measures involving pain and other sensory measures/symptoms (10 studies); standard TENS unit not used (two studies) and treatment delivered at subperceptual levels (one study).

Studies awaiting classification

One paper is awaiting translation and is currently recorded as awaiting classification (Wang 2009). A search of clinical trials registries and abstracts yielded three registered trials and one thesis of interest. We contacted study authors for all three trials. Two authors replied and following this these trials were excluded. We have contacted authors of the remaining trial and the thesis without reply (ICTRPNCT02496351; Samier 2006). These results are recorded as awaiting classification. See Characteristics of studies awaiting classification table.
Ongoing studies
The search identified no ongoing studies.

Risk of bias in included studies
We present a 'Risk of Bias' summary for all included studies in Figure 2, followed by an individual graphical representation for every study across each 'Risk of Bias' domain (Figure 3). In summary, we judged 11 studies as being at high risk of bias overall (Barbarisi 2010; Bi 2015; Celik 2013; Gerson 1977; Ghoname 1999; Koca 2014; Nabi 2015; Prabhakar 2011; Rutgers 1988; Serry 2015; Vitalii 2014). We judged the remaining four studies at unclear risk of bias (Buchmuller 2012; Casale 2013; zkul 2015; Tilak 2016).

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.
Figure 3. Risk of bias summary: review authors’ judgements about each risk of bias item for each included study.

<table>
<thead>
<tr>
<th>Study</th>
<th>Random sequence generation (selection bias)</th>
<th>Allocation concealment (selection bias)</th>
<th>Blinding of participants and personnel (performance bias)</th>
<th>Blinding of outcome assessment (detection bias)</th>
<th>Incomplete outcome data (attrition bias)</th>
<th>Selective reporting (rotating bias)</th>
<th>Other bias</th>
<th>Size of study</th>
</tr>
</thead>
</table>
Allocation

Random sequence generation
We judged six out of the 15 included studies to have adequately described random sequence generation and we classified them as low risk for selection bias (Barbarisi 2010; Bi 2015; Buchmuller 2012; Casale 2013; Gerson 1977; Rutger 1988; Vitalii 2014). Two studies used alternate/sequential allocation to treatment groups and we therefore judged them to be at high risk for selection bias (Celik 2013; Koca 2014).

Allocation concealment
The majority of studies did not provide sufficient detail to allow judgement with respect to allocation concealment and we assigned them unclear risk of bias (Barbarisi 2010; Bi 2015; Casale 2013; Gerson 1977; Rutger 1988; Vitalii 2014). Two studies were cross-over designs and we therefore judged them to be at low risk for selection bias (Ghoma 1999; Gerson 2015), while we judged two parallel controlled trials to have adequately described allocation concealment and were designated low risk of bias in allocation concealment (Buchmuller 2012; Tilak 2016).

Blinding

Blinding of participants/personnel (care providers)
For each study, we assessed and judged blinding of participants and blinding of personnel separately. We considered eight studies to have adequately reported across all outcome measures and were judged at low risk of bias (Barbarisi 2010; Bi 2015; Rutger 1988; Vitalii 2014). One study described adequate blinding of both participants and personnel and was deemed at low risk of bias (Buchmuller 2012). Five studies made comparisons against other comparable active treatments and we assigned unclear risk of bias to blinding of participants and personnel in these studies (Casale 2013; Gerson 1999; Rutger 1988; Vitalii 2014). Two studies used alternate/sequential allocation to treatment groups and we therefore judged them to be at high risk for selection bias (Celik 2013; Koca 2014).

Blinding of outcome assessors
We judged two of the five studies in the pooled analysis investigating changes in pain intensity with TENS versus sham TENS at low risk of bias (Buchmuller 2012; Celik 2013). We rated the remaining three studies in the pooled analysis at unclear risk of bias in this domain (Barbarisi 2010; Bi 2015; Vitalii 2014). We considered studies applying two active comparable treatments at unclear risk for this domain (Casale 2013; Gerson 1977; Rutger 1988; Vitalii 2014), while we judged studies applying invasive or non-comparable treatments compared to TENS at high risk of bias (Gerson 1977; Rutger 1988).

Incomplete outcome data
With regard incomplete outcome data, we separately considered risk of bias assessment for ‘attrition’ and ‘participation exclusion’ domains. However, in a number of studies ‘participant exclusion’ was not explicitly described. In response to this, we used the following guideline when judging ‘attrition’ and ‘participant exclusion’ bias: if ‘participant exclusion’ was not explicitly described but the ‘attrition’ was minor or acceptable and reasonably described, we used this as justification for low risk across both domains. If ‘attrition’ or ‘participant exclusion’ was not adequately described or explained, this was used as justification for the unclear risk ‘participant exclusion from analysis’ decision for the studies Nabi 2015, Prabhakar 2011, Serry 2015, and Vitalii 2014. Furthermore, we judged one cross-over study at unclear risk of bias as no mention was made with regard to any missing data over the many hundreds of data collection points (Ghoma 1999).

With regard incomplete outcome data, we separately considered risk of bias assessment for ‘attrition’ and ‘participation exclusion’ domains. However, in a number of studies ‘participant exclusion’ was not explicitly described. In response to this, we used the following guideline when judging ‘attrition’ and ‘participant exclusion’ bias: if ‘participant exclusion’ was not explicitly described but the ‘attrition’ was minor or acceptable and reasonably described, we used this as justification for low risk across both domains. If ‘attrition’ or ‘participant exclusion’ was not adequately described or explained, this was used as justification for the unclear risk ‘participant exclusion from analysis’ decision for the studies Nabi 2015, Prabhakar 2011, Serry 2015, and Vitalii 2014. Furthermore, we judged one cross-over study at unclear risk of bias as no mention was made with regard to any missing data over the many hundreds of data collection points (Ghoma 1999).

Six studies adequately described both sections in this domain and we judged them at low risk of bias (Barbarisi 2010; Bi 2015; Casale 2013; Celik 2013; Gerson 1999; Koca 2014; Nabi 2015; Rutger 1988; Vitalii 2014). One study specifically excluded participants lost to follow-up and we therefore judged high risk on ‘participant exclusion’ bias (Koca 2014). Two studies reported very significant attrition and employed ‘per protocol’ analysis and we judged these at high risk of bias across both domains (Gerson 1977; Rutger 1988). We obtained data for a neuropathic subgroup of participants in one study, of which there was around 38% loss of outcome data at post-treatment assessment and therefore we judged this study at high risk of attrition bias (Buchmuller 2012).

Selective reporting
We considered eight studies to have adequately reported across all outcome measures and were judged at low risk of bias (Bi 2015; Casale 2013; Celik 2013; Koca 2014; Nabi 2015; Prabhakar 2011; Serry 2015; Tilak 2016; Vitalii 2014. Inconsistencies in presented data led us
to judge two studies at unclear risk (Barbarisi 2010; Buchmüller 2012). Five studies did not adequately describe or present all stated outcome measures and were assigned high risk of bias in this area (Gerson 1977; Ghoname 1999; Prabhakar 2011; Rutgers 1988; Serry 2015).

Other potential sources of bias

We focused on two main factors in this risk of bias section and judged whether baseline characteristics and outcome measure time frames were adequate and comparable. We judged six studies at low risk of bias in this domain (Bi 2015; Buchmüller 2012; Casale 2013; Celik 2013; Gerson 1977; Koca 2014; Nabi 2015; Prabhakar 2011; Rutgers 1988; Serry 2015). Seven studies were at unclear risk due to insufficient detail around baseline comparisons or outcome measure timing (Barbarisi 2010; Ghoname 1999; Koca 2014; Nabi 2015; Özkul 2015; Prabhakar 2011; Rutgers 1988; Serry 2015).

Size of study

We deemed 13 studies to be at high risk of bias with fewer than 50 participants per treatment arm (Barbarisi 2010; Bi 2015; Casale 2013; Celik 2013; Gerson 1977; Koca 2014; Nabi 2015; Özkul 2015; Prabhakar 2011; Rutgers 1988; Serry 2015; Tilak 2016; Vitalii 2014). We assigned two studies unclear risk of bias as their sample size was between 50 and 200 per treatment arm (Buchmüller 2012) or as part of a cross-over trial (Ghoname 1999).

Effects of interventions

See: Summary of findings for the main comparison TENS versus sham TENS

TENS versus sham TENS

Primary outcomes

Change in pain intensity

We included five individual studies that reported change in pain intensity (n = 207) (Barbarisi 2010; Bi 2015; Buchmüller 2012; Celik 2013; Vitalii 2014). Sample sizes ranged from n = 21 (Vitalii 2014), up to n = 122 (Buchmüller 2012). One two-arm parallel design investigated TENS versus sham TENS in participants with PHN (Barbarisi 2010). Three studies ran two-arm parallel group designs in participants with spinal cord injury (Bi 2015; Celik 2013; Vitalii 2014). One study investigated TENS versus sham TENS in participants with chronic radicular low back pain (Buchmüller 2012).

When pooling the data, we entered the pain intensity scores from Barbarisi 2010 as two distinct comparisons: pregabalin 300 mg plus TENS versus pregabalin 300 mg plus sham TENS and pregabalin 600 mg plus TENS versus pregabalin 600 mg plus sham TENS. We considered this a valid approach because it did not cause any unit of analysis issues as it was a parallel study design and participants were not ‘double counted.’

For pain intensity (expressed on a 0-10 scale) pooling of the studies using a random-effects model yielded an MD effect size favouring TENS of -1.58 (95% CI -2.08 to -1.09, P < 0.00001, n = 207, 6 comparisons from 5 studies; very low quality evidence). There was no significant heterogeneity (see Figure 4).

Figure 4. Forest plot of comparison: 1 TENS versus sham TENS, outcome: 1.1 Changes in pain intensity.
Sensitivity analysis yielded the following effect size when using a fixed-effect model (MD -1.57, 95% CI -1.97 to -1.16, P < 0.00001, n = 207, 6 comparisons from 5 studies). Given that we rated the key domains of selection and blinding bias domains as high risk for Celik 2013, we investigated the effect of study quality on the pooled estimate by removing this study from the pooled analysis (see Figure 5). This yielded an effect size of -1.44 (95% CI -1.87 to -1.02, P < 0.001, n = 174, 5 comparisons from 4 studies).

Figure 5. Forest plot of comparison: TENS versus sham TENS, outcome: 1.2 Pain intensity sensitivity analysis (Celik 2013 removed).

With regard to a relative comparison of effect size, three of the five studies in the pooled comparison used concomitant drug treatment and we considered that it would be inappropriate to use these as comparators of effect size. Therefore, using the random-effects result, an MD of -1.58 when expressed relative to the mean baseline values of the study with the largest control group sample size Buchmuller 2012 (n = 58) equated to a 26% reduction in pain intensity post-treatment (95% CI 18% to 34%). Overall, the MD exceeded the 1 unit suggested to be the minimally important difference in between-group change scores for pain intensity (Busse 2015). The very low quality evidence (downgraded due to significant limitations of studies and imprecision) means it is impossible to confidently state whether TENS has a pain relieving effect compared to sham TENS in people with neuropathic pain at short-term postintervention follow-up. The true effect is very likely to be significantly different from the estimate reported.

Changes in health related quality of life

Four of the five studies in the pooled analysis did not investigate HRQoL (Barbarisi 2010; Bi 2015; Celik 2013; Vitalii 2014). The remaining study, whilst assessing HRQoL via the SF-36 questionnaire, did not present baseline data, did not provide neuropathic subgroup data and reported the SF-36 broken into separate physical and mental domains (Buchmuller 2012). Therefore, we were unable to report on HRQoL in this comparison.

Secondary outcomes

Changes in participant global impression of change

No studies reported PGIC.

Change in analgesic medication use

One study assessed concurrent gabapentin use in both TENS and sham TENS groups and reported increases in both (Vitalii 2014). The TENS group increased by a mean of approximately 136 mg of gabapentin while the sham TENS group increased by a mean of 560 mg of gabapentin. This difference in increase was reported as statistically significant but no variance data were given. Pregabalin was used concurrently in another study but there were no comparisons made or planned across pharmacological data (Barbarisi 2010). Drug use was monitored but not explicitly reported or analysed postintervention in a third study (Buchmuller 2012). Two studies did not include medication use as an outcome (Bi 2015;
Overall, we could make no conclusions on the effect of TENS versus sham TENS with respect to medication use.

Incidence/nature of adverse events

Two studies explicitly reported no adverse events associated with TENS treatment (Celik 2013; Vitalii 2014). One study reported minor skin irritation in 11 participants in the active group versus three participants in the sham group. These data related to the whole study which included people without defined neuropathic related pain (Buchmuller 2012). Two studies did not report adverse events (Barbarisi 2010; Bi 2015). We could make no overall conclusion from this with regard to adverse events associated with TENS versus sham TENS.

Planned comparisons

Due to a lack of data we were unable to report on comparisons for TENS versus no treatment or TENS in addition to usual care versus usual care alone. We identified 10 studies that compared TENS to usual care; however, there was great diversity in the treatment provided in the usual care arm of these studies precluding any quantitative data synthesis. A narrative summary of each of these studies is presented below.

TENS versus therapeutic laser

We found one study that compared TENS with laser (Casale 2013).

Primary outcomes

Change in pain intensity

Casale 2013 investigated TENS versus laser in participants with carpal tunnel syndrome. The study reported a statistically significant time-by-group ANOVA interaction indicating statistically significant differences in post-treatment change in pain intensity scores (VAS 0-10) between the laser and TENS groups. Our calculations indicated an MD of -1.2 in favour of laser compared to TENS (95% CI -2.3 to -0.1, P = 0.041).

We found very low quality evidence (downgraded for limitations of study, inconsistency and imprecision) that laser may be more effective than TENS for treatment of pain at short-term postintervention follow-up in participants with carpal tunnel syndrome.

Changes in health related quality of life

The study did not report HRQoL.

Secondary outcomes

Changes in participant global impression of change

The study did not report PGIC.

Change in analgesic medication use

The study did not report change in medication use.

Incidence/nature of adverse events

The study did not report adverse events.

TENS versus carbamazepine plus clomipramine

We found one study that compared TENS versus carbamazepine plus clomipramine (Gerson 1977).

Primary outcomes

Change in pain intensity

Gerson 1977 investigated TENS versus pharmacological intervention (carbamazepine plus clomipramine) in participants with PHN. Analysis of the results was performed on a per-protocol basis and there was a 60% attrition rate across the whole sample. Final analysis was performed on 12 participants for the drug group (including three participants who were initially randomised to TENS) and four participants for the TENS group (including one participant who was initially randomised to drug treatment).

VAS values (0-100) at week eight were reported as means and standard errors of the mean (drug group 21 ± 4.3 mm, TENS group 43 ± 15.6 mm). The study reported this as a statistically significant difference although there was no information on the tests employed.

There was very low quality evidence (downgraded for limitations of study, inconsistency and imprecision) that carbamazepine plus clomipramine drug treatment may be more effective than TENS for treatment of pain in participants with PHN. It should be noted that the drug intervention was completed by week eight and all remaining participants were assessed at this stage. Thus, results reported for the drug arm of this study were short-term postintervention effects while the TENS result related to ‘during use’ effects as the TENS final treatment was not delivered until week 10 of the protocol.

Changes in health related quality of life

The study did not report HRQoL.
Secondary outcomes

Changes in participant global impression of change
The study did not report PGIC.

Change in analgesic medication use
The study reported drug dosage data for participants who competed the protocol as being carbamazepine 150 mg/day to 1000 mg/day and clomipramine 10 mg/day to 75 mg/day. No further analysis or change in analgesic use reported.

Incidence/nature of adverse events
The study did not report adverse events.

TENS versus percutaneous electrical nerve stimulation
We found one study comparing TENS versus PENS (Ghoname 1999).

Primary outcomes

Change in pain intensity
Ghoname 1999 investigated PENS versus TENS in participants with sciatica. The study reported a significant reduction in pain intensity (VAS 0-10) post-treatment for both PENS and TENS. The study reported pain intensity 24 hours post-treatment as significantly lower for PENS compared to TENS (mean ± SD: 4.1 ± 1.4 with PENS versus 5.4 ± 1.9 with TENS). This may be expressed as an MD of -1.3 (95% CI -1.9 to -0.7, P < 0.0001) in favour of PENS compared to TENS. There was very low quality evidence (downgraded for limitations of study, inconsistency and imprecision) that PENS may be more effective than TENS for treatment of pain at short-term post-intervention follow-up in participants with radicular pain secondary to sciatica.

Changes in health related quality of life
Data for quality of life (SF-36) were collected at baseline across all participants and scores reported as physical component summary (PCS) and mental component summary (MCS). The SF-36 was then completed again, 24 hours after completion of all nine treatments of each modality. A repeat baseline SF-36 was not reported prior to each subsequent treatment phase with all post-treatment PCS/MCS scores being compared to the single original baseline assessment. We considered this to be sufficiently problematic such that we did not consider these data further.

Secondary outcomes

Changes in participant global impression of change
The study did not report PGIC.

Change in analgesic medication use
Oral non-opioid analgesic tablet consumption/day reduced by (mean ± SD) 50 ± 19% in the PENS group and 29 ± 17% in the TENS group post-treatment compared to pretreatment for each phase: for PENS this equated to a reduction of approximately 1 tablet/day on average (approximately 2.5 tablets/day to 1.5 tablets/day). The study did not report any statistical analysis for this result.

Incidence/nature of adverse events
The study did not report adverse events.

TENS versus interferential therapy versus splints
We found one study comparing TENS versus IFT (Koca 2014).

Primary outcomes

Change in pain intensity
Koca 2014 investigated TENS versus IFT versus night splints in participants with carpal tunnel syndrome. There was a statistically significant difference (from baseline) in pain intensity (VAS 0-10) for all three interventions post-treatment. The study reported that IFT post-treatment scores were significantly lower than scores for TENS or splint interventions (mean ± SD: 6.4 ± 1.2 with splint, 6.7 ± 1.4 with TENS, 4.80 ± 1.2 with IFT). This represented an MD of -0.3 (95% CI -1.1 to 0.5, P = 0.95) between TENS and splint treatment. In terms of the two active treatments (TENS and IFT), there was an MD of -1.88 (95% CI -2.68 to -1.07, P < 0.0001) in favour of IFT. There were two minor adverse events (skin irritation) in the TENS group. There was very low quality evidence (downgraded for limitations of study, inconsistency and imprecision) that IFT may be more effective than TENS for treatment of pain at medium-term post-intervention follow-up in participants with carpal tunnel syndrome.

Changes in health related quality of life
The study did not report HRQoL.
Secondary outcomes

Changes in participant global impression of change
The study did not report PGIC.

Change in analgesic medication use
The study did not report drug use.

Incidence/nature of adverse events
Skin irritation was “reported in a few” TENS participants.

TENS versus visual illusion
We found one study comparing TENS with visual illusion (VI) (ZKUL 2015).

Primary outcomes

Change in pain intensity
ZKUL 2015 investigated TENS versus VI in participants with pain secondary to spinal cord injury. The study reported a significant difference of ‘present’ pain intensity (VAS 0-10) post day-10 treatment between interventions (mean ± SD): 3.66 ± 1.52 with TENS, 4.66 ± 1.37 with VI). However, from our calculations, this represents a non-significant MD of 1.0 (95% CI -0.16 to 2.15, P = 0.1). Within-treatment analyses were reported as statistically significant in the domains of maximal and minimal pain for TENS only. However, between-group testing was not significantly different for the two groups for mean, maximal or minimal pain intensity post-treatment.

There was very low quality evidence (downgraded for limitations of study, inconsistency and imprecision) that VI was no more effective than TENS for treatment of pain at short-term postintervention follow-up in participants with neuropathic pain following spinal cord injury.

Changes in health related quality of life
The study did not report HRQoL.

Secondary outcomes

Changes in participant global impression of change
The study did not report PGIC.

Change in analgesic medication use
The study did not report drug use.

Incidence/nature of adverse events
The study explicitly reported no adverse events with TENS.

Changes in health related quality of life
The study did not report HRQoL.
TENS versus cervical mobilisation versus exercise
We found one study comparing TENS versus cervical mobilisation versus exercise (Prabhakar 2011).

Primary outcomes

Change in pain intensity
Prabhakar 2011 investigated TENS versus cervical mobilisation versus exercise in participants with cervical radiculopathy. Pain intensity at baseline was not presented or compared between groups. Pain intensity (VAS 0-10) data at three weeks were presented as reduction from baseline and VAS data at six weeks were not supplied. The VAS pain outcomes at three weeks were: reduction from baseline (mean ± SD): -3.53 ± 0.76 with TENS, -4.49 ± 0.76 with mobilisation, -2.16 ± 0.8 with isometric exercise. The results were presented as a series of within-group analyses. Between-group testing was reported as significant; however, it is unclear if this related to VAS pain intensity data and no data were reported for this analysis. We did not undertake any further analysis of the data in the absence of baseline data and sample sizes. We contacted the authors repeatedly for clarification with no reply.

One study provided very low quality evidence (downgraded for limitations of study, inconsistency and imprecision) investigating cervical spine mobilisation, TENS and isometric exercise treatment for pain in participants with cervical radiculopathy. Despite reporting significant differences between groups, it was impossible to draw conclusions on relative efficacy of each intervention due to lack of data and lack of information on statistical testing.

Changes in health related quality of life
The study did not report HRQoL.

Secondary outcomes

Changes in participant global impression of change
The study did not report PGIC.

Change in analgesic medication use
The study did not report drug use.

Incidence/nature of adverse events
The study did not report adverse events.

TENS versus acupuncture
We found one study comparing TENS with acupuncture (Rutgers 1988).

Primary outcomes

Change in pain intensity
Rutgers 1988 investigated TENS versus acupuncture in participants with PHN. The study reported no pain intensity data and undertook no comparisons/analyses. This may be due to the very high attrition rates; at nine weeks, three out of 13 in the TENS group and five out of 10 participants in the acupuncture group remained in the study. At nine weeks, one participant in the TENS group reported a subjective improvement in pain intensity and two participants in the acupuncture group reported moderate subjective improvement. No further analysis of this study was undertaken.

One study (very low quality evidence, downgraded for limitations of study, inconsistency and imprecision) investigated TENS versus acupuncture for pain in participants with PHN. It was impossible to draw conclusions on relative efficacy of each intervention due to significant methodological limitations and incomplete reporting of data.

Changes in health related quality of life
The study did not report HRQoL.

Secondary outcomes

Changes in participant global impression of change
The study did not report PGIC.

Change in analgesic medication use
The study did not report drug use.

Incidence/nature of adverse events
The study did not report adverse events.

TENS versus exercise versus pharmacological therapy
We found one study comparing exercise plus pharmacological therapy versus TENS plus pharmacological therapy versus pharmacological therapy alone for pain in participants with diabetic peripheral neuropathy (Serry 2015).
**Primary outcomes**

**Change in pain intensity**
The study reported pain intensity (VAS 0-10) changes using a within-group analysis. Despite stating using between-group tests there was no reporting of this. Within-group pain intensity percentage changes (comparing pretreatment to post-treatment) were as follows: -41.67% with TENS plus pharmacological therapy, -16.7% with exercise plus pharmacological therapy. The study reported no within-group statistical difference for the pharmacological therapy group. Neither baseline nor post-treatment assessment points had any pain intensity data reported. We did not undertake any further analysis in the absence of useable data. We attempted to contact the authors on a number of occasions with no reply. One study (very low quality evidence, downgraded for limitations of study, inconsistency and imprecision) investigated TENS plus pharmacological therapy versus exercise plus pharmacological therapy versus pharmacological therapy alone for pain in participants with PDN. Despite reporting significant differences between groups, it was impossible to draw conclusions on relative efficacy of each intervention due to lack of data and lack of information on statistical testing.

**Changes in health related quality of life**
The study did not report HRQoL.

**Secondary outcomes**

**Changes in participant global impression of change**
The study did not report PGIC.

**Change in analgesic medication use**
The study did not report drug use.

**Incidence/nature of adverse events**
The study did not report adverse events.

**TENS versus mirror therapy**
We found one study comparing TENS versus mirror therapy (Tilak 2016).

**Discussion**

**Summary of main results**
We were unable to confidently state whether TENS is effective (compare to sham TENS) for pain relief in people with neuropathic pain. The evidence we used in this comparison was very low quality and the true effect is very likely to be substantially different from that reported. The ‘very low’ GRADE judgement was based on the significant methodological limitations of the included studies, and overall small study sizes.
One study provided very low quality evidence that laser was more effective than TENS when treating pain in participants with carpal tunnel syndrome (Casale 2013). While the magnitude of the effect size in this comparison may be considered meaningful, the design of the study was such that allocation and blinding domains in risk of bias assessment were unclear, which, when considered with the small size of the study, necessitates limited confidence in this effect size.

Very low quality evidence investigating TENS versus pharmacotherapy for pain in participants with PHN may be interpreted as favouring carbamazepine plus clomipramine treatment (Gerson 1977). However, serious limitations in methodology and potential bias means this result should be viewed with very limited confidence.

Two studies (very low quality evidence) investigated the efficacy of TENS versus other electrotherapeutic modalities, PENS in participants with radicular pain secondary to sciatica (Ghoname 1999) and IFT in participants with carpal tunnel syndrome (Koca 2014).

Significant concerns with the invasive nature of the PENS intervention and sham PENS intervention (Ghoname 1999), issues with participant selection/allocation (Koca 2014), risk of bias and participant/personnel blinding (Ghoname 1999; Koca 2014) rendered the results very limited in terms of confidence of the reported effects.

One study compared TENS versus PRF sympathectomy for pain intensity in participants with PDN (Nabi 2015). This study did not report variance of the data in the measured outcome and statistical tests did not appear to examine between-group differences. There were also significant differences in final outcome measurement between groups and issues with participant/personnel blinding. We rated this study as providing very low quality evidence and it was impossible to draw conclusions on relative effectiveness.

Two studies investigated aspects of visual manipulation versus TENS on pain intensity (zkul 2015; Tilak 2016). Comparisons were VI versus TENS in participants with spinal cord injury (zkul 2015), and mirror therapy versus TENS in participants with phantom limb pain (Tilak 2016). Upon completion of treatment, there was no significant difference in pain intensity measures between groups in either study. Evidence provided by these studies was rated very low quality. The results should be viewed with limited confidence.

One study investigated cervical spinal joint mobilisation versus TENS versus isometric exercises for pain in participants with cervical radiculopathy (Prabhakar 2011). However, significant issues with methodology/potential risk of bias and data presentation/analysis in this paper meant it was impossible to draw conclusions regarding relative effectiveness of the investigated interventions.

One study investigated TENS versus acupuncture in participants with PHN (Rutgers 1988). This study had very significant methodological issues including high risk of bias across multiple domains, lack of published useable data and no statistical analysis; therefore, we were unable to draw conclusions regarding relative effectiveness of the investigated interventions.

One study investigated exercise plus pharmacotherapy versus TENS plus pharmacotherapy versus pharmacotherapy alone for pain in participants with diabetic peripheral neuropathy (Serry 2015). This study reported significant differences pretreatment to post-treatment in exercise and TENS groups; however, they reported no between-group comparison or presented any pain intensity data. This, combined with issues around participant/personnel blinding, meant we were unable to draw conclusions regarding relative effectiveness of the investigated interventions.

Overall completeness and applicability of evidence

This review included studies investigating TENS treatment for pain across a range of neuropathic conditions and against a number of interventions. We searched multiple databases for both published and unpublished studies. As such, it may be viewed as offering a reasonably complete summation of the evidence in this area. However, there are a number of issues and caveats to consider which may impact on completeness and applicability of the evidence.

Thirteen of the 15 studies in this review applied TENS interventions only in the clinic. This typically consisted of discreet sessions at varying intervals per week for set periods of time applied by and under control of the researcher. This may be due to methodological considerations and most likely addresses attempts to standardise the intervention; however, this is unlikely to be reflective of the manner in which TENS is used by people in daily life. Evidence suggests considerable variability in terms of treatment fidelity (e.g. duration and intensity) when TENS is self-administered at home (Pallett 2014). Therefore, controlled prespecified frequency and duration of treatment may lead to discrepancies in estimate of effect (possible overestimation) compared to that found with self-administered TENS. Conversely, it is possible that this issue might lead studies in this review to underestimate treatment effects as it limits the amount of TENS use possible. It is considered that successful TENS use is often administered for a number of hours per day (Johnson 1991; Johnson 2011). Only one study in this review employed a systematically evaluated self-administration methodology (Buchmuller 2012), implying that the relatively infrequent and limited duration of clinic-administered TENS applications of the rest of the studies in this review might lead to underestimation of TENS effect.

The pooled analysis investigating TENS versus sham TENS rests on the presumption that sham TENS is an effective placebo. However, there are challenges to delivering credible sham treatments for TENS (see How the intervention might work). This further reduces the confidence with which the estimated effect of active TENS versus sham TENS may be viewed. There are devices specifically designed to be a credible TENS sham which switch on, appear ‘live’ and deliver a perceptible sensation for approximately
We did not downgrade the evidence on the GRADE criteria 'indirectness' or 'publication bias.' All included studies investigated either participants with neuropathic pain directly or were able to provide data for subsets of the group with neuropathic pain. The prevalence of small studies, as mentioned previously, increases the risk of publication bias, wherein there is a propensity for small negative studies to not reach full publication. There is evidence that this might lead to an exaggerated estimate of effect (Dechartres 2013; Moore 2012; Nüesch 2010). We did not downgrade any of the GRADE judgements on the basis of publication bias as we had no direct evidence of this, though all comparisons were downgraded for imprecision.

Overall across studies, we found deficiencies in terms of quality of methodology, reporting of methodology and presentation of adequate data to allow reasonable conclusions to be made. A number of studies did not report data on pain outcome measures, instead stating significant differences between groups with no data provided or statistical test results. Some studies did not report variance data for group means (VAS) and one study did not report group sample size. It was not always possible to check baseline characteristics of groups as pain intensity data (in some studies) were presented as change from baseline with no original baseline summary/variance data provided. Several studies did not report adequately on TENS treatment parameters.

Quality of the evidence

We rated the overall quality of the body of evidence as very low according to GRADE criteria. As a consequence, the conclusions drawn from pooled estimates and those taken from individual studies must be viewed with very limited confidence and the true effect is likely to be substantially different from the estimate of the effect. All studies were at unclear or high risk of bias across multiple domains. Within the 10 studies reported narratively, seven were assigned high risk across at least one of the key domains of selection bias: performance bias, detection bias, attrition bias or reporting bias (Gerson 1977; Ghoname 1999; Koca 2014; Nabi 2015; Prabakar 2011; Rutgers 1988; Serry 2015).

In the pooled analysis, we assigned all studies as high risk across at least one of the key domains of selection bias mentioned above. When considering the combined high risk ratings in these domains, the possible bias introduced by small study sizes and the subjective nature of the outcome measure it would suggest the effect sizes estimated here are at risk of being exaggerated, particularly given the subjective nature of the outcome measure (Dechartres 2013; Wood 2008; Savovic 2012). As a consequence, we downgraded the quality of the body of this evidence three times (twice for methodological limitations and once imprecision) from high to very low.
continuous scales can be seen as problematic in chronic pain studies since outcomes in pain studies demonstrate a bimodal distribution for some interventions (Moore 2013). More plainly, some participants demonstrated a substantial response to pain therapies while many demonstrated little or no response with few individual participants demonstrating a response similar to the average. This had led to the recommendation that chronic pain studies employ responder analysis based on predetermined cut-offs for a clinically important response (30% reduction in pain or greater for a moderate benefit, 50% reduction in pain or greater for a substantial benefit) (Dworkin 2008; Moore 2010). No studies identified in this review presented the results of responder analyses and so this type of meta-analysis was impossible. However, it is unclear if a bimodal distribution of outcome represents a bimodal distribution of treatment effect and we are not aware of any evidence to support the presence of bimodally distributed outcomes following TENS.

Agreements and disagreements with other studies or reviews

Due to the very low quality evidence, this Cochrane systematic review was unable to confidently state whether TENS is effective for pain relief compared to sham TENS in people with neuropathic pain. Two reviews investigating treatment modalities in people with neuropathic pain have been published. Cakici 2016 conducted a broad based review investigating all treatment options for people with peripheral diabetic neuropathy and included one study involving TENS and restricted outcomes to commentary in that it was deemed to have a ‘positive’ effect on symptoms. The second review investigated 22 common treatments for people with spinal cord injury (Harvey 2016). The two TENS comparison studies included in this review were also included in our review (Bi 2015; Celik 2013). In line with our finding, the review presented a meta-analysis in favour of TENS as well as similar commentary around quality of evidence.

AUTHORS’ CONCLUSIONS

Implications for practice

For people with neuropathic pain

This review presents very low quality evidence and cannot confidently state whether transcutaneous electrical nerve stimulation (TENS) is effective for pain relief compared to sham TENS in people with neuropathic pain. We have very limited confidence in this estimate of effect given the identified quality issues in the published evidence. People with neuropathic pain should bear in mind the low number of studies, the low quality of this evidence and the fact that the true effect is very likely to be different from that reported here when considering whether or not to use TENS for pain. We are unable to make any judgement on the effect of TENS on health related quality of life, global impression of change or medication use. Some studies reported minor skin irritation with TENS while others reported no adverse events. The majority did not report adverse events and we are, therefore, unable to make meaningful comment on TENS and associated adverse events.

For clinicians

This review is unable to state the effect of TENS versus sham TENS for pain relief due to the very low quality of the included evidence. The low number and small size of included studies and very low quality of the evidence means this result should be viewed with very limited confidence and the true effect is very likely different from that reported here. A small number of studies reported only minor adverse events (skin irritation). The majority of studies did not provide any detail on the safety profile of TENS; this should be explicitly addressed in future studies.

For policy makers and funders

This review neither refutes nor supports the use of TENS in management of neuropathic pain. The results reported here reflect short-term outcome assessment only, are derived from studies that have substantial methodological limitations and may not be reflective of how TENS is typically used by people with pain.

Implications for research

General

TENS is a portable, easily administered modality which is accessed and used by people with pain as required. It is recommended that future studies reflect this (i.e. TENS should be self-administered by the person and investigated in this manner). Blinding in physical interventions such as TENS is challenging. If sham TENS studies are used, at the least the sham TENS devices should be identical and appear ‘active’ in an effort to maintain the perception of treatment validity. Efforts should be made to preserve the naivety of the participant to the intervention and treatment providers/assessors should be blinded to group allocation. Studies in which participants self-administer the intervention would be very helpful in improving this aspect of future TENS research. Consideration may be given to further studies assessing optimal care versus optimal care plus active TENS as an acknowledgment that sham TENS methodologies may be inherently flawed.
Design
Improved quality in study design and reporting would significantly add to the confidence in our estimates of effectiveness. Future studies should consider the IMMPACT recommendations for the design of studies in chronic pain to ensure that outcomes, thresholds for clinical importance and study designs are optimal (Dworkin 2009; Dworkin 2009; Dworkin 2010; Turk 2008). Clear guidance on study design is provided by the CONSORT statement and subsequent checklist (Schulz 2010). Integral to this should be the requirement for clearly defined neuropathic pain participants with suitable diagnostic criteria required for inclusion. Interventions should be clearly described and we recommend active TENS treatments should be of sufficient intensity to be perceived as ‘strong’ with participants titrating intensity to maintain this perception throughout the duration of treatment (Johnson 2011; Moran 2011; Sluka 2013). A recurring feature across reporting of studies in this field was lack of published outcome data. We would strongly recommend all primary specified outcomes be reported in summary form for all comparison groups (mean/median and standard deviation/range/interquartile ranges) at baseline and all assessment times postrandomisation. This would greatly aid future assessment of effect via systematic review of studies.

Outcome measurement
With regard to pain intensity outcome assessment, this review highlights discrepancy in both the nature of the parameter assessed (mean weekly pain, current pain, etc.) and the timing of assessment. Given that TENS is suggested to have both rapid onset and offset of effect (Moran 2011), we would propose that assessment of effect on pain should ideally be assessed during TENS application at each prespecified assessment time with possibly at that time an additional weekly or 24 hour mean measure to assess longer term effects. Possible pain reducing effect of TENS may allow changes in function and self-efficacy which in turn may influence overall longer term perception of pain. It should be noted though that the relationship between efficacy of interventions on pain and disability in people with chronic pain is likely complex and not predictable (Saragiotto 2017). Valid measures of function/quality of life should also be key reportable outcome measures along with pain intensity in future TENS studies.

Acknowledgements
The protocol followed the agreed template for neuropathic pain, which was developed in collaboration with the Cochrane Musculoskeletal Group and Cochrane Neuromuscular Diseases Group. The editorial process was managed by the Cochrane Pain, Palliative and Supportive Care Review Group. The authors would like to thank the following people: Bita Mestgarpour, Jo-Aine Hang and Andrea Wand for generous help with translation; Mark Rockett, Peter Cole and Juliana Ester Martin Lopez for peer review; Joanne Abbott for expertise and help with devising and running literature searches; and Anna Erskine for her patience and ongoing editorial assistance. Many thanks to Andrea Buchmuller and team for kindly supplying additional data on their study.

Cochrane Review Group funding acknowledgement: this project was supported by the National Institute for Health Research (NIHR), via Cochrane Infrastructure funding to the Cochrane Pain, Palliative and Supportive Care Review Group (PaPaS). The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the Systematic Reviews Programme, NIHR, National Health Service or the Department of Health.

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Rutgers 1988 [published data only]

Serry 2015 [published data only]

Tilak 2016 [published data only]

Vitalii 2014 [published data only]

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Bloodworth 2004 [published data only]

Bourke 1994 [published data only]

Casale 1985 [published data only]

Cheing 2005 [published data only]

Chitsaz 2009 [published data only]

Connolly 2013 [published data only]

Finsen 1988 [published data only]

Forst 2004 [published data only]
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Franca 2013 [published data only]

Gosseau 2011 [published data only]

Heidenreich 1988 [published data only]

Ing 2015 [published data only]

Katz 1991 [published data only]

Kumar 1997 [published data only]

Kumar 1998 [published data only]

Lehmkuhl 1978 [published data only]

Marques 2014 [published data only]

Mysliwiec 2012 [published data only]

Norrbrink 2009 [published data only]

Oosterhof 2008 [published data only]

Pourmomeny 2009 [published data only]

Reichstein 2005 [published data only]

Sherry 2001 [published data only]

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Samier A. Neuropathic pain and transcutaneous electrical nerve stimulation (TENS) (effectiveness of TENS for 101 patients with chronic pain after 12 months follow up) [Douleurs neuropathiques et neurostimulation transcutanée (devenir et efficacité de la neurostimulation transcutanée à 1 an sur un échantillon de 101 patients douloureux chroniques consécutifs au sein des structures de prise en charge de la douleur chronique en Aquitaine)]. Thesis, University of Bordeaux 2006.

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Brown 2007

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**Furlan 2009**

**Gebhart 2004**

**Guyatt 2008**

**Guyatt 2011**

**Harvey 2016**

**Higgins 2011**

**Jensen 2011**

**Johnson 1991**

**Johnson 2010**

**Johnson 2011**

**Johnson 2015**

**Johnson 2016**

**Kalra 2001**

**Kennedy 2014**

**Khadilkar 2008**

**Leadley 2012**

**Leadley 2014**
Transcutaneous electrical nerve stimulation (TENS) for neuropathic pain in adults (Review)

Leonard 2010

Leonard 2011

Levinson 2012

Liberati 2009

Maeda 2007

Maier 2010

Matsuo 2014

McDermott 2006

Melzack 1965

Moore 2008

Moore 2010

Moore 2012

Moore 2013

Moore 2014

Moran 2011

Nüesch 2010

O’Connor 2009

Pallett 2014

Rakel 2010

RevMan 2014 [Computer program]

Sabino 2008

Santos 2013
### Characteristics of included studies [ordered by study ID]

**Barbarisi 2010**

<table>
<thead>
<tr>
<th>Methods</th>
<th>RCT, parallel design.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Participants</strong></td>
<td>30 participants with postherpetic neuralgia, divided into 2 groups initially TENS (n = 16) and sham (n = 14). Each group further subdivided by concurrent dose of pregabalin. TENS group (pregabalin 300 mg, n = 9; pregabalin 600 mg, n = 7). Sham group (pregabalin 300 mg, n = 8; pregabalin 600 mg, n = 6). Baseline participant characteristics presented by gender not group Age (mean ± SD): men 65 ± 8.6 years; women 64 ± 8.2 years. Pain duration: men 15.6 ± 8.8 months; women: 14.9 ± 8.6 months. Formal neuropathic pain assessment: no. Sites of pain: left hemithorax: men 9, women 10; right hemithorax: men 3, women 4; leg: men 4, women 2; arm/forearm: men 4, women 4 Concomitant treatment: all participants received pregabalin (300 mg or 600 mg) over initial 8 days’ treatment until a pain intensity VAS of ≤ 60 mm was achieved. Following this, participants were randomised to TENS or sham. TENS/sham treatment continued for 4 weeks following randomisation. All participants continued with pregabalin treatment during the TENS/sham phase</td>
</tr>
<tr>
<td><strong>Interventions</strong></td>
<td><strong>TENS group:</strong> TENS 100 Hz (inconsistent description in text, later described as 50 Hz), 125 µs Intensity: “Clear non-painful paraesthesia.” <strong>Sham TENS group:</strong> as per active TENS but no current passed through electrodes Sham credibility assessment: no. Location: electrodes placed around site of pain. Frequency of treatment: daily for 4 weeks. Duration: 30 minutes per session. Clinic administered.</td>
</tr>
<tr>
<td><strong>Outcomes</strong></td>
<td>Daily pain intensity. 0-10 cm VAS. Outcomes measured daily pretreatment and post-treatment. VAS comparisons presented between baseline (day of randomisation to VAS group), week 3 and final VAS (post-treatment completion - week 4) Did not report adverse events.</td>
</tr>
<tr>
<td><strong>Notes</strong></td>
<td>There may be mistakes in text of the article. VAS comparisons presented at ‘week 3’ and ‘final’ (week 4). It may be ‘week 3’ comparison is in fact ‘week 4’. No conflict of interest stated</td>
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**Risk of bias**

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors’ judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
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Transcutaneous electrical nerve stimulation (TENS) for neuropathic pain in adults (Review)  
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### Barbarisi 2010

<table>
<thead>
<tr>
<th>Bias Type</th>
<th>Risk</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Low risk</td>
<td>Computer generated randomisation.</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Unclear risk</td>
<td>Allocation concealment not reported.</td>
</tr>
<tr>
<td>Blinding of participants and personnel (performance bias)</td>
<td>High risk</td>
<td>Unclear risk for blinding of participants (TENS vs sham, attempted to manage participant expectations of sensation but no detail on whether TENS device appeared 'live' or not). Personnel high risk as the same care provider applied both active and sham treatments</td>
</tr>
<tr>
<td>Blinding of outcome assessment (detection bias)</td>
<td>Unclear risk</td>
<td>TENS vs active sham but see comments above for blinding of participants</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias)</td>
<td>Low risk</td>
<td>No participant dropout after TENS group randomisation. No details regarding dropout during drug titration phase</td>
</tr>
<tr>
<td>Incomplete outcome data (participant exclusion from analysis)</td>
<td>Low risk</td>
<td>No obvious exclusions and dropouts data described.</td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>Unclear risk</td>
<td>Inconsistencies in data presentation. VAS pain data presented in text for week 3 post-randomisation while data in tables presented for final (week 4) VAS</td>
</tr>
<tr>
<td>Other bias</td>
<td>Unclear risk</td>
<td>Baseline characteristics presented by gender not group characteristics</td>
</tr>
<tr>
<td>Size of study</td>
<td>High risk</td>
<td>TENS group: n = 16; sham TENS group: n = 14.</td>
</tr>
</tbody>
</table>

### Bi 2015

<table>
<thead>
<tr>
<th>Methods</th>
<th>RCT, parallel design.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Participants</strong></td>
<td>52 participants with spinal cord injury. 4 dropouts, 2 per group. TENS: 17 men, 7 women; sham TENS 15 men, 9 women. Age (mean ± SD): TENS 35 ± 9 years; sham TENS 33.6 ± 8.5 years. Time since spinal cord injury (mean ± SD): TENS 7 ± 4.1 months; sham TENS 6.8 ± 3.1 months. Formal neuropathic pain assessment: no. Sites of pain: mixed. Concomitant treatment: no details supplied.</td>
</tr>
<tr>
<td><strong>Interventions</strong></td>
<td><strong>TENS group:</strong> TENS 2 Hz, 200 ms. Intensity: 50 mA. No description of perceived sensation. <strong>Sham TENS group:</strong> as per active TENS but no current passed through electrodes Sham credibility assessment: no.</td>
</tr>
<tr>
<td>Location: electrodes placed on region with pain. Frequency of treatment: 3 times per week for 12 weeks. Duration: 20 minutes per session. Clinic administered.</td>
<td></td>
</tr>
</tbody>
</table>

| Outcomes | Current pain intensity. 0-10 cm VAS. Outcomes measured at baseline (pretreatment) and immediately post-treatment at 12 weeks Study did not report adverse events. |

| Notes | No conflict of interest stated. |

| **Risk of bias** |
|---|---|---|
| **Bias** | **Authors’ judgement** | **Support for judgement** |
| Random sequence generation (selection bias) | Low risk | Computer generated random number sequence. |
| Allocation concealment (selection bias) | Unclear risk | Allocation concealment not reported. |
| Blinding of participants and personnel (performance bias) All outcomes | High risk | Unclear risk for blinding of participants (sham control but no attempt to manage participant expectations of sensation and no detail on whether TENS device appeared 'live' or not). Personnel high risk as the same care provider applied both active and sham treatments |
| Blinding of outcome assessment (detection bias) All outcomes | Unclear risk | TENS vs active sham but see comments above for blinding of participants |
| Incomplete outcome data (attrition bias) All outcomes | Low risk | Approximately 4% dropout balanced between groups. |
| Incomplete outcome data (participant exclusion from analysis) | Low risk | No obvious exclusions and dropout data adequately described. |
| Selective reporting (reporting bias) | Low risk | All outcomes adequately reported |
| Other bias | Low risk | Baseline characteristics comparable, outcome assessment times equal |
| Size of study | High risk | n = 24 per group. |
## Buchmuller 2012

### Methods

RCT, parallel design.

### Participants

| 236 participants divided into TENS group: 45 men, 72 women, sham TENS group: 43 men, 76 women, Neuropathic (radicular pain) subgroup n = 139. Of this neuropathic group, VAS pain intensity data provided by authors for radicular pain at baseline and post-treatment for 122 participants (TENS group n = 64, sham TENS group n = 58). At 3 months, 38% dropout with TENS group n = 43, sham TENS group n = 32 |

### Interventions

| TENS group: TENS mixed, 80-100 alternated with 2 Hz, 200 ms. Intensity: alternating low intensity paraesthesia with high intensity perceived sensation including muscle twitches |
| Sham TENS group: as per active TENS but no current passed through electrodes |

### Outcomes

| Primary outcome: RDQ. Secondary outcomes: pain and quality of life (SF-36). Neuropathic subgroup outcomes reported as Pain reduction (3 months) and RDQ (6 weeks). No separate SF-36 reported for neuropathic subgroup |

### Notes

Funding sources acknowledged and no conflict noted. Authors contacted with request for detailed data on pain intensity outcome measures for neuropathic subgroup and kindly provided these data

### Risk of bias

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors' judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Low risk</td>
<td>Computer generated stratified randomisation.</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Low risk</td>
<td>Central allocation.</td>
</tr>
</tbody>
</table>
### Buchmuller 2012 (Continued)

<table>
<thead>
<tr>
<th>Statement</th>
<th>Risk</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blinding of participants and personnel (performance bias) All outcomes</td>
<td>Low</td>
<td>Participants blind (TENS vs sham, attempts made to manage participant expectations of sensation and the TENS device appeared 'live') and treatment self-administered</td>
</tr>
<tr>
<td>Blinding of outcome assessment (detection bias) All outcomes</td>
<td>Low</td>
<td>Participants blinded, sham vs active TENS.</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias) All outcomes</td>
<td>High</td>
<td>At 3 months, 47 participants were missing from the original baseline data for participants with radicular pain. This represents a 38.5% dropout</td>
</tr>
<tr>
<td>Incomplete outcome data (participant exclusion from analysis)</td>
<td>Unclear</td>
<td>No detail provided with respect to missing data and participant exclusion from analysis</td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>Unclear</td>
<td>Low risk for total study. Unable to assess for neuropathic subgroup and lack of SF-36 data for neuropathic subgroup</td>
</tr>
<tr>
<td>Other bias</td>
<td>Low</td>
<td>Baseline characteristics for total study well described.</td>
</tr>
<tr>
<td>Size of study</td>
<td>Unclear</td>
<td>Neuropathic subgroup: TENS group: n = 71; sham TENS group: n = 68</td>
</tr>
</tbody>
</table>

### Casale 2013

<table>
<thead>
<tr>
<th>Methods</th>
<th>RCT, parallel design.</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Interventions</th>
<th>TENS group: TENS 100 Hz, 80 ms. Intensity: &quot;below muscle contraction,&quot; no details on perceived sensation Location: electrodes placed on carpal ligament and course of median nerve Frequency of treatment: daily for 3 weeks, 15 sessions in total Duration: 30 minutes per session. Clinic administered. Laser group: 250 J/cm² 25 W, Probe size 1 cm². Location: 10 cm length along course of median nerve in wrist area. Frequency of treatment: daily for 3 weeks, 15 sessions in total Duration: 100 seconds per session. Clinic administered.</th>
</tr>
</thead>
</table>

Transcutaneous electrical nerve stimulation (TENS) for neuropathic pain in adults (Review)  
Copyright © 2017 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.
Casale 2013  (Continued)

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Pain intensity: no further detail. 0-10 cm VAS. Outcomes measured at baseline (pretreatment) and post-treatment at 3 weeks. Study did not report adverse events.</th>
</tr>
</thead>
</table>

| Notes | No conflict of interest stated. |

**Risk of bias**

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors' judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Low risk</td>
<td>Computer aided sequence generation.</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Unclear risk</td>
<td>No details supplied.</td>
</tr>
<tr>
<td>Blinding of participants and personnel (performance bias)</td>
<td>Unclear risk</td>
<td>Both groups received an 'active' treatment.</td>
</tr>
<tr>
<td>Blinding of outcome assessment (detection bias)</td>
<td>Unclear risk</td>
<td>Participants received active treatment in both groups.</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias)</td>
<td>Low risk</td>
<td>No dropouts reported.</td>
</tr>
<tr>
<td>Incomplete outcome data (participant exclusion from analysis)</td>
<td>Low risk</td>
<td>No obvious exclusions from analysis.</td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>Low risk</td>
<td>All stated outcomes reported.</td>
</tr>
<tr>
<td>Other bias</td>
<td>Low risk</td>
<td>Baseline characteristics between groups adequately tested and described</td>
</tr>
<tr>
<td>Size of study</td>
<td>High risk</td>
<td>n = 10 per group.</td>
</tr>
</tbody>
</table>

Celik 2013

<table>
<thead>
<tr>
<th>Methods</th>
<th>RCT, parallel design.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants</td>
<td>33 participants with spinal cord injury. No participant dropout reported. TENS 4 men, 13 women; sham TENS 11 men, 5 women. Age (mean ± SD): TENS group: 38.18 ± 9.86 years; sham TENS group: 34.81 ± 10.91 years. Mean duration of pain (range): 19.1 (1-170) months for whole sample. No further data supplied. Formal neuropathic pain assessment: LANSS &gt; 12.</td>
</tr>
</tbody>
</table>
### Interventions

**TENS group:** TENS 4 Hz, 200 µs. Intensity: 50 mA. No description of perceived sensation.  
**Sham TENS group:** as per active TENS but no current passed through electrodes  
Sham credibility assessment: no.  
Location: electrodes placed around region with pain.  
Frequency of treatment: 1 application per day for 10 days.  
Duration: 30 minutes per session.

Clinic administered.

### Outcomes

Pain intensity mean of morning, noon, evening and night VAS scores 0-10 cm VAS.  
Outcomes measured at baseline (pretreatment) on day 1 and 1 day following treatment cessation (day 12)  
Study reported adverse events and none occurred.

### Notes

Baseline testing between group for difference in pain location, duration were reported as not being significantly different but no data provided. No description of baseline comparison for LANSS score. No conflict of interest stated.

### Risk of bias

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors’ judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>High risk</td>
<td>Alternate participant group allocation.</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>High risk</td>
<td>Alternate participant group allocation.</td>
</tr>
<tr>
<td>Blinding of participants and personnel (performance bias) All outcomes</td>
<td>High risk</td>
<td>Low risk for blinding of participants (sham controlled study and no sensation reported from either active or sham device given participants had spinal cord injury). Personnel high risk as the same care provider applied both active and sham treatments</td>
</tr>
<tr>
<td>Blinding of outcome assessment (detection bias) All outcomes</td>
<td>Low risk</td>
<td>Participants blinded, sham vs active TENS.</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias) All outcomes</td>
<td>Low risk</td>
<td>No dropout of participants.</td>
</tr>
<tr>
<td>Incomplete outcome data (participant exclusion from analysis)</td>
<td>Low risk</td>
<td>No obvious exclusion from analysis.</td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>Low risk</td>
<td>All outcomes adequately reported.</td>
</tr>
</tbody>
</table>
**Gerson 1977**

<table>
<thead>
<tr>
<th>Methods</th>
<th>Randomised parallel design.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants</td>
<td>29 participants with postherpetic neuralgia. TENS group ( n = 16 ), drugs group ( n = 13 ). No detail on gender across groups. ( n = 10 ) dropouts in TENS group and ( n = 7 ) dropout in drugs group. No baseline characteristics supplied for either group. Formal neuropathic pain assessment: no. Sites of pain: no details. Concomitant treatment: no details.</td>
</tr>
<tr>
<td>Interventions</td>
<td><strong>TENS group:</strong> no detail supplied for TENS application parameters or participant perceived intensity. Location: 'Electrodes placed over the surface of the affected dermatome.' Frequency of treatment: 1 TENS treatment session per week for 4 weeks then 1 treatment applied every second week for 3 weeks. Duration: 15 minutes per session. Clinic administered. <strong>Drug group:</strong> carbamazepine plus clomipramine. No further detail supplied on dosage. Duration of treatment: 8 weeks.</td>
</tr>
<tr>
<td>Outcomes</td>
<td>Pain intensity at each visit. 0-10 cm VAS. No detail whether mean, current or maximal pain recorded at each visit. Outcomes measured at baseline (pretreatment) day 0 then at weeks 2, 4, 6 and 8. Study did not report adverse events.</td>
</tr>
<tr>
<td>Notes</td>
<td>Inconsistencies in text with respect to treatment protocol and duration. Data analysed on per protocol basis. No conflict of interest stated.</td>
</tr>
</tbody>
</table>

**Risk of bias**

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors’ judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Unclear risk</td>
<td>No detail supplied.</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Unclear risk</td>
<td>No detail supplied.</td>
</tr>
<tr>
<td>Blinding of participants and personnel (performance bias) All outcomes</td>
<td>High risk</td>
<td>Given discrepancy in treatment types and application.</td>
</tr>
</tbody>
</table>
Gerson 1977 (Continued)

<table>
<thead>
<tr>
<th>Bias</th>
<th>Risk</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blinding of outcome assessment (detection bias)</td>
<td>High</td>
<td>As above.</td>
</tr>
<tr>
<td>All outcomes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias)</td>
<td>High</td>
<td>Approximately 60% dropout.</td>
</tr>
<tr>
<td>All outcomes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incomplete outcome data (participant exclusion from analysis)</td>
<td>High</td>
<td>Per protocol analysis.</td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>High</td>
<td>No variance in reported TENS data. Follow-up data un-interpretable</td>
</tr>
<tr>
<td>Other bias</td>
<td>High</td>
<td>No baseline characteristics described.</td>
</tr>
<tr>
<td>Size of study</td>
<td>High</td>
<td>TENS group: n = 16; drug group: n = 13.</td>
</tr>
</tbody>
</table>

Ghoname 1999

Methods

3 phase cross-over study.

Participants

64 participants with lumbar radicular pain. 34 women and 30 men. No dropouts reported over entire study. Participants randomised to 3 treatment sequences 1: sham, PENS, TENS; 2: PENS, TENS, sham; and 3: TENS, sham, PENS

Age (mean ± SD): 43 ± 19 years (of the whole sample).

Duration of pain (mean ± SD): 21 ± 9 months.

Formal neuropathic pain assessment: pain radiating below knee, positive straight leg raise testing. Radiological evidence of L5-S1 nerve root compression


Concomitant treatment: non-opioid analgesia.

Interventions

Treatment sequence 1: sham, PENS, TENS.

Treatment sequence 2: PENS, TENS, sham.

Treatment sequence 3: TENS, sham, PENS.

TENS treatment: TENS 4 Hz, 100 ms.

Intensity: maximum tolerated amplitude without producing muscle contraction

Location: 4 electrodes placed on posterior lower limb.

PENS treatment: 4 Hz, 100 ms.

Intensity: highest tolerable sensation without muscle contraction

Location: 10 × 32G acupuncture needles inserted into posterior lower limb

Sham PENS treatment: as per active PENS but no current passed through electrodes

Sham credibility assessment: no.

Frequency of treatment: 3 applications per week for 3 weeks. 1 week washout between treatment modalities

Duration: 30 minutes per session.

Clinic administered.
**Outcomes**

Pain intensity recorded at each visit and 24 hours after last treatment of each modality. Score reflected pain intensity during previous 24 hours. SF-36 completed at baseline and 24 hours after last treatment session of each modality. NSAID use reported as change within modality.

0-10 cm VAS for pain.

Study did not report adverse events.

**Notes**

SF-36 and NSAID use appears to have been taken at initial baseline and then 24 hours following each treatment modality completion. No apparent testing for carry-over effects on outcomes. Similar sham PENS was an invasive procedure compared to TENS. No conflict of interest stated.

**Risk of bias**

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors’ judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Unclear risk</td>
<td>No details supplied.</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Low risk</td>
<td>Cross-over design.</td>
</tr>
<tr>
<td>Blinding of participants and personnel (performance bias)</td>
<td>High risk</td>
<td>Invasive vs non-invasive treatment modalities.</td>
</tr>
<tr>
<td>All outcomes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blinding of outcome assessment (detection bias)</td>
<td>High risk</td>
<td>Invasive vs non-invasive treatment modalities.</td>
</tr>
<tr>
<td>All outcomes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias)</td>
<td>Unclear risk</td>
<td>Missing data or dropouts not reported over the multiple treatment contacts</td>
</tr>
<tr>
<td>All outcomes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incomplete outcome data (participant exclusion from analysis)</td>
<td>Low risk</td>
<td>Not applicable.</td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>High risk</td>
<td>SF-36 data not adequately reported or tested.</td>
</tr>
<tr>
<td>Other bias</td>
<td>Unclear risk</td>
<td>No formal assessment of carry-over effects but data appeared very similar at baseline</td>
</tr>
<tr>
<td>Size of study</td>
<td>Unclear risk</td>
<td>n = 64.</td>
</tr>
</tbody>
</table>
**Methods**

RCT, parallel.

**Participants**

75 participants with carpal tunnel syndrome equally to 3 treatment groups. 12 people dropped out during/follow-up approximately evenly across groups. Splint group, 15 women, 7 men; TENS group 13 women, 7 men; IFT group 15 women, 6 men

Age (mean ± SD): splint group: 35.4 ± 4.2; TENS group: 34.2 ± 5.2; IFT group: 34.9 ± 4.8 years

Mean duration of pain: splint group: 12.4 ± 6.2; TENS group: 13.5.2 ± 6.6; IFT group: 13.0 ± 6.0 months

Formal neuropathic pain assessment: positive nerve conduction studies

Sites of pain: hand.

Concomitant treatment: paracetamol as required daily.

**Interventions**

**Splint group:** wrist-hand resting splint at night for 3 weeks.

**TENS group:** TENS 100 Hz, 80 ms.

Intensity: no description of perceived sensation.

**IFT group:** 4000 Hz with base 20 Hz.

Intensity: no description of perceived sensation.

Location: electrodes for both modalities placed around palmar aspect of hand/wrist/thenar area

Frequency of treatment: 5 times per week for 3 weeks.

Duration: 20 minutes per session.

Clinic administered.

**Outcomes**

Pain intensity: mean levels of pain in previous week.

0-10 cm VAS.

Outcomes measured at baseline and 3 weeks after completion of treatment (6 weeks after randomisation)

2 participants in TENS group reported mild tenderness at application site

**Notes**

No conflicts of interest stated.

**Risk of bias**

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors' judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>High risk</td>
<td>Sequential admission into study.</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>High risk</td>
<td>Sequential allocation.</td>
</tr>
<tr>
<td>Blinding of participants and personnel (performance bias)</td>
<td>High risk</td>
<td>Participant blinding was unclear if comparing TENS to IFT but high when comparing TENS to splint therapy. Personnel high risk as the same care provider applied both TENS and IFT treatments</td>
</tr>
<tr>
<td>All outcomes</td>
<td>High risk</td>
<td></td>
</tr>
<tr>
<td>Blinding of outcome assessment (detection bias)</td>
<td>High risk</td>
<td>Participant blinding was unclear if comparing TENS to IFT but high when comparing TENS to splint therapy. Personnel high risk as the same care provider applied both TENS and IFT treatments</td>
</tr>
<tr>
<td>All outcomes</td>
<td>High risk</td>
<td></td>
</tr>
</tbody>
</table>
### Koca 2014 (Continued)

<table>
<thead>
<tr>
<th>treatments</th>
<th>High risk</th>
<th>Participants lost to follow-up specifically excluded.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incomplete outcome data (attrition bias)</td>
<td>High risk</td>
<td>Participants excluded if they failed to take part in the treatment regimen</td>
</tr>
<tr>
<td>All outcomes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incomplete outcome data (participant exclusion from analysis)</td>
<td>High risk</td>
<td>Stated outcomes adequately reported.</td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>Low risk</td>
<td>Baseline characteristics tested and reported.</td>
</tr>
<tr>
<td>Other bias</td>
<td>Unclear risk</td>
<td></td>
</tr>
<tr>
<td>Size of study</td>
<td>High risk</td>
<td>n = 75 randomised across 3 treatment groups.</td>
</tr>
</tbody>
</table>

### Nabi 2015

**Methods**
- RCT, parallel.

**Participants**
- 65 participants with diabetic neuropathy to 2 treatment groups, TENS and PRF sympathectomy. Overall, 10 participants (15%) described as having dropped out, however, sample sizes for both groups were stated as n = 30 (29 women, 31 men). Unable to accurately state gender composition of each group.
- Age (mean ± SD): TENS group: 56.63 ± 5.86 years; PRF sympathectomy group: 56.76 ± 6.94 years.
- Mean duration of diabetes: TENS group: 12.56 ± 2.96; PRF sympathectomy group: 13.32 ± 3.91.
- Formal neuropathic pain assessment: no - diagnosed by neurologist.
- Sites of pain: lower limb.
- Concomitant treatment: pregabalin 300-600 mg.

**Interventions**
- **TENS group:** TENS 80 Hz, appears to be 200 µs.
  - Intensity: ‘two to three times sensory threshold.”
  - Location: electrodes placed around shin and ankle.
  - Frequency of treatment: 10 treatment sessions delivered on alternate days.
  - Duration: 20 minutes per session.
  - Clinic administered.
- **PRF sympathectomy group:** PRF sympathectomy delivered as one-off invasive intervention.

**Outcomes**
- Pain intensity: mean levels of pain in previous week.
  - 0-10 cm NRS.
  - Outcomes measured at baseline, 1 week, 1 month and 3 months following cessation of treatment (either one-off PRF sympathectomy or 10 sessions of TENS on alternate days). Hence outcomes between groups were measured at differing time points postrandomisation
  - “Skin irritation reported in a few TENS group subjects.”

**Notes**
- Supported by university funding.
### Nabi 2015  
(Continued)

#### Risk of bias

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors’ judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Unclear risk</td>
<td>Block randomisation.</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Unclear risk</td>
<td>No detail supplied.</td>
</tr>
<tr>
<td>Blinding of participants and personnel (performance bias)</td>
<td>High risk</td>
<td>Clearly different treatments and 1 invasive.</td>
</tr>
<tr>
<td>Blinding of outcome assessment (detection bias)</td>
<td>High risk</td>
<td>Impossible to blind given the protocol.</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias)</td>
<td>Unclear risk</td>
<td>Discrepancies in dropout and indicated analysis.</td>
</tr>
<tr>
<td>Incomplete outcome data (participant exclusion from analysis)</td>
<td>Unclear risk</td>
<td>Analysis not fully described and inconsistencies in dropout description</td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>Low risk</td>
<td>All outcomes reported.</td>
</tr>
<tr>
<td>Other bias</td>
<td>Unclear risk</td>
<td>Differences in time postrandomisation outcome measurement between groups</td>
</tr>
<tr>
<td>Size of study</td>
<td>High risk</td>
<td>Reported as TENS group: n = 30; PRF sympathectomy group: n = 30</td>
</tr>
</tbody>
</table>

#### Prabhakar 2011

<table>
<thead>
<tr>
<th>Methods</th>
<th>RCT, parallel design.</th>
</tr>
</thead>
</table>
| Participants                                                          | 75 participants with cervical radicular pain. No participant dropout reported. Randomised into 3 groups: joint mobilisation, TENS and isometric exercises. No details supplied on individual group size or gender composition. Whole sample 48% women, 52% men. Between-group baseline tests for age, body mass and pain duration reported as 'homogenous;' no formal statistical testing.  
Age (mean ± SD): Group A: 36.33 ± 9.4 years; Group B: 37.25 ± 9 years; Group C: 39.33 ± 8.6 years  
Mean duration of pain: no data supplied.  
Formal neuropathic pain assessment: no.  
Sites of pain: cervical spine and unilateral upper limb pain  
Concomitant treatment: heat packs applied to the cervical spine area |
**Interventions**

**Joint mobilisation group:** cervical spine lateral flexion joint mobilisation, 10 sessions on alternate days over 3 weeks  
**TENS group:** TENS 100 Hz, 50 µs. Intensity: no detail supplied, 10 sessions on alternate days over 3 weeks, 30 minute per session. Electrodes placed at cervical spinal segment and distal dermatomal area  
**Exercise group:** isometric neck exercises: isometric flexion, lateral flexion, rotation and extension. 6-8 seconds per contraction. 5 repetitions for each muscle group. No details on intensity of contraction. 10 sessions on alternate days over 3 weeks  
All treatments administered/supervised in clinic.

**Outcomes**

Pain intensity. No details on pain intensity instructions with respect to current pain, mean pain, etc  
0-10 cm VAS.  
Outcomes measured at baseline (pretreatment) week 3 and week 6 (3 weeks post-treatment finished)  
Study did not report adverse events.

**Notes**

Week 3 VAS results were reported as reduction from baseline. Unable to extract baseline data. Week 6 data not reported in text. No conflict of interest stated

**Risk of bias**

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors' judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Unclear risk</td>
<td>No details supplied.</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Unclear risk</td>
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</tr>
<tr>
<td>Blinding of participants and personnel (performance bias) All outcomes</td>
<td>Unclear risk</td>
<td>2 active non-invasive treatments.</td>
</tr>
<tr>
<td>Blinding of outcome assessment (detection bias) All outcomes</td>
<td>Unclear risk</td>
<td>As above in terms of active treatments.</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias) All outcomes</td>
<td>Unclear risk</td>
<td>No details supplied.</td>
</tr>
<tr>
<td>Incomplete outcome data (participant exclusion from analysis)</td>
<td>Unclear risk</td>
<td>No details supplied.</td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>High risk</td>
<td>Key baseline data and week 6 data not supplied.</td>
</tr>
<tr>
<td>Other bias</td>
<td>High risk</td>
<td>Baseline group characteristic testing not described. Age and pain duration at baseline described as homogenous</td>
</tr>
</tbody>
</table>
Rutgers 1988

<table>
<thead>
<tr>
<th>Methods</th>
<th>Randomised parallel design.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants</td>
<td>26 participants with postherpetic neuralgia to 2 treatment groups: TENS group (n = 13) and ACU group (n = 10). At 6 months, 13 dropouts in TENS group and 9 dropouts in ACU group. Total sample = 13 women, 10 men. Age (median (range)): 73 (57-85) years. Mean pain duration: 3 months to &gt; 9 years. Formal neuropathic pain assessment: no. Sites of pain: mixed. Concomitant treatment: no details supplied.</td>
</tr>
<tr>
<td>Interventions</td>
<td>TENS group: TENS 100 Hz, 200 µs. Intensity: amplitude increased until ‘a fairly strong sensation’ was perceived. Location: electrodes placed either side of painful area. Frequency of treatment: 3 clinic administered 30 minute treatments in first week. Then TENS unit loaned for home use for 5 weeks. No information regarding frequency of use given for this period. ACU group: 2 treatment session per week for 6 weeks. Body and auricular stimulation. Steel needles stimulated with current at 5-60 Hz. Duration: no details supplied. Clinic administered.</td>
</tr>
<tr>
<td>Outcomes</td>
<td>Pain intensity, visual stepwise scale, 10 steps. Measured at intake, 6 weeks, 9 weeks and 6 months. No details supplied as to parameters of pain rating (current pain, mean pain, etc.) Study did not report adverse events.</td>
</tr>
<tr>
<td>Notes</td>
<td>No formal statistical tests employed. At 9 weeks, study had 7 participants left in study (73% dropout). Private funding body acknowledged</td>
</tr>
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</table>

Risk of bias

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors’ judgement</th>
<th>Support for judgement</th>
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<td>No details supplied.</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Unclear risk</td>
<td>No details supplied.</td>
</tr>
<tr>
<td>Blinding of participants and personnel (performance bias)</td>
<td>High risk</td>
<td>TENS vs invasive treatment.</td>
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</table>
### Rutgers 1988  (Continued)

<table>
<thead>
<tr>
<th>Bias Type</th>
<th>Risk Level</th>
<th>Description</th>
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<tbody>
<tr>
<td>Blinding of outcome assessment (detection bias)</td>
<td>High risk</td>
<td>Impossible due to treatments being compared.</td>
</tr>
<tr>
<td>All outcomes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias)</td>
<td>High risk</td>
<td>&gt; 70% dropout at 9 weeks.</td>
</tr>
<tr>
<td>All outcomes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incomplete outcome data (participant exclusion from analysis)</td>
<td>High risk</td>
<td>No final statistical tests performed but appears a per protocol approach.</td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>High risk</td>
<td>No data supplied for outcomes.</td>
</tr>
<tr>
<td>Other bias</td>
<td>Unclear risk</td>
<td>No baseline data supplied.</td>
</tr>
<tr>
<td>Size of study</td>
<td>High risk</td>
<td>TENS group: n = 10; ACU group: n = 13.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Serry 2015

**Methods**

- Randomised parallel design.

**Participants**

- 60 participants with chronic DPN were randomised to 3 treatment groups: TENS group n = 20, exercise group n = 20, pharmacological group n = 20. In the total sample, there were 32 women and 28 men.
- Age (mean ± SD): TENS group: 51.6 ± 4.75 years; exercise group: 51.7 ± 4.44 years; pharmacological group: 51.95 ± 4.38.
- Mean duration of DPN: TENS group: 12.05 ± 3.17; exercise group: 12.15 ± 0.38; pharmacological: 12.3 ± 3.38 (unit of measurement not stated).
- Sites of pain: lower limb.
- Concomitant treatment: all groups continued with “regular pharmacological therapy.” There was no description of this for TENS and exercise group in either drugs or dosage. However, the pharmacological group (regular therapy) was described as consisting of “nerve growth stimulant; vitamin B complex and oral hypoglycaemic drugs or insulin.” No further details or comparisons made between groups in this area.

**Interventions**

- **TENS group:** TENS 15 Hz, 250 µs.
  - Intensity: increased until “strong rhythmic muscle contractions” observed.
  - Location: 2 electrodes placed bilaterally on lower aspect of medial tibial condyle and superior to medial malleolus.
  - Frequency of treatment: 3 days per week for 8 weeks.
  - Duration: 30 minutes per session.
  - TENS treatment clinic administered.

- **Exercise group:** aerobic exercise on stationary bicycle.
  - Intensity: following warm-up, participants exercised at 50-70% of maximal heart rate.
  - Frequency of treatment: 3 days per week for 8 weeks.
  - Duration: 50 minutes per session (5 minutes’ warm-up, 40 minutes’ exercise, 5 minutes’ cool down).

- **Pharmacological group:** “regular therapy.” No further information supplied.
Outcomes

Pain intensity recorded pretreatment and post-treatment on a 0-10 VAS. No detail supplied with respect to parameter measured with VAS (e.g. mean pain, minimal pain, maximal pain, etc.). Nerve conduction studies of medial plantar sensory nerve performed pretreatment and post-treatment
Study did not report adverse events.

Notes

Data not supplied for concomitant drug treatment. No data supplied for baseline or post-treatment pain intensity scores. Paper stated Kruskal-Wallis testing was used to assess between-group differences in pain intensity scores post-treatment; however, this analysis was not reported. All significant pain intensity findings are based on within-group analysis and no detail on output of these tests supplied. Pain intensity only presented in descriptive form; percentage change from baseline. Have contacted authors regarding pain intensity data
No conflict of interest reported.

Risk of bias

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors' judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Unclear risk</td>
<td>No information supplied.</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Unclear risk</td>
<td>No information supplied.</td>
</tr>
<tr>
<td>Blinding of participants and personnel (performance bias) All outcomes</td>
<td>Unclear risk</td>
<td>Both interventions were active treatments.</td>
</tr>
<tr>
<td>Blinding of outcome assessment (detection bias) All outcomes</td>
<td>Unclear risk</td>
<td>Self-reported VAS pain intensity data.</td>
</tr>
<tr>
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<td>Unclear risk</td>
<td>No information supplied.</td>
</tr>
<tr>
<td>Incomplete outcome data (participant exclusion from analysis)</td>
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<td>No information supplied.</td>
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<tr>
<td>Selective reporting (reporting bias)</td>
<td>High risk</td>
<td>No data on primary outcome of study. No data on concomitant drug treatment</td>
</tr>
<tr>
<td>Other bias</td>
<td>Unclear risk</td>
<td>No baseline comparison on pain intensity scores.</td>
</tr>
<tr>
<td>Size of study</td>
<td>High risk</td>
<td>n = 20 per group.</td>
</tr>
</tbody>
</table>
**Methods**

RCT, parallel.

**Participants**

26 participants with phantom limb pain to 2 groups. TENS group: 11 men, 2 women, 1 dropout therefore n = 12; mirror group: 12 men, 1 female, n = 13

- Age (mean ± SD): TENS group: 36.38 ± 9.55 years; mirror group: 42.62 ± 10.69 years
- Amputations: TENS group: 3 upper and 10 lower limb amputations; mirror group: 4 upper and 9 lower limb amputations
- Onset of phantom limb pain from date of surgery: TENS group: 13 ± 1.6 days; mirror group: 13 ± 1.4 days
- Formal neuropathic pain assessment: no.
- Sites of pain: upper and lower limb.
- Concomitant treatment: no detail supplied.

**Interventions**

**TENS group:** no TENS frequency details supplied.
- Intensity: "strong but comfortable" without visible muscle contraction
- Location: electrodes placed at site of pain on contralateral limb
- Frequency of treatment: 1 session per day for 4 days.
- Duration: 20 minutes per session.
- Clinic administered.

**Mirror group:** intact limb movements performed with mirror.
- Frequency: 1 session per day for 4 days.
- Duration: 20 minutes per session.
- Clinic administered.

**Outcomes**

Pain intensity: no details supplied as to parameters of pain rating (current pain, mean pain, etc.)
- 0-10 cm VAS.
- Outcomes measured at baseline and 4 days later.
- Study did not report adverse events.

**Notes**

Funding from higher education institution acknowledged.

**Risk of bias**

<table>
<thead>
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<th>Bias</th>
<th>Authors' judgement</th>
<th>Support for judgement</th>
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<td>Opaque sealed envelopes.</td>
</tr>
<tr>
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<td>Unclear risk</td>
<td>Both interventions active treatments.</td>
</tr>
<tr>
<td>All outcomes</td>
<td></td>
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</tr>
<tr>
<td>Blinding of outcome assessment (detection bias)</td>
<td>Unclear risk</td>
<td>Both interventions active treatments.</td>
</tr>
<tr>
<td>All outcomes</td>
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### Tilak 2016

(Continued)

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<tr>
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<th>Author's judgement</th>
<th>Support for judgement</th>
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</thead>
<tbody>
<tr>
<td>Incomplete outcome data (attrition bias) All outcomes</td>
<td>Low risk</td>
<td>1 participant dropout adequately described.</td>
</tr>
<tr>
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<td>Dropout minimal. All participants analysed.</td>
</tr>
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<td>Low risk</td>
<td>All outcomes reported.</td>
</tr>
<tr>
<td>Other bias</td>
<td>Low risk</td>
<td>Adequate description and testing of baseline characteristics</td>
</tr>
<tr>
<td>Size of study</td>
<td>High risk</td>
<td>TENS group: n = 12; mirror group: n = 13.</td>
</tr>
</tbody>
</table>

### Vitalii 2014

Methods
RCT, parallel.

Participants
25 participants with spinal cord injury. 4 participants dropped out. No details on group allocation given. TENS group: 10 men, 1 woman; sham TENS: 9 men, 1 woman Age (mean ± SD): TENS group: 31.72 ± 7.7 years; sham TENS group: 28.9 ± 6.1 years Duration of pain (mean (range)): 12.7 (0.5-14) months for whole sample. No further data supplied Formal neuropathic pain assessment: LANSS > 12; mean (range) score 15.95 (13-20) Sites of pain: mixed. Concomitant treatment: gabapentin started day 1 and increased in 300 mg increments daily to basic dose of 900 mg/day by day 3

Interventions
**TENS group:** TENS 4 Hz, 200 ms. Intensity: 50 mA. No description of perceived sensation. **Sham TENS group:** as per active TENS but no current passed through electrodes Sham credibility assessment: no. Location: electrodes proximal and distal to region with pain Frequency of treatment: 1 application per day for 10 days. Duration: 30 minutes per session. Clinic administered.

Outcomes Pain intensity mean of morning and evening. Mean of these two scores at day 0 and day 10 used in analysis 0-10 cm VAS. Outcomes measured at baseline (pretreatment) on day 0 and day 10 of the study Study reported adverse events and none occurred.

Notes
No conflict of interest stated.

Risk of bias

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors' judgement</th>
<th>Support for judgement</th>
</tr>
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</table>
### Vitalii 2014  
**Methods**  
Randomised cross-over design.

<table>
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<tbody>
<tr>
<td>Allocation concealment (selection bias)</td>
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<td>No details supplied.</td>
</tr>
<tr>
<td>Blinding of participants and personnel (performance bias)</td>
<td>High risk</td>
<td>Unclear risk for blinding of participants (TENS vs sham but no attempt to manage participant expectations of sensation and no detail on whether TENS device appeared 'live' or not). Personnel high risk as the same care provider applied active and sham treatments</td>
</tr>
<tr>
<td>Blinding of outcome assessment (detection bias)</td>
<td>Unclear risk</td>
<td>TENS vs active sham but see comments above for blinding of participants</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias)</td>
<td>Unclear risk</td>
<td>16% dropout rate. No information given with regards to group allocation</td>
</tr>
<tr>
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<td>Unclear risk</td>
<td>No obvious exclusion from analysis; however, dropout rate not fully described with respect to group allocation</td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>Low risk</td>
<td>All outcomes adequately reported.</td>
</tr>
<tr>
<td>Other bias</td>
<td>Low risk</td>
<td>Baseline testing reported albeit without data presented for all tests</td>
</tr>
<tr>
<td>Size of study</td>
<td>High risk</td>
<td>TENS group: n = 11; sham TENS group: n = 10.</td>
</tr>
</tbody>
</table>

### zkul 2015

| Participants | 26 participants with spinal cord injury to 2 treatment groups: 1. VI followed by TENS; 2. TENS followed by VI. n = 12 per group (2 participants dropped out). Total sample: 6 women, 18 men  
Age (mean ± SD): 32.33 ± 12.97 years.  
Mean pain duration: 12.46 ± 17.83 months.  
Sites of pain: at or below level of spinal cord injury.  
Concomitant treatment: pregabalin 300-600 mg. |
| Interventions | TENS treatment: TENS 80 Hz, 180 µs.  
Intensity: perceptible but not uncomfortable.  
Location: electrodes placed bilateral spinal region above level of injury  
Frequency of treatment: 5 days per week for 2 weeks.  
Duration: 30 minutes per session.  
VI treatment: 20 minutes of VI treadmill walking.  
Frequency of treatment: 5 days per week for 2 weeks. |
Duration: 15 minutes per session. Clinic administered.

Outcomes

Pain intensity: mean, maximal and minimal pain intensity levels. Brief pain inventory measured pretreatment and post-treatment. Pain 0-10 cm VAS. Outcomes measured at baseline, pretreatment and post-treatment each treatment session/treatment modality. Study reported adverse events and none occurred.

Notes

No carry-over tests reported. No baseline comparisons between groups reported. No conflict of interest stated.

Risk of bias

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors' judgement</th>
<th>Support for judgement</th>
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<td>Cross-over.</td>
</tr>
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<td>Blinding of participants and personnel (performance bias) All outcomes</td>
<td>Unclear risk</td>
<td>Both active non-invasive treatments.</td>
</tr>
<tr>
<td>Blinding of outcome assessment (detection bias) All outcomes</td>
<td>Unclear risk</td>
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</tr>
<tr>
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<td>Low risk</td>
<td>Dropout from study described and minimal.</td>
</tr>
<tr>
<td>Incomplete outcome data (participant exclusion from analysis)</td>
<td>Low risk</td>
<td>Appears adequate.</td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>Low risk</td>
<td>Adequately reported.</td>
</tr>
<tr>
<td>Other bias</td>
<td>Unclear risk</td>
<td>No formal assessment of carry-over effects but data appeared very similar at baseline.</td>
</tr>
<tr>
<td>Size of study</td>
<td>High risk</td>
<td>n = 12 per group.</td>
</tr>
</tbody>
</table>

µs: microseconds; ACU: electroacupuncture; DN4: Douleur Neuropathique 4; DPN: diabetic peripheral neuropathy; IFT: interferential therapy; LANSS: Leeds Assessment of Neuropathic Symptoms and Signs; n: sample size; NRS: numerical rating scale; NSAID: non-steroidal anti-inflammatory drug; PENS: percutaneous electrical nerve stimulation; PRF: pulsed radiofrequency; RCT: randomised controlled trial; RDQ: Roland-Morris Disability Questionnaire; SD: standard deviation; SF-36: 36-item Short Form; TENS: transcutaneous electrical nerve stimulation; VAS: visual analogue scale; VI: visual illusion.
### Characteristics of excluded studies  
*ordered by study ID*

<table>
<thead>
<tr>
<th>Study</th>
<th>Reason for exclusion</th>
</tr>
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<tbody>
<tr>
<td>Al-Smadi 2003</td>
<td>Not defined neuropathic pain.</td>
</tr>
<tr>
<td>Bahtereva 2009</td>
<td>Not a standard TENS unit application. Unable to contact authors</td>
</tr>
<tr>
<td>Bloodworth 2004</td>
<td>Not randomised/quasi-randomised trial.</td>
</tr>
<tr>
<td>Bourke 1994</td>
<td>Not randomised/quasi-randomised trial.</td>
</tr>
<tr>
<td>Casale 1985</td>
<td>Outcome measure not pain intensity.</td>
</tr>
<tr>
<td>Cheing 2005</td>
<td>Pain intensity scoring in response to stimulus evoked pain. Stimulus applied by researcher</td>
</tr>
<tr>
<td>Chitsaz 2009</td>
<td>Outcome measure a VAS composite of pain and sensory complaints</td>
</tr>
<tr>
<td>Connolly 2013</td>
<td>All participants received perceptual TENS.</td>
</tr>
<tr>
<td>Finsen 1988</td>
<td>Outcome measure not Pain intensity.</td>
</tr>
<tr>
<td>Forst 2004</td>
<td>Outcome measure a VAS composite of pain and sensory symptoms</td>
</tr>
<tr>
<td>Franca 2013</td>
<td>Not defined neuropathic pain.</td>
</tr>
<tr>
<td>Gossrau 2011</td>
<td>TENS applied below perceptual level.</td>
</tr>
<tr>
<td>Heidenreich 1988</td>
<td>Not clearly randomised trial.</td>
</tr>
<tr>
<td>Ing 2015</td>
<td>Not a standard TENS device.</td>
</tr>
<tr>
<td>Kumar 1997</td>
<td>Outcome measure not pain intensity. VAS was a composite of pain intensity, paraesthesia and sleep disturbance. Outcome measure not self-reported</td>
</tr>
<tr>
<td>Kumar 1998</td>
<td>Outcome measure not pain intensity. VAS was a composite of pain intensity, paraesthesia and sleep disturbance. Outcome measure not self-reported</td>
</tr>
<tr>
<td>Lehmkuhl 1978</td>
<td>Outcome measured &lt; 24 hours post-treatment.</td>
</tr>
<tr>
<td>Marques 2014</td>
<td>Not defined neuropathic pain.</td>
</tr>
<tr>
<td>Mysliwiec 2012</td>
<td>Outcome measure not pain intensity. Not defined neuropathic pain participants</td>
</tr>
<tr>
<td>Norrbrink 2009</td>
<td>All participants received TENS.</td>
</tr>
</tbody>
</table>
Oosterhof 2008  No pain intensity follow-up data. Unable to extract potential neuropathic participant data

Pourmomeny 2009  Outcome measure not pain intensity. VAS was a composite measure of pain and non-pain symptoms

Reichstein 2005  Not all participants had pain as a symptom. Outcome measure encompassed non-pain symptoms

Sherry 2001  Not defined neuropathic pain.

Stepanovic 2015  Not defined neuropathic pain.

Thorsteinsson 1977  Outcome measured < 24 hours post-treatment.

Warke 2004  Not defined neuropathic pain condition in study.

Warke 2006  Not defined neuropathic pain condition in study.

Wong 2016  Not randomised/quasi-randomised trial.

Yameen 2011  All participants received TENS.

TENS: transcutaneous electrical nerve stimulation; VAS: visual analogue scale.

**Characteristics of studies awaiting assessment [ordered by study ID]**

<table>
<thead>
<tr>
<th>Study ID</th>
<th>Methods</th>
<th>Participants</th>
<th>Interventions</th>
<th>Outcomes</th>
<th>Notes</th>
</tr>
</thead>
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<td>Not available.</td>
<td>Not available.</td>
<td>Not available.</td>
<td>Unable to contact study authors.</td>
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**Samier 2006**

<table>
<thead>
<tr>
<th>Study ID</th>
<th>Methods</th>
<th>Participants</th>
<th>Interventions</th>
<th>Outcomes</th>
</tr>
</thead>
</table>
**Samier 2006** *(Continued)*

<table>
<thead>
<tr>
<th>Notes</th>
<th>Attempted contact with author. No reply.</th>
</tr>
</thead>
</table>

**Wang 2009**

<table>
<thead>
<tr>
<th>Methods</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Participants</td>
<td>Randomised n = 139 with 'senile radical sciatica' randomised to electroacupuncture (n = 70) or TENS (n = 69) treatments. Awaiting translation. No further details</td>
</tr>
<tr>
<td>Interventions</td>
<td>Awaiting translation.</td>
</tr>
<tr>
<td>Outcomes</td>
<td></td>
</tr>
<tr>
<td>Notes</td>
<td></td>
</tr>
</tbody>
</table>

n: number of participants; TENS: transcutaneous electrical nerve stimulation.
### DATA AND ANALYSES

#### Comparison 1. TENS versus sham TENS

<table>
<thead>
<tr>
<th>Outcome or subgroup title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
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</thead>
<tbody>
<tr>
<td>1 Changes in pain intensity</td>
<td>5</td>
<td>207</td>
<td>Mean Difference (IV, Random, 95% CI)</td>
<td>-1.58 [-2.08, -1.09]</td>
</tr>
<tr>
<td>2 Pain intensity sensitivity analysis (Celik 2013 removed)</td>
<td>4</td>
<td>174</td>
<td>Mean Difference (IV, Random, 95% CI)</td>
<td>-1.44 [-1.87, -1.02]</td>
</tr>
</tbody>
</table>

#### Analysis 1.1. Comparison 1 TENS versus sham TENS, Outcome 1 Changes in pain intensity.

Review: Transcutaneous electrical nerve stimulation (TENS) for neuropathic pain in adults

Comparison: 1 TENS versus sham TENS

Outcome: 1 Changes in pain intensity

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>TENS N</th>
<th>Mean(SD)</th>
<th>Sham N</th>
<th>Mean(SD)</th>
<th>Mean Difference</th>
<th>Weight</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Barbarisi 2010 (1)</td>
<td>9</td>
<td>2.5 (0.97)</td>
<td>8</td>
<td>3.7 (1.19)</td>
<td>-1.20 [-2.24, -0.16]</td>
<td>16.5 %</td>
<td>-1.20 [-2.24, -0.16]</td>
</tr>
<tr>
<td>Barbarisi 2010 (2)</td>
<td>7</td>
<td>2.3 (0.78)</td>
<td>6</td>
<td>3.2 (0.81)</td>
<td>-0.90 [-1.77, -0.03]</td>
<td>21.0 %</td>
<td>-0.90 [-1.77, -0.03]</td>
</tr>
<tr>
<td>Bi 2015</td>
<td>24</td>
<td>2.14 (0.91)</td>
<td>24</td>
<td>3.87 (1.45)</td>
<td>-1.73 [-2.41, -1.05]</td>
<td>27.8 %</td>
<td>-1.73 [-2.41, -1.05]</td>
</tr>
<tr>
<td>Buchmuller 2012</td>
<td>43</td>
<td>3.85 (2.97)</td>
<td>32</td>
<td>5.78 (1.9)</td>
<td>-1.93 [-3.04, -0.82]</td>
<td>15.1 %</td>
<td>-1.93 [-3.04, -0.82]</td>
</tr>
<tr>
<td>Celik 2013</td>
<td>17</td>
<td>3.88 (2.5)</td>
<td>16</td>
<td>6.77 (1.42)</td>
<td>-2.89 [-4.27, -1.51]</td>
<td>10.7 %</td>
<td>-2.89 [-4.27, -1.51]</td>
</tr>
<tr>
<td>Vitalii 2014</td>
<td>11</td>
<td>3.95 (1.7)</td>
<td>10</td>
<td>5.25 (1.86)</td>
<td>-1.30 [-2.83, 0.23]</td>
<td>9.0 %</td>
<td>-1.30 [-2.83, 0.23]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>111</strong></td>
<td><strong>96</strong></td>
<td><strong>100.0 %</strong></td>
<td><strong>-1.58 [-2.08, -1.09]</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Tau² = 0.11; Chi² = 7.04, df = 5 (P = 0.22); I² =29%
Test for overall effect: Z = 6.23 (P < 0.00001)
Test for subgroup differences: Not applicable

(1) P300
(2) P600
Analysis 1.2. Comparison 1 TENS versus sham TENS, Outcome 2 Pain intensity sensitivity analysis (Celik 2013 removed).

Review: Transcutaneous electrical nerve stimulation (TENS) for neuropathic pain in adults

Comparison: 1 TENS versus sham TENS

Outcome: 2 Pain intensity sensitivity analysis (Celik 2013 removed)

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>TENS</th>
<th>Sham TENS</th>
<th>Mean Difference</th>
<th>Weight</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Barbarisi 2010 (1)</td>
<td>7</td>
<td>2.3 (0.78)</td>
<td>6 3.2 (0.81)</td>
<td>23.6 %</td>
<td>-0.90 [-1.77, -0.03]</td>
</tr>
<tr>
<td>Barbarisi 2010 (2)</td>
<td>9</td>
<td>2.5 (0.97)</td>
<td>8 3.7 (1.19)</td>
<td>16.4 %</td>
<td>-1.20 [-2.24, -0.16]</td>
</tr>
<tr>
<td>Bi 2015</td>
<td>24</td>
<td>2.14 (0.91)</td>
<td>24 3.87 (1.45)</td>
<td>37.9 %</td>
<td>-1.73 [-2.41, -1.05]</td>
</tr>
<tr>
<td>Buchmüller 2012</td>
<td>43</td>
<td>3.85 (2.97)</td>
<td>32 5.78 (1.9)</td>
<td>14.5 %</td>
<td>-1.93 [-3.04, -0.82]</td>
</tr>
<tr>
<td>Vitali 2014</td>
<td>11</td>
<td>3.95 (1.7)</td>
<td>10 5.25 (1.86)</td>
<td>7.6 %</td>
<td>-1.30 [-2.83, 0.23]</td>
</tr>
</tbody>
</table>

Total (95% CI) 94 80 100.0 % -1.44 [-1.87, -1.02]  

Heterogeneity: Tau^2 = 0.0; Chi^2 = 3.17, df = 4 (P = 0.53); I^2 = 0.0%

Test for overall effect: Z = 6.71 (P < 0.00001)

Test for subgroup differences: Not applicable

(1) P600

(2) P300

ADDITIONAL TABLES

Table 1. Details of participants and TENS parameters in included studies

<table>
<thead>
<tr>
<th>Study, comparison (admitted sample size)</th>
<th>Group baseline pain intensity VAS/NRS</th>
<th>Neuro-pathic condition</th>
<th>Reported mean duration</th>
<th>Diagnostic criteria</th>
<th>Hz and pulse width</th>
<th>Electrode location</th>
<th>Intensity</th>
<th>Duration, frequency and site of administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Barbarisi 2010 TENS vs sham TENS (30)</td>
<td>P300 + TENS: 4 ± 0.93 P600 + TENS: 3.8 0.95 P300 +</td>
<td>Postherpetic neuralgia</td>
<td>15.25 ± 8.7 months</td>
<td>No formal or clinical neuropathic diagnostic criteria</td>
<td>100 Hz (later described in text as 50 Hz) 125 µs</td>
<td>“Around site of pain”</td>
<td>“Clear non-painful paraesthesia”. Titrated to maintain strength of</td>
<td>30 minutes daily for 4 weeks Clinic administration</td>
</tr>
</tbody>
</table>
Table 1. Details of participants and TENS parameters in included studies  
(Continued)

<table>
<thead>
<tr>
<th>Study Year</th>
<th>Study Design</th>
<th>TENS Parameters</th>
<th>Pain Type/Study Details</th>
<th>Perception TENS Parameters</th>
<th>Perception Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bi 2015</td>
<td>TENS vs sham TENS (52)</td>
<td>TENS: 5.17 ± 2.34, Sham TENS: 5.91 ± 2.12</td>
<td>Lumbar radicular pain, subgroup data supplied by authors</td>
<td>Clinical assessment</td>
<td>Mixed: 80-100 Hz alternated with 2 Hz 200 ms</td>
</tr>
<tr>
<td>Buchmuller 2012</td>
<td>TENS vs sham TENS (122)</td>
<td>TENS: 6.15 ± 2.24, Sham TENS: 5.91 ± 2.12</td>
<td>Spinal cord injury</td>
<td>Clinical assessment</td>
<td>Mixed: 80-100 Hz alternated with 2 Hz 200 ms</td>
</tr>
<tr>
<td>Casale 2013</td>
<td>TENS vs laser? (20)</td>
<td>TENS: 6 ± 0.8, Laser?: 6.6 ± 1.1</td>
<td>Carpal tunnel syndrome</td>
<td>Nerve conduction study</td>
<td>100 Hz 80 ms</td>
</tr>
<tr>
<td>Celik 2013</td>
<td>TENS vs sham TENS (33)</td>
<td>TENS: 5.79 ± 2.17, Sham TENS: 5.64 ± 1.81</td>
<td>Spinal cord injury</td>
<td>LANSS &gt; 12</td>
<td>Place of &quot;on region with pain&quot;</td>
</tr>
<tr>
<td>Gerson 1977</td>
<td>TENS vs drug treatment (29)</td>
<td>TENS: 27.0, Drug: 59.0 (0-100)</td>
<td>Postherpetic neuralgia</td>
<td>No formal or clinical neuropathic diagnostic criteria</td>
<td>No details</td>
</tr>
<tr>
<td>Ghoname 1999</td>
<td>TENS vs PENS (64)</td>
<td>TENS: 7.0 ± 1.9, PENS: 7.2 ± 1.8, Sham PENS: 6.6 ± 1.9</td>
<td>Lumbar radicular pain</td>
<td>Clinical assessment, Radiological assessment of nerve root compression</td>
<td>4 Hz 100 ms</td>
</tr>
<tr>
<td>Study Year</td>
<td>Study Design/Comparison</td>
<td>TENS</td>
<td>IFT</td>
<td>Nerve Conduction Study</td>
<td>Frequency</td>
</tr>
<tr>
<td>------------</td>
<td>-------------------------</td>
<td>------</td>
<td>-----</td>
<td>-------------------------</td>
<td>-----------</td>
</tr>
<tr>
<td>Koca 2014</td>
<td>TENS vs IFT (75)</td>
<td>8.06±0.55</td>
<td>8.25±0.4</td>
<td>13.3±6.3 months</td>
<td>100 Hz</td>
</tr>
<tr>
<td>Nabi 2015</td>
<td>TENS vs PRF sympathectomy (65)</td>
<td>6.10±1.20</td>
<td>6.46 (NRS)</td>
<td>12.9±3 years (since diabetes onset)</td>
<td>Clinical diagnosis</td>
</tr>
<tr>
<td>izkul 2015</td>
<td>TENS vs visual illusion (26)</td>
<td>5.33±1.20</td>
<td>5.33±1.37</td>
<td>≥4 on DN4</td>
<td>80 Hz</td>
</tr>
<tr>
<td>Prabhakar 2011</td>
<td>TENS vs cervical spine mobilisation (75)</td>
<td>Not stated</td>
<td>No details</td>
<td>No formal or clinical neuropathic diagnostic criteria</td>
<td>100 Hz</td>
</tr>
<tr>
<td>Rutgers 1988</td>
<td>TENS vs acupuncture (26)</td>
<td>Not stated</td>
<td>Postherpetic neuralgia</td>
<td>“3 months to 9 years”</td>
<td>No formal or clinical neuropathic diagnostic criteria</td>
</tr>
<tr>
<td>Serry 2015</td>
<td>TENS vs exercise (60)</td>
<td>Not stated</td>
<td>Peripheral diabetic neuropathy</td>
<td>12.2±2.3 years (since onset of neuropathy)</td>
<td>No formal or clinical neuropathic diagnostic criteria</td>
</tr>
</tbody>
</table>
Table 1. Details of participants and TENS parameters in included studies  (Continued)

<table>
<thead>
<tr>
<th>Study</th>
<th>Comparator</th>
<th>TENS:</th>
<th>Phantom</th>
<th>No formal or clinical neuropathic diagnostic criteria</th>
<th>Site of pain contralateral limb</th>
<th>&quot;Strong but comfortable&quot;</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tilak 2016</td>
<td>TENS vs mirror therapy</td>
<td>5.00 ± 1.63</td>
<td>Phantom limb pain</td>
<td>13 ± 1.5 days (since onset of phantom limb pain)</td>
<td>No details</td>
<td>Site of pain contralateral limb</td>
<td>&quot;Strong but comfortable&quot;</td>
</tr>
<tr>
<td>Vitalii 2014</td>
<td>TENS vs sham TENS (25)</td>
<td>8.09 ± 0.97</td>
<td>Spinal cord injury</td>
<td>12.7 months</td>
<td>LANSS &gt; 12</td>
<td>Proximal and distal to pain region</td>
<td>50 mA. No description of perceived sensation</td>
</tr>
</tbody>
</table>

DN4: Douleur Neuropathique 4; IFT: interferential therapy; LANSS: Leeds Assessment of Neuropathic Symptoms and Signs pain scale; NRS: numerical rating scale; P300: pregabalin 300 mg; P600: pregabalin 600 mg; PENS: percutaneous electrical nerve stimulation; PRF: pulsed radiofrequency; TENS: transcutaneous electrical nerve stimulation; VAS: visual analogue scale.

Appendix 1. Search strategies

**CENTRAL**

1. MESH DESCRIPTOR Transcutaneous Electric Nerve Stimulation EXPLODE ALL TREES
2. ("TENS" or "TNS" or "ENS" or "TES"):TI,AB,KY
3. ("transcutaneous electric nerve stimulation" or "transcutaneous electrical nerve stimulation" or "transcutaneous nerve stimulation"):TI,AB,KY
4. ("electric nerve stimulation" or "electrical nerve stimulation" or "electrostimulation therapy" or "electro-stimulation therapy"):TI,AB,KY
5. ("electric nerve therapy" or "electrical nerve therapy" or electroanalgesia"):TI,AB,KY
6. ("transcutaneous electric stimulation" or "transcutaneous electrical stimulation"):TI,AB,KY
7. #1 OR #2 OR #3 OR #4 OR #5 OR #6
8. MESH DESCRIPTOR PAIN EXPLODE ALL TREES
9. MESH DESCRIPTOR Peripheral Nervous System Diseases EXPLODE ALL TREES
10. MESH DESCRIPTOR SOMATOSENSORY DISORDERS EXPLODE ALL TREES
11. ("pain" or discomfort) adj10 (central or complex or rheumat* or muscl* or nerv* or neuralgia* or neuropath*)
12. ("neur*" or nerv*) adj6 (compress* or damage*)
13. #8 OR #9 OR #10 OR #11 OR #12
14. #7 AND #13

**MEDLINE**

1. exp Transcutaneous Electric Nerve Stimulation/
2. ("TENS" or "TNS" or "ENS").ti.
3. ("TENS" or "TNS" or "ENS").ab.
4. ("transcutaneous electric nerve stimulation" or "transcutaneous nerve stimulation").mp.
5. ("electric nerve stimulation" or "electrostimulation therapy" or "electro-stimulation therapy").mp.
6. ("electric nerve therapy" or electroanalgesia").mp.
Transcutaneous electrical nerve stimulation (TENS) for neuropathic pain in adults (Review)

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31. Single Blind Procedure/
32. or/17-31
33. (animal/ or nonhuman/) not human/
34. 32 not 33
35. 16 and 34
36. limit 35 to embase

**PsycINFO**
1. exp Transcutaneous Electric Nerve Stimulation/
2. ("TENS" or "TNS" or "ENS").ti.
3. ("TENS" or "TNS" or "ENS").ab.
4. ("transcutaneous electric nerve stimulation" or "transcutaneous electrical nerve stimulation" or "transcutaneous nerve stimulation").tw.
5. ("electric nerve stimulation" or "electrical nerve stimulation" or "electrostimulation therap$" or "electro-stimulation therap$").tw.
6. ("electric nerve therap$" or "electrical nerve therap$" or electroanalgesi$).tw.
7. ("transcutaneous electric stimulation" or "transcutaneous electrical stimulation").tw.
8. TES.ti,ab.
9. or/1-8
10. exp PAIN/
11. exp PERIPHERAL NEUROPATHY/
12. exp SOMATOSENSORY DISORDERS/
13. ((pain* or discomfor*) adj10 (central or complex or rheumat* or muscl* or nerv* or neuralgia* or neuropath*)).tw.
14. ((neur* or nerv*) adj6 (compress* or damag*)).tw.
15. 10 or 11 or 12 or 13 or 14
16. 9 and 15
17. clinical trials/
18. (randomis* or randomiz*).tw.
19. (random$ adj3 (allocat$ or assign$)).tw.
20. ((clinic$ or control$) adj trial$).tw.
21. ((singl$ or doubl$ or trebl$ or tripl$) adj3 (blind$ or mask$)).tw.
22. (crossover$ or "cross over$").tw.
23. random sampling/
24. Experiment Controls/
25. Placebo/
26. placebo$.tw.
27. exp program evaluation/
28. treatment effectiveness evaluation/
29. ((effectiveness or evaluat$) adj3 (stud$ or research$)).tw.
30. or/17-29
31. 16 and 30

**AMED**
1. exp Transcutaneous Electric Nerve Stimulation/
2. ("TENS" or "TNS" or "ENS").ti.
3. ("TENS" or "TNS" or "ENS").ab.
4. ("transcutaneous electric nerve stimulation" or "transcutaneous electrical nerve stimulation" or "transcutaneous nerve stimulation").tw.
5. ("electric nerve stimulation" or "electrical nerve stimulation" or "electrostimulation therap$" or "electro-stimulation therap$").tw.
6. ("electric nerve therap$" or "electrical nerve therap$" or electroanalgesi$).tw.
7. ("transcutaneous electric stimulation" or "transcutaneous electrical stimulation").tw.
8. TES.ti,ab.
9. or/1-8
10. exp PAIN/
11. exp PERIPHERAL Nervous system disease/
12. ((pain* or discomfor*) adj10 (central or complex or rheumat* or muscl* or nerv* or neuralgia* or neuropath*)).tw.
13. ((neur* or nerv*) adj6 (compress* or damag*)).tw.
14. 10 or 11 or 12 or 13
15. 9 and 14
16. randomized controlled trials/
17. randomized controlled trial.pt.
18. controlled clinical trial.pt.
19. placebo.ab.
20. random*.ti,ab.
21. trial.ti,ab.
22. groups.ab.
23. 16 or 17 or 18 or 19 or 20 or 21 or 22
24. 15 and 23

CINAHL
S26 S16 AND S25
S25 S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23 OR S24
S24 (allocat* random*)
S23 (MH "Quantitative Studies")
S22 (MH "Placebos")
S21 placebo*
S20 (random* allocat*)
S19 (MH "Random Assignment")
S18 (Randomized control* trial*)
S17 (singl* blind* ) or (doubl* blind* ) or (tripl* blind* ) or (trebl* mask* ) or (tripl* mask* ) or (doubl* mask* ) or (singl* mask* )
S16 S9 AND S15
S15 S10 OR S11 OR S12 OR S13 OR S14
S14 ((neur* or nerv*) N6 (compress* or damag*)).
S13 ((pain* or discomfor*) N10 (central or complex or rheumat* or muscl* or nerv* or neuralgia* or neuropath*)).
S12 (MH "Somatosensory Disorders+")
S11 (MH "Peripheral Nervous System Diseases+")
S10 (MH "Pain+")
S9 S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8
S8 TES
S7 ("transcutaneous electric stimulation" or "transcutaneous electrical stimulation").
S6 ("electric nerve therap*" or "electrical nerve therap*" or electroanalgesi*)
S5 "electric nerve stimulation" or "electrical nerve stimulation" or "electrostimulation therap*" or "electro-stimulation therap*").
S4 ("transcutaneous electric nerve stimulation" or "transcutaneous electrical nerve stimulation" or "transcutaneous nerve stimulation")
S3 ("electric nerve stimulation" or "electrical nerve stimulation" or "electrostimulation therap*" or "electro-stimulation therap*").
S2 ("TENS" or "TNS" or "ENS").
S1 (MH "Transcutaneous Electric Nerve Stimulation")

Web of Science
#17 #16 AND #10
Indexes=SCI-EXPANDED, SSCI, CPCI-S, CPCI-SSH Timespan=All years
#16 #15 AND #14
Indexes=SCI-EXPANDED, SSCI, CPCI-S, CPCI-SSH Timespan=All years
#15 TOPIC: (human*)
Indexes=SCI-EXPANDED, SSCI, CPCI-S, CPCI-SSH Timespan=All years
#14 #13 OR #12 OR #11
Indexes=SCI-EXPANDED, SSCI, CPCI-S, CPCI-SSH Timespan=All years
#13 TOPIC: (((((singl* OR doubl* OR trebl* OR tripl*) SAME (blind* OR mask*)))))
Indexes=SCI-EXPANDED, SSCI, CPCI-S, CPCI-SSH Timespan=All years
#12 TOPIC: (((controlled clinical trial OR controlled trial OR clinical trial OR placebo))))
Indexes=SCI-EXPANDED, SSCI, CPCI-S, CPCI-SSH Timespan=All years
#11 TOPIC: (((randomised OR randomized OR randomly OR random order OR random sequence OR random allocation OR randomly allocated OR at random OR randomized controlled trial))))
Appendix 2. Included study methodology description

Pooled studies

Barbarisi 2010 (n = 30) used a two arm parallel design in participants with post-herpetic neuralgia PHN). All participants undertook an initial eight day programme of pregabalin drug treatment at varying doses with the aim of reducing all participants baseline visual analogue scale (VAS) pain intensity scores to 60 mm or less on a 0 to 100 mm VAS scale. There was no information with regard to how many participants were initially enrolled in the drug titration phase. Following this, 30 drug treatment responders were randomised to either transcutaneous electrical nerve stimulation (TENS) or sham TENS applied for 30 minutes per day (clinic administered) for four weeks. Baseline pain intensity post drug titration phase was compared to final pain intensity scores at four weeks. VAS scores of pain intensity appeared to reflect ‘current’ pain intensity. Analysis of participants was subdivided according to the concomitant dose of pregabalin taken during the study. The comparison was: pregabalin 300 mg plus TENS versus pregabalin 300 mg plus sham TENS, pregabalin 600 mg plus TENS versus pregabalin 600 mg plus sham TENS.

Bi 2015 randomised 52 participants with spinal cord injury into TENS versus sham TENS groups. Pain intensity was assessed (on a 0 to 10 VAS) at baseline and then immediately upon cessation of 12 weeks of treatment. The VAS reflected current pain intensity at time of measurement. Participants were treated three times per week for 12 weeks and the TENS/sham TENS was administered in the treating clinic. Celik 2013 carried out a similar sized study in 33 participants with spinal cord injury randomised to TENS or sham TENS. Daily treatment of 30 minute duration was administered in the clinic. Pain intensity VAS scores (on a 0 to 10 VAS) were recorded morning, noon, evening and night pretreatment and post-treatment; day one of the protocol consisted of these four VAS assessments. Participants then had 10 days of treatment intervention. Day 12 of the protocol consisted of assessing the pain intensity with the same four VAS measures used at day one. Means of the four measures obtained at day one and day 12 were calculated and used in the final analysis. It is worth noting that both groups were also taking amitriptyline 10 mg as a concomitant treatment in this study. Vitalii 2014 used a similar methodology with participants who had spinal cord injury. Participants were randomised to TENS or sham TENS groups and then received 30 minute clinic administered treatment daily for 10 days. This study employed concomitant treatment with gabapentin 900 mg. Pain intensity (0 to 10 VAS) scores were a mean of morning and evening reporting. Data were reported as ‘day zero’ baseline and post-treatment ‘day 10’ scores.
Buchmuller 2012 randomised 236 participants with chronic low back pain into two groups receiving either TENS or sham TENS. As a subgroup within this sample, 139 participants were classified as having a neuropathic component to their condition. This classification was made on the basis of clinical assessment. The primary outcome of this study was functional change assessed via the Roland-Morris Disability Questionnaire (RDQ). Secondary outcomes included dichotomising participants according to pain intensity changes (50% decrease in a 0 to 10 VAS classed as criteria for improvement) from baseline to post-treatment. While the paper reported the data in this dichotomised method, following contact the authors were able to provide pain intensity data for participants from the neuropathic group and specifically for those participants with a radicular pain component. These pain intensity data were used when pooling data. Radicular pain was assessed in 122 participants at baseline and then reassessed at three months. In the active TENS group at baseline there were data for 64 participants while in the sham TENS group baseline data were available for 58 participants. Following completion of treatment and with dropout there were data for 43 participants in the active TENS group and 32 participants in the sham TENS group. The TENS/sham TENS units were supplied to the participant for home administration. Participants were instructed to compete four TENS session per day with each session lasting one hour.

Narrative review single studies

Casale 2013 compared laser with TENS for pain intensity (on a 0 to 10 VAS) and paraesthesia in 20 participants with carpal tunnel syndrome. Treatments were applied five times per week for five weeks. Treatment duration was 30 minutes for TENS. Treatment duration for laser application was unclear. There was no information given with respect to the pain intensity VAS measure (mean pain, peak pain, etc.) and timing of assessment was only described as being “evaluated before and after treatment.”

Gerson 1977 compared pharmacological treatment (carbamazepine plus clonipramine) versus TENS in 29 participants with post-therapeutic neuralgia. There were no reported parameters around TENS application beyond stating the duration of treatment was 15 minutes per session. It appears the TENS group initially received four treatments on a weekly basis followed by three TENS sessions at fortnightly intervals (seven TENS sessions in total). This equated to a 10 week treatment period; however, the drug treatment group was reported as being eight weeks in duration and outcomes are reported at eight weeks. Pain intensity (on a 0 to 100 mm VAS) was assessed at initially weekly then fortnightly intervals via a VAS; however, it was not stated whether this was current pain, mean pain or maximal pain.

Ghoname 1999 in a one-arm randomised cross-over study compared percutaneous electrical nerve stimulation (PENS) versus TENS versus sham PENS in participants with lumbar radicular pain. However, the sham treatment was invasive, involving insertion of “acupuncture like needles” into the involved area. We considered this to be very problematic as a sham intervention and therefore only considered the TENS versus PENS comparison. The main comparison involved a non-invasive intervention (TENS) being compared against an inherently invasive procedure (PENS), therefore this study rated high risk across the key domains of participant/personnel bias. Sixty-four participants were randomised to three different treatment sequences 1. sham PENS, PENS, TENS; 2. PENS, TENS, sham PENS; 3. TENS, sham PENS, PENS. Each treatment phase lasted three weeks with a one week washout break between. Participants received three treatment sessions per week (clinical administered) of 30 minutes’ duration. Pain intensity data (0 to 10 VAS) were reported and analysed during treatment and at 24 hours post treatment phase completion.

One three arm study compared TENS, interferential (IFT) and resting splints in participants with carpal tunnel syndrome (Koca 2014). This study randomised 75 participants to one of three treatment groups. Pain intensity was assessed (on a 0 to 10 VAS) as a mean of the previous week's pain at baseline and three weeks after completion of treatment. The splint group were instructed to use resting wrist-hand night splints during the intervention period. The TENS and IFT therapies were delivered in the clinic five times per week for 20 minutes each session.

Nabi 2015 investigated TENS versus pulsed radiofrequency (PRF) sympathectomy in 65 participants with painful peripheral diabetic neuropathy of the lower limb. Participants were randomised to either PRF sympathectomy or TENS interventions and both groups received concomitant treatment with pregabalin 300 mg/day to 600 mg/day. The main comparison involved a non-invasive intervention (TENS) being compared against an inherently invasive procedure (PRF sympathectomy), therefore this study rated high risk across the key domains of participant/personnel bias. Participants assigned to the PRF sympathectomy group initially underwent a sympathetic blockade with local anaesthetic. Participants who reported a 50% reduction in pain then progressed to PRF sympathectomy. There were no data on how many participants underwent the initial local anaesthetic procedure or how many of this group went on to full PRF sympathectomy. Participants in the both groups had pain intensity (0-10 numerical rating scale (NRS)) assessed four times before the procedure (PRF sympathectomy or TENS treatment to completion) and then at one week, one month and three months after completion of the procedure. It was unclear if NRS scores at baseline were a mean of the four preintervention assessments or whether the NRS elicited at each assessment represented current pain, maximal pain or mean pain. The PRF sympathectomy intervention was a one-off single day procedure whereas the TENS was delivered as 10 x 20 minute sessions delivered on alternate days. Given the NRS assessments were completed at fixed times post ‘procedure’ and completion of the TENS treatment was regarded as a procedure, there was an imbalance in outcome assessment timing postrandomisation for the two groups (TENS assessments approximately three weeks later than PRF sympathectomy).
One study investigated TENS versus visual illusion in participants with neuropathic pain following spinal cord injury (Zekul 2015). This two-arm randomised cross-over study allocated 24 participants to groups and received the following intervention sequences: Group one (12 participants) received visual illusion then TENS and Group two (12 participants) received TENS followed by visual illusion. Treatments were delivered five times per week over two weeks followed by one week washout between treatments. TENS sessions lasted 30 minutes while visual illusion sessions lasted 15 minutes. This study was rated overall unclear in terms of bias and was not allocated high risk of bias in any domain. Pain intensity data (0 to 10 VAS) was reported at baseline and immediately upon completion of treatment (two weeks). Group mean pain intensity data were presented across the combined groups preintervention and postintervention. Carry-over testing prior to initiation of second sequence treatment was not reported. Pain intensity reported as present pain (immediately upon cessation of treatment), mean (timeframe not described), minimal and maximal at baseline and post-treatment.

Prabhakar 2011 investigated TENS versus cervical mobilisation versus isometric exercises in participants with cervical radiculopathy. This randomised parallel design allocated 75 participants to one of these three interventions. The number of participants per group was not described. All participants initially received hot pack therapy and treatment interventions were applied on alternate days for 10 sessions over three weeks. TENS sessions lasted approximately 30 minutes. There were no details on duration of treatment in the mobilisation or isometric exercise group. Pain intensity (VAS not specified) was assessed at baseline then at three weeks (completion of treatment) and six weeks (three weeks after treatment completed). The parameters of the VAS pain intensity measure (e.g. mean, minimal, maximal pain) were not described.

One study investigated acupuncture (ACU, 10 participants) and TENS (13 participants) in people with postherpetic neuralgia (Rutgers 1988). All treatment interventions lasted six weeks. The ACU group were treated twice per week for six weeks with body and auricular acupuncture while the TENS group received 3 x 30 minute TENS sessions in the first week (clinic administered) and were then instructed to apply TENS themselves at home for the next five weeks. There were no details on TENS duration, dosage or treatment parameters for the home treatment component of the intervention. Pain intensity was assessed via a 10-point stepwise scale. There was no further detail provided for this scale. Pain intensity was assessed at baseline, six weeks, nine weeks and six months postrandomisation. This study was rated overall at high risk of bias with the key domains blinding of participants and personnel, incomplete outcome data and selective reporting of outcomes being rated high.

Serry 2015 investigated TENS versus exercise in 60 participants with diabetic peripheral neuropathy randomised to TENS, exercise or regular pharmacological therapy groups (20 per group). TENS and exercise groups received treatment three times per week for eight weeks. TENS sessions lasted 30 minutes, aerobic exercise sessions lasted in total 50 minutes. All treatments were applied under supervision. Additionally, participants in the TENS and exercise groups continued with concomitant treatment of their regular pharmacological therapy. This study was rated at overall high risk of bias with particular risk in the ‘selective reporting of outcome’ domain. In this study, pain intensity was assessed at baseline and post-treatment on a 0 to 10 VAS although it was unclear what aspect of the pain experience was assessed (e.g. mean, minimal, maximal pain, etc.).

We include one study investigating TENS versus mirror therapy in participants with phantom limb pain (Tilak 2016). In this study, 26 participants (88% men) were randomised to either TENS (n = 13) or mirror (n = 13) intervention groups. Pain intensity was assessed with a 0 to 10 VAS and a ‘Universal Pain Score’ (participants selects from a range of hand-drawn faces depicting pain expressions which face most closely matches their experience). It was unclear what aspect of the pain experience was assessed (e.g. mean, minimal, maximal pain, etc.). Treatments were applied daily for four days. Each treatment session lasted 20 minutes. Baseline demographics and site of amputation were well described and no significant differences in age, duration of phantom limb pain or pain intensity was found. Overall, this study was rated unclear on risk of bias with the only domain assessed as high being sample size.

**CONTRIBUTIONS OF AUTHORS**

WG: led the design of the review as primary author, implemented the search strategy with the Pain, Palliative and Supportive Care group’s Trials Search Co-ordinator, applied eligibility criteria, assessed studies, extracted and analysed data, led the write up and updating of the review.

BMW: closely informed the design, applied eligibility criteria, assessed studies, extracted and aided in analysis of data, assisted the writing and will aid future updating of the review.

NEO: closely informed the design, acted as third review author when assessing eligibility criteria and during assessment of studies, assisted in analysis of data, assisted the writing and will aid future updating of the review.
DECLARATIONS OF INTEREST

WG: none known.
BMW: none known.
NEO: none known.

All review authors are qualified physiotherapists and involved in the professional training of physiotherapists.

SOURCES OF SUPPORT

Internal sources
- The University of Notre Dame, Australia.
- Brunel University London, UK.

External sources
- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

The protocol of this review contained an error that was overlooked in the review process. In the review, we made the following statement in the 'Assessment of Heterogeneity' section: “We will attempt to deal with clinical heterogeneity by combining studies that examine similar conditions because placebo response rates with the same outcome can vary between conditions, as can the treatment specific effects.”

Following this in the 'Data Synthesis' section we made this statement: “We will pool data from studies of neuropathic pain regardless of the specific diagnosis. We will pool data for adverse events across conditions.”

These are conflicting and incompatible. This was done in error and has now been corrected.

The protocol of this review outlined the criteria involved in grading the quality of evidence according to the GRADE approach. However, we did not explicitly mention that individual criteria may be double downgraded if there were sufficient reasons to do so. In this review, we downgraded twice on “Limitations of studies” due to sample sizes and multiple high risk of bias issues across at least four of the five studies included in the pooled analysis.

In the protocol of this review, we stated that we planned to investigate the following comparisons: TENS versus sham TENS, TENS versus usual care, TENS versus no treatment and TENS in addition to usual care versus usual care alone. We were only able to perform a quantitative synthesis for the comparison of TENS versus sham TENS. No studies investigated TENS versus no treatment and TENS in addition to usual care versus usual care alone. The studies investigating TENS versus usual care employed a wide range of comparative treatments which precluded pooling of data. For the sake of completeness of the evidence, we therefore included a series of individual narrative reviews of studies investigating TENS versus these other active treatments.