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# Transcutaneous Electrical Nerve Stimulation (TENS) for chronic pain - an overview of Cochrane reviews (Protocol)

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# Transcutaneous Electrical Nerve Stimulation (TENS) for chronic pain - an overview of Cochrane reviews (Protocol)

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[Overview of Reviews Protocol]

# Transcutaneous Electrical Nerve Stimulation (TENS) for chronic pain - an overview of Cochrane reviews

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## ABSTRACT

This is the protocol for a review and there is no abstract. The objectives are as follows:

1. To provide an overview of evidence from Cochrane systematic reviews of the effectiveness of TENS to reduce pain in adults with chronic pain (excluding headache or migraine).

2. To provide an overview of evidence from Cochrane systematic reviews of the safety of TENS to reduce pain in adults with chronic pain (excluding headache or migraine).

3. To identify possible sources of inconsistency in the approaches taken to evaluating the evidence related to TENS for chronic pain (excluding headache or migraine) in the Cochrane Library with a view to recommending strategies to improve consistency.

4. To highlight areas of remaining uncertainty regarding the effectiveness of TENS for chronic pain (excluding headache or migraine) with a view to recommending strategies to reduce any uncertainty.

## BACKGROUND

### Description of the condition

Chronic pain is a common problem. When defined as pain of greater than three months duration, prevalence studies indicate that up to half the adult population suffer from chronic pain, and 10% to 20% experience clinically significant chronic pain (Smith 2008). In Europe, 19% of adults report long standing pain of moderate to severe intensity with serious negative implications for their social and working lives. Many of these people receive inadequate pain management (Breivik 2006). Chronic pain clearly impacts the quality of life of those who experience it (Moore 2014a) but also has a substantial economic impact on society, in terms

of reduced productivity, participation and healthcare utilisation (Gaskin 2012; Gustavsson 2012).

Chronic pain is a heterogenous phenomenon with a wide variety of potential causes. These may include both somatic and neuropathic pain conditions in which there is clear evidence of ongoing peripheral tissue pathology, such as rheumatoid arthritis and diabetic neuropathy, as well as many other chronic pain problems, such as fibromyalgia and chronic non-specific low back pain, in which the relationship between peripheral tissue pathology and clinical symptoms is less clear. It is likely that different mechanisms of pain production underpin these different types of chronic pain (Ossipov 2006).

## Description of the interventions

Transcutaneous Electrical Nerve Stimulation (TENS) is the therapeutic application of electrical nerve stimulation over the skin. It is primarily used for pain control in people with a plethora of acute and chronic pain conditions. TENS units typically use adhesive electrodes applied to the skin surface to apply non-invasive pulsed electrical stimulation that can be modified in terms of frequency (stimulation rate), intensity and duration (Johnson 2011). TENS is commonly delivered in either high or low frequency modes. High frequency may be defined as being greater than 50Hz (Sluka 2003), although a number of studies use frequencies at or above 100Hz (Moran 2011; Santos 2013; Sluka 2005). In contrast, low frequency TENS is consistently defined as being 10Hz or less (Bjordal 2003; Moran 2011; Sabino 2008). Low frequency TENS is often used at higher intensities, eliciting muscle contraction, while high frequency TENS has traditionally been used at lower intensities. Modulated TENS applies stimulation across a range of frequencies and may help to prevent the development of tolerance to the electrical stimulation (Sluka 2013).

Intensity appears to be a critical factor in optimising TENS efficacy and it is thought that regardless of frequency of application, the intensity needs to produce a strong, non-painful sensation which ideally is titrated during treatment to maintain the intensity level (Bjordal 2003; Moran 2011; Sluka 2013). Placement of electrodes may also 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 any TENS analgesia induced should peak during or immediately after use (Sluka 2013).

## How the intervention might work

The process by which TENS-induced analgesia is produced is thought to be multifactorial and encompasses likely peripheral, spinal and supraspinal mechanisms. In a recent animal study, the increased mechanical sensitivity caused by peripheral injection of serotonin (a substance naturally produced following injury and inflammation) was decreased by application of TENS (Santos 2013). Importantly, this analgesia was partly mediated by peripheral mechanisms as pre-injection of a peripheral opioid receptor blocker decreased the analgesia produced, implying the TENS effect is 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 initially proposed in 1965 (Melzack 1965). Pain gate theory proposes large diameter (A$\beta$) afferent fibres (carrying sensations such as vibration, touch etc) inhibit nociceptive traffic in the dorsal horn of the spinal cord, with a resultant decrease in pain (Melzack 1965). Clearly, TENS application and the resultant stimulation of afferent neural structures is a source of considerable large diameter afferent activity and this is therefore a plausible means of TENS induced analgesia. However, TENS is 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 glycine, which are thought to be involved in inhibition of nociceptive traffic (Maeda 2007; Somers 2009), and modulation of the activity of the cells which provide support and surround neurons (glial cells) in the spinal cord (Matsuo 2014) have all been suggested means by which TENS may produce analgesia at a spinal segmental level.

TENS also appears to have an effect on endogenous analgesia mediated by higher centres of the nervous system. Descending inhibitory activity relayed via the midbrain periaqueductal grey (PAG) and the rostral ventral medulla (RVM) in the brainstem has anti-nociceptive effects (Gebhart 2004). This PAG-RVM relayed inhibition has been shown to be mediated via opioidergic pathways (Calvino 2006; Gebhart 2004). TENS-induced analgesia is abolished with pre-injection of opioid receptor blockers in both the PAG and RVM in rats with experimentally-induced peripheral inflammation (DeSantana 2009; Kalra 2001), implying this may be an operational pathway by which TENS contributes to analgesia. Support for the effect of TENS on descending inhibitory mechanisms in humans is provided by evidence of increased descending modulation of pain in people with fibromyalgia during TENS treatment compared to no TENS or placebo TENS (Dailey 2013). It is worth noting that low frequency and high frequency TENS effects are mediated via μ and $\delta$ opioid receptor classes, respectively. As such, the effects of low frequency TENS may be limited in patients using opioids for pain relief as they primarily act via μ-opioid receptor pathways (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.

These descending inhibitory mechanisms have also been implicated in placebo analgesia (the phenomena of improvements in

pain which follow the delivery of an inert treatment). It is possible that the suggested mechanisms of TENS-induced analgesia described above may not necessarily represent specific effects of electrical stimulation but could result purely from the therapeutic ritual of using a TENS unit.

### Sham credibility issues in TENS trials

An issue regarding the credibility of sham conditions specifically for TENS studies is whether the sham condition that is employed uses controls adequately for all non-specific aspects of the treatment experience. Various types of sham 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. 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 TENS effectiveness is widely thought to be related to the intensity of the stimulus (Sluka 2013), a true sham that establishes robust blinding of participants is not achievable. This represents a risk of bias to all sham-controlled TENS trials.

### Why it is important to do this overview

TENS is a widely-used and readily available adjunct therapy that has been used and advocated clinically for many years to manage a range of painful conditions. Despite this, its effectiveness remains controversial. There are a number of Cochrane reviews that have assessed the TENS effectiveness in people with persistent pain. There is a need to systematically synthesise the evidence from these reviews to offer a clear summary of the evidence for patients, clinicians and commissioners and to clearly reflect areas of remaining uncertainty. There is also a need to critically scrutinise the evidence that is presented in the Cochrane Library and to identify possible sources of inconsistency in the approaches taken to evaluating the effectiveness of TENS, with a view to developing strategies to improve consistency and quality.

## OBJECTIVES

1. To provide an overview of evidence from Cochrane systematic reviews of the effectiveness of TENS to reduce pain in adults with chronic pain (excluding headache or migraine).

2. To provide an overview of evidence from Cochrane systematic reviews of the safety of TENS to reduce pain in adults with chronic pain (excluding headache or migraine).

3. To identify possible sources of inconsistency in the approaches taken to evaluating the evidence related to TENS for chronic pain (excluding headache or migraine) in the Cochrane Library with a view to recommending strategies to improve consistency.

4. To highlight areas of remaining uncertainty regarding the effectiveness of TENS for chronic pain (excluding headache or migraine) with a view to recommending strategies to reduce any uncertainty.

## METHODS

### Criteria for considering reviews for inclusion

We will include all Cochrane reviews of randomised controlled trials (RCTs) that assessed the effectiveness of TENS in people with chronic pain. In the event of overlap, where more than one review includes evidence relating to the same comparisons for the same conditions, we will compare each review to the most recent review in order to establish whether the older review(s) identifies any RCTs or data that are not included or adequately reported in the most recent review. Where this is not the case, we will not consider the comparisons in the older review(s). We will only consider data from original studies presented in more than one included review once in any new analyses.

#### Types of participants

Adults 18 years or older described as suffering from chronic pain (of > 3 months duration) of any origin, excluding headache or migraine.

#### Types of intervention

We will include reviews which have included studies of all standard modes of TENS, regardless of the device manufacturer, in which the TENS condition delivers a clearly perceptible sensation. Given that self-use and portability are key clinical features of TENS, we will not consider the evidence for non-portable electrical stimulation devices, such as interferential therapy. We will include evidence from studies that used any parameters of TENS treatment. We will exclude studies where current was delivered percutaneously (e.g. electroacupuncture, PENS, neuroreflexotherapy). Where reviews include both comparisons of TENS but also include these interventions that we plan to exclude, we will only consider the evidence relating to TENS as defined above. Comparisons of interest are:

- TENS versus sham.
- TENS versus usual care or no treatment or waiting list control.

- TENS plus active intervention versus active intervention alone.
- Comparisons between different types of TENS or TENS delivered using different stimulation parameters.

### Types of outcome measure

#### Primary outcomes

1. Changes in pain intensity as measured using a visual analogue scale (VAS), numerical rating scale (NRS), verbal rating scale or Likert scale.
2. Incidence and nature of adverse effects.

We will present follow-up scores of primary outcomes and analyse them as between-group differences. Where data are available, we will also present the outcome in a dichotomised format. For dichotomised data (responder analyses), we will consider analyses based upon a $\geq$ 30% reduction in pain to represent a moderately important benefit, and a $\geq$ 50% reduction in pain intensity to represent a substantially important benefit, as suggested by the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) guidelines (Dworkin 2008).

The IMMPACT thresholds are based on estimates of the degree of within-person change from baseline that participants might consider to be clinically important, whereas the trials in this review are most likely to present effect sizes as the average between-group change between intervention-groups. There is little consensus or evidence regarding what the threshold should be for a clinically important difference in pain intensity based on the between-group difference post-intervention. For some pharmacological interventions the distribution of participant outcomes is bimodally distributed (Moore 2013; Moore 2014b; Moore 2014c). That is, some patients experience a substantial reduction in symptoms, some minimal to no improvement, and very few experience intermediate (moderate) improvements. In this instance, and if the distribution of participant outcomes reflects the distribution of treatment effects, then the average effect may be the effect that the fewest participants actually demonstrate (Moore 2013). It is therefore possible that a small average between-group effect size might reflect that a proportion of participants responded very well to the intervention tested. It is unknown whether outcomes are commonly bimodally distributed in TENS trials and the advantage of focusing on the between-group difference is that it is the only direct estimate of the average specific effect of the intervention. Equally it remains possible that a very small average between-group effect might accurately represent generally very small effects of an intervention for most or all individuals.

The OMERACT 12 group have reported recommendations for minimally important difference for pain outcomes (Busse 2015). They recommend a threshold of 10 mm on a 0 to 100 mm VAS as the threshold for minimal importance for average between-group change though stress that this should be interpreted with caution as it remains possible that estimates which fall closely below this point may still reflect a treatment that benefits an appreciable number of patients. We will use this threshold but interpret it appropriately and cautiously.

#### Secondary outcomes

We will analyse the following secondary outcome measures where such data are available:

1. Changes in disability as measured by validated self-report questionnaires or functional testing protocols.
2. Changes in health-related quality of life using any validated tool (e.g. SF-36, EuroQoL).
3. Change in analgesic medication use.
4. Changes in patient global impression of change (PGIC) scales.

Secondary outcomes will be similarly presented and analysed as either change on a continuous scale or in a dichotomised format, depending on what is presented in the included reviews.

## Search methods for identification of reviews

### Electronic searches

We will search the most recent version of the Cochrane Database of Systematic Reviews (CDSR), via the Cochrane Library, across all years. The search strategy is presented in Appendix 1.

## Data collection and analysis

### Selection of reviews

Two review authors (MJC and NEO) will independently screen the results of the electronic search by title and abstract. We will obtain the full-text versions of the reviews that are deemed appropriate and will apply the selection criteria to determine final inclusion. We will resolve any disagreements between review authors through discussion. Where resolution is not achieved, a third overview author (BMW) will consider the review in question and we will make a majority decision.

### Data extraction and management

Two review authors (MJC and NEO) will extract data independently using a standardised form. We will resolve any discrepancies by consensus. Where agreement cannot be reached, a third review author (BMW) will consider the paper and we will make a majority decision. The data extraction form will include the following details:

- Objectives of the review.
- Number of included trials.
- Details of the included participants.
- Details of the interventions studied.
- Outcomes and time points assessed (primary and secondary).
- Comparisons performed and meta-analysis details.
- Details of the approach taken to assessing heterogeneity including subgroup analyses.
- Whether stimulus intensity was titrated to ensure a strong sensation.
- Assessment of the methodological quality and risk of bias of the included evidence (as assessed and presented in each included review).
- GRADE judgements regarding the quality of evidence where present.

We will contact the authors of included reviews in the event that we cannot extract the required information from the reports. We do not plan on contacting authors of individual studies included in the reviews.

### Assessment of methodological quality of included reviews

We will use the AMSTAR tool to assess the methodological quality of the included reviews (Shea 2007; see Table 1). Two overview authors (MJC and NEO) will assess review quality independently. We will resolve any discrepancies by consensus. Where agreement cannot be reached, a third overview author (BMW) will consider the paper and we will make a majority decision. Included reviews may assess the methodological quality and risk of bias of included studies in a variety of ways. Therefore, we will use the judgements made by the authors of the original included reviews regarding the quality of evidence and risk of bias but report it critically within the context of our assessment of the quality of the review itself.

### Data synthesis

It is unlikely that additional data analysis will be required since the included reviews should have undertaken appropriate analyses. Where possible, we will extract data from the included reviews and present it in a 'Summary of findings' table. We will present comparisons, where possible, according to clinical condition and outcome. Comparisons of primary interest are as follows:

- TENS versus sham.
- TENS versus usual care or no treatment or waiting list control.
- TENS plus active intervention versus active intervention alone.
- Comparisons between different types of TENS or TENS delivered using different stimulation parameters.

We will determine the precise comparisons presented by the content of the included reviews. Where possible, we will group extracted data according to clinical diagnosis, outcome and duration of follow-up (during-use effects; short-term: zero to < two weeks post-intervention; mid-term: two to seven weeks post-intervention; and long-term: ≥ eight weeks post-intervention). We will present effect sizes using appropriate metrics including, where possible, the number needed to treat for an additional beneficial outcome (NNTB) and number needed to treat for an additional harmful outcome (NNTH).

We will consider the findings of subgroup analyses presented by the included reviews if they investigate the impact of clinical diagnosis or stimulation parameters on statistical heterogeneity and effect size. Where included reviews have used the GRADE approach (Guyatt 2008) to summarise a body of evidence, we will present their summary assessments. Where reviews do not provide a GRADE assessment of the quality of evidence, we will perform one using the following criteria:

- Limitations of studies: downgrade once if < 75% of included studies are at low risk of bias across all 'Risk of bias' criteria.
- Inconsistency: downgrade once if heterogeneity is statistically significant and the $I^2$ statistic is ≥ 50%.
- Indirectness: downgrade once if > 50% of the participants were outside the target group.
- Imprecision: downgraded once if there are < 400 subjects for continuous data and < 300 events for dichotomous data (Guyatt 2011).
- Publication bias: downgrade once where there is direct evidence of publication bias.

We will present and discuss important limitations within the evidence base and consider the possible influence of publication and small study biases on review findings. Two review authors (MJC and NEO) will independently apply the GRADE criteria. We will resolve any disagreement between review authors through discussion. Where resolution is not achieved, a third review author (BMW) will consider the judgement in question.

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* *Indicates the major publication for the study*

## ADDITIONAL TABLES

**Table 1. AMSTAR review quality assessment tool**

| Criteria | Specific requirements |
|---|---|
| **1. Was an 'a priori' design provided?** | The research question and inclusion criteria should be established before the conduct of the review |
| **2. Was there duplicate study selection and data extraction?** | There should be at least two independent data extractors and a consensus procedure for disagreements should be in place |
| **3. Was a comprehensive literature search performed?** | At least two electronic sources should be searched. The report must include years and databases used (e.g. Central, EMBASE, and MEDLINE). Key words or MESH terms, or both, must be stated and where feasible the search strategy should be provided. All |

**Table 1. AMSTAR review quality assessment tool** (*Continued*)

| | |
|---|---|
| | searches should be supplemented by consulting current contents, reviews, textbooks, specialized registers or experts in the particular field of study, and by reviewing the references in the studies found |
| **4. Was the status of publication (i.e. grey literature) used as an inclusion criterion?** | The review authors should state that they searched for reports regardless of their publication type. The review authors should state whether or not they excluded any reports (from the systematic review), based on their publication status, language etc |
| **5. Was a list of studies (included and excluded) provided?** | A list of included and excluded studies should be provided. |
| **6. Were the characteristics of the included studies provided?** | In an aggregated form such as a table, data from the original studies should be provided on the participants, interventions and outcomes. The ranges of characteristics in all the studies analysed e.g. age, race, sex, relevant socioeconomic data, disease status, duration, severity or other diseases should be reported |
| **7. Was the scientific quality of the included studies assessed and documented?** | 'A priori' methods of assessment should be provided (e.g. for effectiveness studies if the review author(s) chose to include only randomised, double-blind, placebo controlled studies, or allocation concealment as inclusion criteria); for other types of studies alternative items will be relevant |
| **8. Was the scientific quality of the included studies used appropriately in formulating conclusions?** | The results of the methodological rigor and scientific quality should be considered in the analysis and the conclusions of the review, and explicitly stated in formulating recommendations |
| **9. Were the methods used to combine the findings of studies appropriate?** | For the pooled results, a test should be done to ensure the studies were combinable, to assess their homogeneity (i.e. $Chi^2$ test for homogeneity, $I^2$ statistic). If heterogeneity exists a random-effects model should be used or the clinical appropriateness of combining should be taken into consideration (i.e. is it sensible to combine? ), or both |
| **10. Was the likelihood of publication bias assessed?** | An assessment of publication bias should include a combination of graphical aids (e.g. funnel plot, other available tests) or statistical tests (e.g. Egger regression test), or both |
| **11. Was the conflict of interest stated?** | Potential sources of support should be clearly acknowledged in both the systematic review and the included studies |

# APPENDICES

## Appendix 1. CDSR search strategy

1. MeSH descriptor: [Transcutaneous Electric Nerve Stimulation] explode all trees
2 ("TENS" or "TNS" or "ENS") ti,ab,kw
3 ("TENS" or "TNS" or "ENS") ti,ab,kw
4 ("transcutaneous electric* nerve stimulation" or "transcutaneous nerve stimulation") ti,ab,kw
5 ("electric* nerve stimulation" or "electrostimulation therap*" or "electro-stimulation therap*") ti,ab,kw
6 ("electric* nerve therap*" or electroanalgesi*) ti,ab,kw
7 transcutaneous electric* stimulation ti,ab,kw
8 TES ti,ab,kw
9 or/1-8
10 MeSH descriptor: [Pain] explode all trees
11 9 and 10

# WHAT'S NEW

| Date | Event | Description |
|---|---|---|
| 1 October 2015 | Amended | Minor corrections. |

# CONTRIBUTIONS OF AUTHORS

MJC closely informed the protocol development as primary author, will implement the search strategy with the Cochrane PaPaS Group's Trials Search Co-ordinator, apply eligibility criteria, assess studies and extract and analyse data, lead the write-up and updating of the review.

WG closely informed the protocol design and will assist in the analysis of data, the write-up and updating of the review.

BMW closely informed the protocol design, will act as a third review author for conflicts in applying eligibility criteria and assessing included studies and will assist in the analysis of data, the write-up and updating of the review.

NEO led the protocol development, will help to implement the search strategy, apply eligibility criteria, assess studies, extract and analyse data, and assist the write-up and updating of the review.

# DECLARATIONS OF INTEREST

MJC has no relevant conflicts of interest to declare.

BMW has no relevant conflicts of interest to declare.

WG has no relevant conflicts of interest to declare.

CM has no relevant conflicts of interest to declare.

NEO has no relevant conflicts of interest to declare.