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Transcutaneous Electrical Nerve Stimulation (TENS) for neuropathic pain in adults (Protocol)

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[Intervention Protocol]

Transcutaneous Electrical Nerve Stimulation (TENS) for neuropathic pain in adults

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ABSTRACT

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

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.

BACKGROUND

This protocol is based on a template for reviews of drugs used to relieve neuropathic pain.

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 European Union 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 a recent systematic review that estimates 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 and post-herpetic neuralgia. Central neuropathic pain results from injury or disease affecting the central nervous system (the spinal cord, brainstem or brain) and includes central post-stroke pain (CPSP), post spinal cord injury pain (pSCIp) 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 reductions, 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 lesion or disease in a peripheral somatosensory structure (eg 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 plethora of acute and chronic pain conditions (APTA 2001). TENS units typically use adhesive electrodes applied to the skin surface to apply non-invasive pulsed 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 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 is proposed that this protocol will undertake a sub-group 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 a recent animal study, the increased mechanical sensitivity caused 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 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 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 (Melzack 1965). TENS application and its 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. 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 glycine, 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 inhibitory activity relayed via the midbrain periaqueductal grey (PAG) and the rostral ventral medulla

(RVM) in the brainstem has inhibitory effects at the segmental level (Gebhart 2004). This PAG-RVM relayed segmental inhibition is mediated in part via opiodergic pathways (Calvino 2006; Gebhart 2004). TENS induced analgesia has been shown to be reversible with pre-injection 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 protocol proposes a sub-group 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 trials of transcutaneous electrical nerve stimulation

An 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 a low risk profile. This review will supersede two Cochrane reviews: 'Transcutaneous electrical nerve stimulation (TENS) for chronic pain' (Nnoaham 2014); and 'Transcutaneous electrical nerve stimulation (TENS) for neuropathic pain in adults' (Claydon 2014). The original review for chronic pain was split into two titles, one on neuropathic pain and one on fibromyalgia (Claydon in press). This review will replace the original protocol for neuropathic pain that was withdrawn. There are a number of systematic reviews of the effect of TENS in various neuromusculoskeletal conditions (Brosseau 2003; Khadilkar 2008; Mulvey 2010). However, there is no previous review examining the effect of TENS on neuropathic pain and, as such, a review using strictly defined treatment and outcome parameter conditions is important to undertake.

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 will include randomised controlled trials (RCTs) or quasi-randomised trials if TENS was given to treat central or peripheral neuropathic pain of any aetiology. We will exclude studies that are non-randomised, case reports/series, studies of experimental pain, clinical observations or systematic reviews. We will include identified studies regardless of their publication status. We will exclude studies designed to test the immediate effects of a single treatment only with follow-up less than 24 hours.

Types of participants

We will include 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;
- human immunodeficiency virus (HIV) neuropathy;
- painful diabetic neuropathy (PDN);
- phantom limb pain;
- postherpetic neuralgia (PHN);
- postoperative or traumatic neuropathic pain;
- spinal cord injury;
- post-stroke pain;
- trigeminal neuralgia.

We will exclude studies that include participants with a mix of neuropathic and non-neuropathic pain where it is not possible to extract data for the neuropathic pain participants independently. We will exclude studies that include participants with complex regional pain syndrome (Type I or II) or fibromyalgia, as these studies are considered in separate Cochrane reviews (Claydon in press; Smart 2013).

Types of interventions

We will include 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 exclude non-portable electrical stimulation devices such as interferential therapy. We will include any parameters of treatment that evoke sensation, and any frequency or duration of treatment or surface electrode configuration. We will exclude studies delivering intensities of TENS that are sub-perceptual or barely perceptual due to the risk of sub-optimal treatment. We will exclude studies where current was delivered percutaneously (e.g. electroacupuncture, percutaneous electrical nerve stimulation (PENS), neuroreflexotherapy) and where the effect of TENS cannot be separated from the effects of other treatments (i.e. comparison interventions standardised between groups). The comparisons of interest will be 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 will include 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 effects.

Search methods for identification of studies

Electronic searches

We will search the following electronic databases using a combination of controlled vocabulary, that is, medical subject headings (MeSH) and free-text terms, to identify published articles:

- Cochrane Central Register of Controlled Trials (CENTRAL) in *The Cochrane Library*;
- MEDLINE (Ovid);
- EMBASE (Ovid);
- CINAHL (EBSCO);
- PsycINFO (Ovid);
- LILACS;
- PEDro;
- Web of Science (ISI);
- AMED;
- Database of Abstracts of Reviews of Effects in *The Cochrane Library*;
- Health Technology Assessments.

There will be no language restrictions. All database searches will be based on this strategy but adapted to individual databases as necessary. The search strategy for MEDLINE is shown in Appendix 1.

Searching other resources

We will search 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 will check the reference lists of reviews and retrieved articles for additional studies and perform citation searches on key articles. We will contact experts in the field for unpublished and ongoing trials. We will send the list of included studies to content experts to help identify any additional relevant studies.

Unpublished Data

In order to minimise the prospect of publication bias, we will undertake 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) will independently assess the titles and abstracts of potential trials identified by the search strategy for their eligibility. If the eligibility of a study is unclear from the title and abstract, we will assess the full paper. We will exclude studies that do not match the inclusion criteria (see Criteria for considering studies for this review). We will resolve disagreements between review authors regarding a study's inclusion by discussion. A third review author (NEO) will assess relevant studies if resolution and agreement cannot be reached and we will make a majority decision. Studies will not be anonymised prior to assessment.

We plan to include a PRISMA study flow diagram in the full review to document the screening process (Liberati 2009), as recommended in Part 2, Section 11.2.1 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Schünemann 2011).

Data extraction and management

Two review authors (WG and BMW) will independently extract data from all included studies using a standardised and piloted data extraction form. We will resolve discrepancies and disagreements by consensus. In cases where we cannot achieve consensus, a third review author (NEO) will assess the trial for arbitration and we will make a majority decision. We will extract 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 range, gender split);
- 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 effects;
- industry sponsorship;
- author conflict of interest statements.

Assessment of risk of bias in included studies

Two review authors (WG and BMW(will independently assess 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 we cannot reach consensus, a third review author (NEO) will assess the trial for arbitration and we will make a majority decision.

We will assess the following for each study of parallel design.

- **Random sequence generation** (checking for possible selection bias). We will assess the method used to generate the 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). The method used to conceal allocation to group prior to assignment determines whether intervention allocation could have been foreseen in advance of, or during recruitment, or changed after assignment. We will assess the methods 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 do not conceal allocation (e.g. open list)).
- **Blinding of study participants** (checking for possible detection bias). We will assess the methods used to blind participants, care providers and assessors to the treatment provided as follows.

- ○ Blinding of participants: low risk of bias (participants 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 not blinded to allocated intervention OR participants blinded to allocated intervention but it is likely that blinding may have been broken).

○ Blinding of care provider: low risk of bias (care provider 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 (care provider not blinded to allocated intervention and the two interventions clearly identifiable to the care provider as

experimental and control OR care provider blinded to allocated intervention but likely that blinding may have been broken)).

- Blinding of assessor: 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 (drop-outs).** We will first check for possible attrition bias by considering if participant drop-out rate was appropriately described and acceptable.
  - Low: if less than 20% drop-out and appears to be missing at random. Numbers given per group and reasons for drop-out described.
  - Unclear: if less than 20% but reasons not described and numbers per group not given. Unclear that data were missing at random.
  - High: if over 20% even if imputed appropriately.
- **Incomplete outcome data (protocol violations).** We will separately consider if participants were analysed in the group to which they were allocated.
  - Low: if analysed data in group to which originally assigned (with appropriately imputed data or an available-case analysis).
  - Unclear: insufficient information provided to determine if analysis was per protocol or intention to treat.
  - High: 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.** We will assess whether studies were free of the suggestion of selective outcome reporting. We will assess methods as: low risk of bias (study protocol available and all pre-specified 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); high risk of bias (incomplete reporting of pre-specified outcomes; one or more primary outcomes was reported using measurements, analysis methods or sub-sets of data that were not pre-specified; one or more reported primary outcomes were not pre-specified; 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); unclear risk of bias (inadequate information to allow judgement of a study to be classified as 'low risk' or 'high risk').
- **Size of study** (checking for possible biases confounded by small size). We will assess studies as being at 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 will consider other risk factors such as whether trials were stopped early, differences between groups at baseline, timing of outcome assessment, control of co-interventions and author source of funding declarations.

Measures of treatment effect

We will present and analyse primary outcomes on a continuous scale as mean difference with 95% confidence intervals (CI) when the same scale is used and as standardised mean difference with 95% CI when different scales are used. Where data are available, we will also present outcomes in a dichotomised format. For dichotomised data (responder analyses), we will 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). We will calculate risk ratio (RR) and risk difference (RD) with 95% CIs for dichotomised outcome measures. We will calculate the number needed to treat for an additional beneficial outcome (NNTB) as an absolute measure of treatment effect where possible. For HRQoL data, we will consider a minimally important clinical difference to be greater than 10% of the scale employed (Furlan 2009).

The IMMPACT thresholds are based on estimates of the degree of within-person change from baseline that participants might consider clinically important, whereas the trials in this review are most likely to present effect sizes as the mean 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). That is, some participants experience a substantial reduction in symptoms (Moore 2014), some experience 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 mean effect may be the effect that the fewest participants actually demonstrate (Moore 2013). Therefore, it is possible that a small mean 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 trials of TENS and the advantage of focusing on the between-group difference is that it is the only direct estimate of the mean specific effect of the intervention. Equally, it remains possible that a very small mean 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 mean between-group change though they stress that this should be interpreted with caution as it remains possible that estimates that fall closely below this point may still reflect a treatment that benefits an appreciable number of people. We will use this threshold but interpret it appropriately cautiously.

We will present secondary outcomes similarly and analyse them as change on a continuous scale or in a dichotomised format. For example, equivalent measures of treatment effect with respect to PGIC have been defined as: 'much' improved (moderate benefit) and 'very much' improved (substantial benefit).

Unit of analysis issues

We will split the control treatment arm between active treatment arms in a single study if the active treatment arms are not combined for analysis. If we include cross-over studies, we will use first period data only wherever possible (Higgins 2011). Where this is not reported, we will analyse as if the treatment periods were parallel, but draw attention to the potential bias this may introduce. In the unlikely event that the unit of randomisation is not the participant, we will not include the data unless there has been a suitable adjustment for the study design, or an adjustment can be made. If such study designs do occur and the data are reported appropriately, then we will include them using the generic inverse variance option in Review Manager 5 (RevMan 2014).

Dealing with missing data

Where insufficient data are presented in the study report to enter into a meta-analysis, we will contact study authors to request access to the missing data.

Assessment of heterogeneity

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 (Moore 2008). We will not combine studies that compared TENS to usual care with studies that compared TENS to sham/placebo in the same analysis. We will assess heterogeneity using the Chi^2 test to investigate the statistical significance of such heterogeneity, and the I^2 statistic to estimate the amount of heterogeneity. Where significant heterogeneity is present (P value < 0.1), we will explore subgroup analyses. Pre-planned comparisons are described in Subgroup analysis and investigation of heterogeneity.

Assessment of reporting biases

We will consider the possible influence of publication/small study biases on review findings. The influence of small study biases in part will be addressed by the risk of bias criterion 'study size'. We will inspect funnel plots visually to explore the likelihood of reporting biases when at least 10 studies are included in a meta-analysis and included studies differ in size. For continuous outcomes, we will use Egger's test to detect possible small study bias and, for dichotomised outcomes, we will 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. We will interpret the results of this process cautiously since we are aware that all approaches to the quantification of possible reporting biases have important limitations (Moore 2008).

Data synthesis

We will perform pooling of results where adequate data exist using Review Manager 5 (RevMan 2014). We will undertake meta-analyses of outcome data only from suitably homogeneous studies using a random-effects model. Where possible, we will group extracted data according to diagnosis, outcome and duration of follow-up (during use effects; short term: zero to less than two weeks post-intervention; mid-term: two to seven weeks post-intervention; and long term: eight or more weeks post-intervention). We will pool data from studies of neuropathic pain regardless of the specific diagnosis. We will pool data for adverse events across conditions.

For all analyses, we will explicitly and clearly present the outcome of the 'Risk of bias' assessments in the reporting. Where inadequate data are found to support statistical pooling, we will conduct a narrative synthesis of the evidence using the GRADE system (Guyatt 2008). To ensure consistency of GRADE judgements, we will apply the following criteria to each domain equally for all key comparisons of the primary outcomes.

- Limitations of studies: downgrade once if greater than 25% of participants were from studies at high risk of bias across any key 'Risk of bias' criteria.
- Inconsistency: downgrade once if heterogeneity was statistically significant and $I^2 \geq 40\%$ or when reported treatment effects were in opposition directions.
- Indirectness: downgrade once if greater than 50% of the participants were outside the target group.
- Imprecision: downgrade 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 will consider single studies both inconsistent and imprecise (unless sample size is greater than 400 participants for continuous data and greater than 300 events for dichotomous data). We will present pooled effects for all primary outcomes and associated GRADE judgements in 'Summary of findings' tables.

Subgroup analysis and investigation of heterogeneity

Where we find substantial heterogeneity (I^2 < 40%, P value < 0.1), we will conduct subgroup analysis investigating the possible impact of diagnosis and stimulation parameters on effectiveness. Preplanned subgroup analyses will include:

- 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 (subgroups 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).

Sensitivity analysis

Where sufficient data are available, we will conduct 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).

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* *Indicates the major publication for the study*

APPENDICES

Appendix 1. Ovid MEDLINE search strategy

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 therap$" or "electro-stimulation therap$").mp.
6 ("electric$ nerve therap$" or electroanalgesi$).mp.
7 transcutaneous electric$ stimulation.mp.
8 TES.ti,ab.
9 or/1-8
10 exp PAIN/
11 exp PERIPHERAL NERVOUS SYSTEM DISORDERS/
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 randomized controlled trial.pt.
18 controlled clinical trial.pt.
19 randomized.ab.
20 placebo.ab.
21 drug therapy.fs.
22 randomly.ab.

23 trial.ab.
24 groups.ab.
25 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24
26 exp animals/ not humans.sh.
27 25 not 26
28 16 and 27

CONTRIBUTIONS OF AUTHORS

WG: led the design of the review protocol as primary author, will implement the search strategy with the Pain, Palliative and Supportive Care 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.

BMW: closely informed the protocol design, 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.

NEO: 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.

DECLARATIONS OF INTEREST

WG: has no known conflicts of interest to declare that are relevant to the development of this protocol.

BMW: has no known conflicts of interest to declare that are relevant to the development of this protocol.

NEO: has no known conflicts of interest to declare that are relevant to the development of this protocol.

All review authors are qualified physiotherapists and involved in the professional training of physiotherapists. As physiotherapists are often involved in the prescription and use of TENS, it might be perceived that they may have a professional bias in favour of TENS.

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