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Transcutaneous electrical nerve stimulation (TENS) for chronic pain - an overview of Cochrane Reviews (Review)

Gibson W, Wand BM, Meads C, Catley MJ, O'Connell NE

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Transcutaneous electrical nerve stimulation (TENS) for chronic pain - an overview of Cochrane Reviews.
Cochrane Database of Systematic Reviews 2019, Issue 2. Art. No.: CD011890.
DOI: 10.1002/14651858.CD011890.pub2.

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[Overview of Reviews]

Transcutaneous electrical nerve stimulation (TENS) for chronic pain - an overview of Cochrane Reviews

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Editorial group: Cochrane Pain, Palliative and Supportive Care Group.
Publication status and date: New, published in Issue 2, 2019.

Citation: Gibson W, Wand BM, Meads C, Catley MJ, O'Connell NE. Transcutaneous electrical nerve stimulation (TENS) for chronic pain - an overview of Cochrane Reviews. *Cochrane Database of Systematic Reviews* 2019, Issue 2. Art. No.: CD011890. DOI: 10.1002/14651858.CD011890.pub2.

ABSTRACT

Background

Chronic pain, considered to be pain lasting more than three months, is a common and often difficult to treat condition that can significantly impact upon function and quality of life. Treatment typically includes pharmacological and non-pharmacological approaches. Transcutaneous electrical nerve stimulation (TENS) is an adjunct non-pharmacological treatment commonly recommended by clinicians and often used by people with pain.

Objectives

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

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

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 in methodology and reporting.

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

Search methods

We searched the *Cochrane Database of Systematic Reviews* (CDSR), in the Cochrane Library, across all years up to Issue 11 of 12, 2018.

Selection of reviews

Two authors independently screened the results of the electronic search by title and abstract against inclusion/exclusion criteria. We included all Cochrane Reviews of randomised controlled trials (RCTs) assessing the effectiveness of TENS in people with chronic pain.

We included reviews if they investigated the following: TENS versus sham; TENS versus usual care or no treatment/waiting list control; TENS plus active intervention versus active intervention alone; comparisons between different types of TENS; or TENS delivered using different stimulation parameters.

Data extraction and analysis

Two authors independently extracted relevant data, assessed review quality using the AMSTAR checklist and applied GRADE judgements where required to individual reviews. Our primary outcomes included pain intensity and nature/incidence of adverse effects; our secondary outcomes included disability, health-related quality of life, analgesic medication use and participant global impression of change.

Main results

We included nine reviews investigating TENS use in people with defined chronic pain or in people with chronic conditions associated with ongoing pain. One review investigating TENS for phantom or stump-associated pain in people following amputation did not have any included studies. We therefore extracted data from eight reviews which represented 51 TENS-related RCTs representing 2895 TENS-comparison participants entered into the studies.

The included reviews followed consistent methods and achieved overall high scores on the AMSTAR checklist. The evidence reported within each review was consistently rated as very low quality. Using review authors' assessment of risk of bias, there were significant methodological limitations in included studies; and for all reviews, sample sizes were consistently small (the majority of studies included fewer than 50 participants per group).

Six of the eight reviews presented a narrative synthesis of included studies. Two reviews reported a pooled analysis.

Primary and secondary outcomes

One review reported a beneficial effect of TENS versus sham therapy at reducing pain intensity on a 0 to 10 scale (MD −1.58, 95% CI −2.08 to −1.09, P < 0.001, I^2 = 29%, P = 0.22, 5 studies, 207 participants). However the quality of the evidence was very low due to significant methodological limitations and imprecision. A second review investigating pain intensity performed a pooled analysis by combining studies that compared TENS to sham with studies that compared TENS to no intervention (SMD −0.85, 95% CI −1.36 to −0.34, P = 0.001, I^2 = 83%, P < 0.001). This pooled analysis was judged as offering very low quality evidence due to significant methodological limitations, large between-trial heterogeneity and imprecision. We considered the approach of combining sham and no intervention data to be problematic since we would predict these different comparisons may be estimating different true effects. All remaining reviews also reported pain intensity as an outcome measure; however the data were presented in narrative review form only.

Due to methodological limitation and lack of useable data, we were unable to offer any meaningful report on the remaining primary outcome regarding nature/incidence of adverse effects, nor for the remaining secondary outcomes: disability, health-related quality of life, analgesic medication use and participant global impression of change for any comparisons.

We found the included reviews had a number of inconsistencies when evaluating the evidence from TENS studies. Approaches to assessing risk of bias around the participant, personnel and outcome-assessor blinding were perhaps the most obvious area of difference across included reviews. We also found wide variability in terms of primary and secondary outcome measures, and inclusion/exclusion criteria for studies varied with respect to including studies which assessed immediate effects of single interventions.

Authors' conclusions

We found the methodological quality of the reviews was good, but quality of the evidence within them was very low. We were therefore unable to conclude with any confidence that, in people with chronic pain, TENS is harmful, or beneficial for pain control, disability, health-related quality of life, use of pain relieving medicines, or global impression of change. We make recommendations with respect to future TENS study designs which may meaningfully reduce the uncertainty relating to the effectiveness of this treatment in people with chronic pain.

PLAIN LANGUAGE SUMMARY

Transcutaneous electrical nerve stimulation (TENS) for chronic pain - an overview of Cochrane Reviews

Bottom line

For people with chronic pain, this overview of Cochrane Reviews found it was not possible to confidently state whether TENS is effective in relieving pain compared to sham TENS, usual care/no treatment or when TENS is combined with another active treatment versus the active treatment alone. We were unable to find any reliable evidence that the effectiveness of TENS varies when using different delivery modes (e.g. different frequency, intensity or electrode placement).

Background

Chronic pain (pain for longer than three months) is associated with a range of common conditions and can be difficult to treat effectively. TENS is a common treatment for pain conditions and involves using a small battery-operated unit to apply low-intensity electrical current to the body using electrodes attached to the skin. This is suggested to relieve pain. TENS has been previously investigated by a number of Cochrane Reviews.

Review question

By identifying relevant Cochrane Reviews on TENS for common chronic pain conditions, we investigated whether TENS is effective in reducing pain in adults with chronic pain (excluding headache or migraine).

Study characteristics

As of November 2018, we found nine reviews eligible for inclusion. Seven reviews specifically investigated TENS for the treatment of pain/function in a variety of chronic conditions in adults. We also included one review investigating a range of electrotherapy modalities for neck pain and one review examining non-pharmacological interventions in people with spinal cord injury. Both of these reviews included studies investigating TENS. Though the included reviews were of high quality, we found the quality of the evidence presented within the reviews to be very low.

Key findings

We are unable to confidently state whether TENS is effective in relieving pain in people with chronic pain. This is due to the very low quality of the evidence, and the overall small numbers of participants included in studies in the reviews. Issues with quality, study size and lack of data meant we were unable to draw any conclusion on TENS-associated harms or side-effects or the effect of TENS on disability, health-related quality of life, use of pain-relieving medicines or people's impression of how much TENS changed their condition.

BACKGROUND

Description of the condition

Chronic pain is a common problem. When defined as pain of longer 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 (Kennedy 2014; Leadley 2012). In Europe, 19% of adults report long-standing pain of moderate to severe intensity with serious negative implications for their social and working lives and many of these people report inadequate pain management (Reid 2011). Chronic pain clearly impacts the quality of life of those who experience it (Moore 2014a); but it also has a substantial economic impact on society, in terms of reduced productivity, participation and healthcare use (Gaskin 2012; Gustavsson 2012).

Chronic pain is a heterogenous phenomenon with a wide variety of potential causes. These may include both nociceptive 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 underpin these different types of chronic pain (Ossipov 2006; Vardeh 2016).

Description of the interventions

Transcutaneous Electrical Nerve Stimulation (TENS) is the therapeutic application of electrical nerve stimulation through the skin (APTA 2001). It is primarily used for pain control in people across

a range of acute and chronic pain conditions. 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 is commonly delivered in either high- or low-frequency modes. High frequency may be defined as being greater than 50 Hz (Sluka 2003), although a number of studies use frequencies at or above 100 Hz (Moran 2011; Santos 2013; Sluka 2005). In contrast, low-frequency TENS is consistently defined as being 10 Hz 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). Gate control theory proposes large diameter (Aβ) afferent fibres (conveying afferent activity related to vibration, touch perception etc.) inhibit central nociceptive transmission with a resultant decrease in pain perception (Melzack 1965). The application of TENS 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 δ-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 chronic 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 phenomenon 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 can control 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 (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 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 effectiveness/efficacy of TENS 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

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

- To provide an overview of evidence from Cochrane Reviews of the safety of TENS when used to reduce pain in adults with chronic pain (excluding headache or migraine).

- 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 in methodology and reporting.

- 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 included all Cochrane Reviews of randomised controlled trials (RCTs) that assessed the effectiveness of TENS in people with chronic pain. We planned that in the event of overlap between reviews, where more than one review included evidence relating to the same comparisons for the same conditions, we would compare each review to the most recent review in order to establish whether the older review(s) identified any RCTs or data that were not included or adequately reported in the most recent review. Where this was not the case, we did not consider the comparisons in the older review(s). We planned to only consider data from original studies presented in more than one included review once.

Types of participants

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

Types of intervention

We included reviews of all standard methods of TENS delivery, regardless of the device manufacturer, in which the TENS device delivered a clearly perceptible sensation. We did not consider the evidence for non-portable electrical stimulation devices, such as interferential therapy, given that self-use and portability are key clinical features of TENS. We excluded reviews of current delivered percutaneously (e.g. electroacupuncture, PENS, neuroreflexotherapy). Where reviews included both comparisons of TENS and percutaneous stimulation we only considered the evidence relating to TENS. Comparisons of interest were:

- 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

- Pain intensity as measured using a visual analogue scale (VAS), numerical rating scale (NRS), verbal rating scale or Likert scale.
- Incidence and nature of adverse effects.

We planned to present follow-up scores of primary outcomes and analyse them as between-group differences. We planned to present outcomes in a dichotomised format where data were available. 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 Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) guidelines (Dworkin 2008), for dichotomised data (responder analyses).

The IMMPACT thresholds are based on estimates of the degree of within-person change from baseline that participants might consider clinically important, whereas the reviews may 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 2013a; 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 2013a). 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 or treatment effects 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 a minimally important difference for pain outcomes (Busse 2015). They recommend a threshold of 10 mm on a 0 mm 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 planned to use this threshold but interpret it appropriately and cautiously.

Incidence of adverse events also requires careful consideration in studies of TENS. It appears the most commonly reported adverse event involves local reaction to application of electrodes to the skin, which is common to both active and sham interventions. Studies which estimate adverse events by comparing risk between groups may underestimate the true incidence of these events.

Secondary outcomes

We planned to analyse the following secondary outcome measures where such data were available.

- Disability as measured by validated self-report questionnaires or functional testing protocols.
- Health-related quality of life using any validated tool (e.g. SF-36, EuroQoL).
- Analgesic medication use.
- Patient global impression of change (PGIC) scales.

We planned to present secondary outcomes as either change on a continuous scale or in a dichotomised format, depending on what was presented in the included reviews.

Search methods for identification of reviews

Electronic searches

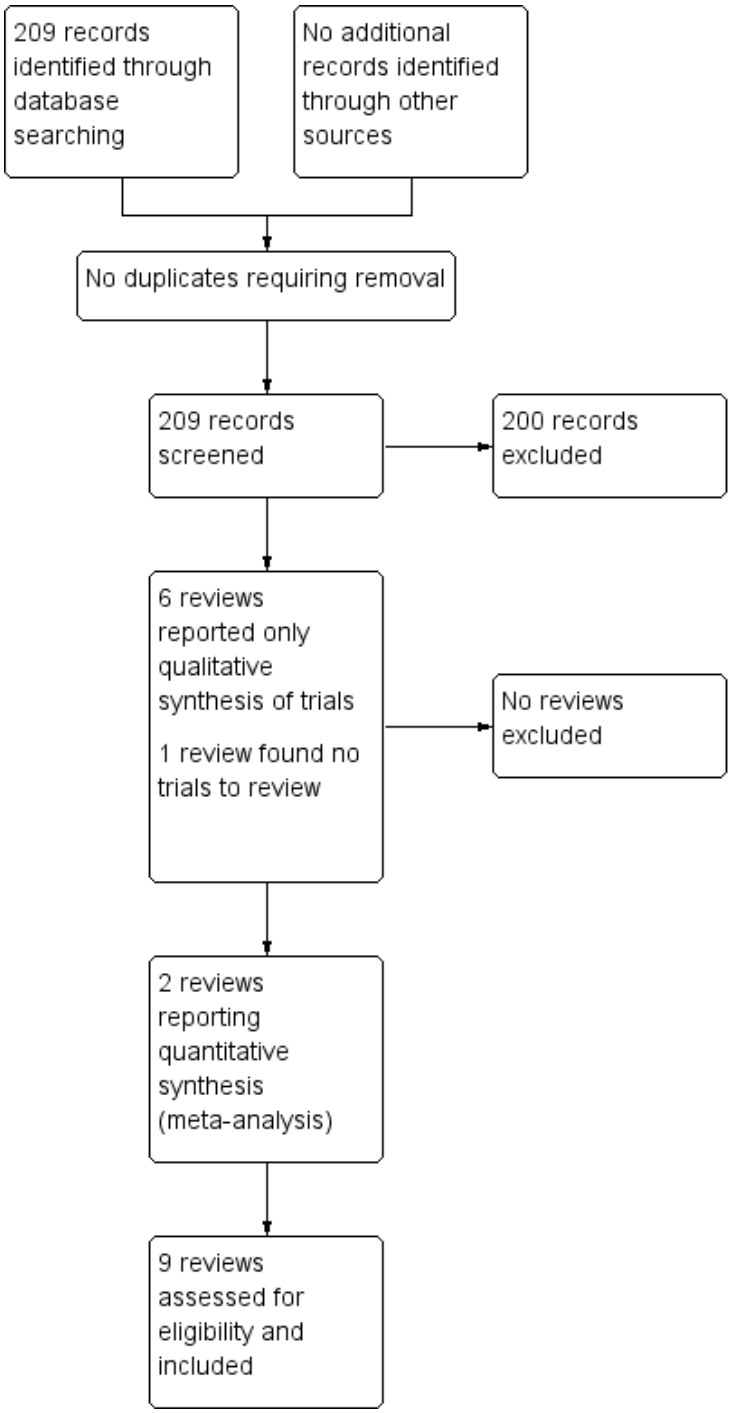
We searched the *Cochrane Database of Systematic Reviews* (CDSR), in the Cochrane Library, across all years up to Issue 11 of 12, 2018. The search strategy is presented in Appendix 1.

Data collection and analysis

Selection of reviews

Two author pairs (WG/NEO or MC/NEO) independently screened the results of the electronic search by title and abstract. We obtained the full-text versions of the reviews deemed appropriate and applied the selection criteria to determine final inclusion. We excluded reviews that did not match the inclusion criteria (see Criteria for considering reviews for inclusion). We resolved disagreements between review authors through discussion. We planned to use an additional reviewer (BMW) where resolution was not achieved; this option was not required. We provide a PRISMA flow diagram documenting the screening and review selection process; see Figure 1.

Figure 1. Study flow diagram.



Data extraction and management

Two author pairs (WG/NEO or MC/NEO) independently extracted data using a standardised form. We resolved any discrepancies by consensus. An additional reviewer (BMW) was available for discussion if agreement could not be reached; however this option was not required. The data extraction form included 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 planned to contact the authors of included reviews in the event that we could not extract the required information from the reports. We did not plan on contacting authors of individual studies included in the reviews.

Assessment of methodological quality of included reviews

We used the AMSTAR tool to assess the methodological quality of the included reviews (Shea 2007). Two overview author pairs (WG/NEO or MC/NEO) assessed review quality independently and resolved differences of opinion by consensus. Where agreement could not be reached, an additional overview author (BMW) was available for consultation; this option was not required. Included reviews assessed the methodological quality and risk of bias of included studies in a variety of ways. Therefore we used the judgements made by the authors of the original included reviews regarding the quality of evidence and risk of bias but have reported it critically within the context of our assessment of the quality of the review itself. In the case of one review that was authored by members of this overview team (Gibson 2017), the quality assessment and extraction was performed by a reviewer not involved in that original review (MC) and checked by and discussed with the primary author of this overview (WG).

Data synthesis

We did not conduct novel analyses for this overview. We extracted data from the included reviews and where possible have presented this in an 'Overview of Reviews' table. We have presented comparisons for each primary and secondary outcome where possible. Comparisons of primary interest were 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 presented the comparisons reported in the included reviews. We intended to group extracted data according to clinical diagnosis, outcome and duration of follow-up (during-use effects; short-term: zero to < 2 weeks post-intervention; mid-term: 2 to 7 weeks post-intervention; and long-term: ≥ 8 weeks post-intervention). We planned to 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 planned to consider the findings of subgroup analyses presented by the included reviews if they investigated the impact of clinical diagnosis or stimulation parameters on statistical heterogeneity and effect size. Where included reviews used the GRADE approach to summarise a body of evidence (Guyatt 2008), we presented their summary assessments. Where reviews did not provide a GRADE assessment of the quality of evidence, we have undertaken this using the following criteria.

- Limitations of studies: downgrade once if less than 75% of included studies are at low risk of bias across all 'Risk of bias' criteria.
- Inconsistency: downgrade once if heterogeneity was statistically significant and the I^2 statistic was greater than 50%.
- Indirectness: downgrade once if greater than 50% of the participants were outside the target group.
- Imprecision: downgrade once if fewer than 400 subjects 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 have presented and discussed important limitations within the evidence base and considered the possible influence of publication and small-study biases on review findings.

RESULTS

The initial search (October 2015) returned 146 Cochrane Review records. We assessed all records and seven reviews were deemed eligible for inclusion (Boldt 2014; Brosseau 2003; Hurlow 2012; Johnson 2015; Khadilkar 2008; Kroeling 2013; Rutjes 2009). One Cochrane Review of TENS for chronic pain had been withdrawn from the Cochrane Library, therefore it was automatically excluded (Nnoaham 2008). An updated search was conducted in October 2017 and returned an additional 59 Cochrane Review records. We assessed a further two reviews as being eligible for inclusion (Gibson 2017; Johnson 2017). A final updated search was conducted in November 2018 and returned a further four records, none of which were eligible for inclusion. Details of the search screening process are presented in Figure 1. Three review protocols were assessed as potentially being eligible for future updates once published; details can be found in Table 1. No review records screened at the full-text stage were excluded.

Description of included reviews

For a detailed description of included reviews see Table 2.

We included seven reviews which specifically investigated the use of TENS for the treatment of pain/function in a variety of defined chronic conditions in adults: TENS for rheumatoid arthritis in the hand (Brosseau 2003), TENS for neuropathic pain (Gibson 2017), TENS for cancer pain (Hurlow 2012), TENS for phantom pain and stump pain following amputation (Johnson 2015), TENS for fibromyalgia (Johnson 2017), TENS for chronic low back pain (Khadilkar 2008), and TENS for osteoarthritis of the knee (Rutjes 2009). We included one review investigating electrotherapy modalities for neck pain (Kroeling 2013); and one review examining non-pharmacological interventions in people with spinal cord injury (Boldt 2014). Both Kroeling 2013 and Boldt 2014 included studies examining TENS.

The nine reviews included 2895 TENS-comparison participants (at time of randomisation) across 51 unique RCTs, with study sizes ranging from n = 10 to n = 350. Of these RCTs, 44 were parallel, seven were cross-over and one was factorial in design. Three of the included reviews explicitly stated a minimum pain duration of more than 3 months (Boldt 2014;Hurlow 2012; Khadilkar 2008), while four reviews included only participants with conditions that were chronic in nature (Brosseau 2003; Gibson 2017; Johnson 2017; Rutjes 2009). One review included participants with acute, subacute or chronic neck pain (Kroeling 2013), although all participants in the TENS studies included in this review were considered to have chronic pain. Johnson 2015 did not specify a minimum pain duration for inclusion and therefore pain duration in some included studies could potentially have been less than the commonly used 3-month definition of chronic pain (Treede 2015); however no relevant studies were found in this review and therefore this review was only further considered in terms of assessment of methods employed.

All nine reviews included pain intensity or pain relief as a primary outcome measure with four reviews having this as the sole primary outcome measure (Boldt 2014; Brosseau 2003; Hurlow 2012; Johnson 2015). All reviews included studies that employed patient-reported assessments of pain, however only two reviews explicitly stated "patient-reported" pain outcomes in the 'Criteria for considering reviews for inclusion' section of the review (Hurlow 2012; Johnson 2015). Two of the included reviews specified parameters around pain-intensity assessment, (pain with movement or resting pain) (Brosseau 2003; Johnson 2017). One review focused on patient-reported pain relief as a primary outcome measure with categorisation into "responder" groups reporting more than 30% and 50% pain relief (Johnson 2017). Other primary outcome measures included disability and function (Khadilkar 2008; Kroeling 2013), health-related quality of life (Gibson 2017; Khadilkar 2008), patient global impression of change (Johnson 2017), and withdrawal due to adverse events (Rutjes 2009). Numerous secondary outcomes were investigated and a summary of the most frequent included adverse events, function, participant impression of change, analgesic use, and quality of life. Two of the nine reviews performed a pooled analysis on the primary outcome of pain intensity (Gibson 2017; Rutjes 2009); and one reported pooled analysis on the secondary outcomes of function and adverse events (Rutjes 2009).

Four reviews reported only on short-term (up to 2 weeks post intervention) outcome assessment time points (Boldt 2014; Brosseau 2003; Gibson 2017; Johnson 2017). Four reviews included a mix of studies with reporting of short- and mid- to long-term (greater than 2 and 8 weeks respectively) follow-up time points (Hurlow 2012; Khadilkar 2008; Kroeling 2013; Rutjes 2009). One review included one study which assessed pain intensity during TENS application (Johnson 2017).

Interventions

All reviews reported variation in TENS application across included studies. Included studies often referred to TENS as AL-TENS which is synonymous with low-frequency TENS (generally < 10 Hz), C-TENS which is synonymous with high-frequency TENS (generally > 50 Hz) and modulated/burst TENS which involves variations in pulse duration/frequency of TENS output. None of the included reviews was able to draw any inferences around relative efficacy of different modes of TENS delivery for pain relief. We found similar variation in terms of intensity of TENS dosage. Four of the nine reviews specifically stated that only TENS interventions which produced (at least) a perceptible sensation would be included (Gibson 2017; Hurlow 2012; Johnson 2015; Johnson 2017). The remaining reviews did not specify minimum dose intensity delivered. Reviews found studies which included a diverse range of reported intensities including "strong"/"strong but comfortable" (Gibson 2017; Hurlow 2012; Johnson 2017), "pleasant tingling" (Johnson 2017) or where parameters were not stated e.g.

Khadilkar 2008.

We found that frequency of application and duration of application (as the second aspect of dosage) was highly variable across reviews. As an example, six of the reviews included studies which evaluated the effect of a one-off TENS intervention (Boldt 2014; Brosseau 2003; Hurlow 2012; Johnson 2017; Kroeling 2013; Rutjes 2009); while one review included a study which used TENS application of four 1-hour sessions per day for 3 months (Gibson 2017). Reviews typically included studies which reported between two to five sessions per week of 20 to 40 minutes' duration commonly for 1 to 4 weeks (e.g. Brosseau 2003; Gibson 2017; Johnson 2017; Khadilkar 2008). It was not possible to identify evidence or consensus on optimal dose paradigms across the included reviews.

Comparisons

All included reviews included TENS versus sham as a pre-specified comparison. The second most common pre-planned comparison was TENS versus no treatment with five of the nine reviews including this (Gibson 2017; Hurlow 2012; Johnson 2015; Johnson 2017; Rutjes 2009). TENS versus usual care and TENS versus non-pharmacological interventions were listed as pre-planned comparisons in five reviews (Boldt 2014; Gibson 2017; Johnson 2015; Johnson 2017; Kroeling 2013), although it appears the distinction between these two comparisons was ambiguous and interventions employed in these comparisons were similar. The credibility of the sham TENS intervention was generally poorly described and potentially problematic. The majority of reviews included studies which reported little specific detail with regard to efforts to create a credible sham. Reviews commonly reported on studies where sham TENS units were simply described as not producing an output (with no description as to whether the device appeared 'live' or not). Two reviews reported on studies where attempts to create a credible sham appeared optimal, with the device either delivering an initial output that quickly declined to zero (Johnson 2017); or employing a device which appeared 'live' (without producing a current) and also captured usage data to add in assessment of sham credibility (Gibson 2017).

We found that most reviews were unable to report across each of the pre-planned comparisons due to a lack of adequate data, with only two reviews able to report on the majority of the stated pre-planned comparisons (Johnson 2017; Kroeling 2013). TENS versus sham was the only pre-planned comparison that was consistently reported on for all reviews that found studies to include.

Quality of evidence

We found all eight reviews (that included studies to analyse) employed formal tools to assess risk of bias: five used the Cochrane 'Risk of bias' tool (Higgins 2011); one used an earlier version of this tool (Higgins 2008); two reviews used the Oxford Quality Scale (Jadad 1996); and one review used an "11 criteria methodological assessment tool" (Van Tulder 2003). Furthermore, four reviews employed the GRADE approach to rate the overall quality of the evidence (Gibson 2017; Johnson 2017; Kroeling 2013; Rutjes 2009). Four reviews assessed risk of bias but did not explicitly rate the quality of included evidence using the GRADE approach (Boldt 2014; Brosseau 2003; Hurlow 2012; Khadilkar 2008).

Gibson 2017 reported a pooled analysis on TENS versus sham and assessed the body of evidence using GRADE as 'very low' due to significant methodological limitations and imprecision. Rutjes 2009 performed a pooled analysis that combined sham and no intervention and used this combined comparator against active TENS. The authors of the review rated the quality of the evidence as 'very low' (methodological limitations and sample size) for pain intensity and 'low' for participants experiencing adverse events (methodological limitations). We deemed the approach of combining sham and no intervention data to be problematic, since we would predict that these different comparisons may be estimating different true effects.

We found similar 'very low' GRADE ratings for another two reviews reporting results of studies in narrative form. Johnson 2017 reported 'very low' GRADE ratings across all studies included due to the small number of studies, participants and events. Specifically for this overview, they reported on pain intensity and adverse effects as outcomes in the comparisons of TENS versus sham TENS, TENS versus no treatment/wait list, TENS plus exercise versus exercise alone and TENS versus other treatment. The same rating was applied to the evidence regarding pain intensity in the comparisons TENS versus sham TENS, TENS plus another treatment versus that treatment alone, TENS versus another treatment and comparisons of TENS delivered with different stimulation parameters from the review by Kroeling 2013 due to methodological limitations, lack of useable data and small studies.

Following consideration of risk of bias decisions across all four reviews that did not explicitly apply GRADE ratings and considering factors such as sample size and study design, we assessed the overall quality of evidence from each of these reviews to be 'very low' given the methodological limitations, significant heterogeneity and small sample sizes of included studies in reviews (Boldt 2014; Brosseau 2003; Hurlow 2012; Khadilkar 2008).

We reviewed risk of bias assessments for all studies in each review and found that blinding of participants, personnel and outcome assessment were particularly problematic, with the majority of included studies in every review assessed as being at 'unclear' or 'high' risk of bias in these domains. Six of the reviews also included a majority of studies which were assessed as being at 'unclear' or 'high' risk of bias across the domains of random sequence generation and allocation concealment (Brosseau 2003; Gibson 2017; Hurlow 2012; Johnson 2017; Kroeling 2013; Rutjes 2009). We also found four reviews which included a majority of studies assessed as being at 'unclear' or 'high' risk of bias for incomplete/selective outcome reporting. Lastly, in terms of common findings across reviews, we found small sample sizes (generally less than 30

per group) consistently across all included studies.

Methodological quality of included reviews

Overall, the quality of the included reviews was high with scores on the AMSTAR methodological rating tool (Table 3) assessed as seven (Hurlow 2012), nine (Brosseau 2003), 10 (Boldt 2014; Johnson 2015; Khadilkar 2008; Rutjes 2009), and 11 out of 11 (Gibson 2017; Johnson 2017; Kroeling 2013). Reviews were not awarded a score on the tool if information pertaining to the AMSTAR item was missing/not mentioned. Where the AMSTAR item was not applicable to any given review, the reviews were awarded the point for that item provided the item had been planned for/mentioned in the Methods section of the review. Reviews were not awarded a point for the following AMSTAR items: 'duplicate study selection and data extraction' (Hurlow 2012); 'status of publication used as an inclusion criterion' (Brosseau 2003; Hurlow 2012; Johnson 2015); 'assessment of publication bias' (Hurlow 2012); and lack of reporting of 'conflict of interest' for both the review and included studies in the review (Boldt 2014; Brosseau 2003; Hurlow 2012; Khadilkar 2008). One study combined the data from sham and no intervention groups and used this combined comparator against active TENS in a pooled analysis (Rutjes 2009). We considered this to be problematic as the two combined comparisons are likely not equivalent in terms of calculated effect size and we did not award a point under the AMSTAR item 'were the methods used to combine the findings of studies appropriate?'.

Effect of interventions

TENS versus sham

Primary Outcomes

Pain intensity

An overview of reviews results summary is provided in Table 4.

One review, on neuropathic pain, performed a pooled analysis of five studies (n = 207) investigating TENS versus sham and reported an MD of −1.58 (95% CI −2.08 to −1.09, P < 0.001, I^2 = 29%, P = 0.22) on a 0 to 10 scale favouring TENS (Gibson 2017). A second review (knee osteoarthritis) performed a pooled analysis of 12 studies (n = 465) investigating TENS versus sham/no intervention (combined) and reported an SMD of −0.85 (−1.36 to −0.34, P = 0.001, I^2 = 83%, P < 0.001) which was interpreted as a large effect size favouring TENS (Rutjes 2009). However, this review found significant asymmetry in the funnel plot, indicating the reported effect size may be affected by small study bias. We considered this pooled comparison to be flawed as the combination of sham/no intervention groups was in our view problematic given the likely differences in underlying effect sizes for these two groups in head-to-head comparisons with active TENS. We therefore have not presented this result in Table 4. Both reviews reporting pooled analysis rated quality of the evidence as very low.

For the remaining reviews (all narrative synthesis of individual studies) we found five that presented limited/sparse data which offered mixed results and no convincing evidence of effect for TENS versus sham in people with rheumatoid arthritis, cancer-related pain, fibromyalgia, chronic low back pain and neck pain (Brosseau 2003; Hurlow 2012; Johnson 2017; Khadilkar 2008; Kroeling 2013). One review assessing non-pharmacological interventions for chronic pain in people with spinal cord injury found just one TENS versus sham comparison study which used a combined scale of pain intensity and unpleasantness as the outcome measure (Boldt 2014). As such, we did not consider this review further.

The very low quality of the evidence across all reviews/conditions means it was not possible to state whether TENS effectively reduces pain intensity compared to sham in people with chronic pain.

Incidence and nature of adverse events

We did not find any reviews that provided pooled analysis data with respect to risk of adverse events. Three reviews explicitly reported no adverse events in the included studies (Boldt 2014; Brosseau 2003; Kroeling 2013). The remaining reviews did not provide further useable data: a minority of included studies provided data on adverse events (typically minor skin irritation at site of application) while the remaining studies either explicitly reported no adverse events or included studies in which no details of adverse events were provided (Gibson 2017; Hurlow 2012; Johnson 2017; Rutjes 2009). One study in one review reported one incident of severe dermatitis in a participant in the sham TENS group (Khadilkar 2008). None of the reviews considered the potential confounding factor that is application of electrodes in both active and sham interventions. Given reaction to local electrode placement appears to be the most frequently reported adverse event, this common exposure to the risk may result in lower accuracy in reporting of adverse events if estimates of these events are based on relative risk analysis.

The very low quality of the evidence and lack of data/reporting across all reviews/conditions means it was not possible to draw conclusions regarding adverse events.

Secondary Outcomes

Disability

We found two reviews that reported disability measures within the comparison TENS versus sham in people with chronic low back pain (Oswestry Disability Index, Low Back Pain Outcomes scale, Roland-Morris Disability Questionnaire) and knee osteoarthritis (WOMAC index) (Khadilkar 2008; Rutjes 2009). One review performed a pooled analysis of five studies (n = 195) investigating TENS versus sham/no intervention (combined) and reported a (non-significant) SMD of −0.33 (95% CI −0.69 to 0.03, P = 0.07, I^2 = 36%, P = 0.18) (Rutjes 2009). However, we considered this pooled comparison to be flawed as the combination of sham/no intervention groups was in our view problematic given the likely differences in underlying effect sizes for these two groups under head-to-head comparisons with active TENS. We therefore have not presented this result in Table 4. A second review provided narrative synthesis of two studies and concluded that TENS offered no improvement in functional status versus sham (Khadilkar 2008). Given the very low quality of the evidence and lack of data we were unable to make any conclusion on the effect of TENS versus sham on function in people with chronic pain.

Health-related quality of life

We did not find any reviews providing useable data or evidence for effect of TENS on this outcome for this comparison.

Analgesic medication use

We did not find any reviews providing useable data or evidence for effect of TENS on this outcome for this comparison.

Participant global impression of change (PGIC)

We did not find any reviews providing useable data or evidence for effect of TENS on this outcome for this comparison.

TENS versus usual care or no treatment or waiting list control

Primary outcomes

Pain intensity

We found three reviews including studies investigating TENS versus various forms of usual care or no treatment/waiting list in participants with neuropathic pain, fibromyalgia and neck pain (Gibson 2017; Johnson 2017; Kroeling 2013). All three of these reviews offered narrative synthesis only of the included studies. Gibson 2017 included 10 studies; Johnson 2017 described five studies; Kroeling 2013 described three studies. These reviews presented limited/sparse data across a range of pain-related outcome measures (e.g. NRS for pain intensity, 'tenderness' of tender points) and offered mixed results providing no convincing evidence of effect for TENS versus usual care or no treatment/wait list control. The limited data and very low quality of the evidence across all reviews/conditions means it was not possible to state whether TENS has a pain relieving effect compared to no treatment/waiting list in people with chronic pain.

Incidence and nature of adverse events

One review reported no adverse events in the included studies (Kroeling 2013). The remaining two reviews both reported minor skin irritation in three of the 15 (Gibson 2017) and three of the eight included studies (Johnson 2017). The very low quality of the evidence and lack of data/reporting across all reviews/conditions means it was not possible to make conclusions regarding adverse events.

Secondary Outcomes

Disability

We did not find any reviews providing useable data or evidence for effect of TENS on this outcome for this comparison.

Health-related quality of life

We did not find any reviews providing useable data or evidence for effect of TENS on this outcome for this comparison.

Analgesic medication use

We did not find any reviews providing useable data or evidence for effect of TENS on this outcome for this comparison.

Participant global impression of change

We did not find any reviews providing useable data or evidence for effect of TENS on this outcome for this comparison

TENS plus active intervention versus active intervention alone

Primary Outcomes

Pain intensity

We found two reviews including studies investigating TENS plus active interventions versus active intervention alone in participants with fibromyalgia and neck pain (Johnson 2017; Kroeling 2013).

Both reviews offered narrative synthesis only of the included studies. Johnson 2017 described two studies while Kroeling 2013 described three. These reviews presented limited/sparse data across a range of outcomes that may be considered proxy measures of the pain experience (e.g. pressure pain threshold, tenderness of tender points, tender point count) and offered either no benefit (Kroeling 2013) or mixed results (Johnson 2017), thus providing no convincing evidence of effect for TENS plus active intervention versus active intervention alone. The limited data and very low quality of the evidence across both reviews/conditions means it was not possible to state whether TENS has a pain-relieving effect when used as an adjunct to active care in people with chronic pain.

Incidence and nature of adverse events

Neither review found any report of adverse events for this comparison. The very low quality of the evidence and lack of data/events across both reviews/conditions means it was not possible to make conclusions regarding adverse events.

Secondary Outcomes

Disability

Neither review provided useable data or evidence for effect of TENS on this outcome for this comparison.

Health-related quality of life

One of the reviews in this comparison included two studies which used health-related quality of life outcome measures (Johnson 2017). However, the results were mixed and provided no convincing evidence of effect for TENS plus active interventions versus active intervention alone on health-related quality of life. The very low quality of the evidence and lack of data across both reviews/conditions means it was not possible to state whether TENS has an effect on health-related quality of life in people with chronic pain.

Analgesic medication use

Neither review provided useable data or evidence for effect of TENS on this outcome for this comparison.

Participant global impression of change

Neither review provided useable data or evidence for effect of TENS on this outcome for this comparison.

Comparisons between different types of TENS or TENS delivered using different stimulation parameters

Primary Outcomes

Pain intensity

We found two reviews reporting on studies investigating differing modes of TENS delivery in participants with chronic pain. Brosseau 2003, a review in participants with rheumatoid arthritis, described one study investigating C-TENS versus AL-TENS applied close to the painful joint with a third C-TENS application at a remote site. No difference between type of TENS in relief of pain intensity was reported. A second review described two studies investigating C-TENS versus frequency modulated TENS and C-TENS versus AL-TENS and 'burst' mode TENS (Kroeling 2013). This review reported no difference in effect across the differing modes of application. The limited data and very low quality of the evidence across both reviews/conditions means it was not possible to derive any conclusion regarding relative efficacy of differing modes of TENS application on pain intensity in people with chronic pain.

Incidence and nature of adverse events

Neither review found any report of adverse events for this comparison. The very low quality of the evidence and lack of data/events across both reviews/conditions means it was not possible to make conclusions regarding adverse events.

Secondary Outcomes

Disability

Neither review provided useable data or evidence for effect of TENS on this outcome for this comparison.

Health-related quality of life

Neither review provided useable data or evidence for effect of TENS on this outcome for this comparison.

Analgesic medication use

Neither review provided useable data or evidence for effect of TENS on this outcome for this comparison.

Participant global impression of change

One review - Brosseau 2003 - included one study that reported 'patient assessment of change in disease', which significantly favoured AL-TENS over C-TENS in people with rheumatoid arthritis; however this study had multiple methodological limitations, lack of data and a small sample size. We therefore concluded neither review provided useable data or evidence for effect of TENS on this outcome for this comparison.

Summary of inconsistencies in review approaches to assessing the evidence

We identified two key areas of methodological inconsistency between reviews that have the potential to influence the conclusions of reviews - blinding and risk of bias; and adequacy of TENS interventions.

Blinding and risk of bias

Reviews differed in approach to assessing risk of bias on the criterion of participant and personnel blinding. Some reviews made a priori decisions to not consider blinding of personnel/outcome assessors given the inherent challenges of doing this using sham TENS devices (Rutjes 2009), while for those reviews that did we found large variation in how risk of bias decisions were made. This inconsistency has the potential to lead to inconsistent conclusions and recommendations between reviews of TENS containing equivalent evidence.

Adequacy of TENS interventions

We found that a number of reviews included studies of single interventions with immediate outcome assessment. Other reviews specifically excluded this type of study as being not informative with respect to treatment effect in studies investigating TENS in people with chronic pain. Similarly some reviews did not specify a minimum dose of TENS in terms of establishing any requirement for interventions to deliver perceptible sensation, whereas others did specify this in their inclusion criteria. This raises the potential issue of including studies of TENS delivered at suboptimal doses.

DISCUSSION

Summary of main results

Our main objectives were to provide an overview of Cochrane Reviews of the effectiveness and safety of TENS to reduce pain in adults with chronic pain. Additionally, we aimed to review and identify inconsistency in approaches taken to evaluate the evidence in Cochrane Reviews of TENS for chronic pain. We planned to use this information to propose strategies that may usefully reduce uncertainty in establishing the effectiveness of TENS in chronic pain. We were primarily interested in the following comparisons: TENS versus sham, TENS versus usual care or no treatment or waiting list control, TENS plus active intervention versus active intervention alone and comparisons between different types of TENS or TENS delivered using different stimulation parameters.
We identified nine reviews across a range of conditions which aimed to either solely investigate TENS for chronic pain (Brosseau 2003; Gibson 2017; Hurlow 2012; Johnson 2015; Johnson 2017; Khadilkar 2008; Rutjes 2009), or assessed TENS as part of a suite of treatment interventions under review (Boldt 2014; Kroeling 2013). Overall, we found the quality of the reviews was high, with seven of the nine reviews scoring either 10 or 11 out of a maximum of 11 on the AMSTAR tool to assess methodological quality in systematic reviews (Shea 2007). We found two reviews which we assessed as scoring nine and seven (respectively) on the AMSTAR tool (Brosseau 2003; Hurlow 2012).
Despite the overall high quality of the methodology of included reviews, we found the evidence within the included reviews to be of very low quality. Four reviews formally rated the evidence using the GRADE approach and self-rated the evidence as very low quality (Gibson 2017; Johnson 2017; Kroeling 2013; Rutjes 2009). The remaining reviews did not explicitly use the GRADE approach; however following consideration of factors such as their risk of bias appraisal results and the size of included studies, we rated them also as offering very low quality evidence. One review employed pooled analysis suggesting a positive effect for TENS versus sham TENS (Gibson 2017); however the authors concluded that due to the very low quality of the evidence it was impossible to confidently state whether TENS had a pain relieving effect versus sham TENS. A second review investigated TENS versus combined sham/no treatment groups for pain intensity, adverse events and function (Rutjes 2009). However, we judged the combination of the sham and no treatment groups in this pooled analysis to be sufficiently problematic that we did not further consider this result.
Due most often to clinical heterogeneity the remaining reviews offered only narrative syntheses across the comparisons we were interested in. Detailed results of these narrative synthesis reviews are presented in the Effects of interventions section above but may be effectively summarised as offering (for all comparisons and outcomes) inconclusive findings derived from very limited data from single studies that provide very low quality evidence.
We found that despite included reviews spanning decades of research, this overview was unable to offer any reliable estimate of the effect of TENS in terms of pain intensity, safety (adverse events), disability, health-related quality of life, analgesic medication use and participant impression of change in people with chronic pain.

Overall completeness and applicability of

evidence

This overview was planned not only to investigate estimates of effect of TENS for chronic pain but to also identify inconsistency in approaches taken to evaluate the evidence in Cochrane Reviews of TENS for chronic pain. We found there was relatively little inconsistency in terms of the manner in which the reviews were conducted. Transparency of search strategies, selection, inclusion and exclusion of studies was overwhelmingly apparent. Three reviews did not explicitly mention status of publication (grey literature) as an inclusion/exclusion criterion (Brosseau 2003; Hurlow 2012; Johnson 2015); however remaining reviews provided reasonably complete reflections of available evidence. All reviews provided clear descriptions of characteristics of included studies, appraised scientific quality with formal tools and used results from this appraisal appropriately in formulating conclusions. The majority of reviews treated the data appropriately and considered publication bias.

We identified a number of areas representing inconsistency in review approach that we propose as worthy of further consideration. Firstly, it may be prudent to consider a reassessment of the decisions made around certain risk of bias domains in reviews with a view to promoting coherence. We found variation with respect to the rigour with which blinding was appraised. One review acknowledged the difficulty with blinding in electrostimulation studies and used this as justification for the decision to "not assess blinding of therapists and outcome assessors" (Rutjes 2009). Another review rated all included studies as being of 'high quality' despite two of the four included studies being judged to be high risk and two to be unclear risk on the domain of blinding of provider/therapist, while two of the four were judged 'unclear' for blinding of outcome assessor (Khadilkar 2008). This may be compared against the rigorous and detailed judgements made in other included reviews, for example Johnson 2017 where critical appraisal in this same risk of bias domain was explicit. Given the empirical evidence behind exaggeration of estimates of effect in studies with inadequate blinding (Savović 2012; Wood 2008), specifically in studies with self-reported outcomes, it is particularly important to ensure internal coherence across risk of bias decisions in these domains in future reviews.

Our second area of focus on inconsistency at the review level concerns the choice of outcome assessment measures for pain. The authors of a very recent review - Johnson 2017 - employed dichotomous categorisation of pain relief as per IMMPACT recommendations (Dworkin 2008) for their primary outcome measure. This responder analyses approach differed from other primary outcome measures in the included reviews in this overview. There may be merit in promoting responder analyses reporting within this field, particularly if TENS trials demonstrate bimodal outcome distributions similar to that reported by Moore 2013a, Moore 2014b and Moore 2014c. However, at present there is no clear evidence this is the case within the body of TENS evidence. Johnson 2017 also reported (as a secondary outcome) the mean group differences on pain intensity as per the remaining reviews. We suggest that continuing to report pain outcomes expressed as an average between-group difference of continuous scales, alongside responder data where they are available, should be encouraged to ensure efficient use of the available evidence.

We suggest that future reviews explicitly exclude studies in which the intervention is a single intervention with immediate post-intervention assessment. Six of the reviews in this overview included studies which were single interventions (Boldt 2014; Brosseau 2003; Hurlow 2012; Johnson 2017; Kroeling 2013; Rutjes 2009). We propose single intervention studies do not offer meaningful insight into treatment effectiveness of TENS as it is generally delivered.

At the level of individual studies there are a number of factors which we deemed important in limiting the ability of reviews to derive reliable estimates of the effect of TENS for chronic pain. Firstly, the majority of studies in the reviews that comprised this overview assessed pain outcomes upon cessation of the intervention with only one review, Johnson 2017, including a study where the effect of TENS on pain was assessed during application. Given that TENS is suggested to have optimal effect during application (Sluka 2013), we suggest future studies assess during use effects coupled with assessment of functional measures. Secondly, we found only four reviews described studies (n = 7) in which TENS was clearly self-administered at home (Gibson 2017; Hurlow 2012; Khadilkar 2008; Rutjes 2009). The remaining majority of studies in the included reviews employed a design whereby TENS was administered in the clinic. The benefits of researchers applying the intervention in this manner are clear in that the intervention can be standardised across all participants. However, this may in fact be a confounder in determining effectiveness of TENS as it is proposed that (optimally) TENS should be self-administered regularly throughout the day and intensities titrated to remain perceived as 'strong but comfortable' during use (Johnson 2011; Moran 2011; Sluka 2013). This is clearly very different from the typically reported model of delivery in included reviews: e.g. 20-minute sessions applied by the researcher in a clinical setting three to five times per week for 2 to 4 weeks.

We found the detail around description/reproducibility of the intervention across studies in the included reviews to be poor. Across all reviews, we were able to identify studies in which key information was missing with regard to the parameters of the TENS intervention. Additionally, in studies investigating TENS versus sham TENS, we found marked disparity in the likely validity of the sham device. Reviews included studies where the sham TENS unit simply did not deliver current and little detail was supplied regarding efforts to manage participant blinding around active/sham intervention with subsequent uncertainty around the credibility of the sham. This contrasts with more rigorous approaches to sham delivery in which demonstrable effort was made to maintain sham credibility; the TENS devices appearing live and featuring inherent data capture capabilities such that frequency and

duration of use can be contrasted between active and sham study arms allowing for inference around sham credibility (Buchmuller 2012; Dailey 2013). While designing a credible sham for TENS is a challenge, reviewers and study authors need to clearly consider and address the potential influence that different approaches to sham TENS may have on outcomes.

Lastly, the overwhelming majority of the primary studies included may be considered to be small in terms of sample size. The prevalence of small studies increases the risk of small-study biases and the related issue 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 overly positive picture in some comparisons (Dechartres 2013; Nüesch 2010).

Quality of the evidence

We found that four of the reviews assessed the quality of the included evidence to be very low and we deemed another four reviews as offering very low quality evidence. Despite 51 studies reviewed by eight reviews, we remain unable to state whether TENS is effective in terms of pain relief or make estimates around safety of TENS in people with chronic pain. Summary estimates of effects presented in this overview and those offered by included reviews should be viewed with very limited confidence and the true effect is likely to be very different.

Potential biases in the overview process

This Cochrane overview used a comprehensive search strategy which was designed and implemented under expert guidance by the Cochrane Pain, Palliative and Supportive Care Review Group. This was an overview of Cochrane Reviews and the search was conducted across all years up to 2018 within the *Cochrane Database of Systematic Reviews*. Given the expert design and implementation of the search, it is reasonable to suggest this overview offers a current summation of the Cochrane Reviews investigating the effect of TENS in people with chronic pain. Of the nine reviews, we found all published well designed, comprehensive search strategies. Of these, eight explicitly stated no language restrictions in their searches, while one appeared to restrict searches to English (Brosseau 2003). Only three of the nine reviews did not explicitly mention searching of unpublished trials/grey literature (Brosseau 2003; Hurlow 2012; Johnson 2015). One review was not eligible for inclusion in this overview as it was withdrawn (Nnoaham 2008). The review in question had been replaced by its host review group with two more focused reviews that utilised more up-to-date review methods - both are included in this overview (Gibson 2017; Johnson 2017). In the interests of completeness, we screened this withdrawn review with respect to whether any additional studies were included which may be missing from the body of evidence assessed in this overview of reviews. The vast majority of studies were either found within reviews included in this overview or were excluded (with reasons given) by the original review authors. We found six studies in the withdrawn review which were not found in the reviews included in this overview; however we assessed three of these studies as not providing useable data (Ballegaard 1985; Köke 2004; Nash 1990), while the remaining three offered ambiguous conclusions derived from small sample-size studies which were designated as (at least) 'unclear' risk of bias (Al-Smadi 2003; Moore 1997; Warke 2006). As such, these studies would have no impact on conclusions drawn in this review. Overall, we are confident this overview of reviews is therefore reflective of the current wider body of studies investigating TENS in people with chronic pain. One of the reviews included in this overview was authored by three members of this overview author team (WG, NEO and BMW). As such, there may have been a risk of potential bias with review and appraisal of this work. We minimised this risk by allocating data extraction and quality assessment to a member of the author team who was not an author on the original review (MC). The authors were not blinded to authors' names or institutions in the review selection process; however review selection was performed by two authors independently, thereby minimising risk of bias.

Agreements and disagreements with other studies or reviews

Due to the very low quality of the evidence and sample sizes across studies in included reviews, this overview is unable to reach any conclusion with respect to effectiveness or safety of TENS for people with chronic pain. This conclusion regarding quality of the evidence and inability to state effectiveness is internally consistent with that reached by every review selected for inclusion. A similar lack of confidence in estimates of the effects of the intervention and significant problems with quality of the evidence was reported in a recent (non-Cochrane) systematic review examining TENS versus placebo/control for pain intensity in participants with chronic low back/neck pain (Resende 2018).

AUTHORS' CONCLUSIONS

Implications for practice

For people with chronic pain

This overview offers a summation of very low quality evidence and we cannot confidently make any statement regarding the effectiveness of TENS for people with chronic pain. The very low

quality of all reviewed evidence means we have very limited confidence in any suggested estimate of effect for all outcomes and the true effect is likely to be different from that summarised here and within individual reviews. A number of reviews reported minor skin irritation at the site of application, one review included one study in which a participant developed a severe skin rash following sham TENS use. Typically, reviews also included studies reporting either no adverse events or did not report adverse events. We therefore cannot make any meaningful comment on adverse events associated with TENS.

For clinicians

This overview is unable to derive any conclusions regarding the efficacy/effectiveness of 1) TENS versus sham, 2) TENS versus usual care or no treatment or waiting list control, 3) TENS plus active intervention versus active intervention alone or 4) comparisons between different types of TENS or TENS delivered using different stimulation parameters in people with chronic pain for pain intensity, disability, health-related quality of life, analgesic medication use or participant impression of change. This is due to limited data, methodological limitations (with subsequent risk of bias) and predominantly small sample sizes leading to the evidence within all reviews being assessed as very low quality. This means estimates of effect summarised here and within individual reviews should be viewed with very limited confidence and the true effect is likely to be different from that reported here. A number of reviews reported mainly minor skin irritation (one case of severe rash in one review), while the remainder either reported no adverse events or did not report on adverse events. We were unable to make any statement regarding risk of adverse events with TENS for chronic pain.

For policy makers and funders

This overview provides no evidence to either support or refute the use of TENS in people with chronic pain. The conclusions reported in this overview reflect review results derived from studies that had overall substantial methodological limitations and were predominantly small in size.

Implications for research

Design of new trials

The overwhelming factors limiting the accurate estimation of effectiveness in TENS for chronic pain are the methodological limitations of studies from all included reviews. Analysis of risk of bias in the reviews reveals a consistent pattern with multiple ratings of high or unclear risk of bias decisions in the domains of allocation concealment, blinding (participants, personnel and outcome assessors), incomplete outcome data, selective reporting and size of study. This speaks to a problem of research waste in TENS research.

Clear published guidelines on reporting of study design for non-pharmacological treatments are available in the public domain through the CONSORT statement and associated checklist (Boutron 2017). Careful analysis and implementation of the checklist into study design would greatly improve many of the common methodological and reporting problems seen in TENS for chronic pain studies. A key part of this should include clear descriptions of the intervention. TENS delivery encompasses multiple factors (frequency of applied stimulation, intensity of stimulation, duration, frequency of application etc.) which may influence outcome and a critical review of methodological quality in TENS studies has been published which may usefully inform future work (Bennett 2011). TENS may be considered a complex non-pharmacologic intervention and published checklists of templates for intervention description and replication are available (TIDieR checklist) which are specifically designed to assist in reporting of complex interventions (Hoffmann 2014). Future researchers and systematic review authors would benefit from the implementation of this template into TENS research designs.

Blinding of participants and care providers in physical interventions is an acknowledged difficulty. However, the observed variation in efforts to maintain naivety of participants/personnel to sham TENS in this overview is another source of ambiguity in estimates of effect of TENS for chronic pain. Devices are now available which appear 'live', deliver initial current before fading to zero and are suggested as being viable devices to maintain blinding (Rakel 2010). Efforts to use similar sham devices combined with the good sham TENS practice employed by Buchmuller 2012, and Dailey 2013 are worth considering for future studies.

TENS is a simple-to-use, portable, self-administered and relatively inexpensive treatment intervention. With this in mind, it is recommended that future studies in this area take advantage of the ease of use and cost to scale up to larger trials possibly through multi-centre designs where the intervention is self-administered but at doses and stimulation parameters consistent with proposed best practice (Sluka 2013). Further repetition of small sample-size studies is unlikely to add any clarity to the ambiguity surrounding estimates of effect for TENS in people with chronic pain. We suggest that given the exaggerated effects associated with meta-analyses of small sample-size studies (Dechartres 2013), researchers seeking to further investigate this area do not replicate the numerous existing small studies and instead aim for samples of sufficient size to produce robust estimates of effectiveness (Guyatt 2011; Higgins 2011). Self-administration (as opposed to clinic administration) may address issues around adequate duration and frequency of treatment as well as allowing the participant to monitor/titrate intensity of stimulation, as optimal effects are suggested when the perception is adjusted to maintain continual 'strong but comfortable' sensation (Johnson 2011; Moran 2011; Sluka 2013).

Large-scale self-administration designs are more likely to provide pragmatic estimates of the effect of TENS in people with chronic pain.

Outcome measures

This overview reviewed evidence from 51 studies across eight reviews. Of these, the majority of interventions were less than 6 weeks' duration and most of the follow-up assessment time points were either immediately post intervention or within two weeks, rendering these short-term follow-up studies. It is worth noting that the nature of conditions included in these reviews means the chronic pain is inherently resistant to change and is by definition persistent. The value of short-term interventions and follow-up in TENS studies must be questioned. We recommend future studies should be designed such that interventions are of sufficient duration to assess change and also that follow-up time points ideally extend to at least three months post-intervention, as well as capturing effects during use.

We found a lack of detail with respect to timing and the specific parameters of pain assessment in the studies from included reviews. No reviews explicitly stated minimal pain level for study inclusion which may influence sensitivity of studies to detect intervention effects. We suggest this be considered for future studies. With respect to timing of assessment, TENS is purported to have a rapid onset and offset of effect (Moran 2011); we therefore suggest pain (and health-related quality of life measures) should be assessed during TENS use or, ideally, during TENS use while undertaking normal daily activities as well as via explicitly stated summary pain measures such as average 24-hour pain or average weekly pain. Additionally, dichotomous categorisation of pain relief as per IMMPACT recommendations (Dworkin 2008), or by assessing the proportion of people who perceive their pain as reduced to 'no worse than mild' may offer outcomes that are directly meaningful to people with pain (Moore 2013b).

Measures of treatment effect are obviously important; however treatment safety is paramount. On balance, the standard of reporting of adverse events across all studies included in reviews was poor. Researchers should consider recording and full reporting of adverse events to be an implicit aspect of good study design.

Design of future systematic reviews

Future reviews of TENS should take a consistent approach to important methodological considerations that affect TENS trials. We recommend this includes taking a clear and consistent approach to assessing blinding of participants and personnel and recognising that, while blinding studies of TENS is challenging, this represents an important risk of bias that must be adequately considered. We would also recommend that studies which deliver TENS at a sub-perceptual level or in a single dose should not be included in future reviews since it is reasonable to predict that such doses are sub-optimal. Finally when pooling data review authors should be careful not to include comparisons of TENS versus sham and TENS versus no treatment in the same analysis.

ACKNOWLEDGEMENTS

We would like to thank Joanne Abbott, Infomation Specialist of the Cochrane PaPaS Group, for her advice in devising the search strategy. Many thanks also to Kerry Harding for ongoing editorial assistance.

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

The authors would like to thank the following peer reviewers: Rae Frances Bell, Mark I. Johnson, Carol G.T. Vance and Corrie Billedeau.

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* *Indicates the major publication for the study*

ADDITIONAL TABLES

Table 1. Details of ongoing reviews

Reference	Review aim	Dates/notes
Odebiyi 2013	To investigate TENS in the management of chronic LBP	Published Issue 4, 2013
Pal 2017	To investigate TENS for pain management in sickle cell disease	Published Issue 8, 2017
Porfírio 2015	To investigate TENS for chronic neck pain	Published Issue 10, 2015

Table 2. Characteristics of included reviews

Review	Date assessed as up to date	Population	Interventions	Comparison interventions	Outcomes for which data were reported	Review limitations
Boldt 2014	1 March 2011	People with spinal cord injury-related pain that has persisted for > 3 months	All standard modes of TENS	Active, sham, waiting list	Pain intensity reported as a subset of 'Descriptor Differentation Scale' (DDS)	Limited studies found. Pain intensity was reported on a composite scale of 'intensity' and 'unpleasantness'. No pooled analysis performed
Brosseau 2003	October 2002	People aged 18 years or more, with clinical and/or radiological confirmation of rheumatoid arthritis of the hand (diagnosis defined accord-	All standard modes of TENS	Comparisons of different TENS modes, sham	Pain intensity (resting and grip pain), disability (functional status), patient global impression of change	Limited studies found. No pooled analysis performed

Table 2. Characteristics of included reviews (*Continued*)

		ing to the criteria of the American Rheumatism Association (ARA 1987))				
Gibson 2017	September 2016	People aged 18 years or more with neuropathic pain from a wide range of conditions	All standard modes of TENS delivered at clearly perceptible levels	Sham, usual care, no treatment, TENS plus usual care versus usual care alone	Pain intensity	Limited, low-quality, small sample studies used in pooled analysis. Only pain intensity reported in pooled analysis
Hurlow 2013	16 November 2011	People aged 18 or more, with cancer-related pain, cancer treatment-related pain or both that has persisted for > 3 months	Conventional TENS, delivered at intensities reported as 'strong but comfortable' at the site of pain or over nerve bundles proximal to the site of pain. Studies where TENS was delivered at intensities reported as 'barely perceptible' or 'mild' were excluded	No active stimulation, no treatment	Pain intensity, adverse events	Limited number of studies. No pooled analysis performed
Johnson 2015	1 March 2015	People aged 16 or more, with any limb amputation resulting in phantom pain, stump pain, or both	All standard modes of TENS, delivered at intensities reported as 'strong and comfortable' at the site of pain, over nerve bundles proximal to the site of pain, on the contralateral limb at the mirror site to the phantom pain, or known	Active, sham, no treatment	None	No studies found

Table 2. Characteristics of included reviews (*Continued*)

			acupuncture points. Studies where TENS was delivered at intensities reported as 'barely perceptible', 'faint' or 'mild' were excluded. Studies that administered TENS using a standard TENS device, Neuromuscular Electrical Stimulation device, Functional Electrical Stimulation, Interferential Current devices or single electrode probes were included			
Johnson 2017	18 January 2017	People aged 18 years or more with fibromyalgia	TENS administered using a standard TENS device and all modes of delivery at a perceptible level	Sham, no treatment/ wait list control, usual care, other treatment	Pain relief, pain intensity, adverse events	No studies reported data in useable dichotomous format for participant-reported pain relief. No pooled analysis performed
Khadilkar 2008	19 July 2007	Outpatients aged 18 or more, with low back pain (localised between the inferior gluteal fold and the costal margin in the absence of malignancy, infection, fracture, inflamma- tory disorder or neurological syndrome) that has	All standard modes of TENS. Studies that administered TENS or sham TENS percutaneously using acupuncture needles were excluded	Active, sham	Pain intensity, adverse effects, disability (back specific function), health-related quality of life (general health)	No pooled analysis performed due to clinical heterogeneity across included studies

Table 2. Characteristics of included reviews (*Continued*)

		persisted for > 12 weeks				
Kroeling 2013	August 2012	People aged 18 or more, with neck pain (non-specific mechanical neck pain including whiplash-associated disorder categories I and II, myofacial neck pain, and degenerative change-related pain) that has persisted for > 12 weeks	All standard modes of TENS	Active, sham, comparisons of different TENS modes	Pain intensity, neck pain disability	No pooled analysis performed due to clinical heterogeneity across included studies
Rutjes 2009	1 February 2009	Studies including at least 75% of patients with clinically and/or radiologically confirmed osteoarthritis of the knee	All standard modes of TENS	Sham, no treatment	Pain intensity, adverse effects, function	Pooled analysis performed for pain intensity, adverse effects and function. However pooled analysis was performed by combining 'sham' and 'no treatment' together and comparing against active TENS intervention

Table 3. AMSTAR quality assessment

AMSTAR item	Author								
	Boldt 2014	Brosseau 2003	Gibson 2017	Hurlow 2013	Johnson 2015	Johnson 2017	Khadilkar 2008	Kroeling 2013	Rutjes 2009
1. a priori design provided?	Y	Y	Y	Y	Y	Y	Y	Y	Y

Table 3. AMSTAR quality assessment (*Continued*)

2. Duplicate study selection and data extraction?	Y	Y	Y	U	Y	Y	Y	Y	Y
3. Comprehensive literature search performed?	Y	Y	Y	Y	Y	Y	Y	Y	Y
4. Status of publication used as inclusion criterion?	Y	N	Y	N	N	Y	Y	Y	Y
5. List of studies included and excluded provided?	Y	Y	Y	Y	Y	Y	Y	Y	Y
6. Characteristics of the included studies provided?	Y	Y	Y	Y	Y	Y	Y	Y	Y
7. Scientific quality of the included studies assessed and documented?	Y	Y	Y	Y	Y	Y	Y	Y	Y
8. Scientific quality of the included studies used appropriately in formu-	Y	Y	Y	Y	N/A	Y	Y	Y	Y

Table 3. AMSTAR quality assessment (*Continued*)

lating conclusions?									
9. Methods used to combine the findings of studies appropriate?	N/A	N/A	Y	N/A	N/A	N/A	N/A	N/A	N
10. Likelihood of publication bias assessed?	Y	N/A	Y	N	N/A	Y	Y	Y	Y
11. Conflict of interest stated?	N	N	Y	N	Y	Y	N	Y	Y
Total score /11	10	9	11	7	10	11	10	11	10

Table 4. Overview of reviews

TENS for Chronic Pain in adults						
Comparison		Illustrative effect estimates (95% CI)	Illustrative relative risk estimates (95% CI)	Number of participants (number of studies included in review)	Quality of the evidence (GRADE)	Comments
Outcome: Pain intensity						
TENS vs sham	Boldt 2014	Limited data, not calculable	Not calculated	40 (1 study)	⊕◯◯◯ Very low	Limited data, pooled analysis not performed
	Brosseau 2003	Limited data, not calculable	Not calculated	78 (3 studies)	⊕◯◯◯ Very low	Limited data, pooled analysis not performed
	Gibson 2017	(0 to 10 VAS) −1.58 (95% CI −2.08 to −1.09)	Not calculated	728 (15 studies) Pooled analysis: 207 (5 studies)	⊕◯◯◯ Very low	Significant methodological limita-

Table 4. Overview of reviews (*Continued*)

						tions across the five pooled trials as well as small sample size of trials and issues with participant blinding in trials
	Hurlow 2012	Limited data, not calculable	Not calculated	88 (3 studies)	⊕◯◯◯ Very low	Limited data, pooled analysis not performed
	Johnson 2015	No data	Not calculable	0 (no studies)	n/a	No studies identified
	Johnson 2017	Not calculable	Not calculated	315 (8 studies)	⊕◯◯◯ Very low	Pooled analysis not performed
	Khadilkar 2008	Not calculable	Not calculated	485 (4 studies)	⊕◯◯◯ Very low	Pooled analysis not performed
	Kroeling 2013	Not calculable	Not calculated	472 (6 studies)	⊕◯◯◯ Very low	Pooled analysis not performed
	Rutjes 2009	Not calculable	Not calculated	465 (12 studies)	⊕◯◯◯ Very low	Pooled analysis was performed but the analysis combined sham and no treatment studies and compared these against active TENS. For this overview, the result is therefore severely compromised. The estimate of the effect is deemed 'not calculable'
TENs vs usual care/no treatment/wait list	No pooled analysis across remaining comparisons in any included reviews	Limited data; not calculable	Limited data; not calculable	No pooled analysis	⊕◯◯◯ Very low	Limited data reported in reviews for this comparison.

Table 4. Overview of reviews (*Continued*)

TENS plus active intervention vs active intervention		Limited data; not calculable	Limited data; not calculable	No pooled analysis	⊕◯◯◯ Very low	Limited data reported in reviews for this comparison.
TENS vs TENS (differing parameters of application)		Limited data; not calculable	Limited data; not calculable	No pooled analysis	⊕◯◯◯ Very low	Limited data reported in reviews for this comparison.
Outcome: Incidence of adverse events						
No pooled analysis across all comparisons in any included review		Limited data; not calculable	Limited data; not calculable	No pooled analysis	⊕◯◯◯ Very low	Limited data reported in reviews for this comparison
Outcome: Change in daily activity						
No pooled analysis across all comparisons in any included review		Limited data; not calculable	Limited data; not calculable	No pooled analysis	⊕◯◯◯ Very low	Limited data reported in reviews for this comparison. Pooled analysis not reported
Outcome: Change in quality of life						
No pooled analysis across all comparisons in any included review		Limited data; not calculable	Limited data; not calculable	No pooled analysis	⊕◯◯◯ Very low	Limited data reported in reviews for this comparison. Pooled analysis not reported
Outcome: Change in medication use						
No pooled analysis across all comparisons in any included review		Limited data; not calculable	Limited data; not calculable	No pooled analysis	⊕◯◯◯ Very low	Limited data reported in reviews for this comparison. Pooled analysis not reported
Outcome: Global impression of change in condition						
No pooled analysis across all comparisons in any included review		Limited data; not calculable	Limited data; not calculable	No pooled analysis	⊕◯◯◯ Very low	Limited data reported in reviews for this comparison. Pooled analysis not reported

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

HISTORY

Protocol first published: Issue 9, 2015

Review first published: Issue 2, 2019

Date	Event	Description
1 October 2015	Amended	Minor corrections.

CONTRIBUTIONS OF AUTHORS

WG closely informed the protocol design, applied eligibility criteria, extracted and analysed data, led full write-up of the overview and will lead in the updating of the overview.

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

CM closely informed the protocol design and contributed to the write-up of the review.

MJC closely informed the protocol development as primary author, implemented the search strategy with the Cochrane PaPaS Group's Information Specialist, applied eligibility criteria, extracted data, contributed to the write-up of the review and will assist in the updating of the overview.

NEO led the protocol development, helped to implement the search strategy, applied eligibility criteria, extracted and analysed data, assisted the write-up and will contribute to updating of the overview.

DECLARATIONS OF INTEREST

WG: none known.

BMW: none known.

CM: none known.

MJC: none known.

NEO: none known.

SOURCES OF SUPPORT

Internal sources

- The University of Notre Dame Australia, Fremantle, Australia.
- Brunel University London, UK.
- Anglia Ruskin University, Cambridge, UK.
- University of South Australia, Adelaide, Australia.

External sources

- No sources of support supplied