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[Intervention Protocol]

Transcutaneous Electrical Nerve Stimulation (TENS) for fibromyalgia in adults

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ABSTRACT

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

To assess the analgesic efficacy and adverse events of TENS for fibromyalgia in adults. We will assess TENS on its own or added to usual care in comparisons with placebo (sham) TENS, usual care, or no treatment.

BACKGROUND

This protocol is based on a template for reviews of drugs used to relieve fibromyalgia. The aim is for all reviews to use the same methods, based on new criteria for what constitutes reliable evidence in chronic pain (Moore 2010a; Appendix 1).

Description of the condition

Fibromyalgia is a long-term medical condition that is characterised by chronic widespread pain in the muscles and joints, with sensitivity to pressure stimuli. The symptoms may vary from person to person, but the main symptom is widespread pain throughout the body. This may be worse in certain areas, such as the back or neck. Pain may be described as aching, burning, stabbing, or sharp and may be accompanied by hyperalgesia (heightened sensitivity to pain) and allodynia (pain on very mild stimulus).

Pain is often continuous but it may fluctuate in severity depending on various factors including stress, physical activity, and the weather. Exposure to certain environmental stimuli (e.g. smoke, certain foods, and bright lights) may cause flare-ups. Other presenting symptoms may include stiffness, especially in the morning; muscle spasm; depression; fatigue; poor sleep quality, including non-restorative sleep; cognitive difficulties in thinking, learning, attention and concentration; headaches, including severe migraines; and irritable bowel syndrome (Wolfe 2014). Originally, the American College of Rheumatology diagnostic criteria for fibromyalgia were widespread pain (axial pain, left- and right-sided pain, upper and lower segment pain) that lasts for longer than three months, with pain on palpation at 11 or more of 18 specified tender points (Wolfe 1990). More recently, a definition of fibromyalgia has been proposed based on symptom severity and the presence of widespread pain, which does not require palpation

of tender points for diagnosis (Wolfe 2010). Thus, fibromyalgia is diagnosed if the patient has: a widespread pain index (WPI) of ≥ 7 and a symptom severity scale score of ≥ 5 , or a WPI of between 3 and 6 and a symptom severity scale score of ≥ 9 ; symptoms have persisted at a similar level for ≥ 3 months; and the pain cannot be explained by another disorder.

While some rheumatologists have thought of fibromyalgia as a specific pain disorder, other investigators have characterised it as a bodily distress syndrome or a physical symptom disorder, or somatoform disorder (Wolfe 2014). It is a heterogeneous condition in which there is abnormal processing of the sensation of pain. The cause, or causes, are not well understood, but it has features in common with neuropathic pain, including changes in the central nervous system (CNS). Moreover, people with neuropathic pain and people with fibromyalgia experience similar sensory phenomena (Koroschetz 2011). Many people with fibromyalgia are significantly disabled, and experience moderate or severe pain for many years. Chronic painful conditions comprised five of the 11 top-ranking conditions for years lived with disability in 2010 (Vos 2012), and are responsible for considerable loss of quality of life, employment, and increased health costs (Moore 2014a).

Fibromyalgia is common. Numerous studies have investigated prevalence in different settings and countries. The Queiroz 2013 review gives a global mean prevalence of 2.7% (range 0.4% to 9.3%), and a mean in the Americas of 3.1%, in Europe of 2.5%, and in Asia of 1.7%. Fibromyalgia is more common in women, with a female to male ratio of 3:1 (4.2%:1.4%). The change in diagnostic criteria does not appear to have significantly affected estimates of prevalence (Wolfe 2013). Estimates of prevalence in specific populations vary greatly, but have been reported to be as high as 9% in female textile workers in Turkey and 10% in metalworkers in Brazil (59% in those with repetitive strain injury; Queiroz 2013). Risk factors for fibromyalgia include: sex (it is more common in women than in men); family history (it is more likely if a relative has the condition); and rheumatic disease (rheumatoid arthritis or lupus). The financial burden of fibromyalgia on society is significant. A cross-sectional study on 299 patients with fibromyalgia in France and Germany estimated that, on average, patients visited their physician 11.6 (France) and 19.6 (Germany) times per year and missed 32.4 and 25.2 days of work per year respectively (Winklemann 2011). Total annual costs to society based on three-month data from 2008 were EUR 7900 in France and EUR 7256 in Germany per person. Direct costs from physician office visits, medications, and out-of-pocket expenses were EUR 910 (France) and EUR 1765 (Germany), and indirect costs from missed days of work and lost productivity were EUR 6990 (France) and EUR 5491 (Germany). Costs were found to increase by more than 200% for mild and severe fibromyalgia. There are no definitive treatments for fibromyalgia. Fibromyalgia pain is difficult to treat effectively, with only a minority of individuals experiencing a clinically relevant benefit from any one intervention. A multidisciplinary approach is now advocated, with

pharmacological interventions being combined with physical or cognitive interventions, or both. Conventional analgesics are usually not effective. Treatment is often by so-called unconventional analgesics, such as antidepressants like duloxetine and amitriptyline (Lunn 2014; Moore 2012a; Sultan 2008), or antiepileptics like gabapentin or pregabalin (Moore 2009; Moore 2011a; Wiffen 2013). The proportion of people who achieve worthwhile pain relief (typically at least a 50% reduction in pain intensity; Moore 2013b) is small, generally only 10% to 25% more than with placebo, with numbers needed to treat to benefit (NNTB) usually between 4 and 10 (Wiffen 2013). Those who do experience good levels of pain relief, however, also benefit from substantial reductions in other symptoms, such as fatigue, function, sleep, depression, anxiety, and ability to work, with significant improvement in quality of life (Moore 2010b; Moore 2014a; Straube 2011). Fibromyalgia is not particularly different from other chronic pain in that only a small proportion of trial participants have a good response to treatment (Moore 2013b).

Description of the intervention

Transcutaneous Electrical Nerve Stimulation (TENS) is the delivery of pulsed electrical currents across the intact surface of the skin to stimulate peripheral nerves, principally for pain relief (APTA 2001; Johnson 2014). TENS treatment is usually self administered by the patient, ideally following instruction from a healthcare practitioner. A portable, battery-powered TENS device is used to produce the electrical currents and these are delivered to the body using self adhering electrodes attached to the surface of the skin. TENS is inexpensive, with a good safety profile compared with medication. TENS devices and accessories (lead wires and self adhering electrodes) are available without prescription. Robust safety guidelines have been published by professional bodies to guide judgements about the appropriateness of TENS in certain situations (Houghton 2010). Contraindications include patients who also have cardiac pacemakers and implantable cardioverter defibrillators. Precautions include pregnancy, epilepsy, active malignancy, deep-vein thrombosis, and frail or damaged skin (Johnson 2011).

TENS devices create pulsed currents with asymmetrical biphasic rectangular or symmetrical biphasic rectangular waveforms. TENS devices are designed so that users can adjust the electrical characteristics of the currents including: pulse frequency (usually < 200 Hz), pulse amplitude (usually < 70 mA), pulse duration (usually 50 to 250 microseconds), and pulse pattern (sometimes termed 'mode' and including continuous, burst, and modulated). Modulated pulse patterns may help to reduce tolerance to TENS caused by repeated use and include modulated frequency, modulated amplitude, and modulated duration (Sluka 2013).

Two TENS techniques have been defined by the International Association for the Study of Pain and are commonly used in the literature (Charlton 2005): conventional TENS administered us-

ing high-frequency, low-intensity currents to produce a strong non-painful TENS sensation; and acupuncture-like TENS (AL-TENS) using low-frequency, high-intensity currents to produce strong non-painful pulsate sensations, phasic muscle contractions (twitching), or both (Claydon 2008a). Low-frequency TENS is consistently defined as the delivery of pulsed current ≤ 10 Hz or low-frequency trains (bursts) of high-frequency pulsed current (i.e. burst mode TENS). High-frequency TENS is often described as pulsed current between ~ 50 Hz and 100 Hz, although this neglects frequencies between 11 Hz and 49 Hz and frequencies above 100 Hz. The term medium-frequency TENS is rarely used in the literature so high-frequency TENS should be used to describe frequencies > 10 Hz to the maximum setting on the TENS device, which is usually 150 Hz to 200 Hz (Johnson 2014). High-frequency TENS is not always applied at a low intensity and low-frequency TENS is not always applied at a high intensity. Low-frequency TENS applied 10% below motor threshold has been shown to generate analgesia in humans and reduce primary and secondary joint inflammation in animal models of nociception (Chen 2008; King 2001; Sluka 1998; Sluka 2013; Vance 2007). The critical factor for response to TENS is the perceptual experience of the intensity of currents during stimulation regardless of frequency. Evidence suggests that optimal hypoalgesia is achieved using pulse amplitudes (mA) that generate a strong, non-painful TENS sensation and therefore pulse amplitude should be titrated during treatment to maintain this intensity level (Bjordal 2003; Moran 2011; Sluka 2013). Thus, this review will include a subgroup analysis of intensity ('strong' versus 'barely perceptible'), frequency (low-frequency versus high-frequency when intensity is 'strong'), and technique (conventional TENS versus AL-TENS). Response to TENS is also influenced by site of stimulation according to the placement of electrodes. Best practice guidelines suggest that electrodes should be placed on healthy sensate skin so that the TENS sensation covers (permeates) the painful area. This is achieved by placing electrodes directly over or 'bracketing' the painful site. This may not always be possible because, for example, skin sensation is altered, there is a skin lesion, or a body part is absent. In these circumstances electrodes are placed over the main nerves proximal to the site of pain, close to vertebrae of spinal segments, over contralateral dermatomes, over acupuncture points (acu-TENS), or over myofascial trigger points. Research findings on the effect of the site of stimulation on treatment outcome are ambiguous (Johnson 2014). Consideration also needs to be given to the duration and regularity of treatment and the timing of outcome measurements. In particular, evidence suggests that the effects of TENS are maximal during stimulation or immediately after stimulation (Sluka 2013), and that some studies have failed to measure outcome during stimulation (Bennett 2011; Bjordal 2003). Thus, this review will include a subgroup analysis: during TENS versus after TENS.

How the intervention might work

The theoretical underpinning for pain relief by electrical stimulation of the skin was established through the publication of the Gate Control Theory of Pain by Melzack and Wall (Melzack 1965). They proposed that neural activity in low-threshold cutaneous afferents (e.g. A-beta axons) would inhibit onward transmission of nociceptive (pain-related) information in the spinal cord and brainstem. Normally, activity in low-threshold cutaneous afferents is generated by low-intensity mechanical stimuli such as 'rubbing the skin'. They suggested that electrical currents could be used to stimulate the low-threshold cutaneous afferents to reduce pain. The physiological intention of using conventional TENS is to generate a strong but non-painful TENS sensation as this is indicative of selective activation of low-threshold cutaneous afferents (A-beta axons). Evidence suggests that this inhibits onward transmission of nociceptive information at the first synapse in the spinal cord or brain stem (i.e. segmental modulation; Garrison 1996; Ma 2001). The intention of using AL-TENS is to generate pulsate sensations in the skin and underlying tissue or non-painful muscle twitching (or both) as this produces neural activity in small diameter muscle afferents leading to activation of descending pain inhibitory pathways (DeSantana 2009; Francis 2011; Kalra 2001; Milan 2002). TENS may also reduce nociceptive input to the central nervous system by blocking incoming afferent activity in peripheral neurons, creating a 'busy-line' effect (Nardone 1989).

Research on animals suggests that low-frequency TENS, when administered just below motor threshold, mediates effects via noradrenaline, serotonin, and mu opioid systems and high-frequency TENS, when administered just below motor threshold, mediates effects via noradrenaline, GABA, and delta opioid systems (Kalra 2001; Leonard 2010; Maeda 2007; Santos 2013; Sluka 1999; Sluka 2006; Somers 2009). Whether the frequency-mediated effects of TENS translate into differential hypoalgesia in humans when the intensity of TENS is kept constant remains in doubt (Chen 2008; Claydon 2008a). There is evidence that long-term use of opioid medication may impact negatively on response to low-frequency TENS but not on response to high-frequency TENS (Sluka 2000). Leonard 2011 found that high-frequency TENS reduced pain in 12 opioid-treated chronic pain patients and 11 opioid-naïve chronic pain patients, whereas low-frequency TENS only reduced pain in the non-opioid group. The lack of pain relief during low-frequency TENS was attributed to the development of μ -opioid receptor tolerance.

Sham credibility issues in trials of TENS

Bennett 2011 examined aspects of fidelity that may contribute to a risk of bias in TENS studies. Factors that contributed to the overestimation of TENS effects included inadequate method of randomisation, small sample sizes, and issues associated with the implementation of a sham (placebo) control such as allocation concealment and how blinding was maintained. Various types of

sham control have been used in TENS studies, including deactivated TENS devices that are identical in appearance but deliver no current and TENS devices that deliver stimulation at the start of treatment and fade to zero current output over a brief period of time (e.g. within 45 seconds) (Rakel 2010). There are threats to the credibility of this approach because active stimulation elicits sensations and introduces a risk of bias to sham-controlled interventions. Thus, it is not possible to truly blind the patient to the sensory experience generated by different types of TENS or the lack of sensation during sham (no current) TENS (or both). However, the nature of the TENS intervention can be concealed during pre-study briefing using a process that calibrates the participant's expectations of sensations from study interventions. Participants can be briefed that some types of non-invasive electrical stimulation techniques do not produce sensations during stimulation (i.e. microcurrent therapy) and that they may or may not experience sensations from the TENS device (Bennett 2011). The sham (no current) device can look and behave similarly to the intervention device (e.g. identical appearance of the device, flashing lights, and functioning display panel) and participants can be instructed to use the device at a pre-determined setting on the display. Blinding can be monitored by asking participants whether they believed that "...the device was functioning properly?" (Deyo 1990). Bennett 2011 also examined aspects of fidelity that may contribute to underestimation of the effects of TENS and found that the adequacy of the TENS intervention (i.e. the appropriateness of the TENS technique) was the main area of concern. Other factors contributing to underestimation of the effects of TENS were: a lack of instruction on how best to administer TENS especially when self administering TENS; assessment of adherence; inadequate reporting of the TENS regimen during use; and failure to standardise or report concurrent analgesia and to assess comparability between groups. We will undertake a subgroup analysis of TENS administered as a sole treatment versus TENS administered in combination with other treatments in this review.

Why it is important to do this review

TENS is used extensively to manage painful conditions because it has few contra-indications or reported side effects and has no potential for overdose (Johnson 2014). A Cochrane review by Johnson 2015a concluded that there was tentative evidence that TENS reduces pain intensity when administered as a stand-alone treatment for acute pain in adults and a non-Cochrane meta-analyses found superiority of TENS over placebo for reducing postoperative analgesic consumption (Bjordal 2003). Another Cochrane review found only limited evidence of effect for labour pain (Dowswell 2009). In 2008, a Cochrane review on TENS for chronic pain was inconclusive (Nnoaham 2008); although the 2008 review has now been withdrawn, our new review will partly serve to update it, focusing on fibromyalgia alone. Most Cochrane reviews on specific chronic pain conditions have found the evi-

dence to be inconclusive (e.g. osteoarthritis of the knee (Rutjes 2009)) or insufficient to make a judgement (e.g. chronic low back pain (Khadilkar 2008), cancer pain (Hurlow 2012), and phantom pain and stump pain (Johnson 2015b)). Non Cochrane meta-analyses have found superiority of TENS over placebo for chronic musculoskeletal pain (Johnson 2007), and osteoarthritis of the knee (Bjordal 2007). Often systematic reviews and meta-analyses are hindered by methodological weaknesses including sub-optimal TENS interventions and inadequate study sample sizes (Bennett 2011; Johnson 2010; Sluka 2013). An overview of Cochrane reviews of TENS for chronic pain is in development (Catley 2015), and a new review on TENS for neuropathic pain in adults, which was developed from Claydon 2010, has been published (Gibson 2015).

There is evidence that electrode placement site, frequency and intensity of stimulation influence TENS outcome although the precise nature of the interaction is unknown (Chesterton 2003; Claydon 2008b; Claydon 2013). Studies on healthy human participants exposed to experimental pain and systematic reviews with meta-analyses of patients with painful conditions have found that a strong, non-painful TENS sensation, at or close to the site of pain, produces optimal analgesic efficacy (Aarskog 2007; Bjordal 2007; Chen 2011; Claydon 2008a; Moran 2011). Central sensitisation contributes to pain associated with fibromyalgia and therefore TENS may be beneficial because it has been shown to reduce this (Ma 2001).

Exercise is recommended as a treatment for fibromyalgia although adherence to exercise programmes may be poor due to pain and fatigue (Bidonde 2014; Busch 2008). As TENS has been shown to reduce pain during movement it may be useful as an adjunct to assist with participation in exercise and activities of daily living. Recently, clinical studies have been published on TENS for managing symptoms associated with fibromyalgia (Andrade 2014; Dailey 2013; Lauretti 2013; Mutlu 2013), and there is a published protocol for a double-blind randomised clinical trial that has yet to be completed (Noehren 2015). To date, there have been no systematic reviews on TENS for fibromyalgia. A systematic review of the current evidence of the effects of TENS for fibromyalgia is needed so that health professionals, researchers, and patients can make informed decisions about its use.

The standards used to assess evidence in chronic pain trials have changed substantially, with particular attention being paid to trial duration, withdrawals, and statistical imputation following withdrawal, all of which can substantially alter estimates of efficacy. The most important change is the move from using average pain scores, or average change in pain scores, to the number of people who have a large decrease in pain (by at least 50%) and who continue in treatment, ideally in trials of eight to 12 weeks or longer. Pain intensity reduction of 50% or more has been shown to correlate with improvements in comorbid symptoms, function, and quality of life. These standards are set out in the reference guide for pain studies (PaPaS 2012). This Cochrane review will assess evidence

using methods that make both statistical and clinical sense, and will use developing criteria for what constitutes reliable evidence in chronic pain (Moore 2010a). The trials included and analysed will need to meet a minimum of reporting quality (blinding, randomisation), validity (duration, dose and timing, diagnosis, outcomes, etc), and size (ideally at least 500 participants in a comparison in which the NNTB is 4 or above; Moore 1998). This approach sets high standards and marks a departure from how reviews were conducted previously.

OBJECTIVES

To assess the analgesic efficacy and adverse events of TENS for fibromyalgia in adults. We will assess TENS on its own or added to usual care in comparisons with placebo (sham) TENS, usual care, or no treatment.

METHODS

Criteria for considering studies for this review

Types of studies

We will include randomised controlled trials (RCTs) or quasi-randomised trials of TENS treatment. We will include single treatment interventions without follow-up but we will give credence to studies that deliver at least two weeks of treatment and have a study duration of at least eight weeks. We will include cross-over and parallel-group trial designs. We require full journal publication, with the exception of online clinical trial results summaries of otherwise unpublished clinical trials, and abstracts with sufficient data for analysis. We will not include short abstracts (usually meeting reports). We will exclude studies that are non-randomised, studies of experimental pain, case reports, and clinical observations.

Types of participants

We will include studies of adult participants aged 18 years or above with pain due to fibromyalgia diagnosed using either the 1990 (Wolfe 1990) or 2010 (Wolfe 2010) criteria.

Types of interventions

We will include studies that evaluate TENS administered using non-invasive techniques for pain relief. We will exclude invasive techniques such as percutaneous electrical nerve stimulation. We will include TENS administered using a standard TENS device

(Johnson 2014), regardless of the device manufacturer, which delivers biphasic or monophasic pulsed electrical currents that are greater than 1 mA using at least two surface electrodes. We will exclude TENS delivered using single probe electrodes (i.e. TENS pens) and studies investigating 'TENS-like' devices such as neuromuscular electrical stimulation (NMES) devices and interferential current devices. We will include studies that administer TENS at intensities that produce perceptible TENS sensations during stimulation. To explore sub-optimal stimulation we will conduct a subgroup analysis to compare TENS at intensities described as 'strong' (optimal) versus those described as 'barely perceptible', 'faint', or 'mild' (sub-optimal). We will include TENS administered on an area of the body that was sensate at either (a) the site of pain or (b) over nerve bundles proximal (or near) to the site of pain. We will include AL-TENS delivered at strong intensities to generate muscle twitches. We will only include TENS delivered at acupuncture points if the point was lying over nerve bundles proximal (or near) to the site of pain. We will include any TENS parameters meeting these criteria; any duration or regularity of TENS treatment; and either self applied or therapist-applied TENS treatment. We will include TENS administered as a sole treatment or in combination with usual care. We will include studies that evaluate TENS versus:

- placebo TENS (e.g. sham (no current) TENS device);
- no treatment or waiting list control;
- usual care;
- another treatment.

Sham credibility is an issue in TENS studies (Deyo 1990). We will define a sham TENS device as a device similar to the one used in the active group but where the current output is modified so that there is: no electrical current, a barely perceptible electrical current, or electrical current that ceases within one minute (Rakel 2010; Sluka 2013). We will exclude studies where it is not possible to isolate the effects of TENS from other treatments.

Types of outcome measures

We anticipate that studies will use a variety of outcome measures, with the majority of studies using standard subjective scales (numerical rating scale (NRS) or visual analogue scale (VAS)) for pain intensity or pain relief, or both. We will include measures of pain at rest and pain on movement. We are particularly interested in Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) definitions for moderate and substantial benefit in chronic pain studies (Dworkin 2008). These are defined as:

- at least 30% pain relief over baseline (moderate);
- at least 50% pain relief over baseline (substantial);
- much or very much improved on Patient Global Impression of Change scale (PGIC; moderate);
- very much improved on PGIC (substantial).

These outcomes concentrate on dichotomous outcomes where pain responses do not follow a normal (Gaussian) distribution. People with chronic pain desire high levels of pain relief, ideally more than 50%, and ideally with no worse than mild pain (Moore 2013a; O'Brien 2010). We will include a 'Summary of findings' table as set out in the author guide (PaPaS 2012). The 'Summary of findings' table will include outcomes of at least 30% and at least 50% pain intensity reduction, PGIC, withdrawals due to adverse events, serious adverse events, and death. We will use the GRADE approach to assess the quality of evidence related to each of the key outcomes listed in 'Types of outcome measures' (Chapter 12, Higgins 2011), as appropriate. We will extract outcome measurement data before, during, and after the intervention, where data are available.

Primary outcomes

- Participant-reported pain relief of 30% or greater.
- Participant-reported pain relief of 50% or greater.
- PGIC much or very much improved.
- PGIC very much improved.

Secondary outcomes

- Any pain-related outcome indicating some improvement (e.g. outcomes from continuous data such as participant-reported change in pain intensity reported as mean data. Baseline status may be heterogeneous and large effects in some individuals may be masked by small effects in others. Therefore, it may only be possible to make generalised statements).
- Any participant-reported change in health-related quality of life, including activities of daily living and fatigue, using any validated tool (e.g. SF-36, SF-6, EuroQol).
- Withdrawals due to lack of efficacy, adverse events, and for any cause.
 - Participants experiencing any adverse event.
 - Participants experiencing any serious adverse event. Serious adverse events typically include any untoward medical occurrence or effect that at any dose results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, is a congenital anomaly or birth defect, is an 'important medical event' that may jeopardise the patient, or may require an intervention to prevent one of the above characteristics or consequences.
 - Specific adverse events, particularly somnolence and dizziness.
 - Any disability-related or mental health-related outcome, if appropriate.

Search methods for identification of studies

Electronic searches

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

- Cochrane Central Register of Controlled Trials (CENTRAL);
- MEDLINE (OVID) from 1950;
- EMBASE (OVID) from 1980;
- CINAHL (EBSCO) from 1982;
- PsycINFO (OVID) from 1806;
- LILACS from 1982;
- PEDRO from 1929;
- Web of Science (ISI);
- AMED (OVID) from 1985;
- SPORTDiscus (EBSCO) from 1975.

There will be no language restrictions. We will tailor the searches to the individual databases. We will adapt the MEDLINE search strategy for the other databases listed. The search strategy will combine the subject-specific search with phase one and two of the Cochrane Sensitive Search Strategy for RCTs (as published in sections 6.4.11.1, 6.3.2.1, and 6.3.3.2 in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011)). The subject-specific search will use a combination of MeSH (upper case) and free-text (lower case) terms based on the MEDLINE search strategy via OVID (Appendix 2). We will identify all relevant studies irrespective of language and translate articles when possible.

Searching other resources

We will review the bibliographies of any RCTs identified and review articles, and we will search clinical trial databases (e.g. ClinicalTrials.gov (www.clinicaltrials.gov), World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP, <http://apps.who.int/trialsearch/>), metaRegister of Controlled Trials (mRCT, www.controlled-trials.com/mrct)) to identify additional published or unpublished data. We will not contact investigators or study sponsors.

Data collection and analysis

Selection of studies

We will determine eligibility by reading the abstract of each study identified by the search. We will eliminate studies that clearly do not satisfy the inclusion criteria, and we will obtain full copies of the remaining studies. Two review authors will make the decisions. Two review authors (LSC, GJ) will read these studies independently and reach agreement by discussion. Disagreements at any stage of the process will be resolved by consensus using a third review author as arbiter (MIJ). We will not anonymise the studies

in any way before assessment. We will create a PRISMA flow chart if appropriate (Higgins 2011; Liberati 2009).

Data extraction and management

Two review authors (LSC, GJ) will extract data independently using a standard form and check for agreement before entry into RevMan (RevMan 2014). Disagreements will be resolved by consensus using the arbiter (MIJ). We will include information about:

- country of origin;
- study design: cross-over, parallel-group;
- study duration;
- study participants: age, gender, fibromyalgia diagnostic criteria used, duration of pain and symptoms;
- sample size: active and comparator groups;
- concomitant treatments: pharmacological and non-pharmacological;
- TENS intervention(s) used: type, electrical parameters, electrode location, perceptual experience during intervention including intensity of stimulation, dosing regimen;
- comparison group(s) used: placebo, no treatment, usual treatment, other treatment, dosing regimen;
- outcomes: time points used including follow-up, withdrawals;
- adverse and serious adverse effects;
- other: sponsorship, country of origin, conflict of interest statements.

We will use the data to populate a table of 'Characteristics of included studies'.

Assessment of risk of bias in included studies

Two review authors (LSC, GJ) will independently assess risk of bias for each study, using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011), with any disagreements resolved by consensus with a third review author (MIJ) acting as arbiter. We will assess the following for each study:

- **Random sequence generation (checking for possible selection bias).** We will assess the method used to generate the allocation sequence as: low risk of bias (any truly random process, e.g. random number table; computer random number generator); unclear risk of bias (method used to generate sequence not clearly stated). We will exclude studies using a non-random process (e.g. odd or even date of birth; hospital or clinic record number).
- **Allocation concealment (checking for possible selection bias).** The method used to conceal allocation to interventions prior to assignment determines whether the intervention allocation could have been foreseen in advance of, or during, recruitment or changed after assignment. We will assess the methods as: low risk of bias (e.g. telephone or central

randomisation; consecutively numbered, sealed, opaque envelopes); unclear risk of bias (method not clearly stated); high risk of bias (studies that do not conceal allocation (e.g. open list).

- **Blinding of outcome assessment (checking for possible detection bias).** We will assess the methods used to blind study participants, care providers, and assessors as follows:

- *Blinding of participants:* low risk of bias (participants blinded to allocated intervention and unlikely that blinding broken); unclear risk of bias (insufficient information to permit judgement of low/high risk of bias); high risk of bias (participants not blinded to allocated intervention OR participants blinded to allocated intervention but it is likely that blinding may have been broken).

- *Blinding of care provider:* low risk of bias (care provider blinded to allocated intervention and unlikely that blinding broken); unclear risk of bias (insufficient information to permit judgement of low/high risk of bias); high risk of bias (care provider not blinded to allocated intervention and the two interventions clearly identifiable to the care provider as experimental and control OR care provider blinded to allocated intervention but likely that blinding may have been broken).

- *Blinding of assessor:* low risk of bias (outcome assessor (including 'participants' with respect to self report outcomes) blinded to participants' allocated intervention and unlikely that blinding broken); unclear risk of bias (insufficient information to permit judgement of low/high risk of bias); high risk of bias (outcome assessor (including 'participants' with respect to self report outcomes) un-blinded to participants' allocated intervention OR outcome assessor blinded to allocated intervention but likely that blinding may have been broken)).

- **Incomplete outcome data (drop-outs).** We will check for possible attrition bias by considering if participant drop-out is acceptable and described: low risk of bias (< 20% drop-out and appears to be random with numbers per group provided along with reasons for drop-out); unclear risk of bias (< 20% and unclear if random with numbers per group and reasons for drop-out not described); high risk of bias (> 20% drop-out).

- **Incomplete outcome data (protocol violations).** We will consider if participants were analysed as per original group allocation: low risk of bias (if participants are analysed in the group to which they were originally assigned); unclear risk of bias (where insufficient information is provided to determine if analysis is per protocol or intention-to-treat); high risk of bias (where per protocol analysis is used, where available data are not analysed or participants' data are included in the group to which they were not originally assigned).

- **Selective reporting.** We will assess whether studies selectively report outcomes. We will assess the methods as: low risk of bias (study protocol is available and all pre-specified outcomes are reported or study protocol not available but all expected outcomes are reported); unclear risk of bias (inadequate information to allow judgement of a study to be classified as 'low

risk' or 'high risk'); high risk of bias (incomplete reporting of specified outcomes. One or more primary outcomes are reported using measurements or analysis that was not pre-specified. One or more of the primary outcomes was not pre-specified. One or more outcomes of interest are reported incompletely and cannot be entered into meta-analysis. Results for a key outcome expected to be reported are excluded).

- **Size of study (checking for biases confounded by small size).** We will assess this as: low risk of bias (≥ 200 participants per treatment arm); unclear risk of bias (50 to 199 participants per treatment arm); high risk of bias (< 50 participants per treatment arm).

- **Other sources of bias.** We will consider other factors such as whether studies were stopped early, differences between groups at baseline, timing of outcome measurement, co-intervention comparability, and funding declarations.

Measures of treatment effect

Where available and appropriate we will present quantitative and intention-to-treat (ITT) data. For dichotomous data (responder analyses) we will use the Initiative on Methods, Measurement and Pain Assessment in Clinical Trials (IMMPACT) definitions for interpreting the clinical importance in change in outcome measures compared to baseline (Dworkin 2008). We will calculate risk ratio (RR) and risk difference (RD) with 95% confidence intervals (CI) for dichotomised outcome measures. We will calculate the number needed to treat to benefit (NNTB) as an absolute measure of treatment effect where possible. We will present pain outcomes collected as continuous data on identical scales as mean difference (MD) with 95% CI. We will present pain outcomes collected as continuous data using different scales as standardised mean difference (SMD) with 95% CI. We will interpret reductions in pain intensity as follows:

- $< 15\%$ - no important change;
- $\geq 15\%$ - minimally important change;
- $\geq 30\%$ - moderately important change;
- $\geq 50\%$ - substantially important change

For health-related quality of life data, we will consider a clinical difference greater than 10% of the scale employed to be minimally important (Furlan 2009).

The IMMPACT thresholds are based on estimates of the degree of within-person change from baseline that participants might consider to be clinically important. The studies in this review are most likely to present effect sizes as the average between-group change between intervention groups. There is little consensus or evidence regarding what the threshold should be for a clinically important difference in pain intensity based on the between-group difference during or after the intervention. It has been found that in pharmacological studies pain outcomes for acute pain (Moore 2011b; Moore 2011c), back pain (Moore 2010d), arthritis (Moore 2010c), and fibromyalgia (Straube 2010), tend to have a U-shaped

rather than a bell-shaped distribution, with some patients experiencing a substantial reduction in symptoms, some minimal to no improvement, and few experiencing average (moderate) improvement. Thus, data expressed as averages may be misleading as a small average between-group effect size may represent a proportion of participants that actually responded very well to the intervention (Moore 2013c; Moore 2014a). It is unknown whether outcomes are commonly bi-modally distributed in trials of TENS. 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 and a small average between-group effect might accurately represent very small effects of the intervention for most or all individuals. We will use a threshold of 10 mm on a 0 to 100 mm VAS for minimally important outcome for pain when analysing average between-group change, in line with the OMERACT 12 group, which states that the proportion of patients achieving one or more thresholds of improvement from baseline pain (e.g. $> 10\%$, $\geq 20\%$, $\geq 30\%$, $\geq 50\%$) should be reported in addition to mean change (Busse 2015). We will interpret these findings with caution as it remains possible that estimates that fall close to this point may reflect a treatment that benefits an appreciable number of patients.

Unit of analysis issues

We will split the control treatment arm between active treatment arms in a single study if the active treatment arms are not combined for analysis. In the unlikely event that the unit of randomisation is not the individual, or where a cross-over design is used, we will not include the data unless a suitable adjustment for the study design has been, or can be, made. We will include cross-over designs but we will only enter the first period data into the meta-analysis. If this is not reported we will note this and not include the data. If such study designs do occur and the data are reported appropriately then we will include the data using the generic inverse variance feature.

Dealing with missing data

We will use intention-to-treat (ITT) analysis where the ITT population consists of participants who were randomised, received at least one dose of the assigned study intervention, and provided at least one post-baseline assessment. We will assign missing participants zero improvement wherever possible.

Assessment of heterogeneity

We will deal with clinical heterogeneity by combining studies that examine similar conditions. We will perform separate analyses where TENS is compared with different control conditions such as placebo or no treatment control. We will examine heterogeneity using visual inspection of forest plots, the I^2 statistic and L'Abbé

Plots (L'Abbé 1987), and the Chi² test. Where significant heterogeneity exists we will explore subgroup analyses. Pre-planned comparisons are described in the section [Subgroup analysis and investigation of heterogeneity](#).

Assessment of reporting biases

The aim of this review is to use dichotomous outcomes of known utility and of value to patients (Moore 2010b; Moore 2010c; Moore 2010d; Moore 2013a). The review will not depend on what the authors of the original studies chose to report or not, though clearly difficulties will arise in studies failing to report any dichotomous results. We will extract and use continuous data, which will probably poorly reflect efficacy and utility and may be useful for illustrative purposes only. We will assess publication bias using a method designed to detect the amount of unpublished data with a null effect required to make any result clinically irrelevant (usually taken to mean a NNTB of 10 or higher; Moore 2008). We will consider the possible influence of small study samples by the risk of bias criterion “study size”. When at least 10 studies are included in a meta-analysis and included studies differ in sample size we will visually inspect funnel plots to explore the likelihood of reporting biases. For studies that have used continuous outcomes we will use Egger's test to detect small study bias (Higgins 2011). We will interpret the results of this process cautiously since we are aware that all approaches to the quantification of possible reporting biases have important limitations (Moore 2008).

Data synthesis

We will perform pooling of results where adequate data exist using Review Manager (RevMan 2014). We will undertake meta-analyses of outcome data only from suitably homogeneous studies using a random-effects model. Where possible, we will group extracted data according to outcome and measurement time points. Time points will include (i) during stimulation or immediately after stimulation at each treatment session, or both; and (ii) post-intervention follow-up at less than two weeks post-intervention (short-term), two to seven weeks post-intervention (mid-term), and eight weeks or more post-intervention (long-term). For all analyses, we will explicitly and clearly present the outcome of the 'Risk of bias' assessments in the reporting. Where inadequate data are found to support statistical pooling we will complete a narrative synthesis of the evidence using GRADE (Grades of Recommendation, Assessment, Development and Evaluation, Guyatt 2008) and we will apply the following criteria to each domain equally for all key comparisons of the primary outcomes:

- Limitations of studies: downgrade once if > 25% of participants are from studies at high risk of bias across all risk of bias criteria;
- Inconsistency: downgrade once if heterogeneity is statistically significant and I² is ≥ 40%;

- Indirectness: downgrade once if > 50% of participants were outside the target group;
- Imprecision: downgrade once if there are fewer than 400 participants for continuous data and 300 events for dichotomous data;
- Publication bias: downgrade once if there is direct evidence of publication bias.

We will consider single studies to be both inconsistent and imprecise (unless the sample size is greater than 400 participants for continuous data and greater than 300 events for dichotomous data). We will present pooled effects for all primary outcomes and associated GRADE judgements in 'Summary of findings' tables.

Subgroup analysis and investigation of heterogeneity

We anticipate too few data for any meaningful subgroup analysis. If sufficient data are available we plan the following analysis: where substantial heterogeneity is found (I² < 40%, P value < 0.1), we will conduct a subgroup analysis investigating the possible impact of TENS technique on analgesic efficacy. If appropriate, we will conduct the following analyses:

- Optimal intensity described as ≥ 'strong' versus sub-optimal intensity described as 'barely perceptible', 'faint', or 'mild';
- Low-frequency (≤ 10 Hz) TENS versus other frequency (e.g. > 10 Hz) TENS;
- Conventional TENS (no visible muscle contraction) versus AL-TENS (visible phasic muscle contractions);
- Assessment during TENS versus after TENS;
- TENS administered as a sole treatment versus TENS administered in combination with other treatments;
- TENS administered as a single dose versus repetitive dose;
- Opioid-treated patients versus opioid-naïve patients.

Sensitivity analysis

We anticipate too few data for any meaningful sensitivity analysis. If sufficient data are available we plan to analyse the effect of excluding studies with high risk of bias and the effect of using a random-effects versus a fixed-effect model.

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* Indicates the major publication for the study

APPENDICES

Appendix 1. Methodological considerations for chronic pain

There have been several recent changes in how the efficacy of conventional and unconventional treatments is assessed in chronic painful conditions. The outcomes are now better defined, particularly with new criteria for what constitutes moderate or substantial benefit (Dworkin 2008); older trials may only report participants with 'any improvement'. Newer trials tend to be larger, avoiding problems from the random play of chance. Newer trials also tend to be of longer duration, up to 12 weeks, and longer trials provide a more rigorous and valid assessment of efficacy in chronic conditions. New standards have evolved for assessing efficacy in neuropathic pain, and we are now applying stricter criteria for the inclusion of trials and assessment of outcomes, and are more aware of problems that may affect our overall assessment. To summarise some of the recent insights that must be considered in this new review:

1. Pain results tend to have a U-shaped distribution rather than a bell-shaped distribution. This is true in acute pain (Moore 2011b; Moore 2011c), back pain (Moore 2010d), and arthritis (Moore 2010c), as well as in fibromyalgia (Straube 2010); in all cases average results usually describe the experience of almost no-one in the trial. Data expressed as averages are potentially misleading, unless they can be proven to be suitable.
2. As a consequence, we have to depend on dichotomous results (the individual either has or does not have the outcome) usually from pain changes or patient global assessments. The Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) group has helped with their definitions of minimal, moderate, and substantial improvement (Dworkin 2008). In arthritis, trials of less than 12 weeks duration, and especially those shorter than eight weeks, overestimate the effect of treatment (Moore 2010c); the effect is particularly strong for less effective analgesics, and this may also be relevant in neuropathic-type pain.
3. The proportion of patients with at least moderate benefit can be small, even with an effective medicine, falling from 60% with an effective medicine in arthritis to 30% in fibromyalgia (Moore 2009; Moore 2010c; Moore 2013a; Moore 2014b; Straube 2008; Sultan 2008). A Cochrane review of pregabalin in neuropathic pain and fibromyalgia demonstrated different response rates for different types of chronic pain (higher in diabetic neuropathy and postherpetic neuralgia and lower in central pain and fibromyalgia) (Moore 2009). This indicates that different neuropathic pain conditions should be treated separately from one another, and that pooling should not be done unless there are good grounds for doing so.
4. Individual patient analyses indicate that patients who get good pain relief (moderate or better) have major benefits in many other outcomes, affecting quality of life in a significant way (Moore 2010b; Moore 2014b).
5. Imputation methods such as last observation carried forward (LOCF), used when participants withdraw from clinical trials, can overstate drug efficacy especially when adverse event withdrawals with drug are greater than those with placebo (Moore 2012b).

Appendix 2. MEDLINE search strategy via Ovid

1. Exp TRANSCUTANEOUS ELECTRIC NERVE STIMULATION/
2. TENS.ti
3. TENS.ab
4. TNS.ti
5. TNS.ab
6. ENS.ab
7. ENS.ti
8. Transcutaneous electric\$ nerve stimulation OR transcutaneous nerve stimulation.mp
9. Electric\$ nerve stimulation OR electrostimulation therap\$ OR electro-stimulation therap\$.mp
10. Electric\$ nerve therap\$ OR electroanalgesi\$.mp
11. OR/ 1-11
12. Exp Fibromyalgia/
13. Fibromyalgi\$. tw
14. Fibrositis.tw
15. OR 12-14
16. 11 AND 15

CONTRIBUTIONS OF AUTHORS

- Mark I Johnson and Leica Claydon led the design of the review protocol. All authors contributed to the writing of the protocol.
- Leica Claydon developed the search strategy and Mark I Johnson, Gareth Jones, and Carole A Paley will implement the search strategy with the PaPaS Group's Trials Search Co-ordinator.
- Leica Claydon, Carole Paley, Gareth Jones, and Mark I Johnson will be responsible for screening articles for eligibility and data management and extraction in the full review.
- G Peter Herbison, Carole Paley, Gareth Jones, and Mark I Johnson will be responsible for data analysis.
- All authors will be responsible for completing the full review and updating the review in future.

DECLARATIONS OF INTEREST

- LSC: no known conflict of interest.
- GPH: no known conflict of interest.
- CAP: no known conflict of interest.
- GJ: no known conflict of interest.
- MIJ: no known conflict of interest.
- LSC, GPH, and CAP are qualified physiotherapists and involved in the professional training of physiotherapists about the use of TENS. MIJ is a physiologist and has been investigating factors that influence the outcome of TENS since undertaking his PhD in 1987. In 2014, he authored a book "*TENS. Research to Clinical Practice*". He is also involved in the professional training of healthcare practitioners about the use of TENS.