MetaTENS_Appendix_BMJO_05-10-2021 – Supplementary File 1

Supplementary Material

Efficacy and Safety of Transcutaneous Electrical Nerve Stimulation (TENS) for Acute and Chronic Pain: A systematic review and meta-analysis (The Meta-TENS study)

Context

This document provides detailed information about all operational processes associated with our systematic review and meta-analysis. The document includes a variety of artefacts including aide memoires used in decision-making. In-text references have been cited using an Author-date format for ease of tracking.

Contents

Table of Contents

SECTION 1 – SUPPLEMENTARY DETAILS OF METHODS

The protocol for this study has been published [1] and is available from https://bmjopen.bmj.com/content/9/10/e029999. An abridged version of the protocol with operational decisions and key findings are described in this Supplementary Material.

The protocol was registered on PROSPERO (CRD42019125054).

This systematic review and meta-analysis were conducted in accordance with

- Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) [2]
- Cochrane Collaboration of Systematic Reviews [3]
- Grading and Recommendations, Assessment, Development and Evaluation (GRADE)[4].

Search Strategy

Search methods for identification of studies

We conducted a literature search to identify RCTs published from date of inception of the database and screened them against our eligibility criteria for inclusion in our review. The purpose of the search was to provide comprehensive coverage of a wide variety of pain conditions (broadly based on the World Health Organisation's (WHO) International Classification of Disease (ICD-11) categories for acute and for chronic pain), at various stages (e.g., acute, chronic) and from various settings (e.g., palliative, community, primary, secondary, tertiary).

In addition, we conducted a literature search to identify systematic reviews on TENS and screened them against our eligibility criteria for the inclusion of previously published systematic reviews in our review. We planned to undertake a descriptive analysis of findings but did not plan to evaluate or quality-assess these systematic reviews. We harvested RCTs from these systematic reviews and mapped inclusion of RCTs across previous systematic reviews.

Electronic searches

We searched the following electronic databases using a combination of controlled vocabulary, i.e., medical subject headings (MeSH) and free-text terms to identify published RCTs and systematic reviews from inception to the date of the search

- Cochrane Library (CENTRAL);
- MEDLINE (via PubMed);
- Embase (via OVID);
- CINAHL (via EBSCO);
- PsycINFO (via EBSCO);
- LILACS (via Bireme);
- PEDRO;
- Web of Science;
- AMED (via OVID);
- SPORTDiscus (via EBSCO).

We tailored searches to the individual databases by adapting the MEDLINE search strategy for the other databases listed. There were no language restrictions and we identified all relevant RCTs irrespective of language and translated articles where possible. We also conducted a literature search to identify systematic reviews on TENS and harvested any outstanding RCTs. We did not search trial registries nor seek data from any unpublished studies identified. We contacted authors

via email to clarify issues relating to inclusion, risk of bias and missing data. The original search was conducted during July 2019; this was updated on 17 May 2020.

MEDLINE Search Terms for RCTs

1. EXP Transcutaneous Electric Nerve Stimulation/
2 TENS.ti,ab
3 TNS.ti,ab
4 ENS.ti,ab
5 transcutaneous electric* nerve stimulation.ti,ab.
6 transcutaneous nerve stimulation.ti,ab
7 electric* nerve stimulation.ti,ab
8 electrostimulation therap*.ti,ab
9 electro-stimulation therap*.ti,ab.
10 electric* nerve therap*.ti,ab
11 electroanalgesi*.ti,ab
12 transcutaneous electric* stimulation.ti,ab.
13 TES.ti,ab
14 or/1-13
15 Pain
16 Randomized controlled trial. pt.
17 Controlled clinical trial.pt.
18 16 OR 17
19 14 AND 15 AND 18

MEDLINE Search Terms for systematic reviews

1. EXP Transcutaneous Electric Nerve Stimulation/
2 TENS.ti,ab
3 TNS.ti,ab
4 ENS.ti,ab
5 transcutaneous electric* nerve stimulation.ti,ab.
6 transcutaneous nerve stimulation.ti,ab
7 electric* nerve stimulation.ti,ab
8 electrostimulation therap*.ti,ab
9 electro-stimulation therap*.ti,ab.
10 electric* nerve therap*.ti,ab
11 electroanalgesi*.ti,ab
12 transcutaneous electric* stimulation.ti,ab.
13 TES.ti,ab
14 or/1-13
15 Pain
16 Systematic review. Pt.
17 Meta-analysis.pt.
18 16 OR 17
19 14 AND 15 AND 18

Eligibility Screening

Description of screening for eligibility

Selection of studies

Two review authors (PGW and MIJ) independently screened records to identify RCTs. We removed duplicates and eliminated records that clearly did not satisfy the inclusion criteria. Full text reports of potentially eligible RCTs were obtained and screened for eligibility by two review authors (PGW and MIJ). Reasons for exclusion were documented and coded against broad exclusion criteria.

Two review authors (PGW and MIJ) screened records to identify systematic reviews on TENS and read full text reports to create a list of RCTs included in each systematic review. Disagreements at any stage of the process were resolved by consensus using a third review author as arbiter (CAP).

We did not anonymise records of systematic reviews or RCTs in any way before assessment. We created a PRISMA flow chart [2].

Types of outcome measures

We included RCTs that measured pain using standard subjective scales (numerical rating scale (NRS) or visual analogue scale (VAS) for pain intensity or pain relief, or both. We included measures of pain at rest and pain on movement. We also planned to extract other pain measures assessed using condition specific questionnaires (e.g., Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), Fibromyalgia Impact Questionnaire (FIQ)). We extracted outcome measurement data before, during, and after the intervention, where data was available.

We extracted data for adverse effects of any type or severity as descriptions from participants and number of withdrawals and/or stopping of treatment. Serious adverse events were defined as untoward medical occurrence or effect resulting in death, threat to life, hospitalisation, significant disability or incapacity, congenital anomaly, or birth defect (see Section Methods of Analysis: Adverse Events). We also planned to extract data on clinical status or health-related quality of life and treatment satisfaction.

Types of studies

We included randomised controlled trials (RCTs) of TENS treatment for acute or chronic pain of any origin. We excluded studies that were non-randomised, case reports and clinical observations. We included studies providing the author used the term ‘randomisation’ in the report. Quasi-RCTs with sequential allocation to groups were excluded. It was noted that some of these studies have been included in previous systematic reviews (e.g., quasi-RCT by [5]).

We included parallel group and crossover trial designs. We included single treatment interventions without follow-up and planned to conduct a subgroup analysis of RCTs that delivered at least two weeks of treatment and had a duration of at least eight weeks as these are considered as best practice. We required full journal publication of a full trial report and did not include, online clinical trial results, summaries of otherwise unpublished clinical trials, abstracts or letters.

Types of participants

We pre-specified that we would include RCTs of adult participants aged 18 years or above with any type of clinical pain, but subsequently decided to include a few RCTs that had a participants with a minimum age of 16 years because more than 95% of the sample were at least 18 years. All RCTs that had at least one participant under 16 years of age (i.e., children) were excluded.

Types of TENS interventions

We included all RCTs that administered TENS as non-invasive electrical stimulation of the skin with the intention of stimulating peripheral nerves to alleviate pain using a standard TENS device [6,7].

Non-invasive

We included RCTs that administered TENS across the intact surface of the skin using surface electrodes and excluded invasive nerve stimulation techniques such as percutaneous electrical nerve stimulation and electro-acupuncture.

Type of TENS Device

We only included RCTs that evaluated TENS using a 'standard TENS device' defined as *"… a portable, battery-powered generator of monophasic or biphasic pulsed electrical current delivered in a repetitive manner, with a maximum peak-to-peak amplitude of approximately 60 milliamperes (mA) into a 1 kilohm load."* p12 [6] and regardless of the device manufacturer.

We excluded RCTs that did not use pulsed electrical currents or administered 'TENS-like' currents not considered output specifications of a standard TENS device (e.g., interferential current, microcurrent), even if the trial authors described the intervention as TENS. We excluded RCTs where the primary intention of TENS was not to stimulate peripheral nerves to alleviate pain (e.g., TENS for bladder dysfunction, constipation, dementia)[7] [6]. We excluded TENS delivered using single probe electrodes (i.e., TENS pens) or using matrix electrodes and electrode arrays. We included TENS administered using electrodes integrated into garments such as knee braces, cuffs, gloves and/or socks providing they did not deviate from the exclusions described previously.

TENS Technique

We included RCTs irrespective of the term used to describe the type of TENS technique (e.g., conventional TENS, acupuncture-Like TENS, high-frequency-low-intensity, low-frequency-high intensity, etc.).

We included RCTs where electrodes were located at (a) the site of pain or (b) over nerve bundles proximal (or near) to the site of pain. We included TENS delivered at acupuncture points only if the point was lying over nerve bundles proximal (or near) to the site of pain.

We included RCTs irrespective of the current amplitude of TENS and/or participant-reported TENS intensity. We planned to exclude RCTs if TENS was administered to areas of the body that were not sensate although there were no instances of this. We considered participant-reported strong but comfortable TENS sensations as optimal and used this as our primary TENS comparison group. We planned to conduct a subgroup analysis to compare TENS at intensities described as 'strong' (optimal) versus those described as 'mild', 'faint', or 'barely perceptible' (sub-optimal), although none of our primary TENS comparisons fell into this latter category.

We included RCTs that delivered TENS at intensities above motor threshold providing TENS was administered using a standard TENS device with the primary intention of stimulating peripheral nerves to alleviate pain.

We included RCTs that administered TENS using pulse frequencies no more than 250 pulses per second (pps) and pulse durations no more than 1 millisecond (1000us). We suspected that some reports had notation errors of SI units expressing microseconds as ms (e.g., 200ms) instead of us (e.g., 200 microseconds). We included any type of pulse pattern.

Determining the primary TENS intervention

We used high frequency pulses delivered using a continuous pulse pattern as our primary TENS comparison group, followed by (i) low frequency TENS delivered either as low frequency pulses or low frequency bursts (trains) of high frequency pulses delivered using a burst pattern of stimulation continuous pulse pattern, (ii) modulated frequency TENS, or (iii) alternating (switching) frequency TENS.

Dosage and Regimen

We included RCTs that administered TENS for any duration or regularity of treatment. We included TENS that was administered by a therapist and/or self-administered by study participants.

TENS alone or as adjunct

We included TENS administered as a sole treatment or in combination with other treatments. We excluded RCTs where it was not possible to isolate the effects of TENS from other treatments.

Evaluation of TENS Treatment Effects

We included RCTs that evaluated TENS versus:

- placebo TENS (e.g., sham (no current) TENS device);
- no treatment or waiting list control;
- standard of care (SoC); and
- another treatment, both pharmacological and non-pharmacological.

Placebo comparators

We included any type of placebo in our analysis but prioritised findings comparing TENS with a placebo (sham) TENS device. Such devices are identical in appearance to the real TENS device but have been modified so that the patient receives no electrical current; or pulses of current that fade to 0mA within one minute [8,9]; or pulses with excessively long inter-stimulus intervals to render them of no physiological consequence. Another approach has been to administer very low amplitude current that is below sensory detection threshold. We included all such approaches and conducted a subgroup analysis of the different approaches.

Ensuring the credibility and blinding of placebo TENS can be problematic because it is not possible to blind participants to TENS sensation. It is possible, however, to generate uncertainty about allocation to active and inactive TENS [10]. We considered the use of a sham TENS device coupled with appropriate briefing information as an adequate method of blinding. We described measures of the adequacy of blinding and/or the perception of participants about the credibility of the placebo intervention in terms of a 'functioning' device on a study by study basis.

No treatment or waiting list control comparators

We considered an intervention as 'no treatment' if we were assured that the participants did not receive any other 'active' treatment. We did not include interventions described as controls that allowed patients any type of active treatment, including medication or exercise. Thus, RCTs that compared TENS in combination with a pharmacological agent versus a control consisting of the pharmacological agent on its own were not included in this analysis.

Standard of care comparators

We considered an intervention as 'standard of care' if trial authors considered the intervention or intervention(s) to be fully or part of 'common', 'routine', or 'standard' practice and/or care, irrespective of whether authors explicitly named the intervention as 'standard of care'. Interventions were either TENS compared head-to-head with a SoC intervention (i.e., TENS vs SoC) or TENS as an adjunct to a SoC intervention (i.e., TENS combined with SoC vs SoC alone).

To avoid 'double-counting' and unit-of-analysis errors, we did not enter several interventions into the same meta-analysis from a study having more than one treatment comparator as this would result in multiple counts of the primary TENS group). There were no instances of this for SoC.

Other treatment comparators

We considered an intervention as 'other treatment' if participants received a comparison intervention that had not been categorised as standard of care (SoC). The purpose of the analysis was to undertake a head-to-head comparison of TENS versus another treatment, so we extracted data that enabled isolation of effects between TENS and another treatment providing any additional care and/or treatment was standardised between groups, e.g., in instances when patients were also given pharmacological, exercise, or physiotherapy-based treatment. The nature of comparisons was either TENS compared head-to-head with another treatment either alone or on a background of care standardised between groups.

To avoid 'double-counting' and unit-of-analysis errors, we pre-specified that we would not enter several interventions into the same meta-analysis from a study having more than one treatment comparator as this would result in multiple counts of the primary TENS group. Unfortunately, there were many instances of a study having more than one treatment comparator for the other treatment analysis.

We decided not to undertake a subgroup analysis comparing Other Treatments because

- This would result in multiple counts of the primary TENS group
- Of the wide variability in the type of interventions.
- None of these other treatment subgroups met our criteria for precision of at least 500 pooled data points in a treatment arm.

We did produce a Forest plot that included multiple treatments from the same study for visual inspection. Also, we calculated overall treatment effect sizes for Other Treatments that had at least 100 pooled data points in each trial arm. These included:

- Interferential therapy
- Pharmacology
- Ultrasound
- Acupuncture and electroacupuncture
- Diadynamic currents
- Electrical muscle stimulation
- Heat therapy
- Percutaneous electrical nerve stimulation

We decided not to report these in the final report because all were below the threshold for pooled data precision. We did not appraise certainty of evidence using GRADE.

Reviewer Aide memoire and Operational Checklist for Eligibility Screening

A. Screening of Titles/Abstracts

Do not carry forward if title/abstract indicates …

1. Definitely NOT non-invasive electrical stimulation
2. Definitely NOT humans
3. Definitely NOT adults with clinical condition
4. Definitely NOT a randomised controlled trial (RCTs)
5. Definitely NOT clinical pain (acute or chronic)
6. Definitely NOT TENS
   - carry forward if on electrotherapy and extract RCTs on TENS – include reports with TENS in scope but fail to identify any TENS SRs
   - carry forward if uncertain whether SR focussed on 'standard TENS' (e.g., TENS characteristics (type of currents), type and location of electrodes (acupoints, single probe electrode etc.) and/or type of device (i.e., TENS-like)

Action

Code gross reasons for 'not carried forward' into the master Excel file

Obtain Full Reports

B. Screening of Full Reports

Do not carry forward if Full Report indicates …

1. Definitely NOT non-invasive electrical stimulation
2. Definitely NOT humans
3. Definitely NOT adults with clinical condition
4. Definitely NOT a randomised controlled trial (RCTs)
5. Definitely NOT clinical pain (acute or chronic)
6. Definitely NOT TENS
   - carry forward if on electrotherapy and extract RCTs on TENS – include reports with TENS in scope but fail to identify any TENS SRs
   - carry forward if uncertain whether SR focussed on 'standard TENS' (e.g., TENS characteristics (type of currents), type and location of electrodes (acupoints, single probe electrode etc.) and/or type of device (i.e., TENS-like)
7. TENS definitely NOT delivered to site of pain or over relevant nerve bundle (i.e., TENS on distal/remote sites)
8. Definitely NOT able to isolate/extract effects due to TENS (combination therapy without appropriate control comparison)
9. TENS treatment given pre-emptively before surgery but not postoperatively whilst patient in pain
10. Other

Screening against specific TENS criteria

Carry forward providing all of the following are met

1. TENS is non-invasive
2. Intention to use TENS to excite peripheral nerves to alleviate pain
3. body sensate
4. participant-reported TENS intensity (irrespective of the current amplitude of TENS)
   a) strong' (optimal) - 'mild', 'faint', or 'barely perceptible' (sub-optimal)

b) muscle twitches if primary goal to alleviate pain

5. pulse frequencies less than 250 pulses per second
6. pulse durations less than 1 millisecond
7. any type of pulse pattern

Carry forward irrespective of the duration or regularity of treatment

Actions:
Code gross reasons for Excluded into the master Excel file
Add to Table of Exclusion with reasons
Add to Table of Awaiting Classification with reasons

C. Reasons for exclusion codes

1. Unrelated to non-invasive electrical stimulation
2. Definitely not humans
    a. TENS but definitely not humans
3. Definitely not adult patients with clinical condition
    a. TENS but healthy humans
    b. NOT adults (<18 years)
4. Definitely not RCT
    a. TENS but definitely not RCT
5. Definitely not pain
    a. TENS but definitely no pain outcomes
    b. Not using intervention as treatment for pain (pain not main outcome measured)
6. Definitely not standard TENS
    a. Not a standard TENS device (i.e., NMES/IFT/TEAS)
    b. Not standard TENS electrodes
    c. Not standard TENS electrical
    d. Invasive technique
7. TENS on remote acupuncture points – none of the acupuncture points are at site of pain
8. Unable to isolate TENS effects
    a. due to an integrated TENS + another modality device
    b. due to combination therapy without a comparable combination therapy without TENS or with a sham TENS
9. TENS treatment given pre-emptively before general anaesthesia surgery and pain recorded postoperatively but TENS not given postoperatively whilst patient in pain
10. Other

Reviewer Aide memoire and Operational Checklist for Extracting Study Characteristics of study

- Study Design
    - Cross-over, parallel-group,
- Setting
- Study duration
- Methods of sequence generation and allocation concealment, blinding, intention-to-treat or per protocol analysis
- Study Participants
    - Age, gender
    - Pain diagnosis, duration of pain and symptoms
- Sample size
- Active and comparator groups
    - TENS
        - Type of TENS device (e.g., standard or 'TENS-like')
        - Electrode placement
        - Electrical characteristics of TENS (pulse frequency, waveform, amplitude/intensity, duration)
        - Dosage (treatment time and frequency)
        - Setting (where TENS was applied and by whom)
        - Adverse effects
    - Comparison group(s)
        - Type
        - Method of delivery (e.g., if placebo TENS then details of electrode placement, characteristics of placebo TENS (pulse frequency, waveform, amplitude/intensity, duration)
        - Dosage (treatment time and frequency)
        - Setting (where it was applied and by whom)
        - Adverse effects
- Concomitant treatments
    - Pharmacological and non-pharmacological
- Outcomes
    - Type
    - Time points used, including follow-up
    - Withdrawals
    - Adverse and serious adverse effects
    - Other
- Sponsorship, country of origin, conflict of interest statements.

Methods to Assess Risk of bias

Description of operational approaches to assess risk of bias in included studies
Two review authors (CAP and MIJ) independently assessed risk of bias for each study against criteria outlined in the Cochrane Handbook for Systematic Reviews of Interventions for selection bias, performance and detection bias, attrition bias, reporting bias [11]. In addition, we assessed the risk of bias associated with the sample size of the primary TENS comparison trial arm, and whether sample size had been determined *a priori*.

We developed an aide memoire adapted for use with TENS to facilitate consistency in the decision-making process.

Selection bias
This includes random allocation sequence generation and allocation concealment. We *excluded* studies that used a non-random process such as odd or even date of birth; hospital or clinic record number (i.e., quasi-randomised). We awarded high risk when there was no attempt to conceal treatment allocation or when allocation was breached (e.g., open list)

Performance bias
There is a longstanding debate about the fidelity of blinding participants and therapists in studies of TENS, impacting on judgements related to the risk of performance bias. Cochrane criteria for judging performance bias is problematic because judgment is an amalgamation of two items, i.e., blinding of participants and blinding of personnel (e.g., therapist). We decided to assess blinding of participants and personnel (therapists) separately.

We argue that blinding of participants is the critical item. It is not possible to blind participants to TENS sensation. It is, however, possible to create uncertainty as to whether a real or fake treatment intervention has been received by informing participants that some types of electrical stimulation devices do not produce sensation during stimulation (e.g., microcurrent therapy), thus creating doubt about the necessity of electrical paraesthesiae during treatment (for detailed discussions see [6,8].

We operationalised decisions about performance bias for *participants* as follows:

- Low risk of performance bias if the report provided a description of an attempt to blind participants (or create uncertainty about active intervention) using a placebo device, with no indication that such blinding was compromised. Thus, we categorised all RCTs that administered placebo TENS using a sham device that was identical in appearance to the active TENS intervention as low risk, providing there was sufficient operational details in the report to assure us there was sufficient operational details in the report to assure us that blinding had not been compromised. Likewise, we categorise all RCTs that compared two active TENS interventions as low risk if devices were identical in appearance and there were sufficient operational details in the report to assure us that blinding had not been compromised.
- We awarded a high risk of bias if the report stated that participants were not blinded (or blinding was clearly compromised) or if interventions were clearly different (e.g., TENS versus exercise).
- We awarded unclear bias to all other permutations

We operationalised decisions about performance bias for *personnel* (e.g., therapists/researchers) as follows:

- Low risk of performance bias if the report provided a description of an attempt to blind personnel to the control intervention (including a placebo device), with no indication that such blinding was compromised. We only categorised RCTs that administered placebo TENS using a sham device as low risk if there were sufficient operational details in the report to assure us that blinding not been compromised – a sham TENS device identical in appearance to the active TENS intervention would be insufficient – there would need to be additional procedural information relating to blinding of personnel. Likewise, we categorise all RCTs that compared two active TENS interventions as low risk if devices were identical in appearance and there were sufficient operational details in the report to assure us that blinding had not been compromised.
- We awarded a high risk of bias if the report stated that personnel were not blinded (or blinding was clearly compromised) or if interventions were clearly different (e.g., TENS versus exercise).
- We awarded unclear bias to all other permutations; insufficient information to permit judgement of low/high risk of bias

We operationalised decisions about performance bias for assessor (*detection bias*) as follows:

- Low risk of bias – stated that outcome assessor blinded to participants' allocated intervention and unlikely that blinding broken (i.e., different personnel to that allocating and/or treating participants)
- 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 was broken

Blinding can be monitored by asking participants about the plausibility and credibility of treatment e.g., '*… do you believe the device (either fake or real) was functioning properly?*' [10]. There were very few studies that monitored blinding.

Attrition bias

We awarded low risk of bias for incomplete outcome data (attrition bias) if it was reported that all participants completed the study with no missing outcome data or missing outcome data was balanced across the groups with similar reasons for loss.

Reporting bias

We awarded low risk of selective reporting (reporting bias) to RCTs that faithfully reported an analysis of data in the Results section from a description of prespecified outcomes in the Methods and/or had previously published a protocol registered on ClinicalTrials.gov and described any deviations from protocol.

Sample size

The influence of small study samples was assessed using the risk of bias criterion 'Sample size' according to numbers of participants analysed in the TENS trial arm. We awarded low risk of bias for sample size if the number of participants receiving TENS in the primary comparison trial arm exceeded 199 and awarded a high risk if it was below 50 participants.

Statement that sample size was estimated a priori

We awarded a low risk of bias if the trial report included a statement and some detail that investigators estimated sample size a priori. We did not attempt to check the validity of power calculations.

Reviewer Aide Memoire and Operational Checklist for Assessment of Risk of Bias

- Random allocation sequence generation (checking for possible selection bias)
    - Low risk of bias - any truly random process, e.g., random number table; computer random number generator
    - Unclear risk of bias - method used to generate sequence not clearly stated
    - High risk of bias - non-random component in the sequence generation process or non-random approaches

  Note: We will exclude studies using a non-random process such as odd or even date of birth; hospital or clinic record number

- Allocation concealment (checking for possible selection bias)
    - Low risk of bias - e.g., telephone or central randomization; 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 participants and blinding of personnel (performance bias)
  Note: Cochrane criteria for judging performance bias is problematic because judgment is an amalgamation of two items, i.e., blinding of participants and blinding of personnel (e.g., therapist). We will assess these two items separately.

  Blinding of participants
    - Low risk - report provided a description of an attempt to blind participants (or create uncertainty about active intervention) using a placebo device, with no indication that such blinding was compromised.
        - Placebo TENS device identical in appearance to the active TENS intervention, providing there was sufficient operational details in the report to assure us that blinding had not been compromised.
        - Likewise, we categorise all RCTs that compared two active TENS interventions as low risk if devices were identical in appearance and there were sufficient operational details in the report to assure us that blinding had not been compromised.
    - High risk - the report stated that participants were not blinded (or blinding was clearly compromised) or if interventions were clearly different (e.g., TENS versus exercise).
    - Unclear bias to all other permutations

  Blinding personnel (e.g., therapists/researchers) as follows:
    - Low risk - description of an attempt to blind personnel to the control intervention (including a placebo device), with no indication that such blinding was compromised. We only categorised RCTs that administered placebo TENS using a sham device as low risk if there were sufficient operational details in the report to assure us that blinding not been compromised – a sham TENS device identical in appearance to the active TENS intervention would be insufficient – there would need to be additional procedural information relating to blinding of personnel. Likewise, we categorise all RCTs that compared two active TENS interventions as low risk if devices were identical in appearance and there were sufficient operational details in the report to assure us that blinding had not been compromised.
    - High risk - if the report stated that personnel were not blinded (or blinding was clearly compromised) or if interventions were clearly different (e.g., TENS versus exercise).

  - Unclear risk - all other permutations; insufficient information to permit judgement of low/high risk of bias

- Blinding of assessor (*detection bias*)
  - Low risk of bias – stated that outcome assessor blinded to participants' allocated intervention and unlikely that blinding broken (i.e., different personnel to that allocating and/or treating participants)
  - 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 was broken

- Incomplete outcome data (drop-outs)
  - Low risk of bias < 20% drop-out and appears to be random with numbers per group provided along with reasons for drop-out, e.g., full data set
  - 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)
  - Low risk of bias - if participants were analysed in the group to which they were originally assigned
  - Unclear risk of bias - where insufficient information is provided to determine if analysis was per protocol or intention-to-treat
  - High risk of bias - where per protocol analysis was used, where available data were not analysed, or participants' data were included in the group to which they were not originally assigned

- Selective reporting
  - Low risk of bias - study protocol was available matched Results reported; all pre-specified outcomes were reported in Methods and reported in Results even if study protocol not published
  - 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 were reported incompletely and could not be entered into meta-analysis. Results for a key outcome expected to be reported were excluded

- Size of study (checking for biases confounded by small size)
  - 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

- Estimation of sample size
  - Low risk of bias – statement that estimation made, even if the actual calculation not present
  - Unclear risk of bias – N/A
  - High risk of bias – No statement

- Other sources of bias
  - Consider other factors including whether studies were stopped early, there were differences between groups at baseline, the timing of outcome measurement, co-intervention comparability, and funding declarations

Cochrane RoB aide memoire annotated for our study on TENS

RANDOM SEQUENCE GENERATION Selection bias (biased allocation to interventions) due to inadequate generation of a randomised sequence.	
Criteria for a judgement of 'Low risk' of bias.	The investigators describe a random component in the sequence generation process such as: • Referring to a random number table; • Using a computer random number generator; • Coin tossing; • Shuffling cards or envelopes; • Throwing dice; • Drawing of lots; • Minimization*. *Minimization may be implemented without a random element, and this is considered to be equivalent to being random.
Criteria for the judgement of 'High risk' of bias.	The investigators describe a non-random component in the sequence generation process. Usually, the description would involve some systematic, non-random approach, for example: • Sequence generated by odd or even date of birth; • Sequence generated by some rule based on date (or day) of admission; • Sequence generated by some rule based on hospital or clinic record number. Other non-random approaches happen much less frequently than the systematic approaches mentioned above and tend to be obvious. They usually involve judgement or some method of non-random categorization of participants, for example: • Allocation by judgement of the clinician; • Allocation by preference of the participant; • Allocation based on the results of a laboratory test or a series of tests; • Allocation by availability of the intervention.
Criteria for the judgement of 'Unclear risk' of bias.	Insufficient information about the sequence generation process to permit judgement of 'Low risk' or 'High risk'.

ALLOCATION CONCEALMENT Selection bias (biased allocation to interventions) due to inadequate concealment of allocations prior to assignment.	
Criteria for a judgement of 'Low risk' of bias.	Participants and investigators enrolling participants could not foresee assignment because one of the following, or an equivalent method, was used to conceal allocation:

	• Central allocation (including telephone, web-based and pharmacy-controlled randomization); • Sequentially numbered drug containers of identical appearance; • Sequentially numbered, opaque, sealed envelopes.
Criteria for the judgement of 'High risk' of bias.	Participants or investigators enrolling participants could possibly foresee assignments and thus introduce selection bias, such as allocation based on: • Using an open random allocation schedule (e.g., a list of random numbers); • Assignment envelopes were used without appropriate safeguards (e.g., if envelopes were unsealed or nonopaque or not sequentially numbered); • Alternation or rotation; • Date of birth; • Case record number; • Any other explicitly unconcealed procedure
Criteria for the judgement of 'Unclear risk' of bias.	Insufficient information to permit judgement of 'Low risk' or 'High risk'. This is usually the case if the method of concealment is not described or not described in sufficient detail to allow a definite judgement – for example if the use of assignment envelopes is described, but it remains unclear whether envelopes were sequentially numbered, opaque and sealed.

BLINDING OF PARTICIPANTS Performance bias due to knowledge of the allocated interventions by participants and personnel during the study.	
Criteria for a judgement of 'Low risk' of bias.	Any one of the following: • No blinding or incomplete blinding, but the review authors judge that the outcome is not likely to be influenced by lack of blinding; • Blinding of participants and key study personnel ensured, and unlikely that the blinding could have been broken. *Low = Statement blinded and no reason to suggest blinding seriously compromised; or blinding inferred, operational process described and no reason to suggest blinding seriously compromised*
Criteria for the judgement of 'High risk' of bias.	Any one of the following: • No blinding or incomplete blinding, and the outcome is likely to be influenced by lack of blinding;

	• Blinding of key study participants and personnel attempted, but likely that the blinding could have been broken, and the outcome is likely to be influenced by lack of blinding. *High = Statement that not blinded; or statements suggesting definitely not blinded*
Criteria for the judgement of 'Unclear risk' of bias.	Any one of the following: • Insufficient information to permit judgement of 'Low risk' or 'High risk'; • The study did not address this outcome. *Unclear = No statement; or blinding inferred but not directly stated*

BLINDING OF PERSONNEL Performance bias due to knowledge of the allocated interventions by participants and personnel during the study.	
Criteria for a judgement of 'Low risk' of bias.	Any one of the following: • No blinding or incomplete blinding, but the review authors judge that the outcome is not likely to be influenced by lack of blinding; • Blinding of participants and key study personnel ensured, and unlikely that the blinding could have been broken. *Low = Statement blinded and no reason to suggest blinding seriously compromised; or blinding inferred, operational process described and no reason to suggest blinding seriously compromised*
Criteria for the judgement of 'High risk' of bias.	Any one of the following: • No blinding or incomplete blinding, and the outcome is likely to be influenced by lack of blinding; • Blinding of key study participants and personnel attempted, but likely that the blinding could have been broken, and the outcome is likely to be influenced by lack of blinding. *High = Statement that not blinded; or statements suggesting definitely not blinded*
Criteria for the judgement of 'Unclear risk' of bias.	Any one of the following: • Insufficient information to permit judgement of 'Low risk' or 'High risk'; • The study did not address this outcome. *Unclear = No statement; or blinding inferred but not directly stated*

BLINDING OF OUTCOME ASSESSMENT Detection bias due to knowledge of the allocated interventions by outcome assessors.	
Criteria for a judgement of 'Low risk' of bias.	Any one of the following: • No blinding of outcome assessment, but the review authors judge that the outcome measurement is not likely to be influenced by lack of blinding; • Blinding of outcome assessment ensured, and unlikely that the blinding could have been broken. *Low = Statement blinded and no reason to suggest blinding seriously compromised; or blinding inferred, operational process described and no reason to suggest blinding seriously compromised*
Criteria for the judgement of 'High risk' of bias.	Any one of the following: • No blinding of outcome assessment, and the outcome measurement is likely to be influenced by lack of blinding; • Blinding of outcome assessment, but likely that the blinding could have been broken, and the outcome measurement is likely to be influenced by lack of blinding. *High = Statement that not blinded; or statements suggesting definitely not blinded*
Criteria for the judgement of 'Unclear risk' of bias.	Any one of the following: • Insufficient information to permit judgement of 'Low risk' or 'High risk'; • The study did not address this outcome. *Unclear = No statement; or blinding inferred but not directly stated*
INCOMPLETE OUTCOME DATA Attrition bias due to amount, nature or handling of incomplete outcome data.	
Criteria for a judgement of 'Low risk' of bias.	Any one of the following: • No missing outcome data; • Reasons for missing outcome data unlikely to be related to true outcome (for survival data, censoring unlikely to be introducing bias); • Missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups; • For dichotomous outcome data, the proportion of missing outcomes compared with observed event risk not enough

	to have a clinically relevant impact on the intervention effect estimate; • For continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes not enough to have a clinically relevant impact on observed effect size; • Missing data have been imputed using appropriate methods.
Criteria for the judgement of 'High risk' of bias.	Any one of the following: • Reason for missing outcome data likely to be related to true outcome, with either imbalance in numbers or reasons for missing data across intervention groups; • For dichotomous outcome data, the proportion of missing outcomes compared with observed event risk enough to induce clinically relevant bias in intervention effect estimate; • For continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes enough to induce clinically relevant bias in observed effect size; • 'As-treated' analysis done with substantial departure of the intervention received from that assigned at randomization; • Potentially inappropriate application of simple imputation.
Criteria for the judgement of 'Unclear risk' of bias.	Any one of the following: • Insufficient reporting of attrition/exclusions to permit judgement of 'Low risk' or 'High risk' (e.g., number randomized not stated, no reasons for missing data provided); • The study did not address this outcome.
SELECTIVE REPORTING Reporting bias due to selective outcome reporting.	
Criteria for a judgement of 'Low risk' of bias.	Any of the following: • The study protocol is available and all of the study's pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way; • The study protocol is not available, but it is clear that the published reports include all expected outcomes, including those that were pre-specified (convincing text of this nature may be uncommon).
Criteria for the judgement of 'High risk' of bias.	Any one of the following: • Not all of the study's pre-specified primary outcomes have been reported;

	• One or more primary outcomes is reported using measurements, analysis methods or subsets of the data (e.g., subscales) that were not pre-specified; • One or more reported primary outcomes were not pre-specified (unless clear justification for their reporting is provided, such as an unexpected adverse effect); • One or more outcomes of interest in the review are reported incompletely so that they cannot be entered in a meta-analysis; • The study report fails to include results for a key outcome that would be expected to have been reported for such a study.
Criteria for the judgement of 'Unclear risk' of bias.	Insufficient information to permit judgement of 'Low risk' or 'High risk'. It is likely that the majority of studies will fall into this category. *Insufficient information to permit judgement of 'Low risk' or 'High risk' as study protocol is not available, and/or suspected study's primary and secondary outcomes were not pre-specified and/or one or more outcomes of interest in the review are reported incompletely so that they cannot be entered in a meta-analysis*

SAMPLE SIZE	
Criteria for a judgement of 'Low risk' of bias.	*Sample size ≥ 200 participants in trial arm of the primary TENS comparison*
Criteria for the judgement of 'High risk' of bias.	*Sample size <50 participants in trial arm of the primary TENS comparison*
Criteria for the judgement of 'Unclear risk' of bias.	*Sample size = 50-199 participants in trial arm of the primary TENS comparison*

SAMPLE SIZE CALCULATION	
Criteria for a judgement of 'Low risk' of bias.	Sample size calculation performed following the CONSORT guidelines. (Moher et al., 2012) *Low Risk = Statement in report that sample size estimated and/or a calculation performed, and no reason suspect that estimation method and/or calculation was incorrect from information in report*
Criteria for the judgement of 'High risk' of bias.	No sample size calculation reported. *High Risk = No statement in report that sample size estimated and/or a calculation performed; or stated in report that sample size estimated and/or a calculation performed, but information in report provided clear evidence that estimation method and/or calculation was incorrect.*

Criteria for the judgement of 'Unclear risk' of bias.	Sample size calculation performed, but lack of information provided. *Unclear Risk = Stated in report that sample size estimated and/or a calculation performed, but lack of information provided.*
CROSSOVER EFFECT Reporting bias due to carryover in crossover studies	
Criteria for a judgement of 'Low risk' of bias.	Order of receiving intervention was randomized, presence of a wash-out period clearly stated, other measures clearly stated to control for crossover effect.
Criteria for the judgement of 'High risk' of bias.	Order of receiving intervention not randomized, presence of a wash-out period not stated, nor measures taken to control for crossover effects.
Criteria for the judgement of 'Unclear risk' of bias.	Insufficient information to permit judgement of low/high risk of bias.

Figure A1 Risk of bias criteria.

Measures and Analysis of treatment effect

Evaluation of Pain Outcomes: Description of principles and operational procedures
Pain outcomes tend to have a U-shaped distribution with some patients experiencing substantial reductions in pain and others experiencing minimal or no improvement [12], so average data may be misleading because small average between-group effect sizes may represent a proportion of participants that responded well to the intervention [13]. Thus, we set responder rate as a primary outcome. The Outcome Measures in Rheumatology (OMERACT 12)[14] group states that the proportion of patients achieving one or more thresholds of improvement from baseline pain should be reported in addition to mean change. We followed the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) definitions when analysing response to treatment and consider reports of pain relief of 30% or greater compared to baseline as responders [15].

Primary Pain Outcomes
Proportion of participant-reported pain relief of ≥30% expressed as frequency (dichotomous) data
Our primary outcome was responder rate. The proportion of participants reporting a reduction in pain intensity of 30% or greater (i.e., at least moderate pain relief) compared with baseline in each group was classed as responders [12,13]. We calculated risk ratio (RR) with 95% confidence intervals (CI). Comparisons between groups were finalised by calculating the number needed to treat to benefit (NNTB) as an absolute measure of treatment effect where possible [15].

Participant-reported pain intensity expressed as mean (continuous) data
We predicted that most RCTs in our review would present effect sizes as the average between intervention groups. We calculated standardised mean difference (SMD) with 95% CI because continuous data was collected on different scales (i.e., both VAS and NRS). We used a between-group difference of ≥10 mm on a 0 to 100 mm VAS for minimally important outcome for pain intensity in-line with IMMPACT criteria for clinically important change, as previously used in Cochrane reviews, where no important change < 15%, minimally important change 15% > 30%, moderately important change 30% > 50% and substantially important change ≥ 50% [15]. We planned to 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.

For standardised mean difference (SMD) we used 'Rules of thumb' based on Cohen's d [3,16] for interpreting effect sizes as follows:

- <0.4 = small effect
- 0.4<0.7 = moderate effect
- ≥0.7 = large effect

We considered a SMD of 0.5 as a rule of thumb for an important difference [3], and were mindful that interpretations of this nature can be problematic due a variety of factors including settings and context in which pain was evaluated.

Secondary Pain Outcomes
We identified the proportion of participants reporting a reduction in pain intensity of 50% or greater (i.e., at least substantial pain relief) as a secondary outcome. In addition, we planned to analyse the frequency of adverse events using the same procedures described for dichotomous and continuous data for primary outcomes.

Evaluation of Adverse Events: Description of principles and operational procedures
For adverse events, we took an exploratory approach 'through opportunistic capture of any adverse effects that happen to be reported' rather than a bespoke search of wider sources [17]. We used the Cochrane Collaboration's definition of adverse event as "*… an unfavourable or harmful outcome that*

occurs during, or after, the use of a drug or other intervention, but is not necessarily caused by it, and an adverse effect (or harm) as an adverse event for which the causal relation between the intervention and the event is at least a reasonable possibility" [17]. Serious adverse events were defined as untoward medical occurrence or effect resulting in death, threat to life, hospitalisation, significant disability or incapacity, congenital anomaly, or birth defect. We extracted data for adverse effects of any type or severity as descriptions from participants and number of withdrawals and/or stopping of treatment.

We conducted a descriptive analysis and calculated relative risk by extracting and pooling data for meta-analysis. We only extracted data as 'zero' when the RCT report included numerical data for the presence of at least one adverse event in one of the trial arms and clearly stated that no adverse events had occurred in the other trial arm(s).

Unit of analysis issues

We included crossover designs and planned to only enter data from the first period into the meta-analysis unless trial authors argued convincingly that there was sufficient washout between interventions to eliminate contamination. If this was not the case, we planned to note this and would not include the data.

There was sufficient washout between interventions to eliminate contamination for all cross trials. For simplicity we analysed crossover data as if parallel group in line with analytical processes undertaken by the trial authors. Analysing crossover data as if parallel group, normally requires generic inverse variance to correct for correlation between groups using the same participants (paired data), but we argue that has negligible impact on outcome because generic inverse variance increases confidence intervals, and this will be negated by the influence of the overwhelming number of data points from parallel group studies.

Dealing with missing data

An intention-to-treat (ITT) analysis was be used when the ITT population were randomised, received at least one dose of TENS, and provided at least one post-baseline outcome measurement. Missing participants were assigned zero improvement wherever possible.

Data synthesis

We used Review Manager 5.3 to pool data and undertake meta-analyses. We grouped data according to outcome and measurement time points prioritising pain at rest at the last during TENS (whilst TENS was switched on) or the first measurement time point immediately after TENS had been switched off. When TENS was applied on more than one occasion as a course of treatment, we selected a measurement time point that was clinically rational, such as the last treatment session and / or as close to an event that precipitated pain (e.g., trauma, operative procedure).

Assessment of heterogeneity

We examined heterogeneity using visual inspection of forest plots, the I^2 statistic and the Chi^2 test [18]. We used the Cochrane Collaboration's rough guide to interpretation and graded heterogeneity as:

- Not important (I^2 = 0% to 40%)
- Moderate (I^2 = 30% to 60%)
- Substantial (I^2 = 50% to 90%)
- Considerable (I^2 = 75% to 100%).

Heterogeneity issues likely at play were:

- Methodological heterogeneity, associated with trial design
- Clinical heterogeneity, associated with pain
- Intervention (treatment) heterogeneity, associated with TENS and comparators

We conducted subgroup and sensitivity analyses to explore heterogeneity further.

Subgroup Analyses: Descriptions of the principles and operational procedures
We pre-specified the following subgroup analyses to investigate sources of heterogeneity and/or estimate treatment effects patient subgroups:

- Type of pain: acute pain, chronic pain, and specific painful conditions
- TENS technique: Optimal intensity described as at least 'strong'; Sub-optimal intensity described as 'barely perceptible', 'faint', or 'mild'; Conventional TENS (high frequency TENS), acupuncture-like TENS (Low frequency TENS)
- TENS dosage: Single TENS treatment, Multiple TENS treatments, use as often as needed
- Measurement time point: during TENS (whilst switched on), after TENS (whilst switched off)
- Contamination from concurrent treatment: TENS administered as a sole treatment, TENS administered in combination with medication, TENS administered in combination with non-pharmacological treatments

It became apparent during screening and data extraction that some pre-specified subgroup analyses would not be possible and/or meaningless.

We refined our pre-specified subgroup analyses as follows:

- Methodological heterogeneity, associated with trial design
    - We conducted subgroup and sensitivity analyses to explore the impact of the following on effect size estimates and statistical heterogeneity:
        - high overall risk of bias (i.e., score of <6 out of 8)
        - trial arm sample sizes of <100, <50 and <30 participants
        - estimation of sample size *a priori*
        - type of placebo
        - TENS administered on its own or with other treatment

- Clinical heterogeneity, associated with pain
    - We conducted subgroup and sensitivity analyses to explore the impact of the following on effect size estimates and statistical heterogeneity
        - duration of pain (acute vs chronic),
        - pain conditions (diagnosis) according to trial author
        - broad ICD-11 categories
        - mechanistic descriptors (nociceptive or neuropathic)
        - anatomical structures involved

- Intervention (treatment) heterogeneity, associated with TENS and comparators
    - Our eligibility criteria biased the inclusion of RCTs that had optimised TENS intervention in terms of generating a strong non-painful TENS sensation at (or close to) the site of pain, irrespective of variations in electrical characteristics of currents produced by a 'standard TENS device' making a subgroup analysis of optimal versus suboptimal intensity or site of stimulation impossible.
    - There was insufficient data to undertake subgroup analyses for high frequency versus low frequency TENS for any comparison
    - Unclear, inconsistent, and inaccurate terminology and the omission of important detail in trial reports rendered subgroup analyses of conventional TENS versus acupuncture-like TENS, and contamination from concurrent treatments meaningless. Such issues would affect the fidelity of subgroup analyses of outcomes at different measurement time points and at following up and therefore we have postponed this analysis until the future.

Subgroup analyses: Interpreting the findings

We followed guidance from [19] when interpreting subgroup analyses using the following criteria

- Criteria 1: report whether a statistically significant subgroup difference (interaction) was detected
- Criteria 2: consider the covariate distribution (i.e., the number of trials and participants contributing to each subgroup)
- Criteria 3: consider the plausibility of the interaction or lack of interaction
- Criteria 4: consider the importance of the interaction or lack of Interaction
- Criteria 5: consider the possibility of confounding

We considered a p-value of less than 0.1 from the test for subgroup differences to indicate a statistically significant difference between the pooled effect estimates for each subgroup (i.e., a subgroup effect (interaction). This indicates that the characteristic under consideration (i.e., the covariate) modifies treatment effect. We also noted whether the direction of each subgroup effect differed and favoured different treatments (i.e., qualitative) or whether the direction of each subgroup effect was the same for the treatment but of different sizes (i.e., quantitative). We also considered the extent to which individual trials differed in treatment effects within each subgroup (i.e., heterogeneity).

If heterogeneity within a subgroup was substantial/considerable, we conducted a further exploration of heterogeneity prior to drawing a conclusion about treatment effect within the subgroup. This included visual inspection of forest plots to evaluate the extent of heterogeneity within the subgroups and across all trials to determine whether the findings of the analyses are trustworthy, whilst acknowledging uncertainty from the inconsistency between individual trial findings.

Reporting (Publication) Biases: Descriptions of operational procedures

Publication bias was assessed 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 numbers needed to treat for benefit (NNTB) of 10 [20]). The influence of small study samples was assessed using the risk of bias criterion 'Sample size' according to numbers of participants analysed in the TENS trial arm.

We visually inspected funnel plots to explore the likelihood of reporting bias if there were at least 10 RCTs in a meta-analysis and if RCTs differed in sample size. Small study effects were analysed using Egger's regression test and the Trim and Fill method was used to analyse potential publication bias

for RCTs using continuous outcomes [3]. For Egger's regression test, the statistical significance was set at ≤0.1.

Quality of the evidence

We considered single RCTs too imprecise, unless the trial arm sample size was greater than 200 participants for continuous data and greater than 150 events for dichotomous data. We considered pooled data to be imprecise if the sample size for a treatment arm was below than 500 participants.

We planned to present pooled effects for outcomes with GRADE judgements in 'Summary of findings' tables. Two review authors (MIJ and PGW) independently rated the quality of outcomes using the Grades of Recommendation, Assessment, Development and Evaluation (GRADE) system (GRADEpro GDT 2015, Supplementary material – S9). We decreased GRADE ratings as follows:

- Limitations to study quality - Serious (- 1) or very serious (- 2)
- Important inconsistency about directness - Some (- 1) or major (- 2)
- Imprecise or sparse data (- 1)
- High probability of reporting bias (- 1)

SECTION 2 – SUPPLEMENTARY DETAILS OF FINDINGS OF THE ANALYSES

Results of the search

The initial search was conducted during July 2019 and identified 6188 potentially relevant records. There were 16 additional records identified through other sources. After removal of duplicates, we screened the titles and abstracts of 4256 records and obtained and read the full texts of 548 records. We excluded 168 records after screening the full text report, with 17 records awaiting classification. We included 348 records of 346 RCTs. Processing of these 346 RCTs (i.e., assessing risk of bias, extracting study characteristics and data, and analysis took 9 months.

We conducted an updated search on 17 May 2020 and identified an additional 1491 potentially relevant records. We removed duplicates and screened titles and abstracts and read the full texts of 75 records. We excluded 37 records after screening the full text report, and included additional 36 RCTs, with 2 records awaiting classification.

In total, our final analysis included 381 RCTs, with 19 RCTs awaiting classification.

Management of multiple records (secondary reports) of one RCT

We categorised multiple records of one RCT as follows.

- An RCT with 1-year follow-up data of 70 patients by [21] as the primary report and 3-month data of the first 23 patients [22] and 3-month data of 36 patients (presumably including the first 23 patients) [23] as secondary reports
- An RCT of TENS in addition to usual primary care management for the treatment of tennis elbow by [24] as the primary report and an economic evaluation by [25] as a secondary report
- An RCT evaluating TENS versus manual therapy for neck pain by [26] reported as the primary report and a Spanish language version by [27] as a secondary report
- The short-term results an RCT evaluating TENS for various chronic pains by [28] as the primary report and an analysis to predict outcome of TENS from the RCT [29], the long-term results of the RCT [30] and the findings of a pilot study investigating different mechanisms for short-term effects of TENS [31] as secondary reports
- An RCT evaluating TENS for knee osteoarthritis by [32] as the primary report and outcomes associated with knee kinematics and kinetics [33] as a secondary report

Management of multiple samples within one report

The following were described and analysed as distinct sample populations within one report of one RCT. We analysed data from these samples separately.

- Chia et al. [34] conducted separate analyses for a sample of participants categorised as nulliparous and multiparous (n = 101) and a sample categorised as nulliparous only (n =20)
- Kayman-Kose et al. [35] conducted separate analyses for a sample of participants categorised as having a Caesarean section (n = 100) and a sample of participants categorised as having a Vaginal delivery (n = 100)

Finally, Lin et al. [36] reported the findings of an RCT of TENS for shoulder pain and Lin et al. [37] reported a similar RCT for chronic shoulder tendonitis. Inspection of reports revealed minor differences in protocols and data, so we categorised these as distinct RCTs with different sample populations.

Thus, we identified 383 distinct samples from 381 RCTs to be included in the review.

Management of errors detected in previous meta-analyses

We conducted a search for systematic reviews on 01 July 2019 and identified 145 systematic reviews that had included RCTs to evaluate the effect of TENS on pain-related outcomes. Our descriptive analysis of systematic reviews found that:

- There were 32/145 Cochrane reviews and 113/145 non-Cochrane reviews
- The mean number of RCTs in a systematic review was 5.6 (maximum: 35; minimum: 1)
- The statements of conclusion in most systematic reviews tended toward inconclusive (70/145) or efficacious (51/145)

The findings of the preliminary descriptive analysis of systematic reviews were disseminated at the European Federation of Chapters of IASP Conference XI held in Valencia, Spain in September 2019.

We cross-checked data presented in meta-analyses of previously published systematic reviews with data extracted from RCTs included in our meta-TENS review. We found very few inconsistencies with data extracted and used in our meta-analysis. We corrected the following errors detected in previous meta-analyses

- double counts of samples from individual RCTs in pooled data (e.g., [38-41])
- the extraction of the area under the curve for pain intensity instead of VAS 100 mm scale (e.g., (i.e., [42] for the RCT by [43])

Description of reasons for excluding studies

Primary reasons for excluding studies are provided in the online Table of Excluded Studies. Often studies were excluded for multiple violations of our inclusion criteria. At least 39 studies were excluded for not being an RCT.

Violations of criteria for 'standard TENS'

The most common reason for exclusion were for violations of our *a priori* criteria for TENS (i.e., electrical characteristics, electrode placement sites, and type of devices; at least 90 studies). The following electrical stimulation techniques were excluded; Transcutaneous electric acupoint stimulation; Transcutaneous spinal electroanalgesia; Acupuncture-like stimulation delivered using a Codetron device; Supraorbital transcutaneous stimulation; Non-invasive interactive neurostimulation using an InterX5000 device); H-wave therapy; Neuromuscular electrical stimulation; Interferential current therapy; 5KHz sine wave currents; Microcurrent electrical stimulation; High voltage pulsed direct current; Frequency rhythmic electrical modulation; and Auto-targeted neurostimulation. Some of these techniques have been included in previous systematic reviews on TENS.

Some original trial authors mistakenly described a technique as 'TENS', despite on close inspection the electrical characteristics of currents did not match those associated with TENS. For example, reports by Itoh et al. state in the title of their report that they evaluated the effect of TENS for knee osteoarthritis [44] and chronic non-specific low back pain [45]. Inspection of the trial report reveals the characteristics of currents akin to interferential therapy "… *a single-channel portable TENS unit (model HVF3000, OMRON Healthcare Co Ltd, Japan), which sends between two electrodes a premixed amplitude-modulated frequency of 122 Hz (beat frequency) generated by two medium frequency sinusoidal waves of 4.0 and 4.122 kHz (feed frequency*" [45] p23. RCTs by Itoh et al., have been previously included in a Cochrane review on osteoarthritis [46] and a non-Cochrane meta-analysis on low back pain [47].

Violations of criteria for appropriate body site for TENS

At least 20 studies were excluded for administering TENS to acupuncture points that we considered to be remote to the site of pain. Many of these studies evaluated transcutaneous electric acupoint stimulation (TEAS, TAES) in which stimulation was delivered to remote acupuncture points using pulsed currents described as 'dense-disperse' using frequencies alternating between 2pps and

100pps. There was a subset of transcutaneous electric acupoint stimulation studies that administered stimulation as a one-off treatment before surgery (i.e., pre-emptive) for post-surgical pain. Some reports implied that transcutaneous electric acupoint stimulation may have been administered to regional acupuncture points but often details were unclear. For consistency, we decided to exclude all studies described as evaluating transcutaneous electric acupoint stimulation.

Four studies were excluded because they administered TENS to an internal body site, i.e., intravaginal [48-50] or intra-oral [51].

Violations of criteria for adult participants

Four studies were excluded because they included at least one child under the age of 16 years [52-55]. We included RCTs by [56], [57] and [58] despite having a sample population with at least one participant no younger than 17 years of age, because the mean age of the sample suggested over 90% of participants were over 18 years of age. We appreciate that including people under 18 can raise issues such as participants between 16-18 years can be included in paediatric studies which may have been missed by our search strategy. It was not possible to isolate the effects of TENS from other treatments given simultaneously or there was no suitable comparison group to assess the contribution of TENS to outcome in at least 17 studies.

Studies Awaiting Classification

There were 19 studies awaiting classification (Online Table of Studies Awaiting Classification) because we were unable to obtain full texts (n = 7 records) and we were unable to translate non-English language full text records (n = 12 records).

Description of Included RCTs

Characteristics of included trials

We included 381 RCTs at entry. A summary of the characteristics of included RCTs is provided in the Online Table of Included Studies and a summary of the conclusion for each RCT is provided the Online Table of RCT Authors' Conclusion.

Study Design

We identified 383 distinct population samples from 381 RCTs. There were 24532 participants at entry with the mean $\pm$ SD study sample size being 64.05 $\pm$ 58.29 participants (n=383 samples, maximum = 607 [59], minimum = 5 [60]).

There were 10615 participants enrolled into the trial arm that we categorised as the primary TENS group, with the mean $\pm$ SD primary TENS trial arm sample size being 27.71 $\pm$ 21.89 participants (maximum = 144 [59]; minimum = 5 participants [60-64].

We categorised 334 RCTs as a parallel-group design, and 47 as crossover design. We categorised 270 RCTs as predominantly pragmatic (efficacious) in focus and 111 RCTs as predominantly explanatory (mechanistic) in focus.

There were 129 reports that stated that an estimation of sample size had been made *a priori*.

RCTs were conducted in 38 countries with the most frequent sample populations being from Turkey (56 RCTs), with high proportions of RCTs conducted in the USA (51 RCTs), Brazil (38 RCTs), UK (37 RCTs), and Sweden (27 RCTs).

Types of pain

We categorised 162/383 samples of participants with acute pain, 176/383 samples of participants with chronic pain, and 10/383samples as including participants with acute and chronic pain.

The category of pain was not reported for 35/383 samples of participants. We categorised samples of participants according to pain condition as follows:

- 95/383 as post-operative pain
- 37/383 as back pain (predominantly chronic low back pain)
- 32/383 as osteoarthritis (predominantly of the knee)
- 26/383 as labour pain
- 23/383 samples of participants with procedural pain
- 22/383 as non-specific musculoskeletal pain of the neck and/or shoulder
- 16/383 as dysmenorrhea
- 15/383 samples of participants with temporomandibular joint pain
- 12/383 samples of participants with myofascial pain
- 11/383 as various pain conditions
- 9/383 samples of participants with fibromyalgia
- 7/383 samples of participants with post stroke pain
- 7/383 samples of participants with rheumatoid arthritis

The remaining samples were from a variety of conditions including peripheral diabetic neuropathy (6 samples), spinal cord injury (5 samples), and neuralgias

There were 231/381 RCTs that had 2 comparison groups, 111/381 RCTs had 3 comparison groups, 29/381 RCTs had 4 comparison groups, 6/381 RCTs had 5 comparison groups, 3/381 RCTs had 6 comparison groups and 1/381 RCT had 12 comparison groups.

Contamination from Concurrent treatment

Many reports described delivering TENS as if it was a sole treatment, although reports often revealed that participants could access other form of treatments including drug medication and or exercise. We categorised at least 216/383 samples as having access to other treatments whilst receiving TENS that may 'contaminate' estimates of TENS effects, although attempts were often made to standardise such access between comparison groups. Analgesic medication or exercise was available informally as part of ongoing standard of care (SoC) or formally as part of a combination treatment. Rescue medication was standardised and/or monitored and/or measured in some but not all RCTs. Generally, there was inadequate monitoring and or reporting of analgesic consumption and/or use other treatments associated with the primary TENS intervention.

Characteristics of TENS interventions

Site of TENS in relation to painful site

TENS was delivered at the site of pain for 376/383 samples, of which TENS was delivered to regional acupuncture points at the site of pain in 7/383 of these samples [65-71].

TENS was not delivered to the site of pain in 3/383 samples. This was due to skin sensitivity and integrity at the site of pain painful diabetic neuropathy so TENS was delivered to the lower back (dermatomal) [60,72]; and to the absence of a limb so TENS was delivered to the contralateral leg for phantom limb pain [73].

There were 2 reports where the statement of the location of TENS was unclear [74,75]. There were 2/381 reports that did not state the location of TENS, although supplementary information within these reports (e.g., descriptions of TENS in Introduction and/or Discussion sections) suggested that the location of TENS was appropriate and did not violate our inclusion criteria [76,77].

Intensity of TENS
TENS was delivered at intensities that were strong and above sensory detection threshold to 342/383 samples. There were 36/381 reports that did not state the intensity of TENS and 7/381 descriptions that were unclear, supplementary information within these reports (e.g., current amplitude (mA), or descriptions of TENS in Introduction and/or Discussion sections) suggested that the intensity of TENS was appropriate and did not violate our inclusion criteria. It should be noted that our eligibility criteria biased our sample of RCTs towards those delivering TENS above sensory detection threshold.

Electrical Characteristics of TENS – Pulse Frequency
The majority of RCT reports described the electrical characteristics of TENS. At face value, reporting appeared to be adequate yet extracting information proved challenging and the resulting categorisation of characteristics (variables) imprecise.

We categorised 363/383 samples as receiving TENS using electrical characteristics associated with standard TENS (i.e., pulsed electrical currents, see Methods). There were 9/383 reports that did not report the electrical characteristics of TENS and 11/383 reports where reporting was unclear, although supplementary information within these reports (e.g., device model) suggested that the electrical characteristics of TENS used did not violate our inclusion criteria.

There were 353/381 reports that included a numerical value for pulse frequency, and we were able to categorise 276/383 of the primary TENS samples as receiving HF TENS (>10 pps). It was less common for reports to include a statement of the pattern (mode) of pulse delivery. The nature of the design of TENS devices means that we can speculate that a continuous pattern of pulse delivery was used to deliver high frequency currents in most of these cases.

We categorised 35/383 samples as receiving low frequency TENS. Often reports did not distinguish between pulses per second and bursts per second when describing low frequency stimulation so it was not possible to ascertain whether low frequency TENS was administered using a continuous pattern of pulses delivered at a low frequency or as a burst pattern of pulses delivering low frequency bursts (trains) of high frequency pulses.

We categorised 17/383 samples as receiving TENS delivered by alternating (or switching) the pattern of stimulation between continuous to burst, as is often recommended for management of labour pain.

We categorised 9/383 samples as receiving alternating frequencies of TENS that used devices that were pre-programmed to intermittently switch between high and low and high frequency pulse delivery; 10/383 samples as receiving modulating frequency TENS; 2/383 samples as receiving random frequency TENS; and 6/383 samples as receiving various frequencies of TENS.

There were 28/381 reports that did not state the numerical pulse frequency of TENS used in the RCT. There were 109/381 reports that stated TENS was delivered at 100Hz; 43/381 reports that stated TENS was delivered at 80Hz; 8/381 reports that stated TENS was delivered at 4Hz; and 3/381 reports that stated TENS was delivered at 2Hz. The remaining reports stated more than one numerical value to describe the frequency of TENS (e.g., TENS was administered between upper and lower frequency boundaries). Participants in some RCTs were instructed to adjust the pulse frequency of TENS as needed.

Often, reports were unclear as to whether frequencies were pre-set and immovable or advisory starting frequencies on which to adjust according to need. Thus, characterisation of the numerical description of the frequency of TENS was imprecise.

There was inconsistency in the use of terms used to describe the type of TENS techniques. Terms used included conventional TENS, AL-TENS, brief intense TENS, high frequency TENS, low frequency TENS, acu-TENS.

Adequacy of TENS intervention
We categorised 336/383 of the primary TENS intervention as meeting all 3 criteria for adequacy: standard electrical characteristics, administered at an appropriate site relative to pain, and at intensities above sensory detection. There were 47/383 samples where there was uncertainty in at least one of these criteria, although overall, we judged the electrical characteristics of TENS used did not violate our inclusion criteria.

TENS regimens varied from single and multiple treatments of less than one minute duration for post-partum uterine contractions [78], dysmenorrhea [79], post-operative surgical abortion [80] or gynaecologic laparoscopic surgery [81] and brief procedural pains such as carboxytherapy [82] to multiple treatments of unspecified duration (e.g., self-administered home treatment for chronic pain as prn).

The longest duration of a course of TENS treatment was in a randomised double-blind evaluation of different types of electrical characteristics of TENS for chronic pain in which participants self-administered TENS until they no longer required TENS or up to a maximum of 2 years [83]. The trial authors concluded that there was no difference in efficacy between pulsed (burst at a low frequency) or continuous (high frequency) TENS.

Characteristics of Outcome Measures
There were 352 or the 381 RCTs that recorded measurements related to our primary outcome, that used a VAS or some other pain continuous or ordinal scale. There were 29/381 RCTs that did not collect data related to our primary outcome measures, but all collected secondary outcome data related to pain, and were therefore included for review.

The most common secondary outcome measurements were analgesic consumption (127 RCTs), range of motion (52 RCTs), McGill Pain Questionnaire scores (both full and short-form versions, 26 RCTs), tenderness via pressure algometry (23 RCTs), WOMAC scores (14 RCTs), Quality of Life (12 RCTs) Roland Morris Disability Questionnaire scores (8 RCTs).

Description of Risk of Bias Assessment

Our assessment of the risk of bias for individual RCTs is available from m.johnson@leedsbeckett.ac.uk on request.

We summarised our assessment of the risk of bias for the included studies as percentages across all included studies.

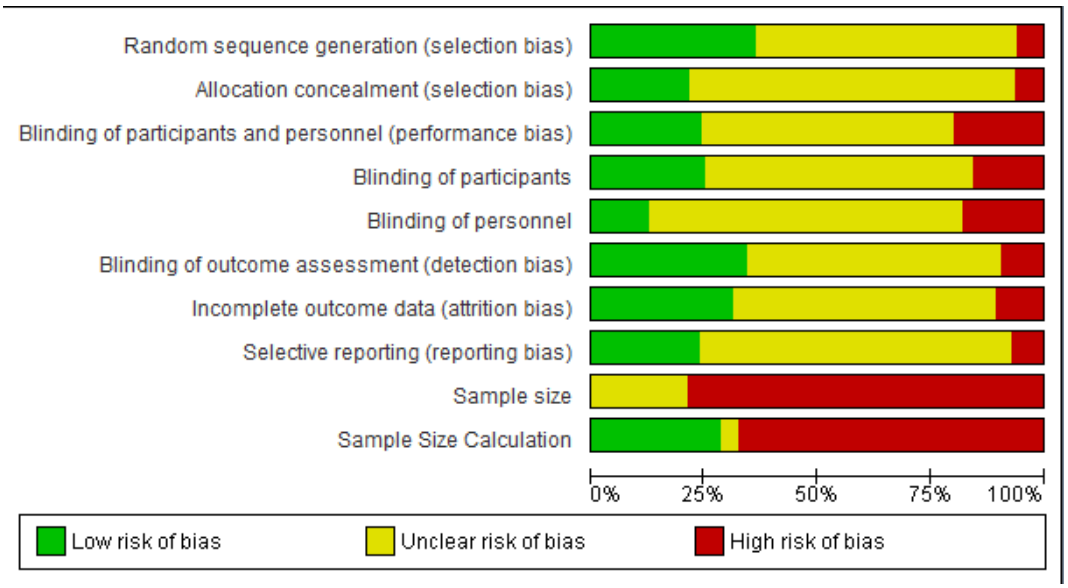

Figure A2 Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

Overall Risk of Bias

Methodological details were superficial and unclear in many reports resulting in unclear RoB assessments. No studies were judged to have a low risk of bias across all 9 RoB items. There were 3/381 RCTs judged to have a low risk of bias across 8 of the 9 items, with unclear or high risk due to low sample sizes [84-86]. There were 9/381 RCTs with 7 or more items judged as low RoB [84-91] and 26/381 RCTS with 6 or more items as low RoB.

We categorised many RCTs as having an unclear risk of bias because study reports lacked omitted or lacked operational details associated with study methodology.

We categorised 341/381 RCTs as having a high risk of bias because of inadequate numbers of participants in the primary TENS trial arm sample (i.e., <50 participants, with no RCTs meeting our criteria for low risk of bias (≥200 participants in the TENS arm). There were 13/381 RCTs that used ≥100 participants in the primary TENS trial arm. The largest TENS trial arm size was 144 participants in a RCT with a total sample of 607 women randomised to receive acupuncture, TENS, or traditional analgesics to manage labour pain [92]. It was found that the use of pharmacological and invasive methods was lower in the acupuncture group compared with TENS (P = 0.031) or traditional analgesics (P < 0.001), although pain scores were comparable across groups.

Randomisation and Allocation (selection bias)

We judged that 136/381 RCTs adequately described the method of random sequence generation and that 82/381 RCTs adequately described the method of allocation concealment.

Blinding (performance bias and detection bias)

There were 94/381 reports that described a method of blinding of participants that was of low risk of performance bias. There were 48/381 reports that described a method of blinding of personnel that was of low risk of performance bias. There were 130/381 reports that described a method of blinding of assessors that was of low risk of detection bias.

Only a few studies attempted to assess seepage of blinding and/or whether participants and/or assessors considered interventions to be functioning correctly (active) or therapeutically plausible/credibility including [85,89,93,94]. Of the studies judged to be of low risk of performance bias [84,85,89] were noteworthy for detailed reporting of well- considered design attributes including the design and delivery of an authentic placebo control and an evaluation of the success or otherwise of blinding of the outcome assessor.

Incomplete outcome data (attrition bias)
We awarded low risk of bias to studies with reports that reported that all participants completed the study with no missing outcome data or missing outcome data was balanced across the groups with similar reasons for loss. There were 118/381 RCTs judged to be of low risk of attrition bias.

Selective reporting (reporting bias)
There were 90/381 RCTs judged to be of low risk of reporting bias.

Sample size
There were 13/381 RCTs with at least 100 participants in the TENS treatment arm and only 2 of these RCTs had extractable data [95](labour pain) [96](fibromyalgia). There were 341/381 RCTs with fewer than 50 participants in the TENS treatment arm.

Sample size estimation
There were 129/381 reports that stated that a calculation had been undertaken to estimate sample size, although often the actual calculation was not provided. Often sample size estimates were stated for total number of participants rather than numbers needed in each trial arm and did not meet our criteria for low risk of bias.

TENS versus placebo: Analysis of effects

There were 202/381 RCTs (203 samples) that compared TENS with a placebo intervention. There were 196 RCTs that delivered placebo TENS in one of the following ways:

- Using a modified TENS device that did not deliver currents (i.e., 0 mA, dead battery, modified circuitry, 155 interventions)
- Using a modified TENS device that delivered currents above that sensory detection threshold for a brief period (< 1 minute) before the amplitude declined to 0 mA (17 interventions)
- Using a modified TENS device that delivered currents above that sensory detection threshold using an interpulse interval of such long duration that it was considered by the authors not to have any physiological action (4 interventions)
- Delivering TENS at amplitudes below sensory detection threshold (12 interventions)
- Delivering TENS above that sensory detection threshold at sites considered to be unrelated to the pain (4 interventions)
- Four reports that did not state the nature of a placebo TENS intervention.

There were 6 RCTs that administered placebo pills and 1 RCT used a non-functioning ultrasound device.

Outcome: Pain intensity - expressed as mean (continuous) data

We extracted data at the last during TENS or the first post-TENS intervention measurement point after a course of TENS treatment (or a single treatment if only one TENS treatment was given) from 91 RCTs (92 samples, 4841 participants). Three of these RCTs were crossover studies deemed to have sufficient washout between interventions to eliminate contamination [89,97,98]. There was a significant overall effect in favour of TENS (SMD -0.96; 95% CI -1.14, -0.78) and substantial heterogeneity I^2 = 88%. (Figure A3).

Visual inspection of the forest plot found reasonable consistency of treatment effects and overlap of confidence intervals with effect estimates and confidence intervals on the side favouring TENS in 50/92 samples. One of these RCTs seems to be an outlier [99] and a sensitivity analysis did not alter the overall effect. We suspected transcriptional errors whereby data had been attributed to the incorrect intervention group in two RCT reports [35,100]. In both instances mean $\pm$ SD data was incorrectly attributed to the placebo group rather than the TENS group in the table of results because all aspects of the report discussed RCT outcome in favour of TENS rather than placebo. We attempted to contact RCT authors for clarification without reply. Cross checking data extracted in a systematic review arising from the same country as Luchesa et al. [100] and published within 3 years of the original report confirmed the transcription error [101] and correct data was entered into our meta-analysis. However, we were unable to confirm the transcription error for [35]. This potential error affected data related to the 'vaginal delivery group' but not a separate sample within the same study (the 'caesarean section group'). Therefore, we entered the data presented in the original report (Table 2 p3) into our meta-analysis. Sensitivity analyses by removing this 'vaginal delivery group' sample from subsequent analyses did not affect tests of overall effect nor tests for subgroup differences.

Forest Plot

MetaTENS_Appendix_BMJO_05-10-2021 – Supplementary File 1

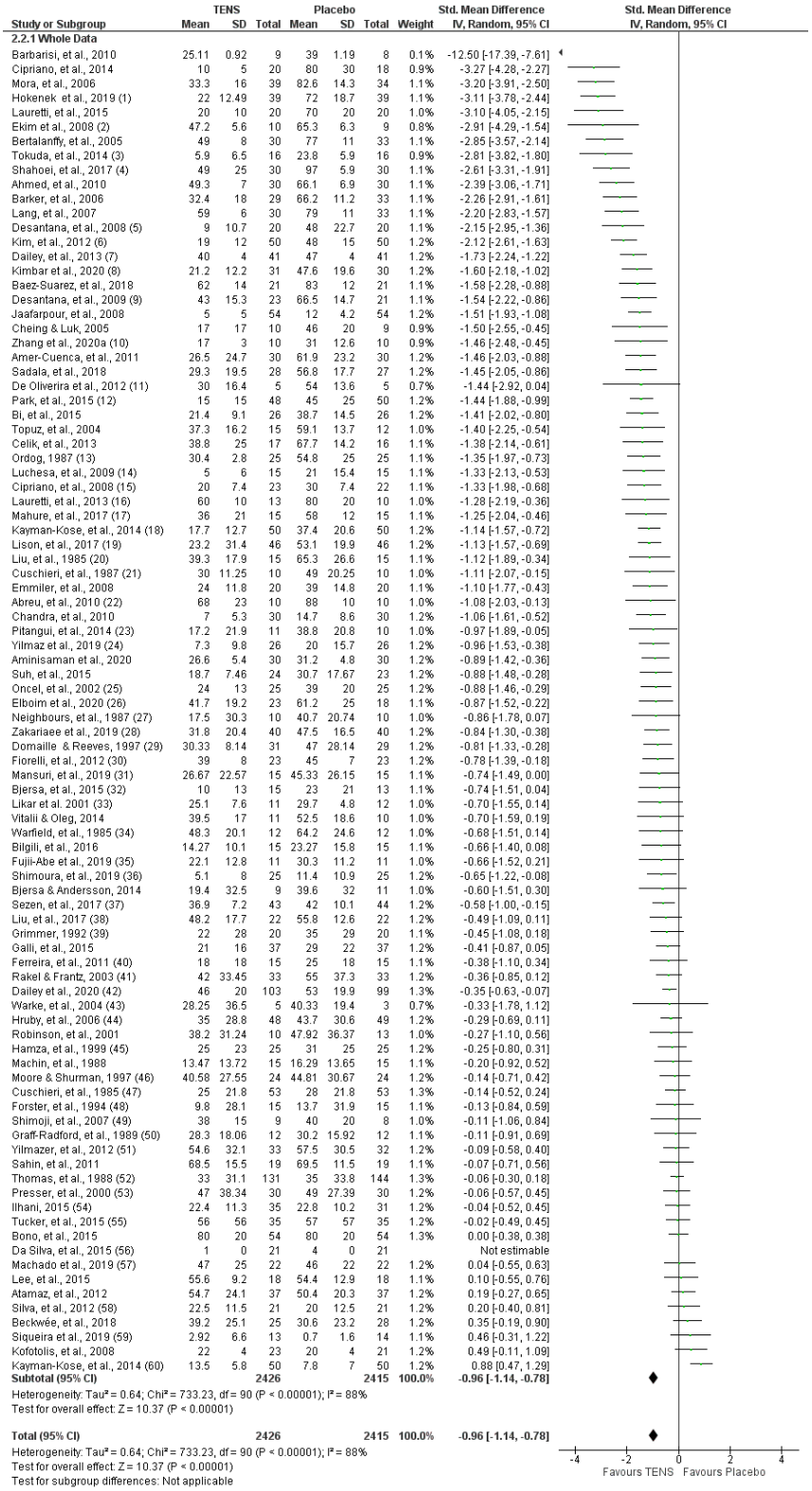

Figure A3 Forest plot of comparison TENS versus placebo. Outcome: pain intensity - expressed as mean (continuous) data.

Subgroup and sensitivity analyses – Methodological Characteristics

Subgroup analyses were conducted to explore the impact of methodological characteristics on effect sizes, tests of overall effect and statistical heterogeneity.

Risk of Bias

A subgroup analysis was conducted to explore the effect of RCTs having an overall low risk of bias (i.e., ≥6 low RoB items out of a total of 9 items). The test for subgroup differences was not statistically significant ($Chi^2 = 1.96$, df = 1 (P = 0.16), suggesting that overall RoB does not modify the effect of TENS in comparison to placebo. There are enough trials and participants in each subgroup, so the covariate distribution is not concerning. There is substantial heterogeneity between results from the trials within each subgroup, therefore the validity of the treatment effect estimate for each subgroup is uncertain (Figure A4).

Forest Plot

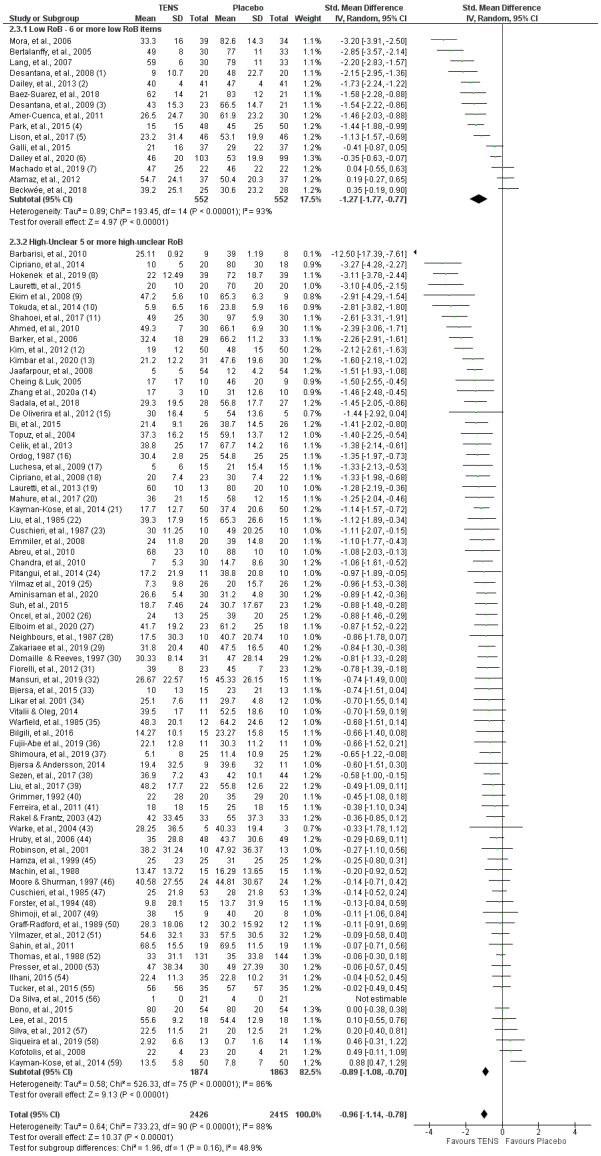

Figure A4 Forest plot of comparison TENS versus placebo with subgroup analysis to explore the effect of RCTs having an overall low risk of bias (i.e., ≥6 low RoB items).

Sample size n ≥ 100 participants in the primary TENS group
There were only 2 studies with extractable data [95](labour pain) [96](fibromyalgia) so analyses was not possible.

Sample size n ≥ 50 participants in the primary TENS group
A subgroup analysis was conducted to explore the effect of studies including 50 participants or more in the primary TENS group. The test for subgroup differences was not statistically significant (Chi^2 = 1.50, df = 1 (P = 0.22), suggesting that whether the trial arm sample size was less than 50 participants does not modify the effect of TENS in comparison to placebo. There are enough trials and participants in each subgroup, so the covariate distribution is not concerning. There is substantial heterogeneity between results from the trials within each subgroup, therefore the validity of the treatment effect estimate for each subgroup is uncertain (Figure A5).
[Forest Plot].

Forest Plot

MetaTENS_Appendix_BMJO_05-10-2021 – Supplementary File 1

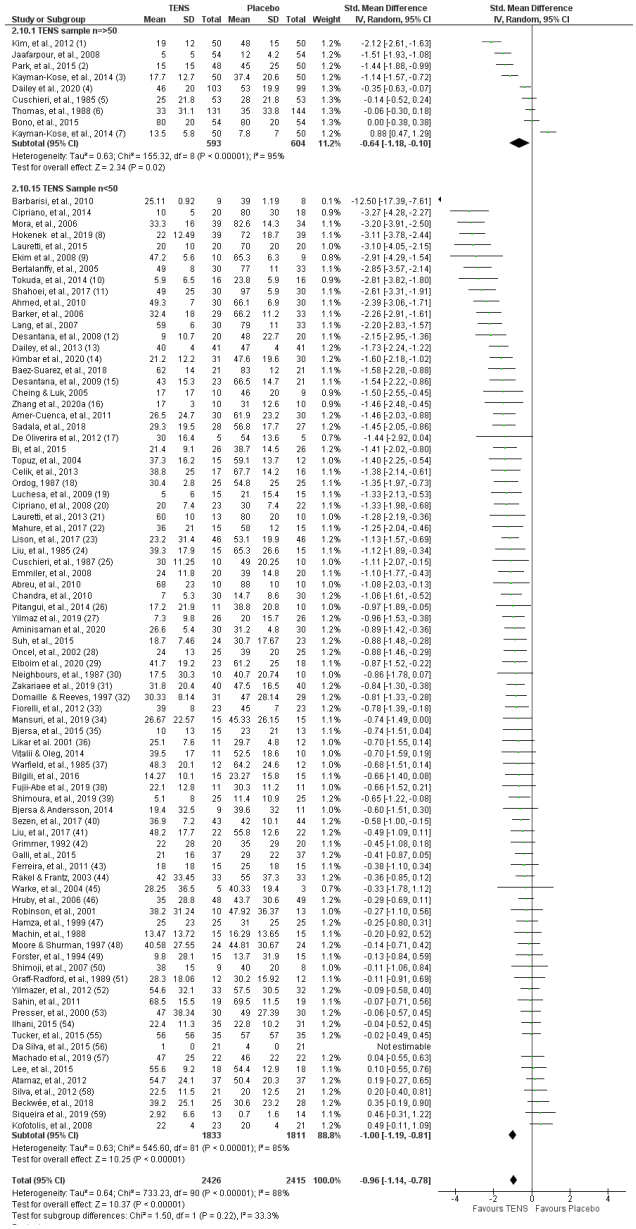

Figure A5 Forest plot of comparison TENS versus placebo with subgroup analysis to explore the effect of studies including 50 participants or more in the primary TENS group.

Estimation of sample size

There was a statistically significant difference in participant-reported pain intensity in favour of TENS both for RCTs that stated in the report that they had undertaken a sample size calculation (49 samples, 2847 participants, P < 0.00001, I^2 = 91%) and for those that did not (44 samples, 1994 participants, P < 0.00001, I^2 = 79%). The test for subgroup differences was statistically significant at our pre-specified threshold of P < 0.1 (Chi^2 = 3.63, df = 1, P = 0.06, I^2 = 72.4%), suggesting that the inclusion of a statement in the report that they had undertaken a sample size calculation does modify the effect of TENS in comparison to placebo. The overall SMD is -1.12 [-1.41, -0.84] in favour of TENS for reports that stated that a sample size calculation had been performed compared with -0.78 [-0.99, -0.57] for those that did not; therefore, the subgroup effect is quantitative. There are enough trials and participants in each subgroup, so the covariate distribution is not concerning.

However, the considerable unexplained heterogeneity combined with frequent unclear reporting of how sample size calculations were undertaken means that we have very low confidence in the precision of the treatment effect estimate for each subgroup.

Type of placebo
There was a statistically significant difference in participant-reported pain intensity in favour of TENS for RCTs used a placebo that did not deliver any electrical currents (74 samples, 3851 participants, P < 0.00001, I^2 = 88%) and for those that used a placebo that administered pulsed electrical currents below sensory detection threshold (7 RCTs, 288 participants, P = 0.01, I^2 = 85%), faded to zero current within one minute (7 RCTs, 549 participants, P = 0.002, I^2 = 89%), with excessive long duration inter-stimulus intervals (2 RCTs, 83 participants, P = 0.02, I^2 = 90%), or placebo pills (2 RCTs, 70 participants, P = 0.0005, I^2 = 0%). The test for subgroup differences was not statistically significant (Chi^2 = 2.03, df = 4 (P = 0.73), I^2 = 0%).

TENS administered on its own or with other treatment
There was a statistically significant difference in participant-reported pain intensity in favour of TENS both for reports that suggested that participants were allowed access to other treatments with the potential to contaminate pain scores (34 samples, 1804 participants, P < 0.00001, I^2 = 87%) and those not allowed access to other treatments (57 samples, 3037 participants, P < 0.00001, I^2 = 87%). The test for subgroup differences was statistically significant at our pre-specified threshold of P < 0.1 (Chi^2 = 3.59, df = 1, P = 0.06, I^2 = 72.1%), suggesting that allowing participants access to other treatments does modify the effect of TENS in comparison to placebo. The overall SMD [95% CI] is -0.74 [-1.02, -0.46] in favour of TENS for reports that suggested that participants were allowed access to other treatments with the potential to contaminate pain scores compared with -1.09 [-1.32, -0.86] for those where participants appeared not to be allowed access to other treatments; therefore, the subgroup effect is quantitative. There are enough trials and participants in each subgroup, so the covariate distribution is not concerning. However, the substantial heterogeneity between results from the trials within each subgroup, combined with the unclear reporting of the consumption of analgesics and/or use of other treatments means that we have very low confidence in the precision of the treatment effect estimate for each subgroup.

Subgroup – Pain Characteristics
Pain Duration - Acute versus chronic
We conducted a subgroup analysis on pain condition categorised as acute and chronic pain according to broad categories of the International Association of Pain and the ICD-11 (i.e., in general terms a pain condition that has persisted for 3 months or more). The test for subgroup differences was not statistically significant (Chi^2 = 1.12, df = 2 (P = 0.57)), suggesting that the duration of painful condition does not modify the effect of TENS in comparison to placebo. There are enough trials and participants in each subgroup, so the covariate distribution is not concerning. . There is substantial heterogeneity between results from the trials within each subgroup, therefore the validity of the treatment effect estimate for each subgroup is uncertain (Figure A6).

Forest Plot

MetaTENS_Appendix_BMJO_05-10-2021 – Supplementary File 1

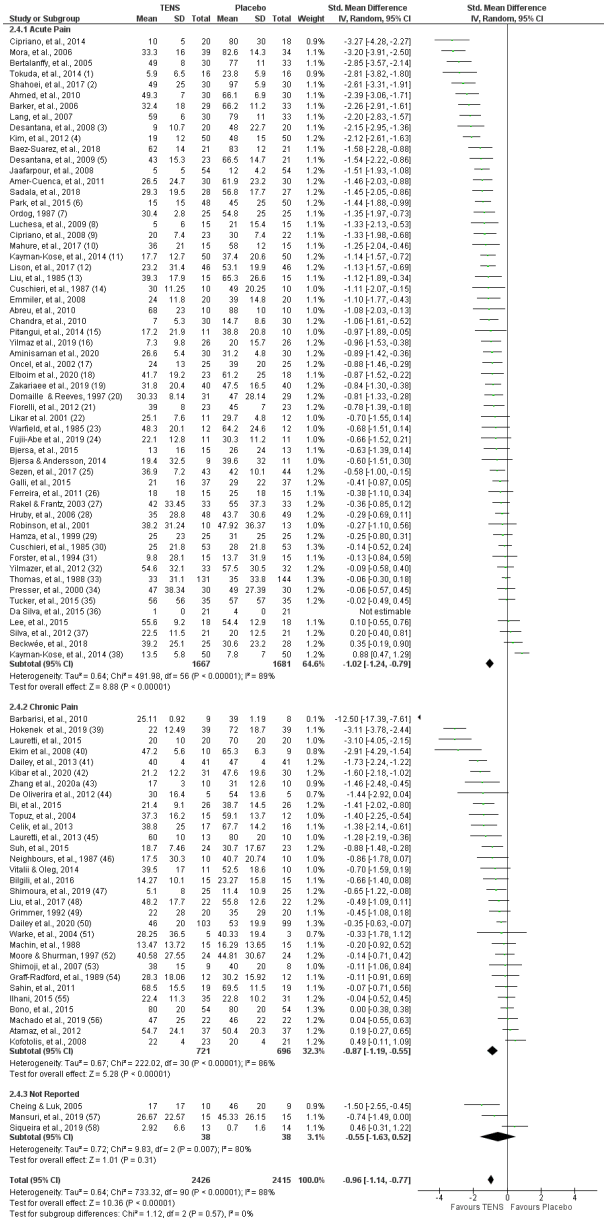

Figure A6 Forest plot of comparison TENS versus placebo with subgroup analysis to explore the effect of pain duration categorised as acute and chonic pain.

Pain Conditions (diagnoses) – as described by RCT author

We conducted a subgroup analysis on pain condition categorised according to authors' description given in the trial report. There was a statistically significant difference in favour of TENS for post-operative pain (36 samples, 1788, P < 0.00001, I^2 = 80%), procedural pain (10 samples, 682 participants, P = 0.001, I^2 = 88%), labour pain (4 sample, 397 participants, P = 0.05, I^2 = 95%) and fibromyalgia (3 samples, 307 participants, P = 0.04, I^2 = 91%). There were no statistically significant differences for back pain (9 samples, 364 participants, P = 0.06, I^2 = 89%) or migraine (3 samples, 230 participants, P = 0.19, I^2 = 97%). The remainder of the subgroups had fewer than 100 participants in the primary TENS trial arm. The test for subgroup differences was statistically significant (Chi^2 = 202.12, df = 23 (P < 0.00001); Figure A7), suggesting that the pain condition categorised according to that stated in the trial report significantly modifies the effect of TENS in

comparison to placebo. The treatment effect favours TENS over placebo for all categories of pain condition; therefore, the subgroup effect is quantitative. However, there are more trials (and participants) contributing data from some pain conditions than others, and there is considerable unexplained heterogeneity between the trials within each of these subgroups. A sensitivity analysis that removed subgroups with pooled sample sizes of fewer than 100 participants in the primary TENS trial arm was not statistically significant ($Chi^2 = 1.25$, df = 5, P =0.94), suggesting that the pain condition categorised according to that stated in the trial report does not significantly modify the effect of TENS in comparison to placebo. Therefore, the validity of the treatment effect estimate for each subgroup is uncertain.

Forest Plot

MetaTENS_Appendix_BMJO_05-10-2021 – Supplementary File 1

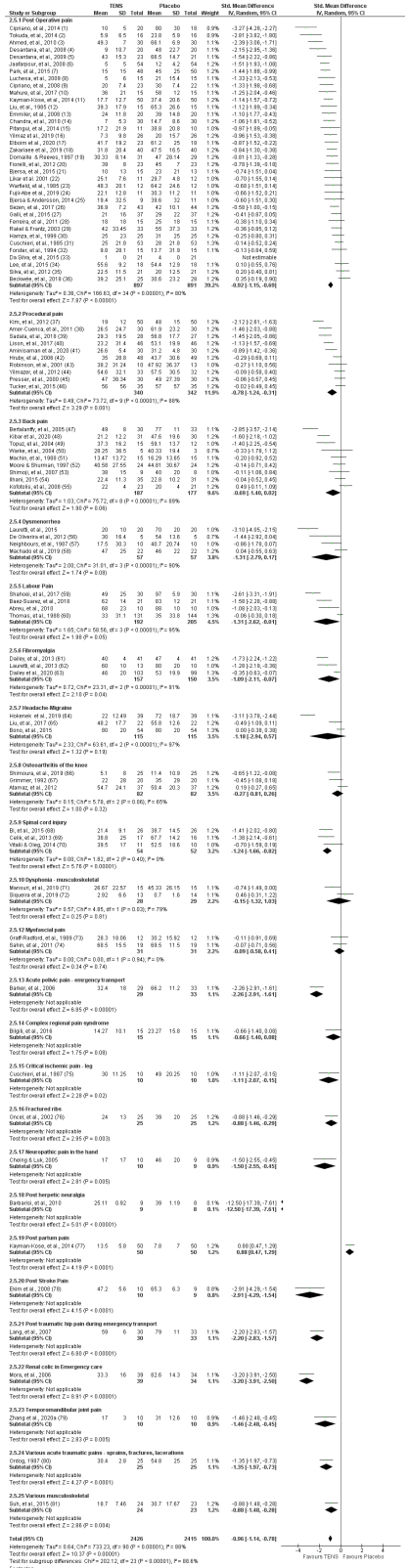
TENS
Placebo
Std. Mean Difference
Std. Mean Difference
Study or Subgroup Mean SD Total Mean SD Total Weight IV, Random, 95% CI
IV, Random, 95% CI
2.5.1 Post Operative pain
Ciprian, et al., 2014 (1) 10 5 20 60 30 18 0.9% -3.27 [-4.26, -2.27]
Tekuta, et al., 2014 (2) 5.9 6.5 16 23.8 5.9 16 0.9% -2.91 [-3.82, -1.99]
Ahmed, et al., 2013 (3) 49.3 7 30 68.1 6.9 30 1.1% -2.39 [-3.06, -1.71]
Desantana, et al., 2008 (4) 9 10.7 20 48 22.7 20 1.1% -2.15 [-2.85, -1.36]
Desantana, et al., 2009 (5) 43 15.3 23 68.5 14.7 21 1.1% -1.54 [-2.22, -0.86]
Jaafarpour, et al., 2008 (6) 5 5 54 12 4.2 54 1.2% -1.51 [-1.93, -1.09]
Paris, et al., 2015 (7) 15 15 48 45 25 50 1.2% -1.44 [-1.86, -0.99]
Lucheva, et al., 2008 (8) 5 6 15 21 15.4 15 1.1% -1.33 [-2.13, -0.53]
Ciprian, et al., 2008 (9) 20 7.4 23 30 7.4 22 1.1% -1.33 [-1.96, -0.69]
Mahure, et al., 2017 (10) 36 21 15 58 12 15 1.1% -1.25 [-2.04, -0.46]
Kayman-Kose, et al., 2014 (11) 17.7 12.7 50 37.4 20.6 50 1.2% -1.14 [-1.57, -0.72]
Liu, et al., 1995 (12) 39.3 17.9 15 65.3 26.6 15 1.1% -1.12 [-1.89, -0.34]
Emmler, et al., 2008 (13) 24 11.8 20 39 14.8 20 1.1% -1.10 [-1.77, -0.43]
Chandra, et al., 2018 (14) 7 5.3 30 14.7 8.6 30 1.2% -1.06 [-1.61, -0.52]
Pitangui, et al., 2014 (15) 17.2 21.9 11 39.8 20.8 10 1.0% -0.97 [-1.89, -0.05]
Yilmaz et al., 2019 (16) 7.3 9.8 26 20 15.7 26 1.2% -0.96 [-1.53, -0.39]
Bloom et al., 2020 (17) 41.7 19.2 23 61.2 25 18 1.1% -0.87 [-1.52, -0.22]
Zalcanaro et al., 2019 (18) 31.8 20.4 40 47.5 16.5 40 1.2% -0.84 [-1.30, -0.38]
Domaille & Rideos, 1987 (19) 30.33 8.14 31 47 28.14 29 1.2% -0.81 [-1.33, -0.28]
Fiorelli, et al., 2012 (20) 39 8 23 45 7 23 1.2% -0.79 [-1.38, -0.19]
Barros, et al., 2015 (21) 10 13 15 23 21 13 1.1% -0.74 [-1.51, 0.04]
Likar et al. 2001 (22) 25.1 7.6 11 29.7 4.8 12 1.0% -0.70 [-1.55, 0.14]
Warfield, et al., 1985 (23) 48.3 28.1 12 84.2 24.6 12 1.0% -0.69 [-1.51, 0.14]
Fujii-Abe et al., 2019 (24) 22.1 12.8 11 38.3 11.2 11 1.0% -0.66 [-1.52, 0.21]
Barsa & Andersson, 2014 (25) 19.4 32.5 9 39.6 32 11 1.0% -0.60 [-1.51, 0.30]
Bezen, et al., 2017 (26) 38.9 7.2 43 42 10.1 44 1.2% -0.58 [-1.00, -0.15]
Gelli, et al., 2015 (27) 21 16 37 29 22 37 1.2% -0.41 [-0.87, 0.05]
Ferreira, et al., 2011 (28) 18 18 15 25 18 15 1.1% -0.38 [-1.10, 0.34]
Rakel & Frantz, 2003 (29) 42 33.45 33 55 37.3 33 1.2% -0.36 [-0.85, 0.12]
Herrera, et al., 1999 (30) 25 23 25 31 25 25 1.2% -0.25 [-0.80, 0.31]
Cuschieri, et al., 1995 (31) 25 21.8 53 28 21.8 53 1.2% -0.14 [-0.52, 0.24]
Forster, et al., 1994 (32) 8.8 28.1 15 13.7 31.9 15 1.1% -0.13 [-0.84, 0.59]
De Silva, et al., 2015 (33) 1 0 21 4 0 21 Not estimable
Lee, et al., 2015 (34) 55.6 9.2 18 54.4 12.9 18 1.1% 0.10 [-0.55, 0.76]
Silva, et al., 2012 (35) 22.5 11.5 21 20 12.5 21 1.2% 0.20 [-0.46, 0.81]
Beckwee, et al., 2018 (36) 39.2 25.1 25 30.6 23.2 28 1.2% 0.35 [-0.18, 0.90]
Subtotal (95% CI) 897 891 20.2% -0.92 [-1.15, -0.69]
Heterogeneity: Tau² = 0.39; Chi² = 166.83, df = 34 (P < 0.00001); I² = 80%
Test for overall effect: Z = 7.87 (P < 0.00001)
2.5.2 Procedural pain
Kim, et al., 2012 (37) 19 12 50 48 15 50 1.2% -2.12 [-2.61, -1.63]
Arnor-Cuenca, et al., 2011 (38) 26.5 24.7 30 61.9 23.2 30 1.2% -1.46 [-2.03, -0.89]
Balsak, et al., 2015 (39) 28.3 19.5 28 58.8 17.7 27 1.2% -1.45 [-2.05, -0.86]
Lison, et al., 2017 (40) 23.2 31.4 46 53.1 19.8 46 1.2% -1.13 [-1.57, -0.69]
Amirsasman et al., 2020 (41) 28.6 5.4 30 31.2 4.8 30 1.2% -0.99 [-1.42, -0.56]
Hruby, et al., 2008 (42) 35 28.8 48 43.7 30.6 49 1.2% -0.29 [-0.69, 0.11]
Robinson, et al., 2001 (43) 38.2 31.24 10 47.82 36.37 13 1.0% -0.27 [-1.10, 0.56]
Yilmazer, et al., 2012 (44) 54.6 32.1 33 57.5 30.5 32 1.2% -0.09 [-0.58, 0.40]
Pressler, et al., 2000 (45) 47 38.34 30 49 27.39 30 1.2% -0.06 [-0.57, 0.45]
Tucker, et al., 2015 (46) 56 56 35 57 57 35 1.2% -0.02 [-0.48, 0.45]
Subtotal (95% CI) 340 342 11.9% -0.70 [-1.24, -0.31]
Heterogeneity: Tau² = 0.49; Chi² = 73.72, df = 9 (P < 0.00001); I² = 88%
Test for overall effect: Z = 3.28 (P = 0.001)
2.5.3 Back pain
Bertolanffy, et al., 2005 (47) 49 8 30 77 11 33 1.1% -2.95 [-3.57, -2.14]
Kibar et al., 2020 (48) 21.2 12.2 31 47.6 19.6 30 1.2% -1.60 [-2.16, -1.02]
Topuz, et al., 2004 (49) 37.3 16.2 15 59.1 13.7 12 1.0% -1.40 [-2.25, -0.54]
Wiehe, et al., 2004 (50) 28.25 38.5 5 40.32 19.4 3 0.7% -0.32 [-1.78, 1.12]
Machin, et al., 1988 (51) 13.47 13.72 15 16.29 13.65 15 1.1% -0.20 [-0.92, 0.52]
Moore & Shurman, 1997 (52) 40.58 27.56 24 44.81 30.67 24 1.2% -0.14 [-0.71, 0.42]
Shimoji, et al., 2007 (53) 38 15 4 40 20 8 1.0% -0.11 [-1.08, 0.84]
Rioni, 2015 (54) 22.4 11.3 35 22.8 10.2 31 1.2% -0.04 [-0.52, 0.45]
Kotsilidis, et al., 2008 (55) 22 4 22 20 4 21 1.2% 0.49 [-0.11, 1.09]
Subtotal (95% CI) 197 177 9.6% -0.69 [-1.40, 0.02]
Heterogeneity: Tau² = 1.03; Chi² = 75.72, df = 8 (P < 0.00001); I² = 89%
Test for overall effect: Z = 1.90 (P = 0.06)
2.5.4 Dysmenorrhea
Laurett, et al., 2015 20 10 20 70 20 20 1.0% -3.10 [-4.05, -2.15]
De Oliveira et al., 2012 (56) 30 16.4 5 54 13.6 5 0.7% -1.44 [-2.92, 0.04]
Neighbours, et al., 1987 (57) 17.5 30.3 10 48.7 20.74 10 1.0% -0.95 [-1.78, 0.07]
Machado et al., 2019 (58) 47 25 22 46 22 22 1.2% 0.04 [-0.55, 0.63]
Subtotal (95% CI) 57 57 3.8% -1.31 [-2.76, 0.17]
Heterogeneity: Tau² = 2.00; Chi² = 31.01, df = 3 (P < 0.00001); I² = 90%
Test for overall effect: Z = 1.74 (P = 0.08)
2.5.5 Labour Pain
Bhanoo, et al., 2017 (59) 49 25 30 97 5.9 30 1.1% -2.61 [-3.31, -1.91]
Baez-Suarez, et al., 2018 62 14 21 83 12 21 1.1% -1.58 [-2.26, -0.89]
Abreu, et al., 2013 68 23 10 88 10 10 1.0% -1.08 [-2.03, -0.13]
Thomas, et al., 1986 (60) 33 31.1 131 35 33.8 144 1.3% -0.06 [-0.35, 0.23]
Subtotal (95% CI) 102 265 6.5% -1.31 [-2.62, 0.01]
Heterogeneity: Tau² = 1.65; Chi² = 58.56, df = 3 (P < 0.00001); I² = 95%
Test for overall effect: Z = 1.99 (P = 0.05)
2.5.6 Fibromyalgia
Dailey, et al., 2013 (61) 40 4 41 47 4 41 1.2% -1.73 [-2.24, -1.22]
Laurett, et al., 2013 (62) 60 10 13 80 20 10 1.0% -1.28 [-2.16, -0.39]
Dailey et al., 2020 (63) 46 20 103 53 19.9 99 1.3% -0.35 [-0.63, -0.07]
Subtotal (95% CI) 157 150 3.5% -1.09 [-2.11, -0.07]
Heterogeneity: Tau² = 0.72; Chi² = 23.31, df = 2 (P < 0.00001); I² = 91%
Test for overall effect: Z = 2.10 (P = 0.04)
2.5.7 Headache-Migraine
Hokenek et al., 2019 (64) 22 12.49 39 72 18.7 39 1.1% -3.11 [-3.78, -2.44]
Liu, et al., 2017 (65) 48.2 17.7 22 59.9 12.6 22 1.2% -0.49 [-1.09, 0.11]
Bono, et al., 2015 60 20 54 60 20 54 1.2% 0.00 [-0.38, 0.38]
Subtotal (95% CI) 115 115 3.5% -1.18 [-2.84, 0.57]
Heterogeneity: Tau² = 2.33; Chi² = 63.61, df = 2 (P < 0.00001); I² = 97%
Test for overall effect: Z = 1.32 (P = 0.19)
2.5.8 Osteoarthritis of the knee
Shimoura, et al., 2019 (66) 5.1 8 25 11.4 10.9 25 1.2% -0.65 [-1.22, -0.09]
Grimmer, 1992 (67) 22 28 30 35 29 20 1.1% -0.45 [-1.08, 0.18]
Alpiraz, et al., 2012 54.7 24.1 27 59.4 20.3 27 1.2% 0.19 [-0.37, 0.75]
Subtotal (95% CI) 82 82 3.5% -0.27 [-0.91, 0.36]
Heterogeneity: Tau² = 0.15; Chi² = 5.78, df = 2 (P = 0.06); I² = 65%
Test for overall effect: Z = 1.00 (P = 0.32)
2.5.9 Spinal cord injury
Bi, et al., 2015 (68) 21.4 9.1 26 38.7 14.5 26 1.2% -1.41 [-2.02, -0.80]
Celik, et al., 2013 (69) 38.8 25 17 67.7 14.2 18 1.1% -1.38 [-2.14, -0.61]
Yilmaz & Oleg, 2014 (70) 39.5 17 11 52.5 18.6 10 1.0% -0.70 [-1.59, 0.19]
Subtotal (95% CI) 54 52 3.2% -1.24 [-1.66, -0.82]
Heterogeneity: Tau² = 0.00; Chi² = 1.82, df = 2 (P = 0.40); I² = 0%
Test for overall effect: Z = 5.76 (P < 0.00001)
2.5.10 Dysphonia - musculoskeletal
Mansur, et al., 2019 (71) 26.67 22.57 15 45.33 26.15 15 1.1% -0.74 [-1.48, 0.00]
Siqueira et al., 2019 (72) 2.92 6.6 13 0.7 1.6 14 1.1% 0.46 [-0.31, 1.22]
Subtotal (95% CI) 28 29 2.2% -0.15 [-1.33, 1.03]
Heterogeneity: Tau² = 0.57; Chi² = 4.85, df = 1 (P = 0.03); I² = 79%
Test for overall effect: Z = 0.25 (P = 0.81)
2.5.12 Myofascial pain
Graff-Radford, et al., 1989 (73) 28.3 18.06 12 30.2 15.92 12 1.1% -0.11 [-0.91, 0.69]
Sahin, et al., 2011 (74) 68.5 15.5 19 69.5 11.5 19 1.1% -0.07 [-0.71, 0.56]
Subtotal (95% CI) 31 31 2.2% 0.00 [-0.58, 0.41]
Heterogeneity: Tau² = 0.00; Chi² = 0.03, df = 1 (P = 0.84); I² = 0%
Test for overall effect: Z = 0.34 (P = 0.74)
2.5.13 Acute pelvic pain - emergency transport
Banker, et al., 2006 32.4 18 29 68.2 11.2 33 1.1% -2.26 [-2.91, -1.61]
Subtotal (95% CI) 29 33 1.1% -2.26 [-2.91, -1.61]
Heterogeneity: Not applicable
Test for overall effect: Z = 6.85 (P < 0.00001)
2.5.14 Complex regional pain syndrome
Bilgili, et al., 2018 14.27 10.1 15 23.27 15.8 15 1.1% -0.66 [-1.40, 0.08]
Subtotal (95% CI) 15 15 1.1% -0.66 [-1.40, 0.08]
Heterogeneity: Not applicable
Test for overall effect: Z = 1.75 (P = 0.08)
2.5.15 Critical ischemic pain - leg
Cuschieri, et al., 1987 (75) 30 11.25 10 49 20.25 10 1.0% -1.11 [-2.07, -0.15]
Subtotal (95% CI) 10 10 1.0% -1.11 [-2.07, -0.15]
Heterogeneity: Not applicable
Test for overall effect: Z = 2.28 (P = 0.02)
2.5.16 Fractured ribs
Orcel, et al., 2002 (76) 24 13 25 39 20 25 1.2% -0.88 [-1.46, -0.29]
Subtotal (95% CI) 25 25 1.2% -0.88 [-1.46, -0.29]
Heterogeneity: Not applicable
Test for overall effect: Z = 2.95 (P = 0.003)
2.5.17 Neuropathic pain in the hand
Chaing & Lue, 2005 17 17 10 46 20 9 0.9% -1.50 [-2.55, -0.45]
Subtotal (95% CI) 10 9 0.9% -1.50 [-2.55, -0.45]
Heterogeneity: Not applicable
Test for overall effect: Z = 2.81 (P = 0.005)
2.5.18 Post herpetic neuralgia
Barbarisi, et al., 2018 25.11 0.82 9 39 1.19 8 0.1% -12.50 [-17.39, -7.61]
Subtotal (95% CI) 9 8 0.1% -12.50 [-17.39, -7.61]
Heterogeneity: Not applicable
Test for overall effect: Z = 5.01 (P < 0.00001)
2.5.19 Post partum pain
Kayman-Kose, et al., 2014 (77) 13.5 5.8 50 7.8 7 50 1.2% 0.88 [0.47, 1.29]
Subtotal (95% CI) 50 50 1.2% 0.88 [0.47, 1.29]
Heterogeneity: Not applicable
Test for overall effect: Z = 4.19 (P < 0.0001)
2.5.20 Post Stroke Pain
Ekim et al., 2006 (78) 47.2 5.6 10 65.3 6.3 9 0.8% -2.91 [-4.28, -1.54]
Subtotal (95% CI) 10 9 0.8% -2.91 [-4.28, -1.54]
Heterogeneity: Not applicable
Test for overall effect: Z = 4.15 (P < 0.0001)
2.5.21 Post traumatic hip pain during emergency transport
Lang, et al., 2007 59 6 30 79 11 33 1.1% -2.20 [-2.83, -1.57]
Subtotal (95% CI) 30 33 1.1% -2.20 [-2.83, -1.57]
Heterogeneity: Not applicable
Test for overall effect: Z = 6.83 (P < 0.00001)
2.5.22 Renal colic in Emergency care
Mora, et al., 2006 33.3 16 39 82.6 14.3 34 1.1% -3.20 [-3.91, -2.50]
Subtotal (95% CI) 39 34 1.1% -3.20 [-3.91, -2.50]
Heterogeneity: Not applicable
Test for overall effect: Z = 8.91 (P < 0.00001)
2.5.23 Temporomandibular joint pain
Zhang et al., 2020a (79) 17 3 10 31 12.6 10 0.9% -1.46 [-2.46, -0.45]
Subtotal (95% CI) 10 10 0.9% -1.46 [-2.46, -0.45]
Heterogeneity: Not applicable
Test for overall effect: Z = 2.83 (P = 0.005)
2.5.24 Various acute traumatic pains - sprains, fractures, lacerations
Ordog, 1987 (80) 30.4 2.8 25 54.8 25 25 1.1% -1.35 [-1.97, -0.73]
Subtotal (95% CI) 25 25 1.1% -1.35 [-1.97, -0.73]
Heterogeneity: Not applicable
Test for overall effect: Z = 4.27 (P < 0.0001)
2.5.25 Various musculoskeletal
Suh, et al., 2015 (81) 18.7 7.46 24 30.7 17.67 23 1.2% -0.88 [-1.48, -0.28]
Subtotal (95% CI) 24 23 1.2% -0.88 [-1.48, -0.28]
Heterogeneity: Not applicable
Test for overall effect: Z = 2.86 (P = 0.004)
Total (95% CI) 2426 2415 100.0% -0.96 [-1.14, -0.78]
Heterogeneity: Tau² = 0.64; Chi² = 733.23, df = 90 (P < 0.00001); I² = 88%
Test for overall effect: Z = 10.37 (P < 0.00001)
Test for subgroup differences: Chi² = 202.12, df = 23 (P < 0.00001), I² = 88.6%
-4 -2 0 2 4
Favours TENS Favours Placebo

Figure A7 Forest plot of comparison TENS versus placebo with subgroup analysis to explore the effect of pain condition (diagnosis) categorised according to authors' description given in the trial report.

Broad ICD-11 categories

We conducted a subgroup analysis on pain condition categorised according to the ICD-11 categories with reference to the classification of top-level diagnoses for chronic pain conditions (i.e., chronic primary pain, chronic cancer-related pain, chronic postsurgical or posttraumatic pain, chronic neuropathic pain, chronic headache or orofacial pain, chronic secondary visceral pain, and chronic secondary musculoskeletal pain, [102]).

There was a statistically significant difference in participant-reported pain intensity in favour of TENS for chronic primary pain (20 samples, 1046, P = 0.0004, I^2 = 86%). The remainder of the subgroups for chronic pain categorised according to ICD-11 had fewer than 100 participants in the primary TENS trial arm. There was a statistically significant difference in participant-reported pain intensity in favour of TENS for acute post-operative pain (36 samples, 1788, P < 0.00001, I^2 = 80%), acute procedural pain (10 RCTs, 682 participants, P = 0.001, I^2 = 88%), and labour pain (4 sample, 397 participants, P = 0.05, I^2 = 95%), as previously reported in the subgroup analysis for pain condition (diagnosis) categorised according to the authors description. In addition, there were no statistically significant differences in participant-reported pain intensity for acute visceral pain (excluding dysmenorrhea and labour pain (3 samples, 235 participants, P = 0.04, I^2 = 95%). The remainder of the subgroups had fewer than 100 participants in the primary TENS trial arm (Figure A8). The test for subgroup differences was statistically significant (Chi^2 = 41.5, df = 10 (P < 0.00001), I^2 = 76.0%).

The sensitivity analysis that removed subgroups with pooled sample sizes of fewer than 100 participants in the primary TENS trial arm was not a statistically significant (Chi^2 = 2.25, df = 4 (P =0.69), I^2 = 0%), suggesting that pain condition categorised according to the ICD-11 does not significantly modify the effect of TENS in comparison to placebo.

MetaTENS_Appendix_BMJO_05-10-2021 – Supplementary File 1

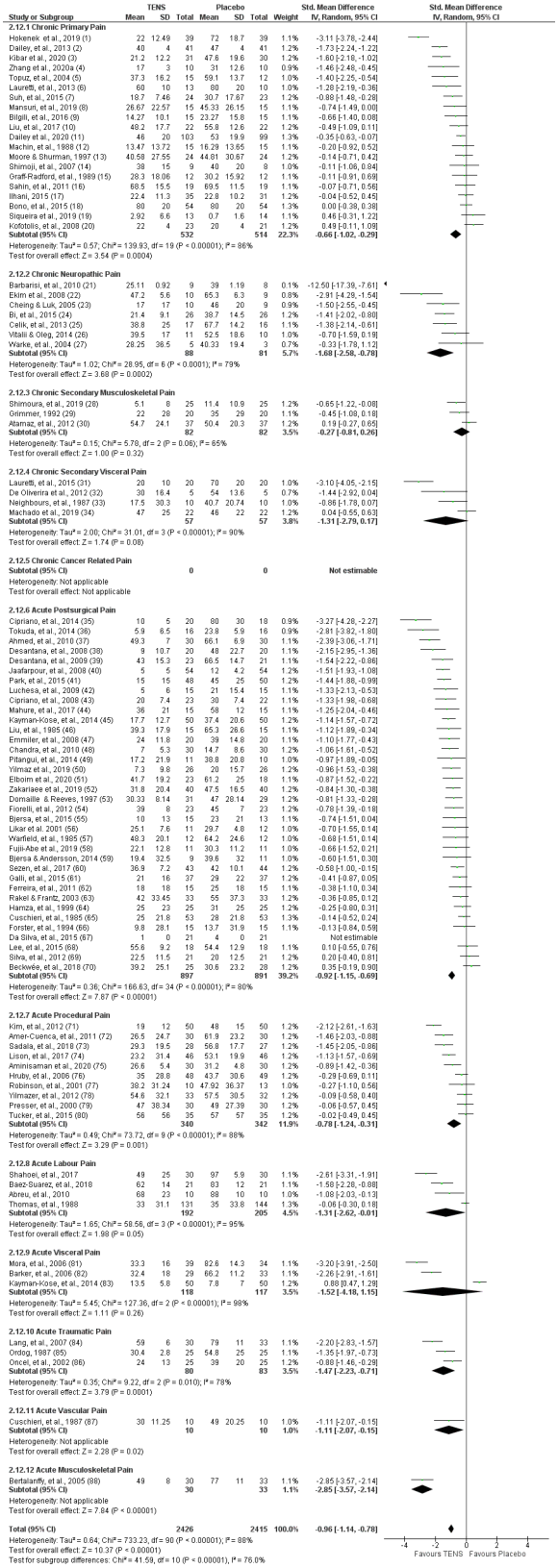

Figure A8 Forest plot of comparison TENS versus placebo with subgroup analysis to explore the effect of pain condition categorised according to authors' description given in the trial report.

Nociceptive or Neuropathic
We conducted a subgroup analysis on pain condition categorised according to mechanistic descriptors of pain as predominantly nociceptive or neuropathic in origin (Kosek et al., 2016). There was a statistically significant difference in participant-reported pain intensity in favour of TENS for pain conditions categorised as predominantly nociceptive in origin (85 samples, 4650 participants, P < 0.00001, I^2 = 88%) and for pain conditions categorised as predominantly neuropathic in origin (7 samples, 191 participants, P < 0.0001, I^2 = 80%). The test for subgroup differences was statistically significant at our pre-specified threshold of P < 0.1 (Chi^2 = 2.83, df = 1 (P = 0.09), I^2 = 64.6%) but there were far fewer trials and participants in pooled neuropathic pain data, meaning that we have very low confidence in the sub- group analysis and the precision of the treatment effect estimate for each subgroup.

Structure Associated with Pain
We conducted a subgroup analysis on conditions categorised by ourselves according to the predominant physiological structures/tissue involved in the painful experience as: Somatosensory (cutaneous); Musculoskeletal; Visceral; Neural; and Bone. We categorised post-operative procedures according to the targeted surgical structure and spasticity irrespective of cause as musculoskeletal.

There was a statistically significant difference in participant-reported pain intensity in favour of TENS for painful experiences with predominant involvement from somatosensory (10 samples, 610 participants, P = 0.002, I^2 = 92%), musculoskeletal (26 samples, 1237 participants, P < 0.00001, I^2 = 83%), visceral (44 samples, 2543 participants, P < 0.00001, I^2 = 89%) and neural (7 samples, 191 participants, P = 0.0001, I^2 = 80%) structures. There were no statistically significant differences in painful experiences with predominant involvement from bone (5 samples, 260 participants, P < 0.06, I^2 = 89%). The test for subgroup differences was not statistically significant (Chi^2 = 7.62, df = 4 (P = 0.11), I^2 = 47.5%).

Plausibility Pain Characteristics - subgroup findings
The subgroup analyses on pain characteristics found no persuasive evidence that the effects of TENS is moderated by pain diagnosis or characteristics. Thus, we posit that TENS may alleviate the intensity of pain, irrespective of pain diagnosis. Treatment effects of TENS were not modified when pain was categorised according to duration (acute versus chronic) or pain diagnoses according to RCT author. The direction subgroup effects were in favour of TENS but of different sizes (i.e., quantitative), although substantial heterogeneity between results from the trials within each subgroup undermined confidence in the magnitude of treatment effect estimates for each subgroup. Nevertheless, the magnitude of any putative subgroup differences was of a scale that would be too small to impact clinical decisions. In summary, the findings of our subgroup analyses on clinical characteristics are consistent with research that has found no relationships between the outcome and type of pain [103].

Analysis of Publication Bias - TENS vs Placebo
We visually inspected funnel plots to explore the likelihood of reporting bias if there were at least 10 RCTs in a meta-analysis. Egger's regression test showed significant evidence of a small-study effect (p <0.0001). Trim and fill analysis showed evidence of publication bias, indicating that eight trials might be missing to right of mean for an adjusted SMD of -0.78 (95% CI -0.995 to -0.565) (random-effects model, Figure A9).

MetaTENS_Appendix_BMJO_05-10-2021 – Supplementary File 1

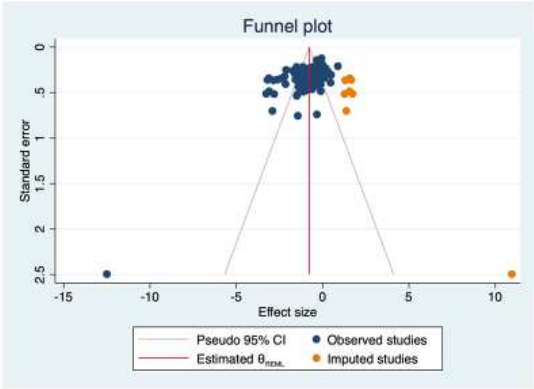

Figure A9 Funnel plot of TENS versus placebo comparison with trim and fill analysis. Actual results displayed in blue. Results corrected for the possibility of a publication bias displayed in orange.

Outcome: ≥30% reduction in pain

There were two RCTs that had extractable data with a total of 118 participants receiving TENS and 114 receiving placebo [89,104]. It was not possible to conduct an analysis of the proportion of participant-reported pain relief of ≥30% expressed as frequency (dichotomous) data because of insufficient data. Nonetheless, the RCT by [89] was of high quality and had a low RoB across 7 of 9 RoB items, with the largest trial arm sample size of any comparison with placebo in our review (TENS = 103 participants vs. placebo TENS = 99 participants). The study provides strong evidence that using TENS for 4 weeks produced clinically meaningful improvement in movement-evoked pain and pain at rest when compared with placebo TENS, for women experiencing pain associated with fibromyalgia who were on a stable medication.

Outcome: ≥50% reduction in pain (i.e., substantial pain relief)

It was possible to extract data from 9 RCTs (460 participants, 9 samples of participants). There were two crossover RCTs and both were deemed to have sufficient washout between interventions to eliminate contamination [105,106]. At the last during TENS or the first post-TENS intervention measurement point, there were 106/241 participants that reported pain relief of ≥50% or greater (responders) for TENS compared with 28/219 participants for any type of placebo. There was a statistically significant difference in the proportion of participants achieving substantial pain relief in favour of TENS with the risk ratio being 2.89 [2.02, 4.13] and no heterogeneity (I^2 = 0%; Figure A10). There are too few RCTs and participants to be entirely certain of the validity of the treatment effect estimate. Therefore, we did not calculate number needed to treat, nor undertake subgroup analyses to explore the effect of methodological or clinical characteristics on outcome.

Forest plot

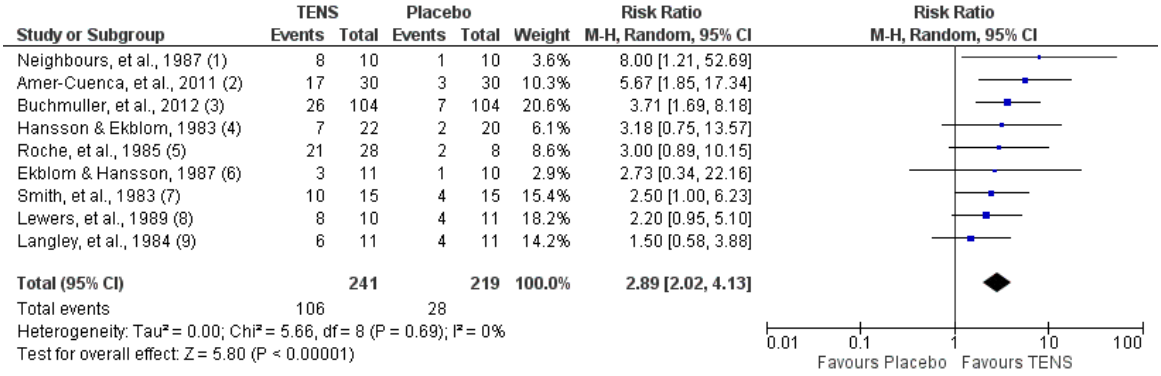

Figure A10 Forest plot of comparison TENS versus placebo. Outcome: ≥50% reduction in pain. NOTE: Favours TENS on the right-hand side of the Forest plot.

TENS versus no treatment - Analysis of effects

We considered an intervention as 'no treatment' if we were assured that the participants did not receive any other 'active' treatment. We did not include interventions described as controls that allowed patients any type of active treatment, including medication or exercise. Thus, RCTs that compared TENS in combination with a pharmacological agent versus a control consisting of the pharmacological agent on its own were not included in this analysis.

There were 16 RCTs that we categorised as comparing TENS with a no treatment intervention. One was a crossover RCT deemed to have enough washout between interventions to eliminate contamination [107].

Outcome: Pain intensity - expressed as mean (continuous) data

We extracted data at the last during TENS or the first post-TENS intervention measurement point from 10 RCTs (10 samples, 602 participant). There was a significant overall effect in favour of TENS (SMD -0.82; 95% CI -1.18, -0.46; Figure A11), and substantial heterogeneity (I^2 = 76%). There was insufficient data to undertake subgroup analyses to explore the effect of methodological nor clinical characteristics on outcome.

Forest plot

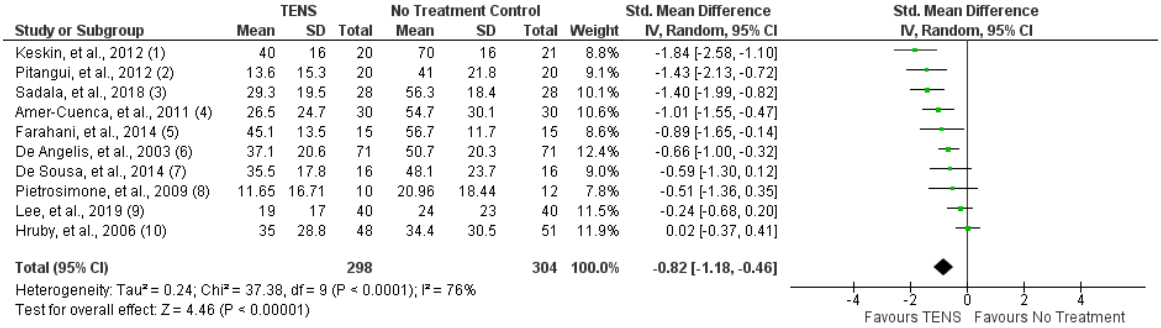

Figure A11 Forest plot of comparison TENS versus no treatment. Outcome: pain intensity - expressed as mean (continuous) data.

Analysis of publication bias – TENS vs No Treatment

We visually inspected funnel plots to explore the likelihood of reporting bias (Figure A12). Egger's regression test showed significant evidence of a small-study effect (p = 0.0878). However, Trim and fill analysis showed no evidence of publication bias.

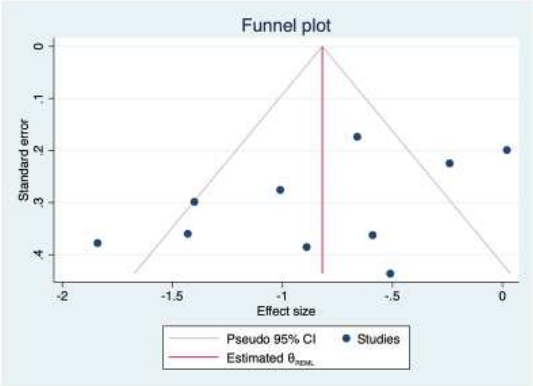

Figure A12 Funnel plot of TENS versus no treatment comparison.

Outcome: ≥30% reduction in pain

It was not possible to conduct an analysis of the proportion of participant-reported pain relief of ≥30% expressed as frequency (dichotomous) data because there were no RCTs with extractable data.

Outcome: ≥50% reduction in pain

It was not possible to conduct an analysis of the proportion of participant-reported pain relief of ≥50% expressed as frequency (dichotomous) data because of insufficient data (There was only one RCT with extractable data; [87]).

TENS versus standard of care - Analysis of effects

We considered an intervention as 'standard of care' if trial authors considered the intervention or intervention(s) to be fully or part of 'common', 'routine', or 'standard' practice and/or care, irrespective of whether authors explicitly named the intervention as 'standard of care'. Interventions were either TENS compared head-to-head with a SoC intervention (i.e., TENS vs SoC) or TENS as an adjunct to a SoC intervention (i.e., TENS combined with SoC vs SoC alone).

There were 127 RCTs (127 samples) that we categorised as comparing TENS with a SoC intervention. There were 8 crossover RCTs and all were deemed to have sufficient washout between interventions to eliminate contamination [79,81,98,108-112]. We categorised 40 of these SoC interventions as RCTs predominantly exercise/physiotherapy based, 71 as predominantly pharmacologically based, 3 as exercise/physiotherapy combined with pharmacological, and 13 RCTs as neither exercise/physiotherapy nor pharmacological (other), and/or unclear.

Outcome: Pain intensity - expressed as mean (continuous) data

We extracted data at the last during TENS or the first post-TENS intervention measurement point from 61 RCTs (61 samples, 3155 participants). There were five crossover RCTs and all were deemed to have sufficient washout between interventions to eliminate contamination [79,81,84,98,110]. There was a significant overall effect in favour of TENS (SMD -0.72; 95% CI-0.95, -0.50) and substantial heterogeneity (I^2 = 88%; Figure A13). The test for subgroup differences was not statistically significant (Chi^2 = 4.16, df = 2, P = 0.12), suggesting that the nature of the SoC intervention does not modify the effect of TENS in comparison with SoC. There are enough trials and participants in each subgroup, so the covariate distribution is not concerning. There is substantial heterogeneity between results from the trials within each subgroup, therefore the validity of the treatment effect estimate for each subgroup is uncertain.

Forest plot

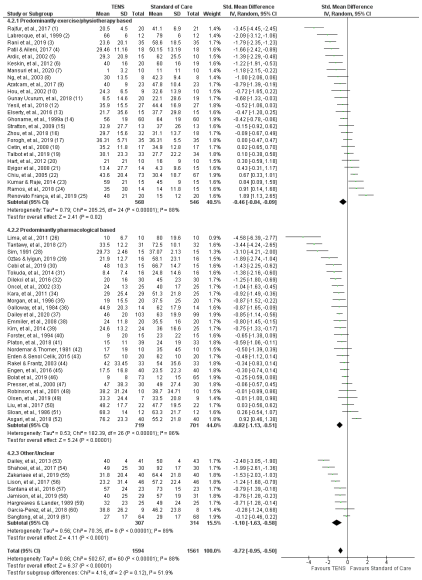

Figure A13 Forest plot of comparison TENS versus standard of care. Outcome: pain intensity - expressed as mean (continuous) data. Subgroup analysis comparing TENS either alone or when added to exercise/physiotherapy based interventions, pharmacologically based interventions, and SoC that was categorised as other/unclear.

Analysis of publication bias – TENS vs SoC

We visually inspected funnel plots to explore the likelihood of reporting bias (Figure A14). Egger's regression test showed significant evidence of a small-study effect (p = 0.0062). Trim and fill analysis showed evidence of publication bias, indicating that 11 trials might be missing to left of mean for an adjusted SMD of -1.032 (-1.31, -0.76) (random-effects model).

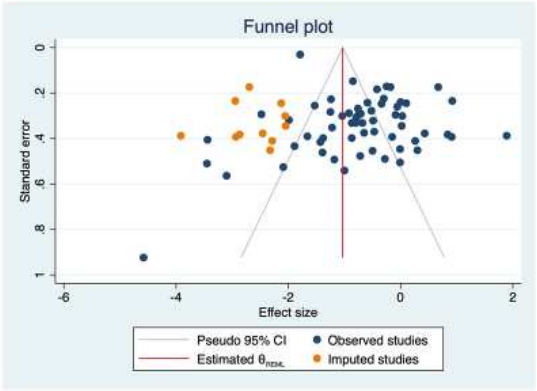

Figure A14 Funnel plot of TENS versus standard of care comparison with trim and fill analysis. Actual results displayed in blue. Results corrected for the possibility of a publication bias displayed in orange.

Interpretation: The finding that 11 trials might be missing to left of mean might be due to ccontamination by additional concurrent treatments in both TENS and comparator groups – participants may titrate concurrent treatments to achieve comparable pain in both groups. This may result in underestimation of TENS effects [113] [114]

Outcome: ≥30% reduction in pain

There were two RCTs with extractable data. It was not possible to conduct an analysis of the proportion of participant-reported pain relief of ≥30% expressed as frequency (dichotomous) data because of insufficient data. The RCT by [89] had low RoB across 7 of 9 RoB items, and provided strong evidence that using TENS for 4 weeks produced clinically meaningful improvement in movement-evoked pain and pain at rest when compared with placebo TENS, for women experiencing pain associated with fibromyalgia who were on a stable medication and routine care. The study by Escortell-Mayor et al. [26] found no differences between TENS and manual therapy the proportion of participants achieving moderate reductions in neck pain of at least 20 mm on a 100 mm VAS (which is below our threshold of ≥30% reduction). Hence, it was not possible to conduct an analysis of the proportion of participant-reported pain relief of ≥30% expressed as frequency (dichotomous) data because of insufficient data.

Outcome: ≥50% reduction in pain

There was one RCT (parallel group) with extractable data. It was not possible to conduct an analysis of the proportion of participant-reported pain relief of ≥50% expressed as frequency (dichotomous) data because of insufficient data.

TENS versus Other Treatments - Analysis of effects

We considered an intervention as 'another treatment' if participants received a comparison intervention that had not been categorised as standard of care (SoC). The purpose of the analysis was to undertake a head-to-head comparison of TENS versus another treatment, so we extracted data that enabled isolation of effects between TENS and another treatment providing any additional care and/or treatment was standardised between groups, e.g., in instances when patients were also given pharmacological, exercise, or physiotherapy-based treatment. The nature of comparisons was either TENS compared head-to-head with another treatment either alone or on a background of care standardised between groups.

We identified 118 RCTs (131 samples) that compared TENS with at least one other treatment. There were four crossover RCTs and all were deemed to have sufficient washout between interventions to eliminate contamination [68,110,115,116]. There were 13 RCTs that compared TENS with more than one treatment intervention. We decided to include all comparisons in the meta-analysis and conducted a sensitivity analysis by removing multiple comparisons from RCTs to explore the effect of duplicate TENS data on outcome.

Outcome: Pain intensity - expressed as mean (continuous) data
We extracted data at the last during TENS or the first post-TENS intervention measurement point from 67 RCTs (131 samples, 3327 participants, including duplicates from primary TENS arm).

We extracted data at the last during TENS or the first post-TENS intervention measurement point from 67 RCTs (131 samples, 3327 participants, including duplicates from primary TENS arm). There were 11 crossover RCTs and all were deemed to have sufficient washout between interventions to eliminate contamination [68,105,110,116-123].

There was not a statistically significant difference in participant-reported pain intensity (Test for overall effect: Z = 1.08, P = 0.28; Random-effects model; Figure A15) and this did not change following the sensitivity analysis that removed multiple samples from the same RCT (favouring samples that were in subgroups with multiple RCTs) and/or removed subgroups with fewer than 2 RCTs.

The test for subgroup differences was statistically significant ($Chi^2 = 82.82$, df = 24, P < 0.00001). It was noted that there was a statistically significant difference in favour of percutaneous electrical nerve stimulation compared with TENS (4 samples, TENS = 157 participants, P < 0.0001), but no other statistically significant differences for subgroups that had more than one RCT in the pooled data sample. The test for subgroup differences was still statistically significant after removing subgroups with fewer than 100 participants pooled in the TENS trial arm.

Subgroup analyses indicate that the type of treatment intervention used as a comparison significantly modifies the effect of TENS. The treatment effect favours TENS in some but not all comparisons; therefore, the subgroup effect is qualitative. However, there are more trials (and participants) contributing data from some of the subgroups, and there is considerable unexplained heterogeneity between the trials within each of these subgroups. Therefore, the validity of the treatment effect estimate for each subgroup is uncertain, as individual trial results are inconsistent.

We choose not to report the meta-analysis in the final report. There is a heterogeneous mix of comparators, the inclusion of duplicate data in the TENS arm, and sub-groups with too few comparisons (Figure A15).

MetaTENS_Appendix_BMJO_05-10-2021 – Supplementary File 1

Forest plot

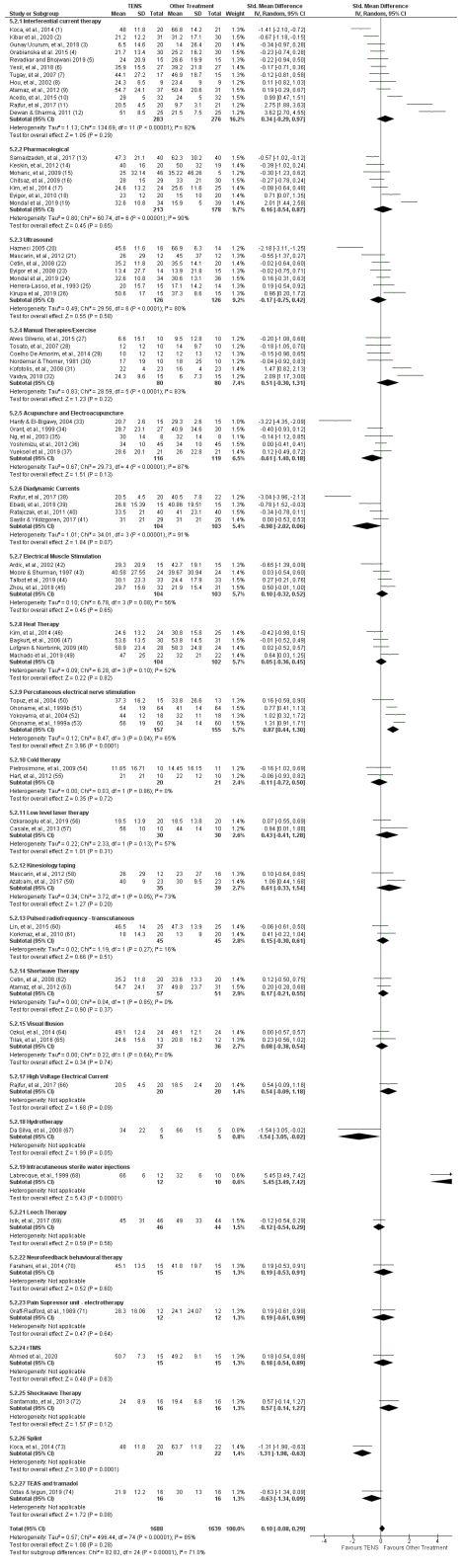
TENS
Other Treatment
Std. Mean Difference
Std. Mean Difference
Study or Subgroup
Mean SD Total Mean SD Total Weight IV, Random, 95% CI
IV, Random, 95% CI
5.2.1 Interferential current therapy
Koca, et al., 2014 (1) 48 11.8 20 66.8 14.2 21 1.3% -1.41 [-2.10, -0.72]
Kilsar et al., 2020 (2) 21.2 12.2 31 31.2 17.1 30 1.5% -0.67 [-1.18, -0.15]
Gunay Urunsm, et al., 2018 (3) 6.5 14.6 20 1.4 26.4 20 1.4% -0.34 [-0.97, 0.28]
Grabiranska et al. 2015 (4) 21.7 13.4 30 25.2 16.2 30 1.5% -0.23 [-0.74, 0.28]
Renodkar and Bhojwani 2019 (5) 24 20.9 15 29.6 18.9 15 1.3% -0.22 [-0.94, 0.50]
Yesil, et al., 2018 (6) 35.9 16.5 27 39.2 21.8 27 1.4% -0.17 [-0.71, 0.38]
Tugay, et al., 2007 (7) 44.1 27.2 17 46.9 18.7 15 1.3% -0.12 [-0.81, 0.58]
Hou, et al., 2002 (8) 24.3 8.5 9 23.4 9 9 1.2% 0.11 [-0.82, 1.03]
Alamuti, et al., 2012 (9) 54.7 24.1 37 50.4 20.6 31 1.5% 0.19 [-0.29, 0.67]
Acedo, et al., 2015 (10) 29 5 32 24 5 32 1.5% 0.89 [0.47, 1.51]
Raftur, et al., 2017 (11) 20.5 4.5 20 9.7 3.1 21 1.2% 2.75 [1.88, 3.63]
Dewan & Sharma, 2011 (12) 51 9.5 25 21.5 7.5 25 1.2% 3.62 [2.70, 4.55]
Subtotal (95% CI) 283 276 16.2% 0.34 [-0.29, 0.97]
Heterogeneity: Tau² = 1.13; Chi² = 134.69, df = 11 (P < 0.00001); I² = 92%
Test for overall effect: Z = 1.05 (P = 0.29)
5.2.2 Pharmacological
Samadzadeh, et al., 2017 (13) 47.3 21.1 40 62.3 30.2 40 1.5% -0.57 [-1.02, -0.12]
Keskin, et al., 2012 (14) 40 16 20 50 32 19 1.4% -0.39 [-1.02, 0.24]
Mohani, et al., 2009 (15) 25 32.14 48 35.22 46.26 5 1.2% -0.30 [-1.23, 0.62]
Chitraz, et al., 2009 (16) 28 15 29 33 21 30 1.5% -0.27 [-0.78, 0.24]
Kim, et al., 2014 (17) 24.6 13.2 24 25.6 11.6 25 1.4% -0.08 [-0.64, 0.48]
Eygor, et al., 2019 (18) 23 12 20 15 10 20 1.4% 0.71 [0.07, 1.35]
Mondal et al., 2019 (19) 32.6 10.8 34 15.9 5 39 1.4% 2.01 [1.44, 2.58]
Subtotal (95% CI) 253 278 9.7% 0.16 [-0.54, 0.87]
Heterogeneity: Tau² = 0.80; Chi² = 60.74, df = 6 (P < 0.00001); I² = 90%
Test for overall effect: Z = 0.45 (P = 0.65)
5.2.3 Ultrasound
Hazneci 2005 (20) 45.6 11.6 16 66.9 6.3 14 1.2% -2.18 [-3.11, -1.25]
Mascarin, et al., 2012 (21) 26 29 12 45 37 12 1.3% -0.55 [-1.37, 0.27]
Celin, et al., 2008 (22) 35.2 11.8 20 35.5 14.1 20 1.4% -0.02 [-0.64, 0.60]
Eygor et al., 2008 (23) 13.4 27.7 14 13.9 21.8 15 1.3% -0.02 [-0.75, 0.71]
Mondal et al., 2019 (24) 32.6 10.8 34 30.6 13.1 36 1.5% 0.16 [-0.31, 0.63]
Herrera-Lasso, et al., 1993 (25) 20 15.7 15 17.1 14.2 14 1.3% 0.19 [-0.54, 0.92]
Kiruga et al., 2019 (26) 50.6 17 15 37.3 8.8 15 1.3% 0.96 [0.20, 1.72]
Subtotal (95% CI) 126 126 9.2% -0.17 [-0.75, 0.42]
Heterogeneity: Tau² = 0.49; Chi² = 29.56, df = 6 (P < 0.0001); I² = 80%
Test for overall effect: Z = 0.55 (P = 0.58)
5.2.4 Manual Therapies/Exercise
Alves Oliveira, et al., 2015 (27) 6.6 15.1 10 9.5 12.8 10 1.2% -0.20 [-1.08, 0.68]
Tosato, et al., 2007 (28) 12 12 10 14 9.7 10 1.2% -0.18 [-1.05, 0.70]
Coelho De Amorim, et al., 2014 (29) 10 12 12 13 12 12 1.3% -0.15 [-0.96, 0.65]
Nordemar & Thorner, 1981 (30) 17 19 10 18 25 10 1.2% -0.04 [-0.92, 0.83]
Hofstede, et al., 2006 (31) 22 4 23 16 4 23 1.4% 1.47 [0.82, 2.13]
Vaidya, 2019 (32) 24.3 9.6 15 6 7.3 15 1.2% 2.09 [1.17, 3.00]
Subtotal (95% CI) 80 80 7.4% 0.51 [-0.30, 1.31]
Heterogeneity: Tau² = 0.83; Chi² = 28.59, df = 5 (P < 0.0001); I² = 83%
Test for overall effect: Z = 1.23 (P = 0.22)
5.2.5 Acupuncture and Electroacupuncture
Hanfy & El-Bigawy, 2004 (33) 20.7 2.6 15 29.3 2.6 15 1.0% -3.22 [-4.35, -2.09]
Grant, et al., 1999 (34) 28.7 23.1 27 40.9 34.6 30 1.5% -0.40 [-0.93, 0.12]
Ng, et al., 2003 (35) 30 14 8 32 14 9 1.1% -0.14 [-1.12, 0.85]
Yoshimizu, et al., 2012 (36) 34 10 45 34 10 45 1.5% 0.00 [-0.41, 0.41]
Yuekiran et al., 2019 (37) 28.6 20.1 21 26 22.8 21 1.4% 0.12 [-0.49, 0.72]
Subtotal (95% CI) 116 119 6.5% -0.61 [-1.49, 0.18]
Heterogeneity: Tau² = 0.67; Chi² = 29.73, df = 4 (P < 0.00001); I² = 87%
Test for overall effect: Z = 1.51 (P = 0.13)
5.2.6 Diadynamic Currents
Raftur, et al., 2017 (38) 20.5 4.5 20 40.5 7.8 22 1.2% -3.04 [-3.98, -2.13]
Ebadi, et al., 2018 (39) 26.6 15.39 15 40.86 19.01 15 1.3% -0.79 [-1.52, -0.03]
Ratajczak, et al., 2011 (40) 33.5 21 40 41 23.1 40 1.5% -0.34 [-0.78, 0.11]
Swain & Yildizgoren, 2017 (41) 31 21 29 31 21 26 1.4% 0.00 [-0.53, 0.53]
Subtotal (95% CI) 104 103 5.4% -0.90 [-2.02, 0.06]
Heterogeneity: Tau² = 1.01; Chi² = 34.01, df = 3 (P < 0.00001); I² = 91%
Test for overall effect: Z = 1.64 (P = 0.07)
5.2.7 Electrical Muscle Stimulation
Ardic, et al., 2002 (42) 29.3 20.9 15 42.7 18.1 15 1.3% -0.65 [-1.39, 0.09]
Moore & Shurman, 1997 (43) 40.58 27.55 24 39.67 30.94 24 1.4% 0.03 [-0.54, 0.60]
Talbot et al., 2019 (44) 30.1 23.3 33 24.4 17.9 33 1.5% 0.27 [-0.21, 0.76]
Zhou, et al., 2018 (45) 29.7 15.6 32 21.9 15.4 31 1.5% 0.50 [-0.01, 1.00]
Subtotal (95% CI) 104 103 5.7% 0.10 [-0.32, 0.52]
Heterogeneity: Tau² = 0.09; Chi² = 6.28, df = 3 (P = 0.10); I² = 52%
Test for overall effect: Z = 0.22 (P = 0.82)
5.2.8 Heat Therapy
Kim, et al., 2014 (46) 24.6 13.2 24 30.8 15.8 25 1.4% -0.42 [-0.98, 0.15]
Bagkurt, et al., 2006 (47) 53.6 13.5 30 53.8 14.5 31 1.5% -0.01 [-0.52, 0.49]
Lotjonen & Nordmark, 2009 (48) 58.9 23.4 28 58.3 24.8 24 1.4% 0.02 [-0.52, 0.57]
Machado et al., 2019 (49) 47 25 22 32 21 22 1.4% 0.64 [0.03, 1.25]
Subtotal (95% CI) 104 102 5.7% 0.05 [-0.36, 0.45]
Heterogeneity: Tau² = 0.10; Chi² = 6.78, df = 3 (P = 0.08); I² = 56%
Test for overall effect: Z = 0.25 (P = 0.80)
5.2.9 Percutaneous electrical nerve stimulation
Topuz, et al., 2004 (50) 37.3 16.2 15 33.8 26.6 13 1.3% 0.16 [-0.59, 0.90]
Ohnsmme, et al., 1998b (51) 54 19 64 41 14 64 1.5% 0.77 [0.41, 1.13]
Yokoyama, et al., 2004 (52) 44 12 18 32 11 18 1.3% 1.02 [0.32, 1.72]
Ohnsmme, et al., 1998a (53) 56 19 60 34 14 60 1.5% 1.31 [0.91, 1.71]
Subtotal (95% CI) 157 155 5.7% 0.87 [0.44, 1.30]
Heterogeneity: Tau² = 0.12; Chi² = 8.47, df = 3 (P = 0.04); I² = 65%
Test for overall effect: Z = 3.96 (P = 0.0001)
5.2.10 Cold therapy
Pietrosimone, et al., 2009 (54) 11.05 16.71 10 14.45 16.15 11 1.2% -0.16 [-1.02, 0.69]
Hart, et al., 2012 (55) 21 21 10 22 12 10 1.2% -0.06 [-0.93, 0.82]
Subtotal (95% CI) 20 21 2.4% -0.11 [-0.72, 0.50]
Heterogeneity: Tau² = 0.00; Chi² = 0.03, df = 1 (P = 0.86); I² = 0%
Test for overall effect: Z = 0.35 (P = 0.72)
5.2.11 Low level laser therapy
Ozbaraoglu et al., 2019 (56) 19.5 13.9 20 18.5 13.8 20 1.4% 0.07 [-0.55, 0.69]
Casale, et al., 2013 (57) 56 10 10 44 14 10 1.2% 0.84 [0.01, 1.68]
Subtotal (95% CI) 30 30 2.6% 0.43 [-0.41, 1.26]
Heterogeneity: Tau² = 0.22; Chi² = 2.33, df = 1 (P = 0.13); I² = 57%
Test for overall effect: Z = 1.01 (P = 0.31)
5.2.12 Kinesiology taping
Mascarin, et al., 2012 (58) 26 29 12 23 27 16 1.3% 0.10 [-0.64, 0.85]
Azakram, et al., 2017 (59) 40 9 23 30 9.5 23 1.4% 1.06 [0.44, 1.68]
Subtotal (95% CI) 35 39 2.7% 0.61 [-0.33, 1.54]
Heterogeneity: Tau² = 0.34; Chi² = 3.72, df = 1 (P = 0.05); I² = 73%
Test for overall effect: Z = 1.27 (P = 0.20)
5.2.13 Pulsed radiofrequency - transcutaneous
Lin, et al., 2015 (60) 46.5 14 25 47.3 13.9 25 1.4% -0.06 [-0.61, 0.50]
Korkmaz, et al., 2010 (61) 18 14.3 20 13 9 20 1.4% 0.41 [-0.22, 1.04]
Subtotal (95% CI) 45 45 2.8% 0.15 [-0.30, 0.61]
Heterogeneity: Tau² = 0.02; Chi² = 1.19, df = 1 (P = 0.27); I² = 16%
Test for overall effect: Z = 0.66 (P = 0.51)
5.2.14 Shortwave Therapy
Celin, et al., 2008 (62) 35.2 11.8 20 33.6 13.3 20 1.4% 0.12 [-0.50, 0.75]
Alamuti, et al., 2012 (63) 54.7 24.1 37 49.8 23.7 31 1.5% 0.20 [-0.28, 0.68]
Subtotal (95% CI) 57 51 2.9% 0.17 [-0.21, 0.55]
Heterogeneity: Tau² = 0.00; Chi² = 0.04, df = 1 (P = 0.85); I² = 0%
Test for overall effect: Z = 0.90 (P = 0.37)
5.2.15 Visual Illusion
Ozkol, et al., 2014 (64) 49.1 12.4 24 49.1 12.1 24 1.4% 0.00 [-0.57, 0.57]
Tilak, et al., 2016 (65) 24.6 15.6 13 20.8 16.2 12 1.3% 0.23 [-0.56, 1.02]
Subtotal (95% CI) 37 36 2.7% 0.08 [-0.38, 0.54]
Heterogeneity: Tau² = 0.00; Chi² = 0.22, df = 1 (P = 0.64); I² = 0%
Test for overall effect: Z = 0.34 (P = 0.74)
5.2.17 High Voltage Electrical Current
Raftur, et al., 2017 (66) 20.5 4.5 20 18.5 2.4 20 1.4% 0.54 [-0.09, 1.18]
Subtotal (95% CI) 20 20 1.4% 0.54 [-0.09, 1.18]
Heterogeneity: Not applicable
Test for overall effect: Z = 1.68 (P = 0.09)
5.2.18 Hydrotherapy
Da Silva, et al., 2009 (67) 34 22 5 66 15 5 0.8% -1.54 [-3.05, -0.02]
Subtotal (95% CI) 5 5 0.8% -1.54 [-3.05, -0.03]
Heterogeneity: Not applicable
Test for overall effect: Z = 1.99 (P = 0.05)
5.2.19 Intracutaneous sterile water injections
Labrecque, et al., 1999 (68) 66 6 12 32 6 10 0.6% 5.45 [3.49, 7.42]
Subtotal (95% CI) 12 10 0.6% 5.45 [3.49, 7.42]
Heterogeneity: Not applicable
Test for overall effect: Z = 5.43 (P < 0.00001)
5.2.21 Leech Therapy
Ilik, et al., 2017 (69) 45 31 46 49 33 44 1.5% -0.12 [-0.54, 0.29]
Subtotal (95% CI) 46 44 1.5% -0.12 [-0.54, 0.29]
Heterogeneity: Not applicable
Test for overall effect: Z = 0.59 (P = 0.56)
5.2.22 Neurofeedback behavioural therapy
Farahani, et al., 2014 (70) 45.1 13.5 15 41.8 19.7 15 1.3% 0.19 [-0.53, 0.91]
Subtotal (95% CI) 15 15 1.3% 0.19 [-0.53, 0.91]
Heterogeneity: Not applicable
Test for overall effect: Z = 0.52 (P = 0.60)
5.2.23 Pain Supressor unit - electrotherapy
Graff-Radford, et al., 1989 (71) 28.3 18.06 12 24.1 24.07 12 1.3% 0.19 [-0.61, 0.99]
Subtotal (95% CI) 12 12 1.3% 0.19 [-0.61, 0.99]
Heterogeneity: Not applicable
Test for overall effect: Z = 0.47 (P = 0.64)
5.2.24 rTMS
Ahmed et al., 2020 50.7 7.3 15 49.2 9.1 15 1.3% 0.18 [-0.54, 0.89]
Subtotal (95% CI) 15 15 1.3% 0.18 [-0.54, 0.89]
Heterogeneity: Not applicable
Test for overall effect: Z = 0.48 (P = 0.63)
5.2.25 Shockwave Therapy
Santarsalo, et al., 2013 (72) 24 8.9 16 19.4 6.8 16 1.3% 0.57 [-0.14, 1.27]
Subtotal (95% CI) 16 16 1.3% 0.57 [-0.14, 1.27]
Heterogeneity: Not applicable
Test for overall effect: Z = 1.57 (P = 0.12)
5.2.26 Splint
Koca, et al., 2014 (73) 48 11.8 20 63.7 11.8 22 1.4% -1.31 [-1.98, -0.63]
Subtotal (95% CI) 20 22 1.4% -1.31 [-1.98, -0.63]
Heterogeneity: Not applicable
Test for overall effect: Z = 3.80 (P = 0.0001)
5.2.27 TEAS and tramadol
Ozlas & Ilgun, 2019 (74) 21.9 12.2 18 30 13 16 1.3% -0.83 [-1.34, 0.03]
Subtotal (95% CI) 18 16 1.3% -0.83 [-1.34, 0.03]
Heterogeneity: Not applicable
Test for overall effect: Z = 1.72 (P = 0.08)
Total (95% CI) 1688 1639 100.0% 0.10 [-0.08, 0.29]
Heterogeneity: Tau² = 0.57; Chi² = 496.44, df = 74 (P < 0.00001); I² = 85%
Test for overall effect: Z = 1.09 (P = 0.28)
Test for subgroup differences: Chi² = 82.82, df = 24 (P = 0.00001), I² = 71.0%
-4 -2 0 2 4
Favours TENS Favours Other Treatment

Figure A15 Forest plot of comparison TENS versus other treatmensts. Outcome: pain intensity - expressed as mean (continuous) data. Subgroup analysis comparing TENS with diffferent treatmenr modalities.

Analysis of publication bias – TENS vs. Other treatment

We did not undertake an analysis of publication bias because we choose not to report the meta-analysis in the final report. There is a heterogeneous mix of comparators, the inclusion of duplicate data in the TENS arm, and sub-groups with too few comparisons

Outcome: ≥30% reduction in pain

There were no RCTs with extractable data, so it was not possible to conduct an analysis of the proportion of participant-reported pain relief of ≥30% expressed as frequency (dichotomous) data because of insufficient data.

Outcome: ≥50% reduction in pain

There was one RCT of crossover design with extractable data and sufficient washout between interventions to eliminate contamination [105]. It was not possible to conduct an analysis of the proportion of participant-reported pain relief of ≥50% expressed as frequency (dichotomous) data because of insufficient data.

High frequency TENS versus low frequency TENS - Analysis of effects

There were 37 RCTs that included at least one comparison of high versus low frequency TENS. There was insufficient extractable data to conduct a subgroup analysis of high versus low frequency TENS for any of the previous analyses of either adverse events or effects of interventions.

Outcome: Pain intensity - expressed as mean (continuous) data

We extracted data at the last during TENS or the first post-TENS intervention measurement point from 13 RCTs (13 samples, 468 participants, no crossover RCTs) that compared high frequency and low frequency TENS. There was not a statistically significant difference in participant-reported pain intensity when data was pooled from samples (SMD -0.19; 95%CI -0.43, 0.06; Figure A16).

Forest plot

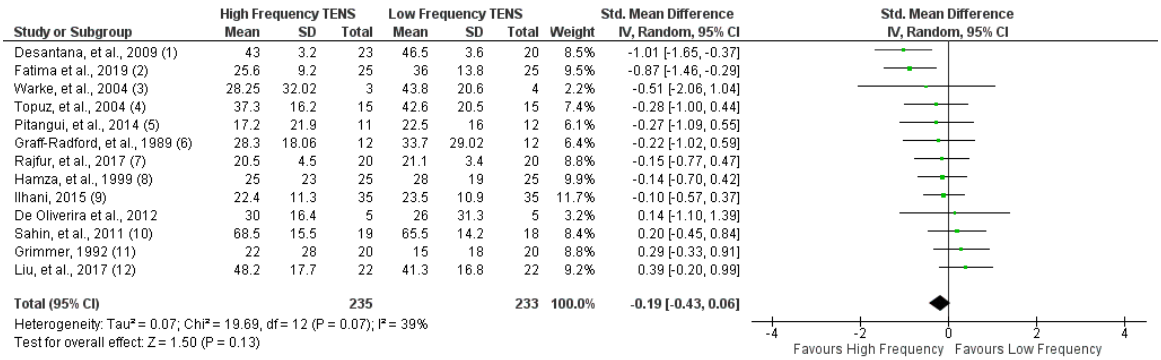

Figure A16 Forest plot of comparison high frequency TENS versus low frequency TENS. Outcome: pain intensity - expressed as mean (continuous) data.

Analysis of publication bias – High vs. low frequency TENS

We visually inspected funnel plots to explore the likelihood of reporting (Figure A17). Egger's regression test showed no evidence of a small-study effect (p = 0.8871). Trim and fill analysis showed no evidence of publication bias.

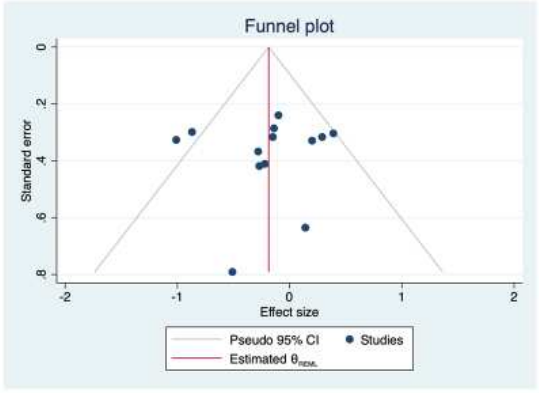

Figure A17 Funnel plot of high frequency versus low frequency TENS comparison.

Outcome: ≥30% reduction in pain

There was one RCT (parallel group) with extractable data [124]. It was not possible to conduct an analysis of high versus low frequency TENS for the proportion of participant-reported pain relief of ≥30% expressed as frequency (dichotomous) data because of insufficient data.

Outcome: ≥50% reduction in pain

It was possible to extract data from 4 RCTs (5 samples, 286 participants). There were two crossover RCTs and all were deemed to have sufficient washout between interventions to eliminate contamination [105,106]. We pooled 4 samples with 28/94 participants that reported pain relief of ≥50% or greater (responders) for high frequency TENS compared with 39/92 participants for low frequency TENS. This was just below our threshold of 100 participants per trial arm for conducting meta-analysis, although the Forest plot is presented for visual inspection (Figure A18).

Forest plot

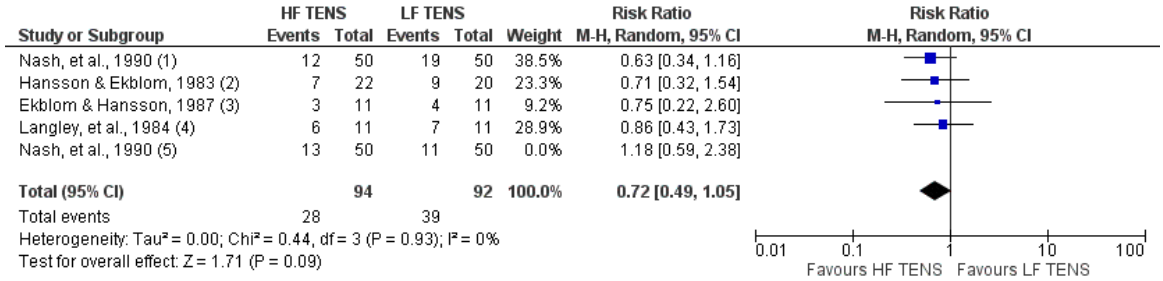

Figure A18 Forest plot of comparison high frequency TENS versus low frequency TENS. Outcome: ≥50% reduction in pain.

Adverse events - Analysis of effects

Textual and numerical information related to adverse events was extracted directly from primary reports via cut and paste into a word document as summarised in the Online Table 4 (11_OL-TABLE4_AdverseEvents.pdf).

Often trial reports did not clearly distinguish adverse events related to the study or not, or whether they were likely a result of a worsening medical condition, including co-morbidity, medical procedures, or treatments other than TENS. Information related to adverse events was summarised and coded in an Excel spreadsheet for descriptive analysis. There were 245/381 reports that did not include a statement about the incidence of adverse events. Out of the 136 reports that included a statement of adverse events, 59/136 reports stated there were no adverse events any of the intervention groups during the RCT and 90/136 reports stated there were no adverse events related to TENS. There were 46 reports that stated the occurrence of adverse events that may be associated with TENS, none of which were deemed by authors to be a serious adverse event directly attributable to TENS. There was one report of the possibility that TENS may contribute to a serious adverse event in an RCT evaluating the effect of electrical stimulation on Botulinum Toxin A therapy in patients with chronic myofascial pain syndrome: "*There was a possible relationship between the treatment and spontaneous abortion. A 36-year-old woman had a spontaneous abortion that occurred 21 days after BTX-A injection and electrical stimulation*." [125] p414. Adverse events associated with TENS were generally described as mild in severity and infrequent in occurrence and included skin irritation, tenderness/soreness and TENS discomfort. Worsening symptoms (e.g., increase in pain-soreness) was identified as a negative consequence of TENS, although often it was unclear whether trial authors considered this to an adverse event or lack of treatment efficacy.

Outcome: Relative Risk

We extracted ratio data from 18 RCTs (1587 participants) for meta-analysis by counting the number of adverse events, irrespective of severity. We were thorough in checking for double counting but not all reports were clear in disclosing adverse events so we cannot guarantee with certainty that there may be an occasional counting of two adverse arising from one participant.

There was not a statistically significant difference in the tally of adverse events between TENS (63 events, 805 participants) and the comparison group (95 events, 782 participants) with the risk ratio being 0.73 (95% CI 0.36, 1.48; Figure A19). The test for subgroup differences in adverse events when TENS was compared with a placebo control (6 RCTs, 828 participants) or active treatment comparison (12 RCTs, 759 participants) was not statistically significant ($Chi^2 = 2.50$, df = 1 (P = 0.11), $I^2 = 60.0\%$), suggesting that the type of comparison intervention does not modify the frequency of adverse effects associated with TENS. There are enough trials and participants in each subgroup, so the covariate distribution is not concerning. There is moderate and substantial heterogeneity between results from the trials within each subgroup, therefore, the validity of the treatment effect estimate for each subgroup is uncertain.

Forest plot

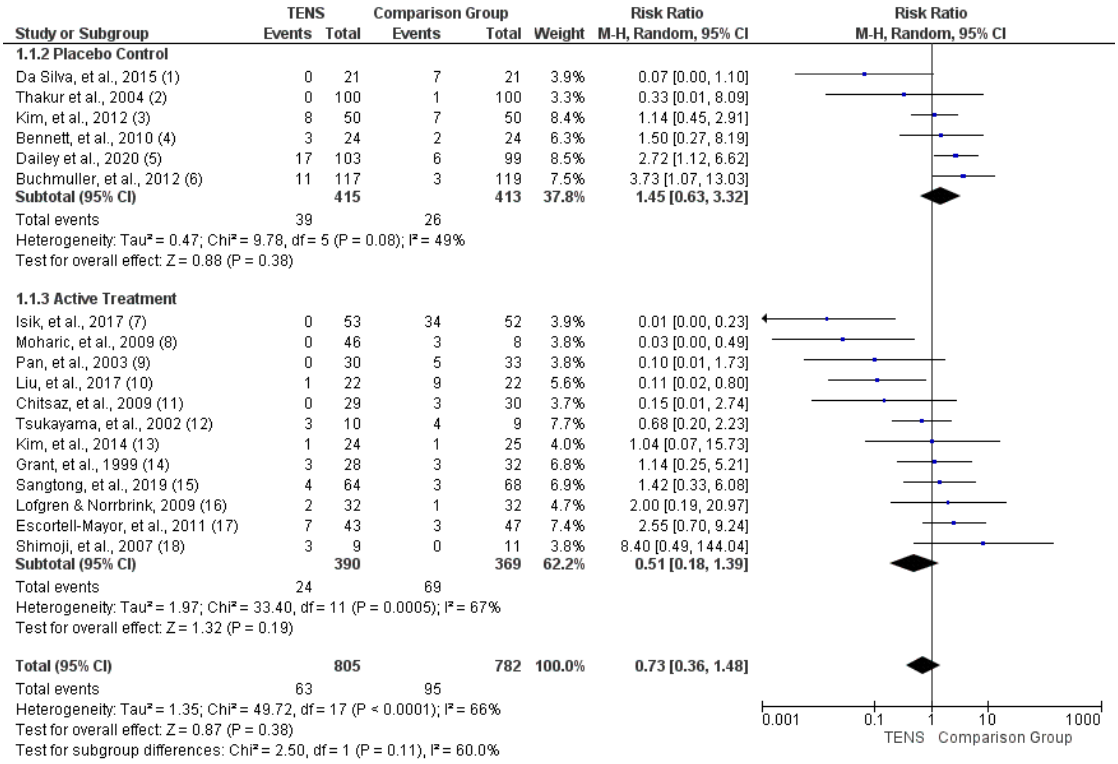

Figure A19 Forest plot of adverse events comparison TENS versus any comparison.

Plausibility: Minor and infrequent adverse events from TENS

Clinical experts claim that TENS hazards associated with TENS are minor and that there is minimal potential for serious, life threatening, adverse events [6,126]. This is consistent with our findings for our descriptive analysis that found that adverse events during and/or after TENS treatment were reported to be minor and included skin irritation, worsening symptoms and TENS discomfort. There were no reports of serious adverse events, although there was one report of a possible relationship between TENS contributing to a spontaneous abortion in a woman although this occurred 21 days after treatment. Having considered overall quality of available evidence, limitations in our review process and physiological and clinical plausibility we are confident that there is minimal harm associated with TENS, although our estimate of risk ratio lacked precision.

SECTION 3 - Potential biases in the review process

Search strategy and screening process - Limitations
Our search strategy for RCTs was broad and involved screening of over 8000 records. We also conducted a search specifically for systematic reviews for a separate analysis and this enabled cross referencing of RCTs between searches. Thus, we are confident that our search was comprehensive.

Our screening processes identified RCTs that had optimised TENS intervention in terms of generating a strong non-painful TENS sensation at (or close to) the site of pain, irrespective of variations in electrical characteristics of currents produced by a 'standard TENS device'. We did not include in our evaluation TENS-like devices (e.g., interferential therapy, transcutaneous electrical acupoint stimulation) that may have been delivered in such a way as to generate a strong comfortable paraesthesia with similar qualities as that experienced with 'standard TENS'. None of our analyses to date suggest that between or within trial variations in specific electrical characteristics of TENS influences clinical outcome to any significant degree.

Effects size estimates - Limitations in the analysis (confounding factors)
Much heterogeneity remained unexplained following subgroup analyses exploring methodological and patient characteristics.

Sample size
We attribute the presence of statistical heterogeneity to the inclusion of lots of RCTs with small sample sizes. It is a matter for debate whether we should have used a higher threshold for trial arm size, although our subgroup analysis of trial arm sizes of $\geq$30 and $\geq$50 participants failed to detect subgroup effects.

RCTs with large total sample sizes compromised statistical power by having multiple intervention groups that markedly reduced the number of participants randomised to trial arms and increased imprecision of estimates of treatment effects.

Quality of reporting - observations
Generally, trial reports lacked recommended levels of detail suggested for reporting TENS trials [113]. It was noticeable that many trial reports focussed on physiological and clinical plausibility of findings rather than the integrity of methods, data, and analyses.

Trial Design - Pragmatic and Exploratory
We included a spectrum of pragmatic and explanatory trials, and it is known that pragmatic trials tend to have higher standard deviations because they recruit a wider range of participants but are more useful to inform options for care in clinical settings [127]. Some RCTs were overly complicated in design and had too many comparison groups and outcome measures, at the expense statistical power.

Cross-over studies - Sensitivity analysis
We included cross-over studies and pre-specified that we would only extract data from the first phase unless we considered there to be sufficient duration of washout between crossover to prevent carry-over effects. We were only able to extract data from a few cross-over trials and in all instances, we considered there to be sufficient washout as evidence suggests that the effects of TENS are generally short-lived. We conducted sensitivity analyses and found that removal of crossover trials did not affect findings of the analysis

- TENS versus placebo
    - All trials

    - SMD [95% CI] = -0.96 [-1.14, -0.78] Test for overall effect: Z = 10.37 (P < 0.00001) Heterogeneity: Tau² = 0.64; Chi² = 733.23, df = 90 (P < 0.00001); I² = 88%).
- After removal of [84,98,128]
    - SMD [95%CI] = -0.97 [-1.16, -0.79] Test for overall effect: Z = 10.35 (P < 0.00001) Heterogeneity: Tau² = 0.66; Chi² = 726.33, df = 88 (P < 0.00001); I² = 88%).

Analysing crossover data as if parallel group, normally requires generic inverse variance to correct for correlation between groups using the same participants (paired data), but we argue that has negligible impact on outcome because generic inverse variance increases confidence intervals and this will be negated by the influence of the overwhelming number of data points from parallel group studies.

Appropriateness of TENS

The electrical characteristics for TENS and the treatment regimens were diverse, but usually appropriate for clinical context, e.g., a single dose of less than five minutes for some procedural pains, to single doses one hour or a single daily dose over a period of a few week. The included studies all administered TENS at a strong intensity that we consider to be optimal. It was difficult to ascertain whether electrical characteristics and/or treatment regimens were advisory or prescribed for longer duration multiple treatment studies. Few studies formally measured frequency of home usage and/or whether there had been adherence to instructions on how best to self-administer TENS.

Many RCTs delivered TENS within clinical settings, which is appropriate for in-patient populations with acute pain, but less so for out-patient populations with chronic pain, where it would be more ecologically valid to monitor outcomes following a period of treatment that was self-administered home use. As TENS is a self-administered technique-based intervention, we argue that RCTs using an enriched enrolment randomised withdrawal design would have utility. There were no such trials in the included studies.

Measurement time points

Few TENS regimens lasted more than one month even for chronic pain. Follow-up after a course of treatment was short and no more than one month. We pre-specified analysis of data during or immediately after a single TENS intervention to account for such diversity so our analysis provides evidence of 'immediate' during treatment effects. We feel that this is ecologically valid but does not address the longer-term outcomes of TENS.

Contamination

We included data of interventions with concurrent use of pharmacological and/or non-pharmacological treatments (e.g., exercise, hot/cold therapies), as background or as rescue, formally as part of the design of the study. Contamination of estimates of treatment effect in RCTs and meta analyses has been recognised as an issue in RCTs of medical interventions [129].

Previously, we have argued that pain scores may be compromised when participants have access to analgesics because participants may titrate analgesic consumption to achieve tolerable levels of pain intensity in each intervention group [114]. Previously we have reported that contamination from the simultaneous use of other treatments is likely to bias toward underestimating treatment effects associated with TENS for pain [113]. We have argued that the influence of TENS on analgesic consumption, and associated side effects, may be a more meaningful measure and we are planning to evaluate the effect of TENS on analgesic consumption.

Risk of Performance Bias (blinding participant)
We used an aide memoire adapted for TENS to support consistency of judgements for risk of bias.

Participant blinding has been central to the debate about the efficacy of TENS. Previous systematic reviews have managed judgements of performance bias associated with blinding participants and therapists inconsistently with some reviewers awarding high risk of performance bias arguing that it is impossible to blind participants to the sensory experience associated with TENS. We argue that the key to blinding is whether participants are uncertain whether an intervention is 'functioning properly' so that participants in treatment and placebo groups are uncertain whether they have received appropriate treatment. Many trials used a modified TENS device without current output coupled with pre-study briefings to create uncertainty about whether a treatment is 'functioning properly'. This has been shown to mitigate over-estimation of effects associated with knowing which intervention is 'placebo' even when participants experience TENS sensations (see discussion in [8]). There were few RCTs that assessed the credibility and outcome of blinding of participants, those that did reported that blinding of this nature was successful.

Adverse events - Limitations in the analysis
All included RCTs focussed on treatment effects rather than adverse events. Adverse effects were rarely pre-specified as an outcome in trial reports and when they were methods and procedures to capture adverse effect data was unclear. We found a lack of clarity in reports and especially whether the likely cause of adverse events was related to TENS or concurrent treatment such as medication, or other medical procedures such as surgery. Some reports categorised worsening symptoms as an adverse event rather treatment failure.

Many reports stated 'no significant adverse effects occurred in the study' or 'there were no side effects in either group' but did not provide comparative numerical data (e.g., tabulated). When pooling data for meta-analysis, we only extracted data as 'zero' if there was clear numerical data or there was a statement that no adverse events occurred in a group, and this was accompanied by numerical data of the occurrence of at least one event in the comparator group(s).

Overall, our analysis is susceptible to bias associated with unclear and selective reporting of adverse events as most investigators reported spontaneous detection of adverse events based on ill-defined criteria. Characterisation and extraction of data to pool for meta-analysis for adverse events was imprecise because most reports inadequately described the monitoring, determination, and analysis. Criteria to recognise adverse events were absent, as were criteria for categorising seriousness. Thus, our estimate of risk ratio for the occurrence of adverse events lacked precision and there is still a need for more robust data.

There are generally few published studies of adverse effects on TENS. Evidence suggests a higher incidence of skin reactions when using monophasic pulsed electrical currents. A laboratory study by [130] found that 52% of 25 healthy participants experienced adverse skin reactions to 10 minutes of subsensory monophasic pulsed transcutaneous electrical stimulation at the knee compared which was higher that reported rates in previous studies using asymmetrically biphasic pulsed electrical currents, which was only 4%. Most studies in our analysis used biphasic pulsed electrical currents.

SECTION 4 - Certainty and Quality of Evidence

GRADE Methodology

GRADE = Grades of Recommendation, Assessment, Development and Evaluation

GRADE judgements were undertaken independently by MIJ and CAP (GJ and PGW as arbiters).

We used GRADEPro software and the Guideline development tool to conduct the assessment of evidence and create evidence tables https://gradepro.org/.

Certainty was assessed against the following criteria and if necessary downgraded:

- Risk of bias - Serious (- 1) or very serious (- 2)
- Inconsistency- Serious (- 1) or very serious (- 2)
- Indirectness - Serious (- 1) or very serious (- 2)
- Imprecision - Serious (- 1) or very serious (- 2)
- Publication bias – Strongly suspected (- 1)

GRADE judgements of pooled effects for outcomes were:

- Very low - The true effect is probably markedly different from the estimated effect
- Low - The true effect might be markedly different from the estimated effect
- Moderate - The authors believe that the true effect is probably close to the estimated effect
- High - The authors have a lot of confidence that the true effect is like the estimated effect.

We created an Aide Memoire to assist decision making (available on request from m.johnson@leedsbeckett.ac.uk). The Aide Memoire was based on the GRADE handbook, Domain-specific guidance for writing useful explanations – from Cochrane and an item checklist developed by [131]

GRADE: Summary of Findings

TENS versus Placebo

TENS versus placebo for pain intensity at last during or first post intervention measurement point

Certainty assessment							Summary of findings				
							Study event rates (%)			Anticipated absolute effects	
Participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	With Placebo (any) at last during or first post intervention measurement	With TENS	Relative effect (95% CI)	Risk with Placebo (any) at last during or first post intervention measurement	Risk difference with TENS
Pain Intensity Rating (assessed with: 0-10 intensity scale (VAS/NRS))											
4841 (91 RCTs)	not serious[a]	serious[b]	not serious[c]	not serious[d]	none[e]	⨁⨁⨁◯ Moderate	2415	2426	-	-	SMD **0.96 SD lower** (1.14 lower to 0.78 lower)
Reduction of pain intensity of 50% or more											
460 (9 RCTs)	not serious	not serious[f]	not serious[c]	serious[g]	publication bias strongly suspected[e]	⨁⨁◯◯ Low[e]	28/219 (12.8%)	106/241 (44.0%)	**RR 2.89** (2.02 to 4.13)	128 per 1,000	**242 more per 1,000** (from 130 more to 400 more)

CI: confidence interval; **RR:** risk ratio; **SMD:** standardised mean difference

Explanations

a. Not serious. Over there was low or unclear RoB, except for sample size. There was low RoB for participant and assessor bias. We considered low sample size within inconsistency

b. Serious. Point estimates varied moderately; Generally, confidence intervals overlapped, although not all overlapped at least one point estimate. The direction of effect was consistent; The magnitude of statistical heterogeneity was high (e.g., I^2 >60%) and unexplained and may be associated with the contribution from small sized studies as detected by Egger's test. We downgraded (-1) for the combined effects of unexplained heterogeneity and possible publication bias associated with small study effect.

c. Not serious. The populations and interventions in included studies were highly applicable. The outcome was directly measured and in a sufficient timeframe. The conclusions were based on direct comparisons

d. Not serious. Pooled data sample size does meet pre-specified (e.g., 500 participants per trial arm). Magnitude of median study sample size was low (<100 participants); Number of included studies was high (>10 studies); Overall effect estimate confidence intervals showing the possibility of an effect above the threshold of important benefit.

e. Not serious. Visual inspection of Funnel plots suggested possible asymmetry and Egger's regression test showed evidence of a small-study effect (p < 0·0001). Trim and fill analysis indicated that eight trials might be missing to the right of the mean for an adjusted SMD of -0·78 (95% CI -0·995 to -0·565) from -0·96 (95% CI -1·14, -0·78). We decided not to downgrade for this item but considered the impact of small study effect under inconsistency.

f. Not serious. Point estimates varied moderately; All confidence intervals overlapped one point estimate. The direction of effect was consistent. The magnitude of statistical heterogeneity was low (e.g., I^2 >0%)

g. Serious. Magnitude of median study sample size was low (<100 participants) and does not meet pre-specified criteria for number of participants for pooled data (≥500 participants per trial arm). Number of included studies was moderate (e.g., 5-10 studies); Outcome was a common event (e.g., >1/100). We downgraded (-1).

TENS versus No Treatment

TENS versus no treatment (waiting list control) for pain intensity at last during or first post intervention measurement point

Certainty assessment							Summary of findings				
							Study event rates (%)			Anticipated absolute effects	
Participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	With No treatment (waiting list control)	With TENS	Relative effect (95% CI)	Risk with No treatment (waiting list control)	Risk difference with TENS
Pain Intensity Rating - last during or first post intervention											
602 (10 RCTs)	not serious[a]	serious[b]	not serious[c]	serious[d]	none[e]	⨁⨁◯◯ Low	304	298	-	-	SMD **0.82 SD lower** (1.18 lower to 0.46 lower)

CI: confidence interval; **RR:** risk ratio; **SMD:** standardised mean difference

Explanations

a. Not serious. Low or unclear RoB except for sample size. Possibility that participants know they are not receiving treatment in some studies. We did not downgrade

b. Serious. Point estimates did not vary widely; Confidence intervals had substantial overlap (all confidence intervals overlap at least one of the included studies point estimate); The direction of effect was consistent; The magnitude of statistical heterogeneity was high (e.g., I2 >60%). We downgraded (-1)

c. Not serious. The populations and interventions in included studies were highly applicable. The outcome was directly measured and in a sufficient timeframe. The conclusions were based on direct comparisons

d. Serious. Pooled data sample size does NOT meet pre-specified (e.g., 500 participants per trial arm). Magnitude of median study sample size was low (<100 participants); Number of included studies was high (>10 studies); Overall effect estimate confidence intervals showing the possibility of an effect above the threshold of important benefit. We downgraded (-1) because pooled data sample size does NOT meet pre-specified

e. Egger's regression test showed potential evidence of a small-study effect (p = 0.0878). although trim and fill analysis showed no evidence of publication bias.

TENS versus Standard of Care (SoC)

TENS versus treatment(s) used as standard of care for pain intensity at last during or first post intervention measurement point

Certainty assessment							Summary of findings				
Participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With Standard of Care	With TENS		Risk with Standard of Care	Risk difference with TENS
Pain Intensity Rating											
3155 (61 RCTs)	not serious[c]	serious[d]	not serious[a]	not serious[e]	publication bias strongly suspected[b]	⨁⨁◯◯ Low	1561	1594	-	-	SMD **0.72 SD lower** (0.95 lower to 0.5 lower)

CI: confidence interval; **RR:** risk ratio; **SMD:** standardised mean difference

Explanations

a. Indirectness - Not serious. The populations and interventions in included studies were highly applicable. The outcome was directly measured and in a sufficient timeframe. The conclusions were based on direct comparisons. We did not downgrade

b. Publication bias - Strongly suspected. Visual inspection of Funnel plots suggested asymmetry. Egger's regression test showed significant evidence of a small-study effect (p = 0.0062). Trim and fill analysis showed evidence of publication bias, indicating that 11 trials might be missing to left of mean for an adjusted SMD of -1.032 (-1.31, -0.76) increasing the effect size (random-effects model). We downgraded (-1) due to small study effect combined with potential RoB associated with blinding.

c. Risk of bias - Not serious. There was low or unclear RoB for all items except sample size. There was a higher RoB associated blinding of participants than for placebo. This was not serious enough to downgrade by one level, so we combined concerns about RoB with concerns about publication bias.

d. Inconsistency - Serious. Point estimates varied moderately; Generally, confidence intervals overlapped, although not all overlapped at least one point estimate. The direction of effect was consistent; The magnitude of statistical heterogeneity was high (e.g., I2 >60%). We downgraded (-1)

e. Imprecision - Not serious. Pooled data sample size does meet pre-specified (e.g., 500 participants per trial arm). Magnitude of median study sample size was low (<100 participants); Number of included studies was high (>10 studies); Overall effect estimate confidence intervals showing the possibility of an effect above threshold. We did not downgrade but Egger's test noted a small study effect which was accounted for under Publication Bias

TENS versus Other Treatment

We did not GRADE.

High Frequency versus Low Frequency TENS

High versus low frequency TENS for pain intensity at last during or first post intervention measurement point

Certainty assessment							Summary of findings				
							Study event rates (%)			Anticipated absolute effects	
Participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	With Low Frequency TENS	With High Frequency TENS	Relative effect (95% CI)	Risk with Low Frequency TENS	Risk difference with High Frequency TENS
Pain Intensity Rating											
468 (13 RCTs)	not serious[a]	not serious[b]	not serious[c]	serious[d]	none[e]	⨁⨁⨁◯ Moderate	233	235	-	-	SMD **0.19 lower** (0.43 lower to 0.06 higher)

CI: confidence interval; **RR:** risk ratio; **SMD:** standardised mean difference

Explanations

a. Not serious. Low or unclear RoB except for sample size which was accounted for in imprecision.
b. Not serious. Point estimates varied moderately; Generally, confidence intervals overlapped. The direction of effect was consistent; The magnitude of statistical heterogeneity was low (e.g., I2 <40%).
c. Not serious. The populations and interventions in included studies were highly applicable. The outcome was directly measured and in a sufficient timeframe. The conclusions were based on direct comparisons.
d. Serious. Pooled data sample size does NOT meet pre-specified threshold (e.g., 500 participants per trial arm). Magnitude of median study sample size was low (<100 participants); Number of included studies was high (>10 studies); Overall effect estimate confidence intervals showed the possibility of no difference in effect. We downgraded (-1).
e. Undetected. Visual inspection of Funnel plots suggested symmetry. Egger's regression test showed no significant evidence of a small-study effect (p = 0.8871). Trim and fill analysis showed no evidence of publication bias.

Adverse events

TENS compared with comparator for adverse events irrespective of severity

Certainty assessment							Summary of findings				
							Study event rates (%)			Anticipated absolute effects	
Participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	With Comparator	With TENS	Relative effect (95% CI)	Risk with Comparator	Risk difference with TENS
Proportion of participants experiencing adverse events irrespective of severity - all comparators											
1587 (18 RCTs)	very serious[a]	not serious[b]	very serious[c]	serious[d]	publication bias strongly suspected[e]	⨁◯◯◯ Very low[d]	95/782 (12.1%)	63/805 (7.8%)	**RR 0.73** (0.36 to 1.48)	121 per 1,000	**33 fewer per 1,000** (from 78 fewer to 58 more)

CI: confidence interval; **RR:** risk ratio

Explanations

a. Very serious. Adverse events were generally capture by spontaneous observation rather than through formal study design. We downgraded by two levels (-2).
b. Not serious. Overall, there is consistency in the direction of results with some inconsistency in the estimates of the treatment effect.
c. Very serious. Most trials did not pre-specify formal measurement of adverse events. The populations and interventions in included studies were highly applicable. The outcome was not directly measured, nor measured in a sufficient timeframe. The conclusions were often based on direct comparisons of spontaneous reports. We downgraded by two levels (-2).
d. Serious. The event rate and trial sample sizes were very low. The optimal information size criterion for benefit was met (i.e., $\geq$500 participants per trial arm) but this needs to be substantially larger for harm. We downgraded by two levels (-2).
e. Strongly suspected. Visual inspection of Funnel plots suggested asymmetry and publication bias.

SECTION 5 – Supplementary Detail to Support Conclusions

Overall completeness and applicability of evidence

Our analysis supports treatment effects during and immediately post TENS. We did not attempt to analyse long-term follow-up following a course of treatment at this stage of the project. We are yet to conduct some pre-specified analyses on secondary outcomes including condition-specific pain-related outcomes (e.g., WOMAC, FIQ), health-related quality of life, including activities of daily living and fatigue, using any validated tool (e.g., Patient Global Impression of Change (PGIC), Short Form Health Survey (SF-36), EuroQol instruments) and participant-reported treatment satisfaction.

Predominance of in-clinic RCTs

There was a predominance of RCTs undertaken in hospital settings with short term outcomes such as post-operative pain and procedural pain, with fewer studies on chronic pain monitoring long term outcome from a long-term course of treatment. Methodological aspects of the study are logistically easier to manage and control in hospital settings than home trials whereby participants are using TENS to self-manage pain. Consequently, these RCTs tended to be judged as having lower risk of bias.

Paucity of long-term follow-up

There was a scarcity of trials with long-term follow-up of say 6 months after treatment had ceased. Interpreting the findings of these types of trials needs careful consideration. The effects of TENS are maximal during or immediately after stimulation so a significant gap between the end of a course of TENS treatment and follow-up measurements may bias towards observing no treatment effect. Trials with a significant gap between the end of a course of TENS treatment and follow-up may detect resolution of pain and/or behaviour changes such as reducing fear-avoidance of movement pain resulting in increased physical activity that may have been catalysed by a course of TENS treatment or by a wide range of other factors.

Paucity of RCTs on prevalent chronic pain conditions

There were too few trials to make confident judgements about treatment effects associated with neuropathic pain, and common types of chronic musculoskeletal pain such as non-specific low back and/or neck pain and osteoarthritis. Despite our review providing evidence that differences in TENS effects between specific conditions is minimal, we feel that a large scale long-term multi-centre trial for these common conditions would still be valuable. This is because differences in the context and practicalities of using TENS between specific conditions and populations of patients (e.g., elderly, cognitively challenged) that may influence whether TENS is indicated in clinical practice. It will also provide guideline panels with more confidence on which to make decisions about specific conditions.

Follow-up analyses emerging from this review are:

- The effect of TENS on analgesic consumption based on the studies included in this review.
- The effect of TENS versus 'TENS-like' devices that were excluded from this review (e.g., transcutaneous electrical acupoint stimulation, interferential currents, etc.). There are some systematic reviews that have recently undertaken similar analyses [41,132,133].

Plausibility of Findings

Physiological Plausibility

Our findings are physiological plausible. There is long-standing evidence that TENS acts physiologically to neuromodulate central nociceptive transmission irrespective of pathophysiology or diagnosis by selectively activating low threshold cutaneous primary afferents which reduces noxious evoked activity in central nociceptive transmission cells in both normal and sensitised states (see [7,134] for reviews). Therefore, TENS is used for symptomatic relief of pain rather than treatment (cure) of pathology in clinical practice.

Clinical Plausibility

Our findings are consistent with expert opinion and clinical experience spanning more than 50 years, that TENS provides symptomatic relief of pain in a manner similar to 'soothing pain' by rubbing, warming or cooling the skin i.e., a therapeutic neuromodulation.

Our findings agree with expert opinion and clinical guidelines that TENS is probably safe and that adverse events are generally mild and restricted to minor skin reactions such as erythema and itchiness at the site of electrodes [6,134-136].

Our findings that pain characteristics do not moderate the effect of TENS agree with research that has found no relationships between TENS outcome and type of pain [103] and that physiological action is via neuromodulation rather than curative (i.e., not dependent on pathology [137,138]).

Our findings that high or low frequency stimulation does not moderate the effect of strong but comfortable TENS is consistent with current clinical practice whereby patients are advised to tailor the electrical output characteristics of the device to maximise comfort accompanying a strong non-painful TENS sensation on a moment-to-moment basis if necessary.

There were few trials and participants to make confident judgements about treatment effects associated with neuropathic pain, and common musculoskeletal pains such as chronic non-specific low back and/or neck pain and osteoarthritis. This review provides evidence that suggests that there are minimal differences in treatment effects between specific conditions. There may, however, be differences in the context and practicalities of using TENS between specific conditions and populations of patients (e.g., elderly, cognitively challenged) that will influence whether TENS is indicated in clinical practice. For TENS we posit that context of pain, rather than pathology is more likely to predict outcome.

Agreements and disagreements with other studies or reviews

As part of this review, we identified and characterised 145 previously published systematic reviews (32 Cochrane reviews) on effect of TENS on pain-related outcomes.

Our descriptive analysis found that statements of conclusion in previous systematic reviews tended toward inconclusive (70/145) or TENS being efficacious (51/145) for acute or chronic pain. Despite being comprehensive and robust in methodological approach, Cochrane reviews consistently report that there are insufficient trials and participants to undertake meta-analyses of pooled data on specific pain conditions.

The recent overview of Cochrane reviews on TENS for chronic pain [139,140] and neuropathic pain [139,140] did not pool data, and were inconclusive. In our review we have argued against using a classical pathology-based categorisation of pain when appraising TENS at a gross level. Our subgroup analyses for common pain conditions such as labour pain, low back pain and osteoarthritis too few

trials and participants to estimate treatment effects with certainty. This is consistent with previous reviews.

Inconsistency in clinical guidelines

At present, TENS is recommended TENS as an adjunct to core treatment for osteoarthritis, rheumatoid arthritis [135,141], but not for non-specific chronic low back pain [142] and intrapartum care (labour pain) [143].

The inconsistency in National Institute for Health and Care Excellence guidelines has been due in part to insufficient data to make recommendations for specific pain conditions. We found that the magnitude of effect between different types of pain is not clinically relevant enabling data pooling from any type of pain. Our review has done this, and our findings should be considered in the development of future clinical guidelines, especially those that do not recommend TENS for specific pain conditions based on insufficient high quality RCTs on specific types of pain

The NICE draft guideline for chronic pain [144] does not recommend TENS for chronic primary pain based on an analysis of two RCTs. In contrast, we analysed data from 20 trials based on the ICD-11 coding, with a statistically significant overall effect in favour of TENS compared with placebo (SMD = -0.66 [-1.20, -0.29], P < 0.0004).

Cost-benefit

Our review did not include a cost-benefit analysis, funders should be aware that previous analyses provide evidence that TENS equipment, running costs and follow-up clinical support is inexpensive and can reduce annual costs for chronic pain [145], chronic low back pain without neurological involvement [146,147] and osteoarthritis of the knee [148].

Summary of Conclusions

TENS produces clinically important reductions in the intensity of acute or chronic pain during and immediately after treatment with minimal risk of adverse events. This is based on a review of 381 RCTs and 24532 participants at entry and various meta-analyses.

- There is moderate-certainty evidence of treatment effects in favour of TENS when compared with placebo based on data from 91 RCTs (92 samples, 4841 participants) with standardised mean difference [95% CI] for pain intensity of -0.96 [-1.14, -0.78]. This surpassed our threshold of magnitude for an important change in pain intensity in-line with IMMPACT criteria [15].
- There is low-certainty evidence of treatment effects in favour of TENS when compared with no treatment (waiting list) controls.
- There is low-certainty evidence of treatment effects in favour of TENS compared with treatments are considered by trial authors to be used fully or partly as standard of care (61 RCTs (61 samples, 3155 participants) with the standardised mean difference of -0.72 [-0.95, -0.50] in favour of TENS.
- There is moderate-certainty evidence of no difference in pain intensity between high and low frequency TENS.
- There is evidence from 381 RCTs that adverse events from TENS are minor and infrequent and not different from placebo, although the estimate of risk ratio had very-low certainty.

We have been judicious in our interpretation of our findings. We are confident in these conclusions because our findings are physiologically plausible and consistent with clinical expertise.

Implications for practice

- TENS can produce clinically important reductions in pain intensity for people experiencing acute or chronic pain, with minimal risk of harm.
- There are no clinically important differences in reductions in pain intensity generated by TENS for different pain conditions (diagnosis) or type of tissue associated with pain.
- TENS should be considered as a potential treatment option as an adjunct or as a stand-alone treatment for individuals experiencing any type of pain.

For people with pain

- TENS is a safe pain-relieving treatment and can be used on its own or in combination with other treatments to reduce the intensity (soothe) acute or chronic pain.
- TENS produces a strong non painful TENS sensation within or close to the site of pain, so TENS needs to be administered frequently to maintain its pain-relieving effect.
- TENS equipment and running costs are relatively inexpensive and TENS can be self-administered either in hospital, clinic, or home settings.

For clinicians

- This review of 381 RCTs provides evidence that clinically meaningful reductions in pain intensity occur during or immediately after delivering strong non painful TENS close to the site of pain.
- There is evidence that the characteristics of pain (e.g., duration or type of pain) do not modify the effects of TENS so any type of pain may respond.
- There is evidence that whether the electrical characteristics of currents are high frequency of low frequency do not modify the effects of TENS.
- Patients may need to use TENS frequently in order to maintain an analgesic effect.

For policymakers

- The findings provide evidence in support of clinical guidelines that recommend TENS as an adjunct to core treatment [135,141].
- The findings provide evidence that the size of treatment effect between different types of pain is small, so efficacy is transferable to any type of pain. This should be considered in the development of clinical guidelines, especially those that do not recommend TENS for specific pain conditions based on insufficient high quality RCTs on specific types of pain, e.g., non-specific chronic low back pain [142] and intrapartum care (labour pain) [143].
- The findings are consistent with physiological plausibility and with clinical experience and expertise in the field.

For funders

- This review did not include a cost-benefit analysis. Previously published analyses provide evidence that TENS equipment, running costs and follow-up clinical support is inexpensive and can reduce annual costs for chronic pain [145], chronic low back pain without neurological involvement [146,147] and osteoarthritis of the knee [149].
- TENS is safe and inexpensive and should be available as a treatment option for the management of pain.

Implications for research

This review should serve to

- Reduce production of systematic reviews on TENS for acute pain, chronic pain, or specific painful conditions unless there is novel angle and/or a dramatic increase in the volume of large multicentre randomised controlled trials.
- Justify a large scale multicentred RCT to assess TENS in a mixed population of chronic pain patients to add further confidence, or otherwise, to the precision of the findings reported in this review. We propose an Enriched Enrolment Randomised Withdrawal design to overcome many

methodological issues encountered in RCTs on TENS [150,151], *trial arm* sample sizes greater than 200 participants, and the use of methodological criteria for RCTs on TENS reported in [113].

- Justify the need for pragmatic ecologically valid studies gathering real-world data about how best to integrate TENS into practice. Such findings can inform educational packages to train and support patients to self-administer TENS [152-154].

References in Supplementary Appendix

1. Johnson, M.I.; Jones, G.; Paley, C.A.; Wittkopf, P.G. The clinical efficacy of transcutaneous electrical nerve stimulation (TENS) for acute and chronic pain: a protocol for a meta-analysis of randomised controlled trials (RCTs). *Bmj Open* **2019**, *9*, e029999, doi:10.1136/bmjopen-2019-029999.
2. Moher, D.; Shamseer, L.; Clarke, M.; Ghersi, D.; Liberati, A.; Petticrew, M.; Shekelle, P.; Stewart, L.A.; Group, P.-P. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Syst Rev* **2015**, *4*, 1, doi:10.1186/2046-4053-4-1.
3. Higgins, J.; Thomas, J.; Chandler, J.; Cumpston, M.; Li, T.; Page, M.; VA, W. *Cochrane Handbook for Systematic Reviews of Interventions*, 2nd ed.; John Wiley & Sons: Chichester (UK), 2019.
4. Guyatt, G.H.; Oxman, A.D.; Vist, G.E.; Kunz, R.; Falck-Ytter, Y.; Alonso-Coello, P.; Schunemann, H.J.; Group, G.W. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ* **2008**, *336*, 924-926, doi:10.1136/bmj.39489.470347.AD.
5. Carbonario, F.; Matsutani, L.; Yuan, S.; Marques, A. Effectiveness of high-frequency transcutaneous electrical nerve stimulation at tender points as adjuvant therapy for patients with fibromyalgia. *European Journal of Physical and Rehabilitation Medicine* **2013**, *49*, 197-204.
6. Johnson, M.I. *Transcutaneous electrical nerve stimulation (TENS). Research to support clinical practice*; Oxford University Press Oxford, UK, 2014.
7. Johnson, M.I. Transcutaneous electrical nerve stimulation. In *Electrophysical agents*, 13 ed.; Watson, T., Nussbaum, E.L., Eds. Elsevier: 2020; pp. 264-295.
8. Rakel, B.; Cooper, N.; Adams, H.J.; Messer, B.R.; Frey Law, L.A.; Dannen, D.R.; Miller, C.A.; Polehna, A.C.; Ruggle, R.C.; Vance, C.G., et al. A new transient sham TENS device allows for investigator blinding while delivering a true placebo treatment. *Journal of pain* **2010**, *11*, 230-238, doi:10.1016/j.jpain.2009.07.007.
9. Sluka, K.A.; Bjordal, J.M.; Marchand, S.; Rakel, B.A. What Makes Transcutaneous Electrical Nerve Stimulation Work? Making Sense of the Mixed Results in the Clinical Literature. *Physical Therapy* **2013**, *93(10):* 1397-402.
10. Deyo, R.; Walsh, N.; Schoenfeld, L.; Ramamurthy, S. Can trials of physical treatments be blinded? The example of transcutaneous electrical nerve stimulation for chronic pain [see comments]. *Am J Phys Med Rehabil* **1990**, *69*, 6-10.
11. Higgins, J.; Altman, D.; Gøtzsche, P.; Jüni, P.; Moher, D.; Oxman, A.; Savović, J.; Schulz, K.; Weeks, L.; Sterne, J. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ* **2011**, *343*, d5928.
12. Moore, A.R.; Eccleston, C.; Derry, S.; Wiffen, P.; Bell, R.F.; Straube, S.; McQuay, H.; Relief, A.W.G.o.t.I.S.I.G.o.S.R.i.P.; Cochrane Pain, P.; Supportive Care Systematic Review Group, E. "Evidence" in chronic pain--establishing best practice in the reporting of systematic reviews. *Pain* **2010**, *150*, 386-389, doi:10.1016/j.pain.2010.05.011.
13. Moore, R.A.; Derry, S.; Wiffen, P.J. Challenges in design and interpretation of chronic pain trials. *Br J Anaesth* **2013**, *111*, 38-45, doi:10.1093/bja/aet126.
14. Busse, J.W.; Bartlett, S.J.; Dougados, M.; Johnston, B.C.; Guyatt, G.H.; Kirwan, J.R.; Kwoh, K.; Maxwell, L.J.; Moore, A.; Singh, J.A., et al. Optimal Strategies for Reporting Pain in Clinical Trials and Systematic Reviews: Recommendations from an OMERACT 12 Workshop. *J Rheumatol* **2015**, 10.3899/jrheum.141440, doi:10.3899/jrheum.141440.
15. Dworkin, R.H.; Turk, D.C.; Wyrwich, K.W.; Beaton, D.; Cleeland, C.S.; Farrar, J.T.; Haythornthwaite, J.A.; Jensen, M.P.; Kerns, R.D.; Ader, D.N., et al. Interpreting the clinical

importance of treatment outcomes in chronic pain clinical trials: IMMPACT recommendations. *J Pain* **2008**, *9*, 105-121.
16. Cohen, J. *Statistical Power Analysis for the Behavioral Sciences.*, 2 ed.; Earlbaum: Hillsdale, NJ, 1988.
17. Peryer, G., Golder, S, Junqueira, D, Vohra, S, Loke, Y.K. Adverse effects. In *Cochrane Handbook for Systematic Reviews of Interventions version 6.0 (updated July 2019)*, Higgins JPT, T.J., Chandler J, Cumpston M, Li T, Page MJ, Welch VA, Ed. Cochrane, 2019. : 2019.
18. Higgins, J.P.; Thompson, S.G.; Deeks, J.J.; Altman, D.G. Measuring inconsistency in meta-analyses. *BMJ* **2003**, *327*, 557-560, doi:10.1136/bmj.327.7414.557.
19. Richardson, M., Garner, P., Donegan, S. Interpretation of subgroup analyses in systematic reviews: A tutorial. *Clinical Epidemiology and Global Health* **2019**, *7*, 192-198.
20. Moore, R.A.; Moore, O.A.; Derry, S.; McQuay, H.J. Numbers needed to treat calculated from responder rates give a better indication of efficacy in osteoarthritis trials than mean pain scores. *Arthritis Res Ther* **2008**, *10*, R39, doi:10.1186/ar2394.
21. Cherian, J.J.; Harrison, P.E.; Benjamin, S.A.; Bhave, A.; Harwin, S.F.; Mont, M.A. Do the Effects of Transcutaneous Electrical Nerve Stimulation on Knee Osteoarthritis Pain and Function Last? *J Knee Surg* **2016**, *29*, 497-501, doi:10.1055/s-0035-1566735.
22. Cherian, J.J.; Kapadia, B.H.; Bhave, A.; McElroy, M.J.; Cherian, C.; Harwin, S.F.; Mont, M.A. Use of Transcutaneous Electrical Nerve Stimulation Device in Early Osteoarthritis of the Knee. *J Knee Surg* **2015**, *28*, 321-327, doi:10.1055/s-0034-1389160.
23. Cherian, J.J.; Kapadia, B.H.; McElroy, M.J.; Johnson, A.J.; Bhave, A.; Harwin, S.F.; Mont, M.A. Knee Osteoarthritis: Does Transcutaneous Electrical Nerve Stimulation Work? *Orthopedics* **2016**, *39*, e180-186, doi:10.3928/01477447-20151222-02.
24. Chesterton, L.; Van Der Windt, D.A.; Sim, J.; Lewis, M.; Mallen, C.D.; Mason, E.; Hay, E. Transcutaneous electrical nerve stimulation for the management of tennis elbow: A pragmatic randomized controlled trial. *Rheumatology* **2013**, *1)*, i38.
25. Lewis, M.; Chesterton, L.S.; Sim, J.; Mallen, C.D.; Hay, E.M.; van der Windt, D.A. An Economic Evaluation of TENS in Addition to Usual Primary Care Management for the Treatment of Tennis Elbow: Results from the TATE Randomized Controlled Trial. *PLoS One* **2015**, *10*, e0135460, doi:10.1371/journal.pone.0135460.
26. Escortell-Mayor, E.; Riesgo-Fuertes, R.; Garrido-Elustondo, S.; Asunsolo-Del Barco, A.; Diaz-Pulido, B.; Blanco-Diaz, M.; Bejerano-Alvarez, E. Primary care randomized clinical trial: manual therapy effectiveness in comparison with TENS in patients with neck pain. *Manual therapy* **2011**, *16*, 66-73, doi:10.1016/j.math.2010.07.003.
27. Escortell Mayor, E.; Lebrijo Perez, G.; Perez Martin, Y.; Asunsolo del Barco, A.; Riesgo Fuertes, R.; Saa Requejo, C. [Randomized clinical trial for primary care patients with neck pain: manual therapy versus electrical stimulation]. *Atencion primaria* **2008**, *40*, 337-343.
28. Oosterhof, J.; De Boo, T.M.; Oostendorp, R.A.; Wilder-Smith, O.H.; Crul, B.J. Outcome of transcutaneous electrical nerve stimulation in chronic pain: short-term results of a double-blind, randomised, placebo-controlled trial. *The journal of headache and pain* **2006**, *7*, 196-205, doi:10.1007/s10194-006-0309-z.
29. Oosterhof, J.; Samwel, H.J.; de Boo, T.M.; Wilder-Smith, O.H.; Oostendorp, R.A.; Crul, B.J. Predicting outcome of TENS in chronic pain: a prospective, randomized, placebo controlled trial. *Pain* **2008**, *136*, 11-20, doi:10.1016/j.pain.2007.06.009.
30. Oosterhof, J.; Wilder-Smith, O.H.; de Boo, T.; Oostendorp, R.A.; Crul, B.J. The Long-Term Outcome of Transcutaneous Electrical Nerve Stimulation in the Treatment for Patients with Chronic Pain: A Randomized, Placebo-Controlled Trial. *Pain Pract* **2012**, 12(7):513-22.
31. Oosterhof, J.; Wilder-Smith, O.H.; Oostendorp, R.A.; Crul, B.J. Different mechanisms for the short-term effects of real versus sham transcutaneous electrical nerve stimulation (TENS) in patients with chronic pain: a pilot study. *J Pain Palliat Care Pharmacother* **2012**, *26*, 5-12, doi:10.3109/15360288.2011.650352.

32. Pietrosimone, B.G.; Saliba, S.A.; Hart, J.M.; Hertel, J.; Kerrigan, D.C.; Ingersoll, C.D. Effects of transcutaneous electrical nerve stimulation and therapeutic exercise on quadriceps activation in people with tibiofemoral osteoarthritis. *The Journal of orthopaedic and sports physical therapy* **2011**, *41*, 4-12, doi:10.2519/jospt.2011.3447.
33. Pietrosimone, B.G.; Saliba, S.A.; Hart, J.M.; Hertel, J.; Kerrigan, D.C.; Ingersoll, C.D. Effects of disinhibitory transcutaneous electrical nerve stimulation and therapeutic exercise on sagittal plane peak knee kinematics and kinetics in people with knee osteoarthritis during gait: a randomized controlled trial. *Clinical Rehabilitation* **2010**, *24*, 1091-1101, doi:10.1177/0269215510375903.
34. Chia, Y.; Arulkumaran, S.; Chua, S.; Ratnam, S. Effectiveness of transcutaneous electric nerve stimulator for pain relief in labour. *Asia Oceania J Obstet Gynaecol* **1990**, *16*, 145-151.
35. Kayman-Kose, S.; Arioz, D.T.; Toktas, H.; Koken, G.; Kanat-Pektas, M.; Kose, M.; Yilmazer, M. Transcutaneous electrical nerve stimulation (TENS) for pain control after vaginal delivery and cesarean section. *Journal of Maternal-Fetal & Neonatal Medicine* **2014**, *27*, 1572-1575, doi:10.3109/14767058.2013.870549.
36. Lin, M.L.; Luo, Y.J.; Hsu, Y.M.; Guo, C.H.; Lin, S.C.; Lin, K.Y.; Lin, S.H.; Chiu, H.W. Randomized controlled trial Comparing of Analgesic Effectiveness of TPRF and TENS in Clinical and Endocrinological Changes for Chronic Shoulder Pain; 4th International Symposium on Bioelectronics and Bioinformatics (ISBB) Oct 14-17, 2015, Tsinghua Univ, Beijing, PEOPLES R CHINA; pp. 23-26.
37. Lin, M.L.; Chiu, H.W.; Shih, Z.M.; Lee, P.Y.; Li, P.Z.; Guo, C.H.; Luo, Y.J.; Lin, S.C.; Lin, K.Y.; Hsu, Y.M. Two Transcutaneous Stimulation Techniques in Shoulder Pain: transcutaneous Pulsed Radiofrequency (TPRF) versus Transcutaneous Electrical Nerve Stimulation (TENS): a Comparative Pilot Study. *Pain Research & Management* **2019**, *2019*, 2823401, doi:10.1155/2019/2823401.
38. Johnson, M.; Martinson, M. Efficacy of electrical nerve stimulation for chronic musculoskeletal pain: a meta-analysis of randomized controlled trials. *Pain* **2007**, *130*, 157-165.
39. Sawant, A.; Dadurka, K.; Overend, T.; Kremenchutzky, M. Systematic review of efficacy of TENS for management of central pain in people with multiple sclerosis. *Mult Scler Relat Disord* **2015**, *4*, 219-227.
40. Kroeling, P.; Gross, A.; Graham, N.; Burnie, S.J.; Szeto, G.; Goldsmith, C.H.; Haines, T.; Forget, M. Electrotherapy for neck pain. *Cochrane Database Syst Rev* **2013**, *8*, CD004251, doi:10.1002/14651858.CD004251.pub5.
41. Zhu, J.; Xu, Q.; Zou, R.; Wu, W.; Wang, X.; Wang, Y.; Ji, F.; Zheng, Z.; Zheng, M. Distal acupoint stimulation versus peri-incisional stimulation for postoperative pain in open abdominal surgery: a systematic review and implications for clinical practice. *BMC complementary and alternative medicine* **2019**, *19*, 192, doi:10.1186/s12906-019-2583-8.
42. Zhou, J.; Dan, Y.; Yixian, Y.; Lyu, M.; Zhong, J.; Wang, Z.; Zhu, Y.; Liu, L. Efficacy of Transcutaneous Electronic Nerve Stimulation in Postoperative Analgesia After Pulmonary Surgery A Systematic Review and Meta-Analysis. *American Journal of Physical Medicine & Rehabilitation* **2020**, *99*, 241-249, doi:10.1097/PHM.0000000000001312.
43. Bjersa, K.; Andersson, T. High frequency TENS as a complement for pain relief in postoperative transition from epidural to general analgesia after pancreatic resection. *Complementary therapies in clinical practice* **2014**, *20*, 5-10, doi:10.1016/j.ctcp.2013.11.004.
44. Itoh, K.; Hirota, S.; Katsumi, Y.; Ochi, H.; Kitakoji, H. A pilot study on using acupuncture and transcutaneous electrical nerve stimulation (TENS) to treat knee osteoarthritis (OA). *Chin Med* **2008**, *3*, 2.

.

45. Itoh, K.; Itoh, S.; Katsumi, Y.; Kitakoji, H. A pilot study on using acupuncture and transcutaneous electrical nerve stimulation to treat chronic non-specific low back pain. *Complementary therapies in clinical practice* **2009**, *15*, 22-25.
46. Rutjes, A.W.; Nuesch, E.; Sterchi, R.; Kalichman, L.; Hendriks, E.; Osiri, M.; Brosseau, L.; Reichenbach, S.; Juni, P. Transcutaneous electrostimulation for osteoarthritis of the knee. *Cochrane Database Syst Rev* **2009**, CD002823.
47. Wu, L.C.; Weng, P.W.; Chen, C.H.; Huang, Y.Y.; Tsuang, Y.H.; Chiang, C.J. Literature Review and Meta-Analysis of Transcutaneous Electrical Nerve Stimulation in Treating Chronic Back Pain. *Reg Anesth Pain Med* **2018**, *43*, 425-433, doi:10.1097/AAP.0000000000000740.
48. Aydin, S.; Arioglu Aydin, C.; Batmaz, G.; Dansuk, R. Effect of vaginal electrical stimulation on female sexual functions: a randomized study. *J Sex Med* **2015**, *12*, 463-469, doi:10.1111/jsm.12788.
49. Murina, F.; Felice, R.; Di Francesco, S.; Oneda, S. Vaginal diazepam plus transcutaneous electrical nerve stimulation to treat vestibulodynia: A randomized controlled trial. *European Journal of Obstetrics, Gynecology, and Reproductive Biology* **2018**, *228*, 148-153, doi:10.1016/j.ejogrb.2018.06.026.
50. Murina, F.; Bianco, V.; Radici, G.; Felice, R.; Di Martino, M.; Nicolini, U. Transcutaneous electrical nerve stimulation to treat vestibulodynia: a randomised controlled trial. *Bjog* **2008**, *115*, 1165-1170.
51. Meechan, J.G.; Gowans, A.J.; Welbury, R.R. The use of patient-controlled transcutaneous electronic nerve stimulation (TENS) to decrease the discomfort of regional anaesthesia in dentistry: Randomised controlled clinical trial. *Journal of Dentistry* **1998**, *26*, 417-420, doi:10.1016/s0300-5712(97)00062-6.
52. Conn, I.G.; Marshall, A.H.; Yadav, S.N.; Daly, J.C.; Jaffer, M. Transcutaneous electrical nerve stimulation following appendicectomy: the placebo effect. *Annals of the Royal College of Surgeons of England* **1986**, *68*, 191-192.
53. Quinton, D.N.; Sloan, J.P.; Theakstone, J. Transcutaneous electrical nerve stimulation in acute hand infections. *Journal of hand surgery* **1987**, *12*, 267-268.
54. VanderArk, G.D.; McGrath, K.A. Transcutaneous electrical stimulation in treatment of postoperative pain. *Am J Surg* **1975**, *130*, 338-340.
55. Wang, W.; George, S.; Wilimas, J. Transcutaneous electrical nerve stimulation treatment of sickle cell pain crises. *Acta Haematol* **1988**, *80*, 99-102.
56. Alm, W.; Gold, M.; Weil, L. Evaluation of transcutaneous electrical nerve stimulation (TENS) in podiatric surgery. *J Am Podiatry Assoc* **1979**, *69*, 537-542.
57. Hanfy, H.M.; El-Bigawy, A. Effects of transcutaneous electrical nerve stimulation versus acupressure in the treatment of primary dysmenorrhea. *Bull. Fac. Phys. Ther. Cairo Univ.* **2004**, *9*, 2.
58. Revadkar, M.T.; Bhojwani, T.M. Comparison of the Effectiveness of Transcutaneous Electrical Nerve Stimulation (Tens) Vs. Interferential Therapy (Ift) for Relief of Pain in Primary Dysmenorrhea. *International Journal of Physiotherapy* **2019**, *6*, 263-267, doi:10.15621/ijphy/2019/v6i6/190223.
59. Borup, L.; Wurlitzer, W.; Hedegaard, M.; Kesmodel, U.S.; Hvidman, L. Acupuncture as pain relief during delivery: a randomized controlled trial. *Birth (Berkeley, Calif* **2009**, *36*, 5-12.
60. Upton, G.A.; Tinley, P.; Al-Aubaidy, H.; Crawford, R. The influence of transcutaneous electrical nerve stimulation parameters on the level of pain perceived by participants with painful diabetic neuropathy: A crossover study. *Diabetes & Metabolic Syndrome* **2017**, *11*, 113-118, doi:10.1016/j.dsx.2016.08.016.
61. Warke, K.; Al-Smadi, J.; Baxter, G.D.; Walsh, D.M.; Lowe-Strong, A.S. A double blind, placebo controlled, randomised, clinical trial investigating the efficacy of transcutaneous electrical nerve stimulation for low back pain in a multiple sclerosis population. *Multiple Sclerosis* **2004**, *10*, S107-S107.

62. Al-Smadi, J.; Warke, K.; Wilson, I.; Cramp, A.; Noble, G.; Walsh, D.; Lowe-Strong, A. A pilot investigation of the hypoalgesic effects of transcutaneous electrical nerve stimulation upon low back pain in people with multiple sclerosis. *Clinical Rehabilitation* **2003**, *17*, 742-749.
63. da Silva, T.F.G.; Suda, E.Y.; Marçulo, C.A.; Paes, F.H.S.; Pinheiro, G.T. Comparison of transcutaneous electrical nerve stimulation and hydrotherapy effects on pain, flexibility and quality of life in patients with fibromyalgia. *Fisioterapia e Pesquisa* **2008**, *15*, 118-124 117p.
64. de Oliveira Guimaraes, C.S.; Santos Tavares, F.C.; Santos, M.N.; Guimaraes, G.C.; Pacheco Olegario, J.G.; Rocha, L.P.; Reis, L.C.; Dos Reis, M.A.; da Cunha Castro, E.C.; Miranda Correa, R.R. Transcutaneous electrical nerve stimulation and placental vascularization in cases of uterine blood flow restriction. *Fetal Pediatr Pathol* **2013**, *32*, 88-96, doi:10.3109/15513815.2012.671648.
65. Chiu, T.T.; Hui-Chan, C.W.; Chein, G. A randomized clinical trial of TENS and exercise for patients with chronic neck pain. *Clinical Rehabilitation* **2005**, *19*, 850-860.
66. Neighbours, L.E.; Clelland, J.; Jackson, J.R.; Bergman, J.; Orr, J. Transcutaneous electrical nerve stimulation for pain relief in primary dysmenorrhea. *Clin J Pain* **1987**, *3*, 17-22.
67. Tsukayama, H.; Yamashita, H.; Amagai, H.; Tanno, Y. Randomised controlled trial comparing the effectiveness of electroacupuncture and TENS for low back pain: a preliminary study for a pragmatic trial. *Acupunct Med* **2002**, *20*, 175-180.
68. Yoshimizu, M.; Teo, A.R.; Ando, M.; Kiyohara, K.; Kawamura, T. Relief of chronic shoulder and neck pain by electro-acupuncture and transcutaneous electrical nervous stimulation: A randomized crossover trial. *Medical Acupuncture* **2012**, *24*, 97-103.
69. Yurtkuran, M.; Kocagil, T. TENS, electroacupuncture and ice massage: comparison of treatment for osteoarthritis of the knee. *Am J Acupunct* **1999**, *27*, 133-140.
70. Grimmer, K. A controlled double blind study comparing the effects of strong burst mode TENS and High Rate TENS on painful osteoarthritic knees. *Australian Journal of Physiotherapy* **1992**, *38*, 49-56.
71. Hsieh, R.L.; Lee, W.C. One-shot percutaneous electrical nerve stimulation vs. transcutaneous electrical nerve stimulation for low back pain: comparison of therapeutic effects. *Am J Phys Med Rehabil* **2002**, *81*, 838-843.
72. Bulut, M.; Özcan, A.; Çakan, T.; Mektas, M.; Çulha, C. The Comparison of Effectiveness of TENS and Placebo TENS in Peripheral Neuropathic Pain in Patients with Type II Diabetes Mellitus. *Turkiye Klinikleri Journal of Medical Sciences* **2011**, *31*, 913-918, doi:10.5336/medsci.2010-18141.
73. Tilak, M.; Isaac, S.A.; Fletcher, J.; Vasanthan, L.T.; Subbaiah, R.S.; Babu, A.; Bhide, R.; Tharion, G. Mirror Therapy and Transcutaneous Electrical Nerve Stimulation for Management of Phantom Limb Pain in Amputees - A Single Blinded Randomized Controlled Trial. *Physiotherapy Research International* **2016**, *21*, 109-115, doi:10.1002/pri.1626.
74. Jensen, J.E.; Conn, R.R.; Hazelrigg, G.; Hewett, J.E. The use of transcutaneous neural stimulation and isokinetic testing in arthroscopic knee surgery. *Am J Sports Med* **1985**, *13*, 27-33.
75. Nash, T.; Williams, J.; Machin, D. TENS:does the type of stimulus really matter? *The Pain Clinic* **1990**, *3*, 161-168.
76. Sherry, E.; Kitchener, P.; Smart, R. A prospective randomized controlled study of VAX-D and TENS for the treatment of chronic low back pain. *Neurol Res* **2001**, *23*, 780-784.
77. Hughes, S.; Dailey, P.; Partridge, C. Transcutaneous electrical nerve stimulation for labour analgesia. *Anesthesia and Analgesia* **1988**, *67*, S99.
78. Olsen, M.F.; Elden, H.; Janson, E.D.; Lilja, H.; Stener-Victorin, E. A comparison of high- versus low-intensity, high-frequency transcutaneous electric nerve stimulation for painful postpartum uterine contractions. *Acta Obstet Gynecol Scand* **2007**, *86*, 310-314.
79. Fagevik Olsen, M.; Bjorndahl, S.; Stahl, A.; Borjesson, S.; Sundemo, A.; Gutke, A. Effects of high-intensity high-frequency transcutaneous electric nerve stimulation in primary

dysmenorrhea-a randomised cross-over pilot study. *European Journal of Physiotherapy.* **2019**.

80. Platon, B.; Andrell, P.; Raner, C.; Rudolph, M.; Dvoretsky, A.; Mannheimer, C. High-frequency, high-intensity transcutaneous electrical nerve stimulation as treatment of pain after surgical abortion. *Pain* **2010**, *148*, 114-119, doi:10.1016/j.pain.2009.10.023.
81. Platon, B.; Mannheimer, C.; Andrell, P. Effects of high-frequency, high-intensity transcutaneous electrical nerve stimulation versus intravenous opioids for pain relief after gynecologic laparoscopic surgery: a randomized controlled study. *Korean Journal of Anesthesiology* **2018**, *71*, 149-156, doi:10.4097/kjae.2018.71.2.149.
82. Sadala, A.Y.; Machado, A.F.P.; Liebano, R.E. Effects of transcutaneous electrical nerve stimulation on pain intensity during application of carboxytherapy in patients with cellulite: A randomized placebo-controlled trial. *Journal of cosmetic dermatology* **2018**, *17*, 1175-1181, doi:10.1111/jocd.12489.
83. Nash, T.P.; Williams, J.D.; Machin, D. TENS: Does the type of stimulus really matter? *Pain Clinic* **1990**, *3*, 161-168.
84. Dailey, D.L.; Rakel, B.A.; Vance, C.G.T.; Liebano, R.E.; Amrit, A.S.; Bush, H.M.; Lee, K.S.; Lee, J.E.; Sluka, K.A. Transcutaneous electrical nerve stimulation reduces pain, fatigue and hyperalgesia while restoring central inhibition in primary fibromyalgia. *Pain* **2013**, *154*, 2554-2562, doi:10.1016/j.pain.2013.07.043.
85. Rakel, B.A.; Zimmerman, M.B.; Geasland, K.; Embree, J.; Clark, C.R.; Noiseux, N.O.; Callaghan, J.J.; Herr, K.; Walsh, D.; Sluka, K.A. Transcutaneous electrical nerve stimulation for the control of pain during rehabilitation after total knee arthroplasty: A randomized, blinded, placebo-controlled trial. *Pain* **2014**, *155*, 2599-2611, doi:10.1016/j.pain.2014.09.025.
86. Tsen, L.C.; Thomas, J.; Segal, S.; Datta, S.; Bader, A.M. Transcutaneous electrical nerve stimulation does not augment epidural labor analgesia. *J Clin Anesth* **2001**, *13*, 571-575.
87. Amer-Cuenca, J.J.; Goicoechea, C.; Girona-Lopez, A.; Andreu-Plaza, J.L.; Palao-Roman, R.; Martinez-Santa, G.; Lison, J.F. Pain relief by applying transcutaneous electrical nerve stimulation (TENS) during unsedated colonoscopy: a randomized double-blind placebo-controlled trial. *Eur J Pain* **2011**, *15*, 29-35, doi:10.1016/j.ejpain.2010.05.006.
88. Atamaz, F.C.; Durmaz, B.; Baydar, M.; Demircioglu, O.Y.; Iyiyapici, A.; Kuran, B.; Oncel, S.; Sendur, O.F. Comparison of the efficacy of transcutaneous electrical nerve stimulation, interferential currents, and shortwave diathermy in knee osteoarthritis: a double-blind, randomized, controlled, multicenter study. *Archives of Physical Medicine and Rehabilitation* **2012**, *93*, 748-756.
89. Dailey, D.L.; Vance, C.G.T.; Rakel, B.A.; Zimmerman, M.B.; Embree, J.; Merriwether, E.N.; Geasland, K.M.; Chimenti, R.; Williams, J.M.; Golchha, M., et al. Transcutaneous Electrical Nerve Stimulation Reduces Movement-Evoked Pain and Fatigue: A Randomized, Controlled Trial. *Arthritis & rheumatology (Hoboken, N.J.)* **2020**, *72*, 824-836, doi:10.1002/art.41170 [doi].
90. Baez-Suarez, A.; Martin-Castillo, E.; Garcia-Andujar, J.; Garcia-Hernandez, J.A.; Quintana-Montesdeoca, M.P.; Loro-Ferrer, J.F. Evaluation of different doses of transcutaneous nerve stimulation for pain relief during labour: a randomized controlled trial. *Trials* **2018**, *19*, 652-652, doi:10.1186/s13063-018-3036-2 [doi].
91. Palmer, S.; Domaille, M.; Cramp, F.; Walsh, N.; Pollock, J.; Kirwan, J.; Johnson, M.I. Transcutaneous electrical nerve stimulation as an adjunct to education and exercise for knee osteoarthritis: a randomized controlled trial. *Arthritis Care Res (Hoboken)* **2014**, *66*, 387-394, doi:10.1002/acr.22147.
92. Borup, L.; Wurlitzer, W.; Hedegaard, M.; Kesmodel, U.S.; Hvidman, L. Acupuncture as pain relief during delivery: a randomized controlled trial. *Birth (berkeley, calif.)* **2009**, *36*, 5-12, doi:10.1111/j.1523-536X.2008.00290.x.

93. Pietrosimone, B.; Luc-Harkey, B.A.; Harkey, M.S.; Davis-Wilson, H.C.; Pfeiffer, S.J.; Schwartz, T.A.; Nissman, D.; Padua, D.A.; Blackburn, J.T.; Spang, J.T. Using TENS to Enhance Therapeutic Exercise in Individuals with Knee Osteoarthritis. *Medicine and science in sports and exercise* **2020**, 10.1249/MSS.0000000000002353 [doi], doi:10.1249/MSS.0000000000002353 [doi].
94. Lison, J.F.; Amer-Cuenca, J.J.; Piquer-Marti, S.; Benavent-Caballer, V.; Bivia-Roig, G.; Marin-Buck, A. Transcutaneous Nerve Stimulation for Pain Relief During Office Hysteroscopy: A Randomized Controlled Trial. *Obstetrics and gynecology* **2017**, *129*, 363-370, doi:10.1097/aog.0000000000001842.
95. Thomas, I.L.; Tyle, V.; Webster, J.; Neilson, A. An evaluation of transcutaneous electrical nerve stimulation for pain relief in labour. *The Australian & New Zealand journal of obstetrics & gynaecology* **1988**, *28*, 182-189.
96. Dailey, D.L.; Vance, C.G.T.; Rakel, B.A.; Zimmerman, M.B.; Embree, J.; Merriwether, E.N.; Geasland, K.M.; Chimenti, R.; Williams, J.M.; Golchha, M., et al. Transcutaneous Electrical Nerve Stimulation Reduces Movement-Evoked Pain and Fatigue: A Randomized, Controlled Trial. *Arthritis Rheumatol* **2020**, *72*, 824-836, doi:10.1002/art.41170.
97. Moore, S.R.; Shurman, J. Combined neuromuscular electrical stimulation and transcutaneous electrical nerve stimulation for treatment of chronic back pain: a double-blind, repeated measures comparison. *Archives Of Physical Medicine And Rehabilitation* **1997**, *78*, 55-60.
98. Rakel, B.; Frantz, R. Effectiveness of transcutaneous electrical nerve stimulation on postoperative pain with movement. *J Pain* **2003**, *4*, 455-464.
99. Barbarisi, M.; Pace, M.C.; Passavanti, M.B.; Maisto, M.; Mazzariello, L.; Pota, V.; Aurilio, C. Pregabalin and transcutaneous electrical nerve stimulation for postherpetic neuralgia treatment. *Clinical Journal of Pain* **2010**, *26*, 567-572, doi:10.1097/AJP.0b013e3181dda1ac.
100. Luchesa, C.A.; Greca, F.H.; Guarita-Souza, L.C.; dos Santos, J.L.; Aquim, E.E. The role of electroanalgesia in patients undergoing coronary artery bypass surgery. *Rev Bras Cir Cardiovasc* **2009**, *24*, 391-396.
101. Sbruzzi, G.; Silveira, S.A.; Silva, D.V.; Coronel, C.C.; Plentz, R.D.M. Transcutaneous electrical nerve stimulation after thoracic surgery: Systematic review and metaanalysis of randomized trials. *Brazilian Journal of Cardiovascular Surgery* **2012**, *27*, 75-87.
102. Treede, R.D.; Rief, W.; Barke, A.; Aziz, Q.; Bennett, M.I.; Benoliel, R.; Cohen, M.; Evers, S.; Finnerup, N.B.; First, M.B., et al. Chronic pain as a symptom or a disease: the IASP Classification of Chronic Pain for the International Classification of Diseases (ICD-11). *Pain* **2019**, *160*, 19-27, doi:10.1097/j.pain.0000000000001384.
103. Johnson, M.I.; Ashton, C.H.; Thompson, J.W. An in-depth study of long-term users of transcutaneous electrical nerve stimulation (TENS). Implications for clinical use of TENS. *Pain* **1991**, *44*, 221-229.
104. Cheing, G.L.Y.; Hui-Chan, C.W.Y. Transcutaneous electrical nerve stimulation: Nonparallel antinociceptive effects on chronic clinical pain and acute experimental pain. *Archives of Physical Medicine and Rehabilitation* **1999**, *80*, 305-312.
105. Ekblom, A.; Hansson, P. Thermal sensitivity is not changed by acute pain or afferent stimulation. *J Neurol Neurosurg Psychiatry* **1987**, *50*, 1216-1220.
106. Hansson, P.; Ekblom, A. Transcutaneous electrical nerve stimulation (TENS) as compared to placebo TENS for the relief of acute oro-facial pain. *Pain* **1983**, *15*, 157-165.
107. Lee, J.E.; Anderson, C.M.; Perkhounkova, Y.; Sleeuwenhoek, B.M.; Louison, R.R. Transcutaneous Electrical Nerve Stimulation Reduces Resting Pain in Head and Neck Cancer Patients: a Randomized and Placebo-Controlled Double-Blind Pilot Study. *Cancer nursing* **2019**, *42*, 218-228, doi:10.1097/NCC.0000000000000594.
108. Dailey, D.L.; Rakel, B.A.; Vance, C.G.; Liebano, R.E.; Amrit, A.S.; Bush, H.M.; Lee, K.S.; Lee, J.E.; Sluka, K.A. Transcutaneous electrical nerve stimulation reduces pain, fatigue and

hyperalgesia while restoring central inhibition in primary fibromyalgia. *Pain* **2013**, *154*, 2554-2562.
109. Dawood, M.Y.; Ramos, J. Transcutaneous electrical nerve stimulation (TENS) for the treatment of primary dysmenorrhea: a randomized crossover comparison with placebo TENS and ibuprofen. *Obstetrics and gynecology* **1990**, *75*, 656-660.
110. Ghoname, E.A.; Craig, W.F.; White, P.F.; Ahmed, H.E.; Hamza, M.A.; Henderson, B.N.; Gajraj, N.M.; Huber, P.J.; Gatchel, R.J. Percutaneous electrical nerve stimulation for low back pain: a randomized crossover study. *Jama* **1999**, *281*, 818-823.
111. Lewis, B.; Lewis, D.; Cumming, G. The comparative analgesic efficacy of transcutaneous electrical nerve stimulation and a non-steroidal anti-inflammatory drug for painful osteoarthritis. *Br J Rheumatol* **1994**, *33*, 455-460.
112. Milsom, I.; Hedner, N.; Mannheimer, C. A comparative study of the effect of high-intensity transcutaneous nerve stimulation and oral naproxen on intrauterine pressure and menstrual pain in patients with primary dysmenorrhea. *Am J Obstet Gynecol* **1994**, *170*, 123-129.
113. Bennett, M.I.; Hughes, N.; Johnson, M.I. Methodological quality in randomised controlled trials of transcutaneous electric nerve stimulation for pain: low fidelity may explain negative findings. *Pain* **2011**, *152*, 1226-1232.
114. Bjordal, J.M.; Johnson, M.I.; Ljunggreen, A.E. Transcutaneous electrical nerve stimulation (TENS) can reduce postoperative analgesic consumption. A meta-analysis with assessment of optimal treatment parameters for postoperative pain. *Eur J Pain* **2003**, *7*, 181-188.
115. Ghoname, E.S.A.; White, P.F.; Ahmed, H.E.; Hamza, M.A.; Craig, W.F.; Noe, C.E. Percutaneous electrical nerve stimulation: an alternative to TENS in the management of sciatica. *Pain* **1999**, *83*, 193-199.
116. Ozkul, C.; Kilinc, M.; Yildirim, S.A.; Topcuoglu, E.Y.; Akyuz, M. Effects of visual illusion and transcutaneous electrical nerve stimulation on neuropathic pain in patients with spinal cord injury: A randomised controlled cross-over trial. *Journal of back and musculoskeletal rehabilitation* **2015**, *28*, 709-719, doi:10.3233/bmr-140573.
117. Alvarez-Arenal, A.; Junquera, L.M.; Fernandez, J.P.; Gonzalez, I.; Olay, S. Effect of occlusal splint and transcutaneous electric nerve stimulation on the signs and symptoms of temporomandibular disorders in patients with bruxism. *J Oral Rehabil* **2002**, *29*, 858-863.
118. Arvidsson, I.; Eriksson, E. Postoperative TENS pain relief after knee surgery: objective evaluation. *Orthopedics* **1986**, *9*, 1346-1351.
119. Gerson, G.R.; Jones, R.B.; Luscombe, D.K. Studies on the concomitant use of carbamazepine and clomipramine for the relief of post-herpetic neuralgia. *Postgraduate medical journal* **1977**, *53 Suppl 4*, 104-109.
120. Ghoname, E.S.; Craig, W.F.; White, P.F.; Ahmed, H.E.; Hamza, M.A.; Gajraj, N.M.; Vakharia, A.S.; Noe, C.E. The effect of stimulus frequency on the analgesic response to percutaneous electrical nerve stimulation in patients with chronic low back pain. *Anesthesia and Analgesia* **1999**, *88*, 841-846.
121. Lofgren, M.; Norrbrink, C. Pain relief in women with fibromyalgia: a cross-over study of superficial warmth stimulation and transcutaneous electrical nerve stimulation. *J Rehabil Med* **2009**, *41*, 557-562.
122. Lundeberg, T. A comparative study of the pain alleviating effect of vibratory stimulation, transcutaneous electrical nerve stimulation, electroacupuncture and placebo. *Am J Chin Med* **1984**, *12*, 72-79.
123. Robb, K.; Newham, D.; Williams, J. Transcutaneous Electrical Nerve Stimulation vs. Transcutaneous Spinal Electroanalgesia for Chronic Pain Associated with Breast Cancer Treatments. *Journal of Pain and Symptom Management* **2007**, *33*, 410-419.
124. Warke, K.; Al-Smadi, J.; Baxter, D.; Walsh, D.; Lowe-Strong, A. Efficacy of transcutaneous electrical nerve stimulation (tens) for chronic low-back pain in a multiple sclerosis

population: a randomized, placebo-controlled clinical trial. *Clinical Journal of Pain* **2006**, *22*, 812-819.

125. Seo, H.G.; Bang, M.S.; Chung, S.G.; Jung, S.H.; Lee, S.-U. Effect of Electrical Stimulation on Botulinum Toxin A Therapy in Patients With Chronic Myofascial Pain Syndrome: A 16-Week Randomized Double-Blinded Study. *Archives of Physical Medicine & Rehabilitation* **2013**, *94*, 412-418.
126. Vance, C.G.; Dailey, D.L.; Rakel, B.A.; Sluka, K.A. Using TENS for pain control: the state of the evidence. *Pain Manag* **2014**, *4*, 197-209, doi:10.2217/pmt.14.13.
127. Rowbotham, M.C.; Gilron, I.; Glazer, C.; Rice, A.S.; Smith, B.H.; Stewart, W.F.; Wasan, A.D. Can pragmatic trials help us better understand chronic pain and improve treatment? *Pain* **2013**, *154*, 643-646, doi:10.1016/j.pain.2013.02.034.
128. Moore, S.; Shurman, J. Combined neuromuscular electrical stimulation and transcutaneous electrical nerve stimulation for treatment of chronic back pain: a double-blind, repeated measures comparison. *Arch Phys Med Rehabil* **1997**, *78*, 55-60.
129. Grovle, L.; Hasvik, E.; Haugen, A.J. Rescue and concomitant analgesics in placebo-controlled trials of pharmacotherapy for neuropathic pain and low back pain. *Pain* **2020**, *161*, 3-10, doi:10.1097/j.pain.0000000000001690.
130. Fary, R.E.; Briffa, N.K. Monophasic electrical stimulation produces high rates of adverse skin reactions in healthy subjects. *Physiother Theory Pract* **2011**, *27*, 246-251, doi:10.3109/09593985.2010.487926.
131. Meader, N.; King, K.; Llewellyn, A.; Norman, G.; Brown, J.; Rodgers, M.; Moe-Byrne, T.; Higgins, J.P.; Sowden, A.; Stewart, G. A checklist designed to aid consistency and reproducibility of GRADE assessments: development and pilot validation. *Syst Rev* **2014**, *3*, 82, doi:10.1186/2046-4053-3-82.
132. Almeida, C.C.; Maldaner da Silva, V.Z.M.; Cipriano Junior, G.; Liebano, R.E.; Quagliotti Durigan, J.L. Transcutaneous electrical nerve stimulation and interferential current demonstrate similar effects in relieving acute and chronic pain: a systematic review with meta-analysis [with consumer summary]. *Brazilian Journal of Physical Therapy* **2018**, *22*, 347-354.
133. Page, M.J.; Green, S.; Mrocki, M.A.; Surace, S.J.; Deitch, J.; McBain, B.; Lyttle, N.; Buchbinder, R. Electrotherapy modalities for rotator cuff disease. *Cochrane Database Syst Rev* **2016**, 10.1002/14651858.CD012225, CD012225, doi:10.1002/14651858.CD012225.
134. Sluka, K.; Walsh, D. Chapter 8: Transcutaneous Electrical Nerve Stimulation and Interferential Therapy In *Mechanisms and Management of Pain for the Physical Therapist*, Second ed.; KA, S., Ed. IASP Press: Philidelphia, USA, 2016; pp. 203-224.
135. National Institute for Health and Care Excellence. *Osteoarthritis: care and management. NICE guidelines [CG177]* London, 2014; pp 1-37.
136. Houghton, P.; Nussbaum, E.; Hoens, A. Electrophysical agents. Contraindications and Precautions: An Evidence-Based Approach to Clinical Decision Making in Physical Therapy. *Physiotherapy Canada* **2010**, *62*, 5-80.
137. DeSantana, J.M.; Walsh, D.M.; Vance, C.; Rakel, B.A.; Sluka, K.A. Effectiveness of transcutaneous electrical nerve stimulation for treatment of hyperalgesia and pain. *Current rheumatology reports* **2008**, *10*, 492-499.
138. Johnson, M.I.; Bjordal, J.M. Transcutaneous electrical nerve stimulation for the management of painful conditions: focus on neuropathic pain. *Expert Rev Neurother* **2011**, *11*, 735-753, doi:10.1586/ern.11.48.
139. Gibson, W.; Wand, B.M.; Meads, C.; Catley, M.J.; O'Connell, N.E. Transcutaneous electrical nerve stimulation (TENS) for chronic pain - an overview of Cochrane Reviews. *Cochrane Database Syst Rev* **2019**, *2*, CD011890, doi:10.1002/14651858.CD011890.pub2.

140. Gibson, W.; Wand, B.M.; O'Connell, N.E. Transcutaneous electrical nerve stimulation (TENS) for neuropathic pain in adults. *Cochrane Database Syst Rev* **2017**, *9*, CD011976, doi:10.1002/14651858.CD011976.pub2.
141. National Institute for Health and Clinical Excellence. *NICE clinical guideline 79 Rheumatoid arthritis: The management of rheumatoid arthritis in adults*; London, 2009; pp 1-35.
142. National Institute for Health and Care Excellence, N. Low back pain and sciatica in over 16s: assessment and management. Clinical guideline [NG59]. National Institute for Health and Care Excellence (NICE): 2016; pp 1-18.
143. National Institute for Health and Clinical Excellence. *NICE clinical guideline 55 Intrapartum care: care of healthy women and their babies during childbirth*; London, 2007; pp 1-65.
144. National Institute for Health and Care Excellence (NICE). Chronic Pain (Primary and Secondary) in over 16s: Assessment of all Chronic Pain and Management of Chronic Primary Pain (NG193). National Institute for Health and Care Excellence (NICE): London, UK, 2021; pp 1–36.
145. Chabal, C.; Fishbain, D.A.; Weaver, M.; Heine, L.W. Long-term transcutaneous electrical nerve stimulation (TENS) use: impact on medication utilization and physical therapy costs. *Clinical Journal of Pain* **1998**, *14*, 66-73.
146. Pivec, R.; Stokes, M.; Chitnis, A.S.; Paulino, C.B.; Harwin, S.F.; Mont, M.A. Clinical and economic impact of TENS in patients with chronic low back pain: analysis of a nationwide database. *Orthopedics* **2013**, *36*, 922-928.
147. Pivec, R.; Minshall, M.E.; Mistry, J.B.; Chughtai, M.; Elmallah, R.K.; Mont, M.A. Decreased Opioid Utilization and Cost at One Year in Chronic Low Back Pain Patients Treated with Transcutaneous Electric Nerve Stimulation (TENS). *Surg Technol Int* **2015**, *27*, 268-274.
148. Woods, B.; Manca, A.; Weatherly, H.; Saramago, P.; Sideris, E.; Giannopoulou, C.; Rice, S.; Corbett, M.; Vickers, A.; Bowes, M., et al. Cost-effectiveness of adjunct non-pharmacological interventions for osteoarthritis of the knee. *PLoS One* **2017**, *12*, e0172749, doi:10.1371/journal.pone.0172749.
149. Ahn, H.; Woods, A.J.; Kunik, M.E.; Bhattacharjee, A.; Chen, Z.; Choi, E.; Fillingim, R.B. Efficacy of transcranial direct current stimulation over primary motor cortex (anode) and contralateral supraorbital area (cathode) on clinical pain severity and mobility performance in persons with knee osteoarthritis: An experimenter- and participant-blinded, randomized, sham-controlled pilot clinical study. *Brain Stimul* **2017**, *10*, 902-909, doi:10.1016/j.brs.2017.05.007.
150. Johnson, M.I.; Claydon, L.S.; Herbison, G.P.; Jones, G.; Paley, C.A. Transcutaneous electrical nerve stimulation (TENS) for fibromyalgia in adults. *Cochrane Database Syst Rev* **2017**, *10*, CD012172, doi:10.1002/14651858.CD012172.pub2.
151. Johnson, M.I. Transcutaneous electrical nerve stimulation (TENS) as an adjunct for pain management in perioperative settings: a critical review. *Expert Rev Neurother* **2017**, *17*, 1013-1027, doi:10.1080/14737175.2017.1364158.
152. Gozani, S.; Kong, X. Real-word effectiveness of fixed-site highfrequency transcutaneous electrical nerve stimulation in chronic low back pain. *Postgraduate Medicine* **2018**, *130 (Supplement 1)*, 78-79.
153. Gozani, S.N.; Ferree, T.C.; Moynihan, M.; Kong, X. Impact of transcutaneous electrical nerve stimulation on sleep in chronic low back pain: a real-world retrospective cohort study. *Journal of Pain Research* **2019**, *12*, 743-752, doi:10.2147/JPR.S196129.
154. Gladwell, P.W.; Cramp, F.; Palmer, S. Matching the perceived benefits of Transcutaneous Electrical Nerve Stimulation (TENS) for chronic musculoskeletal pain against Patient Reported Outcome Measures using the International Classification of Functioning, Disability and Health (ICF). *Physiotherapy* **2020**, *106*, 128-135, doi:10.1016/j.physio.2019.01.017.