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

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

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# ABSTRACT

#### Objective

To investigate the efficacy and safety of transcutaneous electrical nerve stimulation (TENS) for relief of pain.

#### Design

Systematic review and meta-analysis.

#### Data Sources

Medline, Cochrane Central, Embase (and others) from inception to July 2019 and updated on 17 May 2020.

#### Eligibility criteria for study selection

Randomised controlled trials (RCTs) comparing strong non-painful TENS at or close to the site of pain versus placebo or other treatments in adults with any type of pain.

#### Data extraction and synthesis

Reviewers independently screened, extracted data, and assessed risk of bias (RoB, Cochrane tool), and certainty of evidence (GRADE). Mean pain intensity and proportions of participants achieving relief of pain ( $\geq$  30% or  $\geq$  50%) during or immediately after TENS. Random effects models were used to calculate standardised mean differences (SMD) and risk ratios (RR). Subgroup analyses were related to trial methodology and type of pain.

#### Results

The review included 381 RCTs (24532 participants). Pain intensity was lower during or immediately after TENS compared with placebo (91 RCTs, 92 samples, n = 4841, SMD = -0.96 [95% CI, -1.14, -0.78]). Methodological (e.g. RoB, sample size) and pain characteristics (e.g. acute vs chronic, diagnosis) did not modify the effect. Pain intensity was lower during or immediately after TENS compared with pharmacological and non-pharmacological treatments used as part of standard of care (61 RCTs, 61 samples, n = 3155, SMD = -0.72 [95% CI, -0.95, -0.50]). Levels of evidence were downgraded because of small sized trials contributing to imprecision in magnitude estimates. Data was limited for other outcomes including adverse events which were poorly reported, generally mild, and not different to comparators.

#### Conclusion

There was moderate-certainty evidence that pain intensity is lower during or immediately after TENS compared with placebo, irrespective of the type of pain and without serious adverse events.

Systematic review registration PROSPERO - CRD42019125054

#### Keywords

Transcutaneous electrical nerve stimulation (TENS), Pain management, Therapeutic neuromodulation, Metaanalysis

#### Strengths and limitations of this study

- This meta-analysis is the first to pool data from all types of pain and to meet threshold standards for pooling pain data for meta-analysis (i.e. ≥500 participants per trial arm)
- Effect sizes were calculated during or immediately after strong non-painful TENS because this is ecologically valid and overcomes problems of analysing data gathered from a wide variety of TENS regimens, such as prn, where participants are using TENS intermittently
- There was a preponderance of small sample sized studies so a judicious approach was taken in interpretation of findings
- Sub-group analyses were used to explore statistical heterogeneity and the effect of combining different types of pain; the trim and fill method was used to explore publication bias
- GRADE criteria were used to judge the impact of risk of bias, imprecision, inconsistency, indirectness and publication bias on the certainty of effect size estimates

#### BACKGROUND

Pain is a global health problem with negative consequences for patients, society and health care systems <sup>1,2</sup>. Transcutaneous electrical nerve stimulation (TENS) is used for symptomatic relief of pain supported by physiological evidence that TENS inhibits the activity and excitability of central nociceptive transmission neurons (for review see <sup>3</sup>).

Clinicians and policy makers are confused about the benefits and harm associated with TENS and whether they should or should not offer TENS to their patients because of inconsistency in clinical practice guidelines. For example, in 2020, the National Institute of Health and Care Excellence (NICE) in the U.K. released draft guidance for the management of chronic pain that recommends not to offer TENS [GID-NG10069]<sup>4</sup>. The NICE does not recommend TENS for intrapartum care <sup>5</sup> or non-specific chronic low back pain <sup>6</sup> but does recommend TENS as an adjunct for osteoarthritis <sup>7</sup> and rheumatoid arthritis <sup>8</sup>. The situation is similar in other parts of the world. Uncertainty about efficacy resulted in the Centers for Medicare & Medicaid Services in the USA restricting coverage for the use of TENS treatment for chronic lower back pain to individuals enrolled in an approved clinical study. Equipment, running costs and follow-up clinical support for TENS is inexpensive. Treatment can be self-administered without fear of toxicity, potentially offering symptomatic relief of pain throughout the day.

The debate about the efficacy of TENS has been ongoing since it entered mainstream medicine in the 1970s. There are over 100 systematic reviews, including Cochrane reviews, on TENS and many are inconclusive <sup>9</sup>. An overview of eight Cochrane reviews (51 RCTs, 2895 participants) on TENS for chronic pain was inconclusive with reviewers reluctant to meta-analyse data due to methodological and clinical heterogeneity <sup>10</sup>. Meta-analyses of TENS for specific pain conditions are criticised for insufficient pooled data. As research suggests no relationship between TENS outcome and pain diagnosis <sup>11</sup>, amalgamating pain conditions would increase the amount of pooled data for meta-analysis. To date, there has been no attempt to meta-analyse data from all available RCTs irrespective of the type of pain, possibly because of the enormity of the task. Such a meta-analysis would resolve whether strong non-painful TENS administered to painful body parts reduced the intensity of pain.

The aim of our meta-analysis was to evaluate the efficacy and safety of TENS for all types of pain in adults. Concerns of heterogeneity associated with combining pain conditions was offset by subgroup analyses based on pain diagnosis.

#### METHODS

This systematic review and meta-analysis were conducted in accordance with guidelines from the Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA); Cochrane Collaboration of Systematic Reviews; and Grading and Recommendations, Assessment, Development and Evaluation (GRADE). The study was registered on PROSPERO (CRD42019125054) and the protocol published

(https://bmjopen.bmj.com/content/9/10/e029999). Ethical approval for the review was granted by Leeds Beckett University (Application Ref: 78097). See supplementary file 1 for full details of search strategy, eligibility screening, data extraction, and analysis.

#### Search strategy and selection criteria

One reviewer (PGW) searched electronic databases (Medline, Embase, Cochrane Central, CINAHL, PsycINFO, LILACS, PEDRO, Web of Science, AMED, SPORTDiscus) from inception to July 2019 and updated on 17 May 2020, for full text publications of randomised controlled trials (RCTs) and for systematic reviews that evaluated TENS for adults with clinical pain versus:

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

There were no language restrictions and articles were translated where possible.

#### **Types of TENS interventions**

The TENS intervention was defined as pulsed electrical currents generated by a 'standard TENS device' administered across the intact surface of the skin using surface electrodes at the site of pain or over nerve bundles proximal (or near) to the site of pain, with the intention of stimulating peripheral nerves to alleviate pain <sup>3</sup>. We included any type of pulse pattern and excluded pulse frequencies >250 pulses per second (pps), pulse durations >500 microseconds ( $\mu$ s) and peak-to-peak amplitudes >60 milliamperes (mA).

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 We included TENS administered by a therapist and/or participant; as a sole treatment or in combination with other treatments, for any duration or regularity of treatment; as a single or multiple treatment intervention with or without follow-up. We considered participant-reported strong but comfortable TENS sensations as optimal and used this as our primary TENS comparison group. We excluded RCTs evaluating non-painful outcomes (e.g. bladder dysfunction, constipation, dementia), or administering TENS at acupuncture points (unless over nerve bundles at the site of pain), using probes or electrode arrays, or using TENS-like currents (e.g. interferential current, microcurrent).

Two review authors (PGW and MIJ) independently screened titles, abstracts, and full texts, and extracted trial characteristics and numerical data. Disagreements were resolved by consensus with a third review author as arbiter (CAP or GJ). Records were not anonymised before assessment. Reasons for exclusion were coded and tabulated. The characteristics of included trials were extracted and tabulated including design, sample population, TENS intervention, comparator(s) and outcome measures. Decisions, trial characteristics and codes for analyses were documented in Excel spreadsheets.

#### Types of outcome measures

Pain outcomes were mean (continuous data) patient-reported intensity of spontaneous or evoked pain (at rest or on movement) using standard subjective scales (e.g. numerical rating scale (NRS) or visual analogue scale (VAS)), and the proportion of participants reporting a reduction in pain intensity of  $\geq$  30% (moderate) or  $\geq$  50% (substantial) relative to baseline <sup>12</sup>. A between-group difference of  $\geq$ 10 mm on a 100 mm VAS was set as the threshold for clinical importance in-line with IMMPACT criteria <sup>13</sup>. We prioritised measurements at the last during TENS timepoint (i.e. whilst TENS switched on) or the first timepoint immediately after TENS had been switched off. If TENS was administered as a course of treatments, we prioritised the last treatment session. We analysed the proportion of participants experiencing an adverse event, irrespective of severity. 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).

#### Data analysis

Meta-analyses were conducted using Review Manager 5.3 and Stata 16 software. We calculated standardised mean difference (SMD) for continuous data and risk ratio (RR) for dichotomous data. Pre-specified criteria were used to select the primary TENS comparison and we did not enter several interventions into the same meta-analysis to avoid 'double-counting' and unit-of-analysis errors. We used an intention-to-treat analysis and combined data from first and second periods in cross-over trials because there was sufficient washout between interventions to eliminate contamination. Data was considered imprecise if the TENS treatment arm was below 200 participants in single RCTs, or below 500 participants for pooled data <sup>14</sup>.

Two review authors (CAP and MIJ) independently assessed risk of bias (RoB) using the Cochrane tool. We examined heterogeneity using visual inspection of forest plots, the I<sup>2</sup> statistic, the Chi<sup>2</sup> test and the Cochrane Collaboration's rough guide to interpretation. Small study effects were analysed using Egger's regression test (p-value set at  $\leq 0.1$ ), and the Trim and Fill method was used to analyse potential publication bias. Pre-specified subgroup analyses were related to trial methodology and type of pain. We interpreted subgroup analyses by considering: a p-value of  $\leq 0.1$  to indicate a statistically significant subgroup effect (interaction); the direction of each subgroup effect (i.e. qualitative or quantitative); and the extent to which individual trials differed in treatment effects within each subgroup (i.e. heterogeneity), in-line with Richardson et al. <sup>15</sup>. We evaluated the certainty of evidence using the GRADE system (GRADEpro GDT 2015, https://gradepro.org/).

Patient and public involvement

There was no patient or public involvement in any aspect of this study or its write-up.

#### RESULTS

Our searches yielded 7679 records (Figure 1). After removal of duplicates we screened 5747 records and reviewed 623 full text reports of which 381 RCTs were included (383 samples, 24532 participants, 334 parallelgroup, see supplementary file 2 for characteristics of included studies) and 19 RCTs are awaiting classification (supplementary file 3 for studies awaiting classification). Violations of pre-specified criteria for TENS were the most common reasons for excluding studies (supplementary file 4 for reasons for excluding studies). See supplementary file 1 for full details of screening, extraction, main and subgroup analyses, and interpretation, including risk of bias and GRADE judgements. Included trials consist of 176 samples with chronic pain (osteoarthritis = 32 samples), 162 samples with acute pain (post-operative pain = 95 samples), 10 samples mixed and 35 samples unclear. There were 26 trials with overall low RoB (Figure 2). Small sample size was an issue with 341 trials having fewer than 50 participants in the TENS group (mean  $\pm$  SD TENS group =  $27 \cdot 71 \pm 21 \cdot 89$  participants; 13 RCTs had  $\geq 100$  participants in the TENS group). There were at least 216 TENS interventions where participants had access to other treatments, most commonly medication or exercise as part of ongoing SoC, as a combination treatment or as rescue analgesia. Often, monitoring and/or reporting of concurrent treatment(s) was deficient.

There were 352 of 381 RCTs that gathered continuous data for pain intensity and 164 RCTs had extractable data for meta-analysis. Figure 3 summarises overall effect sizes for treatment comparisons with at least 100 pooled data points per arm and Figure 4 summarises subgroup analyses for types of pain. There was insufficient extractable data to conduct responder analyses of participants reporting a  $\geq$ 30% or  $\geq$ 50% pain reduction unless otherwise stated.

#### **TENS versus Placebo**

We extracted mean (continuous) data from 91 of 202 RCTs comparing TENS with placebo. There was a significant overall effect in favour of TENS and substantial statistical heterogeneity (TENS = 2426 participants, placebo = 2415 participants, SMD = -0.96 [95% CI -1.14, -0.78], I<sup>2</sup> = 88%). Subgroup analyses found that the effect of TENS was not modified by methodological variables including RoB, sample size (Figure 3 and supplementary file 5), or by type of pain (Figure 4 and supplementary file 6). The validity of the treatment effect estimate for subgroups were uncertain as individual trial results are inconsistent. 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 the right of the mean for an adjusted SMD of -0.78 (95% CI -0.995 to -0.565). We downgraded to moderate-certainty evidence.

We extracted dichotomous data from nine RCTs and found a statistically significant difference in the proportion of participants reporting a reduction of pain intensity  $\geq$ 50% in favour of TENS (TENS = 106/241 responders, placebo 28/219 responders, RR = 2.89 [2.02, 4.13], p < 0.00001, I<sup>2</sup> = 0%). There were too few RCTs and participants to be entirely certain of the validity of the treatment effect estimate. We downgraded to low-certainty evidence.

#### TENS versus No Treatment

We extracted mean (continuous) data from 10 of 16 RCTs (602 participants) comparing TENS with a no treatment control. There was a statistically significant difference in favour of TENS and substantial statistical heterogeneity (TENS = 298 participants, no treatment = 304 participants, SMD = -0.82 [95% CI -1.18, -0.46], I<sup>2</sup> = 76%) (Figure 3). There was insufficient data to undertake subgroup analyses to explore the effect of methodological nor clinical characteristics on outcome. 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. We downgraded to low-certainty evidence.

#### TENS versus treatment(s) used as part of standard or care

We extracted mean (continuous) data from 61 of 127 RCTs (3155 participants) comparing TENS with treatment(s) used as standard or care (in part or fully). There was a statistically significant difference in favour of TENS and substantial statistical heterogeneity (Figure 3). Subgroup analyses suggested that the nature of the SoC intervention did not modify the effect of TENS. 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 [95% -1.31, -0.76]. We downgraded to low certainty evidence due to small study effect.

We extracted mean (continuous) data from 67 of 118 RCTs that compared TENS with at least one other treatment, not categorised by RCT authors as SoC (67 RCTs, 131 samples, 3327 participants). We chose not to report the meta-analysis due to the heterogeneous mix of comparators, the inclusion of duplicate data in the TENS arm, and sub-groups with too few comparisons. We did not GRADE this evidence.

#### High versus low frequency TENS

We extracted mean (continuous) data from 13 of 37 RCTs (468 participants) that compared high with low frequency TENS and found no statistically significant difference (Figure 3). 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. We downgraded to moderate-certainty evidence of no difference.

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#### Safety

There were 136 reports that included a statement about adverse events (59/136 = no adverse events in all intervention groups, 90/136 = no adverse events related to TENS, see supplementary file 7 for characteristics of adverse events). Often statements were unclear. Adverse events associated with TENS were mild in severity, infrequent in occurrence and included skin irritation, tenderness/soreness and TENS discomfort. There were no reports of a serious adverse event directly attributable to TENS. We extracted dichotomous data from 18 RCTs (1587 participants) and found no statistically significant difference in the risk of an adverse event, irrespective of severity between TENS and comparators (RR = 0.73 [95% CI 0.36, 1.48], p = 0.38, I<sup>2</sup> = 66%). The type of comparator did not modify the effect. We downgraded to very low certainty evidence because of spontaneous detection adverse events based on ill-defined criteria.

All studies met our pre-specified criteria for TENS, although unclear reporting hindered characterisation of specific aspects of TENS technique. We categorised 276 interventions as high frequency TENS (100Hz = 109 interventions) and 35 interventions as low frequency TENS. Participants in some RCTs were instructed to adjust the pulse frequency of TENS as needed. TENS interventions varied considerably; supervised (therapist) or unsupervised (self-administered); prescribed or pro re nata (prn); single or multiple treatments; short treatment duration <1 minute for procedural pain or up to 2 years 'as required' for chronic pain.

#### DISCUSSION

#### Statement of principal findings

Our systematic review of 381 RCTs (24532 participants) is the most comprehensive to date. Our meta-analysis of 91 RCTs (4841 participants) found that pain intensity was lower during or immediately after a treatment of strong non-painful TENS administered to painful body parts compared with placebo. Our analysis has been conducted in a logical, systematic and rigorous manner and we have been diligent and judicious when interpreting the analysis. Risk of bias or trials with fewer than 50 participants per arm did not modify the effect of TENS, allaying concerns that small study size undermines the veracity of conclusions <sup>16</sup>. Types of pain did not modify the effect of TENS compared with placebo. Inconsistency in individual trial results generated uncertainty in the magnitude of effect estimates for different types of pain but this was quantitative in nature (i.e. in the same direction and always in favour of TENS). Thus, we are confident that pain intensity is less during or immediately after TENS treatment when compared with placebo and that there is moderate certainty evidence in the magnitude of the effect estimate.

There was low certainty evidence that more participants report at least 50% reduction in pain during or immediately after TENS than placebo. There was low certainty evidence that TENS added to, or compared with, exercise/physiotherapy or analgesic medications used as part of standard/routine care (61 RCTs, 3155 participants). Adverse events were minor with no serious adverse events reported in 381 RCTs but only very low certainty evidence that the risk ratio of an adverse event, irrespective of severity, is no different to placebo.

#### Strengths of the study

Our meta-analysis provides estimates of effect size during or immediately after treatment and our GRADE judgements account for shortcomings in RCT data. In clinical practice, TENS is used to produce a pleasant sensation to override pain in the moment, i.e. optimal effects occur whilst experiencing a TENS sensation. This is similar to other neuromodulation techniques including warming, cooling and rubbing of the skin. Hence, our analysis during TENS effects is ecologically valid and also overcomes problems of analysing data gathered from a wide variety of TENS regimens, such as prn, where participants are using TENS intermittently. We plan to undertake an analysis of long-term outcome in the future, although this is likely to be inexact due to variability in TENS treatment schedules and of measurement timepoints, contamination by concomitant treatment(s), and a lack of extractable data.

#### Weaknesses of the study

An overview of Cochran reviews on TENS for chronic pain did not pool data from small sized trials because of concern about imprecision <sup>10,17</sup>. We found evidence of a small-study effect and publication bias, although the adjusted SMD using the trim and fill method did not alter the effect size estimate for TENS versus placebo. Our meta-analyses exposed statistical heterogeneity likely to contribute to imprecision, although our pre-specified thresholds for pooling data were met (i.e.  $\geq$ 500 participants per trial arm). Unclear reporting contributed to unclear risk of bias with few reports referring to standards for design and reporting of TENS trials <sup>18</sup>.

In placebo comparisons, blinding of participants was achieved using a sham TENS device (without current) and pre-study briefings to create uncertainty about which intervention was functioning properly. This has been shown to be a valid method of reducing performance bias, although few of the included studies measured

blinding success <sup>19</sup>. Contamination of effect size estimates by concurrent treatment was an issue <sup>20</sup>. We decided not to use generic inverse variance to correct for paired data associated with crossover trial data because of sufficient washout periods and an overwhelming number of parallel group data points.

Most investigators reported spontaneous detection of adverse events based on ill-defined criteria, so our estimate of risk ratio lacked precision. Inadequate adverse event reporting remains a concern in RCTs of non-pharmacological interventions for pain <sup>21</sup>.

Judgements of the impact of risk of bias, imprecision, inconsistency, indirectness and publication bias resulted in downgrading the certainty of all effect size estimates according to GRADE criteria (details provided in the supplementary file 1).

#### Strengths and weaknesses in relation to other studies

Previous systematic reviews and meta-analyses, including Cochrane reviews are inconsistent and/or inconclusive (for review see <sup>3</sup>). The 2020 NICE draft guidelines for chronic pain did not recommend TENS and based on an analysis of two RCTs categorised as chronic *primary* pain <sup>4</sup>. The 2019, overview of Cochrane reviews on TENS for chronic pain was inconclusive based on a descriptive synthesis of 51 RCTs <sup>10, 17</sup>. For chronic pain we extracted data from 31 RCTs and found a statistically significant overall effect in favour of TENS compared with placebo (TENS = 721 participants, placebo = 696 participants, SMD = -0.87 [95% CI - 1.19, -0.55], p < 0.00001, I<sup>2</sup> = 86%). Nonetheless, type of pain did not moderate the effect of TENS and we hope that this will be considered by future guideline panels.

The findings of out meta-analysis are consistent with clinical experience and physiological plausibility. Since its inception over 50 years ago, clinical experience and expert opinion has remained resolute that TENS provides immediate short-term relief of pain by therapeutic neuromodulation in a manner akin to rubbing the skin (for review see <sup>3</sup>). Physiological evidence validates a short-lasting during-stimulation effect, demonstrating that selective activation of low threshold somatosensory peripheral afferents during TENS reduces activity and excitability of central nociceptive transmission cells in normal <sup>22</sup> and sensitised states <sup>23</sup>. Different frequencies of pulsed current influences central neuropharmacological actions in animal studies <sup>24</sup>, but clinical research has failed to find relationships between electrical characteristics, type of pain and TENS outcome <sup>11</sup>. Our finding that adverse events were minor and mostly erythema and itchiness at the site of electrodes is consistent with evaluations of safety by professional bodies <sup>25</sup>.

#### Meaning of the study

At present, clinicians advise patients to self-administer TENS on its own or in combination with other treatments by producing a strong non-painful TENS sensation within or close to the site of pain. Patients are advised to administer TENS frequently to maintain analgesia. Clinicians should be aware that the effects of TENS are not modified by the characteristics of pain, so any type of pain may respond, or by the frequency of currents, providing a strong non-painful TENS sensation is generated within or close to the site of pain. Guideline panels and policy makers should be aware that TENS is efficacious as an adjunct to core treatment and for any type of pain and/or setting i.e. our analysis included TENS administered in hospital, clinic or home (community) settings.

#### Unanswered questions and future research

Our findings justify the need for pragmatic ecologically valid studies gathering real-world data about how best to integrate TENS into practice. Recently, a 30-minute TENS treatment was shown to predict longer-term outcome in women with fibromyalgia <sup>26</sup> and real world data can be used to develop educational packages to train and support patients to optimise TENS treatment within a self-care model of pain management <sup>27,28</sup>. We did not undertake a cost-benefit analysis, although previous analyses provide evidence that TENS equipment, running costs and follow-up clinical support is inexpensive and can reduce annual costs for chronic low back pain and knee osteoarthritis <sup>29,30</sup>.

We hope our findings discourage publication of small sized RCTs on TENS trials. The need for large, multicentred RCTs remains, although we suspect that the effect size estimate from such a trial will be close to that found in our review. We recommend an enriched enrolment randomised withdrawal design with trial arm sample sizes greater than 200 participants to overcome methodological issues <sup>3,18</sup>. We hope our findings discourage publication systematic reviews until such large RCTs become available.

#### Conclusions

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This meta-analysis resolves long-term uncertainty about the efficacy of TENS by providing moderate-certainty evidence that strong non-painful TENS within or close to the site of pain, produces clinically important reductions in the intensity of acute or chronic pain during or immediately after treatment. Adverse events associated with TENS included skin irritation with no reports of serious adverse events. Clinicians, policy makers and funders should consider TENS as adjunct to core treatment for immediate-short-term relief any type of pain.

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- Conceptualization: MIJ
- Data curation: MIJ, PGW, CAP (GJ cross checking)
- Formal Analysis: MIJ, PGW, CAP, MRM, GJ
- Funding acquisition: MIJ
- Investigation: MIJ, PGW, CAP, MRM, GJ
  - Development and delivery of search strategy: PGW, MIJ
  - Screening for eligibility: PGW, MIJ (CAP and GJ as arbiters)
    - Data extraction: MIJ, PGW, (CAP, GJ cross checking)
  - Assessment of risk of bias: MIJ, CAP, (PGW as arbiter)
  - Assessment of adverse events: MIJ, CAP, PGW
  - Assessment of effects of interventions: MIJ, PGW, CAP (GJ and MRM arbiters)
  - Assessment of publication bias: MRM, PGW, MIJ
  - GRADE assessment against criteria: MIJ, CAP (PGW, GJ as arbiters)
  - Overall GRADE judgement: MIJ, CAP, PGW, MRM, GJ
  - Interpreting the results: MIJ, PGW, CAP, MRM, GJ
- Methodology (Protocol development): MIJ, PGW, CAP, GJ
- Project administration: MIJ
- Resources: MIJ
- Software: MIJ, MRM
- Supervision: MIJ
- Validation: MIJ
- Visualization: MIJ
- Writing original draft: MIJ
- Writing review & editing: MIJ, PGW, CAP, GJ, MRM

All authors had access to the data and took responsibility for the integrity of the data and the accuracy of the data analysis. All authors approved the final version of the review.

Data sharing: Extracted data is available on request from Prof. Mark I. Johnson

Transparency declaration: I (Prof. Mark I. Johnson) affirm that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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Competing interests: All authors have completed the ICMJE uniform disclosure form and declare the following:

#### Prof. Mark I. Johnson (taken from ICMJE form)

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- 1. Dissanayaka TD, Pallegama RW, Suraweera HJ, Johnson MI, Kariyawasam AP. (2016). Comparison of the Effectiveness of Transcutaneous Electrical Nerve Stimulation and Interferential Therapy on the Upper Trapezius in Myofascial Pain Syndrome: A Randomized Controlled Study. American Journal of Physical Medicine and Rehabilitation 2016 Sep;95(9):663-72.
- 2. Palmer S, Domaille M, Cramp F, Walsh N, Pollock J, Kirwan J, Johnson MI. (2014) Transcutaneous Electrical Nerve Stimulation as an adjunct to education and exercise for knee osteoarthritis: a randomised controlled trial. Arthritis Care & Research 2014: 66(3), 387–394 Funded by the Physiotherapy Research Foundation (part of the Chartered Society of Physiotherapy Charitable Trust) and Above & Beyond Charities.

- 3. Pallett EJ, Rentowl P. Johnson MI, Watson PJ (2014) Implementation fidelity of self-administered Transcutaneous Electrical Nerve Stimulation (TENS) in patients with chronic back pain: An observational study. Clin J Pain. 2014: Mar;30(3):224-31.
  - 4. Kolen AF, de Nijs RN, Wagemakers FM, Meier AJ, Johnson MI (2012) The effects of spatially targeted transcutaneous electrical nerve stimulation (TENS) using an electrode array that measures skin resistance on pain and mobility in patients with osteoarthritis in the knee: A randomized controlled trial. Pain. 2012 Feb;153(2):373-81. Funded by Phillips Research Europe

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Patient consent for publication: Not required.

Ethical approval: Leeds Beckett University Application Ref: 78097

Dissemination to participants and related patient and public communities: We plan to disseminate our findings to patient organisations and media outlets.

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#### FIGURE LEGENDS

#### Figure 1

PRISMA Flow Chart

#### Figure 2

Methodological quality graph: review authors' judgments about each methodological quality item presented as percentages across all included studies.

#### Figure 3

Summary of standardised mean difference (SMD) and 95% confidence intervals (95%CI) of pain intensity for intervention comparisons and main subgroup group analyses of risk of bias (RoB) and trial arm size.

#### Figure 4

Summary of subgroup group analyses of type of pain for the standardised mean difference (SMD) and 95 % confidence intervals (95%CI) of pain intensity between TENS and placebo. RCTs; randomised controlled trials.

#### SUPPLEMENTARY MATERIALS

#### Supplementary file 1 (File: 12\_12\_SupplementaryAppendix.docx)

Supplementary material providing details of all operational processes associated with our systematic review and meta-analysis including methods, data analyses and interpretation of findings.

#### Supplementary file 2 (File: 08\_OL-TABLE1\_IncludedStudies)

Summary of the characteristics of the included randomised controlled trials

#### Supplementary file 3 (File: 09\_OL-TABLE2\_AwaitingClassification)

Studies awaiting classification

#### Supplementary file 4 (File: 10\_OL-TABLE3\_ExcludedStudies)

Summary of the reasons for excluding studies

#### Supplementary file 5 (File: 06\_OL-Fig1\_SUBMIT)

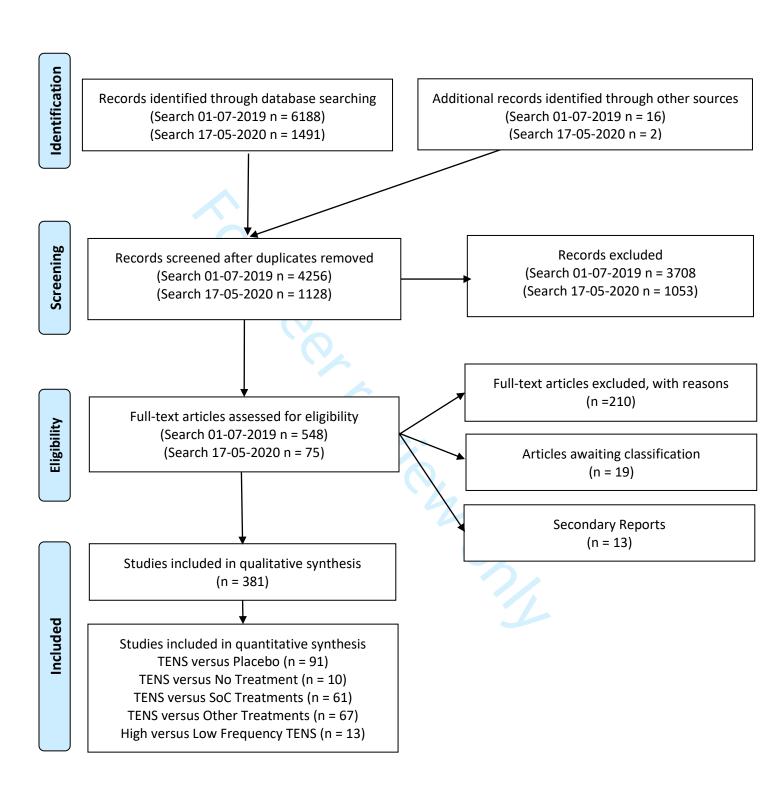
Forest plot of standardised mean difference (SMD) and 95% confidence intervals (95%CI) of pain intensity rating between TENS and placebo with subgroup group analysis of risk of bias (RoB)

#### Supplementary file 6 (File: 07\_OL-Fig2\_SUBMIT)

Forest plot of standardised mean difference (SMD) and 95% confidence intervals (95%CI) of pain intensity rating between TENS and placebo with subgroup group analysis of risk of bias (RoB)

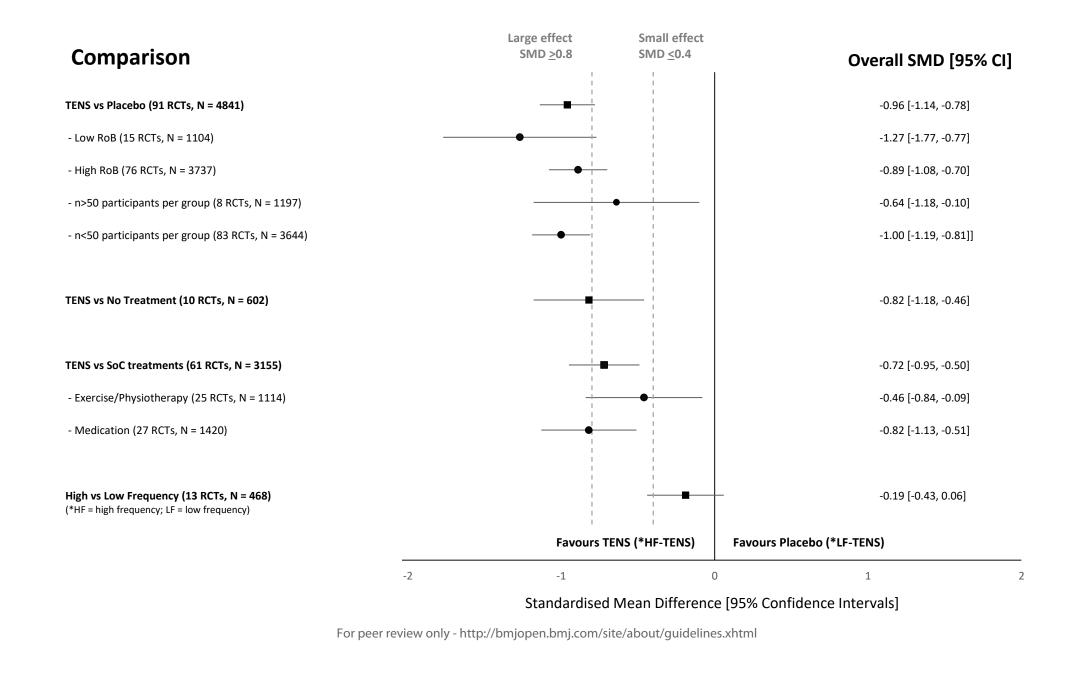
#### Supplementary file 7 (File: 11\_OL-TABLE4\_AdverseEvents)

Summary of the characteristics of TENS-related adverse events



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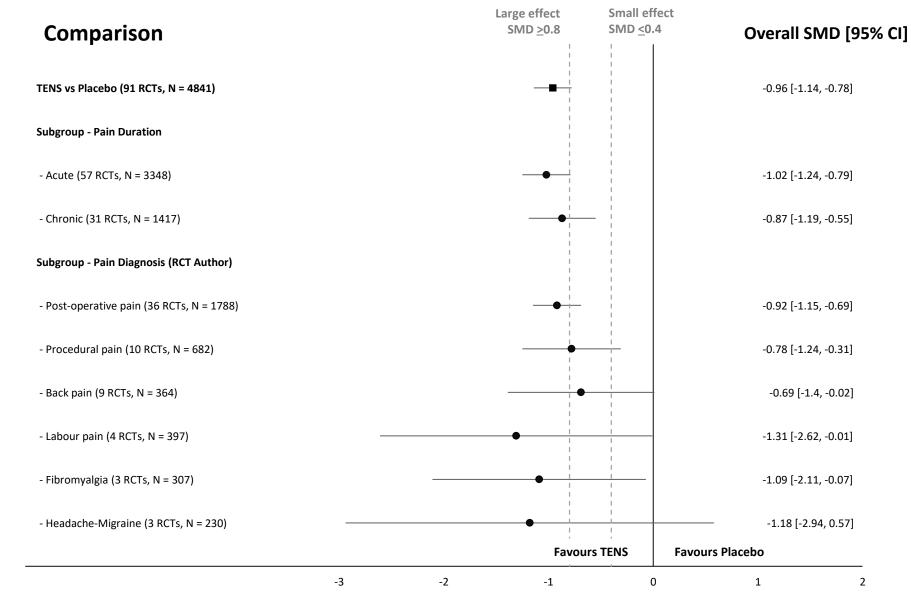
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#### **Appendix - Supplementary Material**

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

#### Context

This document provides detailed information about all operational processes associated with our systematic review and meta-analysis.

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#### METHODS

The protocol for this study has been published <sup>1</sup> and is available from <u>https://bmjopen.bmj.com/content/9/10/e029999</u>. 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)<sup>2</sup>
- Cochrane Collaboration of Systematic Reviews <sup>3</sup>
- Grading and Recommendations, Assessment, Development and Evaluation (GRADE)<sup>4</sup>.

#### 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

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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.

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# **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 <sup>2</sup>.

#### 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 Carbonario et al., 2013 <sup>5</sup>).

We included parallel group and crossover trial designs. We included single treatment interventions without follow-up and planned to conduct a subgroup analyses 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 <sup>6,7</sup>.

#### 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<sup>6</sup> 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)<sup>7 6</sup>. 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  $\mu$ s (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 (e.g. sham (no current) TENS device);
- no treatment or waiting list control;
- standard of care; and
- other 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 <sup>8,9</sup>; 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<sup>10</sup>. 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 analyses 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

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- 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 - Include trial providing TENS

- 1. non-invasive
- 2. intention of exciting peripheral nerves to alleviate pain
- 3. body sensate
- 4. irrespective of the current amplitude of TENS and/or participant-reported TENS intensity
  - 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

Any 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

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# 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
  - o 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
  - о Туре
  - Time points used, including follow-up
  - o Withdrawals
  - Adverse and serious adverse effects
  - o 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<sup>11</sup>. 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 decisionmaking 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 <sup>6,8</sup>.

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?*' <sup>10</sup>. There were very few studies that monitored blinding.

#### Attrition bias

MetaTENS\_SupplementaryAppendix\_FINAL\_23-12-2020

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
  - $\circ$   $\;$  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
  - o 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).

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	• Unclear risk - all other permutations; insufficient information to permit judgement of
4	low/high risk of bias
5	
6	
7	Blinding of assessor (detection bias)
8	<ul> <li>Low risk of bias – stated that outcome assessor blinded to participants' allocated</li> </ul>
9	intervention and unlikely that blinding broken (i.e. different personnel to that allocating
10	and/or treating participants)
11	<ul> <li>Unclear risk of bias - insufficient information to permit judgement of low/high risk of bias</li> </ul>
12	
13	• High risk of bias - outcome assessor (including 'participants' with respect to self-report
14	outcomes) un-blinded to participants' allocated intervention OR outcome assessor
15	blinded to allocated intervention but likely that blinding was broken
16	
17	Incomplete outcome data (drop-outs)
18	<ul> <li>Low risk of bias &lt; 20% drop-out and appears to be random with numbers per group</li> </ul>
19	
	provided along with reasons for drop-out, e.g. full data set
20	<ul> <li>Unclear risk of bias - &lt; 20% and unclear if random with numbers per group and</li> </ul>
21	reasons for drop-out not described
22	<ul> <li>O High risk of bias - ≥ 20% drop-out</li> </ul>
23	Incomplete outcome data (protocol violations)
24	<ul> <li>Low risk of bias - if participants were analysed in the group to which they were</li> </ul>
25	
26	originally assigned
27	<ul> <li>Unclear risk of bias - where insufficient information is provided to determine if</li> </ul>
28	analysis was per protocol or intention-to-treat
29	• High risk of bias - where per protocol analysis was used, where available data were not
30	analysed, or participants' data were included in the group to which they were not
31	originally assigned
32	
52	
33	
	Selective reporting
33	<ul> <li>Selective reporting         <ul> <li>Low risk of bias - study protocol was available matched Results reported; all pre-</li> </ul> </li> </ul>
33 34	<ul> <li>Low risk of bias - study protocol was available matched Results reported; all pre-</li> </ul>
33 34 35	<ul> <li>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</li> </ul>
33 34 35 36 37	<ul> <li>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</li> </ul>
33 34 35 36 37 38	<ul> <li>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</li> <li>Unclear risk of bias - inadequate information to allow judgement of a study to be</li> </ul>
33 34 35 36 37 38 39	<ul> <li>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</li> <li>Unclear risk of bias - inadequate information to allow judgement of a study to be classified as 'low risk' or 'high risk'</li> </ul>
33 34 35 36 37 38 39 40	<ul> <li>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</li> <li>Unclear risk of bias - inadequate information to allow judgement of a study to be classified as 'low risk' or 'high risk'</li> <li>High risk of bias - incomplete reporting of specified outcomes. One or more primary</li> </ul>
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<ul> <li>33</li> <li>34</li> <li>35</li> <li>36</li> <li>37</li> <li>38</li> <li>39</li> <li>40</li> <li>41</li> <li>42</li> <li>43</li> <li>44</li> <li>45</li> <li>46</li> <li>47</li> <li>48</li> </ul>	<ul> <li>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</li> <li>Unclear risk of bias - inadequate information to allow judgement of a study to be classified as 'low risk' or 'high risk'</li> <li>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</li> <li>Size of study (checking for biases confounded by small size)</li> <li>Low risk of bias ≥ 200 participants per treatment arm</li> </ul>
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33         34         35         36         37         38         39         40         41         42         43         44         45         46         47         48         49         50         51         52         53         54         55         56         57         58	<ul> <li>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</li> <li>Unclear risk of bias - inadequate information to allow judgement of a study to be classified as 'low risk' or 'high risk'</li> <li>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</li> <li>Size of study (checking for biases confounded by small size)</li> <li>Low risk of bias - 50 to 199 participants per treatment arm</li> <li>High risk of bias - 50 participants per treatment arm</li> <li>Low risk of bias - 50 participants per treatment arm</li> <li>Unclear risk of bias - statement that estimation made, even if the actual calculation not present</li> <li>Unclear risk of bias - N/A</li> </ul>
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Consider other factors including whether studies were stopped early, there were differences between groups at baseline, the timing of outcome measurement, cointervention comparability, and funding declarations

#### **RANDOM SEQUENCE GENERATION**

Selection bias (biased allocation to interventions) due to inadequate generation of a randomised sequence.

Criteria for a judgement of The investigators describe a random component in the sequence 'Low risk' of bias. 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 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 nonrandom 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.

of 'High 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.	Be at the state of
LOW HSK OF DIdS.	Participants and investigators enrolling participants could not foresee assignment because one of the following, or an equivalent method, was used to conceal allocation:
	<ul> <li>Central allocation (including telephone, web-based and pharmacy-controlled randomization);</li> </ul>
	<ul> <li>Sequentially numbered drug containers of identical appearance;</li> </ul>
	• 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:
	<ul> <li>Using an open random allocation schedule (e.g. a list of random numbers);</li> </ul>
	<ul> <li>Assignment envelopes were used without appropriate safeguards (e.g. if envelopes were unsealed or nonopaque or not sequentially numbered);</li> </ul>
	Alternation or rotation;
	Date of birth;
	Case record number;
	<ul> <li>Any other explicitly unconcealed procedure</li> </ul>
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.
	sequentially numbered, opaque and sealed. BLINDING OF PARTICIPANTS
Performance bias due to kno during the study.	BLINDING OF PARTICIPANTS
	BLINDING OF PARTICIPANTS
during the study.	BLINDING OF PARTICIPANTS weledge of the allocated interventions by participants and personnel Any one of the following: • No blinding or incomplete blinding, but the review authors
during the study. Criteria for a judgement of	<ul> <li>BLINDING OF PARTICIPANTS</li> <li>weldge of the allocated interventions by participants and personnel</li> <li>Any one of the following: <ul> <li>No blinding or incomplete blinding, but the review authors judge that the outcome is not likely to be influenced by lace</li> </ul> </li> </ul>
during the study. Criteria for a judgement of	<ul> <li>BLINDING OF PARTICIPANTS</li> <li>owledge of the allocated interventions by participants and personnel</li> <li>Any one of the following: <ul> <li>No blinding or incomplete blinding, but the review authors judge that the outcome is not likely to be influenced by lac of blinding;</li> <li>Blinding of participants and key study personnel ensured,</li> </ul> </li> </ul>

	but likely that the blinding could have been broken, and t outcome is likely to be influenced by lack of blinding.
Criteria for the judgement	High = Statement that not blinded; or statements suggesting definitely not blinded Any one of the following:
of 'Unclear risk' of bias.	<ul> <li>Insufficient information to permit judgement of 'Low risk' 'High risk';</li> </ul>
	• The study did not address this outcome.
	Unclear = No statement; or blinding inferred but not directly state
	BLINDING OF PERSONNEL
Performance bias due to kno during the study.	owledge of the allocated interventions by participants and personne
Criteria for a judgement of	Any one of the following:
'Low risk' of bias.	<ul> <li>No blinding or incomplete blinding, but the review author judge that the outcome is not likely to be influenced by la of blinding;</li> </ul>
	<ul> <li>Blinding of participants and key study personnel ensured, and unlikely that the blinding could have been broken.</li> </ul>
Cuitoria fontha independent	Low = Statement blinded and no reason to suggest blinding seriou compromised; or blinding inferred, operational process described and no reason to suggest blinding seriously compromised
Criteria for the judgement of 'High risk' of bias.	<ul> <li>Any one of the following:</li> <li>No blinding or incomplete blinding, and the outcome is likely to be influenced by lack of blinding;</li> </ul>
	<ul> <li>Blinding of key study participants and personnel attempted but likely that the blinding could have been broken, and to outcome is likely to be influenced by lack of blinding.</li> </ul>
Criteria for the judgement	High = Statement that not blinded; or statements suggesting definitely not blinded Any one of the following:
of 'Unclear risk' of bias.	<ul> <li>Insufficient information to permit judgement of 'Low risk' 'High risk';</li> </ul>
	• The study did not address this outcome.
	Unclear = No statement; or blinding inferred but not directly state
	BLINDING OF OUTCOME ASSESSMENT

**BMJ** Open

Criteria for a judgement of 'Low risk' of bias.	Any one of the following:
LOW HISK OF DIds.	<ul> <li>No blinding of outcome assessment, but the review authors judge that the outcome measurement is not likely to be influenced by lack of blinding;</li> </ul>
	<ul> <li>Blinding of outcome assessment ensured, and unlikely that the blinding could have been broken.</li> </ul>
Criteria for the judgement	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 Any one of the following:
of 'High risk' of bias.	<ul> <li>No blinding of outcome assessment, and the outcome measurement is likely to be influenced by lack of blinding;</li> </ul>
	<ul> <li>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.</li> </ul>
Criteria for the judgement	High = Statement that not blinded; or statements suggesting definitely not blinded Any one of the following:
of 'Unclear risk' of bias.	<ul> <li>Insufficient information to permit judgement of 'Low risk' or 'High risk';</li> </ul>
	<ul> <li>The study did not address this outcome.</li> </ul>
	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	Any one of the following:
'Low risk' of bias.	No missing outcome data;
	<ul> <li>Reasons for missing outcome data unlikely to be related to true outcome (for survival data, censoring unlikely to be introducing bias);</li> </ul>
	<ul> <li>Missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups;</li> </ul>
	<ul> <li>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;</li> </ul>
	<ul> <li>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;</li> </ul>
	<ul> <li>Missing data have been imputed using appropriate methods.</li> </ul>

Criteria for the judgement	Any one of the following:
of 'High risk' of bias.	<ul> <li>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;</li> </ul>
	<ul> <li>For dichotomous outcome data, the proportion of missing outcomes compared with observed event risk enough to induce clinically relevant bias in intervention effect estimate;</li> </ul>
	<ul> <li>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;</li> </ul>
	<ul> <li>'As-treated' analysis done with substantial departure of the intervention received from that assigned at randomization;</li> </ul>
	<ul> <li>Potentially inappropriate application of simple imputation.</li> </ul>
Criteria for the judgement	Any one of the following:
of 'Unclear risk' of bias.	<ul> <li>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);</li> </ul>
	• The study did not address this outcome.
	SELECTIVE REPORTING
Reporting bias due to selection	ve outcome reporting.
Criteria for a judgement of	Any of the following:
Criteria for a judgement of 'Low risk' of bias.	<ul> <li>Any of the following:</li> <li>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;</li> </ul>
	• 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-
'Low risk' of bias. Criteria for the judgement	<ul> <li>The study protocol is available and all of the study's prespecified (primary and secondary) outcomes that are of interest in the review have been reported in the prespecified way;</li> <li>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)</li> </ul>
'Low risk' of bias.	<ul> <li>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;</li> <li>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).</li> </ul>
'Low risk' of bias. Criteria for the judgement	<ul> <li>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;</li> <li>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).</li> <li>Any one of the following:</li> <li>Not all of the study's pre-specified primary outcomes have</li> </ul>

	<ul> <li>One or more outcomes of interest in the review are reported incompletely so that they cannot be entered in a meta-analysis;</li> </ul>
	<ul> <li>The study report fails to include results for a key outcome that would be expected to have been reported for such a study.</li> </ul>
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 or 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 $\geq$ 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 calculation performed, and no reason suspect that estimation method and/or calculation was incorrect from information in repo
Criteria for the judgement	No sample size calculation reported.
of 'High risk' of bias.	High Risk = No statement in report that sample size estimated and/or a calculation performed; or stated in report that sample siz estimated and/or a calculation performed, but information in repor 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 calculation performed, but lack of information provided.
	CROSSOVER EFFECT

'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.
igure 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 <sup>12</sup>, 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 <sup>13</sup>. Thus, we set responder rate as a primary outcome. The Outcome Measures in Rheumatology (OMERACT 12)<sup>14</sup> 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 <sup>15</sup>.

## Primary Pain Outcomes

Proportion of participant-reported pain relief of  $\geq$ 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 <sup>12,13</sup>. 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 <sup>15</sup>.

## 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  $\geq 10$  mm on a 0 to 100 mm VAS for minimally important outcome for pain intensity inline 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  $\geq 50\%$  <sup>15</sup>. 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.

We used 'Rules of thumb' for interpreting SMD effect sizes as follows <sup>3,16</sup>:

- <0.4 = small effect
- 0.4<0.8 = moderate effect
- >0.8 a large effect

We 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 <sup>17</sup>. 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*" <sup>17</sup>. 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 metaanalysis 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<sup>2</sup> statistic and the Chi<sup>2</sup> test <sup>18</sup>. We used the Cochrane Collaboration's rough guide to interpretation and graded heterogeneity as:

- Not important (I<sup>2</sup> = 0% to 40%)
- Moderate (I<sup>2</sup> = 30% to 60%)
- Substantial (I<sup>2</sup> = 50% to 90%)
- Considerable (I<sup>2</sup> = 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 analysis to explore overall risk of bias, number of participants in the primary TENS group.
- Clinical heterogeneity, associated with pain
  - We conducted subgroup analysis to explore duration of pain (acute vs chronic), diagnostic descriptors (pain conditions), mechanistic descriptors (nociceptive or neuropathic), and structures involved (systems, organs and tissues).
- Intervention (treatment) heterogeneity, associated with TENS and comparators
  - Our eligibility criteria resulted in 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'. Thus, RCTs that did not optimise the delivery of TENS using currents administered at (or close to) the site of pain at intensities that were above sensory detection threshold were excluded rendering a subgroup analysis of optimal versus suboptimal intensity or site of stimulation impossible. We plan to undertake such an analysis by comparing RCTs excluded on this basis

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with those included in this review in the future. 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.

There was insufficient data to undertake subgroup analyses for high frequency versus low frequency TENS for any comparison

There were sufficient RCTs to undertake a head-to-head comparison of high versus low frequency TENS for pain intensity (continuous data).

#### Subgroup analyses: Interpreting the findings

We followed guidance from Richardson <sup>19</sup> 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 numbers needed to treat for benefit (NNTB) of 10<sup>20</sup>). 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  $\leq 0.1$ .

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# 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)

# Sensitivity analysis

We analysed the effect of excluding RCTs with high risk of bias.

# RESULTS

# **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 <sup>21</sup> as the primary report and 3-month data of the first 23 patients <sup>22</sup> and 3-month data of 36 patients (presumably including the first 23 patients) <sup>23</sup> as secondary reports
- An RCT of TENS in addition to usual primary care management for the treatment of tennis elbow <sup>24</sup> as the primary report and an economic evaluation <sup>25</sup> as a secondary report
- An RCT evaluating TENS versus manual therapy for neck pain <sup>26</sup> reported as the primary report and a Spanish language version <sup>27</sup> as a secondary report
- The short-term results an RCT evaluating TENS for various chronic pains <sup>28</sup> as the primary report and an analysis to predict outcome of TENS from the RCT <sup>29</sup>, the long-term results of the RCT <sup>30</sup> and the findings of a pilot study investigating different mechanisms for short-term effects of TENS <sup>31</sup> as secondary reports
- An RCT evaluating TENS for knee osteoarthritis <sup>32</sup> as the primary report and outcomes associated with knee kinematics and kinetics <sup>33</sup> 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 <sup>34</sup> 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 <sup>35</sup> 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, <sup>36</sup> reported the findings of an RCT of TENS for shoulder pain and <sup>37</sup> 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. <sup>38-41</sup>)
- the extraction of the area under the curve for pain intensity instead of VAS 100 mm scale (e.g. (i.e. <sup>42</sup> for the RCT by <sup>43</sup>)

#### 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 <sup>44</sup> and chronic non-specific low back pain <sup>45</sup>. 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" <sup>45</sup> p23. RCTs by Itoh et al., have been previously included in a Cochrane review on osteoarthritis <sup>46</sup> and a non-Cochrane meta-analysis on low back pain <sup>47</sup>.

#### 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 <sup>48-50</sup> or intra-oral <sup>51</sup>.

# Violations of criteria for adult participants

Four studies were excluded because they included at least one child under the age of 16 years <sup>52-55</sup>. We included RCTs by <sup>56</sup>, <sup>57</sup> and <sup>58</sup> 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 <sup>59</sup>, minimum = 5 <sup>60</sup>).

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 <sup>59</sup>; minimum = 5 participants <sup>60-64</sup>.

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 10/383 samples 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 <sup>65-71</sup>.

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 <sup>74,75</sup>. 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 <sup>76,77</sup>.

# 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

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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 postpartum uterine contractions <sup>78</sup>, dysmenorrhea <sup>79</sup>, post-operative surgical abortion <sup>80</sup> or gynaecologic laparoscopic surgery <sup>81</sup> and brief procedural pains such as carboxytherapy <sup>82</sup> 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 selfadministered TENS until they no longer required TENS or up to a maximum of 2 years <sup>83</sup>. 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).

### **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 <sup>84-86</sup>. There were 9/381 RCTs with 7 or more items judged as low RoB <sup>84-91</sup> 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  $\geq$ 100 participants in the primary TENS trial arm. The largest TENS trial arm size was 144 participants in an RCT with a total sample of 607 women randomised to receive acupuncture, TENS, or traditional analgesics to manage labour pain <sup>92</sup>. 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 <sup>85,89,93,94</sup>. Of the studies judged to be of low risk of performance bias <sup>84,85,89</sup> 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 <sup>95</sup>(labour pain) <sup>96</sup>(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.

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## **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 <sup>89,97,98</sup>. 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 A2).

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 <sup>99</sup> 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 <sup>35,100</sup>. In both instances mean + 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. and published within 3 years of the original report confirmed the transcription error <sup>101</sup> and correct data was entered into our metaanalysis. However, we were unable to confirm the transcription error for <sup>35</sup>. 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

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1 2	
3 4 5	
5 6 7	
8 9	
10 11 12	
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50 59	

Study or Subgroup	Mean		Total	Mean			Weight	Std. Mean Difference IV, Random, 95% Cl	Std. Mean Difference IV, Random, 95% Cl
Barbarisi, et al., 2010 Gioriana, et al., 2014	25.11	0.92	9	39	1.19	8	0.1%	-12.50 [-17.39, -7.61]	۹ I <del></del>
Cipriano, et al., 2014 More, et al., 2005	10	5	20	80	30	18	0.9%	-3.27 [-4.28, -2.27]	
Mora, et al., 2006 Hokenek et al., 2019	33.3 22	16 12.49	39 39	82.6 72	14.3 18.7	34 39	1.1% 1.1%	-3.20 [-3.91, -2.50] -3.11 [-3.78, -2.44]	
Lauretti, et al., 2015	20	10	20	70	20	20	1.0%	-3.10 [-4.05, -2.15]	[
Ekim et al., 2008	47.2	5.6	10	65.3	6.3	9	0.7%	-2.91 [-4.29, -1.54]	
Bertalanffy, et al., 2005	49	8	30	77	11	33	1.1%	-2.85 [-3.57, -2.14]	<u> </u>
Tokuda, et al., 2014	5.9	6.5	16	23.8	5.9	16	0.9%	-2.81 [-3.82, -1.80]	<u> </u>
Shahoei, et al., 2017	49	25	30	97	5.9	30	1.1%	-2.61 [-3.31, -1.91]	<u> </u>
Ahmed, et al., 2010	49.3	7	30	66.1	6.9	30	1.1%	-2.39 [-3.06, -1.71]	
Barker, et al., 2006	32.4	18	29	66.2	11.2	33	1.1%	-2.26 [-2.91, -1.61]	
Lang, et al., 2007	59	6	30	79	11	33	1.1%	-2.20 [-2.83, -1.57]	
Desantana, et al., 2008 Kim, et al., 2012	9 19	10.7 12	20 50	48 48	22.7 15	20 50	1.0% 1.2%	-2.15 [-2.95, -1.36] -2.12 [-2.61, -1.63]	
Dailey, et al., 2013 (1)	40	4	41	40	4	41	1.2%	-1.73 [-2.24, -1.22]	
Kibar et al., 2020	21.2	12.2	31	47.6	19.6	30	1.2%	-1.60 [-2.18, -1.02]	
Baez-Suarez, et al., 2018	62	14	21	83	12	21	1.1%	-1.58 [-2.28, -0.88]	
Desantana, et al., 2009	43	15.3	23	66.5	14.7	21	1.1%	-1.54 [-2.22, -0.86]	
Jaafarpour, et al., 2008	5	5	54	12	4.2	54	1.2%	-1.51 [-1.93, -1.08]	
Cheing & Luk, 2005	17	17	10	46	20	9	0.9%	-1.50 [-2.55, -0.45]	
Zhang et al., 2020a	17	3	10	31	12.6	10	0.9%	-1.46 [-2.48, -0.45]	
Amer-Cuenca, et al., 2011	26.5	24.7	30	61.9	23.2	30	1.2%	-1.46 [-2.03, -0.88]	
Sadala, et al., 2018 De Oliverira et al., 2012	29.3 30	19.5 16.4	28 5	56.8 54	17.7 13.6	27 5	1.1% 0.7%	-1.45 [-2.05, -0.86] -1.44 [-2.92, 0.04]	
Park, et al., 2015	15	15	48	45	25	50	1.2%	-1.44 [-1.88, -0.99]	
Bi, et al., 2015	21.4	9.1	40	38.7	14.5	26	1.1%	-1.44 [-1.88, -0.99]	
Topuz, et al., 2004	37.3	16.2	15	59.1	13.7	12	1.0%	-1.40 [-2.25, -0.54]	
Celik, et al., 2013	38.8	25	17	67.7	14.2	16	1.1%	-1.38 [-2.14, -0.61]	<u> </u>
Ordog, 1987	30.4	2.8	25	54.8	25	25	1.1%	-1.35 [-1.97, -0.73]	——
Luchesa, et al., 2009	5	6	15	21	15.4	15	1.0%	-1.33 [-2.13, -0.53]	[
Cipriano, et al., 2008	20	7.4	23	30	7.4	22	1.1%	-1.33 [-1.98, -0.68]	
Lauretti, et al., 2013 De Silve, et al., 2015	60	10	13	80	20	10	1.0%	-1.28 [-2.19, -0.36]	
Da Silva, et al., 2015 Mabura, et al., 2017	1 26	0.795	21	4	3.18	21	1.1%	-1.27 [-1.94, -0.60]	
Mahure, et al., 2017 Kayman-Kose, et al., 2014 (2)	36 17.7	21 12.7	15 50	58 37.4	12 20.6	15 50	1.0% 1.2%	-1.25 [-2.04, -0.46] -1.14 [-1.57, -0.72]	
Kayman-Kose, et al., 2014 (2) Lison, et al., 2017	23.2	31.4	50 46	37.4 53.1	20.6 19.9	50 46	1.2%	-1.14 [-1.57, -0.72] -1.13 [-1.57, -0.69]	
Lison, et al., 1985	39.3	17.9	15	65.3	26.6	15	1.1%	-1.12 [-1.89, -0.34]	<u> </u>
Cuschieri, et al., 1987	30	11.25	10	49	20.25	10	1.0%	-1.11 [-2.07, -0.15]	<u> </u>
Emmiler, et al., 2008	24	11.8	20	39	14.8	20	1.1%	-1.10 [-1.77, -0.43]	——
Abreu, et al., 2010	68	23	10	88	10	10	1.0%	-1.08 [-2.03, -0.13]	
Chandra, et al., 2010	7	5.3	30	14.7	8.6	30	1.2%	-1.06 [-1.61, -0.52]	
Pitangui, et al., 2014	17.2	21.9	11	38.8	20.8	10	1.0%	-0.97 [-1.89, -0.05]	
Yilmaz et al., 2019	7.3	9.8	26	20	15.7	26	1.2%	-0.96 [-1.53, -0.38]	
Aminisaman et al., 2020 Subject of 1, 2015	26.6	5.4	30	31.2	4.8	30	1.2%	-0.89 [-1.42, -0.36]	
Suh, et al., 2015 Oncel, et al., 2002	18.7 24	7.46 13	24 25	30.7 39	17.67 20	23 25	1.1% 1.2%	-0.88 [-1.48, -0.28] -0.88 [-1.46, -0.29]	
Elboim et al., 2020	41.7	19.2	23	61.2	25	18	1.1%	-0.87 [-1.52, -0.22]	
Neighbours, et al., 1987	17.5	30.3	10	40.7	20.74	10	1.0%	-0.86 [-1.78, 0.07]	
Zakariaee et al., 2019	31.8	20.4	40	47.5	16.5	40	1.2%	-0.84 [-1.30, -0.38]	
Domaille & Reeves, 1997	30.33	8.14	31	47	28.14	29	1.2%	-0.81 [-1.33, -0.28]	
Fiorelli, et al., 2012	39	8	23	45	7	23	1.1%	-0.78 [-1.39, -0.18]	
Mansuri, et al., 2019	26.67	22.57	15	45.33	26.15	15	1.1%	-0.74 [-1.49, 0.00]	
Bjersa, et al., 2015	10	13	15	23	21	13	1.1%	-0.74 [-1.51, 0.04]	
Likar et al. 2001	25.1	7.6	11	29.7	4.8	12	1.0%	-0.70 [-1.55, 0.14]	
Vitalii & Oleg, 2014 Warfield, et al., 1985	39.5 48.3	17 20.1	11	52.5 64.2	18.6 24.6	10 12	1.0% 1.0%	-0.70 [-1.59, 0.19] -0.68 [-1.51, 0.14]	
Bilgili, et al., 2016	14.27	10.1	15	23.27	15.8	15	1.1%	-0.66 [-1.40, 0.08]	
Fujii-Abe et al., 2019	22.1	12.8	11	30.3	11.2	11	1.0%	-0.66 [-1.52, 0.21]	
Shimoura, et al., 2019	5.1	8	25	11.4	10.9	25	1.2%	-0.65 [-1.22, -0.08]	
Bjersa & Andersson, 2014	19.4	32.5	9	39.6	32	11	1.0%	-0.60 [-1.51, 0.30]	+
Sezen, et al., 2017	36.9	7.2	43	42	10.1	44	1.2%	-0.58 [-1.00, -0.15]	
Liu, et al., 2017	48.2	17.7	22	55.8	12.6	22	1.1%	-0.49 [-1.09, 0.11]	
Grimmer, 1992	22	28	20	35	29	20	1.1%	-0.45 [-1.08, 0.18]	
Galli, et al., 2015 Forreiro, et al., 2011	21	16	37	29	22	37	1.2%	-0.41 [-0.87, 0.05]	
Ferreira, et al., 2011 Rakel & Frantz, 2003 (3)	18 42	18 33.45	15 33	25 55	18 37.3	15 33	1.1% 1.2%	-0.38 [-1.10, 0.34] -0.36 [-0.85, 0.12]	
Dailey et al., 2020	42 46	33.45 20	33 103	53	37.3	33 99	1.2%	-0.35 [-0.63, -0.07]	
Warke, et al., 2004	28.25	36.5		40.33	19.4	3	0.7%	-0.33 [-1.78, 1.12]	
Hruby, et al., 2006	35	28.8	48	43.7	30.6	49	1.2%	-0.29 [-0.69, 0.11]	+
Robinson, et al., 2001	38.2	31.24	10	47.92	36.37	13	1.0%	-0.27 [-1.10, 0.56]	<u> </u>
Hamza, et al., 1999	25	23	25	31	25	25	1.2%	-0.25 [-0.80, 0.31]	-+
Machin, et al., 1988		13.72			13.65	15	1.1%	-0.20 [-0.92, 0.52]	
Moore & Shurman, 1997 (4)	40.58	27.55	24	44.81	30.67	24	1.2%	-0.14 [-0.71, 0.42]	-+
Cuschieri, et al., 1985 Foreter, et al., 1994	25	21.8	53	28	21.8	53	1.2%	-0.14 [-0.52, 0.24]	
Forster, et al., 1994 Shimoji, et al., 2007	9.8 38	28.1 15	15 9	13.7 40	31.9 20	15 8	1.1% 1.0%	-0.13 [-0.84, 0.59] -0.11 [-1.06, 0.94]	
Shimoji, et al., 2007 Graff-Radford, et al., 1989		15 18.06	12		20 15.92	12	1.0%	-0.11 [-1.06, 0.84] -0.11 [-0.91, 0.69]	
Yilmazer, et al., 2012	20.3 54.6	32.1	33	57.5	30.5	32	1.2%	-0.09 [-0.58, 0.40]	_ <del></del>
Sahin, et al., 2011	68.5	15.5	19	69.5	11.5	19	1.1%	-0.07 [-0.71, 0.56]	<u> </u>
Thomas, et al., 1988	33	31.1	131	35	33.8	144	1.3%	-0.06 [-0.30, 0.18]	+
Presser, et al., 2000	47	38.34	30	49	27.39	30	1.2%	-0.06 [-0.57, 0.45]	
llhani, 2015	22.4	11.3	35	22.8	10.2	31	1.2%	-0.04 [-0.52, 0.45]	-+-
Tucker, et al., 2015	56	56	35	57	57	35	1.2%	-0.02 [-0.49, 0.45]	+
Bono, et al., 2015	80	20	54	80	20	54	1.2%	0.00 [-0.38, 0.38]	1
Machado et al., 2019 Los, et al., 2016	47 55 6	25	22	46 54.4	22	22	1.1%	0.04 [-0.55, 0.63]	
Lee, et al., 2015 Atamaz, et al., 2012	55.6 64.7	9.2	18	54.4 50.4	12.9	18	1.1%	0.10 [-0.55, 0.76]	
Atamaz, et al., 2012 Silva, et al., 2012	54.7 22.5	24.1	37	50.4 20	20.3	37	1.2%	0.19 [-0.27, 0.65] 0.20 [-0.40, 0.81]	<u> </u>
Silva, et al., 2012 Beckwée, et al., 2018	22.5 39.2	11.5 25.1	21 25	20 30.6	12.5 23.2	21 28	1.1% 1.2%	0.20 [-0.40, 0.81] 0.35 [-0.19, 0.90]	<u> </u>
Siqueira et al., 2019	2.92	6.6	13	0.7	1.6	14	1.270	0.35 [-0.31, 1.22]	<u> </u>
Kofotolis, et al., 2008	2.92	4	23	20	4	21	1.1%	0.49 [-0.11, 1.09]	+
Kayman-Kose, et al., 2014 (5)	13.5	5.8	50	7.8	7	50	1.2%	0.88 [0.47, 1.29]	
									. [
Total (95% CI)			2426				100.0%	-0.96 [-1.14, -0.78]	•
Heterogeneity: Tau <sup>2</sup> = 0.64; Chi <sup>2</sup>			1 (P <	0.00001	); I² = 88	3%			-4 -2 0 2
Test for overall effect: Z = 10.49	(P < 0.0)	JOO1)							Favours TENS Favours Placebo
Footnotes									
(1) *Crossover									
(2) *Cesarian delivery sample									
<ul><li>(2) "Cesarian delivery sample</li><li>(3) *Crossover</li></ul>									

Figure A2 Forest plot of comparison TENS versus placebo. Outcome: pain intensity - expressed as mean (continuous) data.

#### Subgroup – 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 1 († .o. Thei .ncerning. 1) .p. therefore the 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 A3).

Forest Plot

#### $MetaTENS\_SupplementaryAppendix\_FINAL\_23-12-2020$

L Low Rob E- for more low R r, et al., 2005 taiandr, et al., 2005 (a), et al., 2007 (a), et al., 2007 (a), et al., 2007 (b), et al., 2008 (c), et al., 2018 (c), et al., 2019 (c), et al., 2010 (c), et al., 2010 (c), et al., 2010 (c), et al., 2010 (c), et al., 2017 (c), et al., 2016 (c), et al., 2017 (c), et al., 2018 (c), et al., 2018 (c), et al., 2018 (c), et al., 2019 (c), et al., 2014 (c), et al., 2014	33.3 49 59 9 40 62 43 26.5 15 23.2 21 46 47 54.7 39.2 = 193.45, < 0.0000	16 8 6 10.7 4 4 15.3 24.7 15 31.4 16 20 25 24.1 25.1 112.49 10 5.6 6.5 5 6.6 5.6 6.5 5 7 7 112.49 10 5.6 8.5 5 7 112.49 10 5.1 12.49 10 5.1 12.49 10 5.1 12.49 10 5.1 12.49 10 5.1 12.49 10 5.1 12.49 10 5.1 12.49 10 5.1 12.49 10 5.1 12.49 10 5.1 12.49 10 5.1 12.49 10 5.1 12.49 10 5.1 12.49 10 5.1 12.49 10 5.1 12.49 10 5.5 11.4 11.4 11.4 11.4 11.4 11.4 11.4	39 30 200 41 21 23 30 48 46 46 552 552 552 20 39 20 39 20 39 20 39 20 39 20 39 20 39 39 20 39 39 20 39 30 30 41 103 22 552 552 552 552 552 552 20 552 20 552 20 552 20 552 20 552 20 552 20 552 20 552 20 552 20 552 20 552 20 30 30 20 10 41 10 30 20 20 41 10 30 20 20 41 10 30 20 20 30 30 30 30 20 20 30 30 30 20 20 30 30 30 30 30 30 30 30 30 30 30 30 30	82.6 77 79 84 86.5 66.5 61.9 45 53.1 29 53.4 65.4 30.6 50.4 30.6 50.4 30.6 50.4 30.6 50.4 30.6 50.4 30.6 50.4 30.6 50.2 23.8 97 66.1 23.8 80 72 76 30 80 72 76 30 80 72 76 30 80 72 76 30 80 72 76 30 80 72 76 30 80 76 53 30 80 76 53 30 80 76 53 30 80 76 53 30 80 55 50 50 50 50 50 50 50 50 50 50 50 50	14.3 11 11 22.7 25 19.9 22 23.2 19.9 22 23.2 1.19 30 18.7 20 6.3 5.9 6.9 11.2 20 3.2 1.19 3.0 1.19 3.0 1.19 3.0 1.2 2.1 2.2 2.3 2.2 2.3 2.2 2.3 2.2 2.3 2.2 2.3 2.2 2.3 2.2 2.3 2.2 2.3 2.2 2.3 2.3	8 18 39 20 9 16 30 30	1.1% 1.1% 1.1% 1.2% 1.2% 1.2% 1.2% 1.2%	$\begin{array}{c} 32 \ 01 \ 317 \ .2 \ 001 \ .2 \ 01 \ .2 \ 01 \ .2 \ 01 \ .2 \ 01 \ .2 \ 01 \ .2 \ .2 \ .2 \ .2 \ .2 \ .2 \ .2 \ .$	
taianff, et al., 2005 taianff, et al., 2008 (1) saritaria, et al., 2008 (1) saritaria, et al., 2008 (2) saritaria, et al., 2008 (2) saritaria, et al., 2019 saritaria, et al., 2019 (2) saritaria, et al., 2011 (b, et al., 2015 (4) on, et al., 2017 (5) (1), et al., 2015 (4) on, et al., 2011 (1), et al., 2011 (1), et al., 2010 (1), et al., 2011 (1), et al., 2010 (1), et al., 201	49 49 59 9 40 0 62 43 23.2 21 46 47 54.7 23.2 21 46 47 54.7 23.2 21 1 46 47 54.7 23.2 25.1 1 1 1 0 25.1 1 1 1 1 1 1 1 1 1 1 1 1 1	8 6 10.7 4 14, 15.3 24.7 15.3 31.4 16 25 24.1 25, 12.49 10, 5.6 6 6 6 6 7 7 18 12 5 12.5 12.5 10, 12.5	30 30 200 41 21 23 30 48 46 46 37 552 552 552 (P < 0 9 9 20 10 39 20 0 10 39 20 39 20 0 10 39 20 30 30 30 30 30 30 30 30 30 3	777 799 488 66.5 53.1 29 50.4 30.6 50.4 30.6 50.4 30.6 000001); 70 65.3 23.8 97 66.1 66.2 97 66.4 48	111 111 122.7 23.2 25 19.9 22 20.3 23.2 23.2 1.19 30 18.7 20 8.9 22 20.3 23.2 7 8 9 9 22 20.3 23.2 7 8 9 9 9 22 20.3 23.2 23.2 25 25 20.3 23.2 25 25 25 25 20.3 23.2 25 25 25 20.3 23.2 25 25 20.3 23.2 25 25 20.3 23.2 25 25 25 25 25 25 25 25 25 2	33 33 20 41 21 21 30 50 46 47 37 99 22 28 552 552 552 552 552 8 8 8 8 8 8 8	1.1% 1.1% 1.2% 1.2% 1.2% 1.2% 1.2% 1.2%	$\begin{array}{c} -2.86(+3.7,-2.14)\\ -2.86(+3.7,-2.14)\\ -2.10(+2.34,-1.57)\\ -2.16(+2.34,-1.53)\\ -2.16(+2.34,-1.32)\\ -1.56(+2.24,-0.86)\\ -1.56(+2.24,-0.86)\\ -1.46(+2.22,-0.86)\\ -1.46(+2.22,-0.86)\\ -1.32(+1.57,-0.86)\\ -2.8(+1.57$	
ng, et al., 2007 samtana, et al., 2008 (1) lev, et al., 2013 (2) samtana, et al., 2018 (2) samtana, et al., 2018 (2) samtana, et al., 2018 (2) lev, et al., 2016 (2) lev, et al., 2017 (5) lev, et al., 2017 (5) lev, et al., 2017 (5) lev, et al., 2019 (7) maz, et al., 2019 (7) tor overail effect Z = 4 97 (P 2 Ugb, Uncleant S or over S lig barsis, et al., 2019 (3) barsis, et al., 2019 (3) barsis, et al., 2014 barsis, et al., 2016 (3) res, et al., 2016 (1) dampour, et al., 2016	9 9 40 0 62 43 3 45 75 15 15 15 15 15 15 15 15 15 15 15 15 15	10.7 4 14 15.3 24.7 15 31.4 16 20 25 24.1 25.1 (df=14 11) ar RoB 6.5 25 12.49 10 5.6 6.5 25 12.49 10 5.12 12 25 15 15 15 15 15 15 24.1 15 15 24.1 15 25.1 15 15 24.1 15 25.1 15 15 24.1 15 25.1 15 15 24.1 15 25.1 15 15 24.1 15 25.1 15 15 24.1 15 25.1 15 15 24.1 15 25.1 15 15 24.1 15 25.1 15 15 25.1 15 15 25 15 15 25 15 15 25 15 15 15 15 15 15 15 15 15 1	200 411 213 300 488 466 37 103 225 552 552 20 39 200 106 30 39 200 106 300 300 300 300 31 551 400 31 31 550 31 31 30 30 30 30 30 30 30 30 30 30 30 30 30	48 47 83 66.5 51.1 29 53 46 50.4 50.4 50.4 30.6 30.6 30.6 30.6 72 70 65.3 80 72 70 66.1 66.2 48	22.7 4 12 14,7 23.2 25 19.9 22 20.3 22 23.2 7 = 93% 1.19 30 18.7 20 8.5 9 5.8 6.9 5.8 5.8 5.9	20 41 21 30 50 46 46 37 99 92 23 77 28 552 % 8 8 8 8 8 8 8 8 8 8 8 8 9 9 20 9 9 16 30 30 30 30 30 30 30 30 30 30 30 30 30	1.1% 1.2% 1.1% 1.2% 1.2% 1.2% 1.2% 1.2%	$\begin{array}{c} -215(2.96,-1.30)\\ -1.73(2.24,-1.22)\\ -1.73(2.24,-1.22)\\ -1.73(2.24,-1.22)\\ -1.65(2.23,-0.80)\\ -1.46(2$	+ + + + + +
lev, et al., 2013 (2) Sc Juaroz, et al., 2018 Sc Juaroz, et al., 2018 Sc Juaroz, et al., 2016 (4), 2017 (5), 2017 (	40 62 43 26.5 55 51 55 47 54.7 54.7 54.7 54.7 54.7 54.7 54.	4 14 15.3 24.7 15 31.4 16 20 25 24.1 25.1 0.92 5 12.49 10 6 6.5 25 12.49 10 6 6.5 25 7 18 12 2 12.2 9 10.5 12.49 10.5 12.49 10.5 12.49 10.5 12.49 10.5 11.5 11.5 11.5 11.5 11.5 11.5 11.5	41 21 23 30 48 46 37 103 22 37 55 55 25 20 39 20 39 20 39 20 39 20 39 20 30 39 20 39 20 39 20 39 20 39 20 39 30 30 30 30 30 30 30 30 30 30	47 83 86 55 61.9 45 53.1 29 53 46 50.4 30.6 00001); 00001); 00001); 00001); 00001); 000010 72 70 65.3 80 72 70 66.1 94 80 53 50 53 50 53 53 53 53 53 53 53 53 53 53 53 53 53	4 14.7 23.2 25 19.9 22 20.3 23.2 20.3 23.2 P=93: 1.19 30 18.7 20 6.3 5.9 6.9 6.9 1.2	41 21 30 50 50 46 37 99 22 37 28 552 552 % 8 8 8 8 8 8 8 8 9 20 9 16 30 30	1.2% 1.1% 1.2% 1.2% 1.2% 1.2% 1.2% 1.2%	$\begin{array}{c} -1.73 (\pm 2.4, \pm 1.22) \\ -1.58 (\pm 2.8, \pm 0.88) \\ -1.58 (\pm 2.8, \pm 0.88) \\ -1.48 (\pm 2.03, \pm 0.88) \\ -1.44 (\pm 2.03, \pm 0.88) \\ -1.44 (\pm 1.88, \pm 0.98) \\ -0.41 (\pm 0.87, \pm 0.88) \\ -0.42 (\pm 0.47, \pm 0.88) \\ -0.42 (\pm 0.47, \pm 0.88) \\ -0.42 (\pm 0.47, \pm 0.88) \\ -0.42 (\pm 0.48, \pm 0.48) \\ -0.41 (\pm 0.48, \pm $	
25-Surany, et al., 2018 santany, et al., 2008 (3), (4), et al., 2015 (4), (4), et al., 2015 (4), (5), et al., 2015 (4), (6), et al., 2016 (7), (6), et al., 2018 (7), (7), et al., 2016 (7), (7), et al., 2016 (7), (7), et al., 2016 (7), (7), et al., 2017 (7), (7), et al., 2018 (7), (7), et al., 2008 (19), (7), et al., 2009 (19), (7), et al., 2009 (19), (7), et al., 2018 (19), (7), et al., 2018 (19), (7), et al., 2019 (19), (7), et al., 2019, (7), et al., 2019, (7), et al., 2014 (10), (7), et al., 2015 (10), (7), et al., 2014 (10), (7), et al.,	62 43 26.5 15 52.2 21 46 47 54.7 25.11 10 22 20 0 22 20 0 22 20 0 22 20 0 22 20 20	14 15.3 24.7 15 31.4 16 20 25 24.1 10 4f=144 11) <b>ar RoB</b> 0.92 5 5 12.49 5 12.49 5.25 5 25 5 25 5 7 7 18.4 10 5 12.49 5.25 5 12.49 5.25 5.25 5.25 5.25 7 7 18 10 5.25 5.25 12.49 5.25 7 7 18 10 5.25 5.25 7 7 10 5.25 7 10 5.25 7 10 5.25 7 10 5.25 7 10 5.25 7 10 5.25 7 10 5.25 7 10 5.25 7 10 5.25 7 10 5.25 7 10 5.25 7 10 5.25 7 10 5.25 7 10 5.25 7 11 5 7 11 5 7 12 5 7 7 11 5 7 10 7 10 7 5 7 7 11 10 7 7 11 10 7 7 10 10 10 10 10 10 10 10 10 10 10 10 10	21 23 30 48 46 37 103 22 552 552 552 552 20 39 20 10 16 30 20 10 16 30 30 29 50 31 50 21 10 31 10 30 30 10 30 30 10 30 30 10 30 30 10 30 30 30 10 30 30 30 30 30 30 30 30 30 30 30 30 30	83 66.5 61.9 45 53.1 29 53.4 46 50.4 30.6 50.4 30.6 70 70 70 72 70 65.3 23.8 97 66.3 23.8 97 66.4 48	12 14.7 23.2 25 19.9 22 20.3 23.2 23.2 1.19 9 30 18.7 20 6.3 5.9 6.3 5.9 6.9 11.2	21 21 30 50 46 50 37 37 22 37 28 552 38 552 38 552 39 20 9 8 18 39 20 9 16 30 30	1.1% 1.2% 1.2% 1.2% 1.2% 1.2% 1.2% 1.2%	$\begin{array}{c} -1.56[2,26],0.68[\\ -1.56[2,20],0.68[\\ -1.56[2,20],0.68[\\ -1.46[2,20],0.68[\\ -1.46[1,457],0.68[\\ -0.36[1,457],0.68[\\ -0.36[1,457],0.68[\\ -0.36[1,457],0.68[\\ -0.36[1,457],0.68[\\ -0.36[1,45],0.90[\\ -1.227[1,47],0.77]\\ -1.225[1,47],0.77]\\ -1.225[1,47],0.75[1]\\ -2.16[1,40],0.75[1$	
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terogeneity: Tau" = 0.98; Ch <sup>2</sup> = 4.97 (P 2 High-Unclear 5 or more high thanks, et al., 2010 thanks, et al., 2010 thanks, et al., 2010 thanks, et al., 2010 thanks, 2011 thanks, 2014 thanks, 2014 thanks, 2010 there, et al., 2000 then 6 al., 2020 than et al., 2020 thanks, 2025 thanks,	= 193.45 < 0.0000 ph-uncles 25.11 100 22 20 47.2 5.9 49 49.3 32.4 19 21.2 5 17 17 29.3 30.4 30.4 30.4	df=14 1) ar RoB 0.92 5 12.49 10 5.6 8.5 25 7 18 122 12.2 5 17 3 19.5 16.4 9.1	552 (P < 0) 9 20 39 20 10 16 30 29 50 31 54 10	00001); 39 80 72 70 65.3 23.8 97 66.1 66.2 48	F = 939 1.19 30 18.7 20 6.3 5.9 5.9 6.9 11.2	552 % 8 18 39 20 9 16 30 30	17.5% 0.1% 0.9% 1.1% 1.0% 0.8% 0.9% 1.1%	-12.50 [-17.39, -7.61] -3.27 [-4.28, -2.27] -3.11 [-3.78, -2.44] -3.10 [-4.29, -1.54] -2.81 [-3.82, -1.80] -2.81 [-3.82, -1.80] -2.61 [-3.31, -1.91]	• =
terogeneity: Tau" = 0.98; Ch <sup>2</sup> = 4.97 (P 2 High-Unclear 5 or more high thanks, et al., 2010 thanks, et al., 2010 thanks, et al., 2010 thanks, et al., 2010 thanks, 2011 thanks, 2014 thanks, 2014 thanks, 2010 there, et al., 2000 then 6 al., 2020 than et al., 2020 thanks, 2025 thanks,	<ul> <li>&lt; 0.0000</li> <li>(h-uncles)</li> <li>25.11</li> <li>10</li> <li>22</li> <li>20</li> <li>47.2</li> <li>5.9</li> <li>49.3</li> <li>32.4</li> <li>19</li> <li>21.2</li> <li>5</li> <li>17</li> <li>17</li> <li>29.3</li> <li>30</li> <li>21.4</li> <li>37.3</li> <li>38.8</li> <li>30.4</li> </ul>	II) ar RoB 0.92 5 12.49 10 5.6 8.5 25 7 18 12 12.2 5 12.2 5 17 3 19.5 16.4 9.1	(P < 0. 9 20 39 20 10 16 30 29 50 31 54 10	39 80 72 70 65.3 23.8 97 66.1 66.2 48	1.19 30 18.7 20 6.3 5.9 5.9 6.9 11.2	% 8 18 39 20 9 16 30 30	0.1% 0.9% 1.1% 1.0% 0.8% 0.9% 1.1%	-12.50 [-17.39, -7.61] -3.27 [-4.28, -2.27] -3.11 [-3.78, -2.44] -3.10 [-4.29, -1.54] -2.81 [-3.82, -1.80] -2.81 [-3.82, -1.80] -2.61 [-3.31, -1.91]	
2 High-Unclear 5 or more High barist, et al., 2010 harner, et al., 2014 harner, et al., 2016 (8) harner, et al., 2016 (8) horist al., 2016 (9) horist al., 2016 (9) horist al., 2016 (9) horist al., 2016 (9) horist al., 2016 hard al., 2016 (13) hard al., 2016 (13) hard al., 2016 hard al., 2016 hard al., 2016 horist al., 2016 hard al., 2016 hard al., 2016 hard al., 2016 hard al., 2016 (10) harner, al., 2001 hard, 14, 2006 (16) harner, al., 2000 (17) harner, al., 2000 (15) harner, al., 2000 (17) harner, al., 2000 (15) harner, al., 2000 (17) harner, al., 2000 (15) harner, al., 2000 (17) harner, al., 2000 (15) harner,	h-uncles 25.11 10 22 20 47.2 5.9 49 49.3 32.4 19 21.2 5 17 17 29.3 30 21.4 37.3 38.4 30.4 30.4	ar RoB 0.92 5 12.49 10 5.6 8.5 25 7 18 12 12.2 5 12.2 5 12.2 5 19.5 18.4 9.1	20 39 20 10 16 30 29 50 31 54 10	80 72 70 65.3 23.8 97 66.1 66.2 48	30 18.7 20 6.3 5.9 5.9 6.9 11.2	18 39 20 9 16 30 30	0.9% 1.1% 1.0% 0.8% 0.9% 1.1%	-3.27 [-4.28, -2.27] -3.11 [-3.78, -2.44] -3.10 [-4.05, -2.15] -2.91 [-4.29, -1.54] -2.81 [-3.82, -1.80] -2.61 [-3.31, -1.91]	
banis, et al., 2010 trano, et al., 2014 stemek, et al., 2015 m et al., 2019 (1) (2) (2) (2) m et al., 2000 (2) (2) (2) m et al., 2000 (2) (2) (2) med, et al., 2010 (2) (2) (2) (2) (3) (2) (2) (2) (3) (2) (2) (2) (3) (2) (2) (2) (4) (2) (2) (2) (4) (2) (2) (2) (4) (2) (2) (4) (2) (2) (2) (4) (2) (2) (5) (2) (2) (5) (2) (2) (6) (2) (2) (6) (2) (2) (7) (2) (2) (2) (7) (2) (2) (2) (7) (2) (2) (2) (7) (2) (2) (2) (2) (7) (2) (2) (2) (2) (2) (7) (2) (2) (2) (2) (2) (2) (2) (2) (2) (2	25.11 10 22 20 47.2 5.9 49 49.3 32.4 19 21.2 5 17 29.3 30 21.4 37.3 38.8 30.4	0.92 5 12.49 10 5.6 8.5 25 7 18 12.2 12.2 5 17 3 19.5 18.4 9.1	20 39 20 10 30 30 29 50 31 54 10	80 72 70 65.3 23.8 97 66.1 66.2 48	30 18.7 20 6.3 5.9 5.9 6.9 11.2	18 39 20 9 16 30 30	0.9% 1.1% 1.0% 0.8% 0.9% 1.1%	-3.27 [-4.28, -2.27] -3.11 [-3.78, -2.44] -3.10 [-4.05, -2.15] -2.91 [-4.29, -1.54] -2.81 [-3.82, -1.80] -2.61 [-3.31, -1.91]	
riano, et al., 2014 kenek, et al., 2019 (8) arefit, et al., 2019 (8) urda, et al., 2019 (8) urda, et al., 2014 (10) urda, et al., 2014 (10) kene, et al., 2017 (11) kene, et al., 2012 (2) har et al., 2020 (2) har et al., 2020 (2) urda per et al., 2020 (10) diang, et al., 2020 (14) diala, et al., 2012 (15) et al., 2015 urd, 1015 urda, 1016 urda, 1017 har et al., 2000 (17) riano, et al., 2000 (15) riano, et al., 2009 (15) riano, et al., 20	22 20 47.2 5.9 49.3 32.4 19 21.2 5 17 17 29.3 30 21.4 37.8 30.2 21.4 37.8 30.4	12.49 10 5.6 8.5 25 7 18 12 12.2 5 17 3 19.5 16.4 9.1	39 20 10 30 30 29 50 31 54 10	72 70 65.3 23.8 97 66.1 66.2 48	30 18.7 20 6.3 5.9 5.9 6.9 11.2	18 39 20 9 16 30 30	0.9% 1.1% 1.0% 0.8% 0.9% 1.1%	-3.27 [-4.28, -2.27] -3.11 [-3.78, -2.44] -3.10 [-4.05, -2.15] -2.91 [-4.29, -1.54] -2.81 [-3.82, -1.80] -2.61 [-3.31, -1.91]	
nreth, et al., 2015 one et al., 2008 (Ø) suda, et al., 2014 (10) ahoel, et al., 2017 (11) nred, et al., 2010 nred, et al., 2021 (12) nred, 12, 2021 (21) hose ret al., 2020 (21) hose ret al., 2020 (21) hose ret al., 2020 (21) data, et al., 2018 (20) nred, 12, 2013 (0) retring at al., 2014 (10) nr, et al., 2014 (IN, et al., 2014 (10) (IN, 10) (10) (10) (IN, 10) (10) (10) (IN, 10) (10) (10) (IN, 10) (10) (10) (10) (IN, 10) (10) (10) (10) (IN, 10) (10) (10) (10) (10) (10) (IN, 10) (10) (10) (10) (10) (10) (10) (10)	20 47.2 5.9 49 32.4 19 21.2 5 17 17 29.3 30 21.4 37.3 38.8 30.4	10 5.6 6.5 25 7 18 12 12.2 5 17 3 19.5 16.4 9.1	20 10 30 29 50 31 54 10	70 65.3 23.8 97 66.1 66.2 48	20 6.3 5.9 5.9 6.9 11.2	20 9 16 30 30	1.0% 0.8% 0.9% 1.1%	-3.10 [-4.05, -2.15] -2.91 [-4.29, -1.54] -2.81 [-3.82, -1.80] -2.61 [-3.31, -1.91]	
me tal., 2008 (e) uda, et al., 2014 (10) ahoel, et al., 2017 (11) here, et al., 2017 (11) here, et al., 2012 (12) here at al., 2020 (12) here at al., 2020 (12) here at al., 2020 (14) dalas, et al., 2012 (15) here at al., 2013 (15) here at al., 2008 (15) here at al., 2008 (15) here at al., 2009 (15) here at al., 2009 (15) here at al., 2008 (15) here at al., 2018 (15) here at al., 2008 (15) here at al., 2018 (15) here at al., 2008 (15) here at al., 2018 (15) here at al., 2018 (15) here at al., 2008 (15) here at al., 2018 (15) here at al., 2008 (15) here at al., 2018 (15) here at al., 2018 (15) here at al., 2008 (15) here at al., 2018 (15) here	47.2 5.9 49 49.3 32.4 19 21.2 5 17 17 29.3 30 21.4 37.3 30.2 1.4 37.3 30.8 8.8 30.4	5.6 8.5 7 18 122 12.2 5 17 3 19.5 16.4 9.1	10 16 30 29 50 31 54 10	65.3 23.8 97 66.1 66.2 48	6.3 5.9 5.9 6.9 11.2	9 16 30 30	0.8% 0.9% 1.1%	-2.91 [-4.29, -1.54] -2.81 [-3.82, -1.80] -2.61 [-3.31, -1.91]	
unda, etal., 2014 (10) shoel, etal., 2010 treed, etal., 2010 treed, etal., 2010 treed, etal., 2010 etal., 2012 (12) etal., 2012 (12) etal., 2012 (12) etal., 2014 (10) etal., 2014 (10	5.9 49 49.3 32.4 19 21.2 5 17 17 29.3 30 21.4 37.3 38.8 30.4	8.5 25 7 18 12 12.2 5 17 3 19.5 16.4 9.1	16 30 29 50 31 54 10	23.8 97 66.1 66.2 48	5.9 5.9 6.9 11.2	16 30 30	0.9% 1.1%	-2.81 [-3.82, -1.80] -2.61 [-3.31, -1.91]	
ahoei, et al., 2017 (11) eted, et al., 2010 ker, et al., 2012 (21) hab ar et al., 2022 (21) hab ar et al., 2022 (21) hab ar et al., 2020 (21) hab ar et al., 2020 (21) hab ar, et al., 2020 (21) hab ar, et al., 2021 (21) hab ar, et al., 2021 (21) hab ar, et al., 2021 (21) hab ar, et al., 2020 (12) riano, et al., 2009 (15) riano, et al., 2009 (	49 49.3 32.4 19 21.2 5 17 17 29.3 30 21.4 37.3 38.8 30.4	25 7 18 12 12.2 5 17 3 19.5 16.4 9.1	30 30 29 50 31 54 10	97 66.1 66.2 48	5.9 6.9 11.2	30 30	1.1%	-2.61 [-3.31, -1.91]	
need, et al., 2010 keer, et al., 2006 n, et al., 2020 (13) fanpour, et al., 2020 (13) fanpour, et al., 2020 ing at Luk, 2020 (14) talae, et al., 2015 cilae, et al., 2016 Oliverina et al., 2012 (15) et al., 2015 iux, et al., 2013 iux, et al., 2013 iux, et al., 2013 iux, et al., 2003 (15) read, 2009 (17) riano, et al., 2009 (17) riano, et al., 2009 (16) riano, et al., 2009 (17) riano, et al., 2009 (13) riano, et al., 2009 (13) riano, et al., 2009 (13) riano, et al., 2009 (13) riano, et al., 2009 (15) riano, et al., 2009 (17) riano, et al., 2009 (13) riano, et al., 2009 (15) riano, et	32.4 19 21.2 5 17 17 29.3 30 21.4 37.3 38.8 30.4	7 18 12 12.2 5 17 3 19.5 16.4 9.1	30 29 50 31 54 10	66.1 66.2 48	6.9 11.2	30	4.4.00		I
ker, et al., 2006 n, et al., 2012 (12) ubar et al., 2020 (13) rhar et al., 2020 (13) rhar pour, et al., 2008 eing & Luk, 2005 ing et al., 2010 Oliverina et al., 2012 (15) et al., 2015 uzz, et al., 2004 ing, 1997 (16) hesa, et al., 2009 (17) ririano, et al., 2008 (18) refut, et al., 2008 (18) refut, et al., 2018 (16)	19 21.2 5 17 29.3 30 21.4 37.3 38.8 30.4	12 12.2 5 17 3 19.5 16.4 9.1	29 50 31 54 10	66.2 48	11.2		1.1%	-2.39 [-3.06, -1.71]	
hbar et al., 2020 (13) har et al., 2020 (13) harpour, et al., 2008 et al., 2020 a (14) Jala, et al., 2012 Oliverina et al., 2012 et al., 2015 forg. 1997 (16) hesa, et al., 2009 (17) ririano, et al., 2008 (18) refut, et al., 2018 (18) refut, et al., 2018 (18)	21.2 5 17 29.3 30 21.4 37.3 38.8 30.4	12.2 5 17 3 19.5 16.4 9.1	31 54 10			33	1.1%	-2.26 (-2.91, -1.61)	
farpour, et al., 2008 eing & Luk, 2005 ang et al., 2020a (14) Jala, et al., 2012 (15) Oliverira et al., 2012 (15) Oliverira et al., 2012 (15) et al., 2014 lik, et al., 2014 lik, et al., 2014 itis, et al., 2004 (17) rirano, et al., 2008 (18) refut, et al., 2013 (19)	5 17 29.3 30 21.4 37.3 38.8 30.4	5 17 3 19.5 16.4 9.1	54 10	47.0	19.6	50 30	1.2% 1.2%	-2.12 [-2.61, -1.63] -1.60 [-2.18, -1.02]	I
ang et al., 2020a (14) dala, et al., 2018 Oliverira et al., 2012 (15) et al., 2015 puz, et al., 2004 lik, et al., 2004 lik, et al., 2003 iog, 1987 (16) hesa, et al., 2009 (17) ritano, et al., 2008 (18) vetti. et al., 2013 (19)	17 17 29.3 30 21.4 37.3 38.8 30.4	17 3 19.5 16.4 9.1	10	12	4.2	54	1.2%	-1 51 [-1 93 -1 08]	<u> </u>
ang et al., 2020a (14) dala, et al., 2018 Oliverira et al., 2012 (15) et al., 2015 puz, et al., 2004 lik, et al., 2004 lik, et al., 2003 iog, 1987 (16) hesa, et al., 2009 (17) ritano, et al., 2008 (18) vetti. et al., 2013 (19)	29.3 30 21.4 37.3 38.8 30.4	3 19.5 16.4 9.1		46	4.2 20	54 9	0.9%	-1.50 (-2.55, -0.45)	
tala, et al., 2018 Oliverira et al., 2012 (15) et al., 2015 Juz, et al., 2004 lik, et al., 2004 icog, 1987 (16) :hesa, et al., 2009 (17) riano, et al., 2009 (18) refut, et al., 2013 (19)	30 21.4 37.3 38.8 30.4	16.4 9.1		31	12.6	10	0.9%	-1.46 (-2.480.45)	—— I
et al., 2015 Juz, et al., 2004 like, et al., 2013 log, 1987 (16) ihesa, et al., 2009 (17) iriano, et al., 2008 (18) jurétti, et al., 2013 (19)	21.4 37.3 38.8 30.4	9.1	28 5	56.8	17.7 13.6	27 5	1.2% 0.7%	-1.45 [-2.05, -0.86] -1.44 [-2.92, 0.04]	
ouz, et al., 2004 lik, et al., 2013 log, 1987 (16) :hesa, et al., 2009 (17) iriano, et al., 2008 (18) iriano, et al., 2013 (19)	37.3 38.8 30.4	9.1	5 26	54 38.7	13.6 14.5	5 26	0.7%	-1.44 [-2.92, 0.04] -1.41 [-2.02, -0.80]	
log, 1987 (16) :hesa, et al., 2009 (17) riano, et al., 2008 (18) #etti, et al., 2013 (19)	38.8 30.4		26	38.7 59.1	14.5	26 12	1.2%	-1.41 [-2.02, -0.80] -1.40 [-2.25, -0.54]	
log, 1987 (16) :hesa, et al., 2009 (17) riano, et al., 2008 (18) #etti, et al., 2013 (19)		16.2 25	15 17	67.7	14.2	16	1.1%	-1.38 [-2.14, -0.61]	
riano, et al., 2008 (18) uretti, et al., 2013 (19)	5	2.8	25	54.8	25	25	1.1%	1.35 [-1.97, -0.73]	
riano, et al., 2008 (18) uretti, et al., 2013 (19)		6	15	21	15.4	15	1.1%	-1.33 [-2.13, -0.53]	—— I
new, et al., 2013 (19)	20 60	7.4	23 13	30 80	7.4	22 10	1.1%	-1.33 [-1.98, -0.68] -1.28 [-2.19, -0.36]	
hure, et al., 2017 (20)	60 36	10	13	80 58	20	10	1.0%	-1.28 [-2.19, -0.36] -1.25 [-2.04, -0.46]	
man-Kose, et al., 2014 (21)	17.7	12.7	50	37.4	20.6	50	1.2%	-1.14 [-1.57, -0.72]	
/man-Kose, et al., 2014 (21) , et al., 1985 (22)	39.3	17.9	50 15	65.3	26.6	15	1.2% 1.1%	-1.14 [-1.57, -0.72] -1.12 [-1.89, -0.34]	—— I
schieri, et al., 1987 (23)	30	11.25	10	49	20.25	10	1.0%	-1.11 [-2.07, -0.15]	
miler, et al., 2008	24 68	11.8 23	20 10	39 88	14.8 10	20 10	1.1%	-1.10 [-1.77, -0.43] -1.08 [-2.03, -0.13]	
eu, et al., 2010 andra, et al., 2010	68 7	23 5.3	10 30	88 14.7	10 8.6	10 30	1.0%	-1.08 [-2.03, -0.13] -1.06 [-1.61, -0.52]	
angui, et al., 2014 (24)	17.2	21.9	11	38.8	20.8	10	1.0%	-0.97 [-1.89, -0.05]	
naz et al., 2019 (25)	7.3	9.8 5.4	26	20	15.7	26	1.2%	-0.96 [-1.53 -0.38]	
naz et al., 2019 (25) inisaman et al., 2020	26.6	5.4	30	31.2	4.8	30	1.2%	-0.89 [-1.42, -0.36]	
n, et al., 2015	18.7	7.46	24	30.7	17.67	23	1.2%	-0.88 [-1.48, -0.28]	
cel, et al., 2002 (26) oim et al., 2020 (27)	24 41.7	13 19.2	25 23	39 61.2	20 25	25 18	1.2% 1.1%	-0.88 [-1.46, -0.29] -0.87 [-1.52, -0.22]	
oim et al., 2020 (27) ighbours, et al., 1987 (28)	41.7	30.3	10	40.7	25 20.74	18	1.1%	-0.87 [-1.52, -0.22] -0.86 [-1.78, 0.07]	
(ariaee et al., 2019 (29)	31.8	20.4	40	47.5	16.5	40	1.2%	-0.84 [-1.30, -0.38]	
maille & Reeves, 1997 (30)	30.33	8.14	31	47	28.14	29	1.2%	-0.81 [-1.33 -0.28]	
relli, et al., 2012 (31)	39	8	23	45	7	23	1.2%	-0.78 [-1.39, -0.18]	
nsuri, et al., 2019 (32)	26.67 10	22.57 13	15 15	45.33 23	26.15 21	15 13	1.1% 1.1%	-0.74 [-1.49, 0.00]	
rsa, et al., 2015 (33) ar et al. 2001 (34)	25.1	13 7.6	15	23 29.7	4.8	13	1.1%	-0.74 [-1.51, 0.04] -0.70 [-1.55, 0.14]	
alii & Oleg, 2014	39.5	17	11	52.5	4.0 18.6	10	1.0%	-0.70 [-1.55, 0.14]	+
rfield, et al., 1985 (35)	48.3	20.1	12	64.2	24.6	12	1.0%	-0.68 [-1.51, 0.14]	
pili. et al., 2016	14.27	10.1	15	23.27	15.8	15	1.1%	-0.66 [-1.40.0.08]	
ii-Abe et al., 2019 (36)	22.1 5.1	12.8 8	11	30.3 11.4	11.2 10.9	11 25	1.0% 1.2%	-0.66 [-1.52, 0.21]	
moura, et al., 2019 (37) rsa & Andersson, 2014	5.1 19.4	32.5	25 9	11.4 39.6	10.9	25	1.2%	-0.65 (-1.22, -0.08) -0.60 (-1.51, 0.30)	
rsa & Andersson, 2014 ten, et al., 2017 (38)	36.9	7.2	43	42	10.1	44	1.2%	-0.60 (-1.51, 0.30) -0.58 (-1.00, -0.15)	
, et al., 2017 (39)	48.2	17.7	22	55.8	12.6	22	1.2%	-0.49 (-1.09. 0.11)	+
mmer, 1992 (40)	22	28 18	20 15	36	29 18	20 15	1.1%	-0.45 [-1.08, 0.18] -0.38 [-1.10, 0.34]	+
reira, et al., 2011 (41) kel & Frantz, 2003 (42)	18 42	18 33.45	15 33	25 55	18 37.3	15 33	1.1% 1.2%	-0.38 [-1.10, 0.34] -0.36 [-0.85, 0.12]	
kel & Frantz, 2003 (42) rke, et al., 2004 (43)	42 28.25	33.45 36.5	33	55 40.33	37.3	33	1.2%	-0.36 [-0.85, 0.12] -0.33 [-1.78, 1.12]	
iby, et al., 2006 (44)	35	28.8	48	43.7	30.6	49	1.2%	-0.29 I-0.69. 0.111	+
binson et al. 2001	38.2	31.24	10	47.92	36.37	13	1.0%	-0.27 [-1.10, 0.56]	-+-
mza, et al., 1999 (45) chin, et al., 1988	25	23	25	31	25	25	1.2%	-0.25 [-0.80, 0.31]	-+
chin, et al., 1988 ore & Shurman, 1997 (46)	13.47 40.58	13.72 27.55	15	16.29 44.81	13.65 30.67	15	1.1%	-0.20 [-0.92, 0.52] -0.14 [-0.71, 0.42]	<u>_</u> _
ore & Shurman, 1997 (46) schieri, et al., 1985 (47)	40.58 25	27.55 21.8	24 53	44.81 28	30.67 21.8	24 53	1.2% 1.3%	-0.14 [-0.71, 0.42] -0.14 [-0.52, 0.24]	<b>T</b>
	25 9.8	21.8	53 15	13.7	21.8 31.9	15	1.3%	-0.13 [-0.84, 0.59]	
moji, et al., 2007 (49) iff-Radford, et al., 1989 (50)	38	15	9	40	20	15 8	1.0%	-0.11 [-1.06, 0.84]	
df-Radford, et al., 1989 (50)	28.3	18.06	12	30.2	15.92	12	1.1%	-0.11 [-0.91, 0.69]	
nazer, et al., 2012 (51)	54.6	32.1	33	57.5	30.5	32	1.2%	-0.09 [-0.58, 0.40]	
nin, et al., 2011 omas, et al., 1988 (52) sser, et al., 2000 (53)	68.5 33	15.5 31.1	19 131	69.5 35	11.5 33.8	19 144	1.1% 1.3%	-0.07 [-0.71, 0.56] -0.06 [-0.30, 0.18]	
sser. et al., 1900 (52)	33 47	38.34	30	35 49	27.39	30	1.3%	-0.06 [-0.57, 0.45]	-
ini, 2016 (54)	22.4	11.3	35	22.8	10.2	31	1.2%	-0.04 (-0.52, 0.45)	+
:ker. et al., 2015 (55)	56	56	35	57	57	35	1.2%	-0.02 [-0.49, 0.45]	+
Silva, et al., 2015 (56)	1	0	21	4	0	21		Not estimable	
no, et al., 2015	80	20	54	80	20	54	1.3%	0.00 [-0.38, 0.38]	<u> </u>
e, et al., 2015 ra, et al., 2012 (57)	55.6 22.5	9.2 11.5	18 21	54.4 20	12.9 12.5	18 21	1.1% 1.2%	0.10 [-0.55, 0.76] 0.20 [-0.40, 0.81]	<u> </u>
ueira et al., 2019 (58)	2.92	6.6	13	0.7	12.5	14	1.1%	0.46 [-0.31, 1.22]	
otolis, et al., 2008 /man-Kose, et al., 2014 (59)	2.82	4	23	20	4	21	1.2%	0.49 [-0.11, 1.09]	+
/man-Kose, et al., 2014 (59)	13.5	5.8	50	7.8	7	50	1.2%		.
ototal (95% CI)	F00 ( -		1874			1863	82.5%	-0.89 [-1.08, -0.70]	•
terogeneity: Tau <sup>e</sup> = 0.58; Chi <sup>e</sup> = at for overall effect: Z = 9.13 (P	= 526.33	df = 75	(P < 0.	00001);	Pf = 869	85			
st for overall effect: Z = 9.13 (P	< 0.0000	(I)							
al (95% CI)			2426				100.0%	-0.96 [-1.14, -0.78]	♦
terogeneity: Tau# = 0.64; Chi# = at for overall effect: Z = 10.37 (F	= 733.23	df= 90	(P < 0	00001);	P= 889	%			-4 -2 0 2 4

Figure A3 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.  $\geq 6$  low RoB items).

#### Sample 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<sup>2</sup> = 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 A4). [Forest Plot].

Forest Plot

#### $MetaTENS\_SupplementaryAppendix\_FINAL\_23-12-2020$

Study or Subgroup 2.10.1 TENS sample n=>50	TENS Mean SD Total	Mean SD Total	Weight I	V, Random, 95% Cl	Std. Mean Difference IV, Random, 95% Cl	
Kim, et al., 2012 (1)	19 12 50	48 15 50	1.2%	-2.12 [-2.61, -1.63]		
Jaafarpour, et al., 2008 Park, et al., 2015 (2)	5 5 54 15 15 48	12 4.2 54 45 25 50	1.2% 1.2%	-1.51 [-1.93, -1.08] -1.44 [-1.88, -0.99]		
Kayman-Kose, et al., 2014 (3)	17.7 12.7 50	37.4 20.6 50	1.2%	-1.14 [-1.57, -0.72]		
Dailey et al., 2020 (4) Cuschieri, et al., 1985 (5)	46 20 103 25 21.8 53	53 19.9 99 28 21.8 53	1.3% 1.3%	-0.35 [-0.63, -0.07] -0.14 [-0.52, 0.24]	7	
Thomas, et al., 1988 (6)	33 31.1 131	35 33.8 144	1.3%	-0.06 [-0.30, 0.18]	+	
Bono, et al., 2015 Kayman-Kose, et al., 2014 (7)	80 20 54 13.5 5.8 50	80 20 54 7.8 7 50	1.3% 1.2%	0.00 (-0.38, 0.38) 0.88 (0.47, 1.29)	+	
Subtotal (95% CI)	593	604	11.2%	0.64 [-1.18, 0.10]	•	
Heterogeneity: Tau <sup>2</sup> = 0.63; Chi <sup>2</sup> Test for overall effect: Z = 2.34 (P		0001); I² = 95%				
2.10.15 TENS Sample n<50	- 0.02/					
Barbarisi, et al., 2010	25.11 0.92 9	39 1.19 8	0.1% -1	2.50 [-17.39, -7.61]	(	
Cipriano, et al., 2014 Mora, et al., 2006	10 5 20 33.3 16 39	80 30 18 82.6 14.3 34	0.9%	-3.27 [-4.28, -2.27] -3.20 [-3.91, -2.50]		
Hokenek et al., 2019 (8)	22 12.49 39	72 18.7 39	1.1%	-3.11 [-3.78, -2.44]		
Lauretti, et al., 2015	20 10 20 47.2 5.6 10	70 20 20 65.3 6.3 9	1.0% 0.8%	-3.10 [-4.05, -2.15]		
Ekim et al., 2008 (9) Bertalanffy, et al., 2005	49 8 30	77 11 33	1.1%	-2.91 [-4.29, -1.54] -2.85 [-3.57, -2.14]		
Tokuda, et al., 2014 (10) Shahoei, et al., 2017 (11)	5.9 6.5 16 49 25 30	23.8 5.9 16 97 5.9 30	0.9% 1.1%	-2.81 [-3.82, -1.80] -2.61 [-3.31, -1.91]		
Ahmed, et al., 2010	49.3 7 30	66.1 6.9 30	1.1%	-2.39 [-3.06, -1.71]		
Barker, et al., 2006 Lang, et al., 2007	32.4 18 29 59 6 30	66.2 11.2 33 79 11 33	1.1%	-2.26 [-2.91, -1.61] -2.20 [-2.83, -1.57]		
Desantana, et al., 2008 (12)	9 10.7 20	48 22.7 20	1.1%	-2.15 [-2.95, -1.36]		
Dailey, et al., 2013 (13) Kimbar et al., 2020 (14)	40 4 41 21.2 12.2 31	47 4 41 47.6 19.6 30	1.2% 1.2%	-1.73 [-2.24, -1.22] -1.60 [-2.18, -1.02]	<u> </u>	
Baez-Suarez, et al., 2018	62 14 21	83 12 21	1.1%	-1.58 [-2.28, -0.88]		
Desantana, et al., 2009 (15) Cheing & Luk, 2005	43 15.3 23 17 17 10	66.5 14.7 21 46 20 9	1.1% 0.9%	-1.54 [-2.22, -0.86] -1.50 [-2.55, -0.45]		
Cheing & Luk, 2005 Zhang et al., 2020a (16)	17 3 10	31 12.6 10	0.9%	-1.50 [-2.55, -0.45] -1.46 [-2.48, -0.45]		
Amer-Cuenca, et al., 2011	26.5 24.7 30 29.3 19.5 28	61.9 23.2 30 56.8 17.7 27	1.2% 1.2%	-1.46 [-2.03, -0.88]	<u> </u>	
Sadala, et al., 2018 De Oliverira et al., 2012 (17)	30 16.4 5	54 13.6 5	0.7%	-1.45 [-2.05, -0.86] -1.44 [-2.92, 0.04]		
Bi, et al., 2015	21.4 9.1 26	38.7 14.5 26	1.2%	-1.41 [-2.02, -0.80]		
Fopuz, et al., 2004 Celik, et al., 2013	37.3 16.2 15 38.8 25 17	59.1 13.7 12 67.7 14.2 16	1.0% 1.1%	-1.40 [-2.25, -0.54] -1.38 [-2.14, -0.61]		
Ordog, 1987 (18)	30.4 2.8 25	54.8 25 25	1.1%	-1.35 [-1.97, -0.73]		
uchesa, et al., 2009 (19) Cipriano, et al., 2008 (20)	5 6 15 20 7.4 23	21 15.4 15 30 7.4 22	1.1%	-1.33 [-2.13, -0.53] -1.33 [-1.98, -0.68]		
auretti, et al., 2013 (21)	60 10 13	80 20 10	1.0%	-1.28 [-2.19, -0.36]		
dahure, et al., 2017 (22) Lison, et al., 2017 (23)	36 21 15 23.2 31.4 46	58 12 15 53.1 19.9 46	1.1% 1.2%	-1.25 [-2.04, -0.46] -1.13 [-1.57, -0.69]		
.iu, et al., 1985 (24)	39.3 17.9 15	65.3 26.6 15	1.1%	-1.12 [-1.89, -0.34]		
Cuschieri, et al., 1987 (25) Emmiler, et al., 2008	30 11.25 10 24 11.8 20	49 20.25 10 39 14.8 20	1.0%	-1.11 [-2.07, -0.15] -1.10 [-1.77, -0.43]		
breu, et al., 2010	68 23 10	88 10 10	1.0%	-1.08 [-2.03, -0.13]		
Chandra, et al., 2010 Pitanqui, et al., 2014 (26)	7 5.3 30 17.2 21.9 11	14.7 8.6 30 38.8 20.8 10	1.2%	-1.06 [-1.61, -0.52] -0.97 [-1.89, -0.05]		
'ilmaz et al., 2019 (27)	7.3 9.8 26	20 15.7 26	1.2%	-0.96 [-1.53, -0.38] -0.89 [-1.42, -0.36]		
Aminisaman et al., 2020 Suh, et al., 2015	26.6 5.4 30 18.7 7.46 24	31.2 4.8 30 30.7 17.67 23	1.2% 1.2%	-0.88 [-1.48, -0.28]		
Oncel, et al., 2002 (28) Elboim et al., 2020 (29)	24 13 25 41.7 19.2 23	39 20 25 61.2 25 18	1.2%	-0.88 [-1.46, -0.29] -0.87 [-1.52, -0.22]		
leighbours, et al., 1987 (30)	17.5 30.3 10	40.7 20.74 10	1.0%	-0.86 [-1.78, 0.07]		
Zakariaee et al., 2019 (31) Domaille & Reeves, 1997 (32)	31.8 20.4 40 30.33 8.14 31	47.5 16.5 40 47 28.14 29	1.2% 1.2%	-0.84 [-1.30, -0.38] -0.81 [-1.33, -0.28]	=	
Fiorelli, et al., 2012 (33)	39 8 23	45 7 23	1.2%	-0.78 [-1.39, -0.18]		
Mansuri, et al., 2019 (34) Bjersa, et al., 2015 (35)	26.67 22.57 15 10 13 15	45.33 26.15 15 23 21 13	1.1% 1.1%	-0.74 [-1.49, 0.00] -0.74 [-1.51, 0.04]		
.ikar et al. 2001 (36)	25.1 7.6 11	29.7 4.8 12	1.0%	-0.70 [-1.55, 0.14]		
/italii & Oleg, 2014 Varfield, et al., 1985 (37)	39.5 17 11 48.3 20.1 12	52.5 18.6 10 64.2 24.6 12	1.0%	-0.70 [-1.59, 0.19] -0.68 [-1.51, 0.14]		
Bilgili, et al., 2016	14.27 10.1 15	23.27 15.8 15	1.1%	-0.66 [-1.40, 0.08]		
ujii-Abe et al., 2019 (38) Shimoura, et al., 2019 (39)	22.1 12.8 11 5.1 8 25	30.3 11.2 11 11.4 10.9 25	1.0% 1.2%	-0.66 [-1.52, 0.21] -0.65 [-1.22, -0.08]		
Bjersa & Andersson, 2014	19.4 32.5 9	39.6 32 11	1.0%	-0.60 [-1.51, 0.30]	+	
Sezen, et al., 2017 (40) Liu, et al., 2017 (41)	36.9 7.2 43 48.2 17.7 22	42 10.1 44 55.8 12.6 22	1.2%	-0.58 [-1.00, -0.15] -0.49 [-1.09, 0.11]		
Grimmer, 1992 (42)	22 28 20	35 29 20	1.1%	-0.45 [-1.08, 0.18]		
Galli, et al., 2015 Enmoire, et al., 2011 (42)	21 16 37 18 18 15	29 22 37 25 18 15	1.2%	-0.41 [-0.87, 0.05]		
Ferreira, et al., 2011 (43) Rakel & Frantz, 2003 (44)	42 33.45 33	55 37.3 33	1.1% 1.2%	-0.38 [-1.10, 0.34] -0.36 [-0.85, 0.12]	- <b>T</b>	
Narke, et al., 2004 (45)	28.25 36.5 5	40.33 19.4 3	0.7%	-0.33 [-1.78, 1.12]	<u> </u>	
Hruby, et al., 2006 (46) Robinson, et al., 2001	35 28.8 48 38.2 31.24 10	43.7 30.6 49 47.92 36.37 13	1.2% 1.0%	-0.29 [-0.69, 0.11] -0.27 [-1.10, 0.56]		
Hamza, et al., 1999 (47)	25 23 25	31 25 25	1.2%	-0.25 [-0.80, 0.31]	_+	
Machin, et al., 1988 Moore & Shurman, 1997 (48)	13.47 13.72 15 40.58 27.55 24	16.29 13.65 15 44.81 30.67 24	1.1% 1.2%	-0.20 [-0.92, 0.52] -0.14 [-0.71, 0.42]		
Forster, et al., 1994 (49)	9.8 28.1 15	13.7 31.9 15	1.1%	-0.13 [-0.84, 0.59]	-+-	
Shimoji, et al., 2007 (50) Graff-Radford, et al., 1989 (51)	38 15 9 28.3 18.06 12	40 20 8 30.2 15.92 12	1.0% 1.1%	-0.11 [-1.06, 0.84] -0.11 [-0.91, 0.69]		
Yilmazer, et al., 2012 (52)	54.6 32.1 33	57.5 30.5 32	1.2%	-0.09 [-0.58, 0.40]	+	
Sahin, et al., 2011 Presser, et al., 2000 (53)	68.5 15.5 19 47 38.34 30	69.5 11.5 19 49 27.39 30	1.1% 1.2%	-0.07 [-0.71, 0.56] -0.06 [-0.57, 0.45]	±	
Ilhani, 2015 (54)	22.4 11.3 35	22.8 10.2 31	1.2%	-0.04 [-0.52, 0.45]	+	
Tucker, et al., 2015 (55) Do Silvo, et al., 2015 (56)	56 56 35	57 57 35 4 0 21	1.2%	-0.02 [-0.49, 0.45]	+	
Da Silva, et al., 2015 (56) Machado et al., 2019 (57)	1 0 21 47 25 22	4 0 21 46 22 22	1.2%	Not estimable 0.04 (-0.55, 0.63)	+	
Lee, et al., 2015	55.6 9.2 18	54.4 12.9 18	1.1%	0.10 [-0.55, 0.76]	±	
Atamaz, et al., 2012 Silva, et al., 2012 (58)	54.7 24.1 37 22.5 11.5 21	50.4 20.3 37 20 12.5 21	1.2% 1.2%	0.19 [-0.27, 0.65] 0.20 [-0.40, 0.81]	<del>—</del>	
Beckwée, et al., 2018	39.2 25.1 25	30.6 23.2 28	1.2%	0.35 [-0.19, 0.90]	+	
Siqueira et al., 2019 (59) Kofotolis, et al., 2008	2.92 6.6 13 22 4 23	0.7 1.6 14 20 4 21	1.1%	0.46 [-0.31, 1.22] 0.49 [-0.11, 1.09]	<u>+</u>	
Subtotal (95% CI)	1833	1811	88.8%	-1.00 [-1.19, -0.81]	•	
Heterogeneity: Tau <sup>#</sup> = 0.63; Chi <sup>#</sup> Test for overall effect: Z = 10.25 (	= 545.60, af = 81 (P < 0 P < 0.00001)	uudu1); I*= 85%				
Total (95% CI)	2426	2415	100.0%	-0.96 [-1.14, -0.78]	•	
Listeregeneity Teut - 0.64: Chill.	= 733.23, df = 90 (P < 0	00001); I# = 88%			-4 -2 0 2 4	_
est for overall effect: Z = 10.37 (	D = 0.000041				Favours TENS Favours Placebo	

Figure A4 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.

#### 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 A5). Std. Mean Difference

#### Forest Plot Study or Subgroup Mean St 2.4.1 Acute Pain

Study or Subgroup	TE Mean	ENS SD	Total	Plac	ebo SD T	etal	Weight	Std. Mean Difference IV, Random, 95% CI	Std. Mean Difference IV, Random, 95% Cl	
Study or Subgroup 2.4.1 Acute Pain	modif	эр	rvidi	moull	av 1	Juli	. rogut	w, runuotti, 95% Cl	rv, rvandulli, 93% Ci	
ipriano, et al., 2014	10	5	20	80	30	18	0.9%	-3.27 [-4.28, -2.27]		
ora, et al., 2006	33.3 49	16	39	82.6 1 77	14.3	34	1.1%	-3.20 [-3.91, -2.50]		
ertalanffy, et al., 2005 ikuda, et al., 2014 (1)	49 5.9	8 6.5	30 16		11 5.9	33 16	0.9%	-2.85 [-3.57, -2.14] -2.81 [-3.82, -1.80]		
nahoei, et al., 2017 (2)	49	25 7 18	30 30 29	97	5.9	30 30 33	1.1%	-2.61 (-3.311.91)		
Ahmed, et al., 2010 Barker, et al., 2006	49.3	7	30	66.1	6.9	30	1.1%	-2.39 [-3.06, -1.71] -2.26 [-2.91, -1.61]		
ang, et al., 2006 ang, et al., 2007	32.4 59	18	29	66.2 1 79	11.2	33	1.1% 1.1%	-2.26 [-2.91, -1.61] -2.20 [-2.83, -1.57]		
Ging, et al., 2008 (3) Gin, et al., 2008 (3)	9	10.7	30 20 50 21 23 54 30 28 48 25 15 23 15		22.7	33 20 50 21 21 54 30 27 50 25 15	1.1%	-2.15 [-2.95, -1.36]		
Gm, et al., 2012 (4)	19	12	50	48	15	50	1.2%	-2.12 [-2.61, -1.63]		
Baez-Suarez, et al., 2018 Desantana, et al., 2009 (5)	62 43 5	14	21	83 66.5 1	12	21	1.1%	-1.58 [-2.28, -0.88] -1.54 [-2.22, -0.86]		
esantana, et al., 2009 (5) aafarpour, et al., 2008	43	15.3 5	23	66.5 1 12	4.2	21	1.1%	-1.54 [-2.22, -0.86] -1.51 [-1.93, -1.08]	I	
analapour, et al., 2000 amer-Cuenca, et al., 2011 Sadala, et al., 2018	26.5	24.7	30	61.9 2 56.8 1	7.2 23.2 17.7	30	1.2%	-1.46 [-2.03, -0.88] -1.45 [-2.05, -0.86]		
Sadala, et al., 2018	29.3	19.5	28	56.8 1	17.7	27	1.2%	-1.45 [-2.05, -0.86]		
Park, et al., 2015 (6)	15	15	48	45	25 25	50	1.2%	-1.44 [-1.88, -0.99]		
Ordog, 1987 (7) Luchesa, et al., 2009 (8)	30.4 5	2.8 6	25	54.8 21 1	25	25	1.1% 1.1%	-1.35 [-1.97, -0.73] -1.33 [-2.13, -0.53]		
Cipriano, et al., 2008 (9)	20	7.4	23	30 58	7.4	22 15	1.1%	-1.33 [-1.980.68]		
Vahure, et al., 2017 (10)	36	21	15	58	12	15	1.1%	-1.25 [-2.04, -0.46] -1.14 [-1.57, -0.72]		
Kayman-Kose, et al., 2014 (11)	17.7	12.7	50 46 15 10 20 10	37.4	20.6	50 46 15	1.2%	-1.14 [-1.57, -0.72]		
ison, et al., 2017 (12) iu, et al., 1985 (13)	23.2 39.3	31.4 17.9	15	53.1 1 65.3 2	19.9 26.6	15	1.2% 1.1%	-1.13 [-1.57, -0.69] -1.12 [-1.89, -0.34]		
Cuschieri, et al., 1987 (14)	30 1	11.25	10	49 20	0.25	10	1.0%	-1.11 [-2.070.15]		
mmiler, et al., 2008 breu, et al., 2010	24	11.8 23	20	39 1	14.8 10	20 10	1.1%	-1.10 [-1.77, -0.43] -1.08 [-2.03, -0.13]		
Abreu, et al., 2010	68 7	23	10	88	10	10	1.0%	-1.08 [-2.03, -0.13]		
Chandra, et al., 2010 Pitangui et al., 2014 (15)		5.3 21.9	30 11 26	14.7 38.8 1	8.6 20.8	30 10 26	1.2%	-1.06 [-1.61, -0.52] -0.97 [-1.89, -0.05]		
ritangui, et al., 2014 (15) filmaz et al., 2019 (16)	7.3	9.8	26	20 1	15.7	26	1.2%	-0.96 [-1.53]-0.38]		
minisaman et al., 2020	26.6	5.4	30	31.2 39	4.8 20	30	1.2%	-0.89 [-1.42, -0.36] -0.88 [-1.46, -0.29]		
Oncel, et al., 2002 (17) Elboim et al., 2020 (18)	24 41.7	13 19.2	25	39 61.2	20 25	30 25 18	1.2%	-0.88 [-1.46, -0.29] -0.87 [-1.52, -0.22]		
⊏noom et al., 2020 (18) Zakariaee et al., 2019 (19)	41.7	19.2	23 40	47.5 1	25 16.5	18	1.1%	-0.87 [-1.52, -0.22] -0.84 [-1.30, -0.38]		
Zakariaee et al., 2019 (19) Domaille & Reeves, 1997 (20)	30.33	20.4 8.14	30 25 23 40 31 23 11 12 11 15 9	47.5 1 47 28 45	16.5 3.14 7	40 29 23 12 12 11 13	1.2% 1.2%	-0.84 [-1.30, -0.38] -0.81 [-1.33, -0.28]		
Fiorelli, et al., 2012 (21)	39	8	23	45	7	23	1.2%	-0.78 [-1.390.18]		
Likar et al. 2001 (22) Warfield, et al., 1985 (23)	25.1 48.3	7.6 20.1	11	29.7	4.8 24.6	12	1.0%	-0.70 (-1.55, 0.14) -0.68 (-1.51, 0.14)		
/vartield, et al., 1985 (23) Fujii-Abe et al., 2019 (24)	48.3	20.1	12	20.2 1	24.6 11.2	12	1.0%	-0.68 [-1.51, 0.14]		
Biersa, et al., 2015	13	16	15	26	24	13	1.1%	-0.66 [-1.52, 0.21] -0.63 [-1.39, 0.14]		
Bjersa & Andersson, 2014	19.4	32.5	9	39.6	32	11	1.0%	-0.60[-1.51_0.30]		
Sezen, et al., 2017 (25) Galli, et al., 2015	36.9 21	7.2 16	43 37 15 33 48	42 1 29	10.1	11 44 37 15	1.2% 1.2%	-0.58 [-1.00, -0.15] -0.41 [-0.87, 0.05]		
Galli, et al., 2015 Ferreira, et al., 2011 (26)	18	16 18	37	29	22 18	37	1.2%	-0.38 [-1.10, 0.34]		
Rakel & Frantz, 2003 (27) Hruby, et al., 2006 (28)	42 3 35	33.45 28.8	33	25 55 3 43.7 3	37.3	33 49	1.2%	-0.36 [-0.85, 0.12] -0.29 [-0.69, 0.11]		
Hruby, et al., 2006 (28)	35	28.8	48	43.7 3	30.6	49	1.2%	-0.29 [-0.69, 0.11]		
Robinson, et al., 2001	38.2 3	31.24	10	47.92 36	6.37	13	1.0%	-0.27 [-1.10, 0.56]		
Hamza, et al., 1999 (29) Cuschieri, et al., 1985 (30)	25 25	23 21.8	10 25 53 15 33	31 28 2	25 21.8	13 25 53 15 32	1.2% 1.3%	-0.25 [-0.80, 0.31] -0.14 [-0.52, 0.24]		
Forster, et al., 1994 (31)	9.8	28.1 32.1	15	13.7 3	31.9 30.5	15	1.1%	-0.13 [-0.84, 0.59]		
Yilmazer, et al., 2012 (32) Thomas, et al., 1988 (33)	54.6	32.1	33	57.5 3	30.5	32	1.2%	-0.09 (-0.58, 0.40)	-	
Thomas, et al., 1988 (33)	33 47 3	31.1	131	35 3 49 21	33.8	144	1.3%	-0.06 [-0.30, 0.18]	+	
Presser, et al., 2000 (34) Tucker, et al., 2015 (35)	47 : 56	38.34 56	30 35 21 18	49 21	7.39 57	30 35	1.2%	-0.06 [-0.57, 0.45] -0.02 [-0.49, 0.45]		
Da Silva, et al., 2015 (36)	1	0	21	4	0	21	1.2.10	Not estimable		
Lee, et al., 2015 Silva, et al., 2012 (37)	55.6	9.2	18	54.4 1	12.9	18	1.1%	0.10.60.55.0.761		
Silva, et al., 2012 (37)	22.5	11.5	21	20 1	12.5	21	1.2%	0.20 (-0.40, 0.81)	+	
Beckwée, et al., 2018 Kayman-Kose, et al., 2014 (38)	39.2 13.5	25.1 5.8	25 50	30.6 2 7.8	23.2 7	28 50	1.2%	0.35 (-0.19, 0.90) 0.88 (0.47, 1.29)	Τ	
Subtotal (95% CI)			1667		1	681	64.6%	-1.02 [-1.24, -0.79]	♦	
Heterogeneity: Tau <sup>a</sup> = 0.64; Chi <sup>a</sup> = Test for overall effect: Z = 8.88 (P	491.98, 0 < 0.00001	df = 5ช  )	(P < U.I	00001); P	= 89%					
		· ·								
2.4.2 Chronic Pain Barbarisi, et al., 2010	25.11	0.92	9	39 1	1.19	8	0.1%	-12.50 [-17.39, -7.61]		
3arbarisi, et al., 2010 Hokenek et al., 2019 (39)		0.92	9 39		1.19 18.7	8 39	0.1%	-12.50 [-17.39, -7.61] • -3.11 [-3.78, -2.44]		
auretti, et al., 2015	20	10	20	70	20	20	1.0%	-3.10 [-4.05, -2.15]		
.auretti, et al., 2015 Ekim et al., 2008 (40)	47.2	5.6	20 10	65.3	6.3	20 9	0.8%	-3.10 [-4.05, -2.15] -2.91 [-4.29, -1.54]		
Dailey, et al., 2013 (41)	40	4	41	47	4	41 30	1.2%	-1.73 [-2.241.22]	<u> </u>	
(Ibar et al., 2020 (42) Thang et al., 2020a (43)	21.2 17	12.2 3	41 31 10		19.6 12.6	30	1.2% 0.9%	-1.60 [-2.18, -1.02] -1.46 [-2.48, -0.45]		
De Oliverira et al., 2012 (44)	30	3 16.4	5	54 1	13.6	10 5 26	0.9%	-1.44 [-2.92, 0.04]		
De Oliverira et al., 2012 (44) 31, et al., 2015	21.4	9.1	5 26	38.7 1	14.5	26	1.2%	-1.44 [-2.92, 0.04] -1.41 [-2.02, -0.80]		
Topuz. et al., 2004	37.3	16.2	15	59.1 1	13.7	12	1.0%	-1.40 [-2.250.54]		
celik, et al., 2013 auretti, et al., 2013 (45)	38.8 60	25 10	15 17 13	67.7 1 80	14.2 20	16 10	1.1% 1.0%	-1.38 [-2.14, -0.61] -1.28 [-2.19, -0.36]		
Rub et al. 2015	60 18.7	10 7.46	24	80 30.7 17	20 7.67	23	1.0%	-1.20 (-2.19, -0.36) -0.88 (-1.48, -0.28)	<u> </u>	
veighbours, et al., 1987 (46) /italii & Oleg, 2014	17.5	30.3	24 10 11 15 25	40.7 20	0.74	23 10	1.0%	-0.88 [-1.48, -0.28] -0.86 [-1.78, 0.07]		
fitalii & Oleg, 2014	39.5	17	11	52.5 1	18.6	10	1.0%	-0.70[-1.59_0.19]		
Bilgili et al. 2016	14.27	10.1	15	23.27 1	15.8	15 25	1.1%	-0.66 [-1.40, 0.08] -0.65 [-1.22, -0.08]		
3himoura, et al., 2019 (47) .iu, et al., 2017 (48)	5.1 48.2	8 17.7	25	11.4 1 55.8 1	10.9 12.6	25 22	1.2%	-0.65 [-1.22, -0.08] -0.49 [-1.09, 0.11]		
3rimmer, 1992 (49)	40.2	28	20	35	29	20	1.1%	-0.45 [-1.08, 0.18]		
Grimmer, 1992 (49) Dailey et al., 2020 (50)	22 46	28 20	103	53 1	19.9	20 99	1.1% 1.3%	-0.45 [-1.08, 0.18] -0.35 [-0.63, -0.07]		
Varke, et al., 2004 (51)	28.25	36.5	22 20 103 5	40.33 1	19.4	3	0.7%	-0.33 [-1.78, 1.12]		
fachin, et al., 1988 foore & Shurman, 1997 (52)	13.47 1 40.58 2	13.72 27.55	15		3.65	15 24	1.1%	-0.20 (-0.92, 0.52) -0.14 (-0.71, 0.42)		
Moore & Shurman, 1997 (52) Shimoji et al. 2007 (52)	40.58 1	27.55	24	44.81 3L 40	0.67 20	24	1.2%	-0.14 [-0.71, 0.42] -0.11 [-1.06, 0.84]		
Shimoji, et al., 2007 (53) Graff-Radford, et al., 1989 (54)	28.3 1	18.06	9 12 19	30.2 15	5.92	12	1.1%	-0.11 [-0.91, 0.69]		
Bahin, et al., 2011	68.5	15.5	19	69.5 1	11.5	19	1.1%	-0.07 [-0.71, 0.56]		
lhani, 2015 (55)	22.4 80	11.3 20	35	22.8 1 80	10.2	31 54	1.2%	-0.04 [-0.52, 0.45]	+	
Bono, et al., 2015 Machado et al., 2019 (56)	80 47	20 25	54	80 46	20 22	54 22	1.3% 1.2%	0.00 (+0.38, 0.38) 0.04 (+0.55, 0.63)	土	
wasmauu eran, 2019 (56) Mamaz, et al., 2012	47 54.7	20	35 54 22 37 23	+0 50.4 3	22	22 37	1.2%	0.19 (-0.27, 0.65)		
Atamaz, et al., 2012 Kofotolis, et al., 2008	54.7 22	24.1 4	23	50.4 2 20	4	37 21	1.2%	0.49 [-0.11, 1.09] -0.87 [-1.19, -0.55]	. +	
Subtotal (95% CI)			721			696	32.3%	-0.87 [-1.19, -0.55]	◆	
Heterogeneity: Tau# = 0.67; Chi# = Test for overall effect: Z = 5.28 (P	222.02, 0	df = 30	(P < 0.1	00001); P	= 86%					
	- 0.00001	v								
.4.3 Not Reported										
Cheing & Luk, 2005 Appound at al., 2010 (67)	17	17	10	46	20	9	0.9%	-1.50 [-2.55, -0.45]		
Mansuri, et al., 2019 (57) Siqueira et al., 2019 (58)	26.67 2 2.92	22.57 6.6	15	45.33 26 0.7	1.6	15 14	1.1% 1.1%	-0.74 [-1.49, 0.00] 0.46 [-0.31, 1.22]		
Subtotal (95% CI)			38			38	3.1%	-0.55 [-1.63, 0.52]	-	
Heterogeneity: Tau <sup>a</sup> = 0.72; Chi <sup>a</sup> = Test for overall effect: Z = 1.01 (P	9.83, df=	= 2 (P =	= 0.007)	; I <sup>2</sup> = 80%						
	= 0.31)									
Fotal (95% CI)			2426		2	415	100.0%	-0.96 [-1.14, -0.77]	•	
leterogeneity: Tau <sup>2</sup> = 0.64; Chi <sup>2</sup> =	733.32, 0	df = 90	(P < 0.	00001); P	= 88%				-4 -2 0 2	4
est for overall effect: Z = 10.36 (P est for subgroup differences: Ch	< 0.0000	J1) df= 2 :	(D = 0 -	7) 8-0~					Favours TENS Favours Placebo	
sciol subgroup differences: Ch	i = 1.12,	ai≓∠i	(r = 0.5		,					

Std. Mean Difference

Figure A5 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 – 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 postoperative pain (36 samples, 1788, P < 0.00001, I<sup>2</sup> = 80%), procedural pain (10 samples, 682 participants, P = 0.001, I<sup>2</sup> = 88%), labour pain (4 sample, 397 participants, P = 0.05, I<sup>2</sup> = 95%) and fibromyalgia (3 samples, 307 participants, P = 0.04, I<sup>2</sup> = 91%). There were no statistically significant differences for back pain (9 samples, 364 participants, P = 0.06, I<sup>2</sup> = 89%) or migraine (3 samples, 230 participants, P = 0.19, I<sup>2</sup> = 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<sup>2</sup> = 202.12, df = 23 (P < 0.00001); Figure A6), suggesting that the pain condition categorised according to

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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<sup>2</sup> = 1.25, df = 5, P =0.94; figure not shown), 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, as individual trial results are inconsistent.

Forest Plot

ert, ..25, df. .ng to that s .h to placebo. T. ., as individual trial

tudy or Subgroup 5.1 Post Operative pain ipriano, stal., 2014 (1)	10 5 20 80 30	otal Weight	Std. Mean Difference IV, Random, 95% Cl -3.27 [-4.28, -2.27]	Std. Mean Difference IV, Random, 95% Cl	
5.1 Pead Operative pain (strains, of str., 2014 (2) (strains, of st., 2014 (2) (strains, et st., 2010 (4) examinar, et st., 2010 (4) examinar, et st., 2010 (5) (strains, et st., 2010 (6) (strains, et st., 2010 (6) (strains, et st., 2010 (7) symmatri-loops, et st., 2000 (6) (strains, et st., 2010 (7) (strains, et st., 2010 (13) (strains, et st., 2010	$\begin{array}{cccccccccccccccccccccccccccccccccccc$	16         0.9%           30         1.1%           20         1.1%           21         1.1%           54         1.2%           55         1.2%           56         1.2%           57         1.1%           50         1.2%           50         1.2%           50         1.2%           30         1.2%           30         1.2%           30         1.2%           30         1.2%           30         1.2%           30         1.2%           40         1.2%	$\begin{array}{c} -3.27 [+38,-227] \\ -2.01 [-38,2,-1.01] \\ -2.01 [-38,2,-1.01] \\ -2.05 [+28,-1.38] \\ -1.55 [+28,-1.38] \\ -1.55 [+138,-0.93] \\ -1.55 [+138,-0.93] \\ -1.55 [+138,-0.93] \\ -1.33 [+23,-0.53] \\ -1.33 [+130,-0.63] \\ -1.33 [+130,-0.63] \\ -1.35 [+130,-0.64] \\ -1.45 [+154,-0.52] \\ -0.97 [+152,-0.72] \\ -0.97 [+152,-0.33] \\ -0.07 [+152,-0.23] \\ -0.07 [+152,-0.23] \\ \end{array}$		
umathic Reverse, 1997 (19) umathic Reverse, 1997 (19) (1974, 241, 2015 (21) (1974, 241, 2015 (21) (1974, 241, 2015 (22) (1974, 241, 2015 (22) (1974, 241, 2015 (22) (1974, 2015 (22) (1974, 2015 (22) (1974, 2015 (22) (1974, 2015 (22) (1976, 2015 (23) (1976, 2015 (23) (1976, 2015 (23) (1976, 2015 (25) (1976, 2015 (25) (1976, 2015 (25) (1977, 2015 (25) (19	1         1.0         2.0         2.1         2.0         2.1	$\begin{array}{cccccccccccccccccccccccccccccccccccc$	$\begin{array}{c} 0.811+1.33,-0.28\\ 0.78+1.33,-0.18\\ 0.78+1.35,0.018\\ 0.70+1.55,0.14\\ 0.98+1.55,0.14\\ 0.98+1.55,0.14\\ 0.98+1.55,0.21\\ 0.98+1.55,0.21\\ 0.98+1.55,0.21\\ 0.98+1.55,0.21\\ 0.98+1.55,0.21\\ 0.98+1.0,0.16\\ 0.98+1.0,0.16\\ 0.98+1.0,0.34\\ 0.98+0.85,0.12\\ 0.98+0.85,0.12\\ 0.98+0.85,0.12\\ 0.98+0.85,0.12\\ 0.98+0.85,0.12\\ 0.98+0.85,0.12\\ 0.98+0.85,0.12\\ 0.98+0.85,0.12\\ 0.98+0.85,0.12\\ 0.98+0.85,0.12\\ 0.98+0.85,0.12\\ 0.98+0.85,0.12\\ 0.98+0.85,0.12\\ 0.98+0.85,0.12\\ 0.98+0.85,0.12\\ 0.98+0.05\\ 0$		
aclovda, et al., 2018 (36) ubtotal (95% CB) eterogeneity: Tau <sup>2</sup> = 0.36; Ch <sup>2</sup> = est for overall effect Z = 7.87 (P +	39.2 25.1 25 30.8 23.2 897 168.63, df= 34 (P < 0.00001), P= 00% 0.00001)	28 1.2% 891 39.2%	0.35[-0.19]0.90 0.92[-1.15, 0.69]	•	
adala, et al., 2018 (35) ison, et al., 2017 (45) iminisama et al., 2020 (41) ruby, et al., 2006 (42) obinosor, et al., 2001 (43) imazer, et al., 2001 (44) imazer, et al., 2000 (45) ucker, et al., 2015 (46) ucker, et al., 2015 (46) ucker, et al., 2015 (46)	28.3         19.5         28         58.8         17.7           23.2         31.4         46         53.1         19.9           26.6         6.4         30         31.2         4.8           35         28.8         48         43.7         30.6           36.2         31.24         10         47.92         36.37           54.6         32.1         33         57.5         30.5           47         38.34         30         40         27.53	50 1.2% 30 1.2% 46 1.2% 46 1.2% 48 1.2% 48 1.2% 30 1.2% 30 1.2% 31 1.0% 32 1.2% 30 1.2% 34 1.2%	$\begin{array}{c} -2.12 \left[ 2.81 , -1.63 \right] \\ -1.46 \left[ 2.20 , -0.83 \right] \\ -1.45 \left[ 2.20 , -0.81 \right] \\ -1.13 \left[ 1.57 , -0.01 \right] \\ -0.39 \left[ 1.42 , -0.31 \right] \\ -0.29 \left[ -0.09 , 0.31 \right] \\ -0.29 \left[ -0.09 , 0.31 \right] \\ -0.09 \left[ 0.45 , 0.40 \right] \\ -0.09 \left[ 0.45 , 0.40 \right] \\ -0.02 \left[ 0.40 , 0.45 \right] \\ -0.28 \left[ -0.24 , 0.431 \right] \\ -0.28 \left[ -0.24 , 0.431 \right] \\ \end{array}$	• • •	
5.3 Back pain stalarty, et al., 2005 (47) bits et al., 2020 (48) post, et al., 2020 (48) post, et al., 2020 (46) stahs, et al., 2004 (50) stahs, et al., 2004 (51) bits, et al., 2020 (53) bits, et al., 2020 (55) ubstal (55) ethorogenety, Tau" = 1.03, Ch" = stfor coveral feet 12 = 1.90 (PT 2005 (25) bits (2005 (25)) bits (	75.72 df = 8 dP < 0.000011 P = 8P%	33 1.1% 30 1.2% 12 1.0% 3 0.7% 15 1.1% 24 1.2% 8 1.0% 31 1.2% 4177 9.6%	$\begin{array}{c} -2.85\left[3.57,-2.14\right]\\ -1.60\left[2.10,-1.02\right]\\ -1.40\left[2.25,-0.54\right]\\ -0.23\left[1.73,112\right]\\ -0.21\left[402,25,0.52\right]\\ -0.14\left[4.10,27\right],0.42\right]\\ -0.14\left[4.10,0.84\right]\\ -0.04\left[4.022,0.45\right]\\ -0.04\left[4.022,0.45\right]\\ -0.04\left[4.022,0.45\right]\\ -0.04\left[4.022,0.45\right]\\ -0.04\left[4.022,0.45\right]\\ -0.04\left[4.022,0.45\right]\\ -0.04\left[4.022,0.45\right]\\ -0.04\left[4.022,0.45\right]\\ -0.04\left[4.022,0.45\right]\\ -0.02\left[4.04,0.02\right]\\ -$		
5.4 Dysmenorrhea auretti, et al., 2015 e Oliverna et al., 2012 (56) eightours, et al., 1987 (57) achado et al., 2019 (58) utototal (955 C0)	20 10 20 70 20 30 16.4 5 54 13.6 17.5 30.3 10 40.7 20.74 47 25 22 46 22 57 31.01, at = 3.6 < 0.000011; #= 90%	20 1.0% 5 0.7% 10 1.0% 22 1.2% 57 3.8%	-3.10 [-4.05, -2.15] -1.44 [-2.02, 0.04] -0.08 [-1.70, 0.07] 0.08 [-1.70, 0.07] 0.08 [-0.55, 0.63] -1.34 [-2.79, 0.17]		
5.5 Labour Pain hahoei, et al., 2017 (58) aec-Suarez, et al., 2018 breu, et al., 2010 homas, et al., 1988 (60) ueteral (465, Ch		30 1.1% 21 1.1% 10 1.0% 144 1.3% 205 4.5%	-2.81 [-3.31, -1.91] -1.58 [-2.23, -0.03] -1.08 [-2.03, -0.13] -0.08 [-0.30, 0.18] -1.31 [-2.62, -0.01]		
5.6 Fibromyskipia S.6 Fibromyskipia olifey, et al., 2013 (51) auretti, et al., 2013 (52) alley et al., 2020 (53) abbotal (55% CD) abstrageneity. Trai= 0.72; Chi <sup>2</sup> = est for overall effect Z = 2.10 (P)		41 1.2% 10 1.0% 99 1.3% 150 3.5%	-1.73 [-2.24, -1.22] -1.28 [-2.19, -0.38] -0.35 [-0.63, -0.07] -1.09 [-2.11, -0.07]	-	
5.7 Headache Migraine loisnek: et al., 2019 (54) lu, et al., 2017 (55) ono, et al., 2015 luktotal (15% Ct) eterogeneity: Tau <sup>a</sup> = 2.33, Ch <sup>a</sup> = est for overall effect Z = 1.32 (P	22 12.49 38 72 18.7 48.2 17.7 22 55.8 12.6 80 20 54 80 20 115 83.61, at = 2 dP < 0.000011; P = 97% 0.19)	39 1.1% 22 1.2% 54 1.3% 115 3.5%	-3.11 [-3.78,-2.44] -0.49 [-1.09,0.11] 0.00 [-0.38,0.38] -1.18 [-2.94, 0.57]		
eterogeneity: Tau*= 0.15; Chi*= est for overall effect Z = 1.00 (P = 5.9 Solval cord interv	5.1 8 25 11.4 10.9 22 28 20 35 29 54.7 24.1 37 50.4 20.3 82 5.70, df = 2 (P = 0.06), P = 65% 0.32)	25 1.2% 20 1.1% 37 1.2% 82 3.5%	-0.65 [-1.22, -0.08] -0.45 [-1.08, 0.18] 0.19 [-0.27, 0.65] -0.27 [-0.81, 0.26]	•	
i, et al., 2015 (66) enix, et al., 2013 (60) maris (04), 2014 (70) ubtotal (85% C0) etenogeneity: Tau" = 0.00; Chi" = est for overall effect Z = 5.76 (P +	1.82, df = 2 (P = 0.40); P = 0% 0.00001)	26 1.2% 16 1.1% 10 1.0% 52 3.2%	-1.41 [-2.02,-0.80] -1.38 [-2.14,-0.61] -0.70 [-1.59,0.19] -1.24 [-1.66,-0.92]	•	
ansuri, et al., 2019 (71) iqueira et al., 2019 (72) ubtotal (95% C0) eterogeneity: Tau*= 0.57; Chi*= est for overall effect Z = 0.25 (P =	26.67 22.57 15 45.33 26.15 2.92 6.6 13 0.7 1.6	15 1.1% 14 1.1% 29 2.2%	-0.74 [-1.49, 0.00] 0.46 [-0.31, 1.23] -0.15 [-1.32, 1.03]	-	
eterogeneity: Tau" = 0.00; Chi" =	0.00, df = 1 (P = 0.94); P = 0%	12 1.1% 19 1.1% 31 2.2%	-0.11 [-0.91, 0.69] -0.07 [-0.71, 0.56] -0.09 [-0.58, 0.41]	•	
est for overall effect Z = 6.85 (P +		33 1.1% 33 1.1%	-2.26 [-2.91, -1.61] -2.26 [-2.91, -1.61]	•	
5.14 Complex regional pain syn ligil, et al., 2016 ubtotal (85% CB) eterogeneity: Not applicable est for overall effect. Z = 1.75 (P =	14.27 10.1 15 23.27 15.8 15			•	
est for overall effect Z = 2.28 (P =	30 11.25 10 40 20.25 10 0.02)	10 1.0% 10 1.0%	-1.11 [-2.07, -0.15] -1.11 [-2.07, -0.15]	•	
5.16 Fractured rills ncel, et al., 2002 (76) ubtotal (95% CI) eterogeneity: Not applicable est for overall effect Z = 2.95 (P =		25 1.2% 25 1.2%	-0.88 [-1.46, -0.29] -0.88 [-1.46, -0.29]	•	
5.17 Neuropathic pain in the har heing & Luk, 2005 ubtotal (95% CI) intercogeneity: Not applicable est for overall effect Z = 2.81 (P =	17 17 10 45 20 10	8 0.9% 9 0.9%	-1.50 [-2.55, -0.45] -1.50 [-2.55, -0.45]	-	
eterogeneity: Not applicable est for overall effect $Z = 5.01$ (P $\leq$	25.11 0.92 9 38 1.19 9	8 0.1% 8 0.1%	-12.50 [-17.39, -7.81] • -12.50 [-17.39, -7.61] •		
eterogeneity: Not applicable est for overall effect Z = 4.19 (P +	13.5 5.8 50 7.8 7 50	50 1.2% 50 1.2%	0.88 [0.47, 1.29] 0.08 [0.47, 1.29]	Ť	
5.20 Post Stroke Pain	47.2 5.8 10 65.3 6.3 10	9 0.8% 9 0.8%	-2.91 [4.29, -1.54] -2.91 [-4.28, -1.54]	•	
5.21 Post traumatic hip pain du ang, et al., 2007 ubtotal (95% CD) eterogeneity: Not applicable et for coveral effect Z = 6.00 /P =	ring emergency transport 59 6 30 79 11 30 0.00001)			<b>→</b>	
5.22 Renal colic in Emergency o lora, et al., 2006 lutotata (955 CI) eterogeneity. Not applicable est for overall effect Z = 8.91 (P	care 33.3 16 39 82.6 14.3 39	34 1.1% 34 1.1%	-3.20 [-3.91, -2.50] -3.20 [-3.91, -2.50]	•	
5.23 Temporomandibular joint p hang et al., 2020a (76) ubtotal (95% C0) eterogeneity: Not applicable est for overall effect Z = 2.83 (P =	nain 17 3 10 31 12.6 10			•	
5.24 Various acute traumatic p rdog, 1987 (80) ubtotal (95% CD) eterogeneity: Not applicable est for overall effect Z = 4.27 PP «	ains - sprains, fractures, lacerations 30.4 2.8 25 54.8 25 25 0.0001)	25 1.1% 25 1.1%	-1.35 [-1.97, -0.73] -1.35 [-1.97, -0.73]	•	
5.25 Various musculoskeletal uh, et al., 2015 (01) ubtotal (95% C0) eterogeneity: Not applicable est for overall effect Z = 2.86 (P =	18.7 7.46 24 30.7 17.67 24 0.004)	23 1.2% 23 1.2%	-0.88 [-1.48, -0.28] -0.88 [-1.48, -0.28]	•	
otal (95% CI) eterogeneity: Tau <sup>2</sup> = 0.84; Chi <sup>2</sup> = est for overall effect Z = 10.37 (P	733.23, df= 90 (P < 0.00001); P= 88%	415 100.0% 8.8%	-0.96 [-1.14, -0.78]	Favours TENS Favours Placeb	

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Figure A6 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.

#### Plausibility Pain Characteristics - subgroup findings

The subgroup analyses on pain characteristics provides support to claims that TENS is beneficial for any type of pain. 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 <sup>102</sup>.

## 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).

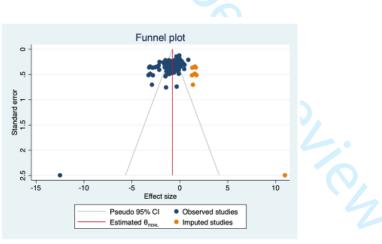


Figure A7 Funnel plot of TENS versus placebo comparison with trim and fill analysis. Actual results displayed in blue. Results corrected for the possibility of a publication bias displayed in orange.

There were two RCTs that had extractable data with a total of 118 participants receiving TENS and 114 receiving placebo <sup>89,103</sup>. It was not possible to conduct an analysis of the proportion of participant-reported pain relief of  $\geq$ 30% expressed as frequency (dichotomous) data because of insufficient data. Nonetheless, the RCT by <sup>89</sup> 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.

## 

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 <sup>104,105</sup>. At the last during TENS or the first post-TENS intervention measurement point, there were 106/241 participants that reported pain relief of  $\geq$ 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 A8). 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	pl	lot

<i>FULEST μΙΟ</i> Γ							
	TENS	s	Place	bo		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
Neighbours, et al., 1987 (1)	8	10	1	10	3.6%	8.00 [1.21, 52.69]	
Amer-Cuenca, et al., 2011 (2)	17	30	3	30	10.3%	5.67 [1.85, 17.34]	
Buchmuller, et al., 2012 (3)	26	104	7	104	20.6%	3.71 [1.69, 8.18]	<b>→</b>
Hansson & Ekblom, 1983 (4)	7	22	2	20	6.1%	3.18 [0.75, 13.57]	
Roche, et al., 1985 (5)	21	28	2	8	8.6%	3.00 [0.89, 10.15]	
Ekblom & Hansson, 1987 (6)	3	11	1	10	2.9%	2.73 [0.34, 22.16]	
Smith, et al., 1983 (7)	10	15	4	15	15.4%	2.50 [1.00, 6.23]	
Lewers, et al., 1989 (8)	8	10	4	11	18.2%	2.20 [0.95, 5.10]	
Langley, et al., 1984 (9)	6	11	4	11	14.2%	1.50 [0.58, 3.88]	
Total (95% CI)		241		219	100.0%	2.89 [2.02, 4.13]	◆
Total events	106		28				
Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup>	²= 5.66, d	lf = 8 (F	e = 0.69);	l <sup>2</sup> = 0%			
Test for overall effect: Z = 5.80 (	P < 0.000	01)					0.01 0.1 1 10 100 Favours Placebo Favours TENS

Figure A8 Forest plot of comparison TENS versus placebo. Outcome: <a>>50%</a> 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 <sup>106</sup>.

#### 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 A9), and substantial heterogeneity (I<sup>2</sup> = 76%). There was insufficient data to undertake subgroup analyses to explore the effect of methodological nor clinical characteristics on outcome.

#### Forest plot

		TENS		No Treatment Control			9	Std. Mean Difference	Std. Mean Difference	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% Cl	IV, Random, 95% Cl	
Keskin, et al., 2012 (1)	40	16	20	70	16	21	8.8%	-1.84 [-2.58, -1.10]	_ <b>-</b>	
Pitangui, et al., 2012 (2)	13.6	15.3	20	41	21.8	20	9.1%	-1.43 [-2.13, -0.72]	_ <b>—</b>	
Sadala, et al., 2018 (3)	29.3	19.5	28	56.3	18.4	28	10.1%	-1.40 [-1.99, -0.82]		
Amer-Cuenca, et al., 2011 (4)	26.5	24.7	30	54.7	30.1	30	10.6%	-1.01 [-1.55, -0.47]		
Farahani, et al., 2014 (5)	45.1	13.5	15	56.7	11.7	15	8.6%	-0.89 [-1.65, -0.14]	_ <b></b>	
De Angelis, et al., 2003 (6)	37.1	20.6	71	50.7	20.3	71	12.4%	-0.66 [-1.00, -0.32]	-	
De Sousa, et al., 2014 (7)	35.5	17.8	16	48.1	23.7	16	9.0%	-0.59 [-1.30, 0.12]		
Pietrosimone, et al., 2009 (8)	11.65	16.71	10	20.96	18.44	12	7.8%	-0.51 [-1.36, 0.35]	+	
Lee, et al., 2019 (9)	19	17	40	24	23	40	11.5%	-0.24 [-0.68, 0.20]		
Hruby, et al., 2006 (10)	35	28.8	48	34.4	30.5	51	11.9%	0.02 [-0.37, 0.41]	+	
Total (95% CI)			298			304	100.0%	-0.82 [-1.18, -0.46]	◆	
Heterogeneity: Tau <sup>2</sup> = 0.24; Chi	<sup>2</sup> = 37.38	, df = 9	(P < 0.0	001); I <sup>2</sup> =	76%			_		
Test for overall effect: Z = 4.46 (									-4 -2 U 2 4 Favours TENS Favours No Treatment	

Figure A9 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. 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.

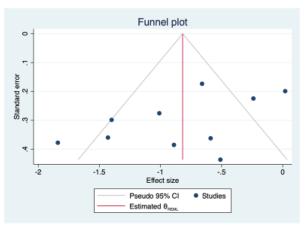


Figure A10 Funnel plot of TENS versus no treatment comparison.

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

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It was not possible to conduct an analysis of the proportion of participant-reported pain relief of  $\geq$ 50% expressed as frequency (dichotomous) data because of insufficient data (There was only one RCT with extractable data; <sup>87</sup>.

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# **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 <sup>79,81,98,107-111</sup>. 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 <sup>79,81,84,98,109</sup>. 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 A11). 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. iez oni

# Forest plot

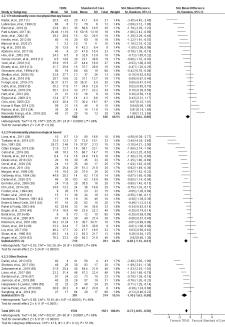


Figure A11 Forest plot of comparison TENS versus standard of care. Outcome: pain intensity expressed as mean (continuous) data. Subgroup analysis comparing TENS either alone or when added to exercise/physiotherapy based interventions, pharmacologically based interventions, and SoC that was categorised as other/unclear.

# Analysis of publication bias – TENS vs SoC

We visually inspected funnel plots to explore the likelihood of reporting bias. 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).

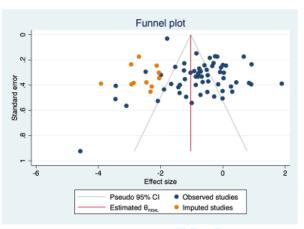


Figure A12 Funnel plot of TENS versus standard of care comparison with trim and fill analysis. Actual results displayed in blue. Results corrected for the possibility of a publication bias displayed in orange.

The finding that 11 trials might be missing to left of mean might be due to ccontamination by other 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 <sup>112</sup> <sup>113</sup>

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There were two RCTs that collected dichotomous data. The RCT by <sup>89</sup> 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 <sup>26</sup> 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  $\geq$ 30% reduction). Hence, it was not possible to conduct an analysis of the proportion of participant-reported pain relief of  $\geq$ 30% expressed as frequency (dichotomous) data because of insufficient data.

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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  $\geq$ 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 <sup>68,109,114,115</sup>. 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 <sup>68,104,109,115-122</sup>.

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 analysis 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 A13).

Forest plot

Test for overall effect Z = 0.45 (P = 0.65) 5.2.3 Ultrasound Hazneci 2005 (20) 45.	3         21.1         40         62.3         30           10         16         20         50         3           15         32.14         46         35.22         46.2           18         15         29         33         5           6         13.2         24         25.6         11           13         12         20         15         1           6         10.8         34         15.9         15.9	2 21 1 30 9 15 9 9 9 8 215 7 15 9 9 9 8 31 15 32 276 276 276 276 130 20 20 21 21 21 21 21 21 21 21 21 21		$\begin{array}{c} -1.41 \left[-2.10, -0.72\right]\\ -0.67 \left[-1.18, -0.15\right]\\ -0.34 \left\{-0.37, 0.28\right]\\ -0.23 \left\{-0.74, 0.28\right]\\ -0.22 \left\{-0.34, 0.50\right]\\ -0.22 \left\{-0.34, 0.50\right]\\ -0.17 \left\{-0.71, 0.36\right]\\ -0.17 \left\{-0.71, 0.36\right]\\ -0.12 \left\{-0.81, 0.58\right]\\ 0.11 \left\{-0.82, 1.03\right]\\ -0.9 \left[0.32, 0.67\right]\\ -0.98 \left[0.47, 1.51\right]\\ -2.75 \left[1.83, 0.63\right]\\ -0.34 \left[-0.28, 0.97\right]\end{array}$			
52 / Planniaccongical Semializative, 142, 2017 (1.3) 47, Menanice, 441, 2009 (1.5) 47, Kinger, 441, 2009 (1.5) 47, Kinger, 441, 2019 (1.6) 42, Menali 441, 2014 (1.7) 44, Anger, 441, 2010 (1.6) 42, Menali 441, 2014 (1.7) 44, Menali 441, 2014 (1.7) 44, Menali 441, 2014 (1.7) 45, Menali 441	3         21.1         40         62.3         30           10         16         20         50         3           15         32.14         46         35.22         46.2           18         15         29         33         5           6         13.2         24         25.6         11           13         12         20         15         1           6         10.8         34         15.9         15.9	.2 40 32 19 26 6 21 30 .6 24			-		
Hazneci 2005 (20) 45.		10 20 5 39 178	1.5% 1.4% 1.5% 1.4% 1.4% 1.4% 9.7%	$\begin{array}{c} -0.57\left[+1.02,-0.12\right]\\ -0.39\left[+1.02,0.24\right]\\ -0.30\left[+1.23,0.82\right]\\ -0.019\left[+0.84,0.40\right]\\ -0.019\left[+0.84,0.40\right]\\ 0.71\left[0.07,125,0.24\right]\\ -0.019\left[+0.84,0.40\right]\\ 0.71\left[0.07,125,0.24\right]\\ -0.019\left[-0.54,0.87\right]\end{array}$			
Heterogeneity: Tau <sup>a</sup> = 0.49; Chi <sup>a</sup> = 29.56, df = Test for overall effect Z = 0.55 (P = 0.56)	6         11.6         16         66.9         6           16         29         12         45         3           2.1         11.8         20         35.5         14           4         27.7         14         13.9         21           8         10.8         34         30.8         13           10         15.7         15         17.1         14           6         17         15         37.3         8           26         (P < 0.0001); P = 80%	.3 14 37 12 1 20 8 16 1 36 2 14 .6 15 126	1.2% 1.3% 1.4% 1.3% 1.5% 1.3% 1.3% 9.2%	-2.18 [-3.11, -1.25] -0.55 [-1.37, 0.27] -0.02 [-0.54, 0.60] -0.02 [-0.75, 0.71] 0.16 [-0.31, 0.63] 0.19 [-0.54, 0.92] 0.66 [0.20, 1.72] -0.47 [-0.75, 0.42]			
S.2.4 Manual Therapies/Exercise           Areas Bineno, et al. 2016 (27)         6.           Tossino, et al. 2007 (28)         1           Coelho Da Amorin, et al. 2014 (29)         1           Nordemiar & Thome, 1981 (30)         1           Kobis, et al. 2008 (31)         2           Stated and (2002)         24.           Stated (95% CI)         1           Heterogeneity Travel = 0.63; ChP = 20.59, df =           Test for oreal affect Z = 1.33 0° = 0.22	6         15.1         10         9.5         12           2         12         10         14         9           0         12         12         12         12           7         19         10         18         2           2         4         23         15         3           3         9.6         15         6         7           80         =         6(P < 0.0001); P = 83%	.8 10 .7 10 13 12 25 10 4 23 .3 15 80	1.2% 1.2% 1.3% 1.2% 1.4% 1.2% 7.4%	+0.20 [+1.08, 0.88] -0.18 [+1.05, 0.70] +0.15 [+0.96, 0.85] +0.04 [+0.92, 0.93] 1.47 [0.82, 2.13] 2.09 [+1.7, 3.00] 0.51 [-0.30, 1.31]	 ●		
		.8 15 .8 30 14 8 10 45 .8 21 119	1.0% 1.5% 1.1% 1.5% 1.4% 6.5%	-3.22 [-4.35, -2.09] -0.40 [-0.83, 0.12] -0.14 [-1.12, 0.85] 0.00 [-0.41, 0.41] 0.12 [-0.49, 0.72] -0.61 [-1.40, 0.18]			
S.2.8 Diadynamic Currents           Rajtar, et al., 2017 (35)         20.           Esold, et al., 2018 (36)         26.           Rajtar, et al., 2011 (40)         3.           Subirt & Histopenet, 2017 (41)         3.           Subirt & Histopenet, 2017 (41)         3.           Feedersen, 2017 (41)         3.           Subirt & Histopenet, 2017 (41)         3.           Feedersen, 2017 (41)         3.           Subirt & Histopenet, 2018 (40)         3.	= 3 (P < 0.00001); P = 91%		1.4% 5.4%	-3.04 [-3.96, -2.13] -0.78 [-1.52, -0.03] -0.34 [-0.78, 0.11] 0.00 [-0.50, 0.53] -0.98 [-2.02, 0.06]			
Artit: et al. 2002 (42)         20.           Moore & Shurman, 1997 (43)         40.5           Tatiost et al., 2019 (44)         30.           Zhou, et al., 2018 (45)         20.           Subtotal (95% CI)         28.           Heterogeneith: Tau" = 0.10; Chi" = 6.78, df =         Test for overall effect Z = 0.45 (P = 0.65)	3 (P = 0.08); P = 56%			-0.65 [-1.39, 0.09] 0.03 [-0.54, 0.60] 0.27 [-0.21, 0.76] 0.50 [-0.01, 1.00] 0.10 [-0.32, 0.52]			
Heterogeneity: Tau <sup>a</sup> = 0.09; Chi <sup>a</sup> = 6.28, df = : Test for overall effect: Z = 0.22 (P = 0.82) 5.3.0 Decontaneous: electrical second efford	lation		1.25	-0.42 [-0.98, 0.15] -0.01 [-0.52, 0.49] 0.02 [-0.52, 0.57] 0.54 [-0.52, 0.57] 0.05 [-0.36, 0.45] 0.05 [-0.59, 0.90]	•		
$\begin{array}{llllllllllllllllllllllllllllllllllll$	3 (P = 0.04); P = 65%	100	1.2%	0.77 [0.41, 1.13] 1.02 [0.32, 1.72] 1.31 [0.391, 1.71] 0.87 [0.44, 1.30] -0.16 [-1.02, 0.69] -0.06 [-0.83, 0.82]			
Sabitatia (95% C) Heterogeneity: Tau' = 0.00; Chi* = 0.03; df = Taol for overall affect Z = 0.15 (9° = 0.72) 52.11 Low level laser therapy Obsistogiu et al.; 2019 (60) 19. Sabitatia (95% C) Heterogeneity: Tau' = 0.22; Chi* = 2.33; df = Test for overall effect Z = 1.01 (9° = 0.31)	1 (P = 0.86); P = 0%		1.2% 2.4% 1.4% 1.2% 2.6%	-0.06 [-0.83, 0.82] -0.11 [-0.72, 0.50] 0.07 [-0.55, 0.89] 0.84 [0.01, 1.88] 0.43 [-0.41, 1.28]	• 		
$ \begin{array}{llllllllllllllllllllllllllllllllllll$	16 29 12 23 2 10 9 23 30 9 35 1 (P=0.05); P=73%	27 16 .5 23 39	1.3% 1.4% 2.7%	0.10 [-0.64, 0.85] 1.06 [0.44, 1.86] 0.61 [-0.33, 1.54]	-		
S., 21.3 Funded Tablor (equinery, ir trainscaladed (in c) et al., 2015 (0) (in c) et al., 2010 (01) (in c) et al., 201			1.4% 1.4% 2.8% 1.4% 1.5% 2.9%	-0.06 [-0.81, 0.50] 0.41 [-0.22, 1.04] 0.15 [-0.30, 0.61] 0.15 [-0.30, 0.61] 0.12 [-0.50, 0.75] 0.20 [-0.28, 0.88] 0.37 [-0.21, 0.55]	•		
5.2.15 Visual Illusion         Columbra         49.           Columbra         2014 (04)         49.           Tisk, et al., 2015 (05)         24.           Subtotal (95% Cl)         14.           Heleorgeneiky: Tau? = 0.00; Chi? = 0.22, df =         Test for overall effect Z = 0.34 (P = 0.74)	1 12.4 24 49.1 12 8 15.6 13 20.8 16 37 1 (P=0.64); P=0%		1.4% 1.3% 2.7%	0.00 (-0.57, 0.57) 0.23 (-0.58, 1.02) 0.08 (-0.38, 0.54)	•		
5.2.17 High Voltage Electrical Current Raybur, et al., 2017. (86)         20.           Stathotal (95% CD)         20.           Histerogeneity: Not applicable         20.           Test for overall effect. Z = 1.08 (P = 0.09)         5.2.18 Hydrother app           Das Binx, et al., 2008 (97)         3           Statetopel (95% CI)         1	5 4.5 20 10.5 2 20 14 22 5 66 1		1.4% 1.4% 0.8% 0.8%	0.54 [-0.09, 1.18] 0.54 [-0.09, 1.18] -1.54 [-3.05, -0.02] -1.54 [-3.05, -0.02]	•		
Test for overall effect 2 = 1.99 (P = 0.05) \$2.19 Intracutaneous sterile water injectio Labrecous, et al., 1992 (66) Satoria (1955: 4) Satoria (1955: 4) Satoria (1955: 4) Satoria (1955: 4) Satoria (1955: 4) Satoria (1955: 4) Satoria (1955) Satoria (1955) Sato	16 6 12 32 12		0.6% 0.6%	5.45 [3.49, 7.42] 5.45 [3.49, 7.42]	-	- -	
Isin, et al., 2017, 7(8)         4           Subtotal (95% C)         4           Heterogenety, Not applicable         5           Test for ownail effect. Z = 0.59 0° = 0.56)         5           Szazza Saworőseöback: behavisural therapy         5           Szazza Saworőseöback: behavisural therapy         45           Skatotal (95% C)         45           Heterogenetiy, Not applicable         45           Teat for ownail effect Z = 0.52 0° = 0.50)         60	15 31 46 49 3 46 1 1 13,5 15 41,8 19 15		1.5% 1.5% 1.3% 1.3%	-0.12[-0.54, 0.29] -0.12[-0.54, 0.29] 0.19[-0.53, 0.91] 0.19[-0.53, 0.91]	•		
5.2.23 Pain Supressor unit - electrotherary	7 3 18.08 12 24.1 24.0 12	07 12 12	1.3% 1.3%	0.19 [-0.61, 0.99] 0.19 [-0.61, 0.99]	-		
Heterogeneily: Not applicable Test for overall effect: Z = 0.48 (P = 0.63) 5.2.25 Shockwave Therapy	7 7.3 15 49.2 9 15			0.18 [-0.54, 0.89] 0.18 [-0.54, 0.89]	•		
Santamato, et al., 2013 (72)         2           Subtotal (99% C1)         1           Haterogeneity, Not applicable         1           Test for overall effect. Z = 1.67 (P = 0.12)         5.2.26 Splint           Koza, et al., 2014 (73)         4           Subtotal (95% C1)         4	14 8.9 16 19.4 6 16 18 11.8 20 83.7 11 20		1.3% 1.3% 1.4%	0.57 [-0.14, 1.27] 0.57 [-0.14, 1.27] -1.31 [-1.98, -0.63] -1.31 [-1.98, -0.63]	-		
Haterogeneily: Not applicable Test for overall effect: Z = 3.80 (P = 0.0001) 5.2.27 TEAS and tramadol	9 12:2 16 30 1 16	13 16 16	1.3% 1.3%	-0.63 [-1.34, 0.09] -0.63 [-1.34, 0.09]	•		

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Figure A13 Forest plot of comparison TENS versus other treatments. Outcome: pain intensity - expressed as mean (continuous) data. Subgroup analysis comparing TENS with different treatment 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 metaanalysis 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

### 

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  $\geq$ 30% expressed as frequency (dichotomous) data because of insufficient data.

## 

There was one RCT of crossover design with extractable data and sufficient washout between interventions to eliminate contamination  $^{104}$ . It was not possible to conduct an analysis of the proportion of participant-reported pain relief of  $\geq$ 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 comparted 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 A14).

### Forest plot

	High Fre	equency 1	ENS	Low Fre	quency 1	rens		Std. Mean Difference	Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% Cl	IV, Random, 95% Cl
Desantana, et al., 2009 (1)	43	3.2	23	46.5	3.6	20	8.5%	-1.01 [-1.65, -0.37]	<b>_</b>
Fatima et al., 2019 (2)	25.6	9.2	25	36	13.8	25	9.5%	-0.87 [-1.46, -0.29]	_ <b>-</b>
Warke, et al., 2004 (3)	28.25	32.02	3	43.8	20.6	4	2.2%	-0.51 [-2.06, 1.04]	
Topuz, et al., 2004 (4)	37.3	16.2	15	42.6	20.5	15	7.4%	-0.28 [-1.00, 0.44]	
Pitangui, et al., 2014 (5)	17.2	21.9	11	22.5	16	12	6.1%	-0.27 [-1.09, 0.55]	
Graff-Radford, et al., 1989 (6)	28.3	18.06	12	33.7	29.02	12	6.4%	-0.22 [-1.02, 0.59]	
Rajfur, et al., 2017 (7)	20.5	4.5	20	21.1	3.4	20	8.8%	-0.15 [-0.77, 0.47]	
Hamza, et al., 1999 (8)	25	23	25	28	19	25	9.9%	-0.14 [-0.70, 0.42]	
llhani, 2015 (9)	22.4	11.3	35	23.5	10.9	35	11.7%	-0.10 [-0.57, 0.37]	
De Oliverira et al., 2012	30	16.4	5	26	31.3	5	3.2%	0.14 [-1.10, 1.39]	
Sahin, et al., 2011 (10)	68.5	15.5	19	65.5	14.2	18	8.4%	0.20 [-0.45, 0.84]	<b>-</b>
Grimmer, 1992 (11)	22	28	20	15	18	20	8.8%	0.29 [-0.33, 0.91]	_ <del></del>
Liu, et al., 2017 (12)	48.2	17.7	22	41.3	16.8	22	9.2%	0.39 [-0.20, 0.99]	+
Total (95% CI)			235			233	100.0%	-0.19 [-0.43, 0.06]	•
Heterogeneity: Tau <sup>2</sup> = 0.07; Chi	r = 19.69, i	df = 12 (P	= 0.07);1	I <b>²</b> = 39%					- <u>tttt_</u>
Test for overall effect: Z = 1.50 (	P = 0.13)								-4 -2 U 2 4 Favours High Frequency Favours Low Frequency
									ravouis migh riequency ravouis Low riequency

Figure A14 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. 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.

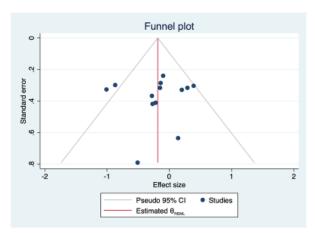


Figure A15 Funnel plot of high frequency versus low frequency TENS comparison.

### Outcome: <u>></u>30% reduction in pain

There was one RCT (parallel group) with extractable data <sup>123</sup>. It was not possible to conduct an analysis of high versus low frequency TENS for the proportion of participant-reported pain relief of  $\geq$ 30% expressed as frequency (dichotomous) data because of insufficient data.

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 <sup>104,105</sup>. We pooled 4 samples with 28/94 participants that reported pain relief of  $\geq$ 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 A16).

#### Forest plot

,	HF TE	NS	LF TE	NS		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	I M-H, Random, 95% Cl
Nash, et al., 1990 (1)	12	50	19	50	38.5%	0.63 [0.34, 1.16]	]
Hansson & Ekblom, 1983 (2)	7	22	9	20	23.3%	0.71 [0.32, 1.54]	]
Ekblom & Hansson, 1987 (3)	3	11	4	11	9.2%	0.75 [0.22, 2.60]	]
Langley, et al., 1984 (4)	6	11	7	11	28.9%	0.86 [0.43, 1.73]	]
Nash, et al., 1990 (5)	13	50	11	50	0.0%	1.18 [0.59, 2.38]	1
Total (95% CI)		94		92	100.0%	0.72 [0.49, 1.05]	. ◆
Total events	28		39				
Heterogeneity: Tau <sup>2</sup> = 0.00; Chi	i <sup>z</sup> = 0.44, d	lf = 3 (F	<sup>o</sup> = 0.93);	l <sup>2</sup> = 0%			0.01 0.1 1 10 100
Test for overall effect: Z = 1.71 (	(P = 0.09)						Favours HF TENS Favours LF TENS

Figure A16 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 interactive online table - Adverse Events.

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 ... that occurred 21 days after BTX-A injection and electrical stimulation." <sup>124</sup> 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 A17). 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<sup>2</sup> = 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

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1.1.2 Placebo Control         Da Silva, et al., 2015 (1)       0       21       7       21       3.9%       0.07 [0.00, 1.10]         Thakur et al., 2014 (2)       0       100       1       100       3.3%       0.33 [0.01, 8.09]         Kim, et al., 2010 (4)       3       24       2       24       6.3%       1.14 [0.45, 2.91]         Bennett, et al., 2010 (4)       3       24       2       24       6.3%       1.50 [0.27, 8.19]         Dailey et al., 2012 (6)       11       117       3       119       7.5%       3.73 [1.07, 13.03]         Subtotal (95% CI)       415       413       37.8%       1.45 [0.63, 3.32]       1.45 [0.63, 3.32]         Total events       39       26       141       145       433       37.8%       0.01 [0.00, 0.23]         Heterogeneity: Tau <sup>2</sup> = 0.47; Chi <sup>2</sup> = 9.78, df = 5 (P = 0.08); P = 49%       145 [0.63, 3.32]       1.45 [0.63, 0.30 [0.00, 0.49]       9.7%         Pan, et al., 2007 (10)       1       22       9.22       5.6%       0.01 [0.01, 0.7.3]       1.45 [0.03, 0.00 [0.0]       1.40 [0.07, 15.73]         Grant, et al., 2009 (11)       0       29       3       30       3.7%       0.15 [0.01, 2.74]       1.34 [0.23, 6.08]         Tsukayama, et al.	Chucha or Cultura un	TEN		Comparison	•	Mainht	Risk Ratio	Risk Ratio
Da Silva, et al., 2015 (1) 0 21 7 21 3.9% 0.07 [0.00, 1.10] Thakur et al., 2004 (2) 0 100 1 100 3.3% 0.33 [0.01, 8.09] Kim, et al., 2012 (3) 8 50 7 50 8.4% 1.14 [0.45, 2.91] Dailey et al., 2010 (4) 3 24 2 24 6.3% 1.50 [0.27, 819] Dailey et al., 2020 (5) 17 103 6 99 8.5% 2.72 [1.12, 6.62] Buchmuller, et al., 2012 (6) 11 117 3 119 7.5% 3.73 [1.07, 13.03] Subtotal (95% CI) 415 413 37.8% 1.45 [0.63, 3.32] Total events 39 26 Heterogeneity: Tau <sup>2</sup> = 0.47; Chi <sup>2</sup> = 9.78, df = 5 (P = 0.08); P = 49% Test for overall effect: Z = 0.88 (P = 0.38) 1.1.3 Active Treatment Isik, et al., 2009 (8) 0 46 3 8 3.8% 0.03 [10.00, 0.49] Pan, et al., 2009 (8) 0 46 3 8 3.8% 0.01 [10.00, 0.23] (		Events	Total	Events	Total	weight	M-H, Random, 95% CI	M-H, Random, 95% C
Thakur et al., 2004 (2) 0 100 1 100 3.3% 0.33 [0.01, 8.09] Kim, et al., 2012 (3) 8 50 7 50 8.4% 1.14 [0.45, 2.91] Bennett, et al., 2010 (4) 3 24 2 24 6.3% 1.50 [0.27, 8.19] Dalley et al., 2020 (5) 17 103 6 99 8.5% 2.72 [1.12, 6.62] Buchmuller, et al., 2012 (6) 11 117 3 119 7.5% 3.73 [1.07, 13.03] Subtotal (95% CI) 415 413 37.8% 1.45 [0.63, 3.32] Total events 39 26 Heterogeneity: Tau <sup>2</sup> = 0.47; ChF <sup>2</sup> = 9.78, df = 5 (P = 0.08); P <sup>2</sup> 49% Test for overall effect $Z = 0.88$ (P = 0.38) 1.1.3 Active Treatment Isik, et al., 2017 (7) 0 53 34 52 3.9% 0.01 [0.00, 0.23] Moharic, et al., 2009 (8) 0 46 3 8 3.8% 0.03 [0.00, 0.49] Pan, et al., 2009 (9) 0 30 5 33 38% 0.10 [0.01, 1.74] Liu, et al., 2017 (10) 1 22 9 22 5.6% 0.11 [0.02, 0.80] Chitsaz, et al., 2009 (11) 0 29 3 30 3.7% 0.68 [0.20, 2.23] Kim, et al., 2009 (11) 0 29 3 30 3.7% 0.68 [0.20, 2.23] Kim, et al., 2009 (14) 3 1 24 1 25 4.0% 1.04 [0.07, 15.73] Grant, et al., 2019 (15) 4 64 3 68 6.9% 1.42 [0.33, 6.08] Lofgren & Northrink, 2001 (15) 3 90 369 62.2% 0.51 [0.18, 1.39] Total events 24 69 Heterogeneity: Tau <sup>2</sup> = 1.97; ChF = 33.40, df = 11 (P = 0.0005); P = 67% Test for overall effect $Z = 1.32$ (P = 0.19) Total events 63 95 Heterogeneity: Tau <sup>2</sup> = 1.97; ChF = 33.40, df = 11 (P = 0.0005); P = 67% Test for overall effect $Z = 1.32$ (P = 0.19) Total events 63 95			~ ~ ~	_	~ ~ ~			
Kim, et al., 2012 (3)       8       50       7       50       8.4%       1.14 [0.45, 2.91]         Bennett, et al., 2010 (4)       3       24       2       24       6.3%       1.50 [0.27, 8.19]         Dailey et al., 2020 (5)       17       103       6       99       8.5%       2.72 [1.12, 6.62]         Buchmuller, et al., 2012 (6)       11       117       3       119       7.5%       3.73 [1.07, 13.03]         Subtotal (95% CI)       415       413       37.8%       1.45 [0.63, 3.32]         Total events       39       26         Heterogeneity: Tau <sup>2</sup> = 0.47; Chi <sup>2</sup> = 9.78, df = 5 (P = 0.08); P = 49%         Test for overall effect: Z = 0.88 (P = 0.38)         1.1.3 Active Treatment         Isik, et al., 2017 (7)       0       53       34       52       3.9%       0.01 [0.00, 0.23]         Pan, et al., 2009 (8)       0       46       3       8       3.8%       0.03 [0.00, 0.49]         Pan, et al., 2009 (11)       0       29       32       5.6%       0.11 [0.02, 0.23]         Chitsaz, et al., 2009 (11)       0       29       30       3.7%       0.15 [0.01, 2.74]         Tsukayama, et al., 2009 (12)       3       10       4       9       7.7% <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td>								
Bennett, et al., 2010 (4) 3 24 2 24 6.3% 1.50 [0.27, 8.19] Dailey et al., 2020 (5) 17 103 6 99 8.5% 2.72 [1.12, 6.62] Buchmuller, et al., 2012 (6) 11 117 3 119 7.5% 3.73 [1.07, 13.03] Subtotal (95% CI) 415 413 37.8% 1.45 [0.63, 3.32] Total events 39 26 Heterogeneity: Tau <sup>2</sup> = 0.47; Chi <sup>2</sup> = 9.78, df = 5 (P = 0.08); P = 49% Test for overall effect: $Z = 0.88$ (P = 0.38) 1.13 Active Treatment Isik, et al., 2017 (7) 0 53 34 52 3.9% 0.01 [0.00, 0.23] Moharic, et al., 2009 (8) 0 46 3 8 3.8% 0.03 [0.00, 0.49] Pan, et al., 2009 (8) 0 46 3 8 3.8% 0.10 [0.01, 1.73] Liu, et al., 2009 (8) 0 30 5 33 3.8% 0.10 [0.01, 1.73] Liu, et al., 2009 (11) 0 29 3 30 3.7% 0.15 [0.01, 2.74] Tsukayama, et al., 2000 (12) 3 10 4 9 7.7% 0.68 [0.20, 2.23] Kim, et al., 2019 (15) 4 64 3 68 6.9% 1.14 [0.07, 15.73] Grant, et al., 2019 (15) 4 64 3 68 6.9% 1.14 [0.02, 5.21] Sangtong, et al., 2019 (15) 4 64 3 68 6.9% 1.42 [0.33, 6.08] Lofgren & Northrink, 2019 (16) 2 32 1 32 4.7% 2.05 [0.70, 9.24] Shimoji, et al., 2017 (18) 3 9 0 11 3.8% 8.40 [0.49, 144.04] Subtotal (95% CI) 390 369 62.2% 0.51 [0.18, 1.39] Total events 24 69 Heterogeneity: Tau <sup>2</sup> = 1.97; Chi <sup>2</sup> = 33.40, df = 11 (P = 0.0005); P = 67% Test for overall effect: $Z = 1.32$ (P = 0.19) Total events 6 3 95 Heterogeneity: Tau <sup>2</sup> = 1.26; ChiE = 40.27, df = 12 (C = 0.00015); P = 67% Test for overall effect: $Z = 1.32$ (P = 0.19)	,							
Dailey et al., 2020 (5)       17       103       6       99       8.5%       2.72 [1.2, 6.62]         Buchmuller, et al., 2012 (6)       11       117       3       119       7.5%       3.73 [1.07, 13.03]         Subtotal (95% CI)       415       413       37.8%       1.45 [0.63, 3.32]         Total events       39       26         Heterogeneity: Tau <sup>2</sup> = 0.47; Ch <sup>2</sup> = 9.78, df = 5 (P = 0.08); P = 49%         Test for overall effect Z = 0.88 (P = 0.38) <b>1.1.3 Active Treatment</b> Isik, et al., 2009 (8)       0       46       3       8       3.8%       0.03 [0.00, 0.49]								
Buchmuller, et al., 2012 (6) 11 117 3 119 7.5% $3.73$ [1.07, 13.03] Subtotal (95% CI) 415 413 37.8% 1.45 [0.63, 3.32] Total events 39 26 Heterogeneity: Tau <sup>2</sup> = 0.47; Chi <sup>2</sup> = 9.78, df = 5 (P = 0.08); P = 49% Test for overall effect $Z = 0.88$ (P = 0.38) 1.1.3 Active Treatment Isik, et al., 2017 (7) 0 53 34 52 3.9% 0.01 [0.00, 0.23] Moharic, et al., 2009 (8) 0 46 3 8 3.8% 0.03 [0.00, 0.49] Pan, et al., 2009 (8) 0 46 3 8 3.8% 0.01 [0.01, 1.73] Liu, et al., 2003 (9) 0 30 5 33 3.8% 0.10 [0.01, 1.73] Liu, et al., 2009 (11) 0 29 3 30 3.7% 0.15 [0.01, 2.74] Tsukayama, et al., 2002 (12) 3 10 4 9 7.7% 0.68 [0.20, 2.23] Kim, et al., 2019 (15) 4 64 3 68 6.9% 1.04 [0.07, 15.73] Grant, et al., 2019 (15) 4 64 3 68 6.9% 1.04 [0.07, 15.73] Grant, et al., 2019 (15) 4 64 3 68 6.9% 1.42 [0.33, 6.08] Lofgren & Norrbrink, 2009 (16) 2 32 1 32 4.7% 2.00 [0.19, 20.97] Escontel-Mayor, et al., 2011 (17) 7 43 3 47 7.4% 2.55 [0.70, 9.24] Shimoji, et al., 2017 (18) 3 9 0 11 3.8% 8.40 [0.49, 144.04] Subtotal (95% CI) 390 369 62.2% 0.51 [0.18, 1.39] Total events 24 69 Heterogeneity: Tau <sup>2</sup> = 1.97; Chi <sup>2</sup> = 33.40, df = 11 (P = 0.0005); P = 67% Test for overall effect $Z = 1.32$ (P = 0.19) Total events 63 95 Heterogeneity: Tau <sup>2</sup> = 1.97; Chi <sup>2</sup> = 33.40, df = 11 (P = 0.0005); P = 67% Test for overall effect $Z = 1.32$ (P = 0.19) Total events 63 95		-						
Subtotal (95% Cl)       415       413       37.8%       1.45 [0.63, 3.32]         Total events       39       26         Heterogeneity: Tau <sup>2</sup> = 0.47; Chi <sup>2</sup> = 9.78, df = 5 (P = 0.08); P = 49%         Test for overall effect: Z = 0.88 (P = 0.38) <b>1.13 Active Treatment</b> Isik, et al., 2017 (7)       0       53       34       52       3.9%       0.01 [0.00, 0.23]         Moharic, et al., 2009 (8)       0       46       3       8       3.8%       0.03 [0.00, 0.49]         Pan, et al., 2003 (9)       0       30       5       33       3.8%       0.01 [0.01, 1.73]         Liu, et al., 2017 (10)       1       22       9       22       5.6%       0.11 [0.02, 0.80]         Chitsaz, et al., 2009 (11)       0       29       3       30       3.7%       0.15 [0.01, 2.74]         Tsukayama, et al., 2002 (12)       3       10       4       9       7.7%       0.68 [0.20, 2.23]         Kim, et al., 1999 (14)       3       28       32       6.8%       1.14 [0.25, 5.21]       3         Sangtong, et al., 2019 (15)       4       64       3       68       6.9%       1.42 [0.33, 6.08]       5         Subtotal (95% Cl)       39       0       11<								_ <b></b>
Heterogeneity: Tau <sup>2</sup> = 0.47; Chi <sup>2</sup> = 9.78, df = 5 (P = 0.08); I <sup>2</sup> = 49% Test for overall effect: $Z = 0.88$ (P = 0.38) <b>1.1.3 Active Treatment</b> Isik, et al., 2017 (7) 0 53 34 52 3.9% 0.01 [0.00, 0.23] Moharic, et al., 2009 (8) 0 46 3 8 3.8% 0.03 [0.00, 0.49] Pan, et al., 2003 (9) 0 30 5 33 3.8% 0.10 [0.01, 1.73] Liu, et al., 2017 (10) 1 22 9 22 5.6% 0.11 [0.02, 0.80] Chitsaz, et al., 2009 (11) 0 29 3 30 3.7% 0.15 [0.01, 2.74] Tsukayama, et al., 2002 (12) 3 10 4 9 7.7% 0.68 [0.20, 2.23] Kim, et al., 2014 (13) 1 24 1 25 4.0% 1.04 [0.07, 15.73] Grant, et al., 2019 (15) 4 64 3 68 6.9% 1.14 [0.25, 5.21] Sangtong, et al., 2019 (15) 4 64 3 68 6.9% 1.42 [0.33, 6.08] Lofgren & Norrbrink, 2009 (16) 2 32 1 32 4.7% 2.00 [0.19, 20.97] Escortel-Mayor, et al., 2011 (17) 7 43 3 347 7.4% 2.55 [0.70, 9.24] Shimoij, et al., 2007 (18) 3 9 0 11 3.8% 8.40 [0.49, 144.04] Subtotal (95% CI) 390 369 62.2% 0.51 [0.18, 1.39] Total events 24 69 Heterogeneity: Tau <sup>2</sup> = 1.97; Chi <sup>2</sup> = 33.40, df = 11 (P = 0.0005); P = 67% Test for overall effect: $Z = 1.32$ (P = 0.19) Total events 63 95 Hotorogeneity: Tau <sup>2</sup> = 1.96 (Di <sup>2</sup> = 40 72) df = 17 (P = 6.0001); P = 66%		11		3				•
Test for overall effect: $Z = 0.88 (P = 0.38)$ <b>1.1.3 Active Treatment</b> Isik, et al., 2017 (7)       0       53       34       52       3.9%       0.01 [0.00, 0.23]         Moharic, et al., 2009 (8)       0       46       3       8       3.8%       0.03 [0.00, 0.49]         Pan, et al., 2003 (9)       0       30       5       33       3.8%       0.10 [0.01, 1.73]         Liu, et al., 2017 (10)       1       22       9       22       5.6%       0.11 [0.02, 0.80]         Chitsaz, et al., 2009 (11)       0       29       3       30       3.7%       0.15 [0.01, 2.74]         Tsukayama, et al., 2012 (12)       3       10       4       9       7.7%       0.68 [0.20, 2.23]         Kim, et al., 2014 (13)       1       24       1       25       4.0%       1.04 [0.07, 15.73]         Grant, et al., 1999 (14)       3       28       3       32       6.8%       1.14 [0.25, 5.21]         Sangtong, et al., 2019 (15)       4       64       3       68       6.9%       1.42 [0.33, 6.08]         Lofgren & Norrbrink, 2009 (16)       2       32       1       32       4.7%       2.00 [0.19, 20.97]         Escortell-Mayor, et al., 2017 (18)	Total events	39		26				
<b>1.1.3 Active Treatment</b> Isik, et al., 2017 (7)       0       53       34       52 $3.9\%$ 0.01 [0.00, 0.23]         Moharic, et al., 2009 (8)       0       46       3       8 $3.8\%$ 0.03 [0.00, 0.49]         Pan, et al., 2003 (9)       0       30       5       33 $3.8\%$ 0.10 [0.01, 1.73]         Liu, et al., 2017 (10)       1       22       9       22 $5.6\%$ 0.11 [0.02, 0.80]         Chitsaz, et al., 2009 (11)       0       29       3       30 $3.7\%$ 0.15 [0.01, 2.74]         Tsukayama, et al., 2002 (12)       3       10       4       9 $7.7\%$ 0.68 [0.20, 2.23]         Kim, et al., 2014 (13)       1       24       1       25       4.0%       1.04 [0.07, 15.73]         Grant, et al., 1999 (14)       3       28       3       32       6.8%       1.14 [0.25, 5.21]         Sangtong, et al., 2019 (15)       4       64       3       68       6.9%       1.42 [0.33, 6.08]         Lofgren & Norrbrink, 2009 (16)       2       32       1       32       4.7%       2.00 [0.19, 20.97]         Escortell-Mayor, et al., 2011 (17)       7       43       3       47	Heterogeneity: Tau <sup>2</sup> = 0.47; Chi <sup>2</sup> =	9.78, df=	5 (P =	0.08); I <sup>2</sup> = 49%				
Isik, et al., 2017 (7)       0       53       34       52       3.9%       0.01 [0.00, 0.23]         Moharic, et al., 2009 (8)       0       46       3       8       3.8%       0.03 [0.00, 0.49]         Pan, et al., 2003 (9)       0       30       5       33       3.8%       0.10 [0.01, 1.73]         Liu, et al., 2007 (10)       1       22       9       22       5.6%       0.11 [0.02, 0.80]         Chitsaz, et al., 2009 (11)       0       29       3       30       3.7%       0.15 [0.01, 2.74]         Tsukayama, et al., 2002 (12)       3       10       4       9       7.7%       0.68 [0.20, 2.23]         Kim, et al., 2014 (13)       1       24       1       25       4.0%       1.04 [0.07, 15.73]         Grant, et al., 2019 (14)       3       28       3       32       6.8%       1.14 [0.25, 5.21]         Sangtong, et al., 2019 (15)       4       64       3       68       6.9%       1.42 [0.33, 6.08]         Lofgren & Norrbrink, 2009 (16)       2       32       1       32       4.7%       2.00 [0.19, 20.97]         Escortell-Mayor, et al., 2011 (17)       7       43       3       47       7.4%       2.55 [0.70, 9.24]				~				
Moharic, et al., 2009 (8)       0       46       3       8 $3.8\%$ $0.03[0.00, 0.49]$ Pan, et al., 2003 (9)       0       30       5       33 $3.8\%$ $0.10[0.01, 1.73]$ Liu, et al., 2017 (10)       1       22       9       22 $5.6\%$ $0.11[0.02, 0.80]$ Chitsaz, et al., 2009 (11)       0       29       3 $30$ $3.7\%$ $0.15[0.01, 2.74]$ Tsukayama, et al., 2002 (12)       3       10       4       9 $7.7\%$ $0.68[0.20, 2.23]$ Kim, et al., 2014 (13)       1       24       1       25 $4.0\%$ $1.04[0.07, 15.73]$ Grant, et al., 1999 (14)       3       28       3       32 $6.8\%$ $1.14[0.25, 5.21]$ Sangtong, et al., 2019 (15)       4       64       3       68 $6.9\%$ $1.42[0.33, 6.08]$ Lofgren & Norrbrink, 2009 (16)       2       32       1       32 $4.7\%$ $2.00[0.19, 20.97]$ Escortell-Mayor, et al., 2011 (17)       7       43       3 $47$ $7.4\%$ $2.05[0.70, 9.24]$ Shimoij, et al., 2007 (18)       3       9       0 $11$ $3.8\%$ $8.40[$	1.1.3 Active Treatment							
Pan, et al., 2003 (9)       0       30       5       33       3.8%       0.10 [0.01, 1.73]         Liu, et al., 2017 (10)       1       22       9       22       5.6%       0.11 [0.02, 0.80]         Chitsaz, et al., 2009 (11)       0       29       3       30       3.7%       0.15 [0.01, 2.74]         Tsukayama, et al., 2002 (12)       3       10       4       9       7.7%       0.68 [0.20, 2.23]         Kim, et al., 2014 (13)       1       24       1       25       4.0%       1.04 [0.07, 15.73]         Grant, et al., 1999 (14)       3       28       3       32       6.8%       1.14 [0.25, 5.21]         Sangtong, et al., 2019 (15)       4       64       3       68       6.9%       1.42 [0.33, 6.08]         Lofgren & Norrbrink, 2009 (16)       2       32       1       32       4.7%       2.00 [0.19, 20.97]         Escortell-Mayor, et al., 2011 (17)       7       43       3       47       7.4%       2.55 [0.70, 9.24]         Shimoij, et al., 2007 (18)       3       9       0       11       3.8%       8.40 [0.49, 144.04]         Subtotal (95% CI)       390       369       62.2%       0.51 [0.18, 1.39]       •         Total event	lsik, et al., 2017 (7)	0	53	34	52	3.9%	0.01 [0.00, 0.23]	←─────────────────────────────────────
Liu, et al., 2017 (10) 1 22 9 22 5.6% 0.11 $[0.02, 0.80]$ Chitsaz, et al., 2009 (11) 0 29 3 30 3.7% 0.15 $[0.01, 2.74]$ Tsukayama, et al., 2002 (12) 3 10 4 9 7.7% 0.68 $[0.20, 2.23]$ Kim, et al., 2014 (13) 1 24 1 25 4.0% 1.04 $[0.07, 15.73]$ Grant, et al., 2019 (15) 4 64 3 68 6.9% 1.42 $[0.33, 6.08]$ Lofgren & Norbrink, 2009 (16) 2 32 1 32 4.7% 2.00 $[0.19, 20.97]$ Escortell-Mayor, et al., 2011 (17) 7 43 3 47 7.4% 2.55 $[0.70, 9.24]$ Shimoji, et al., 2007 (18) 3 9 0 11 3.8% 8.40 $[0.49, 144.04]$ Subtotal (95% CI) 390 369 62.2% 0.51 $[0.18, 1.39]$ Total events 24 69 Heterogeneity: Tau <sup>2</sup> = 1.97; Chi <sup>2</sup> = 33.40, df = 11 (P = 0.0005); P = 67% Test for overall effect: Z = 1.32 (P = 0.19) Total events 63 95 Hotorogeneity: Tau <sup>2</sup> = 1.26; Chi <sup>2</sup> = 0.72 df = 12 (P = 0.0004); P = 66%	Moharic, et al., 2009 (8)	0	46	3	8	3.8%	0.03 [0.00, 0.49]	
Chitsaz, et al., 2009 (11)       0       29       3       30 $3.7\%$ $0.15 [0.01, 2.74]$ Tsukayama, et al., 2002 (12)       3       10       4       9 $7.7\%$ $0.68 [0.20, 2.23]$ Kim, et al., 2014 (13)       1       24       1       25 $4.0\%$ $1.04 [0.07, 15.73]$ Grant, et al., 1999 (14)       3       28       3       32 $6.8\%$ $1.14 [0.25, 5.21]$ Sangtong, et al., 2019 (15)       4       64       3       68 $6.9\%$ $1.42 [0.33, 6.08]$ Lofgren & Norrbrink, 2009 (16)       2       32       1       32 $4.7\%$ $2.00 [0.19, 20.97]$ Escortell-Mayor, et al., 2011 (17)       7       43       3       47 $7.4\%$ $2.55 [0.70, 9.24]$ Shimoji, et al., 2007 (18)       3       9       0       11 $3.8\%$ $8.40 [0.49, 144.04]$ Subtotal (95% CI)       390       369       62.2% $0.51 [0.18, 1.39]$ $4.69$ Heterogeneity: Tau <sup>2</sup> = 1.97; Chi <sup>2</sup> = 33.40, df = 11 (P = 0.0005); P = 67\%       Test for overall effect: $Z = 1.32$ (P = 0.19) $782 100.0\%$ $0.73 [0.36, 1.48]$ $4.04$ Total events       63       95 $95$	Pan, et al., 2003 (9)	0	30	5	33	3.8%	0.10 [0.01, 1.73]	
Tsukayama, et al., 2002 (12)       3       10       4       9       7.7%       0.68 [0.20, 2.23]         Kim, et al., 2014 (13)       1       24       1       25       4.0%       1.04 [0.07, 15.73]         Grant, et al., 1999 (14)       3       28       3       32       6.8%       1.14 [0.25, 5.21]         Sangtong, et al., 2019 (15)       4       64       3       68       6.9%       1.42 [0.33, 6.08]         Lofgren & Norrbrink, 2009 (16)       2       32       1       32       4.7%       2.00 [0.19, 20.97]         Escortell-Mayor, et al., 2011 (17)       7       43       3       47       7.4%       2.55 [0.70, 9.24]         Shimoji, et al., 2007 (18)       3       9       0       11       3.8%       8.40 [0.49, 144.04]         Subtotal (95% CI)       390       369       62.2%       0.51 [0.18, 1.39]       10         Total events       24       69       69       67%       11 (P = 0.0005); P = 67%       12 (P = 0.19)         Total (95% CI)       805       782       100.0%       0.73 [0.36, 1.48]       4         Total events       63       95       95       95       95       95          70.2 of = 12 (P = 0.0001)	Liu, et al., 2017 (10)	1	22	9	22	5.6%	0.11 [0.02, 0.80]	
Kim, et al., 2014 (13)       1       24       1       25       4.0%       1.04 [0.07, 15.73]         Grant, et al., 1999 (14)       3       28       3       32       6.8%       1.14 [0.25, 5.21]         Sangtong, et al., 2019 (15)       4       64       3       68       6.9%       1.42 [0.33, 6.08]         Lofgren & Norrbrink, 2009 (16)       2       32       1       32       4.7%       2.00 [0.19, 20.97]         Escortell-Mayor, et al., 2011 (17)       7       43       3       47       7.4%       2.55 [0.70, 9.24]         Shimoji, et al., 2007 (18)       3       9       0       11       3.8%       8.40 [0.49, 144.04]         Subtotal (95% CI)       390       369       62.2%       0.51 [0.18, 1.39]         Total events       24       69         Heterogeneity: Tau <sup>2</sup> = 1.97; Chi <sup>2</sup> = 33.40, df = 11 (P = 0.0005); I <sup>2</sup> = 67%         Test for overall effect: Z = 1.32 (P = 0.19)       805       782       100.0%       0.73 [0.36, 1.48]         Total events       63       95         Hotorogeneity: Tau <sup>2</sup> = 1 25; Chi <sup>2</sup> = 10 72; df = 17 /P < 0.0001; I <sup>2</sup> = 65%       63       95	Chitsaz, et al., 2009 (11)	0	29	3	30	3.7%	0.15 [0.01, 2.74]	
$\begin{array}{c ccccccccccccccccccccccccccccccccccc$	Tsukayama, et al., 2002 (12)	3	10	4	9	7.7%	0.68 [0.20, 2.23]	
Sangtong, et al., 2019 (15) 4 64 3 68 6.9% $1.42 [0.33, 6.08]$ Lofgren & Norrbrink, 2009 (16) 2 32 1 32 4.7% 2.00 [0.19, 20.97] Escortell-Mayor, et al., 2011 (17) 7 43 3 47 7.4% 2.55 [0.70, 9.24] Shimoji, et al., 2007 (18) 3 9 0 11 3.8% 8.40 [0.49, 144.04] Subtotal (95% CI) 390 369 62.2% 0.51 [0.18, 1.39] Total events 24 69 Heterogeneity: Tau <sup>2</sup> = 1.97; Chi <sup>2</sup> = 33.40, df = 11 (P = 0.0005); I <sup>2</sup> = 67% Test for overall effect: $Z = 1.32$ (P = 0.19) Total events 63 95 Hotorogeneity: Tau <sup>2</sup> = 1.25; Chi <sup>2</sup> = 40.72, df = 12 (P = 0.0004); I <sup>2</sup> = 66%	Kim, et al., 2014 (13)	1	24	1	25	4.0%	1.04 [0.07, 15.73]	
Lofgren & Norrbrink, 2009 (16) 2 32 1 32 4.7% 2.00 [0.19, 20.97] Escortell-Mayor, et al., 2011 (17) 7 43 3 47 7.4% 2.55 [0.70, 9.24] Shimoji, et al., 2007 (18) 3 9 0 11 3.8% 8.40 [0.49, 144.04] Subtotal (95% CI) 390 369 62.2% 0.51 [0.18, 1.39] Total events 24 69 Heterogeneity: Tau <sup>2</sup> = 1.97; Chi <sup>2</sup> = 33.40, df = 11 (P = 0.0005); I <sup>2</sup> = 67% Test for overall effect: $Z = 1.32$ (P = 0.19) Total events 63 95 Hotorogeneity: Tau <sup>2</sup> = 1.25; Chi <sup>2</sup> = 40.72, df = 12 (P < 0.0004); I <sup>2</sup> = 66%	Grant, et al., 1999 (14)	3	28	3	32	6.8%	1.14 [0.25, 5.21]	
Escortell-Mayor, et al., 2011 (17) 7 43 3 47 7.4% 2.55 $[0.70, 9.24]$ Shimoji, et al., 2007 (18) 3 9 0 11 3.8% 8.40 $[0.49, 144.04]$ Subtotal (95% CI) 390 369 62.2% 0.51 $[0.18, 1.39]$ Total events 24 69 Heterogeneity: Tau <sup>2</sup> = 1.97; Chi <sup>2</sup> = 33.40, df = 11 (P = 0.0005); P = 67% Test for overall effect: Z = 1.32 (P = 0.19) Total events 63 95 Hotorogeneity: Tou <sup>2</sup> = 1.26; Chi <sup>2</sup> = 40.72, df = 17 (P < 0.0004); P = 66%	Sangtong, et al., 2019 (15)	4	64	3	68	6.9%	1.42 [0.33, 6.08]	<b></b>
Shimoji, et al., 2007 (18)       3       9       0       11       3.8%       8.40 [0.49, 144.04]         Subtotal (95% Cl)       390       369       62.2%       0.51 [0.18, 1.39]         Total events       24       69         Heterogeneity: Tau <sup>2</sup> = 1.97; Chi <sup>2</sup> = 33.40, df = 11 (P = 0.0005); I <sup>2</sup> = 67%         Test for overall effect: Z = 1.32 (P = 0.19)         Total (95% Cl)       805       782       100.0%       0.73 [0.36, 1.48]         Total events       63       95         Hotorogeneity: Tau <sup>2</sup> = 1.25; Chi <sup>2</sup> = 40.72; df = 12 (P < 0.0004); I <sup>2</sup> = 65%       65%	Lofgren & Norrbrink, 2009 (16)	2	32	1	32	4.7%	2.00 [0.19, 20.97]	
Subtotal (95% CI)       390       369       62.2%       0.51 [0.18, 1.39]         Total events       24       69         Heterogeneity: Tau <sup>2</sup> = 1.97; Chi <sup>2</sup> = 33.40, df = 11 (P = 0.0005); I <sup>2</sup> = 67%         Test for overall effect: Z = 1.32 (P = 0.19)         Total events       63         95         Hotorogeneity: Tau <sup>2</sup> = 1.25; Chi <sup>2</sup> = 40.72; df = 17 (P < 0.0004); I <sup>2</sup> = 56%	Escortell-Mayor, et al., 2011 (17)	7	43	3	47	7.4%	2.55 [0.70, 9.24]	+
Total events       24       69         Heterogeneity: Tau <sup>2</sup> = 1.97; Chi <sup>2</sup> = 33.40, df = 11 (P = 0.0005); l <sup>2</sup> = 67%         Test for overall effect: Z = 1.32 (P = 0.19)         Total (95% Cl)       805       782       100.0%       0.73 [0.36, 1.48]         Total events       63       95         Hotorogeneity: Tau <sup>2</sup> = 1.25; Chi <sup>2</sup> = 40.72; df = 12 (P ≤ 0.0004); l <sup>2</sup> = 56%	Shimoji, et al., 2007 (18)	3	9	0	11	3.8%	8.40 [0.49, 144.04]	
Heterogeneity: Tau <sup>2</sup> = 1.97; Chi <sup>2</sup> = 33.40, df = 11 (P = 0.0005); l <sup>2</sup> = 67% Test for overall effect: Z = 1.32 (P = 0.19) <b>Total (95% CI) 805 782 100.0% 0.73 [0.36, 1.48] •</b> Total events 63 95 Hotorogeneity: Tou <sup>2</sup> = 1 25; Chi <sup>2</sup> = 40.72, df = 17 (P < 0.0004); l <sup>2</sup> = 65%	Subtotal (95% CI)		390		369	62.2%	0.51 [0.18, 1.39]	
Test for overall effect: Z = 1.32 (P = 0.19)         Total (95% Cl)       805       782       100.0%       0.73 [0.36, 1.48]         Total events       63       95         Hotorographity: Toulis = 1.25: Chill = 40.72; df = 17 (B < 0.0004); B = 56%	Total events	24		69				
Total (95% Cl)         805         782         100.0%         0.73 [0.36, 1.48]           Total events         63         95           Underscreen bits         70.2 (f = 12 /B = 0.0004); B = 56%         100.0 (f = 12 /B = 0.0004); B = 56%			= 11 (P	= 0.0005); I <sup>2</sup> =	67%			
Total events 63 95		,	805		782	100.0%	0 73 [0 36 4 49]	
Hotorrogonolity: Touiz = 1.25: Chiz = 40.72, df = 17./P < 0.0001): IZ = 66%		60	005	05	102	.00.070	0.75 [0.50, 1.40]	
			- 17/0		CON			
Test for overall effect: Z = 0.87 (P = 0.38)			= 17 (P	< 0.0001); I==	0070			0.001 0.1 1 10

Figure A17 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 <sup>6,125</sup>. 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.

#### Potential biases in the review process: Description

#### 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 and this has contributed to risk of bias and imprecision in data for all pooled analyses. 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 <sup>112</sup>. 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 <sup>126</sup>.

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: Tau<sup>2</sup> = 0.64; Chi<sup>2</sup> = 733.23, df = 90 (P < 0.00001); I<sup>2</sup> = 88%).
  - After removal of <sup>84,98,127</sup>
    - SMD [95%CI] = -0.97 [-1.16, -0.79] Test for overall effect: Z = 10.35 (P < 0.00001) Heterogeneity: Tau<sup>2</sup> = 0.66; Chi<sup>2</sup> = 726.33, df = 88 (P < 0.00001); I<sup>2</sup> = 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 <sup>128</sup>.

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 <sup>113</sup>. 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 <sup>112</sup>. 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 <sup>8</sup>). 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 <sup>129</sup> 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.

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## **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 <u>https://gradepro.org/.</u>

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)
- Large effect according to Cohens d Large (+1) or very large effect (+2).

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 [GRADE - Aide Memoire\_LIVE.docx]. The Aide Memoire was based on the GRADE handbook, Domain-specific guidance for writing useful explanations – from Cochrane and an item checklist developed by <sup>130</sup>

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### **GRADE:** Summary of Findings

#### TENS versus Placebo

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

	tudies) Ilow upof biasInconsistencyIndirectnessImprecisionPublication biascer en Intensity Rating (assessed with 0-10 intensity scale (V/ 4841 1 RCTs)not serious aserious bnot serious cnot serious dpublication biasMOaserious bnot serious cnot serious cnot serious dpublication biasMO							Sumn	nary of f	indings	
							Study event ra	ites (%)		Anticipated effec	
Participants (studies) Follow up	of	Inconsistency	Indirectness	Imprecision		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 Inter	nsity R	ating (asses	ssed with (	D-10 inten	sity scale	(VAS/NRS	))				
4841 (91 RCTs)	serious	serious <sup>b</sup>	not serious <sup>c</sup>	not serious <sup>d</sup>	bias strongly suspected	⊕⊕⊕⊖ MODERATE	2415	2426	-	-	SMD 0.96 SD lower (1.14 lower to 0.78 lower)
Reduction	of pai	n intensity	of 50% or	more							
460 (9 RCTs)	not serious ª	not serious <sup>g</sup>	not serious <sup>c</sup>	serious <sup>h</sup>	publication bias strongly suspected <sup>e,i</sup>	⊕⊕⊖⊖ LOW º	28/219 (12.8%)	106/241 (44.0%)		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; VAS: Visual analogue scale; NRS: Numerical rating scale

### Explanations

a. Not serious. We did not rate down because overall, 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

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- 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. I2 >60%) and unexplained and probably associated with the contribution from small sized studies. We downgraded (-1)
- c. Not serious. We did not rate down because 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. We did not rate down because 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. Strongly suspected. Visual inspection of Funnel plots suggested asymmetry and Egger's test detected publication bias. We downgraded (-1)
- f. Large. Effect size was large based on pre-specified criteria by Cohen and remained large after trim-and-fit method. Upgraded (+1)
- g. Not serious. We did not rate down because 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. I2 >0%)
- h. 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).
- participants per trial arm). Number or included studies was inouerate (e.g., 9-10 studies), octione neo consistent evidence from at least 2 large studies i. No - effect not large. The Re = 2.89 and greater than >2.0 or <0.5 generally considered large. However, there was not consistent evidence from at least 2 large studies and there were plausible confounders, so we did not upgrade

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### **TENS versus No Treatment**

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

		Cert	ainty assess	sment				Sur	nmary of fir	ndings	
						li	Study eve (%				ed absolute fects
Participant (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 <sup>b</sup> rious <sup>a</sup>	not serious <sup>c</sup>	serious <sup>d</sup>	publication bias strongly suspected strong association <sup>e</sup>	⊕⊕⊖⊖ Low	304	298	-	-	SMD 0.82 SD lower (1.18 lower to 0.46 lower)	
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CI: Confidence interval; RR: Risk ratio; SMD: Standardised mean difference

### Explanations

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

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. We did not rate down because 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. Strongly suspected. 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. We downgraded for the small study effect (-1)

## TENS versus Standard of Care (SoC)

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

		Cert	ainty assess	sment				Sur	nmary of fir	ndings	
Participants	Risk				Publication	Overall	Study ev (%	ent rates 6)	Relative		ted absolute ffects
(studies) Follow up	of bias	Inconsistency	Indirectness	Imprecision	bias	certainty of evidence	With Standard of Care	With TENS	effect (95% CI)	Risk with Standard of Care	Risk difference with TENS
Pain Inte	nsity F	Rating	~								
3155	not	serious <sup>d</sup>	not serious a	not serious e	nublication		1561	150/	_		

	3155 (61 RCTs)	not serious c	serious <sup>d</sup>	not serious <sup>a</sup>	not serious <sup>e</sup>	publication bias strongly suspected <sup>b,f</sup>	⊕⊕⊖⊖ LOW	1561	1594	-	-	SMD 0.72 SD lower (0.95 lower to 0.5 lower)	
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CI: Confidence interval; RR: Risk ratio; SMD: Standardised mean difference

# Explanations

a. Not serious. We did not rate down because 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.

b. 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) further increasing the effect size (random-effects model). We downgraded (-1) due to small study effect

c. Not serious. We did not rate down because overall RoB was low or unclear except for sample size. We did not downgrade

d. 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. Not serious. We did not rate down because the 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

f. No large effect. SMD categorised as moderate effect size by Cohen's d. Not upgraded

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*TENS versus Other Treatment* We did not GRADE

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## High Frequency versus Low Frequency TENS

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

		Cer	rtainty asse	ssment			Sumn	hary of fir	ndings		
							Study ev (%	ent rates 6)			ed absolute ects
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 Inte	nsity F	Rating									
468 (13 RCTs)	not serious ª	not serious <sup>b</sup>	not serious <sup>c</sup>	serious <sup>d</sup>	none <sup>e,f</sup>	⊕⊕⊕⊖ MODERATE	233	235	-	-	SMD 0.19 lower (0.43 lower to 0.06 higher)
Reduction	n of pa	in intensity	of 50% o	r more		7					
186 (4 RCTs)	not serious ª	not serious <sup>b</sup>	not serious <sup>c</sup>	very serious	publication bias strongly suspected <sup>e,f</sup>	⊕⊖⊖⊖ VERY LOW	39/92 (42.4%)	28/94 (29.8%)	RR 0.72 (0.49 to 1.05)	424 per 1,000	119 fewer per 1,000 (from 216 fewer to 21 more)

CI: Confidence interval; RR: Risk ratio; SMD: Standardised mean difference

## Explanations

a. Not serious. We did not rate down because overall RoB was generally low or unclear except for sample size which was accounted for in imprecision.

b. Not serious. We did not rate down because 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. We did not rate down because 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

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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 showing 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. We did not downgrade

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f. No large effect so we did not upgrade

g. Very 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 (<10 participants); Number of included studies was low (<10 studies); Overall effect estimate confidence intervals showing the possibility of no effect above the threshold of important benefit. We downgraded (-2)

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### Adverse events

# TENS compared with comparator for adverse events irrespective of severity

		Certa	ainty assess	ment				Sun	nmary of fir	ndings	
Participants	Risk				Dublication	Overall	Study event	rates (%)	Relative		d absolute ects
(studies) Follow up	of bias	Inconsistency	Indirectness	Imprecision	Publication bias	certainty of evidence	With Comparator	With TENS	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 <sup>b</sup>	very serious <sup>c</sup>	serious <sup>d</sup>	publication bias strongly suspected <sup>e</sup>	⊕⊖⊖⊖ VERY LOW	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			C						

## Explanations

a. Very serious (-2). Adverse events were generally capture by spontaneous observation rather than through formal study design.

b. Not serious. We did not rate down because overall, there is consistency in the direction of results with some inconsistency in the estimates of the treatment effect c. Very serious (-2). Most trials did not pre-specify formal measurement of AEs. 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

d. Serious (-1). The event rate and trial sample sizes are very low. The optimal information size criterion for benefit was met (i.e. >500 participants per trial arm) but this needs to be substantially larger for harm

e. Strongly suspected. Visual inspection of Funnel plots suggested asymmetry and publication bias

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### **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 <sup>7,131</sup> 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 safe and that adverse events are generally mild and restricted to minor skin reactions such as erythema and itchiness at the site of electrodes <sup>6,131-133</sup>.

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 <sup>102</sup> and that physiological action is via neuromodulation rather than curative (i.e. not dependent on pathology <sup>134,135</sup>).

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.

### 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 <sup>41,136,137</sup>.

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#### 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 <sup>138,139</sup> and neuropathic pain <sup>138,139</sup> 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 <sup>132,140</sup>, but not for non-specific chronic low back pain <sup>141</sup> and intrapartum care (labour pain) <sup>142</sup>.

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

### 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 <sup>143</sup>, chronic low back pain without neurological involvement <sup>144,145</sup> and osteoarthritis of the knee <sup>146</sup>.

#### Conclusions

The debate about the efficacy of TENS has been ongoing since the late 1960s. The novelty of our systematic review is that it is the first to pool all available TENS data for meta-analyses, irrespective of the type of pain.

In conclusion, 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<sup>15</sup>.

- 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 when compared with, or added to, interventions that 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 a 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 <sup>132,140</sup>.
- 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 <sup>141</sup> and intrapartum care (labour pain) <sup>142</sup>.
- 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 <sup>143</sup>, chronic low back pain without neurological involvement <sup>144,145</sup> and osteoarthritis of the knee <sup>147</sup>.
- 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 <sup>148,149</sup>, *trial arm* sample sizes greater than
  200 participants, and the use of methodological criteria for RCTs on TENS reported in <sup>112</sup>.
- 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 <sup>150-152</sup>.

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#### 08\_OL-TABLE1\_IncludedStudies

### ONLINETABLE1

Summary Characteristics	of	in RCT bed
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Reference	Design	Type	Condition	Sample size (women)	Primary TENS comparison	Comparison interventions	TENS regimen	Primary Outcome	Secondary Outcome
Abbasi et al., 2019 <sup>1</sup>	Р	Pr	Procedural - Throughout Pleurodesis	66 (NR)	TENS (HF) + Diclofenac = 33	Placebo TENS (0mA) + diclofenac = 33	Fixed 1 x 50 mins during procedure	Pain intensity (VAS)	Analgesic consumption Blood pressure, heart rate
Abelson et al., 1983 <sup>2</sup>	Р	Pr	Rheumatoid arthritis 🧹	32 (26W)	TENS (HF) = 13	Placebo TENS = 13 (0mA)	Fixed 1 x 15 mins / week x 3 weeks 3 sessions	Pain intensity (VAS) Resting pain Pain on movement (grip task)	Grip strength
Abreu et al., 2010 <sup>3</sup>	Р	Pr	Labour pain	20 (20W)	TENS (HF) = 10	Placebo TENS = 10 (mA barely perceptible)	PRN during labour - first stage	Pain intensity (VAS)	Time to analgesia Duration of analgesia
Acedo et al., 2015 <sup>4</sup>	Р	Pr	Neck pain - chronic non -specific	64 (64W)	TENS (LF, burst, - 100pps) = 32	IFT = 32	Fixed 30 mins / day on days 2, 3, 5 3 sessions	Pain intensity (VAS)	Muscle relaxation (EMG microV)
Adedoyin et al., 2005 <sup>5</sup>	Р	Pr	Osteoarthritis - knee	46 (28W)	TENS (HF) + Exercise = 15	IFT + Exercise = 16 Exercise alone (SoC, no TENS) = 15	Fixed 2 x 20min / week x 4 weeks 8 sessions	Pain intensity (NRS)	WOMAC
Ahmed, 2010 <sup>6</sup>	Р	Pr	Post-op – inguinal hernia repair	60 (0W)	TENS (HF) + paracetamol + diclofenac as needed = 30	Placebo TENS (0mA) + paracetamol + diclofenac as needed = 30	Fixed 2 x 30 mins / day x 5 days 10 sessions	Pain intensity (VAS)	Analgesic consumption Assessment of serum cortisol level
Ahmed et al., 2020 <sup>7</sup>	Р	Pr	Diabetic neuropathic pain	30 (19W)	TENS (LF, AL-TENS) + aerobic exercise = 15	Repetitive transcranial magnetic stimulation (rTMS) + aerobic exercise = 15	Fixed 1 x 20 mins / day x 5 days 10 sessions	Pain intensity (VAS)	Blood β-endorphin level
Alcidi et al., 2007 <sup>8</sup>	Р	Pr	Osteoarthritis - knee - acute	40 (35W)	TENS (HF) = 20	Electromagnetic radiation = 20	Fixed 1 x 20 mins /day x 5 days 5 sessions	Pain intensity (VAS)	Lequesne's index for knee OA
Ali et al., 1981 <sup>9</sup>	Р	Pr	Post-op – abdominal	40 (24W)	TENS (HF) + Demerol = 15	Placebo TENS (0mA) + Demerol = 10 Demerol + No TENS (SoC, no TENS) = 15	PRN 48h Post-operation	No primary outcome	Analgesic consumption Vc FRc arterial PO2
Alizade and Ahmadizad, 2009 <sup>10</sup>	Р	Pr	Back pain – low, chronic	24 (24W)	TENS (HF) + NSAIDs (ibuprofen and diclofenac) = 8	NSAIDs (ibuprofen and diclofenac) + exercise = 8 NSAIDs (ibuprofen and diclofenac, SoC, no TENS) = 8	Fixed 30 mins / day x 3 days / week x 5 weeks	No primary outcome	Modified Oswestry low back pain disability questionnaire

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							15 sessions		
Allais et al., 200311	Р	Pr	Migraine - transformed	60 (60W)	TENS (HF, MF, LF) = 20	Infrared laser therapy = 20 Acupuncture = 20	Fixed 30 mins / day x 5 day / week x 2 weeks 10 sessions	No primary outcome	Number of days with headache per month
Alm et al., 1979 <sup>12</sup>	Р	Е	Post-op – podiatric surgery		TENS (HF) = 50	Placebo TENS (0mA) =25 Control Group (patient records) = 25	PRN Mean duration 20-40 mins / treatment repeated	Pain relief (4- point category scale)	Analgesic consumption
Al-Smadi et al., 2003 <sup>13</sup>	Р	Pr	Back pain – low, multiple sclerosis	15 (n/r)	TENS (HF) = 5 (110 Hz, 200 ms)	Placebo TENS = 5 (0mA) TENS (LF) = 5 (4Hz, 200 ms)	Fixed 1 x 45min / day x 3 days / week x 6 weeks 18 sessions	Pain intensity (VAS)	McGill Pain Questionnaire Roland Morris Disability Questionnaire Leeds MS Specific Quality of Life Questionnaire
Altay et al., 2010 <sup>14</sup>	Р	Pr	Osteoarthritis - knee	40 (30W)	TENS (HF) = 20	Placebo TENS = 20 (0mA)	Fixed 1 x 40 min / day x 3 weeks 21 sessions	Pain intensity (VAS)	WOMAC Beck Depression Inventory Short Form 36 10 steps stairs climbing up-down time 6-minute walk distance
Alvarez-Arenal et al., 2002 <sup>15</sup>	С	Ε	Temporomandibular disorder – bruxism	24 (9W)	TENS (LF) = 24	Splint = 24	Fixed 1 x 45-60 mins every 2 days 15 sessions	Pain intensity on palpation (4-point scale)	Tenderness on palpation (4-point scale) Severity of TMD (pantographic reproducibility index -PRI) Joint noises associated with oral opening and closing (number of 'click' noises)
Alves Silverio et al., 2015 <sup>16</sup>	Р	Pr	Dysphonic – Muscle tension	20 (20W)	TENS $(LF) = 10$	Laryngeal manual therapy = 10	Fixed 2 x 20mins / week x 6 weeks 12 sessions	Pain intensity (VAS)	Nordic musculoskeletal sympton questionnaire Vocal quality - auditory perceptual analysis of voice.
Amer-Cuenca et al., 2011 <sup>17</sup>	Р	Pr	Procedural pain – colonoscopy	90 (50W)	TENS (RF) = 30	Placebo TENS = 30 (0mA) No treatment (unsedated) = 30	Fixed During procedure	Pain intensity (VAS and 5-point Likert scale)	Unusual or adverse events
AminiSaman et al., 2020 <sup>18</sup>	Р	Pr	Procedural pain - Needle insertion - Spinal anaesthesia	60 (25W)	TENS (HF) = 30	Placebo TENS (0mA) = 30	Fixed During needle insertion procedure	Pain intensity (VAS)	Number of attempts to insert needle Duration insertion time
Angulo and Colwell Jr, 1990 <sup>19</sup>	Р	Pr	Post-op – knee replacement	48 (28W)	TENS (sensory threshold) + continuous passive motion + opioids as needed (SoC, No TENS control) = 18	Placebo TENS (active <sdt) +<br="">continuous passive motion + opioids as needed = 18 No TENS + continuous passive motion + opioids as needed (SoC, no TENS) = 12</sdt)>	PRN 20 hours / day x 3 days	Pain intensity (VAS)	Analgesic consumption (Narcotic Knee flexion range of motion
Ardic et al., 2002 <sup>20</sup>	Р	Pr	Myofascial pain	40 (36W)	TENS (HF) + Exercise = 15	Exercises (SoC, no TENS) = 10 Electrical muscle stimulation + Exercises = 15	Fixed 1 x 20mins / day x 2 weeks 14 sessions	Pain intensity (VAS)	Pain threshold on palpation Range of motion
Arvidsson and Eriksson, 1986 <sup>21</sup>	С	Е	Post-op –	15(3W)	TENS (HF) $= 15$	Placebo TENS = 15 (0mA)	Fixed 1 x 15-20 mins	Pain intensity (0- 20 Borg scale)	Quadriceps contraction ability (EMG)

			knee ACL reconstruction			Epidural injection (lidocaine 2.5ug/ml) = 15	1 session	Resting pain Pain on movement (quadriceps contraction)	
Asgari et al., 2018 <sup>22</sup>	Р	Pr	Procedural pain – gynaecologic laparoscopy (shoulder pain)	80 (80W)	TENS $(LF) = 40$	Fentanyl (SoC, no TENS) = 40	Fixed 20 mins during procedure	Pain intensity (VAS)	Analgesic consumption
Atamaz et al., 2012 <sup>23</sup>	P	Pr	Osteoarthritis - knee	203 (167W)	TENS (HF) + Exercise + Education = 37	Placebo TENS + Exercise + Education = 37 (0mA) IFT + Exercise + Education = 31 Placebo IFT + Exercise + Education = 35 Shortwave diathermy + Exercise + Education = 31 Placebo shortwave diathermy + Exercise + Education = 32	Fixed 1 x 20 mins / day x 5 / week x 3 weeks 15 sessions	Pain intensity (VAS)	Analgesic consumption (Paracetamol) Pain free range of motion Patient's satisfaction with the treatment (VAS) WOMAC Nottingham Health Profile
Aydin et al., 2005 <sup>24</sup>	Р	Pr	Spasticity – SCI, lower limb pain	21 (15W)	TENS (HF) + exercise (range of motion, every morning) = 11	Baclofen + exercise (range of motion, every morning) (SoC) = 10	Fixed 1 x 15 min / day x 15 days 15 sessions	Painful spasm scale (3-point scale)	Clinical assessment of spasticity Self-reported and clinical examination Electrophysiologic Assessment of Spasticity H-reflex
Azatcam et al., 2017 <sup>25</sup>	Р	Pr	Myofascial pain	69 (38W)	TENS (HF) + Exercise (Trapezius stretching) = 23	Exercise (Trapezius stretching)(SoC, no TENS) = 23 Kinesiology taping + Exercise (Trapezius stretching) = 23	Fixed 1 x 20 mins / day x 5 days / week x 2 weeks 10 sessions	Pain intensity (VAS)	Pain threshold (algometry) Neck Disability Index Cervical range of motion
Báez-Suárez et al., 2018 <sup>26</sup>	Р	Pr	Labour pain	63 (63W)	TENS (HF) $= 21$	Placebo TENS = 21 (0mA) TENS (MF) = 21	PRN >30 mins / treatment during labour	Pain intensity (VAS)	Care in Obstetrics Measure for Testing Satisfaction (COMFORTS) scale
Bai et al., 2017 <sup>27</sup>	Р	Pr	Dysmenorrhea	134 (134W)	TENS (AF) + Ibuprofen as needed = 67	Placebo TENS (0mA) + ibuprofen as needed) = 67 (0mA)	Fixed 1 x 30 mins / day x 3 days x 3 menstrual cycles 9 sessions	Pain intensity (NRS)	Analgesic consumption (Ibuprofen) Pain relief duration World Health Organization quality of life (WHOQOL)-BREF
Baki et al., 2015 <sup>28</sup>	Р	Pr	Post-op – thoracotomy	40 (15W)	TENS (HF) + tramadol PCA = 20	Paravertebral block+ tramadol PCA = 20	PRN 24 h post op	Pain intensity (VAS) • Resting pain • During cough	Analgesic consumption (Tramadol) Respiratory function FEV1, FEV1/FVC, mean arteria pressure, heart rate, saturation of oxygen
Ballegaard et al., 1985 <sup>29</sup>	С	E	Pancreatitis – chronic	16(NR)	TENS (HF, conventional followed by LF, acupuncture -like) + morphine on request = 11	Placebo TENS (NR) + morphine on request = 11	Fixed 1 x 30 mins / day x 1 week 7 sessions Repeated at each of 3 body sites	Pain intensity (VAS)	Analgesic consumption (Morphine) Treatment preference Daily assessment of well-being (VAS)

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Barbarisi et al., 201030	Р	Pr	Post herpetic neuralgia	30 (15W)	TENS (HF) + Pregabalin =	Placebo TENS + Pregabalin (0mA)	21 sessions Fixed	Pain intensity	SF-McGill Pain Questionnai
Baibailsi et al., 2010	r	rı	Fost herpetic neuraigia	50 (15 W)	16	= 14	1 x 30 mins / day x 9 visits (over 4 weeks) 9 sessions	(VAS)	Sleep interference
Barker et al., 2006 <sup>31</sup>	Р	Pr	Pelvic pain – acute, during transport to hospital	62 (62W)	TENS (HF) = 29	Placebo TENS (0mA) = 33	PRN ~ 30 mins during transportation to hospital 1 session	Pain intensity (VAS)	Oscillometric blood pressure Heart rate Anxiety (VAS) Signs of sympathetic Activity (vasoconstriction/di of arms)
Barker et al., 2008 <sup>32</sup>	P	Pr			TENS (HF) = 28	$\mathbf{e}_{1}$	PRN 2 x 30 min / day x 3 weeks 21 sessions	<ul> <li>Pain intensity (VAS)</li> <li>present pain</li> <li>average pain over a week</li> <li>worst pain over a week</li> </ul>	Oswestry Disability Index Functional physical tests • 5-minute walking distance • 1-minute stair climb • 1 minute standing up and s down from a chair Health Anxiety and Depressi Scale Tampa Scale Kinesiophobia Pain Coping Scale Pain Self Efficacy Questionnaire Patient Global Impression of Change scale
Başkurt et al., 2006 <sup>33</sup>	Р	Е	Shoulder impingement - stage I	92 (60W)	TENS (HF) = 30	Heat (39°, SoC no TENS) = 31 Heat + TENS = 31	Fixed 1 x 20 mins 1 session	Pain intensity (VAS)	Pressure algometry (pressure threshold)
Bayindir et al., 1991 <sup>34</sup>	Р	Е	Post-op – cardiac surgery	89 (29W)	TENS (LF, burst) = 59	Placebo TENS = 30 (0mA)	Fixed 1 x 180 mins	Pain intensity (VAS)	None
Beckwée et al., 2018 <sup>35</sup>	Р	Pr	Post-op – total knee arthroplasty	53 (34W)	TENS (LF, burst) + analgesics + physiotherapy (SoC) = 25	Placebo TENS + analgesics + physiotherapy (SoC) = 28 (0mA)	Fixed 1x 40 mins / day during passive mobilisation x 5 days 5 sessions	Pain intensity (VAS)	Analgesic consumption • Daily opioid analgesia • cumulative opioid analgesia • Non-opioid analgesia Range of motion - Knee flex
Benedetti et al., 1997 <sup>36</sup>	Р	Е	Post-op – thoracic	324 (NR)	TENS (HF) = 103	Placebo TENS (0mA) = 106 Conventional drugs (SoC, no TENS) = 115 (Control)	Fixed 2 x 60 mins in recovery room first 12 h only 2 sessions	Pain intensity (NRS)	Analgesic consumption Time to request further analg
Bennett et al., 2010 <sup>37</sup>	С	E	Cancer bone pain	24 (6W)	TENS (HF) =24	Placebo TENS = 24 (0mA)	Fixed 1 x 60 mins 1 session	Pain intensity (NRS and VRS 4 categories) • Resting pain • Pain on movement	SF-McGill Pain Questionnai Satisfaction questionnaire
Bergeron-Vezina et al., 2018 <sup>38</sup>	С	Е	Back pain – chronic, low, non-specific	21 (11W)	TENS (HF) = 21 (maintaining pulse amplitude)	TENS (HF) = 21 (pulse amplitude fading)	Fixed 1 x 25 mins 1 session	Pain intensity (VAS)	Pain unpleasantness (VAS) Patient's Global Impression Change scale

Bertalanffy et al., 2005 <sup>39</sup>	Р	Pr	Back pain - acute, low, during emergency transport	74 (30W)	TENS (HF) = 35	Placebo TENS = 36 (0mA)	Fixed 1 x ~30 mins during transportation 1 session	Pain intensity (VAS)	Anxiety (VAS) Oscillometric blood pressure Heart rate
Bi et al., 2015 <sup>40</sup>	Р	Pr	Spinal cord injury	52 (16W)	TENS (LF) = 26	Placebo TENS = 26 (0mA)	Fixed 1 x 20mins/day x 3 / week x 12 weeks 36 sessions	Pain intensity (VAS)	McGill Pain Questionnaire
Bilgili et al., 2016 <sup>41</sup>	Р	Pr	Complex regional pain syndrome	30 (16W)	TENS (HF) + contrast bath + whirlpool bath + exercise = 15	Placebo TENS (0mA) + contrast bath + whirlpool bath + exercise = 15	Fixed 1 x 20 mins / day x 15 days 15 sessions	Pain intensity (VAS) at rest	LANSS Douleur Neuropathique en 4 Questions (DN-4) Volumetric oedema (mm) Hand mobility (distance betweer the 2nd and 5th finger pulp and distal palmar line in cm) Range of motion - wrist Hand grip strength Duruöz Hand Index
Binder et al., 2011 <sup>42</sup>	Р	Pr	Post-op – caesarean	42 (42W)	TENS (HF) + morphine PCA = 22	Morphine PCA (SoC, no TENS) = 20	PRN Over 24 hours	Pain intensity (VAS)	Analgesic consumption (Morphine) - PCA Sedation perception (VAS)
Bjersa and Andersson, 2014 <sup>43</sup>	Р	E	Post-op – pancreatic surgery	20 (N/R)	TENS (HF) + SoC (medication) = 9	Placebo TENS = 11 (stimulation as low as possible) + SoC (medication)	PRN >30m/session	Pain intensity (VAS) • Resting (lying) • On movement (walking + deep breathing)	Analgesic consumption (Morphine) Quality of Recovery 40 (QoR-40 EDA infusion rate (ml/h) Total time of TENS usage in minutes during the day of EDA termination and the day after.
Bjersa et al., 2015 <sup>44</sup>	Р	E	Post-op – colon surgery	30 (14W)	TENS (HF) + SoC (medication) = 24	Placebo TENS = 26 (stimulation as low as possible) + SoC (medication)	PRN >30m/session	Pain intensity (VAS) • Resting (lying) • On movement (walking + deep breathing)	Analgesic consumption (oxycodone) Time of TENS usage during the 24 hours after EDA termination Quality of Recovery 40 (QoR-40
Bloodworth et al., 2004 <sup>45</sup>	С	E	Radiculopathy – chronic	13 (7W)	TENS (HF, conventional TENS back) = 13	Placebo TENS (0mA, back) = 13 Placebo TENS (0mA, leg) = 13 TENS (HF, leg) = 13 TENS (RF, back) = 13 TENS (RF, leg) = 13	Fixed 1 x 10 mins 1 session	Pain intensity (VAS)	McGill Pain Questionnaire Walking speed (feet per second)
Bolat et al., 2019 <sup>46</sup>	Р	Pr	Procedural pain - transrectal prostatic biopsy	138 (0W)	TENS (HF) + antibiotic = 73	SoC - intrarectal administration of 60 mg lidocaine gel, an additional infiltration of 5 mL of prilocaine and bupivacaine mixture (5 mL of 2% prilocaine and 5 mL of 0.25% bupivacaine) = 65	Fixed During procedure	Pain intensity (NRS) • probe insertion • biopsy • post-biopsy	Biopsy times
Bono et al., 2015 <sup>47</sup>	Р	Pr	Migraine / tension-type headache - Chronic	160 (127W)	TENS (HF, occipital) + acute medications = 108	Placebo TENS + acute medications = 52 (0mA)	Fixed 3 x 30 mins / day x 14 days	Pain intensity (VAS)	Analgesic consumption Headache-free days per month

Borjesson et al., 1997 <sup>48</sup>	Р	E	Angina – unstable	30 (11W)	TENS (HF) + mediation (angina/analgesia) = 14	Placebo TENS (low level stimulation <10mA on hips) + mediation	14 sessions Fixed 4 x 30 mins / day plus PRN for attacks	Pain intensity (VAS) • Rest	Allodynia symptom check list (12-item) Migraine Disability Assessmen Questionnaire Beck Depression Inventory-II Hamilton Anxiety Rating Scale Analgesic consumption Ischemic episodes, ECG and biochemical outcomes
Borjesson et al., 1998 <sup>49</sup>	С	E	Procedural Pain - oesophageal manometry pain	18 (10W)	TENS (HF) = 18 (at pain - neck)	(angina/analgesia) = 16 Placebo TENS = 18 (active, >SDT, remote to pain - hips)	Fixed Before and during procedure	<ul><li>Pain intensity (11- point Borg scale)</li><li>Oesophageal distension</li></ul>	Treatment feasibility including AEs Hemodynamic BP, heart rate, ECG Manometric variables Oesophageal pH
Borup et al., 2009 <sup>50</sup>	Р	E	Labour pain	607 (607W)	TENS (HF) + analgesics as needed = 144	Traditional analgesics (Control) (SoC, no TENS) = 149 Acupuncture + analgesics as needed = 314	PRN 20-45 mins / sessions	Pain intensity (VAS)	Analgesic consumption Non-or requirements Duration of labour Use of oxytocin Mode of deliv Postpartum Haemorrhage Apgar score Umbilical cord blood pH value
Breit and Van der Wall, 2004 <sup>51</sup>	Р	Е	Post-op - total knee arthroplasty	67 (37W)	TENS (NR) + morphine PCA = 25	Placebo TENS (0mA) + morphine PCA = 22 Morphine PCA (SoC, no TENS) = 22	PRN 1 x 24h post op	Pain intensity (VAS)	<ul> <li>Analgesic consumption</li> <li>Cumulative dose morphine PCA</li> </ul>
Buchmuller et al., 2012 <sup>52</sup>	Р	Pr	Back pain – chronic low non-specific with and without radicular pain	236 (148W)	TENS (HF+LF burst) + daily analgesic medication as required = 117	Placebo TENS (0mA) + daily analgesic medication as required = 119	Fixed 4 x 60 mins / day x 3 months ~?? sessions	Pain intensity (VAS) • Weekly	Analgesic consumption (anti-inflammatory) Roland Morris Disability Questionnaire Dallas questionnaire SF-36 Compliance with TENS treatr Quality of life
Bulut et al., 2011 <sup>53</sup>	Р	Pr	Neuropathic pain – chronic peripheral	40 (23W)	TENS (HF) = 20	Placebo TENS = 20 (0mA)	Fixed 1 x 30 mins / day x 20 days 20 sessions	Pain intensity (VAS)	Pain grade (6 categories)
Bundsen et al., 1982 <sup>54</sup>	Р	Pr	Labour pain	24 (24W)	TENS (HF + LF burst) = 15	Conventional analgesia, control) (SoC, no TENS) = 9	PRN >1 x 15-30 mins During Labour	Pain intensity (5- point categorical scale) • low-back / abdominal pain	Pain experience questionnaire Uterine activity Foetal and neonatal condition
Can et al., 2003 <sup>55</sup>	Р	Е	Knee – chronic, patellofemoral pain	30 (22W)	TENS (HF) = $16 (23 \text{ knees})$	Diadynamic current = 14 (19 knees)	Fixed	Pain intensity (VAS)	Lysholm knee scoring scale a squat

							1 x 30 mins x 4 to 5 / week x 6 weeks <30 sessions		Number of squats performed in 30 seconds 4-level activity test
Casale et al., 2013 <sup>56</sup>	Р	Pr	Carpal tunnel syndrome	20 (10W)	TENS (HF) = 10	Low level laser therapy = 10	Fixed 1 x 30 mins / day x 3 weeks 15 sessions	Pain intensity (VAS)	Severity paraesthesia Median nerve distal motor latence and sensory nerve conduction velocity
Çebi, 2019 <sup>57</sup>	Р	Pr	Post op - pain after impacted third molar surgery	30 (15W)	TENS (HF) = ?15	Routine care (SoC, Pharmacological - Flurbiprofen 100 mg, amoxicillin, chlorhexidine gluconate) = ? 15	Fixed 1 x 15 mins / day x 5 days	Pain intensity (VAS)	None
Celik et al., 2013 <sup>58</sup>	Р	Pr	Spinal cord injury, neuropathic pain	33 (9W)	TENS (LF) = 17	Placebo TENS = 16 (0mA) = 16	Fixed 1x 30m /day x 10 days 10 sessions	Pain intensity (VAS)	None
Cetin et al., 2008 <sup>59</sup>	Р	Pr	Osteoarthritis - knee	100 (100W)	TENS (HF) + hot packs + isokinetic exercise = 20 (Group 2)	Hot packs + isokinetic exercise) (SoC, no TENS) = 20 Shortwave diathermy + hot packs + isokinetic exercise = 20 Ultrasound + hot packs + isokinetic exercise = 20 Isokinetic exercise = 20	Fixed 1 x 20 mins x 3 / week x 8 weeks 24 sessions	Pain intensity (VAS) • After walk	Ambulation Activity - time (secs to walk 50 m Lequesne index Peak torque levels (N·m) knee flexion and extension
Chandra et al., 2010 <sup>60</sup>	Р	E	Post-op – thoracotomy	60 (29W)	TENS (HF) + epidural 10 ml of 0.125% bupivacaine at 2- hourly = 30	Placebo TENS (0mA) + epidural 10 ml of 0.125% bupivacaine at 2- hourly = 30	Fixed 1 x 45 mins	Pain intensity (VAS)	Systolic blood pressure Side effects.
Cheing and Hui-Chan, 1999 <sup>61</sup>	Р	Е	Back pain - chronic low non-specific	30 (9W)	TENS (HF) = 15	Placebo TENS = 15 (0mA)	Fixed 1 x 60 mins	Pain intensity (VAS)	Pain intensity (VAS) to electrically-evoked pain
Cheing and Luk, 2005 <sup>62</sup>	Р	Е	Neuropathic pain	19 (3W)	TENS (HF) = 10	Placebo TENS = 9 (0mA)	Fixed 1x 20m/day x5 days x 2weeks 10 sessions	Pain intensity (VAS)	Downey Hand Centre Hand Sensitivity Test Flexion reflex
Cheing et al., 2002 <sup>63</sup>	Р	Е	Osteoarthritis - knee	62 (52W)	TENS (HF) = 16	Placebo TENS = 16 (0mA) Exercise (SoC, no TENS control) = 15 TENS + Exercise =15	Fixed 1 x 60 mins/day x 5 days / week x 4 weeks 20 sessions	Pain intensity (VAS)	None
Cheing et al., 2003 <sup>64</sup>	Р	Е	Osteoarthritis - knee	38 (34W)	TENS (HF) = 10 (60 mins)	Placebo TENS = 8 (0mA) TENS = 10 (20 mins) TENS = 10 (40 mins)	Fixed 1 x 60 mins/day x 5 days / week x 2 weeks 10 sessions	Pain intensity (VAS) • On movement	Time of 'half-life' for analgesic effect
Chellappa and Thirupathy, 2020 <sup>65</sup>	Р	Pr	Temporomandibular joint disorder	60 (NR)	TENS (HF) = 30	LLLT = 30	Fixed 1 x 15 min/day x 2 / week x 3 weeks	Pain intensity (VAS, may be categorical scale)	Range of motion Palpation
Cherian et al., 2016 <sup>66</sup> – Primary Report	Р	Pr	Osteoarthritis - knee	70 (46)	TENS (AF) = 33	Standard of care = corticosteroid injections + exercises + pharmaceutical management) (SoC, no TENS) = 10	PRN mean = 27 hours / week x 3 months	Pain intensity (VAS)	Analgesic consumption Knee Society Scale (KSS) Lower extremity functional scale (LEFS)

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#### 08\_OL-TABLE1\_IncludedStudies

Secondary Reports Cherian et al., 2015 <sup>67</sup> Cherian et al., 2016 <sup>68</sup>									SF-36 Timed up and-go (TUG) 5-repetition chair rise Timed stair climb test 6-inch step test 2-minute walk test Isokinetic strength Active and passive range of
Chesterton et al., 2013 <sup>69</sup> Secondary Report Lewis, et al., 2015 <sup>70</sup>	P	Pr	Tendinitis - Lateral epicondylitis - Tennis elbow	241 (109W)	TENS (HF) + Primary care management = 121	Primary care management (exercises + education) (SoC, no TENS) = 120	PRN > 1 x 45 mins / day whenever symptoms x 6 weeks	Pain intensity (NRS)	motion. Global change in elbow pain point adjectival scale Pain and limitation in functi (patient-rated tennis elbow evaluation) Number of days of sick leav to tennis elbow EuroQoL EQ-5D (Quality of SF-12 Changes in health beliefs an perceptions Adherence to treatment prot
Chia et al., 1990 <sup>71</sup>	Р	Pr	Labour pain	Sample 1: 101 (101W) Sample 2: 20 (20W) -	Sample 1: TENS (AF) = 48 Sample 2: TENS (AF) = 10	Sample 1: Inhalation analgesia = 53 (ENTONOX) Sample 2: Inhalation analgesia = 10 (ENTONOX)	PRN During labour	Pain intensity (categorical scale) Pain relief (categorical scale)	Analgesic consumption • Request Treatment failure - request t change type of treatment Duration of use of treatment Cervical dilatation and num contractions / 10 mins
Chiou et al., 2019 <sup>72</sup>	Р	Pr	Myofascial pain in neck and shoulder from spinal cord injury	64 (12W)	TENS (LF/HF, on trigger points) = 30	TENS (HF, on remote acupuncture Points) = 30	Fixed 1 x 20 mins / day x 7 days x 1 week	Pain intensity (VAS)	Short-form McGill Pain Questionnaire Hospital Anxiety and Depre Scale Pittsburgh Sleep Quality Inc
Chitsaz et al., 2009 <sup>73</sup>	Р	Pr	Spasticity – multiple sclerosis	59 (44W)	TENS (HF) = 29	Nortriptyline = 30	PRN >20-30 mins x 3/day x 8 weeks	Pain intensity (VAS) • Average	Intensity of sensory complai (VAS)
Chiu et al., 2005 <sup>74</sup>	Р	Pr	Neck pain - chronic non -specific	218 (149W)	TENS (HF) + infrared radiation = 78	Exercise + Infrared radiation = 67 Infrared radiation alone (warmth) = 78	Fixed 1 x 30 mins / day x 2 / week x 6 weeks 12 sessions	Pain intensity (NRS, verbal)	Analgesic consumption Northwick Park Neck Pain questionnaire Percentage subjects on sick Peak isometric strength nech muscles.
Cipriano et al., 2008 <sup>75</sup>	Р	Pr	Post-op – cardiac surgery	45 (13W)	TENS (HF) = 23	Placebo TENS = 22 (active, >SDT-infrequent pulses)	Fixed 1 x 240mins (4h) on the third postoperative	Pain intensity (VAS) • Cough	Spirometry • vital capacity • tidal volume • respiratory rate Electrical muscle activity (E
Cipriano et al., 2014 <sup>76</sup>	Р	Е	Post-op cardiac surgery	38 (18W)	TENS (HF) + pethidine HCl, 20 mg = 20	Placebo TENS (active, >SDT- infrequent pulses) + pethidine HCl, 20 mg = 18 (active)	Fixed 4 x 30mins/day x 5 days 5 sessions	Pain intensity (VAS)	Analgesic consumption (Opioid) Physiological measurements Mean arterial pressure

									Femoral blood flow Femoral vascular conductance Beta-Endorphin levels Sympathetic stimulation test 6-min walking test
Coelho de Amorim et al., 2014 <sup>77</sup>	Р	Pr	Osteoarthritis - knee	24 (20W)	TENS (HF) = 12	Manual therapy = 12	Fixed 1 x 20 mins / day x 3 / week x 4 weeks 12 sessions	Pain intensity (VAS)	WOMAC Stiffness Function
Cooperman et al., 1977 <sup>78</sup>	Р	Pr	Post-op – abdomen	50 (36W)	TENS (HF) + analgesics as rescue (diazepam, 10 mg i.m., meperidol, 75-100 mg i.m.) = 26	Placebo TENS = 24 (0mA)	PRN x 5 days	No primary outcomes	Analgesic consumption
Coyne et al., 1995 <sup>79</sup>	Р	Е	Procedural pain - intravenous needlesticks	61 (35W)	TENS (HF) = 19	Placebo TENS = 21 (not described)	Fixed 1 x 12-32 mins 1 session	Pain intensity (VAS)	Pain unpleasantness (VAS)
Crompton et al., 1992 <sup>80</sup>	Р	Pr	Procedural pain – cervical laser treatment	100 (100W)	TENS (HF) = 34	Local anaesthetic (SoC, no TENS) = 35 TENS + local anaesthetic (lignocaine) = 29	Fixed 1 x <20 mins (duration of procedure)	Pain intensity (VAS)	Satisfaction and utility of TENS
Cuschieri et al., 1985 <sup>81</sup>	Р	Pr	Post-op – abdomen	106 (62W)	TENS (HF) + morphine = 53	Placebo TENS + morphine = 53 (0mA)	PRN 72 hours	Pain intensity (VAS)	Analgesic consumption (Morphine) Arterial blood gas analysis Pulmonary complications
Cuschieri et al., 1987 <sup>82</sup>	Р	Pr	Ischaemic pain - critical leg at rest	20 (10W)	TENS (NR) + morphine = 10	Placebo TENS + morphine = 10 (0mA)	PRN 48 hours	Pain intensity (VAS)	Analgesic consumption (Morphine)
da Silva et al., 2008 <sup>83</sup>	Р	Pr	Fibromyalgia	10 (9W)	TENS (HF) = 5	Hydrotherapy = 5	Fixed 1 x 40 mins/day x3/week x 3 weeks 9 sessions	Pain intensity (VAS)	SF-36 Nottingham Health Profile Beck Depression Index Finger-to-floor test (flexibility test)
da Silva et al., 2015 <sup>84</sup>	Р	Pr	Post-op – liposuction	42 (42W)	TENS (HF) + analgesics (morphine + dipyrone) = 21	Placebo TENS + analgesics (morphine + dipyrone) = 21 (0mA)	Fixed 1 x 30 mins (2h after procedure 1 session)	Pain intensity (VAS)	Analgesic consumption Number and types of adverse effects McGill Pain Questionnaire Patient satisfaction
Dailey et al., 2013 <sup>85</sup>	С	E	Fibromyalgia	43 (40W)	TENS (HF) + other treatments (stable) = 43	Placebo TENS = 43 (fading) + other treatments (stable) No TENS + other treatments (stable) (SoC, no TENS) = 43	Fixed 1 x 60-75 mins 1 session	Pain intensity (VAS) • Resting pain • Pain on movement	Pressure pain threshold at tende points (algometry) Conditioned pain modulation Fatigue at rest and movement (VAS) 6 Minute Walk Test Range of Motion Sit to Stand Test Single Leg Stance
Dailey et al., 2020 <sup>86</sup>	Р	Pr	Fibromyalgia	301 (301W)	TENS (MF) + routine care (pharmacology) = $103$	Placebo TENS (F) = 99	PRN	Pain intensity (NRS)	Brief Pain Inventory

						No TENS (SoC, pharmacology) = 99	At home during activity > 1 x 2 hours / day x 4 weeks	<ul> <li>Resting pain</li> <li>Pain on movement (during 6min walk test)</li> </ul>	Fatigue to 6MWT (NRS) and Multidimensional Assessment of Fatigue Function - International Physical Activity Questionnaire (IPAQ) short form Disease impact Quality of life Global impression of change Fear of Movement Other psychological factors
Davies, 1982 <sup>87</sup>	Р	Pr	Post-op – caesarean	35 (35W)	TENS (HF) + analgesics (papaveretum i.m., paracetamol, Dextropropoxphene as required) = 21	Placebo TENS (0mA) + analgesics (papaveretum i.m., paracetamol, Dextropropoxphene as required) = 14	PRN 24 hours	Pain intensity (VAS)	Analgesic consumption (opioid)
Dawood and Ramos, 1990 <sup>88</sup>	C	Е	Dysmenorrhea - primary	32 (32W)	TENS (HF) + ibuprofen if needed = 32	Placebo TENS + ibuprofen if needed = 32 (0mA) Ibuprofen (SoC, no TENS) = 32	PRN continuously for first 8 hours then PRN	Pain intensity (5 item categorical scale)	Analgesic consumption (Ibuprofen) Pain relief (5 item category sca Menstrual symptoms including pain intensity (5 categories)
De Angelis et al., 2003 <sup>89</sup>	Р	Pr	Procedural pain – hysterectomy	142 (142W)	TENS (HF) = 71	No treatment = 71	Fixed Duration of procedure	Pain intensity (VAS) during procedure	Pain relief Duration of hysteroscopy CO <sub>2</sub> flow Heart rate
De Giorgi et al., 2017 <sup>90</sup>	Р	Pr	Myalgia - Chronic facial (temporomandibular joint)	49 (49W)	TENS (HF) = 34	No treatment (waiting list control) = 15	Fixed 1 x 60 mins /day x 10 weeks 10 sessions	Pain intensity (VAS)	Pericranial Muscle Tenderness Score Cervical Muscle Tenderness Score
de Oliveira, 2012 <sup>91</sup>	Р	E	Dysmenorrhea - primary	15 (15W)	TENS (HF) = 5	Placebo TENS = 5 (0mA) TENS (LF) = 5	Fixed 1 x 30 mins 1 session	Pain intensity (NRS)	Pain interference with daily activities (NRS)
de Orange et al., 2003 <sup>92</sup>	Р	Pr	Labour pain	22 (22W)	TENS (HF) + (Bupivacaine + Sufentanyl epidural) – 11	Analgesic - (Bupivacaine + Sufentanyl epidural (SoC, no TENS) = 11	PRN	Pain intensity (VAS)	Duration of labour Frequency of hypoxia Apgar score
de Sousa et al., 2014 <sup>93</sup>	Р	Е	Post-partum uterine contraction pain	32 (32W)	TENS (HF) = 16	No treatment = 16	Fixed 40 mins during breast feeding 1 session	Pain intensity (NRS)	Treatment satisfaction
DeSantana et al., 200894	Р	Pr	Post-op – inguinal herniorrhaphy	40 (0W)	TENS (HF) + Metamizole (Dipyrone) = 20	Placebo TENS (0mA) + Metamizole (Dipyrone) = 20	Fixed 12 x 30 mins at 2h then 4h Post-op	Pain intensity (NRS) • Resting pain	Analgesic consumption (Metamizole) Nausea medication consumption TENS-Related Questions
DeSantana et al., 2009 <sup>95</sup>	Р	E	Post-op – laparoscopic tubal ligation	64 (64W)	TENS (HF) + medication (Ketoprophen, Hioscin plus Dipyrone and Metochlopramide) = 23	Placebo TENS + medication (Ketoprophen, Hioscin plus Dipyrone and Metochlopramide) = 21 (0mA)	Fixed 1 x 20min 1 sessions	Pain intensity (NRS)	McGill Pain Questionnaire

						TENS (LF) + medication (Ketoprophen, Hioscin plus Dipyrone and Metochlopramide) = 20			
Dewan and Sharma, 2011 <sup>96</sup>	Р	Pr	Adhesive capsulitis	50 (NR)	TENS (HF) = 25	IFT= 25	Fixed 1 x 20 mins x 2 to 3 / week x 4 weeks 10 sessions	Pain intensity (VAS)	Range of motion Constant Murley Assessment (CMA) score
Deyo et al. (1990 <sup>97</sup>	Р	Pr	Back pain – chronic, low, non-specific	125 (73)	TENS (AF, HF, LF burst) = 31	Placebo TENS = 29 (0mA) Placebo TENS + exercises = 29 (0mA) TENS + exercises = 34	Fixed 1 x 45 min x 3/day 3 sessions	Pain intensity (VAS)	Pain improvement (6-point scal Pain improvement (VAS) Pain frequency (5-point scale) Sickness Impact profile Level of activity (self-assessed categories) Straight leg raising test Schober test Use of medical providers
Dibenedetto et al., 1993 <sup>98</sup>	P	Pr	Fibromyalgia	30 (29W)	TENS (HF) = 15	S = Adenosyl–L methionine = 15	Fixed 1 x 20 mins / day at each of 4 MTPs 5 days / week x 6 weeks 30 sessions	Pain intensity (VAS)	Total tender point score • Number • Tenderness intensity (5-point scale) Pressure pain threshold (algometry) Hamilton Rating Scale for Depression Fatigue, sleep, and well-being (VAS) Laboratory tests (complete blood picture) Overall evaluation of efficacy
Dilekci et al., 2016 <sup>99</sup>	Р	Pr	Tendinitis - Lateral epicondylitis	65 (43W)	TENS (HF) + SoC including NSAIDs =30	Standard of care (SoC, no TENS) = 30	Fixed 1 x 30 mins / day 10 sessions	Pain intensity (VAS) • At rest • On movement	Patient-Rated Tennis Elbow Evaluation (PRTEE) questionnaire
Dissanayaka et al., 2016 <sup>100</sup>	Р	Pr	Myofascial pain – syndrome patients with up/ trapezius myofascial trigger point	105 (58W)	TENS (HF) + SoC = $35$	Standard care (SoC, no TENS) = 35 IFT+ standard care = 35	Fixed 1 x 20 mins x 2 / week x 4 weeks 8 sessions	Pain intensity (VAS)	Range of motion – cervical
Dogu et al., 2008 <sup>101</sup>	Р	Pr	Myofascial pain and temporomandibular disorders	30 (28W)	TENS (HF) + rescue analgesic (paracetamol) = 14	Occlusal splint (SoC) = 16	Fixed 1 x 30 mins / day x 5 days / week x 4 weeks 20 sessions.	No pain intensity	Pressure-pain threshold (algometry) during rest and functional activities Pain and range of motion Quality of life both general and specific to masticatory functions SF-36
Domaille and Reeves, 1997 <sup>102</sup>	Р	Е	Post-op – coronary artery bypass	60 (0W)	TENS (HF) + 1 mg morphine PCA = 31	Placebo TENS+ 1 mg morphine PCA = 29 (0mA)	Fixed 1 x 3h	Pain intensity (VAS)	Analgesic consumption (Morphine) - PCA

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Ebadi et al., 2018 <sup>103</sup>	Р	E	Back pain – chronic, low, non-specific	30 (15W)	TENS (HF) = 15	Diadynamic = 15	Fixed 1 x 15 mins	Pain intensity (VAS)	Pressure pain threshold (algometry) Depression Anxiety and Stress Scale (DASS)
Ekblom and Hansson, 1987 <sup>104</sup>	С	E	Oral – acute pain from teeth and/ or surrounding tissue	40 (17W)	TENS (HF) = 11	Placebo TENS = 5 (0mA) TENS (LF) = 11 Vibration = 8 Placebo vibration = 5	Fixed 1 x 30 mins 1 session	Pain intensity (VAS)	Thermal threshold (heat and cold
Ekim et al., 2008 <sup>105</sup>	Р	Pr	Hemiplegic Shoulder Pain	19 (8W)	TENS (HF) + Hemiplegia rehabilitation = 10	Placebo TENS (0mA) + Hemiplegia rehabilitation = 9	Fixed 1 x 20 minutes / day x 5 / week x 3 weeks 15 sessions	Pain Intensity (VAS)	Barthel Index Range of motion - upper limb
Elboim-Gabyzon et al., 2019 <sup>106</sup>	Р	Pr	Post op - following Gamma-nail surgical fixation of extracapsular hip fractures	41 (32W)	TENS (HF) + SoC – physiotherapy = 23	Placebo TENS (0mA) + SoC – physiotherapy = 18	Fixed 1 x 30 mins / day x 5 days 5 sessions	Pain Intensity (NRS) • rest • during night during ambulation	Functional Ambulation Classification instrument Time to complete five sit-to-stand tests Two-minute walk test
Elserty et al., 2016 <sup>107</sup>	Р	Pr	Back pain – chronic, low, non-specific	45 (31W)	TENS (HF) + exercise = 15 (pulse amplitude adjusted every 5 mins, Group B)	Exercises only (SoC, no TENS, Group C) = 15 TENS + exercise = 15 (Fixed pulse amplitude, Group A)	Fixed 1 x 40 mins x 3 / week x 4 weeks	Pain intensity (VAS)	Oswestry Disability Index (ODI) Lumbar range of motion (flexion and extension)
Emmiler et al., 2008 <sup>108</sup>	Р	Pr	Post-op – open cardiac operation	60 (18W)	TENS (HF) + analgesia (pethidine and metamizole) = 20	Placebo TENS + analgesia (pethidine and metamizole) = 20 (0mA) Analgesia (pethidine and metamizole (SoC, no TENS) = 20	Fixed 1 x 60 mins then 60 mins rest then 1 x 60 mins	Pain intensity (VAS)	Analgesic consumption
Engen et al., 2016 <sup>109</sup>	Р	Pr	Post-op – video assisted thoracoscopic surgery	40 (23W)	TENS (VF) + Opioids (morphine - oral) = 20	Opioids (morphine - oral) (SoC, no TENS) = 20	PRN for 48 hours after surgery	Pain intensity (VAS)	Analgesic consumption (opioids blocks) Rating of physical status TENS satisfaction and utility
Erden and Senol Celik, 2015 <sup>110</sup>	Р	Pr	Post-op -posterolateral thoracotomy	40 (10W)	TENS (HF) + analgesics (tramadol / tamoxicam) = 20	No TENS + analgesics (tramadol / tamoxicam) (SoC, no TENS) = 20	Fixed 3 x 30 mins / day x 2 days then 2 x 30 mins / day	Pain intensity (VAS) • Resting pain • During cough	Analgesic consumption (Opioid)
Erdogan et al., 2005 <sup>111</sup>	Р	Pr	Post-op thoracotomy pain	116 (46W)	TENS (HF) + standard medication as needed) = 60	Placebo TENS (0mA) + standard medication as needed = 56	PRN for 48 hours then 1 x 20 mins at 3-hour intervals for 2 days 5 days in total	Pain intensity (VAS) • Resting pain • During cough	Analgesic consumption Spirometric breath functions (FEV1 and FVC) Blood gases (PaO2 and PaCO2)
Erkkola et al., 1980 <sup>112</sup>	Р	Pr	Labour pain	200 (200W)	TENS (NR) + meperidine = 100	No TENS + meperidine (SoC, no TENS) = 100	PRN throughout delivery	Pain intensity (5- point categorical scale)	Pain questionnaire (no description) Desire for analgesics
Escortell-Mayor et al., 2011 <sup>113</sup> Secondary Report	Р	Е	Neck pain - chronic non -specific ('mechanical neck disorder')	90 (80W)	TENS (HF) + exercises and education = 43	Manual therapy + exercises and education (SoC, no TENS) = 47	Fixed 1 x 30 mins / day every 2 days total 10 sessions	Pain intensity (VAS)	Neck Disability Index SF-12 Physical Component Summary (PSC-12)

Escortell Mayor et al., 2008 <sup>114</sup>									Mental Component Summary (MCS-12) Duration of crisis (days) General Health Questionnaire-
Esteban Gonzalez et al., 2015 <sup>115</sup>	Р	Pr	Post-op - thoracotomy (shoulder pain)	50 (10W)	TENS (HF) + analgesics (epidural - paracetamol and ibuprofen or metamizole) = 25	Placebo TENS = 25 (0mA) + analgesics (epidural - paracetamol and ibuprofen or metamizole)	Fixed 1 x 30 mins every 8 hours x 3 days	Pain intensity (VAS) • on movement	Range of motion
Eyigor et al., 2008 <sup>116</sup>	Р	Pr	Osteoarthritis - Knee	45(34W)	TENS (HF) + superficial heat and exercise = 14	Control - superficial heat and exercise (SoC, no TENS) = 15 US + superficial heat and exercise = 15	Fixed 1 x 20 mins / day x 5 days / week x 3 weeks 15 sessions	Pain intensity (VAS)	20-meter walking test Lequesne index WOMAC Isokinetic muscle testing SF 36
Eyigor et al., 2010 <sup>117</sup>	Р	Pr	Tendinitis – rotator cuff	40 (29W)	TENS (HF) + exercises (Codman) + Paracetamol = 20	Intra articular injection of corticosteroid (+ exercises (Codman) + Paracetamol) = 20	Fixed 5 x 30 mins / week for 3 weeks 15 sessions	Pain intensity (VAS) • Resting pain	Analgesic consumption (Paracetamol) Range of motion Shoulder disability questionna (SDQ) Beck depression inventory Doctors satisfaction
Facci et al., 2011 <sup>118</sup>	Р	Pr	Back pain – Chronic, low, non- specific	150 (109W)	TENS (HF) = 50	No treatment (waiting list) = 50 IFT= 50	Fixed 1 x 30 mins / day x 5 days x 2 weeks 10 sessions	Pain intensity (VAS)	McGill Pain Questionnaire Analgesic consumption Duration of pain relieve post intervention
Farahani et al., 2014 <sup>119</sup>	Р	Ε	Headache – primary	45 (20W)	TENS (NR) = 15	No treatment = 15 Neurofeedback behavioural therapy = 15	Fixed 1 x 20 mins / day x 20 days 20 sessions	Pain intensity (? VAS – 100mm)	Frequency of pain Duration of headache Blanchard headache diary
Farina et al., 2004 <sup>120</sup>	Р	Pr	Upper trapezius Myofascial pain syndrome	40 (30W)	TENS (HF) = 21	Frequency modulated neural stimulation = 19	Fixed 1 x 20 mins / day x 5 days / week x 2 weeks 10 sessions	No pain intensity	Disability (NPDVAS) Myofascial trigger point characteristics Pressure pain threshold (algometry). Range of motion
Fatima and Sarfraz, 2019 <sup>121</sup>	Р	Pr	Post op - Caesarean	50 (50W)	TENS (HF) + exercises + analgesics as needed = 25	TENS (LF, 4Hz) + exercises + analgesics as needed = 25	Fixed 2 x 20 mins / day x 3 days 6 sessions	Pain intensity (NRS)	Analgesic consumption
Ferraz and Moreira, 2009 <sup>122</sup>	Р	Е	Post-op - cardiac surgery	20 (6W)	TENS (HF) = 10	Placebo TENS = 10 (0mA)	Fixed 1 x 20 mins 1 session	Pain intensity (NRS)	Analgesic consumption
Ferreira et al., 2011 <sup>123</sup>	Р	Е	Post-op - thoracotomy	30 (12W)	TENS (HF) + fentanyl / bupivacaine = 15	Placebo TENS (0mA) + fentanyl / bupivacaine = 15	Fixed 1 x 60 mins 1 h after epidural on second Post-op day 1 session	Pain intensity (VAS) • Resting pain • Changing decubitus • Pain on movement	None

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								<ul> <li>During cough</li> </ul>	
Ferreira et al., 2017 <sup>124</sup>	Р	Е	Temporomandibular disorder – chronic	40 (30W)	TENS (LF then HF) $= 20$	Placebo TENS = 20 (current fade away to 0mA after 40s)	Fixed 1 x 50 mins 1 session	Pain intensity (VAS)	Pressure pain threshold (algometry) EMG activity
Finsen et al., 1988 <sup>125</sup>	Р	Pr	Post op - major amputation	51 (24W)	TENS (LF) + analgesics (NR) = 17	Placebo TENS + analgesics (NR) = 19 (0mA) Chlorpromazine + placebo TENS (0mA) + analgesics (NR) = 15	Fixed 2 x 30 mins / day x 2 weeks 28 sessions	No primary outcome	Analgesic consumption Presence of phantom pain (tall yes or no answers)
Fiorelli et al., 2012 <sup>126</sup>	Р	Pr	Post-op - thoracotomy	50 (19W)	TENS (HF) + morphine PCA = 25	Placebo TENS + morphine PCA = 25 (0mA)	Fixed 1 x 30 mins at 4h intervals for first 48h then 2 x 30 mins / day from day 3-5 16 sessions	Pain intensity (VAS)	Analgesic consumption (morphine-PCA) Serum cytokines measurement Respiratory function (FVC, FE 1)
Fodor-Sertl et al., 1990 <sup>127</sup>	Р	Pr	Post-op - thoracotomy	40 (7W)	TENS (HF, segmental) + medication = 16	Placebo TENS (non-segmental, placebo control) + analgesic medication = 18	Fixed 15-30 mins 6 post-operative days	No primary outcomes	Analgesic consumption
Forogh et al., 2019 <sup>128</sup>	Р	Pr	Rehabilitation – following ACL surgery	70 (0W)	TENS (HF) + exercise = 35	Exercise (SoC, no TENS) = 35	Fixed 1 x 35 mins / day x 5 days / week x 4 weeks 20 sessions	Pain intensity (VAS)	International knee documentati committee (IKDC) questionnai Range of motion
Forst et al., 2004 <sup>129</sup>	Р	Pr	Peripheral diabetic neuropathy	19 (9W)	TENS (LF) = 12	Placebo TENS = 7 (0mA)	PRN >30 mins / day /leg for 12 weeks	Pain intensity (VAS)	New total symptom score (NT = 6) Sensory nerve threshold (temperature, vibration, pain) Neuropathy total symptom sco 6 (NTSS - 6) Intensity of dysaesthesia, hypaesthesia and muscle weakness (VAS) Peripheral nerve function – vibration perception and temperature thresholds Microvascular blood flow
Forster et al., 1994 <sup>130</sup>	Р	Pr	Post-op - coronary artery bypass graft surgery	45 (0W)	TENS (HF) + Analgesics (morphine/paracetamol) = 15	Placebo TENS Analgesics (morphine/paracetamol) = 15 (0mA) Control Analgesics (morphine/paracetamol), (SoC, no TENS) = 15 (no description)	PRN up to 72 hours post op	Pain intensity (NRS) • Resting pain • During cough	Analgesic consumption (Narcotic)
Fujii-Abe et al., 2019 <sup>131</sup>	Р	Е	Post op – Wisdom tooth extraction	44 (23W)	HF TENS (non-noxious) = 11	Placebo TENS (0mA) = 11 TENS (noxious, conditioned pain modulation = 11 Combined TENS (non-noxious + noxious) = 11	Fixed 1 x 20 mins	Pain intensity (VAS)	None
Galli et al., 2015 <sup>132</sup>	Р	Е	Post-op - nephrectomy	74 (39W)	TENS (HF) + analgesics (unknown) = 37	Placebo TENS (fading) + analgesics (unknown) = 37	Fixed 1 x 60 mins	Pain intensity (NRS) • Resting pain	Respiratory muscle strength Pulmonary function Walk function

								<ul> <li>During cough</li> <li>During pulmonary testing</li> <li>During walking</li> </ul>	
Galloway et al., 1984 <sup>133</sup>	Р	Pr	Post-op - abdominal	40 (30W)	TENS (PRN) + analgesic (Cyclimorph) as required = 14	No treatment (SoC, no TENS) + analgesic (Cyclimorph) as required = 14 TENS + analgesic Ccyclimorph) as required = 12 (Remote - non = segmental)	PRN for 48 hours	Pain intensity (VAS, Likert scale)	Analgesic consumption Wound pain discomfort (VAS)
Garcia-Perez et al., 2018 <sup>134</sup>	Р	Pr	Pressure ulcers (injury)	17 (15W)	TENS (HF) + standard wound care = 9	Standard wound care (SoC, no TENS) = 8	Fixed 1 x 60 mins / day x 3 weeks total 20 sessions	No primary outcome	Pressure injury area Pressure injury healing rate Blood flow in affected lower limb Skin tempOerature Pain Assessment in Advanced Dementia Scale
Gerson et al., 1977 <sup>135</sup>	С	Е	Post herpetic neuralgia	29 (NR)	TENS (NR) = 13	Carbamazepine + Clomipramine = 16	Fixed 1 x 15 mins / week x 4 weeks then one x 15 mins put 2 weeks x 6 weeks ? x 8 weeks too	Pain intensity (VAS).	Analgesic consumption Plasma concentrations of drugs Physical activity and mental outlook (VAS)
Ghoname et al., 1999 <sup>136</sup>	С	E	Back pain - low	60 (31W)	TENS (LF) + analgesics (non-opioid) as required = 60	Placebo PENS (0mA) + analgesics as required = =64 PENS + analgesics as required = = 64 Exercise therapies + analgesics as required = (SoC, no TENS) = 64	Fixed 1 x 30 mins x 3 / week x 3 weeks 9 sessions	Pain intensity (VAS)	Analgesic consumption SF-36 Physical component summary Mental component summary Quality of sleep Well-being)
Ghoname et al., 1999 <sup>137</sup>	С	E	Back pain - Sciatica	64 (34W)	TENS (LF) + analgesics (non-opioid) as required = 64	Placebo PENS + analgesics as required (0mA) = 64 PENS + analgesics as required = 64	Fixed 1 x 30 mins / day x 3 weeks 21 sessions	Pain intensity (VAS)	Analgesic consumption SF-36 Physical activity and quality of sleep during the 24 h interval prior to each treatment session (VAS)
Gilbert et al., 1986 <sup>138</sup>	Р	Pr	Post-op - inguinal herniorrhaphy	40 (0W)	TENS (HF) + Pethidine as required = $20$	Placebo TENS + Pethidine as required = 20 (0mA)	PRN	Pain intensity (VAS)	Analgesic consumption (Pethidine) Expiratory peak flow
Grabiańska et al., 2015 <sup>139</sup>	Р	Pr	Back pain low	60 (NR)	TENS (HF) $= 30$	IFT = 30	Fixed 10 x 20 mins / day	Pain intensity (VAS)	Laitinen Pain Questionnaire
Graff-Radford et al., 1989 <sup>140</sup>	Р	E	Myofascial pain and trigger point sensitivity	60 (45W)	TENS (HF) =12	Sham Control (Staodynamics unit or Pain Suppressor unit. 0mA). =12 TENS (LF, 2hz, 250us, >MDT) = 12 TENS (HF, 50us, SBC) = 12 TENS (Pain Supressor, 4mA, 15Hz burst of 20Khz, active <sdt) 12<="" =="" td=""><td>Fixed 1 x 30 mins 1 session</td><td>Pain intensity (VAS)</td><td>Pressure algometry</td></sdt)>	Fixed 1 x 30 mins 1 session	Pain intensity (VAS)	Pressure algometry
Grant et al., 1999 <sup>141</sup>	Р	Е	Back pain	60 (54W)	TENS (HF) = 28	Acupuncture = 32	PRN	Pain intensity (VAS)	Analgesic consumption Pain subscale of Nottingham Health Profile

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							1 x <30 mins / session and < 6h / day for 4 weeks		Spinal flexion measured from C to S1
Gregorini et al., 2010 <sup>142</sup>	Р	Е	Post-op - cardiac surgery	25 (7W)	TENS (HF) = 13	Placebo TENS (>SDT – infrequent pulses) = 12	Fixed 1 x 4 hours ?? on 3rd post-op day	Pain intensity (VAS)	Respiratory muscle strength Lung volumes and capacity
Grimmer, 1992 <sup>143</sup>	Р	E	Osteoarthritis - knee	60 (37W)	TENS (HF) = 20	Placebo TENS = 20 (0mA) TENS (LF, burst) = 20	Fixed 1 x 30 mins 1 session	Pain intensity (VAS)	Stiffness change (VAS) Pain relief time (in hours) Stiffness relied time (hours) Change on knee circumference Change in knee range of motio Physiological respiratory rate, heart rate and blood pressure
Gschiel et al., 2010 <sup>144</sup>	Р	Pr	Osteoarthritis – knee (gonarthrosis)	45 (32W)	TENS (AF) = 25	Placebo TENS (0mA) = 20	PRN >2 x 30 mins / day for 3-weeks	Pain intensity (VAS)	SF-36 WOMAC Lysholm score
Gunay Ucurum et al., 2018 <sup>145</sup>	Р	Pr	Shoulder impingement syndrome	79 (65W)	TENS (NR) + exercise = 20	Exercise (SoC, no TENS) = 19 IFT + Exercise = 20 US + Exercise = 20	Fixed 1 x ?? mins x 3 / week x 4 weeks 12 sessions	Pain intensity (VAS)	Short Form-36 (SF-36) Disabilities of the Arm, Shoulder and Hand questionnaire (DASH)
Guo and Jia, 2005 <sup>146</sup>	Р	Pr	Fibromyalgia	66 (45W)	TENS (HF) = 22	Routine medication (SoC, no TENS) = 22 EA = 22	Fixed 1 x 30 mins / day for 20 days [repeated for another 20 days] ?? 40 sessions	Pain intensity (VAS)	Analgesic consumption
Hamza et al., 1999 <sup>147</sup>	Р	Pr	Post-op - gynaecological	100 (100W)	TENS (HF) + morphine PCA = 25	Placebo TENS + morphine PCA = 25 (0mA) TENS (LF) + morphine PCA = 25 TENS (AF) + morphine PCA = 25	Fixed 1 x 30 mins at intervals of 2 h or longer while patient awake	Pain intensity (VAS)	Analgesic consumption (PCA morphine) levels of sedation, fatigue, discomfort and nausea
Hanfy and El-Bigawy, 2004 <sup>148</sup>	Р	Pr	Dysmenorrhea – primary	30 (30W)	TENS (HF) = 15	Acupressure = 15	Fixed 1 x 20 mins x 3 days x 3 menstrual cycles	Pain intensity (6- point scale)	Pain relief (5-point scale)
Hansson and Ekblom, 1983 <sup>149</sup>	С	Е	Orofacial pain – acute	62 (36W)	TENS (HF) = 22	Placebo TENS (0mA) = 20 TENS (LF, burst) = 20	Fixed 1 x 30 mins 1 session	Pain intensity (5- point verbal scale)	None
Hansson et al., 1986 <sup>150</sup>	Р	E	Post-op - oral	28 (16W)	TENS (HF) + naloxone = $6$	TENS (LF, burst) + naloxone = 7 Vibration + Naloxone = 7 Naloxone = 8	Fixed 1 x 45 mins 1 session	Pain intensity (5- point verbal scale)	None
Hargreaves and Lander, 1989 <sup>151</sup>	Р	E	Post-op dressing changes following abdominal surgery	75 (34W)	TENS (HF) + meperidine and morphine = 25	Placebo TENS (0mA) + meperidine and morphine = 25 No treatment (+ meperidine and morphine, SoC, no TENS) = 25	Fixed 1 x 15 to 60 mins depending on duration of dressing change 1 session	<ul><li>Pain intensity (VAS)</li><li>During dressing change</li></ul>	Analgesic consumption (prescription and administration
Harrison et al., 1986 <sup>152</sup>	Р	Pr	Labour pain	150 (150W)	TENS (HF+LF burst) = 76	Placebo TENS = 73 (0mA)	PRN During labour	Pain intensity (5- point scale)	Analgesic consumption Hours pf labour Mode of delivery Pain relief reported by the midwife (5-point scale)

Hart et al., 2012 <sup>153</sup>	Р	Pr	Rehabilitation - Anterior cruciate ligament	30 (10W)	TENS (HF) + exercise = 10	Exercise alone (SoC, no TENS) = 10 Cryotherapy + Exercise = 10	PRN Daily x 2 weeks and during in clinic exercise session	Pain intensity (VAS)	Various functional outcomes for knee Tegner activity rating International Knee Documentation Committee subjective knee evaluation form. Circumferential girth (measured at mid-patella)
Hazneci et al., 2005 <sup>154</sup>	Р	Pr	CRPS - reflex sympathetic dystrophy syndrome upper limb	30 (0W)	TENS (HF) +, contrast bathing and exercise programme = 16	Pulsed US on stellate ganglion + contrast bathing and exercise programme = 14	Fixed 1 x 20 mins / day for 3 weeks 21 sessions	Pain intensity (???) • spontaneous pain • provocative pain	Range of motion Quadriceps central activation Loss of mobility, muscle power Oedema
Herrera-Lasso et al., 1993 <sup>155</sup>	Р	Pr	Shoulder – painful syndrome	29 (23W)	TENS (HF) + Exercises + Heat (superficial) = 15	US + Exercises + Heat (superficial) = 14	Fixed 1 x 20 mins / day x 2-5 / week 13 sessions	Pain intensity (VAS)	Range of motion
Hershman, 1989 <sup>156</sup>	Р	Pr	Post op - colorectal or cholecystectomy	95 (47W)	TENS (HF) + omnopon (opiate) = 48	Placebo TENS + omnopon (opiate) (0mA) = 47	PRN 48h post-operative	No primary outcome	Analgesic consumption - Opiate Anti- emetic consumption Duration of hospital stay
Hokenek et al., 2020 <sup>157</sup>	Р	Pr	Migraine – presenting to emergency department	83 (NR)	TENS (HF) + rescue medication = 39	Placebo TENS (0mA) + rescue medication = 39	Fixed 1 x 20mins	Pain intensity (VAS)	Analgesic consumption
Hou et al., 2002 <sup>158</sup>	P	Е	Cervical Myofascial Pain and Trigger Point Sensitivity	71 (59W)	TENS (HF) + hot pack active ROM + stretch with spray (B5) = 9	Hot pack + active ROM + stretch with spray (SoC, no TENS) (B4) = 10 Ischemic compression + TENS (HF) + hot pack + active range of motion + = 9 Hot pack + active range of motion + ischemic compression = 12 Hot pack + active range of motion = 21 IFT+ myofascial release + Hot pack + active range of motion (B6) = 9	Fixed 1 x 20 mins 1 session	Pain intensity (VAS)	Pressure pain threshold and tolerance (algometry) Range of motion
Hruby et al., 2006 <sup>159</sup>	Р	Pr	Procedure pain - Office-based flexible cystoscopy	148 (40W)	TENS (HF) = 48	Placebo TENS (0mA) = 49 No treatment (no analgesics) = 51	Fixed < 5min During procedure 1 session	Pain intensity (VAS)	International Prostate Symptom Score questionnaire Changes in vital signs and IPSS
Hsieh and Lee, 2002 <sup>160</sup>	Р	E	Back pain - chronic low non-specific	133 (89W)	TENS + Medication = 49	Medication - Diclofenac (NSAID), mephenoxalone (muscle relaxant) and antacid (SoC, no TENS) = 31 PENS + medication = 53	Fixed 1 x 15 mins 1 session	Pain intensity (VAS)	Pain drawing instrument Pressure pain threshold (algometry) Quebec Back Pain Disability sc
Hsueh et al., 1997 <sup>161</sup>	Р	Е	Myofascial trigger points	60 (35W)	TENS (HF) = 20	Placebo electrotherapy (0mA) = 18	Fixed 1 x 20 mins	Pain intensity (VAS)	Pressure algometry (pain threshold)

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						Functional electrical muscle stimulation = 22	1 session		Range of motion
Hughes et al., 1988 <sup>162</sup>	Р	Pr	Labour pain	89 (89W)	TENS (NR) + opioids rescue = 29	Placebo TENS (0mA) + opioids rescue = 30 Conventional medication, opioids (SoC, no TENS) = 30	PRN 24h	Pain intensity (VAS)	Analgesic consumption Pain relief (5-point category ran scale) Infant condition Apgar
Husch et al., 2020 <sup>163</sup>	Р	Pr	Post op - thoracotomy	45 (25W)	TENS (HF) + physiotherapy + analgesics = 15	Placebo TENS (fading to 0mA) + physiotherapy + analgesics = 15 Control (SoC, physiotherapy) + analgesics = 15	Fixed 3 x 30 mins / day x 2 days 6 sessions	Pain intensity (VAS)	Analgesic consumption Pulmonary function, respiratory muscle strength
Ilhanli, 2015 <sup>164</sup>	Р	Pr	chronic low back pain with lumbar disc herniation	160 (108W)	Conventional TENS (HF) Hot pack, ultrasound and exercise	Group1= Group2= Acupuncture- like TENS, Group3= Brief-intense TENS, Group4= Sham TENS.	Fixed 5 days/week for 3 weeks	Pain intensity (VAS) Rest Movement	Ostwestry Low Back Pain Disability Questionnaire Short-Form 36 physical component Mental component Scores Modified Lumbar Schober test, Straight Leg Raising test and Femoral Stretching test
Inal et al., 2016 <sup>165</sup>	Р	Pr	Osteoarthritis - knee	90 (90W)	TENS (HF) + physiotherapy (hot pack, US, exercise) = 30	Placebo TENS (0mA) + physiotherapy (hot pack, US, exercise) = 30 TENS (LF) physiotherapy (hot pack, US, exercise) = 30	Fixed 1 x 20 mins / day x 5 weeks 35 sessions	Pain intensity (VAS) • Resting pain • Pain on movement	WOMAC Walking speed (50 metres) Climbing stairs speed (ten stairs
Isik et al., 2017 <sup>166</sup>	Р	Pr	Osteoarthritis - knee	105 (80W)	TENS (HF) = 53	Leech therapy = 52	Fixed 1 x 20min / day x 5 days / week x 3 weeks (in clinic) 15 sessions	Pain intensity (VAS)	WOMAC
Jaafarpour et al., 2008 <sup>167</sup>	Р	Pr	Post-op - caesarean	108 (108W)	TENS (MF) $= 54$	Placebo TENS (0mA) = 54	PRN 24h continuous	Pain intensity (VAS)	Analgesic consumption
Jamison et al., 2019 <sup>168</sup>	Р	Pr	Back pain - chronic low non-specific	68 (41W)	TENS (HF) = 35	Usual treatment (SoC, no TENS) = 33	PRN daily x 3 months	Pain intensity (NRS) • Current pain • Average pain	Pressure algometry (PPT) Quantitative sensory testing Anxiety, depression, and irritability (NRS) Brief Pain Inventory Pain Disability Inventory (PDI) Pain Catastrophizing Scale (PC Hospital Anxiety and Depression Scale (HADS).
Jarzem et al., 2005 <sup>169</sup>	С	Е	Back pain - chronic low non-specific	50 (21W)	TENS (NR, conventional) = 25	Placebo TENS (0mA) = 25	Fixed 3 x 20 mins 3 sessions	Pain intensity (VAS)	Range of motion Straight leg raising Sit-ups and oblique sit-ups
Jensen et al., 1985 <sup>170</sup>	Р	Pr	Arthroscopic knee surgery	90 (18W)	TENS (HF) = 30	Placebo TENS (0mA) = 30 Analgesic (SoC, no TENS control) = 30	PRN < 7 days - discontinuation day measured	Pain intensity (6- point category scale)	Analgesic consumption Medicine rating Range of motion Isokinetic muscle examination Leg volume

Jensen et al., 1991 <sup>171</sup>	Р	Pr	Osteoarthritis - knee	20 (18W)	TENS (HF) = 10	TENS (LF) = 10	Fixed 1 x 30 mins / day x 5 days 5 sessions	Pain intensity (4- point Likert scale) • Resting pain • Pain on movement • Exercise induced	Analgesic consumption (NSAID)
Jones and Hutchinson, 1991 <sup>172</sup>	С	E	Post-op pain – abdominal	31 (16W)	TENS (HF, Para incision) + physiotherapy = 31	Placebo TENS ('modified placebo' remote site, leg) + physiotherapy = 31 Entonox + physiotherapy = 31	Fixed 1 x 20 mins 1 session	Pain intensity (VAS)	Respiratory function Peak expiratory flow rate
Kara et al., 2011 <sup>173</sup>	Р	Pr	Post-op spinal surgery	54 (28W)	TENS (AF,) + Meperidine PCA = 25	Meperidine PCA (SoC, no TENS control) = 29	Fixed 2 x 30- 40 mins with a 3 to 4-hour rest interval	Pain intensity (VAS) • Resting pain • Pain on movement	Analgesic consumption Beck Depression Inventory Timed Up and Go (TUG) test
Kararmaz et al., 2004 <sup>174</sup>	Р	Pr	Procedural pain - during extracorporeal shock wave lithotripsy	66 (42W)	TENS (HF, conventional) = 22	Placebo TENS (active, <sdt) 22<br="" =="">TENS (LF, acupuncture-like) = 22</sdt)>	Fixed ~45-60mins throughout the procedure 1 session	Pain intensity (VAS)	Analgesic consumption (Alfentanil) Nausea and vomiting (tally of yes/no) Aldrete score Patients' satisfaction (4-point scale)
Kayman-Kose et al., 2014 <sup>175</sup>	Р	E	Post-partum pain following (a) Caesarean section – post operative pain + uterine contractions (b) Vaginal delivery – post trauma pain + uterine contractions	(a) = 50 (50W) (b) = 50 (50W)	(a) TENS (HF) = 50 (b) TENS (HF)= 50	(a) Placebo TENS (0mA) = 50 (b) Placebo TENS (0mA) = 50	Fixed 1 x 30min 1 session	Pain intensity (VAS and verbal rating scale)	Analgesic consumption
Keskin et al., 2012 <sup>176</sup>	Р	Pr	Back pain – low, pregnancy-related	79 (79W)	TENS (HF) = 20	Control group (no treatment control) = 21 Exercise (SoC) = 19 Acetaminophen = 19	2 x ? mins / week x 3 weeks	Pain intensity (VAS)	Roland Morris Disability Questionnaire
Kibar et al., 2020 <sup>177</sup>	Р	Pr	Back pain - chronic low non-specific	123 (87W)	TENS (HF) + hot pack + exercise + rescue paracetamol = 31	Placebo TENS (Sham TENS/IFT device, 0mA) + hot pack + exercise + rescue paracetamol = 30 IFT + hot pack + exercise + rescue paracetamol = 30 TENS + IFT + hot pack + exercise + rescue paracetamol = 32	1 x 30 mins / day x 5 / week x 3 weeks 15 sessions	Pain intensity (VAS) • During activity	Lumbar range of motion (ROM) via inclinometer and modified Schober test, patient and physician global assessment Rolland-Morris Disability Questionnaire
Kim et al., 2012 <sup>178</sup>	Р	E	Pain during venous cannulation	100 (60W)	TENS (HF) = 50	Placebo TENS (0mA) = 50	Fixed 1 x 20 min before cannulation 1 session	Pain intensity (NRS)	Adverse effects
Kim et al., 2014 <sup>179</sup>	Р	Pr	Myofascial pain syndrome Mixed	99 (86W)	TENS (NR) + Ketoprofen (NSAID) patch = 24	Ketoprofen (NSAID) patch (SoC) = 25	Fixed 2 x 20 mins / day x 2 weeks	Pain intensity (NRS)	Active range of motion Pressure pain threshold (algometry)

						Heating pad + ketoprofen (NSAID) patch = 25 Topical capsaicin + ketoprofen (NSAID) patch = 25	28 sessions		Neck Disability Index (NDI Safety
Kirupa et al., 2019 <sup>180</sup>	Р	Pr	Temporomandibular joint	30 (NR)	TENS (HF) = 15	Ultrasound = 15	Fixed 1 x 15 mins / day x unclear /week x 4 weeks ? 10 sessions	Pain intensity (VAS)	None
Knobel et al., 2005 <sup>181</sup>	Р	Pr	Labour pain	60 (60W)	TENS (HF, 'tablet electrode') = 20	Placebo TENS (0mA) = 20 TENS using silver spike point electrode = 20	PRN 1 x 120 mins	Pain intensity (VAS)	Analgesic consumption Epidural analgesia Pain relief (calculated from intensity (VAS) Discomfort (NR)
Koca et al., 2014 <sup>182</sup>	Р	Pr	Carpal tunnel syndrome	75 (43W)	TENS (HF) = 25	IFT= 25 Splint therapy = 25	Fixed 1 x 20 mins / day x 5 days / week x 3 weeks 15 sessions	Pain intensity (VAS)	Symptom severity scale BCTQ Neurophysiology (median m nerve latency and sensory no conduction velocity)
Kofotolis et al., 2008 <sup>183</sup>	Р	Pr	Back pain - chronic low non-specific	92 (92W)	TENS (LF) = 23	Placebo TENS (0mA) = 23 Rhythmic stabilisation = 23 TENS (LF) + Rhythmic stabilisation = 23	Fixed 1 x 40-45 mins x 5 days/week x 4 weeks 20 sessions	Pain intensity (VAS/BORG)	Physical activity questionna Oswestry Low Back Pain Disability Questionnaire Range of motion Flexion and extension trunk endurance tests
Koke et al., 2004 <sup>184</sup>	С	Pr	Chronic pain	180 (116W)	TENS (HF, HI, >SDT) = 62	Control (HF, intensity of choice) = 60 TENS (HF, LI, SDT) = 58	PRN 30 mins (HI) or 60 mins (LI) 4 to 6 times / day x 2 weeks 56 sessions	Pain intensity (VAS)	Desire to continue (TENS continuation questionnaire)
Korkmaz et al., 2010 <sup>185</sup>	Р	Pr	Shoulder pain	40 (28W)	TENS (HF) + exercise = 20	Pulsed radiofrequency + exercise = 20	Fixed 1 x 20 mins /day x 5 / week 20 sessions	<ul> <li>Pain intensity (VAS)</li> <li>Resting pain (maximum and mean)</li> <li>Pain on movement (maximum and mean)</li> <li>Pain at night (maximum and mean)</li> </ul>	Range of motion Shoulder Pain and Disability Index SF-36
Kumar and Raje, 2014 <sup>186</sup>	Р	Pr	Tension-type headache	36 (20W)	TENS (LF) = 17	Exercises - Progressive muscular relaxation (SoC) = 19	Fixed 1 x 15 mins / day x 7 days 7 sessions	Pain intensity (VAS)	Lakaev Academic Stress Response Scale
Labrecque et al., 1999 <sup>187</sup>	Р	E	Labour pain (Low back pain)	34 (34W)	TENS (HF) =12	Standard care (massage, whirlpool bath, mobilisation, SoC, no TENS) = 12	PRN During labour	Pain intensity (VAS)	Analgesic consumption (narcotics) Pain unpleasantness (VAS) Labour Agentry Scale (LAS

						Intracutaneous sterile water injections (as a treatment) = 11			Labour and Delivery Satisfaction Index
Laitinen and Nuutinen, 1991 <sup>188</sup>	Р	Pr	Post-op cholecystectomy	60 (53W)	TENS (HF) + Indomethacin = 20	Control opioid analgesics (SoC, no TENS or Indomethacin) = 10 Indomethacin = 10 TENS (LF) + Indomethacin = 20	Unclear > 16 hours	Pain intensity (4 point categorical)	Analgesic consumption (Opioid Blood pressure Heart rate Respiratory frequency Reported side effects
Lang et al., 2007 <sup>189</sup>	Р	Pr	Acute Posttraumatic hip pain during emergency transport	101 (58W)	TENS (HF) $= 30$	Placebo TENS (0mA) = 33	Fixed ~30 mins throughout transport to hospital	Pain intensity (VAS)	Anxiety (VAS) Morphometric characteristics
Langley et al., 1984 <sup>190</sup>	Р	Е	Rheumatoid arthritis (hand) + chronic pain (hand)	33 (24W)	TENS (HF) =11	Placebo TENS (0mA) = 11 TENS (LF, acupuncture -like) = 11	Fixed 1 x 20 mins 1 session	Pain intensity (VAS) • Resting pain • Pain on movement (grip)	Pressure algometry (joint tenderness) Grip strength
Lauretti et al., 2013 <sup>191</sup>	Р	Pr	Fibromyalgia	39 (34W)	TENS (AF, single device) + placebo TENS device = 13	Placebo TENS (0mA, 2 devices) = 10 TENS (AF, two devices) = 13	Fixed 1 x 20min every 12 h x 7 days	Pain intensity (VAS)	Analgesic consumption Quality of sleep and fatigue
Lauretti et al., 2015 <sup>192</sup>	Р	Pr	Dysmenorrhea	40 (40W)	TENS (Alternating between HF continuous, LF burst) = 20	Placebo TENS (0mA) = 20	Fixed 1 x 30mins at 8 h interval x 7 days ~14 sessions	Pain intensity (VAS)	Analgesic consumption (Diclofenac) Quality of life questionnaire
Law and Cheing, 2004 <sup>193</sup>	Р	Pr	Osteoarthritis - knee	34 (unclear)	TENS (HF) = 12	Placebo TENS (0mA) = 10 TENS (LF) = 13 TENS (AF 2/100pps) = 13	Fixed 1 x 40 mins / day x 5 / week x 2 weeks 10 sessions	Pain intensity (VAS) • Pain on movement	Range of motion Time-up-and-Go
Law et al., 2004 <sup>194</sup>	Р	Pr	Osteoarthritis - knee	39 (37W)	TENS (HF) = 22	Placebo TENS (0mA) = 17	Fixed 1 x 40 mins / day x 5 days x 2 weeks 10 sessions	Pain intensity (VAS) • Pain on movement	Range of motion Timed-up-and-Go
Leandri et al., 1990 <sup>195</sup>	Р	Pr	Post stroke - Hemiplegic shoulder pain	60 (44W)	TENS (HF) = 20	Placebo TENS (0mA) = 20 TENS (HF, LI) = 20	Fixed 3 days week x 4 weeks 12 sessions	No primary outcome	Range of motion - pain free
Lee et al., 1990 <sup>196</sup>	Р	Pr	Labour pain	125 (125W)	TENS (HF continuous, LF burst) + analgesics on demand = 58	Placebo TENS (0mA) + analgesics on demand = 33 No treatment (pethidine injections and Entonox inhalation) (SoC, no TENS) = 34	PRN During labour	Pain intensity (NRS)	Analgesic consumption Pain interval TENS satisfaction questionnair
Lee et al., 2015 <sup>197</sup>	Р	Pr	Post-op Colle's fracture	36 (NR)	TENS (HF) = 18	Placebo TENS (0mA) = 18	Fixed 1 x 15min / day x 5 days	Pain intensity (VAS)	Analgesic consumption (PCS morphine and Cataflan)
Lee et al., 2019 <sup>198</sup>	С	E	Cancer pain - head and neck	41 (6W)	TENS (HF) = 40	Placebo TENS (fading) = 40 No treatment = 40	Fixed 1 x 30 mins x 1 / week 1 session	Pain intensity (VAS)	McGill Pain Questionnaire Perception of TENS effectiven (VAS) Oral function tasks Fatigue (VAS)
Leo et al., 1986 <sup>199</sup>	C	Е	Mixed pain	192 (NR)	TENS (HF, 60pps, 250us, tolerance) = 16	TENS (HF, 60pps, 50us, tolerance) = 16	Fixed 1 x 30 mins 1 session	Pain intensity (VAS)	None

						TENS (HF, 60pps, 250us, <sdt) =<br="">16 TENS (HF, 60pps, 50us, <sdt) =<="" th=""><th></th><th></th><th></th></sdt)></sdt)>			
						16 TENS (HF, 60pps, 250us, SDT) = 16			
						TENS (HF, 60pps, 50us, SDT) = 16 TENS (LF, 3pps, 250us, tolerance) = 16			
						TENS (LF, 3pps, 50us, tolerance) = 16			
						TENS (LF, 3pps, 250us, SDT) = 16 TENS (LF, 3pps, 50us, SDT) = 16 TENS (LF, 3pps, 250us, <sdt) =<="" td=""><td></td><td></td><td></td></sdt)>			
						16 TENS (LF, 3pps, 50us, <sdt) 16<="" =="" td=""><td></td><td></td><td></td></sdt)>			
Leonard et al., 2011 <sup>200</sup>	С	Е	Chronic pain - various	23 (15W)	TENS (HF, conventional) = 23	TENS (LF, acupuncture-like) = 23	Fixed 1 x 25 mins 1 session	Pain intensity (NRS)	Pain unpleasantness (NRS) The Patient Global Impress Change (PGIC) scale
Lewers et al., 1989 <sup>201</sup>	Р	Е	Dysmenorrhea - primary	21 (21W)	TENS (LF, acupuncture-like) =10	Placebo pill = 11	Fixed 1 x 30 mins 1 session	Pain intensity (VAS)	McGill Pain Questionnaire Pain rating index
Lewis et al., 1984 <sup>202</sup>	С	Е	Osteoarthritis - knee	30 (22W)	TENS (HF) = 30	Placebo TENS (0mA) = 30	Fixed 3 x 30-60 mins / day x 3 weeks 21 sessions	Pain intensity (VAS)	Analgesic consumption Paracetamol intake Duration of pain relief Pain free range of motion Questionnaire of patients'
Lewis et al., 1994 <sup>203</sup>	С	Е	Osteoarthritis - knee	36 (21W)	TENS (HF) + placebo pills = 36	Placebo TENS (0mA) + placebo pills = 36 Placebo TENS (0mA) + Naproxen (SoC, sham TENS) = 36	PRN > 3 x 30-60 mins / day x 3 weeks	Pain intensity (VAS)	Pain relief (VAS) Pain Index for the Knee Patient Opinion of Treatme Efficacy Piper Pain Intensity Scale
Likar et al., 2001 <sup>204</sup>	Р	Pr	Postop pain	30 (9W)	TENS (HF) + analgesics = 11	Placebo TENS (0mA) + analgesics	PRN	Pain intensity (VAS) • At rest • On movement (abduction)	Analgesic consumption - ti taking the 1st analgesic Blood pressure, Heart rate, Respiratory rate, Side effects,
Lim et al., 1983 <sup>205</sup>	Р	Pr	Postop pain - abdominal	30 (17W)	TENS (NR) = 15	Placebo TENS (0mA) = 15	PRN	Pain intensity (VAS)	Analgesic consumption (morphine)
Lima et al., 2011 <sup>206</sup>	Р	Pr	Post-op - coronary artery bypass graft	20 (10W)	TENS (HF) + usual care (Physiotherapy and analgesics) = 10	Usual care (Physiotherapy and analgesics, SoC, no TENS) = 10	Fixed 1 x 30 mins x 3 / day	Pain intensity (VAS)	Analgesic consumption Muscle strength (MIP) and expiratory muscle strength (MEP) Functional residual capacit (FRC)
Limoges and Rickabaugh, 2004 <sup>207</sup>	Р	Pr	Procedural pain - Screening flexible sigmoidoscopy	90 (39 W)	TENS (HF) = 30	Placebo TENS (0mA) = 30 Verbal encouragement (SoC, no TENS) = 30	Fixed	Pain intensity (NRS, categorical scale)	McGill Pain Questionnaire 12-item questionnaire (Blo nausea, electrode site burn

							10-20 mins throughout procedure 1 session		tingling, present versus previous SFS pain comparison, and degree of procedural difficulty)
Lin et al., 2015 <sup>208</sup>	Р	Pr	Shoulder pain – chronic	33 (25W)	TENS (LF, 2Hz) = 17	Transcutaneous pulsed radiofrequency = 16	Fixed 1 x 15 mins x 3 / week x 1 week 3 sessions	Pain intensity (VAS)	Serum cortisol level
Lin et al., 2019 <sup>209</sup>	Р	Pr	Shoulder pain – chronic	50 (34W)	TENS (HF) = 25	Transcutaneous pulsed radiofrequency = 25	Fixed 1 x 15 mins every other day x 1 week 3 sessions	Pain intensity (VAS)	Treatment comfort level Constant–Murley shoulder (CMS score PEG (pain, enjoyment of life, and general activity) score
Linde et al., 1995 <sup>210</sup>	Р	Pr	Temporomandibular joint disk displacement	31 (26W)	TENS (HF) = 16	Flat occlusal splint (SoC, no TENS) = 15	Fixed 3 x 30 mins / day x 6 weeks 66 sessions	Pain intensity (VAS)	Frequency and intensity of complaints (6-step verbal scale) Pain-Track system (pain intensity VAS, sleep or waking hours, mealtimes)
Linn et al., 1999 <sup>211</sup>	Р	Pr	Post-stroke – shoulder subluxation	40 (22W)	TENS (HF, AM) + standard care (conventional physiotherapy and occupational therapy) = 20	Standard care (conventional physiotherapy and occupational therapy, SoC, no TENS) = 20	Fixed 4 x 30-60 mins / day x 4 weeks 112 sessions	Pain intensity (5- point NRS)	Pain free range of motion Shoulder subluxation (radiological) Upper arm girth
Lison et al., 2017 <sup>212</sup>	Р	Pr	Procedural pain - office hysteroscopy	138 (138W)	TENS (RF) = 46	Placebo TENS (0mA) = 46 Standard care without analgesia (SoC, no TENS) = 46	Fixed 5-30 mins throughout procedure 1 session	Pain intensity (VAS and 5-point verbal scale)	Duration of the procedure Vital parameters Vasovagal symptoms Unusual or adverse TENS events Level of satisfaction with the procedure (NRS)
Liu et al., 1985 <sup>213</sup>	Р	Pr	Post-op - thoracotomy	30 (8W)	TENS $(NR) = 15$	Placebo TENS (active, <sdt) 15<="" =="" td=""><td>Fixed 1 x 20min / day x 10days 10 sessions</td><td>Pain intensity (NRS)</td><td>Passive range of motion Functional activities score</td></sdt)>	Fixed 1 x 20min / day x 10days 10 sessions	Pain intensity (NRS)	Passive range of motion Functional activities score
Liu et al., 2017 <sup>214</sup>	Р	Pr	Migraine	110 (87W)	TENS (HF, TONS) = 22	Placebo TENS (0mA) = 22 Topiramate (SoC, no TENS) = 22 TENS (LF, TONS) = 22 TENS (AF, TONS) = 22	Fixed 1 x 30m/day x 4 weeks 28 sessions	Pain intensity (VAS)	Analgesic consumption Headache diary (frequency, headache intensity, duration) Self-rating depression scale (SDS Self-rating anxiety scale (SAS) Headache Impact Test Patient satisfaction with treatmen
Lofgren and Norrbrink, 2009 <sup>215</sup>	С	Е	Fibromyalgia	32 (32W)	TENS (HF) = 16	Heat therapy (Superficial warmth) = 16	PRN 1 x >30 mins / session as needed x 3 weeks	Pain intensity (VAS, NRS)	Duration of analgesia Fibromyalgia impact questionnaire Treatment preference
Luchesa et al., 2009 <sup>216</sup>	Р	Pr	Post-op coronary artery bypass graft	30 (5W)	TENS (HF) = 15	Placebo TENS (0mA) = 15	PRN 2 x 50 min / day x 5 days	Pain intensity (NRS)	Expiratory flux peak Forced vital capacity Forced expiratory volume
Lundeberg, 1984 <sup>217</sup>	С	Pr	Myalgia - chronic	36 (20W)	TENS (HF) = 9	Placebo pill = 9 EA = 9 Vibration = 9	Fixed ~ 2 x 45 mins / week x 3 weeks 6 sessions	Pain intensity (VAS)	Duration of pain relief

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Lundeberg et al., 1985 <sup>218</sup>	С	Е	Dysmenorrhea - primary	21 (21W)	TENS (HF) = 21	Placebo TENS =21 (0mA) TENS (LF, burst) = 21	Fixed 1 x 45 mins 1 session	Pain intensity (VAS)	Analgesic consumption McGill Pain Questionnaire Duration of pain relief
Machado et al., 2019 <sup>219</sup>	Р	E	Dysmenorrhea	88 (88W)	TENS (HF) + placebo thermotherapy = 22	Placebo TENS + placebo thermotherapy = 22 Thermotherapy (microwave diathermy) + placebo TENS = 22 TENS + Thermotherapy (microwave diathermy) = 22	Fixed 1 x 30 mins 1 session	Pain intensity (NRS)	McGill Pain Questionnaire Conditioned pain modulation tes
Machin et al., 1988 <sup>220</sup>	Р	E	Back pain - chronic low non-specific	30 (?NR)	TENS (HF) = 15	Placebo TENS = 15 (0mA)	Fixed 1 x 20 mins/day, unclear x days/week x 3 weeks 15 sessions	Pain intensity (VAS and verbal descriptive scale)	Pain diary information
Mahure et al., 2017 <sup>221</sup>	Р	Pr	Post-op arthroscopic rotator cuff repair	37 (19W)	TENS (HF) = 21	Placebo TENS = 16 (0mA)	Fixed 4 x 45 min /day x 7 days 28 sessions	Pain intensity (VAS)	Analgesic consumption (Narcotic)
Manigandan et al., 2014 <sup>222</sup>	Р	Pr	Post stroke - subluxation	24 (7W)	TENS (HF, at supraspinatus, posterior deltoid + long head of biceps) + physiotherapy + occupational therapy = 12	TENS (HF, at supraspinatus and posterior deltoid) + physiotherapy + occupational therapy = 12	Fixed 1 x 30-60mins / day x 5 weeks 35 sessions	No primary outcome	Shoulder subluxation in mm (x- ray) Pain - free range of passive later rotation and active shoulder abduction range of motion
Mannheimer and Carlsson, 1979 <sup>223</sup>	С	Е	Rheumatoid arthritis	20 (13W)	TENS (HF) = 20	TENS (LF) = 20 TENS (LF, burst) = 20	Fixed 1 x 10 mins 1 session	Pain intensity (5- point scale)	Loading test (time patient could hold weight) Duration of analgesia
Mannheimer and Whalen, 1985 <sup>224</sup>	Р	Pr	Dysmenorrhea	27 (27W)	TENS (HF) $= 9$	Placebo TENS (0mA) = 9 TENS (LF, acupuncture-like) = 9	Fixed 1 x 30 mins 1 session	Pain intensity (VAS)	Total number of painful days Duration of pain relief
Mannheimer et al., 1978 <sup>225</sup>	С	Е	Rheumatoid arthritis	19 (17W)	TENS (HF, SBC at pain, Group 1) = 19	TENS (SDT at pain, group 2) = 19 TENS (HF, SDT at remote site, Group 3) = 19	Fixed 5 mins / day x 15 days 15 sessions	No primary outcome	Degree of pain relief Loading test (time patient could hold weight)
Mannheimer et al., 1985 <sup>226</sup>	Р	Pr	Severe angina pectoris	23 (4W)	TENS (HF) + antianginal medication as needed = 12	Antianginal medication (SoC, no TENS, 'no treatment' control) = 11	Fixed 3 x 60 mins / day x 10 weeks during anginal attacks 30 sessions	Pain intensity (5- point scale)	Recovery time (min) Frequency of anginal attacks Consumption nitroglycerin Work during exercise Pulse rate, blood pressure Dyspnoea (5-point scale) Electrocardiograms
Mansourian et al., 2019 <sup>227</sup>	Р	Pr	TMJ - Myofascial pain	108 (88W)	TENS (HF) + medication = NR (36)	Medication Control (SoC, no intervention) = NR (36) LLLT + medication = NR (36)	Fixed 1 x 10 mins / day x 3 / week x 3 weeks 10 sessions	Pain intensity (VAS) • at rest • on movement - variety of face and jaw movements	Mouth opening Lateral protrusive movements

Mansuri et al., 2019 <sup>228</sup>	Р	E	Musculoskeletal pain - Muscle tension dysphonia	30 (20W)	TENS (HF) = 15	Placebo TENS (0mA) = 15	Fixed 1 x 20 mins 1 session	Pain intensity (VAS)	Vocal tract discomfort scale Extended Nordic musculoskeletal symptoms questionnaire Auditory-perceptual assessment
Mansuri et al., 2020 <sup>229</sup>	Р	Pr	Musculoskeletal pain - Muscle tension dysphonia	20 (20W)	TENS (LF) + vocal tract training = 10	Vocal tract training (SoC) = 10	Fixed 1 x 50 mins / day x 2 / week x 2 weeks 10 sessions	Pain intensity (VAS)	Extended Nordic Musculoskeleta Symptoms Questionnaire Vocal tract discomfort
Marchand et al., 1993 <sup>230</sup>	Р	Pr	Back pain - chronic low non-specific	42 (22W)	TENS (HF) = 14	Placebo TENS (0mA) = 12 No treatment = 16	Fixed 1 x 30 mins / day x 2 / week x 10 weeks 20 sessions	Pain intensity (VAS)	Pain unpleasantness (VAS)
Mascarin et al., 2012 <sup>231</sup>	Р	Pr	Osteoarthritis - knee	38 (38W)	TENS (MF) = 12	Kinesiology taping = 16 Ultrasound = 10	Fixed 1 x 20 mins / day x 2 / week x 12 weeks 24 sessions	Pain intensity (VAS)	WOMAC Range of motion - knee flexion and extension Six-minute walking test (6-MWT
McCallum et al., 1988 <sup>232</sup>	Р	Pr	Post-op decompressive lumbar laminectomy	20 (13W)	TENS (HF) = 10	Placebo TENS (0mA) = 10	PRN (NR)	No primary outcome	Analgesic consumption Plasma morphine concentrations
Melzack et al., 1983 <sup>233</sup>	Р	Pr	Back pain – acute and chronic low non- specific	41 (22W)	TENS (LF) = 20	Gentle massage = 21	Fixed 2 x 30 mins / week x 5 weeks 10 sessions	Pain intensity (PPI)	McGill Pain Questionnaire Range of motion
Merrill, 1989 <sup>234</sup>	Р	Pr	Post-op urologic surgery	96 (0W)	TENS (NR) + analgesics as needed = 48	Analgesics (SoC, no TENS) = 48	PRN	No primary outcome	Analgesic consumption
Miller et al., 2007 <sup>235</sup>	С	Pr	Spasticity – multiple sclerosis	32 (17W)	TENS (HF, for 8 hrs) = 32	TENS (HF, for 60 mins) = 32	Fixed 1 x 8 hours or 60 mins / day x 2 weeks 14 sessions	Pain intensity (VAS)	Global Spasticity Scale (GSS) Penn Spasm Scale (PSS) TENS experience questionnaire
Milsom et al., 1994 <sup>236</sup>	С	Е	Dysmenorrhea - primary	12 (12W)	TENS (HF, HI) = 12	Naproxen (500 mg, SoC not TENS) = 12	Unclear 1 x 10 seconds repeated as necessary	Pain intensity (5- point scale)	Uterine contractility and intrauterine pressure
Moharic et al., 2009 <sup>237</sup>	Р	Pr	Peripheral diabetic neuropathy	65 (NR)	TENS (HF) = 46	Pregabalin = 5 TENS (HF) + Pregabalin = 14	Fixed 1 x 3h / day x 7 days / week 3 weeks 21 sessions	Pain intensity (VAS)	Pain unpleasantness (VAS Pain interference with daily activities and sleep (VAS) SF-36
Mondal et al., 2019 <sup>238</sup>	Р	Pr	Myofascial pain	109 (86W)	TENS (HF) + + SoC (exercises + heat + medication) = 34	Ultrasound therapy + SoC (exercises + heat + medication) = 36 Trigger point injection (steroid + local anaesthetic) + SoC (exercises + heat + medication) = 39	Fixed 1 x 20 mins per trigger point / day x 2 weeks 14 sessions	Pain intensity (VAS)	Index score of trigger point after palpation Neck disability Index
Moore and Shurman, 1997 <sup>239</sup>	С	Е	Chronic back pain	24 (16W)	TENS (HF) = 24	Placebo TENS (0mA) = 24 NMES = 24 NMES + TENS = 24	Fixed 1 x 5 hours / day x 2 days 2 sessions	Pain intensity (VAS)	Pain relief (VAS)
Mora et al., 2006 <sup>240</sup>	Р	Pr	Renal colic in Emergency care	100 (29W)	TENS (HF) = 39	Placebo TENS (sham, 0mA) = 34	Fixed 1 x 30 mins 1 session	Pain intensity (VAS)	Anxiety (VAS) Morphometric characteristics

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Morgan et al., 1996 <sup>241</sup>	Р	Pr	Procedural pain - Distention shoulder arthrography	60 (32W)	TENS (HF) + Lignocaine = 20	Placebo TENS (active, $\leq$ SDT) + Lignocaine = 20 Lignocaine (SoC, no TENS, control) = 20	Fixed 1 x 20 mins before procedure then throughout procedure 1 session	Pain intensity (VAS)	None
Møystad et al., 1990 <sup>242</sup>	С	Е	Rheumatic disease involving the temporomandibular joint.	19 (17W)	TENS (HF) = 19	Placebo TENS (0mA) = 19 TENS (LF) = 19	Fixed 1 x 30 mins 1 session	Pain intensity (VAS) • At rest • on movement	Muscle tenderness to palpation (3- point scale) Range of motion
Murray et al., 2004 <sup>243</sup>	C	E	Angina pectoris	10 (2W)	TENS (HF) = 10	Placebo pills = 10	Fixed 3 x 60 mins / day x 2 / week 10 sessions	No primary outcome	Treadmill exercise tests • exercise time • Time to maximum ST depression • Rate-pressure product at peak exercise • Time to onset of angina
Mutlu et al., 2013 <sup>244</sup>	Р	Pr	Fibromyalgia	66 (66W)	TENS + Exercise (supervised) = 33	Supervised exercise (SoC, no TENS) = 33	Fixed 1 x 30 mins / day x 5 days x 5 weeks 25 sessions	Pain intensity (VAS – within FIQ)	Fibromyalgia Impact Questionnaire (FIQ) Tender point count) Myalgic pain score SF-36
Nabi et al., 2015 <sup>245</sup>	Р	Pr	Peripheral diabetic neuropathy	65 (29W)	TENS (HF) = 30	Pulsed radiofrequency = 30	Fixed 1 x 20 mins every 2 days x 2 weeks 10 sessions	Pain intensity (NRS)	None
Nash et al., 1990 <sup>246</sup>	Р	Е	Chronic pain	200 (126W)	TENS (HF, continuous, 100pps) = 50	TENS (HF, continuous, 10pps) = 50 TENS (LF, burst, 10pps) = 50 TENS (LF, burst 100pps) = 50	PRN < 2 years	Pain intensity (VAS)	Responders (≥50% reduction in pain) Time to ≥50% reduction in pain
Navarathnam et al., 1984 <sup>247</sup>	Р	Pr	Post-op cardiac surgery	31 (6W)	TENS (NR) + analgesics on demand = 14	Placebo TENS (0mA) + analgesics on demand = 17	PRN	Pain intensity (5- point scale)	Analgesic consumption Spirometry Experience of cardiac surgery (Questionnaire)
Neary, 1981 <sup>248</sup>	Р	Pr	Post incisional surgical pain	200 (NR)	TENS (HF) = 100	Morphine sulphate or Meperidine Hydrochloride (SoC, no TENS) = 100	PRN 1 x 30 mins or as needed	No primary outcome	Analgesic consumption
Neighbours et al., 1987 <sup>249</sup>	Р	Е	Dysmenorrhea	20 (20W)	TENS (LF, acupuncture-like) = 10	Placebo pill = 10	Fixed 1 x 30 mins 1 session	Pain intensity (VAS)	Analgesic consumption McGill Pain Questionnaire Pain rating index
Nesheim, 1981 <sup>250</sup>	Р	Pr	Labour pain	70 (70W)	TENS (LF, burst) = 35	Placebo TENS (0mA) = 35	PRN during labour	No primary outcome	Pain relief (4-point category scale)
Neumark et al., 1978 <sup>251</sup>	Р	Pr	Labour pain	30 (30W)	TENS (NR) = 10	Pethidine (SoC, no TENS) = 5 Placebo TENS (0mA) = 5 Remote TENS (electrodes in wrong positions) = 5 No treatment = 5 (no analgesia	Fixed 70 mins 1 session	Pain intensity (6- point scale)	None
Ng et al., 2003 <sup>252</sup>	Р	Pr	Osteoarthritis - knee	24 (23W)	TENS (LF) + Education about knee care = 8	Education about knee care (SoC, no TENS) = 8 EA + Education about knee care = 8	Fixed 1 x 20 mins on alternative days x each session over 2 weeks	Pain intensity (NRS)	Range of motion Timed Up-and-Go test

							8 sessions		
Nordemar and Thorner, 1981 <sup>253</sup>	Р	Pr	Neck pain - acute cervical pain	30 (18W)	TENS (HF) + neck collar + analgesics = 10	Neck collar + analgesics (SoC, no TENS) = 10 Manual therapy + neck collar + analgesics = 10	Fixed 1 x 30 mins x 3 / week 3 session	Pain intensity (VAS) • at rest • on movement	Analgesic consumption Range of motion
Norrbrink, 2009 <sup>254</sup>	С	Pr	Spinal cord injury neuropathic pain	24 (4W)	TENS (HF) = 24	TENS (LF) = 24	Fixed 3 x 30 to 40 mins / day x 7 days x 2 weeks 42 sessions	Pain intensity (Borg CR-10)	Pain unpleasantness (BORG CR 10) Global pain relief (5-point scale) Multidimensional Pain Inventory Hospital Anxiety and Depression Scale Nordic Basic Sleep Questionnair Life Satisfaction Instrument-9 Ability to cope with pain (NRS)
Olsén et al., 2007 <sup>255</sup>	Р	E	Postpartum uterine contractions	21 (21W)	TENS (HF, brief HI) = 12	TENS (HF, LI) = 8	Fixed 1 x 1 min repeated 2 times if necessary 1 session	Pain intensity (VAS)	Uterine contraction discomfort (5 point verbal scale) Discomfort from treatment (5- point verbal scale)
Olsen et al., 2019 <sup>256</sup>	C	E	Dysmenorrhea - primary	16 (16W)	TENS (HF, brief HI) = 7 (7W)	Control (SoC, no TENS, 'delayed intervention) = 9 (9W)	PRN 1 x 60 seconds repeated as needed	Pain intensity (VAS)	Analgesic consumption Limitation in physical function (VAS) Discomfort from the treatment
Oncel et al., 2002 <sup>257</sup>	Р	Pr	Minor rib fracture	100 (41W)	TENS (HF) = 25	Placebo TENS (0mA) + Naproxen NSAID = 25 Naproxen NSAID (SoC, no TENS) = 25 Placebo pills = 25	Fixed 2 x 30 mins / day x 3 days 6 sessions	Pain intensity (VAS)	None
Oosterhof et al., 2006 <sup>258</sup> Secondary reports Oosterhof et al., 2008 <sup>259</sup> , Oosterhof et al., 2012 <sup>260</sup> , Oosterhof et al., 2012 <sup>261</sup>	Р	Pr	Chronic pain, various types	163 (97W)	TENS (HF) = 81	Placebo TENS = 82 (0mA)	PRN x 10 days	Pain intensity (VAS)	TENS satisfaction
Ordog, 1987 <sup>262</sup>	Р	Pr	Acute traumatic pain	100 (NR)	TENS (NR) = 25	Placebo TENS (0mA) = 25 TENS (NR) + acetaminophen with codeine = 25 Placebo TENS (0mA) + acetaminophen with codeine = 25	PRN	Pain intensity (VAS)	TENS satisfaction Side effects
Ozkaraoglu et al., 2020 <sup>263</sup>	Р	Pr	Back pain - low non- specific	40 (19W)	TENS (HF) + ultrasound, hot pack and exercise = 20	High Intensity Laser Therapy (HILT) + ultrasound, hot pack and exercise = 20	Fixed 1 x 20 mins / day x 5 days a week for a total of 20 sessions.	Pain intensity (VAS)	Range of motion Oswestry Disability Questionnai Beck Depression Inventory
Ozkul et al., 2015 <sup>264</sup>	С	Pr	Neuropathic pain in patients with spinal cord injury	24 (6W)	TENS (HF) = 12	Visual illusion = 12	Fixed 1 x 30 mins / day x 5 days x 2 weeks 10 sessions	Pain intensity (VAS)	Neuropathic sign and symptoms (DNa) McGill pain questionnaire Neuropathic Pain Scale (NPS) Brief Pain Inventory

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Oztas and Iyigun, 2019 <sup>265</sup>	Р	Pr	Post-op abdominal surgery	48 (10W)	TENS (LF-HF) + Tramadol PCA + rescue Pethidine = 16	Analgesic Medication (tramadol PCA + rescue pethidine (SoC, no TENS) = 16 TAES + tramadol PCA + rescue pethidine = 16	Fixed 1 x 30 mins at 2h, 18h, 22h, 42, 46h post-op 5 sessions	Pain intensity (VAS)	Analgesic consumption (Tramadol - PCA) Nausea severity (VAS) Vomiting (frequency) Antiemetic consumption Pulmonary function tests
Ozturk et al., 2016 <sup>266</sup>	Р	Pr	Post-op cardiac surgery	120 (39W)	TENS (HF) + morphine (PCA) = 40	Placebo TENS + placebo parasternal block (saline) + morphine (PCA) (Control) = 37 Placebo TENS + Parasternal block = 38	PRN 60 mins treatments with 60 mins rest as needed	Pain intensity (VAS)	Analgesic consumption (morph - PCA) Mean arterial pressure, heart rai and arterial blood gas analysis Duration of extubating, ICU an hospital stay Opioid-related side effects
Padma et al., 2000 <sup>267</sup>	Р	Pr	Labour pain	70 (70W)	TENS (HF) = 50	Placebo TENS (0mA) = 20	PRN	No primary outcome	<ul> <li>Pain relief (4 categories)</li> <li>Subjective assessment (by the patient)</li> <li>Observer Assessment</li> <li>Monitoring mother and foetus</li> <li>Duration of labour APGAR score</li> </ul>
Paker et al., 2006 <sup>268</sup>	Р	Pr	Knee AO	60 (NR)	TENS (HF) = NR	Intra-articular hyaluronic acid injection = NR	Fixed 1 x 20 mins / day x 5 / week x 3 weeks 15 sessions	Pain intensity (5- point scale) from WOMAC	WOMAC Lequesne Index SF-36
Palmer et al., 2014 <sup>269</sup>	Р	Pr	Osteoarthritis - knee	224 (141W)	TENS (HF) + Exercise + education = 73	Placebo TENS (0mA) + Exercise + education = 74 Exercise + education + exercise (SoC, no TENS control) = 77	PRN x 6 weeks	Pain intensity (5- point scale) from WOMAC	WOMAC Maximum knee extensor torque Patient global assessment of change scale Self-efficacy for exercise
Pan et al., 2003 <sup>270</sup>	Р	Е	Tendinitis - Chronic calcific of the Shoulders	60 (39W)	TENS (HF) + hydrocollator pack = 28 (30 shoulders)	Extracorporeal shock wave = 32 (33 shoulders)	Fixed 1 x 20 mins / day x 3 / week x 4 weeks 12 sessions	Pain intensity (VAS)	Constant score Manual muscle test (MMT)
Park et al., 2015 <sup>271</sup>	Р	Pr	Post op thyroidectomy - neck pain	100 (NR)	TENS (HF) = 50	Placebo TENS = 50 (0mA)	Fixed throughout surgery 1 session	Pain intensity (NRS) • Anterior wound pain	Analgesic consumption post- operative
Patil and Aileni, 2017 <sup>272</sup>	Р	Pr	Temporomandibular disorder	36 (23W)	TENS (HF) = 18	Exercise home programme = 18	Fixed 1 x 30 mins / day x once / week x 4 weeks 1 session	Pain intensity (VAS)	Pain free range of motion masticatory muscle tenderness (VAS)
Peacock et al., 2019 <sup>273</sup>	Р	Pr	Chronic pain - Various	100 (22W)	TENS (LF, AL-TENS) + SoC =30	Tennant Biomodulator + SoC = 34 Acupuncture + SoC = 36	PRN 2 x 20min / day x 6 weeks 12 sessions	Pain intensity (VAS, as pain log)	Million visual analogue scale PTSD checklist – military Center for Epidemiological Studies - depression scale
Pietrosimone et al., 2009 <sup>274</sup>	Р	Е	Tibiofemoral OA	33 (16W)	TENS (HF) = 10	No treatment (control) = 12 Focal joint knee cooling = 11	Fixed 1 x 45 mins 1 session	Pain intensity (VAS)	WOMAC Quadriceps CAR

									Peak knee extension torque with maximal voluntary isometric contractions (MVIC)
Pietrosimone et al., 2011 <sup>275</sup> Secondary report Pietrosimone et al., 2010 <sup>276</sup>	Р	Pr	Tibiofemoral OA	36 (21W)	TENS (HF) + Exercises (strengthening) = 12	Placebo TENS (Fading) = 12 Exercise (strengthening, SoC, no TENS control) = 12	PRN >8 hours / day x 4 weeks 21 sessions	No primary outcome	WOMAC Quadriceps strength Peak knee extension torque wit maximal voluntary isometric contractions
Pietrosimone et al., 2020 <sup>277</sup>	Р	Pr	OA, knee [during therapeutic exercise]	90 (39W)	TENS (HF) + Exercises (strengthening) = 30	Placebo TENS (0mA) + Exercises Exercises = 30	PRN during all exercise sessions and during activities of daily living for 4 weeks	No primary outcomes	WOMAC Quadriceps Strength and Voluntary activation Peak knee extension torque with maximal voluntary isometric contractions
Pike, 1978 <sup>278</sup>	Р	Pr	Post-op hip replacement	40 (19W)	TENS (HF) + medication (pethidine) = 20	Medication (pethidine, SoC, no TENS control) = 20	PRN > 8 hours / day	No primary outcome	Analgesic consumption (Pethidine) Pain relief (4 categories) Nausea and vomiting (frequence
Pitangui et al., 2012 <sup>279</sup>	Р	Pr	Post episiotomy pain	40 (40W)	TENS (HF) = 20	No treatment = 20	Fixed 1 x 60 mins 1 session	Pain intensity (NRS) • rest • standing • walking	McGill Pain Questionnaire TENS–related questions Functional limitations
Pitangui et al., 2014 <sup>280</sup>	Р	Е	Post episiotomy pain	33 (40W)	TENS (HF) = 11	Placebo TENS (0mA) = 10 TENS (LF) = 13	Fixed 1 x 30 mins pre- injection 1 session	Pain intensity (NRS) • Resting pain • Pain on movement	Treatment satisfaction TENS–related questions
Platon et al., 2010 <sup>281</sup>	Р	Pr	Post-op surgical abortion	200 (200W)	TENS (HF, HI) = 100	Fentanyl i.v. (SoC, no TENS control) = 100	Fixed 1 x 1 min (repeated if necessary)	Pain intensity (VAS)	Analgesic consumption Nausea (VAS) Time in recovery ward Ramsay sedation score
Platon et al., 2018 <sup>282</sup>	С	Е	Post-op gynaecologic laparoscopic surgery	93 (93W)	TENS (HF, HI) = 47	Morphine i.v. (SoC, no TENS control) = 46	Fixed 1 x 1 min (repeated if necessary)	Pain intensity (VAS)	Analgesic consumption (Opioids) Nausea (VAS) Time in recovery ward Ramsay sedation score
Prabhakar and Ramteke, 2011 <sup>283</sup>	Р	Е	Radiculopathy - cervical	75 (39W)	TENS (HF) + Hot fomentation + Exercises, Isometric neck (Group B) = 25	Hot fomentation + Exercises, Isometric neck (SoC, no TENS control, Group C) = $25$ Cervical contralateral lateral flexion mobilization + Hot fomentation + Exercises, Isometric neck (Group A) = $25$	Fixed 1 x 30 mins 1 session	Pain intensity (VAS)	Northwick Park neck pain questionnaire Neuropathic pain scale, SF-McGill Pain Questionnaire
Presser et al., 2000 <sup>284</sup>	Р	Е	Procedural pain - Injection of epidural steroids	90 (30W)	TENS (HF) = 30	Placebo TENS (active, <sdt) +<br="">Local anaesthetic = 30 Local anaesthetic (SoC, no TENS control) = 30</sdt)>	Fixed Throughout procedure	Pain intensity (VAS)	None

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Rainov et al., 1994 <sup>285</sup>	Р	Pr	Post-op spinal surgery	234 (121W)	TENS (Alternating F) + analgesic medication = 126	Analgesic medication (SoC, no TENS control) = 108	Fixed 1 x 60 mins every 2 hours ? how many days?	Pain intensity (VAS)	Analgesic consumption Pain unpleasantness (VAS)
Rajfur et al., 2017 <sup>286</sup>	Р	Pr	Back pain - chronic low non-specific	127 (73W)	TENS (HF) + exercise = 20	Exercise (SoC, no TENS control) = 21 TENS (LF, acupuncture = like) + exercise = 20 High-voltage electrical stimulation) + exercise = 22 IFT) + exercise = 22 Diadynamic current) + exercise = 22	Fixed 1 x 60 mins / day x 5 / week x 3 weeks 15 sessions	Pain intensity (VAS)	Modified Laitinen pain scale The Oswestry questionnaire Roland-Morris Disability Questionnaire Lasègue test Schober test Postural stability
Rajpurohit et al., 2010 <sup>287</sup>	Р	Pr	Masticatory muscle pain	60 (24W)	TENS (HF) = 30	Microcurrent electrical nerve stimulation (= 30	Fixed 1 x 20 mins / day x 7 days 7 sessions	Pain intensity (VAS)	Muscle tenderness (algometry)
Rakel and Frantz, 2003 <sup>288</sup>	С	Е	Post-op abdominal surgery	33 (17W)	TENS (MF) + analgesics = 33	Placebo TENS (0mA) + analgesics = 33 Analgesics (SoC, no TENS control) = 33	Fixed 1 x 15 mins for duration of measurements	Pain intensity (NRS)	Iowa Gait Test Pulmonary status
Rakel et al., 2014 <sup>289</sup>	Р	Pr	Post-op knee arthroplasty (control of pain during exercises)	317 (173W)	TENS (HF) + analgesics = 122	Placebo TENS (Fading) + analgesics = 123 Analgesics (SoC, no TENS control) = 72	Fixed 1 x 20 mins before exercise, then during exercise x 1 to 2 / day x 6 weeks	Pain intensity (NRS) • At rest • On movement	Pain catastrophizing State and trait anxiety" Geriatric depression scale Knee injury and osteoarthritis outcome score Quantitative sensory testing Range of motion Gait speed test
Ramanathan et al., 2017 <sup>290</sup>	Р	Pr	Pot op knee arthroplasty	116 (30W)	TENS (NR) + opioid analgesics + femoral nerve block = 58	Placebo TENS (Fading to 0mA) + opioid analgesics + femoral nerve block = 58	PRN 1 x 2 hours followed by 30 mins rest as needed for 6 weeks	Pain intensity (VAS)	Analgesic consumption Time up and go test Range of motion Knee injury and osteoarthritis outcome score SF-12
Ramos et al., 2018 <sup>291</sup>	Р	Pr	Back pain - low, lumbar disc herniation	29 (14W)	TENS (HF) = 14	Exercises (segmental stabilisation, SoC) = 15	Fixed 1 x 60 mins / day x 2 / week x 8 weeks 18 sessions	Pain intensity (VAS)	LM Muscular Fatigue Fatigue Test Transversus abdominis activatior capacity Oswestry Disability Index
Rani et al., 2020 <sup>292</sup>	Р	Pr	Rotator cuff	76 (34W) 70 (32W) analysed	TENS (HF) + SoC + rescue meds = 35	Exercises (SoC, no TENS control) + rescue meds = 35	Fixed 1 x 20mins /day x 5 days	Pain intensity (NRS, pain item from Shoulder Pain and Disability Index)	Shoulder Pain and Disability Index
Ratajczak et al., 2011 <sup>293</sup>	Р	Pr	Back pain – low, desmopathy	80 (57W)	TENS = 40	Diadynamic currents = 40 Healthy participants groups (no TENS) = 40	Fixed 1 x 30 mins / day x 5 days / week x 2 weeks 10 sessions	Pain intensity (VAS)	Functional pain index by Lequesne Range of motion

Rawat et al., 1991 <sup>294</sup>	Р	Pr	Procedural pain - during biliary extracorporeal shockwave lithotripsy	100	TENS (MF, on back) = 25	Placebo TENS (0mA, on back) = 25 TENS (MF, back and acupoints on leg) = 25 Placebo TENS (0mA, on back and acupoints on leg) = 25	PRN throughout procedure	Pain intensity (5- point scale)	Analgesic consumption
Renovato França et al., 2019 <sup>295</sup>	Р	Pr	Radiculopathy – lumbar disc herniation	40 (25W)	TENS = 20	Exercises (Motor control training, SoC) = 20	Fixed 2 x 60 mins / week x 8 weeks 16 session	Pain intensity (VAS)	McGill Pain Questionnaire Oswestry Disability Index Transversus Abdominis Activation Capacity
Reuss et al., 1988 <sup>296</sup>	Р	Pr	Post-op cholecystectomy	64 (50W)	TENS (HF) = 30	No treatment (+ meperidine on demand) = 34	PRN	No primary outcomes	Analgesic consumption Complications
Revadkar and Bhojwani, 2019 <sup>297</sup>	Р	Pr	Dysmenorrhea	30 (30W)	TENS (HF) + rescue medication = 15	IFT + rescue medication= 15	Fixed 1 x 20mins 1 session	Pain intensity (NRS)	None
Ringel and Taubert, 1991 <sup>298</sup>	Р	Pr	Migraine	57 (48W)	TENS (NR) = 31	Ergocomb (prophylactic buccal tablets for migraine) (SoC, no TENS) = 26	PRN >1 x 30 mins / day as needed for 3 months	Pain intensity (4- point scale)	Number of headache days
Robb et al., 2007 <sup>299</sup>	С	Е	Chronic pain associated with breast cancer treatment	41 (411W)	TENS (HF) = 41	Placebo TENS (0mA) = 41 Transcutaneous spinal electroanalgesia = 41	PRN >10-30 mins / day x 3 weeks	Pain intensity (NRS) – from BPI	Analgesic consumption BPI Hospital Anxiety and Depression (HAD) Scale Range of motion Patient satisfaction questionnaire
Robinson et al., 2001 <sup>300</sup>	Р	E	Procedural pain – colonoscopy	33 (NR)	TENS (various F) + standard medication = 10	Placebo TENS (0mA) + standard medication = 13 Standard medication (SoC, no TENS control) = 10	Fixed 1 x 5mins pre- procedure, 1x 5 mins during procedure, 1 x 5 mins post procedure 1 session	Pain intensity (NRS)	Post-procedure evaluation questionnaire
Roche et al., 1985 <sup>301</sup>	Р	Pr	Haemophilia	36 (NR)	TENS (HF) = 28	Placebo TENS (0mA) = 8	PRN 1 x 25 mins continuous from recovery room for 5 days as needed	Pain intensity (NRS)	McGill Pain Questionnaire
Rooney et al., 1983 <sup>302</sup>	Р	E	Post-op – thoracotomy	44 (17W)	TENS (HF) $= 22$	Placebo TENS (0mA) = 22	Fixed 1 x 25 mins 1 session	No primary outcome	Analgesic consumption – (Narcotic)
Rosenberg et al., 1978 <sup>303</sup>	Р	Pr	Post-op cholecystectomy	12 (NR)	TENS (HF) + analgesics = $6$	Analgesics (SoC, no TENS control) = 6	PRN 3 days as needed	No primary outcome	Analgesic consumption Pulmonary function
Rutgers et al., 1988 <sup>304</sup>	Р	Pr	Postherpetic neuralgia	23 (13W)	TENS (HF) = 13	Acupuncture = 10	PRN 3 x 30 mins / week x 1 week then as needed for 6 weeks	Pain intensity (NRS)	None
Sadala et al., 2018 <sup>305</sup>	Р	Е	Procedural pain - during carboxytherapy	84 (84W)	TENS (HF) = 28	Placebo TENS (Fading) – 28 No treatment (Control) = 28	Fixed 1 min / puncture 1 session	Pain intensity (VAS)	None
Sahin et al., 2011 <sup>306</sup>	Р	Е	Cervical myofascial pain syndrome	80 (40W)	TENS (HF, conventional) = 20	Placebo TENS (Fading) = 20 TENS (LF, acupuncture = like) = 20	Fixed 1 x 30min/day x 3 / week	Pain intensity (VAS)	SF-36 Bodily pain subscale

						TENS (LF, burst) = $20$	?? no. weeks? 1 session		
Samadzadeh et al., 2017 <sup>307</sup>	Р	Pr	Labour pain	120 (120W)	TENS (HF, continuous, LF, burst) + meperidine as rescue analgesia = 40	Entonox + meperidine as rescue analgesia = 40 TENS + Entonox + meperidine as rescue analgesia = 40	PRN During labour	Pain intensity (VAS)	Analgesic consumption
Sangtong et al., 2019 <sup>308</sup>	Р	Pr	Osteoarthritis - knee	148 (135W)	TENS (HF) + US = $64$	US = 68	Fixed 1 x 10 mins / day x 5 days x 2 weeks 10 session	Pain intensity (NRS) • At rest • On movement (walking, climbing stairs)	6-min walk test Patient global assessment Adverse events
Santamato et al., 2013 <sup>309</sup>	Р	Pr	Botulinum toxin type A injection for post - stroke spasticity	32 (18W)	TENS (LF) = 16	Shock wave therapy = 16	Fixed 1 x 30 mins / day x 2 / day x 5 days 10 sessions	Pain intensity (VAS)	Spasticity scale Spasm scale
Santana et al., 2016 <sup>310</sup>	Р	Pr	Labour pain	46 (46W)	TENS (HF) + routine obstetric care = 23	Routine obstetric care (SoC, no TENS control) = 23	Fixed 1 x 30 mins / day x 5 days x 2 weeks 10 sessions	Pain intensity (VAS)	Time to analgesic requireme Pain location
Saranya et al., 2019 <sup>311</sup>	Р	Pr	Muscle pain – Temporomandibular Masticatory Muscle Pain	60 (42W)	TENS (HF) + jaw exercises + hot fomentation = 30	Microcurrent electrical stimulation + jaw exercises + hot fomentation = 30	Fixed 1 x 20min / day x 5 days 5 sessions	Pain intensity (VAS)	Mouth opening and function assessment
Sayilir and Yildizgoren, 2017 <sup>312</sup>	Р	Pr	Back pain - chronic low non-specific	55 (32W)	TENS (HF) = 26	Diadynamic currents = 29	Fixed 1 x 30 mins / day x 5 days/week x 2 weeks 10 sessions	Pain intensity (VAS) • Rest • On movement	Roland Morris Disability Questionnaire Oswestry Disability Index (ODI) Hand finger floor distance (HFFD)
Seo et al., 2013 <sup>313</sup>	Р	Pr	Chronic myofascial pain syndrome	76 (64W)	TENS (LF, burst) + Botulinum toxin A = 38	Botulinum toxin A + electrical stimulation with muscle contraction = 38	Fixed 1 x 30 mins / day x 3 days 3 sessions	Pain intensity (VAS)	Neck Pain and Disability Sc (NPAD) Global Assessment of Improvement Scale (GAS) Pressure algometry (pain threshold)
Serry et al., 2016 <sup>314</sup>	Р	Pr	Peripheral diabetic neuropathy	60 (32W)	TENS (HF) + pharmacological therapy = 20	Pharmacological therapy (SoC, no TENS control) = 20 Exercise (aerobic) + pharmacological therapy =20	Fixed 1 x 30 mins / day x 3 / week x 8 weeks 24 sessions	Pain intensity (VAS)	Nerve conduction studies
Sezen et al., 2017 <sup>315</sup>	Р	Pr	Post-op thoracotomy	87 (25W)	TENS (HF) + Analgesics (diclofenac i.m., tramadol i.v. + paracetamol i.v.) = 43	Placebo TENS + Analgesics (diclofenac i.m., tramadol i.v. + paracetamol i.v.)= 44 (0mA)	PRN During labour at 8 h intervals	Pain intensity (VAS)	Analgesic consumption Pulse rate Blood pressure Saturation Complication
Shahoei et al., 2017 <sup>316</sup>	Р	Pr	Labour pain	90 (90W)	TENS (PRN) = 30	Placebo TENS = 30 (0mA) Routine care (SoC, no TENS control) = 30	PRN During labour	Pain intensity (VAS)	

Shehab and Adham, 2000 <sup>317</sup>	Р	Pr	Shoulder pain	50 (50W)	TENS (HF) + cold pack + stretching exercises = 26	Ultrasound therapy + cold pack + stretching exercises = 24	Fixed 1 x 30 mins / day x 3 to 5 / week x 3 to 5 weeks 13 sessions	Pain intensity (VAS)	Range of motion
Sherry et al., 2001 <sup>318</sup>	Р	Pr	Back pain - chronic low non-specific	44 (21W)	TENS (NR) + analgesics if needed = 22	Vertebral axial decompression = 22	Fixed 1 x 10 mins / day x 20 days then 1 x 10 mins / week x 4 weeks 24 sessions	Pain intensity (VAS)	Disability (4-point scale)
Shimoji et al., 2007 <sup>319</sup>	Р	E	Back pain - chronic low non-specific	28 (24W)	TENS (HF) $= 9$	Placebo TENS (0mA) = 8 TENS (Bidirectional modulated sine waves) = 11	Fixed 1 x 15 mins 1 session	Pain intensity NRS	None
Shimoura et al., 2019 <sup>320</sup>	Р	E	Osteoarthritis - knee	50 (35W)	TENS (MF) = 25	Placebo TENS = 25 (0mA)	Fixed Details NR 1 session	Pain intensity (VAS) • on movement	Climb test Timed Up and Go (TUG) 6-minute walk test (6MWT) Knee extensor strengths 2-step test Stand-up test in the locomotive syndrome risk test.
Shoukry and Al-Ansary, 2019 <sup>321</sup>	Р	Pr	Procedural pain - during Extracorporeal Shock-Wave Lithotripsy (ESWL)	60 (26W)	TENS (HF) + IV fentanyl = 30	IV fentanyl = 30	Fixed 1 treatment Duration not reported but less than 40 mins	Pain intensity (VAS)	Analgesic consumption Modified Post- Anaesthetic Discharge Scoring System adverse effect during or after the procedure Discharge time
Siemens et al., 2020 <sup>322</sup>	С	Pr	Cancer pain - advanced cancer, inpatients	25 (12W)	TENS (HF) + medication = 20	Placebo TENS (0mA) + medication = 20	PRN For 1 day Mean $\pm$ SD = 9.1+7.5h for TENS and 7 $\pm$ 5.6 for placebo 24 h washout	Pain intensity (NRS)	Analgesic consumption Brief Pain Inventory (BPI) Edmonton Classification System for Cancer Pain Douleur Neuropathique en 4 Questions 7-point verbal pain rating scale EORTC QLQC30
Sikiru et al., 2008 <sup>323</sup>	Р	Pr	Pelvic pain, prostatitis - chronic	24 (24M)	TENS (HF) + antibiotics = 8	Placebo pill + antibiotics = 8 Analgesics (Ibuprofen 400mg) + antibiotics (SoC, no TENS control) = 8	Fixed 1 x 20 mins / day x 5 / week x 4 weeks 20 sessions	Pain intensity (NRS)	NIH chronic prostatitis symptom index questionnaire (pain domain
Silva et al., 2012 <sup>324</sup>	Р	Pr	Post-op cholecystectomy	42 (39W)	TENS (HF) + analgesics (Tramadol + Dipyrone) = 21	Placebo TENS (0mA) + analgesics (Tramadol + Dipyrone) = 21	PRN 1 x 30 mins / session as needed	Pain intensity (VAS, verbal NRS)	Occurrence of nausea and emesis
Silva et al., 2014 <sup>325</sup>	Р	Е	Post-mastectomy pain syndrome – chronic, intercostobrachial	18 (18W)	TENS (LF, burst) = 9	TENS (MF, acupuncture-like,) = 9	Fixed 1 x 10-15 mins 1 session	Pain intensity (VAS)	Electroencephalography (EEG) measures
Sim, 1991 <sup>326</sup>	Р	Pr	Post-op cholecystectomy	30 (27W)	TENS (HF) + analgesics (Papaveretum) = 15	Papaveretum, i.m. on demand (SoC, no TENS control) = 15	PRN 1 x 60 mins / day? x 5 days 5 sessions	Pain intensity (VAS) • Resting pain • Coughing • Deep breathing.	Analgesic consumption Spirometer function

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Siqueira et al., 2019 <sup>327</sup>	Р	Pr	Musculoskeletal pain – behavioural dysphonia	27 (27W)	TENS (LF) + vocal training	Placebo TENS (0mA) + vocal therapy	Fixed 1 x 20mins / day 12 sessions	Pain intensity (VAS)	Self-perception of musculoskeletal pain frequent (4-point Likert scale) and intensity Pressure algometry - Pain Threshold
Sloan et al., 1986 <sup>328</sup>	Р	Pr	Rib fracture	24 (NR)	TENS (HF) + paracetamol + dihydrocodeine as required = 12	Naproxen + paracetamol + dihydrocodeine as required (SoC, no TENS control) = 12	PRN 2 post op days	Pain intensity (VAS)	Pain relief (VAS) Arterial blood assays Peak expiratory flow rate Treatment effectiveness (VA
Smania et al., 2005 <sup>329</sup>	Р	Pr	Myofascial pain syndrome	53 (36W)	TENS (HF) = 18	Placebo (ultrasound turned off) = 18 Repetitive magnetic stimulation = 17	Fixed 1 x 20 mins / day x 5 days / week x 2 weeks 10 sessions	Pain intensity (Pain and disability VAS)	Pressure pain threshold (algometry) Range of motion
Smedley et al., 1988 <sup>330</sup>	Р	Pr	Post-op inguinal herniorrhaphy	62 (62W)	TENS (HF) + Omnopon = 34	Placebo TENS (0mA) + Omnopon = 28	PRN 2 days continuously post op Unclear	Pain intensity (VAS)	Analgesic consumption Expiratory flow
Smith et al., 1983 <sup>331</sup>	Р	Pr	Osteoarthritis - knee	30 (20W)	TENS (HF) = 15	Placebo TENS (0mA) = 15	Fixed 1 x 20 mins / day x 8 occasions over 4 weeks 8 sessions	Pain intensity (VAS)	Analgesic consumption Pain chart Sleep disturbance (VAS)
Smith et al., 1986 <sup>332</sup>	Р	Pr	Post-caesarean pain	18 (18W)	TENS (HF) + analgesics = 9	Placebo TENS (0mA) + analgesics = 9	PRN Continuous with 15 mins rest for 3 days post up	Pain intensity (5- point scale)	Analgesic consumption McGill Pain Questionnaire
Sodipo et al., 1980 <sup>333</sup>	Р	Pr	Post-op	30 (NR)	TENS (NR) + analgesics = 15	Narcotic medication (SoC, no TENS control) = 15	PRN 2 days post op	No primary outcome	Analgesic consumption Pulmonary function
Solak et al., 2007 <sup>334</sup>	Р	Pr	Post-op thoracotomy	40 (8W)	TENS (LF) + (no morphine PCA) = 20	Morphine (PCA) (SoC, no TENS control) = 20	Fixed 1 x 30 mins / day ? x 10 days 10 sessions	Pain intensity (VAS)	Analgesic consumption (Morphine - PCA) Prince Henry pain scale Pulmonary function
Solak et al., 2009 <sup>335</sup>	Р	Pr	Post-op coronary bypass grafting	100 (13W)	TENS (HF, continuously) + morphine (PCA) = 25	Placebo TENS + morphine (PCA) = 25 Morphine (PCA)(SoC, no TENS control) = 25 TENS (HF, intermittently) + morphine (PCA) = 25	PRN continuously one day Continuously = on for 24h without break Intermittently = 1h on 1 hr off	Pain intensity (VAS)	Analgesic consumption Duration operation, extubati hospital stay Oximetry Respiratory function
Sonde et al., 1998 <sup>336</sup>	Р	Pr	Post stroke – shoulder pain	44 (17W)	TENS (LF) + Physiotherapy (usual care) = 26	Physiotherapy (SoC, no TENS control) = 18	Fixed 1 x 60 mins / day x 5 days / week x 12 weeks 60 sessions	Pain intensity (VAS)	Fugl-Meyer Ashworth scale Autonomy in activities of da living
Stepanovic et al., 2015 <sup>337</sup>	Р	Pr	Post-herpetic neuralgia	222 (133W)	TENS (HF) = 36	Analgesics (SoC, no TENS control) = 38 Antiviral agents = 71 TENS + antiviral agents = 77	Fixed 1 x 30 mins / day 10 to 15 sessions	Pain intensity (VAS)	Analgesic consumption Allodynia, hyperalgesia or paraesthesia
Steptoe and Bo, 1984 <sup>338</sup>	Р	Pr	Labour pain	25 (25W)	TENS $(HF + LF) = 12$	Placebo TENS $(0mA) = 13$	PRN	Pain intensity	Analgesic consumption

							1 x 30 mins?		
Stratton and Smith, 1980 <sup>339</sup>	Р	Pr	Plantar fasciitis	26 (NR)	TENS (HF) + exercise (stretching) + orthoses = 13	Exercise (stretching) + orthoses (SoC, no TENS control) = 13	Fixed 1 x 20 mins / day x 7 days x 4 weeks 28 sessions	Pain intensity (VAS)	Activities of daily living subsca of Foot and Ankle Ability Measure
Stubbing and Jellicoe, 1988 <sup>340</sup>	Р	Pr	Post-op thoracotomy	40 (12W)	TENS (HF) + opioids (Papaveretum, i.v.) = 20	Papaveretum (i.v.) (SoC, no TENS control) = 20	PRN for 48 hours	Pain intensity (5- categories)	Analgesic consumption Time to transfer to oral analges Peak expiratory flow rate
Suh et al., 2015 <sup>341</sup>	Р	Pr	Musculoskeletal pain - (various types, work- related)	47 (36W)	TENS (HF) = 24	Placebo TENS = 23 (0mA)	Fixed 1 x 60 mins 1 session	Pain intensity (VAS) • resting • on movement	Pressure pain threshold (algometry) Range of motion Fatigue (VAS) • Resting pain • Pain on movement
Talbot et al., 2020 <sup>342</sup>	P	Pr	Knee pain, Patellofemoral pain syndrome	130 (29W)	TENS (HF) + exercise (home programme) = 33	Exercise (home programme) alone (SoC) = 34 Neuromuscular electrical stimulation + exercise (home programme) = 33 Alternating Neuromuscular electrical stimulation and TENS + exercise (home programme) = 30	Fixed 1x 20 mins / day 1 x every 2 days X 9 weeks	Pain intensity (VAS)	Lower Extremity Isometric Strength 30-Second Chair Stand Test (30 SCST) Timed Stair Climb Test (SCT) Forward Step-Down Test Six-Minute Timed Walk Test ( MWT)
Tantawy et al., 2018 <sup>343</sup>	Р	Pr	Chronic orchialgia	71 (0W)	TENS (HF) + analgesic medication = 36	Analgesic medication (SoC, no TENS control) = 35	Fixed 1 x 30 mins / day x 5 / week x 4 weeks 20 sessions	Pain intensity (VAS)	Pin prick Quality of life
Taylor et al., 1981 <sup>344</sup>	C	Е	Osteoarthritis - knee	10 (9W)	TENS (Freq. PRN) = 10	Placebo TENS (0mA) = 10	PRN 1 x 30 to 60 mins or continuously / day 2 weeks at home	Pain intensity (5- point category scale)	Analgesic consumption (5 categories) Ambulation (5 categories)
Taylor et al., 1983 <sup>345</sup>	Р	Pr	Post op abdominal surgery	77 (45W)	TENS (HF) + analgesics = 30	Placebo TENS (0mA) + analgesics = 22 Analgesic medication (SoC, no TENS control) = 25	Fixed 1 x 60 mins x 4 / day (q4h) x 3 post days 12 sessions	Pain intensity (NRS)	Analgesic consumption (Morphine) Physiological depression Patient ambulation Fluid intake
Thakur and Patidar, 2004 <sup>346</sup>	Р	Pr	Labour pain	300 (300W)	TENS (HF) = 100	No treatment = 100 Tramadol (100mg) = 100	PRN	No primary outcome	Pain relief (5 categories) Time taken for onset of analges action Duration of analgesia
Thomas et al., 1988 <sup>347</sup>	Р	Pr	Labour pain	280 (280W)	TENS (NR) = 132	Placebo TENS (0mA) = 148	PRN	Pain intensity (VAS)	Analgesic consumption Labour questionnaire
Thomas et al., 1995 <sup>348</sup>	C	E	Dysmenorrhea - primary	29 (29W)	TENS (HF) = 12	Placebo TENS (0mA) = 12 TENS (LF) = 12	Fixed 1 x 20 mins / day x 2 days 2 sessions	Pain intensity (VAS)	Analgesic consumption Patients perception of improvement (3 category scale) Blood loss (3 category scale) Nausea and vomiting (4 catego scale) Hours of work lost (3 category scale)

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### 08\_OL-TABLE1\_IncludedStudies

Thorsteinsson et al., 1978 <sup>349</sup>	С	E	Chronic pain	93 (53W)	TENS (NR) = 93	Placebo TENS = 93 (0mA)	Fixed 1 x treatment at each of the following (i) at painful site (ii) over main nerve bundle (iii) at remote site 3 sessions	No primary outcomes	<ul> <li>Pain relief (4-categories)</li> <li>Minnesota</li> <li>Multiphasic</li> <li>Personality Inventory</li> <li>Duration of pain relief</li> </ul>
Tilak et al., 2016 <sup>350</sup>	Р	Pr	Phantom limb pain	26 (3W)	TENS (LF, burst) = 13	MVF = 13	Fixed 1 x 20 mins x 4 days 4 sessions	Pain intensity (VAS)	Universal pain score
Tokuda et al., 2014 <sup>351</sup>	Р	Pr	Post-op abdominal	48 (19W)	TENS (HF) + Fentanyl (PCA) + No TENS (Control) = 16	Placebo TENS (fading) + Fentanyl (PCA) = 16 Fentanyl (PCA) (SoC, no TENS control) = 16	PRN 1 x 60 min/day x 3 days	Pain intensity (VAS) • Resting pain • Coughing • Seating	Pulmonary Functions
Tonella et al., 2006 <sup>352</sup>	Р	E	Post-op abdominal	48 (20W)	TENS (HF) + usual care (analgesics and physiotherapy) = NR	Placebo TENS (0mA) + usual care (analgesics and physiotherapy)) = NR Usual care ((analgesics and physiotherapy) SoC, no TENS control) = NR	Fixed 1 x 30 mins for one day? 1 session	Pain intensity (VAS)	Analgesic consumption
Topuz et al., 2004 <sup>353</sup>	Р	Pr	Back pain - chronic low non-specific	60 (41W)	TENS (HF, conventional) = 15	Placebo TENS (0mA) = 12 TENS (LF) =15 Percutaneous neuromodulation therapy = 13	Fixed 1 x 20 min/day x 5 days x 2 weeks 10 sessions	Pain intensity (VAS) • Resting • On movement	Low back pain outcome scale Oswestry disability index Beck Depression Inventory
Tosato et al., 2007 <sup>354</sup>	Р	Е	Temporomandibular disorders	20 (20W)	TENS (NR) = 10	Massage therapy = 10	Fixed 1 x 30 mins 1 session	Pain intensity (VAS)	Electromyography (EMG) measures
Treacy, 1999 <sup>355</sup>	Ρ	Pr	Bruxism	23 (10W)	TENS (LF) = 8	Placebo TENS (0mA) = 8 Relaxation (muscular awareness training) = 8	Fixed 20 to 30 mins / day x 2 / week x 4 months 20 sessions	No primary outcome	Muscle pain from physical examination Degree of discomfort (7-point scale) EMG Cognitive-Somatic Anxiety Questionnaire Beck Depression Inventory Multidimensional health locus of control scales
Tsen et al., 2000 <sup>356</sup>	Р	Pr	Labour pain	40 (40W)	TENS (MF) = NR	Placebo TENS (0mA) = NR	PRN During labour 1 session	Pain intensity (VAS)	Duration of analgesia Pin Prick
Tsen et al., 2001 <sup>357</sup>	Р	Pr	Labour pain	40 (40W)	TENS (MF) = NR	Placebo TENS (0mA) = NR	PRN During labour 1 session	Pain intensity (VAS)	Duration of analgesia Pin Prick
Tsukayama et al., 2002 <sup>358</sup>	Р	Pr	Back pain - chronic low non-specific	20 (16W)	TENS $(LF) = 10$	Electroacupuncture = 9	Fixed 1 x 15 mins / day x 2 / week x 2 weeks 4 sessions	Pain intensity (VAS)	Back pain profile Adverse events
Tucker et al., 2015 <sup>359</sup>	Р	Pr	Procedural pain - bone marrow sampling	70 (32W)	TENS (HF) = 35	Placebo TENS (sub threshold) = 35	Fixed	Pain intensity (NRS)	Treatment perception questionnaire

							throughout procedure 1 session		
Tugay et al., 2007 <sup>360</sup>	Р	E	Dysmenorrhea - primary	32 (32W)	TENS (HF) = 17	IFT = 15	Fixed 1 x 20 mins 1 session	Pain intensity (VAS) • Menstrual pan • Referred lower limbs pain • Low back pain	None
Tulgar et al., 1991 <sup>361</sup>	С	Е	Several painful conditions	27 (11W)	TENS (HF, conventional) = 27	TENS (LF, burst = 27 TENS (modulated frequency) = 27	Fixed 1 x 30 mins / day switch next day 3 days	Pain intensity (VAS)	None
Tulgar et al., 1991 <sup>362</sup>	С	E	Several painful Conditions	14 (7W)	TENS (HF, conventional) = 14	TENS (LF, burst) = 27 TENS (high rate frequency modulation) = 27 TENS (low rate frequency modulation) = 27	Fixed 1 x 20 mins / day switch each day 4 days equals 4 tests 1 session	Pain intensity (VAS)	Duration of pain relief
Unterrainer et al., 2010 <sup>363</sup>	Р	Pr	Post-op lumbar	38 (19W)	TENS + PCA = 13	Placebo TENS + PCA (control) = 11 Placebo TENS + PCA (Pre) + TENS + PCA (post) = 14	Fixed 1 x 30 mins pre-op + 1 x 8 hours post-op + 1 x 30 mins post- op day 1 2 sessions	Pain intensity (VAS)	Analgesic consumption Mini Mental State Examination The Short Cognitive Performance Test
Unterrainer et al., 2012 <sup>364</sup>	Р	Pr	Post-op lumbar interbody fusion	35 (17W)	TENS (HF) + placebo PCA = 17	PCA (piritramide) + Placebo TENS (0mA) (SoC, sham TENS control) = 18	Fixed 1 x 30 mins pre-op 1 x 24 hours post up 1 session	Pain intensity (VAS)	Analgesic consumption (PCA - rescue meds)
Upton et al., 2017 <sup>365</sup>	C	Е	Peripheral diabetic neuropathy	5	TENS (HF, conventional) = 5	TENS (LF, acupuncture-like) = 5	Fixed 1 x 30 mins / day x 10 days 10 sessions	Pain intensity (NRS)	McGill Pain Questionnaire Mechanical detection threshold Patient's Global Impression of Change
Vaidya, 2018 <sup>366</sup>	Р	Pr	Pregnancy induced posterior pelvic pain	30 (30W)	TENS (HF) = 15	Mobilisation of sacroiliac Joint = 15	Fixed 1 x 30 mins / day x 3 / week 5 sessions	Pain intensity (VAS)	Roland Morris disability Questionnaire
Vaillancourt et al., 2019 <sup>367</sup>	Р	Pr	Chronic pain - Various	18 (18W)	TENS (HF) + exercise = 7	Placebo TENS (0mA) + exercise = 8	Fixed 2 x 45mins / session x 2 / week x 4 weeks, 8 sessions	Pain intensity (NRS)	Short-Form McGill Pain Questionnaire Brief Pain Inventory Beck Depression Inventory
Valenza et al., 2016 <sup>368</sup>	Р	Е	Knee pain - anterior	84 (52W)	TENS = 28	No treatment = 28 Stretching = 28	Fixed 1 x 20 mins 1 session	No primary outcome	Analgesic consumption Roland Morris disability score Pressure algometry
van der Ploeg et al., 1996 <sup>369</sup>	Р	Pr	Labour pain	94 (94W)	TENS (HF, continuous + LF, burst) + analgesics (pethidine/promethazine PCA) = 46	Placebo TENS (NR) + analgesics (pethidine/promethazine, PCA) = 48	PRN	Pain intensity (VAS)	Duration of stages of labour Mode of delivery, Foetal status Apgar scores

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van der Spank et al., 2000 <sup>370</sup>	Р	E	Labour pain	59 (94W)	TENS (HF, continuous, burst) + Epidural (drug NR) = 24	Epidural (drug NR) (SoC, no TENS control) = 35	PRN	Pain intensity (VAS)	Analgesic consumption TENS satisfaction questionnaire
Vance et al., 2012 <sup>371</sup>	Р	E	Osteoarthritis - knee	75 (46W)	TENS (HF) = 25	Placebo TENS (Fading) = 25 TENS (LF) = 25	Fixed 1 x 40 to 50 mins 1 session	Pain intensity (VAS) • Rest • On movement (Timed-up-and- go) • Heat evoked - temporal summation	Quantitative sensory testing Pressure algometry, Cutaneous mechanical pain threshold, pressure pain threshold (PPT), heat pain threshold, heat temporal summation] Timed up and go
Vitalii and Oleg, 2014 <sup>372</sup>	Р	Pr	Neuropathic pain associated with spinal cord injury	21 (2W)	TENS (LF) + gabapentin = 11	Placebo TENS (no current stimulation) + gabapentin = 10	Fixed 1 x 30 mins / day x 10 days 10 sessions	Pain intensity (VAS)	Analgesic consumption
Vrouva et al., 2019 <sup>373</sup>	Р	Pr	Rotator cuff	42 (20W)	TENS (HF) + kinesiotherapy	microcurrent electrical nerve stimulation + kinesiotherapy	Fixed 1 x 20 mins / day x 5 / week x 3 weeks 15 sessions	Pain intensity (NRS)	Shoulder pain and disability inde (SPADI) EuroQoL-5 (Quality of life)
Walker et al., 1991 <sup>374</sup>	Р	Pr	Post-op (rehabilitation - total knee arthroplasty	48 (NR)	TENS (HF) + continuous passive motion + analgesic (various opioids) = 18	TENS (subthreshold) + continuous passive motion + analgesics (various opioids) = 18 Continuous passive motion + analgesics (various opioids) (SoC, no TENS control) = 12	PRN continuously 3 days post op	No primary outcome	Analgesic consumption
Wang et al., 2009 <sup>375</sup>	C	E	Dysmenorrhea - primary	21 (21W)	TENS (HF) = 21	Placebo TENS (0mA) = 21	Fixed 1 to 2 x 30 mins / day x 2 days	Pain intensity (NRS, 11-point scale)	Pain location Autonomic and related symptom questionnaire SF-36
Warfield et al., 1985 <sup>376</sup>	Р	Pr	Post-op thoracotomy	24 (NR)	TENS (NR) + opioids = 12	Placebo TENS (0mA) + opioids = 12	PRN Continuous stimulation x ? days	Pain intensity (NRS)	Analgesic consumption Ability to tolerate chest physica therapy (3 categories) Recovery room stay
Warke et al., 2004 <sup>377</sup>	Р	Pr	Back pain – low, multiple sclerosis	15 (NR)	TENS (HF) = 5	Placebo TENS (0mA) = 5 TENS (LF) = 5	Fixed 1 x > 45 mins/day x 6 weeks >42 sessions	Pain intensity (VAS)	Roland Morris Disability Questionnaire Barthel Activities of Daily Livin Rivermead Mobility Index McGill Pain Questionnaire Leeds Multiple Sclerosis Qualit of Life Questionnaire SF-36
Warke et al., 2006 <sup>378</sup>	Р	Pr	Back pain – low, multiple sclerosis	90 (69W)	TENS (HF) = 30	Placebo TENS (0mA) = 30 TENS (LF) = 30	PRN >2 x 45 mins / day x 6 weeks >42 sessions	Pain intensity (VAS)	Analgesic consumption McGill Pain Questionnaire Roland Morris Disability Questionnaire Barthel Index Rivermead Mobility Index Multiple Sclerosis Quality of Life-54 Instrument

#### 08\_OL-TABLE1\_IncludedStudies

Yameen et al., 2011 <sup>379</sup>	Р	Pr	Neuralgia - trigeminal	31 (20W)	TENS (HF, continuous pattern) = 16	TENS (LF, Burst) = 15	PRN x 3 weeks	Pain intensity (VAS)	None
Yesil et al., 2018 <sup>380</sup>	Р	Pr	Neck pain - chronic non -specific	81 (56W)	TENS (HF) + Exercise (neck stabilisation) = 27	Exercise (neck stabilisation) (SoC, no TENS control) = 26 IFT + Exercise (neck stabilisation) = 27	Fixed 1 x 25 mins / day x 5 / week x 3 weeks 15 sessions	Pain intensity (VAS)	Range of motion Neck Disability index SF-36 Beck Depression Inventory
Yilmaz et al., 2020 <sup>381</sup>	Р	Pr	Post op - inguinal herniorrhaphy	52 (3W)	TENS (HF) + intramuscular NSAID = 26	Placebo TENS (0mA) + intramuscular NSAID = 26	Fixed 5 x 30 mins / day x 1 day 5 sessions	Pain intensity (VAS)	Analgesic consumption, Newcastle Satisfaction with Nursing Care Scale Vital signs
Yilmazer et al., 2012 <sup>382</sup>	Р	Pr	Procedural pain - office endometrial biopsy	65 (65W)	TENS (NR) + Oral naproxen = 33	Placebo TENS + oral naproxen (0mA) = 32	Fixed 10 mins pre and during procedure 1 session	Pain intensity (VAS)	Blood pressure and pulse Vasovagal symptoms questionnaire
Yokoyama et al., 2004 <sup>383</sup>	Р	Pr	Back pain - chronic low non-specific	53 (30W)	TENS (HF) + analgesics = 18	Percutaneous electrical nerve stimulation + analgesics = 18 PENS + TENS + analgesics = 17	Fixed 1 x 20 mins / day x 2 / week x 8 weeks 16 sessions	Pain intensity (VAS)	Analgesic consumption Degree of impairment (5 categories)
Yoshimizu et al., 2012 <sup>384</sup>	С	Е	Neck pain - chronic non -specific ('Shoulder and neck pain')	90 (52W)	TENS (LF) = 90	Electroacupuncture = 90	Fixed 1 x 15 mins 1 session	Pain intensity (VAS)	SF-36
Yüksel et al., 2019 <sup>385</sup>	Р	E	Fibromyalgia	42 (NR)	TENS (HF) = 21	Acupuncture = 21	Fixed 1 x 20 mins 1 session	Pain intensity (VAS)	Pressure algometry pain threshold Beck Depression Inventory Fibromyalgia Impact Questionnaire
Yurtkuran and Kocagil, 1999 <sup>386</sup>	Р	Pr	Osteoarthritis - knee	100 (91W)	TENS (LF) = 25	Electroacupuncture = 25 Ice massage = 25 Placebo TENS (no current) = 25	Fixed 1 x 20 mins / day x 5 / week x 2 weeks 10 sessions	Pain intensity (5 categories) • Present pain • Overall pain	50-foot walking time Quadriceps muscle strength Range of motion
Zakariaee et al., 2019 <sup>387</sup>	Р	Pr	Post op - episiotomy	120 (120W)	TENS (HF) + routine care = 40	Placebo TENS (0mA) + routine care = 40 Routine care = 40	Fixed 1 x 60 mins 1 session	Pain intensity (NRS)	TENS' complications satisfaction rate
Zhang et al., 2020 <sup>388</sup>	Р	E	Chronic TMJ pain (TMJ disc displacement without reduction)	20 (10W)	TENS (LF, AL-TENS) = 10	Placebo TENS (0mA) = 10	Fixed 1 x 45 mins 1 session	Pain intensity (NRS) • Movement – jaw opening and closing	Mandibular motor function using Cranio-Mandibular Evaluation System
Zhou et al., 2018 <sup>389</sup>	Р	Pr	Hemiplegic shoulder pain	90 (19W)	TENS (HF) + rehab programme = 32	NMES + rehabilitation programme = 31 Conventional rehab programme (SoC, no TENS control) = 18	Fixed 1 x 60 mins / day x 5 days x 4 weeks 20 sessions	Pain intensity (NRS)	Fugl-Meyer Modified Ashworth scale Barthel Index Stroke specific quality of life scale

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- Design: P = Parallel group; C = Crossover.
- Type: E = Predominantly Explanatory; Pr = Predominantly Pragmatic (mixed).
- Sample: W = women
- Primary TENS intervention group as selected by reviewers: Size of sample arm '=' on enrolment; HF = high frequency >10 pps); LF = low frequency < 10 pps or LF burst pattern. AF = alternating frequency, MF = modulated frequency; VF = various frequencies; burst = burst pattern of pulse delivery; HI = High Intensity TENS
- Comparison Intervention(s). Listed in reviewers' order of priority; number in trial arm '='; Placebo TENS (0mA sham device or dead batteries); Fading = TENS current administered briefly and then turned off e.g. applied for 30 seconds and then drifted off to 0mA over a 15 second time frame; Active = Placebo TENS used currents above 0mA, >SDT- infrequent pulses = current above sensory detection threshold and time between pulses modified so that they were delivered very infrequently (e.g. inter-pulse interval adjusted from 330 ms to 33 s to avoid any analgesic effect), >SDT- TENS remote = current above sensory detection threshold and delivered at a site considered to be completely unrelated to the site of the pain; categorised as considered as standard of care (SoC)
- TENS regimen: Fixed = regimen either delivered as such or advice given to patient on regimen to use themselves; PRN = 'pro re nata', when necessary; Extracted elements of regimen as min. each session / no. sessions / day / session days 10 / week / weeks / course of treatment (no. of TENS sessions));
  - Primary outcome measures in relation to this review: Pain intensity as dichotomous or continuous data
  - Secondary outcomes: Analgesic consumption general term to encompass any time of measurement associated with analgesic medication
- 12 • Other Abbreviations: IFT=Interferential current therapy; NSAID = Non-Steroidal Anti-Inflammatory Drugs; PENS = Percutaneous electrical nerve stimulation, TONS = transcutaneous occipital nerve stimulation EA = electroacupuncture; 13 VAS = visual analogue scale; NRS = Numerical rating scale; PCA = Patient controlled analgesia; BPI = Brief Pain Inventory LANSS = Leeds Assessment of Neuropathic Symptoms and Signs; WOMAC = Western Ontario and McMaster 14 Universities Osteoarthritis Index; NR = Not reported

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# Online Table 2

## **Records Awaiting Classification**

Reference	Language	Reason
Aiyejusunle et al. 2007 <sup>1</sup>	Not reported	Need to obtain PDF
Chen et al. 2007 <sup>2</sup>	Chinese	Needs translation
Houshyar et al. 2015 <sup>3</sup>	Persian	Needs translation
Kim et al. 2020 <sup>4</sup>	Not reported	Need to obtain PDF
Kumar and Rahim 2019 <sup>5</sup>	Not reported	Need to obtain PDF
Mehlhorn et al. 2005 <sup>6</sup>	German	Needs translation
Pourmomeny et al. 2009 <sup>7</sup>	Persian	Needs translation
Renklitepe et al. 1995 <sup>8</sup>	Not reported	Need to obtain PDF
Sakai et al. 2001 <sup>9</sup>	Japanese	Needs translation
Tokuda et al. 2013 <sup>10</sup>	Japanese	Needs translation
Tunc et al. 2002 <sup>11</sup>	Not reported	Need to obtain PDF
van der Pierjil et al. 1998 <sup>12</sup>	Not reported	Needs translation
Wang et al. 2005 <sup>13</sup>	Not reported	Need to obtain PDF
Xiao et al. 2002 <sup>14</sup>	Not reported	Need to obtain PDF
Zati et al. 2004 <sup>15</sup>	Italian	Needs translation
Zheng et al., 2011 <sup>16</sup>	Chinese	Needs translation
Zhang et al. 2014 <sup>17</sup>	Chinese	Needs translation
Zhong and Zhang 2017 <sup>18</sup>	Not reported	Need to obtain PDF
Zhou et al. 2009 <sup>19</sup>	Not reported	Need to obtain PDF

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\*Note: Reference numbering in this list relates only to studies cited in this table

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#### 10\_OL-TABLE3\_ExcludedStudies

#### **ONLINE TABLE 3**

#### Excluded studies, with reasons, based on screening full text records

Reference	Reason for exclusion	Description of study
Aguilar Ferrandiz et al., 2016 <sup>1</sup>	Not standard TENS - auto-targeted neurostimulation	Evaluated Nervomatrix Soleve® auto-targeted neurostimulation device providing TENS-stimulation and mechanical pressure for chronic low back pain. Technical specifications differ from a standard TENS device
Albayrak, 2017 <sup>2</sup>	Not an RCT	Evaluated TENS on persistent post-surgical pain after total knee arthroplasty. Retrospective study of prospectively collected data
Alhusaini et al., 2019 <sup>3</sup>	No pain outcomes – Primary outcomes grip strength and function; secondary outcome manual ability	Evaluated TENS combined with therapeutic exercises for hand function by reducing spasticity in children with hemiplegic cerebral palsy
Altas et al., 2019 <sup>4</sup>	Not possible to isolate TENS	Evaluated the effect of physical therapy modalities on pain, sleep, mental status, and quality of life of patients with osteoarthritis
Al Zamil et al., 2019 <sup>5</sup>	Not full report - Abstract of conference presentation	Evaluated TENS of median nerves and acupuncture in the treatment of carpal tunnel syndrome
Askin et al., 2014 6	Not possible to isolate effect of TENS	Evaluated ultrasound therapy for stellate ganglion blockade in complex regional pain syndrome type I. TENS delivered in combination with drug medication, contrast bath and exercise to all groups.
Atalay et al., 2009	No pain outcomes	Evaluated TENS for viability of skin flaps created during mastectomy in breast cancer patients. No pain outcomes
Augustinsson et al., 1977 <sup>8</sup>	Not an RCT	Evaluated TENS for pain during delivery labour pain). Open label pre-post study single group study without comparison intervention(s)
Avramidis et al., 2003 <sup>9</sup>	Not standard TENS – neuromuscular electrical stimulation	Evaluated electric muscle stimulation during rehabilitation after total knee arthroplasty - MicroStim 2-channel (MS-2) neuromuscular stimulator
Aydın et al., 2015	TENS administered internally - intravaginal	Evaluated vaginal electrical stimulation for sexual function using the insertion of a vaginal probe inserted delivering medium- frequency (50 Hz) alternating current (duty cycle 5 seconds on followed by 5 seconds off) generated by a MyoBravo electro stimulation instrument (MTR+ Vertiebs GmbH, Berlin)
Aydogan et al., 2014 11	Not standard TENS - Frequency Rhythmic Electrical Modulation System	Evaluated pre-emptive frequency rhythmic electrical modulation using a Phyback device (PBK2C) in patients undergoing lumba stabilization
Ayyildiz et al. 2004 <sup>12</sup>	Not an RCT	Evaluated TENS for pain associated with extracorporeal short-wave lithotripsy. Open label pre-post study single group study without comparison intervention(s).
Bai et al., 2018 <sup>13</sup>	Not standard TENS - transcutaneous electric acupoint stimulation	Evaluated transcutaneous electric acupoint stimulation (TEAS) on stress response during extubation after general anaesthesia in patients undergoing elective supratentorial craniotomy. Primary purpose of TEAS was not to treat pain. TEAS was administered using a Hwato electronic acupuncture treatment instrument (model no.: SDZ-II) delivering an alternate dense- disperse frequenc of 2/10 Hz (2 Hz for 10 s and 10 Hz) to various acupuncture points
Behm et al., 2019	Not pain outcomes - Fatigue rather than pain	Evaluated if TENS-induced pain suppression would augment force output during a fatiguing protocol in the treated and contralateral muscles.
Belmonte et al., 2012 <sup>15</sup>	Not standard TENS - microcurrent electrical stimulation and bioresonance device	Evaluated low-frequency low-intensity electrotherapy in the treatment of chronic upper limb breast cancer-related lymphoedema Used a Flowave2Home device delivering microcurrents via a wave of carrier frequency ranging from 0.31 to 6.16 Hz and a modulation between 400 and 2120 Hz; the low offset voltage is always between +12 and -12 V.
Bouafif and Ellouze, 2019 <sup>16</sup>	Not an RCT	Evaluated modulated PWM-TENS for non-cancer pain. PWM-TENS used sinusoidal waves sinusoidal carrier whose frequency varies according to the mode of stimulation. There was a comparison with 'classical TENS' but this was not a RCT.
Bundsen et al., 1981 <sup>17</sup>	Not an RCT	Evaluated TENS for labour pain. Retrospective (stated as prospective in title) open label questionnaire with each patient matche with a control without randomisation.
Burch et al., 2008	Not standard TENS - low-current TENS (0.5mA used as control	Evaluated combination of interferential and patterned muscle stimulation for osteoarthritis of knee. Control group received low- current TENS biphasic square wave with a 0.2 Hz frequency and a fixed amplitude of 60 mA, with pulse width adjusted to provide a net output of 73 nC and delivered across 300 microseconds equivalent to a peak output of 0.5 mA. This did not meet of criteria for standard TENS
Burssens et al., 2003 <sup>19</sup>	No pain outcomes	Evaluated burst TENS on the healing of Achilles tendon suture
Carbonario et al., 2013 <sup>20</sup>	Not an RCT	Evaluated TENS for tender points in fibromyalgia. Patients were allocated 'sequentially' and there was no mention of randomisation within the report (quasi-RCT). This was included in the Cochrane review on Fibromyalgia.

Reference	Reason for exclusion	Description of study
Chao et al., 2007 <sup>21</sup>	TENS delivered to acupuncture points distant to pain	Evaluated TENS on acupuncture points for pain during the first stage of labour using two pairs of electrodes placed at bilateral Li 4 (Hegu) points (midpoint between first and second carpal bones, first web space dorsal side) and Sp6 (Sanyinjiao) points (5 cm above medial malleolus in lower leg)
Chee and Walton 1986 22	Not standard TENS - microcurrent electrical stimulation	Evaluated treatment of trigger points with micro amperage TENS using an Electro-acuscope 80 stimulator
Cheing and Hui- Chan, 2004 <sup>23</sup>	No pain outcomes	Evaluated addition of TENS to exercise training for knee osteoarthritis but measured functional outcomes only. There were no pain outcomes in report
Chen et al., 2013 <sup>24</sup>	Not standard TENS electrodes	Evaluated TENS for knee osteoarthritis using silver spike point electrodes, similar to IFT suction cups, rather than self-adhering carbon-rubber TENS electrodes
Chen et al. 2013 25	TENS on acupuncture points using TEAS	Evaluated electroacupuncture, TENS and acupoint massage on periarthritis of shoulder.
Chen et al., 2015 <sup>26</sup>	Not standard TENS - transcutaneous electric acupoint stimulation	Evaluated transcutaneous electric acupoint stimulation on post-procedural abdominal pain after colonoscopy at Jiaji (EX-B2) points were located on both sides of the spinous column using a Han's Acupoint Nerve Stimulator (HANS-200A, Nanjing Jishen Medical Technology Co., Ltd., Nanjing, China), delivering a dense-and-disperse frequency at 2/100 Hz for 30 min prior to induction.
Chen et al., 2015 <sup>27</sup>	Not standard TENS - transcutaneous electric acupoint stimulation	Evaluated transcutaneous electric acupoint stimulation for remifentanil-induced hyperalgesia in patients undergoing thyroidectomy and delivered as 30 min of stimulation (6-9 mA, 2/10 Hz) on the Hegu (LI4) and Neiguan (PC6) before anaesthesi (pre-emptive) and terminated before the end of surgery. Stimulation was not at site of pain or over nerve bundles.
Chen et al., 2015 <sup>28</sup>	Not standard TENS - transcutaneous electric acupoint stimulation	Evaluated transcutaneous electric acupoint stimulation on postoperative quality of recovery after thyroidectomy with general anaesthesia administered at bilateral Hegu (LI4) and Neiguan (PC6) before induction of anaesthesia (pre-emptive). TEAS was delivered at a disperse-dense frequency of 2/10 Hz and an intensity of 6-9 mA for 30 min using the Hans electronic acupuncture apparatus (HANS-100A)
Chen et al., 2020 29	Not Standard TENS -TEAS	Evaluated efficacy of TEAS for sedation and postoperative analgesia in lung cancer patients undergoing thoracoscopic pulmonar resection.
Cheng and Pomeranz, 1986 <sup>30</sup>	Not standard TENS - Codetron	Evaluated 'acupuncture-like stimulation' using a Codetron device for chronic musculoskeletal pain and delivering currents randomly to acupuncture points at different locations on the body via seven electrodes.
Chiu et al., 1999 <sup>31</sup>	TENS delivered to acupuncture points distant to pain	Evaluated TENS for pain during hemorrhoidectomy. Electrodes were positioned on acupuncture points distant to the painful area (i.e. dorsal web between the first and the second metacarpal bones (Hegu, Large Intestine meridian, 4th ampoint, negative electrode) and on radial side 3 cm proximal to the wrist crease (Lieque, Lung meridian, 7th ampoint, positive electrode) using a Han Acutens, WQ1002F device
Coletta et al., 1988	Unable to isolate TENS effects	Evaluated TENS vs. TENS + ointment containing Etofenamate. Not possible to isolate effects of TENS
Conn et al., 1986 33	Some participants not adults	Evaluated TENS for pain following appendicectomy. Included children (minimum age = 13 years (TENS), 15 (sham) and 13 (control))
Cornell et al., 1984 34	Not an RCT	Evaluated TENS for pain following foot surgery. Data gathered prospectively during TENS was compared with retrospective dat of patients that did not receive TENS harvested from medical records
Demidas et al., 2019 <sup>35</sup>	Healthy humans	Evaluated touch and pain sensations and the correlation between them in diadynamic current and TEN.S
Duzyj et al., 2020	Not full report – Abstract of conference poster presentation	Evaluated effect of TENS therapy in the pain management of women after caesarean delivery.
Dodick et al., 2015	Not standard TENS - invasive technique	Evaluated peripheral nerve stimulation (PNS) of the occipital nerves for managing chronic migraine using implanted with a neurostimulation system Not TENS
Eidy et al., 2016 <sup>38</sup>	TENS given pre-emptive to general anaesthesia / surgery - pain measured after surgery with no TENS post op	Evaluated effects of preoperative TENS on post inguinal hernia repair pain
Ertzgaard et al., 2018 39	Not standard TENS electrodes	Evaluation of TENS for spasticity using an AT Mollii® electrotherapy system consisting of a two-piece garment equipped with selectrodes and a control unit.
Fagade and Obilade, 2003 40	No pain outcomes	Evaluated TENS on post-IMF trismus and pain in Nigerian Patients. No pain outcomes

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#### 10\_OL-TABLE3\_ExcludedStudies

Reference	Reason for exclusion	Description of study
Fargas-Babjak et al., 1989 41	Not standard TENS – Codetron	Evaluated 'acupuncture-like stimulation' for osteoarthritis of the hip or knee using a Codetron device
Fargas-Babjak et al., 1992 42	Not standard TENS – Codetron	Evaluated 'acupuncture-like stimulation' for chronic pain syndrome or osteoarthritis using a Codetron device
Fary et al., 2011 <sup>43</sup>	Not standard TENS - subsensory pulsed electrical stimulation	Evaluated pulsed electrical stimulation for osteoarthritis of the knee using a commercially available TENS stimulator (Metron Digi-10s) that was modified by a biomedical engineer to deliver pulsed, asymmetrically biphasic, exponentially decreasing waveform currents with a frequency of 100 Hz and pulse width of 4 msec. Author's state " <i>Participants attached the device an turned the intensity up until they could feel pins and needles or a prickling sensation under one or both electrodes. After achiev sensory output, participants were instructed to turn the intensity down until they could no longer feel any electrical stimulation this stage, a built-in locking mechanism was engaged that prevented subsequent adjustment of intensity without restarting the device." Thus, subsensory stimulation.</i>
Fletcher-Smith et al., 2019 <sup>44</sup>	Not standard TENS - Neuromuscular Electrical Stimulation " current intensity was increased to produce an alternating contraction of the flexors and extensors using a flex-hold-extend-hold pattern, ensuring that a pure movement was produced with no/minimal ulnar or radial deviation."	Evaluated feasibility of initiating electrical stimulation treatment of wrist extensors and flexors in patients early after stroke to prevent muscle contractures and pain.
Gadsby et al., 1997 45	TENS delivered to acupuncture points distant to pain	Evaluated acupuncture-like TENS within palliative care delivered to acupuncture points PC6 (Neiguan) and LI4 (Hegu) of the dominant hand
Gao et al., 2017 46	Not standard TENS - transcutaneous electric acupoint stimulation	Evaluated transcutaneous electric acupoint stimulation for procedural pain during and post thyroidectomy administered at PC6 (Neiguan) and LI4 (Hegu) and distant from the painful site. Full article in Chinese.
Garaud et al., 2018 47	Cannot isolate effects of TENS	Evaluated efficacy of TENS in the treatment LBP when associated to a therapeutic education program (TEP).
Garland et al., 2007 <sup>48</sup>	Not standard TENS - highly optimized, capacitively coupled, pulsed electrical stimulator	Evaluated highly optimized, capacitively coupled, pulsed electrical stimulator for osteoarthritis of the knee using a knee garmed with flexible, embedded electrodes and a small battery-operated generator that produced a 100-Hz, negative pulsed signal (BioniCare Medical Technologies, Inc., Sparks, Maryland.). Authors state - "They then turned on the device, increased the sign amplitude to between 0 and 12 V by rotating a dial until a tingling sensation was felt over the knee or thigh, and then reducing amplitude until this sensation disappeared. Thus, active treatment remained imperceptible and indistinguishable from placebor P631 and "In fact, TENS and PES differ in many ways." P635
Gaul et al., 2016 49	Not standard TENS - invasive vagus nerve stimulation	Evaluated non-invasive vagus nerve stimulation for prevention and acute treatment of chronic cluster headache using " a low voltage electrical signal (5-kHz sine wave series that occurred for 1 ms and repeated every 40 ms (25Hz))." p 535
Geirsson et al., 1993 <sup>50</sup>	Not standard TENS - posterior tibial nerve stimulation	Evaluated TENS of the tibial nerve in patients with interstitial cystitis using electrodes positioned over the tibial nerve on the f Thus, TENS delivered distant to symptoms. Posterior tibial nerve stimulation is a neuromodulation technique to treat overactive bladder and associated symptoms. TENS is administered over tibial nerve distant from sensations associated with urinary urge
Ghoname et al., 1999c <sup>51</sup>	Not standard TENS - percutaneous electrical nerve stimulation	Evaluated the effect of stimulus frequency on response to percutaneous electrical nerve stimulation in patients with chronic low back pain delivered via ten, 32-gauge (0.2 mm) stainless steel acupuncture-like needle probes placed into soft tissue and/or mu in the low back region to a depth of 2–4 cm.
Gokce et al., 2020	Not RCT	Evaluated bilateral transcutaneous tibial nerve stimulation on constipation severity in geriatric patients with refractory chronic constipation.
Gottfried et al., 2019 <sup>53</sup>	Not focussed on pain - Not TENS - abstract	Evaluated transcutaneous vagal nerve stimulation improves symptoms, pain, and gastric emptying in patients with idiopathic gastroparesis.
Govil et al., 2020 54	Not RCT	Evaluated extent to which genetic variability modifies Transcutaneous Electrical Nerve Stimulation (TENS) effectiveness in osteoarthritic knee pain
Gu et al., 2019 55	Not standard TENS - TEAS	Evaluated effects of TEAS on gastrointestinal function recovery after laparoscopic radical gastrectomy
Gorodetskyi et al., 2007 <sup>56</sup>	Not standard TENS - non-invasive interactive neurostimulation (InterX)	Evaluated non-invasive interactive neurostimulation in the post-operative recovery of patients with a trochanteric fracture of the femur. Currents delivered using a handheld, non-invasive, interactive neurostimulation device (InterX 5000; Neuro Resource Group, Plano, Texas) device that " generates a high peak amplitude averaging 17 volts on the skin with a low current of ab 6 mA, and damped biphasic electrical impulses which are delivered to the tissue through a pair of concentric electrodes place direct contact with the target area. The device is able to adjust its strength and damping of the biphasic stimulus changes in accordance with the impedance of the underlying tissue (Fig. 1), resulting in a highly sensitive and variable voltage in order t maintain constant peak current."

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Reference	Reason for exclusion	Description of study
Harrison et al., 1987 <sup>57</sup>	Not an RCT – May also be using part of sample in Harrison 1986	Evaluated TENS for labour pain. Patient self-selected treatment – not random allocation/RCT "All patients were informed about the methods of analgesia available, including TENS. They were asked if they had decided upon a specific form of analgesia and what it was. Information regarding the trial and its aims was then given to all potential participants and those giving informed consent were enrolled in their specific group of choice."
Hedner et al., 1996	Not an RCT – narrative review	This is a narrative overview that describes the RCT by Milson et al., 1994 - included
Herman et al., 1994 <sup>59</sup>	Not standard TENS - Codetron	Evaluated 'acupuncture-like stimulation' using a Codetron device for acute occupational low back pain. Codetron is a neuromodulation technique described as the delivery of acupuncture-like stimulation to six locations on the body in a random order.
Hettrick et al., 2004 60	No pain outcome – measured itch	Evaluated the role of TENS for the management of burn-related pruritus
Hsieh et al., 1992	Not an RCT – analysis of scales used in an RCT by <sup>62</sup> which was excluded	Evaluated reliability of instruments used in a RCT of transcutaneous muscle stimulation on chronic low back pain. This publication pre-empted publication of RCT by Pope et al., 1994
Huang et al., 2017	Not standard TENS - transcutaneous electric acupoint stimulation	Evaluated transcutaneous electrical acupoint stimulation at different frequencies on perioperative anaesthetic dosage, recovery, complications, and prognosis in video-assisted thoracic surgical lobectomy delivered to acupoints Neiguan (PC6), Hegu (LI4), Lieque (LU7), and Quchi (LI11) distant from pain and using a HANS-200A Acupoint Stimulator and frequency set as 2/100, 2, or 100 Hz in the dense-and-disperse mode before, during and post-surgery
Huang et al., 2018	Not standard TENS - transcutaneous electric acupoint stimulation	Evaluated transcutaneous electrical acupoint stimulation for recovery after laparoscopic colorectal cancer resection delivered to ST36 (leg) distant to pain before and during surgery
Huang et al., 2019 65	Not standard TENS - transcutaneous electrical acupoint stimulation	Evaluated transcutaneous electrical acupoint stimulation for pain in patients "in expansion process of skin soft tissue dilator on forehead by water injection applied to acupuncture points at the wrist (PC6), forehead (shangxing) and diwei points. Article in Chinese
Ing et al., 2015 66	Not standard TENS - microampere rather than milliampere	Evaluated TENS for chronic postherpetic neuralgia using electronic neuroadaptive regulation (SCENAR) delivered using a Tennant Biomodulator (TBM) device. The authors state " <i>The major difference between SCENAR and TBM devices and the traditional TENS units is that the former devices utilize microamps, not the milliamps utilized by the TENS units.</i> " P477
Issenman et al., 1985 <sup>67</sup>	Not an RCT	Evaluated TENS for pain control after spinal fusion with Harrington rods and assessed 'hospital charts' of patients who used TENS with sex and age matched controls. It was described as an evaluation of the effectiveness of their postoperative pain management programme with no statement that this was a prospective study with randomisation
Itoh et al., 2008 68	Not standard TENS – electrical characteristics are interferential therapy	Evaluated TENS for osteoarthritis of the knee versus acupuncture or acupuncture combined with TENS or topical poultice. The authors describe this as TENS but inspection of the reported electric characteristics suggest this is IFT "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)."
Itoh et al., 2009 69	Not standard TENS – electrical characteristics are interferential therapy	Evaluated TENS for chronic low back pain versus acupuncture or acupuncture combined with TENS or topical poultice. The authors describe this as TENS but inspection of the reported electric characteristics suggest this is IFT "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)."
Jarden et al., 1999 70	Conference abstract - ? reporting RCT by Jarzem et al., 2005 (included	Evaluated conventional transcutaneous electrical nerve stimulation [TENS] with sham therapy using a randomized double-blind crossover design. Transcutaneous electrical nerve stimulation for non-acute low back pain: a randomized double-blind study of conventional, nu-waveform, acupuncture-type and sham therapies.
Jeans et al., 1979 71	Not an RCT	Evaluated the effect of brief, intense transcutaneous electrical stimulation on chronic pain
Jiang et al., 2019 72	Not standard TENS - Cefaly	Evaluated efficacy and safety of combination therapy of flunarizine plus transcutaneous supraorbital neurostimulation (tSNS) compared with either flunarizine or tSNS alone for migraine prophylaxis
Juarez-Albuixech et al., 2019 <sup>73</sup>	Not RCT	Evaluated efficacy of Volta Therapy and transcutaneous electrical nerve stimulation (TENS) in the treatment of lumbosciatica

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#### 10\_OL-TABLE3\_ExcludedStudies

Reference	Reason for exclusion	Description of study
Junger et al., 2008 74	Not standard TENS - microcurrent electrical stimulation	Evaluated Local therapy and treatment costs of chronic, venous leg ulcers treated with electrical stimulation using a Dermapuls device (Gerromed, Hamburg, Germany) delivering currents with varying polarity at a pulse frequency of 128 Hz and an averag current strength of 300 microamperes (initially 300 mA, if pain or paraesthesia was noted, it was reduced)
Kaplan et al., 1994	Not an RCT	Evaluated TENS for dysmenorrhea. Open label single group without a comparison group
Katz and Melzack 1991 <sup>76</sup>	TENS delivered to acupuncture points distant to pain	Evaluated low frequency high intensity auricular TENS for phantom limb pain.
Kempf et al., 2018	Not standard TENS – H wave	Evaluated short-term application of High-Tone Electrical Muscle Stimulation (HTEMS) compared to Transcutaneous Electrica Nerve Stimulation (TENS) with chronic sciatica.
Kho et al., 1991 78	Unable to isolate TENS effects	Evaluated transcutaneous stimulation combined with acupuncture for surgery for retroperitoneal lymph node dissection major surgery. Not possible to isolate the effects of TENS from those of acupuncture
Kocyigit et al., 2012 <sup>79</sup>	Not an RCT – experimental study	Evaluated effects of Low-frequency Transcutaneous Electrical Nerve Stimulation on Central Pain Modulation in patients with subacromial impingement syndrome of the shoulder. The experimental paradigm was to evaluate pain-induced activation in the brain during low-frequency TENS application in response to experimentally induced painful stimuli although the nature of the stimuli unclear " <i>The involved arm of the patient was grasped by the researcher</i> "
Kolen et al., 2012	Not standard TENS device or electrodes	Evaluated different ways of delivering TENS for osteoarthritis of the knee. Used a prototype TENS device with a matrix electr array.
Kolu et al., 2018 81	Unable to isolate TENS effects	Evaluated transcutaneous nerve stimulation combined with high-intensity laser therapy and ultrasound treatment in patients wi chronic lumbar radiculopathy. Not possible to isolate TENS
Koo et al., 2015 82	Unable to isolate TENS effects	Evaluated Noxipoint Therapy to conventional physiotherapy that consisted of TENS, exercise, and manual and heat therapies is the treatment of chronic neck and shoulder. Noxipoint Therapy is a modified technique to deliver TENS over tender muscle per to produce a sore pain and does not meet our criteria for standard TENS and the comparator group included TENS combined vertex other treatments
Kumar et al., 1997 83	Not standard TENS – H-wave therapy	Evaluated transcutaneous electrostimulation for chronic painful peripheral neuropathy. The authors state "Electrotherapy was given by a portable, rechargeable unit, the H-Wave machine (Electronic Waveform Lab, Huntington Beach, CA), which has output parameters that are distinct from the other available transcutaneous electrical nerve stimulation (TENS) modalities." P Current is biphasic, exponentially decaying waveform with pulse widths of 4 ms and $\leq$ 35 V The electric current strength varie with voltage setup to a maximum of 35 mA, and the pulse frequency is user adjustable (2-70 Hz).
Kumar et al., 1998 84	Not standard TENS - H-wave therapy	Evaluated transcutaneous electrostimulation for chronic painful peripheral neuropathy using H-Wave device with parameters distinct from standard TENS.
Labrunee et al., 2015 85	No pain outcomes	Evaluated randomized placebo control study to determine whether applying TENS before exercise in PAD patients could delay onset of pain and lead to longer walking distances
Lan et al., 2012 86	TENS delivered to acupuncture points distant to pain	Evaluated TENS on six acupuncture points for pain after total hip arthroplasty for elderly patients. Acupuncture points were generally distant to the site of pain (bilateral P6 on anterior surface of the forearm; L14 on dorsum of hand; ipsilateral to the surgery ST36 anterior crest of the tibia; GB31 between greater trochanter of femur and hiatus of sacrum).
Lanham et al., 1984 <sup>87</sup>	Not an RCT	Evaluated TENS combined with hypothermia in podiatric surgery by describing a series of 69 patients that received treatment. There was no comparison group
Lee et al., 1997 <sup>88</sup>	Not standard TENS - medium frequency AC plus galvanic	Evaluated electrical stimulation for pain associated with myofascial trigger points. The type of current was a combination of medium-frequency AC current and Galvanic current at a frequency of 50-100Hz Not standard TENS - combination of medium frequency AC plus galvanic
Lee et al., 2015 89	Unable to isolate TENS effects	Evaluated effect of a device combining high-frequency transcutaneous electrical nerve stimulation and thermotherapy (I-Rune 200L, Midirune Co.) for primary dysmenorrhea. Not possible to isolate TENS because TENS and thermal therapies combined
Lehmann et al., 1983 <sup>90</sup>	Not standard TENS characteristics – delivered below sensory detection threshold (subthreshold TENS – reporting data from same sample as Lehmann et al., 1986	Evaluated subthreshold TENS versus placebo TENS and electroacupuncture for chronic low back pain. Analysis of nonorgani- findings.
Lehmann et al., 1986 <sup>91</sup>	Not standard TENS characteristics – delivered below sensory detection threshold (subthreshold TENS – probably reporting same data as Lehmann et al., 1983	Evaluated subthreshold TENS versus placebo TENS and electroacupuncture for chronic low back pain. Analysis of efficacy.

Reference	Reason for exclusion	Description of study
Lerma et al., 2020	Not full report – Abstract of conference poster	Evaluated TENS for pain control during first-trimester abortion.
Li et al., 2019 93	Not standard TENS - TEAS	Explored effect and mechanisms of TEA on postoperative recovery after caesarean section
Lin et al., 2017 94	Not standard TENS – TEAS delivered to acupuncture points	Evaluated regulatory effects of acupoint electric stimulation on the analgesic substances and the relevant indices of nerve- immunity-endocrine system in the patients undergoing general anaesthesia anorectal operation
Liu et al., 2015 95	Not standard TENS - transcutaneous electric acupoint stimulation	Evaluated transcutaneous electrical acupuncture stimulation combined with sufertanil anaesthesia for intraoperative and postoperative supratentorial craniotomy. Electrodes applied at five pairs of acupuncture points: Hegu (L14) and Waiguan (TE5), Jinmen (BL63) and Taichong (LR3), Zusanli (ST36) and Qiuxu (GB 40), and Fengchi (GB20) with Tianzhu (BL10) and Cuanzh (BL2) with Yuyao (EX-HN4) on the craniotomy side and currents delivered using a Han's acupoint nerve stimulator (LH202H, Beijing Huawei Co, Ltd, Beijing, China) with a dense-disperse frequency of 2/100 Hz (alternated once every 3 s; 0.6 ms at 2 Hz and 0.2 ms at 100 Hz).
Loeser et al., 1975	Not an RCT	Evaluated TENS for various chronic pains. No comparison groups
Lone et al., 2003 97	Not an RCT	Evaluated TENS for osteoarthritis of the knee. Authors state "The results of this non-randomised controlled single-blind continuous trial" p481
Lorenzana et al., 1999 98	TENS on remote acupuncture points	Evaluated the efficacy of transcutaneous electrical nerve stimulation (TENS) versus lidocaine in the relief of episiotomy pain
Lv et al., 2018 99	Not standard TENS - transcutaneous electric acupoint stimulation	Evaluated transcutaneous acupoint electrical stimulation combined with sufentanil pre-treatment on incidence and severity of etomidate-induced myoclonus delivered bilaterally, at hegu and waiguan acupoints (on arm) using to 2/100Hz "dilatational waves". Acupoint not covering painful site
Macdonald and Coates, 1995 <sup>100</sup>	Not standard TENS - transcutaneous spinal electroanalgesia and TENS control group not applied at site of pain	Evaluated Transcutaneous Spinal Electroanalgesia for Chronic Pain. Used TENS as a control for comparison but stated "Normal one would not apply TENS to these locations" p656
Malmir et al., 2017	Not clinical pain - sample of pain-free participants	Evaluated TENS on experimentally induced delayed onset muscle soreness in Amateur Athletes
Maria Fernandez- Seguin et al., 2019	Not TENS	Evaluated radiological changes after combining static stretching and transcutaneous electrical stimulation of the plantar fascia in adults with idiopathic cavus foot
Matsuse et al., 2020 <sup>103</sup>	No pain outcomes - Not treating pain	Evaluated effectiveness of a hybrid training system with walking that simultaneously applies electrical stimulation to the knee extensors/flexors during walking in obese women with knee pain
McGough et al., 2019 104	No pain outcomes - Not pain	Evaluated efficacy and safety of TNS for Attention-Deficit/Hyperactivity Disorder and potential changes in brain spectral power using resting state quantitative electroencephalography
Meade et al., 2010	Not standard TENS - transcutaneous electric acupoint stimulation	Evaluated transcutaneous electric acupoint stimulation as adjunctive treatment for opioid detoxification using a Han's Acupoint Nerve Stimulator to deliver currents to "hegu" and "neiguan" acupoints on dorsal and palmar surface of one hand, and dorsal and ventral surface of the other forearm. Frequency of stimulation alternated between 2 and 100 Hz at 3-second intervals. Primary outcome was opioid consumption although physical pain in past 24 hours assessed using the Brief Pain Inventory was a secondar outcome.
Meechan et al., 1998 <sup>106</sup>	TENS administered internally – intra-oral	Evaluated transcutaneous electronic nerve stimulation for discomfort associated with regional anaesthesia in dentistry using an injection-assist TENS machine (3M, St Paul, Minnesota, USA) with electrodes positioned in the mouth either side of the needle puncture point.
Melzack et al., 1975 107	Not standard TENS device and electrodes	Evaluated TENS for various chronic pains using a Grass model S8 stimulator and EEG disc electrode to deliver currents
Melzack et al., 1980 <sup>108</sup>	Not an RCT - "Patients were assigned alternately, as they arrived at the clinic, to each order of treatment."	Evaluated TENS versus ice massage in patients with chronic low back pain
Mi et al., 2018 <sup>109</sup>	Not standard TENS - transcutaneous electric acupoint stimulation	Evaluated the effect of transcutaneous electrical acupoint stimulation (TEAS) on the quality of recovery during the early period after laparoscopic cholecystectomy and the dosage of anaesthetic and analgesic
Miller Jones et al., 1980 110	Not an RCT	Evaluated TENS for labour Pain. Not prospective randomisation -patients were given TENS and followed. Then retrospectively they were compared with a sample taken from patients who had not received TENS - EXCLUDE AS NOT RADMOSIED
Monaco et al., 2013 <sup>111</sup>	No pain outcomes	Evaluated effect of TENS on electromyographic and kinesiographic activity in patients with temporomandibular disorder. No pa outcomes

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#### 10\_OL-TABLE3\_ExcludedStudies

Reference	Reason for exclusion	Description of study
Mucuk and Baser, 2014 <sup>112</sup>	Not standard TENS - TENS-acupuncture pen	Evaluated non-invasive electroacupuncture on labour pain using a TENS-acupuncture pen with a maximum output of 0.6mA administered to acupuncture points LI4 (hand)SP6 (leg/foot)
Mummolo et al., 2019 113	Not RCT – retrospective evaluation	Evaluated effects of ultra-low-frequency transcutaneous electrical nerve stimulation (ULF-TENS) on pain and electromyographic values in subjects affected by temporomandibular disorder
Murina et al., 2008	TENS administered internally - intravaginal	Evaluated TENS to treat vestibulodynia using a dual channel portable TENS unit (YSY-EST device) and a commercially availabl plastic vaginal probe with two gold metallic transversal rings as electrodes (Periprobe VAG2ST Beac, Pavia, Italy) inserted 20 mm into the vagina
Murina et al., 2018	TENS administered internally - intravaginal	Evaluated TENS plus diazepam to treat vestibulodynia using a dual channel portable TENS unit (NeuroTrac Continence; VerityMedical, London, UK) and a commercially available plastic vaginal probe with two gold metallic transversal rings (Periprobe VAG2ST Beac, Pavia, Italy) inserted 20 mm into the vagina
Mysliwiec et al., 2011 116	No pain outcomes	Evaluated effect of cervical traction and TENS on strength of painless grip
Naeser et al., 2002	Not standard TENS – microcurrent electrical stimulation	Evaluated carpal tunnel syndrome pain treated with low-level laser and microamperes transcutaneous electric nerve stimulation
Nakano et al., 2019	Not RCT	Evaluated effects of TENS on pain and other physical symptoms in 20 in-patients with advanced cancer receiving palliative care
Ngai et al., 2010 119	Not clinical pain	Evaluated Acu-TENS on functional capacity and beta-endorphin level in subjects with chronic obstructive pulmonary disease
Noehren et al., 2015 <sup>120</sup>	Protocol – ongoing study	Protocol of an RCT to evaluate TENS for fibromyalgia: a double-blind randomized clinical trial. Full RCT published <b>after our</b> search Dailey et al., 2019 Arthritis Rheumatol, 2019 Nov 18, doi: 10.1002/art.41170.
Nourbakhsh and Fearon, 2008 <sup>121</sup>	Not standard TENS device or electrodes	Evaluation of noxious level electrical stimulation on chronic lateral epicondylitis administered using a MRL Neuroprobe System V (CR Kesner Company, Geneva, IL, USA) as painful stimulation of trigger points for 30s using 4Hz interupted DC current and a probe electrode
Okonkwo et al., 2018 122	Not an RCT	Evaluation of TENS for post-injection sciatic pain in a non-randomized controlled clinical trial.
Oyibo et al., 2004	Not standard TENS - microcurrent electrical stimulation	Evaluated electrical stimulation therapy through silver-plated nylon-Dacron <sup>™</sup> stocking electrodes (Micro-Z, Prizm Medical, Duluth, GA, USA) for painful diabetic neuropathy. Pulsed electric current were delivered a subsensory dose approximately 50 micro amps at 80 pulses per second for the first 10 min, then 8 pulses per second for the next 10 min each hour over an 8-h period
Ozen et al., 2019	Cannot isolate TENS - hotpack, transcutaneous electrical nerve stimulation (TENS, and ultrasound	Evaluated effects of physiotherapy modalities with those of acupuncture on pain, daily function, and quality of life in FMS patients.
Park et al., 2014 125	No pain outcomes	Evaluated TENS with exercise on spasticity, balance, and gait in patients with chronic stroke. No pain outcomes.
Patel et al., 2016	Unable to isolate TENS effects	Evaluated TENS with McKenzie method for lumbar radiculopathy. Not possible to isolate the effects of TENS from McKenzie
Peng et al., 2010	Not an RCT	Evaluated TENS on Acupoints for labour pain. Stated a Non-randomized Controlled Study
Polat et al., 2017	Not an RCT	Evaluated TENS combined with hot pack and home exercise program for osteoarthritis of the knee with and without neuropathic pain. There was no comparison intervention
Pope et al., 1994	Not standard TENS - neuromuscular electrical stimulation	Evaluated transcutaneous muscle stimulation for sub-acute low back pain using a Myocare PLUS device which is considered to b a neuromuscular stimulator and thus excluded. Note: Currents produced physiological stimulation that could be considered within the scope of 'standard TENS' Biphasic pulses 37pps pulse duration 225 us with pulse amplitude modulated (ramped up in 2 s hele for 6s then ramped off in 2s then a pause before cycle repeated. 4 electrodes placed on back around pain and current delivered to maintain sensation as high as possible – no mention of muscle twitching
Pour et al., 2012 <sup>130</sup>	TENS applied to acupuncture points away from painful area [TENS applied to acupuncture points on foot and SP6 for labour pain]	Evaluated effect of two methods of compressive medicine and electrical stimulation of the skin on the severity of labour pains in the first pregnant women.
Quinton et al., 1987 131	Some participants not adults	Evaluated TENS in acute hand infections. Sample included at least one child under 16years of age (age range from 15 to 66 years).
Radhakrishna et al., 2020 <sup>132</sup>	TENS applied pre-emptive before general surgery and pain measured post operatively without TENS	Evaluated the effect of immediate preoperative TENS on intraoperative anaesthetic drug consumption in patients undergoing lumbar discectomy under general anaesthesia

Reference	Reason for exclusion	Description of study
Rapoport et al., 2019 <sup>133</sup>	Not TENS - secondary report of Yartisky	Performed a post-hoc analysis on a subgroup of participants with migraine from a randomized, double-blind, parallel-group, sham-controlled, multicentre study
Razavi and Jansen, 2004 134	Not standard TENS - placebo TENS only	Evaluated acupuncture and placebo TENS in addition to exercise in treatment of rotator cuff tendinitis. No active TENS intervention.
Reich et al., 1989	Unable to isolate TENS effects	Evaluated various non-invasive treatments for vascular and muscle contraction headache including an 'Electrical Group' that received either traditional TENS or electrical neurotransmitter modulation, either singly or in combination. Data was analysed at group rather than modality level.
Reichstein et al., 2005 136	Not standard TENS – H wave characteristics delivered using a CEFAR Dumo TENS device	Evaluated effects of high-frequency external muscle stimulation HF) with those of TENS in patients with diabetic distal symmetrical sensory polyneuropathy.
Rodriguez- Fernandez et al., 2011 <sup>137</sup>	Not clinical pain - sample of pain-free participants	Evaluated burst-type TENS on cervical range of motion and latent myofascial trigger point sensitivity in a sample of individuals recruited from a pain-free population with at least 1 latent myofascial trigger point in their upper trapezius. Sample not recruited from clinical pain population.
Rooney et al., 1986	No pain outcomes	Evaluated cryoanalgesia and TENS on pulmonary function tests post thoracotomy. No pain outcome
Roth and Thrash, 1986 <sup>139</sup>	Not standard TENS - microampere currents, and not standard electrodes and invasive technique	Evaluated TENS for pain associated with orthodontic tooth movement. In one group TENS was applied externally over zygomatic arches using sponge pad electrodes – not standard TENS electrodes (0.5 Hz with an intensity of 500 mA). In one group TENS was applied internally (intraoral) directly to teeth using one probe electrode on the crown of each tooth and the other electrode on the palatal mucosa adjacent to the tooth (0.5 Hz, intensity of 50 mA) – Internal Currents were delivered using Alpha-Stim model 2000 which produces a biphasic waveform with varying pulse widths in the millisecond range and intensities in the microampere range (i.e. microcurrent). It is probable that 500mA and 50mA were typographical errors that should read 500 microampere and 50 microamperes. "Both groups were told that the intensity of the current was so small that the most they would feel was a very slight tingling, if anything at all." p133
Santiesteban et al., 1985 140	TENS delivered to acupuncture points distant to pain	Evaluated TENS on acupuncture points for primary spasmodic dysmenorrhea using a MRL pain control system (5Hz, 250us, intensity to patient tolerance). Acupuncture points were not covering painful site (GB34, Sp6, (leg).
Sari et al., 2019 <sup>141</sup>	Unable to isolate TENS	Evaluated intermittent pneumatic compression along with conventional treatment with cold pack treatment along with conventional treatment on clinical outcomes in patients with knee osteoarthritis
Schuster et al., 1980 <sup>142</sup>	Not an RCT - 26 control patients were selected at random. Records were matched as closely as possible	Evaluated use of TENS and narcotic analgesics in relieving post-operative pain.
Schoenen et al., 2013 <sup>143</sup>	Not standard TENS - supraorbital transcutaneous stimulator	Evaluated trigeminal neurostimulation with a supraorbital transcutaneous stimulator (Cefaly, STX-Med., Herstal, Belgium) for migraine prevention. Neurostimulation delivered with one 30 mm 3x94 mm self-adhesive electrode on forehead and delivery of biphasic rectangular pulsed currents (250 µs, 60 Hz, 16 mA).
Schomburg and Carter-Baker, 1983	Not an RCT	Evaluated TENS for post laparotomy pain compared with chart review to 75 patients who had undergone similar surgical procedures performed by the same surgeon before TENS postoperative pain management had been instituted.
Selfe et al., 2008	Not standard TENS - noninvasive interactive neurostimulation (InterX5000 device	Evaluated Noninvasive Interactive Neurostimulation on Symptoms of Osteoarthritis of the Knee using an InterX5000 device (Neuro Resource Group, Plano, TX)
Shirazi et al., 2014	Not an RCT	Evaluated TENS on joint position sense in patients with knee joint osteoarthritis. Pre-post study without a comparison group.
Silberstein et al., 2016 <sup>147</sup>	Not standard TENS - 5KHz sine wave	Evaluated non-invasive vagus nerve stimulation for chronic migraine headache prevention using low voltage 5KHz sine wave lasting 1 millisecond with such bursts repeated every 40 milliseconds (Electrocore Ltd)
Silberstein et al., 2016 <sup>148</sup>	Not standard TENS - 5KHz sine wave	Evaluated non-invasive vagus nerve stimulation for the acute cluster headache using low voltage 5KHz sine wave lasting 1 millisecond with such bursts repeated every 40 milliseconds (Electrocore Ltd)
Simon et al., 2015	Not an RCT	Evaluated TENS for chronic axial low back pain on a single cohort stratified for age. Dose-response study with no other intervention comparison groups.
Simpson and Ward, 2004 <sup>150</sup>	Not standard TENS - transcutaneous spinal electroanalgesia	Evaluated transcutaneous spinal electroanalgesia for pain from chronic critical limb ischemia. Transcutaneous spinal electroanalgesia uses two electrodes placed over dorsal spine and delivers currents that do not cause action potentials in peripheral nerves and no sensation of paraesthesia (4 us, 1800–2500 Hz, 100–300 V, Advanced Pain Management)

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#### 10\_OL-TABLE3\_ExcludedStudies

Reference	Reason for exclusion	Description of study
Solomon and Guglielmo, 1985	Not standard TENS - microcurrent electrical stimulation	Evaluated TENS for headache using a device that " differs from most other TENS equipment by its low amperage (maximum 4 milliamperes), high frequency (12,000 to 20,000 Hz rectified to monophasic wave form) and short pulse width (approximately 30 microsec)" p 12
Solomon et al., 1989 <sup>152</sup>	Not standard TENS - microcurrent electrical stimulation	Evaluated Cranial Electrotherapy in the Treatment of Tension Headache using " extremely low level, high frequency current applied transcranially" – microcurrent p 445
Sonde et al., 2000	No pain outcomes	Evaluated TENS for post-stroke paretic arm on functional outcomes including spasticity and activities of daily function but not pain
Stralka et al., 1998	Not standard TENS - high voltage pulsed direct current	Evaluated high voltage pulsed direct current built into a wrist splint for hand and wrist pain
Stratton and Smith, 1980 155	No pain outcomes	Evaluated TENS for postoperative thoracotomy on ventilatory function including forced vital capacity but not pain
Strayhorn et al., 1983 156	Not an RCT	Evaluated TENS on use of narcotic analgesics and occurrence of postoperative complications following gastric bypass surgery fo control of obesity from chart review
Sun et al., 2017 <sup>157</sup>	Not standard TENS - transcutaneous electric acupoint stimulation	Evaluated Perioperative Transcutaneous Electrical Acupoint Stimulation for Postoperative Pain Relief Following Laparoscopic Surgery using a HANS Acupoint Nerve Stimulator (HANS-200A, Nanjing Jisheng Medical Technology Company, Nanjing, China) delivering an alternating dense and disperse stimulation (2Hz (0.6 ms pulse width) alternated with 100 Hz stimulation (0.2 ms pulse width) every 3 seconds to maximum current tolerated but subnoxious) to Hegu (L14) and Neiguan (P6) distant from pair
Sunshine et al., 1996 <sup>158</sup>	Not standard TENS – microcurrent electrical stimulation	Evaluated microcurrent TENS and massage for fibromyalgia (Electroacuscope device)
Takla and Rezk- Allah, 2018 <sup>159</sup>	Not standard TENS - combination therapy, unable to isolate effect of TENS	Evaluated simultaneous application of TENS and ultrasound phonophoresis on active myofascial trigger points as a combined therapy using an Intelect Advanced Combo therapy system (2752CC; Chattanooga DJO France SAS Industries; Mexico) device. Using an ultrasound treatment head as an electrode and not possible to isolate TENS - Combined therapy
Takla et al., 2018	Not standard TENS - combination therapy, unable to isolate effect of TENS	Evaluated low-frequency high-intensity versus medium-frequency low-intensity TENS delivered as combined therapy with ultrasound phonophoresis for management of active myofascial trigger points using an Intelect Advanced Combo therapy system (2752CC; Chattanooga DJO France SAS Industries; Mexico) device. Using an ultrasound treatment head as an electrode and not possible to isolate TENS - Combined therapy
Thiese et al., 2013	Not an RCT	Evaluated electrical stimulation for chronic non-specific low back pain in a working-age population – Report of a Protocol
Thompson et al., 2008 <sup>162</sup>	Not standard TENS - transcutaneous spinal electroanalgesia	Evaluated transcutaneous spinal electroanalgesia (TSE) on low back pain. "TSE bears a superficial resemblance to transcutaneous electrical nerve stimulation (TENS) but differs in that it is applied to the skin overlying the vertebral spine and uses stimulation frequencies far higher (2500+ Hz) than those used for TENS (circa 1–150 Hz) The pulse widths used for the two systems are also substantially different (4 ls for TSE compared with 50–200 ls for TENS)."
Tok et al., 2011 <sup>163</sup>	Unable to isolate TENS effects	Evaluated electrical stimulation combined with continuous passive motion on symptoms, functional capacity, quality of life and balance in knee osteoarthritis. Combination therapy not possible to isolate contribution of TENS.
Tousignant- Laflamme et al., 2017 <sup>164</sup>	Not an RCT - only one intervention	Evaluated acupuncture-like TENS for chronic low back pain. Design was a randomized, crossover study to determine the duration of analgesia following 15- and 30-minute treatment. No comparison intervention group.
Tu et al., 2019 <sup>165</sup>	TENS delivered to acupuncture points distant to pain	Evaluated transcutaneous electrical acupoint stimulation on postoperative analgesia after ureteroscopic lithotripsy delivered to bilateral Shenyu (BL23) outside spinous process of L2 and SP9 between posterior tibia border and gastrocnemius muscle using a HANS LH-202 electrical stimulator.
Vance et al., 2018	Not an RCT	Development of a method to maximize intensity of TENS used for fibromyalgia by analysing baseline data from an ongoing clinical RCT investigating the effects of TENS in women with fibromyalgia – the Fibromyalgia Activity Study with TENS (FAST: NCT01888640).
VanderArk and McGrath, 1975 <sup>167</sup>	Some participants not adults	Evaluated TENS for post-operative pain. Some participants were not adults (13 years to 87 years).
Vincenti et al., 1982 <sup>168</sup>	Not an RCT	Evaluated TENS for labour pain.
Vinterberg et al. 1978 <sup>169</sup>	Not an RCT	Evaluated TENS for rheumatoid arthritis.

Reference	Reason for exclusion	Description of study
Wang et al., 1988	Some participants not adults	Evaluated TENS for sickle cell pain crises. Some participants were not adults (12years to 27 years)
Wang, 1997 171	Not standard TENS - transcutaneous electric acupoint stimulation	Evaluated transcutaneous electrical acupoint stimulation on analgesic consumption post operation lower abdomen surgery at acupuncture points (Hegu (LI14) and either side of the incision site) using dense-disperse current.
Wang et al., 2007	Not standard TENS - acupuncture acupoint stimulator	Evaluated TENS applied to acupoints for labour pain using an acupuncture acupoint stimulator (G-6502-2A). Acupuncture point LI4 PC6 SP6 LR3 not at site of pain.
Wang et al., 2007	TENS delivered to acupuncture points distant to pain	Evaluated abdominal acupuncture TENS on leg shoulder loin and neck pain using acupuncture points that are distant from pain LI4 PC6 SP6 LR3 – in Chinese Excluded based on abstract.
Wang et al., 2007	Not standard TENS - 'pen shaped' electrodes	Evaluated acupuncture-like electrical stimulation on chronic tension-type headache using a 'pen shaped' electrode with a tip diameter of 1mm delivering dense-and-disperse currents (TAO, MibiTech ApS, Helsingør, Denmark) to six acupoints distant to the pain , bilateral EX-HN5, GB 20, LI 4
Wang et al., 2008	Not standard TENS - transcutaneous electric acupoint stimulation	Evaluated pre and during surgery TEAS on blood bioactive compounds involving cerebral injury during craniotomy at LI4, LI1 ST36 SP6 distant to pain not at site of pain. No pain measure in Chinese Excluded based on abstract.
Wang et al., 2009	Not standard TENS - transcutaneous electric acupoint stimulation	Wang, Z. X. (2009) Clinical observation on electroacupuncture at acupoints for treatment of senile radical sciatica. [Chinese]. Zhongguo zhen jiu = Chinese acupuncture & moxibustion 29 (2), 126-128.
Wang et al., 2014	Not standard TENS - transcutaneous electric acupoint stimulation	Evaluated transcutaneous electric acupoint stimulation on intra-operative remifentanil consumption and postoperative side-effec in patients undergoing sinusotomy delivered to Hegu (LI4), Neiguan (PC6), and Zusanli (ST36) a 6–9mA,2/10 Hz before anaesthesia.
Ward et al., 2009	Not clinical pain - sample of pain-free participants	Evaluated A efficacy of medium frequency alternating current and TENS on healthy participants.
Wattrisse et al., 1993 179	Not standard TENS - Limoges currents	Evaluated effect of transcutaneous cranial electrical stimulation with Limoges currents – French. Excluded based on abstract.
Weng et al., 2005	Not standard TENS - 5KHz currents modulated at lower frequencies	Evaluated modulated-frequency mode of AL-TENS on tennis elbow pain. " treated with either 5 KHz modulated by 2 Hz frequency mode (LF group), 5 KHz modulated by 100 Hz frequency mode of TENS (HF group) on acupuncture points (L110 and L111)". Output characteristics seems to be a carrier wave of 5KHz modulated at 2Hz or 100Hz.
Whitehair et al., 2019 <sup>181</sup>	Not TENS	Evaluated acute effects of TENS, transcutaneous neuromuscular electrical stimulation and no stimulation on pain-free passive range of motion of the shoulder in subjects with hemiplegic shoulder pain
Wieselmann- Penkner et al., 2001 <sup>182</sup>	No pain outcomes	Evaluated TENS and EMG-biofeedback on muscular relaxation in bruxism.
Williams et al., 2019 <sup>183</sup>	Not TENS Not RCT - healthy humans	Evaluated conditioned pain modulation efficiency in persons with and without migraine headaches
Williams 2019 184	Not RCT - Abstract	Evaluated feasibility of TENS as adjunctive treatment for post-operative orthopaedic pain.
Wilson and Stanczak, 2020 <sup>185</sup>	Not an RCT - Review	Round-up of the current body of evidence of using TENS for pain control in patients with advanced cancer and palliative pain.
Wong et al., 2003	Not standard TENS - Codetron	Evaluated acupuncture-like TENS for radiation-induced xerostomia associated with radical radiotherapy using Codetron device that delivers electrical currents randomly between 6 electrodes. Report of phase 1 of the RCT trial. Not an RCT
Wong et al., 2012	Not standard TENS - Codetron	Evaluated acupuncture-like TENS for radiation-induced xerostomia associated with radical radiotherapy using Codetron device. " This particular TENS devicediffers from conventional TENS units, because it embeds a random circuit that enables rando switching among 6 electrodes to prevent brain habituation to continuous stimulation" page 4245. Report of phase 2 of the RCT
Wu et al., 2012 <sup>188</sup>	Not standard TENS - middle frequency electrical stimulation	Evaluation of middle frequency electrical stimulation for dysmenorrhea. Currents delivered at frequency of 1000 -10,0000 Hz to acupuncture points not covering pain site (LI4 SP6) using a GM390TE, GEMORE device
Xu et al., 2014 <sup>189</sup>	Cannot isolate TENS because all groups received identical TENS as combined therapy	Evaluated TENS in combination with cobalamin injection for postherpetic neuralgia.
Xie et al., 2017 <sup>190</sup>	Not standard TENS - transcutaneous electric acupoint stimulation	Evaluated transcutaneous electrical acupoint stimulation combined with palonosetron on chemotherapy-induced nausea and vomiting. No pain outcomes.
Yang et al., 2017	Not an RCT	Evaluated accupuncture like TENS on knee osteoarthritis (KOA) with low pain. Single intervention group divided according to lo and high pai.n

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#### 10\_OL-TABLE3\_ExcludedStudies

Reference	Reason for exclusion	Description of study
Yang et al., 2017	Not clinical pain - slow-transit constipation	Evaluated transcutaneous electrical stimulation in women with slow-transit constipation. Primary purpose of study was to evaluat slow-transit constipation and associated symptoms of constipation, including abdominal pain as a secondary outcome. Target sample was women with slow-transit constipation rather than patients with clinical pain.
Yao et al., 2015 <sup>193</sup>	Not standard TENS - transcutaneous electric acupoint stimulation	Evaluated transcutaneous electric acupoint stimulation on quality of recovery and postoperative analgesia after gynaecological laparoscopic surgery to Hegu (LI4), Neiguan (PC6), Zusanli (ST36), and Sanyinjiao (SP6) acupoints distant from pain using a Hans electronic acupuncture apparatus (dense-disperse frequency (2/10 Hz), 6–9mA, HANS-100B, Nanjing Jisheng Medical Technology Company, Nanjing, China).
Yarnitsky et al., 2017) <sup>194</sup>	Not standard TENS - Remote Electrical Neuromodulation	<ul> <li>Evaluated remote nonpainful electrical upper arm skin stimulation for reducing migraine attack pain.</li> <li>Remote Electrical Neuromodulation uses the principles of conditioned pain modulation applying high intensity TENS to the arm for migraine. Authors argue that REN on arm has neural relationship to migraine pain - we exclude because authors do not call this technique TENS, location of electrodes are remote, and currents delivered using parameters to simulate elicit conditioned pair modulation systems.</li> </ul>
Yarnitsky et al., 2019) <sup>195</sup>	Not standard TENS and not at site of pain much debate in team on this though	Evaluated efficacy and safety of a remote electrical neuromodulation (REN) device for the acute treatment of migraine.
Yeh et al., 2010 <sup>196</sup>	Not standard TENS - transcutaneous electric acupoint stimulation	Evaluated transcutaneous acupoint electrical stimulation for postoperative pain in patients with patient-controlled analgesia. TEA delivered at acupoints distant from pain, BL40, GB34, HT7, P6
Yeh et al., 2018 197	Not standard TENS - transcutaneous electric acupoint stimulation	Evaluated transcutaneous acupoint electrical stimulation on post-hemorrhoidectomy-associated pain, anxiety, and heartrate variability at acupoints distant from pain, <i>chengshan</i> (BL57) and <i>erbai</i> (EX-UE2) and a stimulator (D0205KL, Ching-Ming Co., Taiwan) delivering dense disperse currents
Yilmaz et al., 2020	Not possible to isolate the effects of TENS - "a combination of US, TENS"	Evaluated high-intensity laser therapy (HILT) and a combination of transcutaneous nerve stimulation (TENS) and ultrasound (Ut treatment on pain, range of motion (ROM) and functional activity on cervical pain associated with cervical disc herniation (CDH
Yip et al., 2007 <sup>199</sup>	Unable to isolate TENS effects	Evaluated combined transcutaneous acupoint electrical stimulation and electromagnetic millimetre waves for spinal pain. Not possible to isolate TENS
Yousesef et al., 2015 <sup>200</sup>	Not standard TENS - posterior tibial nerve stimulation	Evaluated transcutaneous electrical posterior tibial nerve stimulation versus lateral internal sphincterotomy for treatment of chronic anal fissure. Transcutaneous electrical nerve stimulation of posterior tibial nerve is used for faecal and urinary incontinence and was applied using an Endomed 182 device (Enraf Nonius, Holland) with the negative contact electrode on the ankle skin behind the medial malleolus, and the positive electrode, 10 cm above the negative electrode.
Yu et al., 2019 201	Not standard TENS - TEAS	Evaluated TEAS on early recovery in patients undergoing gynaecological laparoscopic surgery.
Zeb et al., 2019 202	Not RCT	Evaluated effectiveness TENS in management of neuropathic pain in post-traumatic incomplete spinal cord injury patients.
Zhan and Tian 2019 <sup>203</sup>	Not standard TENS - TEAS	Evaluated effect and adverse effects of transverse abdominis plane block and TEAS on postoperative outcomes.
Zhang et al., 2014 204	Not standard TENS - transcutaneous electric acupoint stimulation	Evaluated pre-treatment with transcutaneous electrical acupoint stimulation on the quality of recovery after ambulatory breast surgery. Transcutaneous electrical acupoint stimulation was delivered at acupoints distant from pain LI4, PC4, ST36 (hand and arm) using a TEAS - SDZ-V dense and disperse device.
Zhang et al., 2016 205	Not standard TENS - transcutaneous electric acupoint stimulation	Evaluated TEAS before the anaesthesia induction on opioids consumption in patients undergoing off-pump coronary artery bypac grafting at distal-proximal acupoints combination (LI4 and CV17) and regional acupoints combination (CV17 and CV14) using a <i>Hwato</i> electronic acupuncture treatment instrument (model No. SDZ-V, Suzhou Medical Appliances Co., Ltd, Suzhou, China) InJClinExpMed 9(12)
Zhang et al., 2017	TENS delivered to body sites distant to pain	Evaluated TENS of foot for postoperative bladder spasms and pain. Stimulation not on pain site
Zhang et al., 2020	E - Not pain	Evaluated effect of transcutaneous electrical stimulation treatment in combination with intraoperative nerve staining on sexual function after radical surgery.
Zhao et al., 2015 208	Not standard TENS - transcutaneous electric acupoint stimulation	Evaluated transcutaneous electrical acupoint stimulation for spasticity following Brain Injury using an acupoint nerve electrical stimulator (HANS-100A, Nanjing Gensun medical technology company, Nanjing, China) at Hegu (LI4)–Yuji (LU10) and Zusan (ST36)–Chengshan (BL57). Pain on Disability Assessment Scale was a secondary outcome.
Zhou et al., 2018 209	Not standard TENS - transcutaneous electric acupoint stimulation	Evaluated Transcutaneous Electrical Acupoint Stimulation for gastrointestinal dysfunction after caesarean section SP6 and ST36 acupoints using a Hwato electric acupuncture treatment instrument (model No. SDZV; Suzhou Medical Appliances Co. Ltd, Suzhou, China) with a dilatational wave of 2/10 Hz (2-second cycle) for 30 min. TEAS delivered at acupoints distant from pain.

	Reason for exclusion	Description of study
Cizic et al., 1995	Not standard TENS – microcurrent electrical stimulation	Evaluated pulsed electrical stimulation for osteoarthritis of the knee using low voltage (mean = 6.2V peak volts). Characteristics like those of microcurrent electrical stimulation although no overt statement to this effect in the report.
Note: Reference Aguilar H Aguilar H Albayrak in after Total K Alhusain miplegic cerebr Altas EU ndomized-contr Al Zamil ndrome. Europe Askin A, ndomised placel Atalay C Augustin Avramid chives of physic Avagustin Avramid chives of physic Aydogan ian spine journa Aydogan ian spine journa Aydogan ian spine journa Bai WY, nesthesia in Eldo Behm Do urnal of applied Belmonte inical rehabilita Bouafif I	<ul> <li>116; 19(5): E707-19.</li> <li>14. Apiliogullari S, Dal CN, Levendoglu F, Ozerbil OM. Efficine Arthroplasty. <i>Journal of Knee Surgery</i> 2017; 30(2): 134-4</li> <li>14. A, Fallatah S, Melam GR, Buragadda S. Efficacy of transcal palsy. <i>Somatosensory &amp; motor research</i> 2019; 36(1): 49-55</li> <li>14. Demirdal U. The effect of physical therapy and rehabilitation olled study. <i>Turkish journal of physical medicine and rehabili</i></li> <li>15. M, Kulikova N, Bezrukova O, Volkova I, Stahurlova V. Corr<i>ean Journal of Neurology</i> 2019; 26: 729.</li> <li>16. Savas S, Koyuncuoglu HR, Baloglu HH, Inci MF. Low dose bo controlled trial. <i>International Journal of Clinical and Expe</i>, Yilmaz KB. The effect of transcutaneous electrical nerve stinesson L, Bohlin P, Bundsen P, et al. Pain relief during delivery is K, Strike PW, Taylor PN, Swain ID. Effectiveness of electrical <i>medicine and rehabilitation</i> 2003; 84(12): 1850-3.</li> <li>17. Artoğlu Aydın Ç, Batmaz G, Dansuk R. Effect of vaginal electrical and <i>Link Uroloji Dergisi</i> 2004; 30(4): 446-50.</li> <li>18. Yang YC, Teng XF, Wan YX, Wei W, Zhu JC. Effects of Traerly Patients Undergoing Elective Supratentorial Craniotomy: G, Colwell EM, Power GMJ, et al. Transcutaneous electrical nerve stringent and refuging Elective Supratentorial Craniotomy: G, Colwell EM, Power GMJ, et al. Efficacy of low-frequency low-<i>ttion</i> 2012; 26(7): 607-18.</li> <li>19. Peterson L, Selstam U. Pain relief in labor by transcutaneous</li> </ul>	imulation Is Not Superior to Placebo in Chronic Low Back Pain: A Fourfold Blind Randomized Clinical Tria eacy of Pulsed Radiofrequency Therapy to Dorsal Root Ganglion Adding to TENS and Exercise for Persisten 42. cutaneous electrical nerve stimulation combined with therapeutic exercise on hand function in children with 5. n modalities on sleep quality in patients with primary knee osteoarthritis: A single-blind, prospective, <i>itation</i> 2020; <b>66</b> (1): 73-83. nparative analysis between transcutaneous electroneurostimulation and acupuncture in treatment of carpal tur- high frequency ultrasound therapy for stellate ganglion block ade in complex regional pain syndrome type I:

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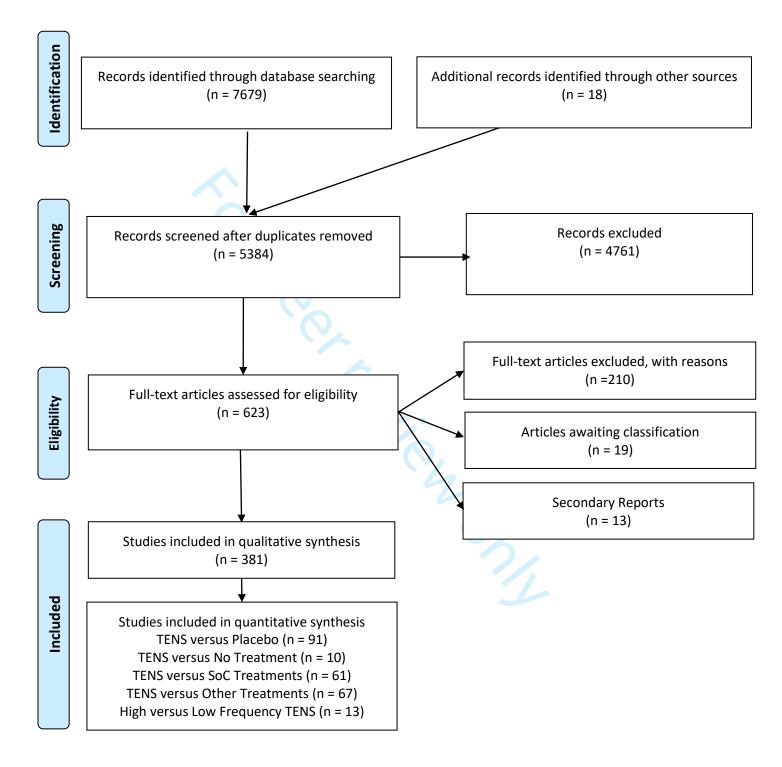
Zizic TM, Hoffman KC, Holt PA, et al. The treatment of osteoarthritis of the knee with pulsed electrical stimulation. *The Journal of rheumatology* 1995; 22(9): 1757-61. 210. 

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Lika Koleg, 2014         39.5         17         11         52.5         18.6         10         -0.70 [-1.59, 0.19]           Warfield, et al., 1985         48.3         20.1         12         64.2         24.6         12         1.0%         -0.70 [-1.59, 0.19]           Warfield, et al., 1985         48.3         20.1         12         64.2         24.6         12         1.0%         -0.66 [-1.51, 0.14]           Bilgili, et al., 2016         14.27         10.1         15         23.27         15.8         15         1.1%         -0.66 [-1.40, 0.08]           Fujii-Abe et al., 2019         22.1         12.8         11         30.3         11.2         11         1.0%         -0.66 [-1.52, 0.21]           Shimoura, et al., 2019         5.1         8         25         11.4         10.9         25         1.2%         -0.66 [-1.52, 0.21]           Shimoura, et al., 2017         54.9         32.5         9         32         11         1.0%         -0.66 [-1.51, 0.30]           Sezen, et al., 2017         36.9         7.2         43         42         10.1         44         1.2%         -0.58 [-1.00, -0.15]	Std. Mean Difference IV, Random, 95% Cl
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$ \begin{array}{c} \mbox{Amer-Cuenca, et al., 2011} 26.5 & 24.7 & 30 & 61.9 & 23.2 & 30 & 12\% & -1.46 [+38.0.98] \\ Lison, et al., 2017 & 23.2 & 31.4 & 46 & 53.1 & 19.9 & 46 & 12\% & -1.14 [+138.0.98] \\ \mbox{Lison, et al., 2017 & 23.2 & 31.4 & 46 & 53.1 & 19.9 & 96 & 12\% & -1.34 [+138.0.98] \\ \mbox{Lison, et al., 2017 & 23.2 & 31.4 & 46 & 53.1 & 19.9 & 99 & 13\% & -0.35 [+0.63, 0.07] \\ \mbox{Machado te al., 2019 & 46 & 20 & 103 & 53 & 19.9 & 99 & 13\% & -0.35 [+0.63, 0.07] \\ \mbox{Machado te al., 2019 & 54.7 & 24.1 & 37 & 50.4 & 20.3 & 71 & 12\% & 0.04 [+0.55, 0.63] \\ \mbox{Machado te al., 2016 & 29.2 & 25. & 26 & 22 & 21 & 11\% & 0.04 [+0.55, 0.63] \\ \mbox{Machado te al., 2016 & 29.2 & 55.2 & 55.2 & 55.2 & 55.2 & 55.2 \\ \mbox{Test for overall effect. Z = 4.97 (P < 0.00001); P = 93\% & -1.250 [+7.39, -7.61] \\ \mbox{Test for overall effect. Z = 4.97 (P < 0.00001); P = 93\% & -1.250 [+7.39, -7.61] \\ \mbox{Test for overall effect. Z = 4.97 (P < 0.00001); P = 93\% & -3.27 [+4.28, -2.27] \\ \mbox{Hokenek et al., 2014 & 10 & 52 & 08 & 97 & 18.7 & 91 & 11\% & -3.11 [+3.78, -2.44 \\ \mbox{Lison, et al., 2014 & 10 & 52 & 08 & 97 & 15.9 & 01 & 11\% & -3.01 [+3.8, -4.4] \\ \mbox{Lison, et al., 2017 & 49 & 25 & 30 & 77 & 59 & 11\% & -2.91 [+3.2, -1.54] \\ \mbox{Tokenek et al., 2017 & 49 & 25 & 09 & 97 & 50 & 11.1\% & -2.91 [+3.2, -1.54] \\ \mbox{Tokenek et al., 2017 & 49 & 25 & 09 & 97 & 50 & 11.1\% & -2.91 [+3.2, -1.54] \\ \mbox{Tokenek et al., 2017 & 49 & 25 & 09 & 75 & 50 & 11.2\% & -2.16 [+3.82, -1.61] \\ \mbox{Amado, et al., 2010 & 49.3 & 7 & 30 & 661 & 6.9 & 30 & 11.1\% & -2.91 [+3.2, -1.54] \\ \mbox{Tokenek et al., 2017 & 49 & 25 & 04 & 815 & 50 & 11.2\% & -2.21 [+2.61, -1.61] \\ \mbox{Amado, et al., 2010 & 49.3 & 7 & 30 & 661 & 6.9 & 30 & 11.1\% & -2.91 [+3.0, -1.61] \\ \mbox{Amado, et al., 2010 & 47.7 & 10 & 31 & 12.6 & 10 & 0.9\% & -1.61 [-2.61, -1.61] \\ \mbox{Amado, et al., 2016 & 17.7 & 10 & 46 & 29 & 0.9\% & 1.16 [-2.46, 0.45] \\ \mbox{Amado, et al., 2016 & 17.7 & 10 & 46 & 29 & 0.9\% & 1.16 [-2.46, 0.45] \\ \mbox{Amado, et al., 2016 & 17.7 & 10 $	•
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Gall, et al., 2015         21         16         37         29         22         37         1.2%         -0.41 [0.87, 0.05]           Daley et al., 2019         47         25         22         46         22         22         1.1%         0.04 [0.63, 0.07]           Manaz, et al., 2019         47         25         22         46         22         22         1.1%         0.04 [0.65, 0.63]           Backwise, et al., 2018         32         251         252         17.3%         -0.37 [0.17, 0.77]           Heterogeneity, Tau" = 0.99; Ch" = 193.45, df = 14 (P < 0.00001); P = 93%	•
Dealey at al., 2020 46 20 103 53 19.9 99 1.3% - 0.35 [ $0.63$ , $0.07$ ] Machado et al., 2019 547 24.1 37 50.4 20.3 37 1.2% 0.19 [ $0.27$ , $0.65$ ] Backweis, et al., 2018 39.2 25.1 25 30.6 21 28 1.2% 0.35 [ $0.19$ , $0.90$ ] Subtotal (65% CI) 519 19.3 45, df at $1/4$ ( $P < 0.00001$ ); $P = 33%$ . Test for overall effect: $Z = 4.97$ ( $P < 0.00001$ ) if $P = 33%$ . Test for overall effect: $Z = 4.97$ ( $P < 0.00001$ ); $P = 33%$ . Test for overall effect: $Z = 4.97$ ( $P < 0.00001$ ); $P = 33%$ . Test for overall effect: $Z = 4.97$ ( $P < 0.00001$ ); $P = 33%$ . Test for overall effect: $Z = 4.97$ ( $P < 0.00001$ ); $P = 33%$ . Test for overall effect: $Z = 4.97$ ( $P < 0.00001$ ); $P = 33%$ . Test for overall effect: $Z = 4.97$ ( $P < 0.00001$ ); $P = 33%$ . Test for overall effect: $Z = 4.97$ ( $P < 0.00001$ ); $P = 33%$ . Test for overall effect: $Z = 4.97$ ( $P < 0.00001$ ); $P = 33%$ . Test for overall effect: $Z = 4.97$ ( $P < 0.00001$ ); $P = 33%$ . Test for overall effect: $Z = 4.97$ ( $P < 0.00001$ ); $P = 33%$ . Test for overall effect: $Z = 4.97$ ( $P < 0.00001$ ); $P = 33%$ . Test for overall effect: $Z = 4.97$ ( $P < 0.00001$ ); $P = 33%$ . Test for overall effect: $Z = 4.97$ ( $P < 0.00001$ ); $P = 33%$ . Test for overall effect: $Z = 4.97$ ( $P < 0.00001$ ); $P = 33%$ . Test for overall effect: $Z = 4.27$ ( $Z = 2.27$ ). Test for $Z = 2.27$ ( $Z = 2.27$ ), $Z = 2.27$ ( $Z = 2.27$ ). Test for $Z = 2.27$ ( $Z = 2.27$ ), $Z = 2.27$ ( $Z = 2.27$ ). Test for $Z = 2.27$ ( $Z = 2.27$ ), $Z = 2.27$ ( $Z = 2.27$ ). Test for $Z = 2.27$ ( $Z = 2.27$ ), $Z = 2.27$ ( $Z = 2.27$ ), $Z = 2.27$ ( $Z = 2.27$ ), $Z = 2.27$ ( $Z = 2.27$ ), $Z = 2.27$ ( $Z = 2.27$ ), $Z = 2.27$ , $Z = 2.$	+ + + + + + + + + + + + + + + + + + +
Machado et al., 2019         47         25         22         46         22         22         1.1%         0.04 [.0.55, 0.65]           Backwie, et al., 2018         392         25.1         25         352         552         17.3%         .0.27, 0.65]           Subtotal (PSW CI)         552         552         17.3%         .1.27, [1.77, -0.77]           Heterogeneity: Tau" = 0.49; Ch" = 193.45, df = 14 (P < 0.00001); P = 93%         110         8         0.1%         -12.50 [.17.39, -7.61]           Chrome, et al., 2014         10         5         20         9         39         1.19         8         0.1%         -3.27 [.4.28, -2.27]           Hokenek et al., 2019         22         12.49         39         72         18.7         39         1.1%         -3.11 [.37, 8.2.4]           Laurett, et al., 2014         10         5         20         10         20.1         20.1         23.1 [.42, 9.1.54]           Taking, et al., 2014         5.9         6.5         16         23.8         5.9         10         1.1%         -2.26 [.2.9, 1.61]           Barker, et al., 2016         23.1         33.1         19         2         13.3         1.19         2         11.19         2.26 [.2.9, 1.61]	+
Alama, et al., 2012       54.7       24.1       37       50.4       20.3       37       1.2%       0.03 [ $-0.27$ , $0.63$ ]         Beckwie, et al., 2016       39.2       25.1       25.3       25.2       15.2       17.3%       0.35 [ $-0.10$ , $0.90$ ]         Subtotal (65% (C)       Tate 10.8; (C) P = 193.45; (C) = 113.45; (C) = 10.92       9       39       1.19       8       0.1%       -12.50 [ $-17.39, -7.61$ ]       -12.50 [ $-17.39, -7.61$ ]         Test for overall effect Z = 4.97 (P < 0.00001); P = 93%       39       1.19       8       0.1%       -32.7 [ $4.28, -2.27$ ]         Hokenek et al., 2010       25.1       0.2       0.30       18       0.9%       -3.31 [ $-3.8, -2.44$ ]          Eximate al., 2019       22.12.49       39       7.18       9.1%       -3.11 [ $-3.8, -2.41$ ]          Chrone et al., 2019       22.14.29       5.6       10       0.53       6.3       9.0%       -2.81 [ $-3.31, -1.91$ ]          Shaheel, et al., 2017       49       25       30       97       5.9       30       1.1%       2.2.2.2.2.2.2.2.1.2.2.1.3       1.61 [ $-2.18, -1.02$ ]         Shaheel, et al., 2017       49       15       50       1.2.5%       -2.5.5 $-0.45$ [       2.2.5 [ $-1.18, -1.02$ ]       <	◆ - - - - - - - - - - - - -
Subtotal (65% CI)         552         552         17.3%         -1.27 [-1.77, -0.77]           Heterogeneity: Tar J = 0.89; Chr = 193.45, df = 14 (P < 0.00001); P = 93%	
$\begin{aligned} & Heterogeneity: Tar' = 0.89; Chi' = 193.45, df = 14 (P < 0.00001); P = 93%\\ \text{Test for overall effect: Z = 4.97 (P < 0.00001); P = 93%\\ \text{Test for overall effect: Z = 4.97 (P < 0.00001); P = 93%\\ \text{Test for overall effect: Z = 4.97 (P < 0.00001); P = 93%\\ \text{Cipriano, et al., 2014 10 5 20 80 30 18 0.9% - 3.27 [-4.28, -2.44]\\ \text{Lauretti, et al., 2015 20 10 20 70 20 20 1.0% - 3.10 [-4.05, -2.44]\\ \text{Lauretti, et al., 2015 20 10 20 70 20 20 1.0% - 3.10 [-4.05, -2.44]\\ \text{Lauretti, et al., 2015 20 10 20 70 20 20 1.0% - 3.10 [-4.05, -2.45]\\ \text{Tokuda, et al., 2014 5.9 6.5 16 23.8 5.9 16 0.9% - 2.81 [-3.82, -1.54]\\ \text{Tokuda, et al., 2014 5.9 6.5 16 23.8 5.9 16 0.9% - 2.81 [-3.82, -1.54]\\ \text{Tokuda, et al., 2010 49.3 7 30 66.1 6.9 30 1.1% - 2.62 [-2.91, -1.61]\\ \text{Tokuda, et al., 2006 32.4 18 29 66.2 11.2 33 1.1% - 2.26 [-2.91, -1.61]\\ \text{Him, et al., 2006 12.4 19 12 50 48 15 50 1.2% - 2.12 [-2.61, -1.63]\\ \text{Kibar et al., 2020 21.2 12.2 31 47.6 19.6 30 1.2% - 1.60 [-2.18, -1.02]\\ Jaafarpour, et al., 2020 17 3 10 31 12.6 10 0.9% - 1.46 [-2.48, -0.45]\\ \text{Sadala, et al., 2015 17 17 10 46 20 9 0.9% - 1.50 [-2.55, -0.45]\\ \text{Sadala, et al., 2015 21.4 9.1 26 58.7 14.5 26 1.1% - 1.48 [-2.26, -0.46]\\ \text{Sadala, et al., 2015 21.4 9.1 26 58.7 14.5 26 1.1% - 1.48 [-2.26, -0.46]\\ \text{Sadala, et al., 2013 38.8 25 17 67.7 14.2 16 1.1% - 1.38 [-2.14, -0.61]\\ \text{Orlog, 1897 30.4 2.2 5 56.8 17.7 27 1.1% - 1.38 [-2.14, -0.61]\\ \text{Orlog, 1897 30.4 2.2 5 56.8 17.7 14.2 16 1.1% - 1.38 [-2.14, -0.61]\\ \text{Curbica, et al., 2015 27.7 14.2 15 9.1 15.7 14.2 16 1.1% - 1.38 [-2.14, -0.61]\\ \text{Curbica, et al., 2015 20.7 7.4 23 30 7.4 22 1.1% - 1.33 [-1.96, -0.66]\\ \text{Lauretti, et al., 2015 10 10 13 8.0 20 10 1.0% - 1.33 [-1.96, -0.66]\\ \text{Lauretti, et al., 2015 10 10.7 3 6.2 17 6.0 37.4 20.6 10 1.0% - 1.38 [-2.40, -0.61]\\ \text{Curbica, et al., 2015 10 10.7 5 2.1 4 3.18 21 1.1% - 1.77 [-0.43]\\ \text{Abreu, et al., 2015 10 7.7 12.7 50 37.4 20.6 10 1.0% - 1.38 [-1.47, -0.73]\\ \text{Luchesa, et al., 2015 10 10.7 5 2.1 4 3.18 221 1.1.0% - 1.40 [-2.26, -0.54]\\ \text{Ceinit, et $	
Test for overall effect: Z = 4.97 (P < 0.00001)	
Barbaris, et al., 2010         25.11         0.92         9         38         1.19         8         0.1%         -12.56 [r13.97.61]           Cipriano, et al., 2014         10         5         20         80         30         18         0.9%         -3.27 [4.28, -2.27]           Hokenek et al., 2015         20         10         20         70         20         10.%         -3.10 [4.36, 2.15]           Ekim et al., 2014         5.9         6.5         16         63.5         6.9         90         1.1%         -2.281 [4.29, 1.54]           Shahoe, et al., 2010         49.3         7         30         66.1         69         90         1.1%         -2.28 [5.291, 1.61]           Shahoe, et al., 2006         32.4         18         29         66.2         11.2         31         1.4%         -2.29 [2.261, 1.63]           Kim, et al., 2012         12         12.2         31         47.6         19.6         30         1.2%         -1.60 [2.48, 0.45]           Jaafarpour, et al., 2020         17         3         10         12.6         10         9.9%         -1.51 [-19.3, 1.08]           Cheing & Luk, 2005         17         17         10         46         20         9	
Hokenek et al., 2019         22         12.49         39         72         18.7         39         1.11         3.11         2.341         2.441           Lauretti, et al., 2015         20         10         20         70         20         20         10.%         -3.10         [-4.05, 2.15]           Tokuda, et al., 2014         5.9         6.5         16         23.8         5.9         16         0.9%         -2.26         [-2.91, 1.61]           Tokuda, et al., 2010         49.3         7         30         66.1         6.9         30         1.1%         -2.26         [-2.91, 1.61]           Kim, et al., 2010         49.3         7         30         66.1         6.9         30         1.1%         -2.26         [-2.91, 1.61]         1.11           Kim, et al., 2010         21.2         21         31         47.6         19.6         30         1.2%         -1.26         [-2.8, 0.42]         Jaafarpour, et al., 2018         20.2         31         12.6         10         9.9         9.68.8         17.7         7         1.1%         -1.46         22.80.068]         Jaafarpour, et al., 2018         20.2         30         7.4         22         1.1%         -1.44         22.9	
Lauretti, et al., 2015 20 10 20 70 20 20 10% -3.01 [+4.29, -1.5] Ekim et al., 2008 47.2 5.6 10 65.3 6.3 9 0.7% -2.81 [-3.22, -1.54] Shahoei, et al., 2017 49 25 30 97 5.9 30 1.1% -2.81 [-3.32, -1.80] Takuda, et al., 2017 49 25 30 97 5.9 30 1.1% -2.81 [-3.32, -1.61] Barker, et al., 2010 42.3 7 30 66.1 6.9 30 1.1% -2.39 [-3.06, -7.7] Barker, et al., 2010 22.4 18 29 66.2 11.2 33 1.1% -2.39 [-3.06, -7.7] Ekim et al., 2010 19 12 50 48 15 50 12% -2.12 [-2.61, -1.61] Kibar et al., 2020 21.2 12.2 31 47.6 19.6 30 1.2% -1.61 [-1.83, -1.08] Jaafarpour, et al., 2008 5 5 54 12 4.2 54 1.2% -1.50 [-2.55, -0.45] Zhang et al., 2012 17 17 10 46 20 9 0.9% -1.46 [-2.48, -0.45] Sadala, et al., 2012 17 3 10 31 12.6 10 0.9% -1.46 [-2.48, -0.45] Sadala, et al., 2013 016.4 5 54 13.6 5 0.7% -1.44 [-2.92, 0.04] El, et al., 2015 21.4 9.1 26 38.7 14.5 26 1.1% -1.45 [-2.5, 0.54] Coliverina et al., 2012 30 16.4 5 54 13.6 5 0.7% -1.44 [-2.92, 0.04] El, et al., 2015 21.4 9.1 26 38.7 14.5 26 1.1% -1.45 [-2.5, 0.54] Coliverina et al., 2013 38.8 25 17 67.7 14.2 16 1.1% -1.38 [-1.97, 0.30] Cipriano, et al., 2004 37.3 16.2 15 59.1 13.7 12 1.0% -1.40 [-2.25, 0.54] Celik, et al., 2015 10.795 21 4 3.18 21 1.1% -1.38 [-1.97, 0.3] Luchesa, et al., 2004 20 7.4 23 30 7.4 22 1.1% -1.38 [-1.97, 0.3] Luchesa, et al., 2015 1 0.795 21 4 3.18 21 1.1% -1.28 [-1.9, 0.36] Da Silva, et al., 2015 1 0.795 21 4 3.18 21 1.1% -1.28 [-1.9, 0.36] Da Silva, et al., 2015 1 0.795 21 4 3.18 21 1.1% -1.28 [-1.9, 0.36] Da Silva, et al., 2017 7 36 21 5 58 12 15 1.0% -1.28 [-2.04, -0.46] Kayman-Kose, et al., 2014 (2) 17.7 12.7 50 37.4 20.6 50 1.2% -1.48 [-1.27, 0.73] Luchesa, et al., 2010 7 5.3 30 14.7 8.6 30 1.2% -0.88 [-1.48, -0.28] Da Silva, et al., 2014 77.2 [-1.94 138 20.8 10 10 1.0% -1.28 [-2.04, -0.46] Kayman-Kose, et al., 2014 77.2 [-1.94 138 20.8 10 10 1.0% -0.88 [-1.48, -0.28] Ornel, et al., 2019 7.3 9.8 26 20 15.7 26 1.2% -0.98 [-1.42, -0.46] Kayman-Kose, et al., 2019 7.3 9.8 26 30 17.7 62 31 1.1% -0.74 [-1.48, -0.28] Dradid, et al., 2019 7.	
Ekim et al., 2008         47.2         5.6         10         65.3         6.3         9         0.7%         -2.91         [1.3.8], 1.9.1]           Tokuda, et al., 2014         5.9         6.5         16         23.8         5.9         16         0.9%         -2.81         [1.3.8], 1.9.1]           Ahmed, et al., 2010         49.3         7         30         66.1         6.9         30         1.1%         -2.28         [2.2.1, 1.61]         -           Barker, et al., 2000         21.2         12.2         31         4.76         19.6         30         1.2%         -2.16         1.61         -           Jaafarpour, et al., 2020         21.2         21.2         31         4.76         19.6         30         1.2%         -1.60         1.28         -1.61         -           Jaafarpour, et al., 2020         17         3         10         31         12.6         10         9.%         -1.61         -2.55         -0.45           Sadala, et al., 2018         29.3         19.5         28         56.8         17.7         27         1.1%         -1.41         -2.29         -0.64           De Oliverina et al., 2013         38.8         25         17.6         13.7 <td></td>	
Tokuda, et al., 2014         5.9         6.5         16         2.3.8         5.9         16         0.9%         -2.8.1         1.3.2         1.8.01           Shahoei, et al., 2017         49         25         30         97         5.9         30         1.1.%         -2.3.8         1.3.3.1         1.1.1         -2.3.8         1.3.3.1         1.1.1         -2.3.8         1.3.3         1.1.%         -2.3.8         1.3.6         1.3.8         -2.3.8         1.3.6         1.3.8         -2.3.8         1.3.6         1.3.8         -2.3.8         1.3.6         1.3.8         -2.3.8         1.3.6         1.3.8         -2.3.8         1.3.6         1.3.8         -2.3.8         1.3.6         1.3.8         1.3.6         1.3.8         -2.3.8         1.3.6         1.3.8         1.3.6         1.3.8         1.3.6         1.3.8         1.3.6         1.3.8         1.3.6 <td></td>	
Shahosi, et al., 2017         49         25         30         97         59         30         1.1%         -2.61 [3.3], -1.91]           Ahmed, et al., 2010         49.3         7         30         66.2         11.2         33         1.1%         -2.28 [2.91, -1.61]         T           Kim, et al., 2020         21.2         2.2         31         4.76         19.6         1.2%         -2.28 [2.91, -1.61]         T           Jaafarour, et al., 2008         5         5         54         12         4.2         54         -1.50 [-2.55, -0.45]           Zhang et al., 2020         17         17         10         46         20         9         9.%         -1.50 [-2.55, -0.45]           Sadata, et al., 2018         2.93         19.5         2.8         56.8         17.7         27         1.1%         -1.44 [2.92, 0.04]         T           De Oliverira et al., 2013         38.8         25         17.6         67.7         14.2         10         -1.44 [2.92, 0.04]         T           Celik, et al., 2013         38.8         25         17.6         67.7         14.2         16         1.1%         -1.33 [-2.13, -0.6]           Ordog, 1987         30.4         2.8         58.4	
Ahmed, et al., 2010       49.3       7       30       66.1       69.30       1.1%       -2.36       2.36.61.71       T         Barker, et al., 2006       32.4       18       29       66.2       11.2       33       1.1%       -2.36       [2.9.1, -1.61]       T         Kin, et al., 2020       21.2       12.2       21       47.6       19.6       30       1.2%       -1.26       [2.1.61]       T         Jaafargour, et al., 2008       5       54       12       4.2       54       1.2%       -1.50       [2.55, -0.45]         Zhang et al., 2012       30       16.4       5       56.8       1.7       7       1.1%       -1.44       [2.20, -0.80]       T         Back al., 2015       21.4       9.1       26       58.7       14.2       26       1.1%       -1.41       [2.20, -0.80]       T         Ordog, 1987       30.4       2.8       25       54.8       25       51.1       1.41       16       1.1%       -1.33<[2.13, -0.53]	
Link of all 2017         20.7         7.0         7.1         2.5.7         7.0	
Link of all 2017         20.7         7.0         7.1         2.5.7         7.0	
Links Gale, 2014         39.5         17         11         25.7         47.8         12         1.0%         -0.70 [-1.59, 0.19]           Warlie & Oleg, 2014         39.5         17         11         52.5         18.6         10         1.0%         -0.70 [-1.59, 0.19]           Warlie & Oleg, 2014         39.5         17         11         52.5         18.6         10         1.0%         -0.70 [-1.59, 0.19]           Warlie & Oleg, 2014         48.3         20.1         12         64.2         24.6         12         1.0%         -0.68 [-1.51, 0.14]           Biglii, et al., 2016         14.27         10.1         15         23.27         15.8         15         1.1%         -0.66 [-1.52, 0.21]           Fujii-Abe et al., 2019         22.1         12.8         11         30.3         11.2         11         1.0%         -0.66 [-1.52, 0.21]           Shimoura, et al., 2019         5.1         8         25         11.4         10.9         25         1.2%         -0.65 [-1.22, -0.08]           Bjersa & Andersson, 2014         19.4         32.5         9         39.6         32         11         1.0%         -0.65 [-1.20, -0.08]           Stezen, et al., 2017         36.9         7.2 <t< td=""><td></td></t<>	
Links of al.         Dot         20.1         12         64.0         12         1.0%         -0.70         [-1.59, 0.19]           Warfield, et al., 1985         48.3         20.1         12         64.2         24.6         12         1.0%         -0.70         [-1.59, 0.19]           Warfield, et al., 1985         48.3         20.1         12         64.2         24.6         12         1.0%         -0.68         [-1.51, 0.14]           Bilgili, et al., 2016         14.27         10.1         15         23.27         15.8         15         1.1%         -0.66         [-1.40, 0.08]           Fujii-Abe et al., 2019         22.1         12.8         11         30.3         11.2         11         1.0%         -0.66         [-1.22, -0.08]           Shimoura, et al., 2019         5.1         8         25         11.4         10.9         25         1.2%         -0.66         [-1.22, -0.08]           Bjersa & Andersson, 2014         19.4         32.5         9         39.6         32         11         1.0%         -0.66         [-1.20, -0.08]           Sezen, et al., 2017         36.9         7.2         43         42         10.1         44         1.2%         -0.58         [-1.00, -	
Vitali & Oleg, 2014         39.5         17         11         52.5         17         11         52.5         16.6         10         10.7         -0.70 [-1.59, 0.19]           Warlie & Oleg, 2014         39.5         17         11         52.5         17         11         52.5         18.6         10         1.0%         -0.70 [-1.59, 0.19]           Warlie & Oleg, 2014         39.5         17         11         52.5         17         11         10.2         14.8         10         1.0%         -0.70 [-1.59, 0.19]           Warlie & Oleg, 2014         34.3         20.1         12         64.2         24.6         12         1.0%         -0.68 [-1.51, 0.14]           Bilgili, et al., 2019         22.1         12.8         11         30.3         11.2         11         1.0%         -0.66 [-1.52, 0.21]           Shimoura, et al., 2019         22.1         12.8         13.1.2         11         1.0%         -0.66 [-1.52, 0.21]           Bjersa & Andersson, 2014         19.4         32.5         9         39.6         32         11         1.0%         -0.66 [-1.51, 0.30]           Sezen, et al., 2017         36.9         7.2         43         42         10.1         44         1.2%	
Linka Gale         2017         30.7         17         20.7         43.0         12         10.70         -0.70         [1.50,0]         -0.70         [1.20,0]         -0.70         [1.20,0]	 
Vitali & Oleg, 2014         39.5         17         11         52.5         17         11         52.5         16.6         10         10.7         -0.70 [-1.59, 0.19]           Warlie & Oleg, 2014         39.5         17         11         52.5         17         11         52.5         18.6         10         1.0%         -0.70 [-1.59, 0.19]           Warlie & Oleg, 2014         39.5         17         11         52.5         17         11         10.2         14.8         10         1.0%         -0.70 [-1.59, 0.19]           Warlie & Oleg, 2014         34.3         20.1         12         64.2         24.6         12         1.0%         -0.68 [-1.51, 0.14]           Bilgili, et al., 2019         22.1         12.8         11         30.3         11.2         11         1.0%         -0.66 [-1.52, 0.21]           Shimoura, et al., 2019         22.1         12.8         13.1.2         11         1.0%         -0.66 [-1.52, 0.21]           Bjersa & Andersson, 2014         19.4         32.5         9         39.6         32         11         1.0%         -0.66 [-1.51, 0.30]           Sezen, et al., 2017         36.9         7.2         43         42         10.1         44         1.2%	
Linka Gale         2017         30.7         17         20.7         43.0         12         10.70         -0.70         [1.50,0]         -0.70         [1.20,0]         -0.70         [1.20,0]	<u>—</u>
Untail & Oleg, 2014         39.5         17         11         52.7         43.6         10         10.76         -0.70 [-1.59, 0.19]           Warfield, et al., 1985         48.3         20.1         12         64.2         24.6         12         1.0%         -0.70 [-1.59, 0.19]           Warfield, et al., 1985         48.3         20.1         12         64.2         24.6         12         1.0%         -0.70 [-1.59, 0.19]           Bilgili, et al., 2016         14.27         10.1         15         23.27         15.8         15         1.1%         -0.66 [-1.51, 0.14]           Bilgili, et al., 2019         22.1         12.8         11         30.3         11.2         11         1.0%         -0.66 [-1.52, 0.21]           Shimoura, et al., 2019         22.1         12.8         11.4         10.9         25         1.2%         -0.66 [-1.52, 0.21]           Bjersa & Andersson, 2014         19.4         32.5         9         39.6         32         11         1.0%         -0.66 [-1.51, 0.30]           Sezen, et al., 2017         36.9         7.2         43         42         10.1         44         1.2%         -0.58 [-1.00, -0.15]	
Links of al.         Dot         20.1         12         64.0         12         1.0%         -0.70         [-1.59, 0.19]           Warfield, et al., 1985         48.3         20.1         12         64.2         24.6         12         1.0%         -0.70         [-1.59, 0.19]           Warfield, et al., 1985         48.3         20.1         12         64.2         24.6         12         1.0%         -0.68         [-1.51, 0.14]           Bilgili, et al., 2016         14.27         10.1         15         23.27         15.8         15         1.1%         -0.66         [-1.40, 0.08]           Fujii-Abe et al., 2019         22.1         12.8         11         30.3         11.2         11         1.0%         -0.66         [-1.22, -0.08]           Shimoura, et al., 2019         5.1         8         25         11.4         10.9         25         1.2%         -0.66         [-1.22, -0.08]           Bjersa & Andersson, 2014         19.4         32.5         9         39.6         32         11         1.0%         -0.66         [-1.20, -0.08]           Sezen, et al., 2017         36.9         7.2         43         42         10.1         44         1.2%         -0.58         [-1.00, -	——
Untail & Oleg, 2014         39.5         17         11         52.7         43.6         12         10.7         40.6         12         10.7         40.7         [1.5]         11         20.7         43.6         12         10.7         40.7         [1.5]         10         10.7	
Links of al.         Dot         20.1         12         64.0         12         1.0%         -0.70         [-1.59, 0.19]           Warfield, et al., 1985         48.3         20.1         12         64.2         24.6         12         1.0%         -0.70         [-1.59, 0.19]           Warfield, et al., 1985         48.3         20.1         12         64.2         24.6         12         1.0%         -0.68         [-1.51, 0.14]           Bilgili, et al., 2016         14.27         10.1         15         23.27         15.8         15         1.1%         -0.66         [-1.40, 0.08]           Fujii-Abe et al., 2019         22.1         12.8         11         30.3         11.2         11         1.0%         -0.66         [-1.22, -0.08]           Shimoura, et al., 2019         5.1         8         25         11.4         10.9         25         1.2%         -0.66         [-1.22, -0.08]           Bjersa & Andersson, 2014         19.4         32.5         9         39.6         32         11         1.0%         -0.66         [-1.20, -0.08]           Sezen, et al., 2017         36.9         7.2         43         42         10.1         44         1.2%         -0.58         [-1.00, -	
Linko Gal, 2014         20.1         7.6         7.2         7.7         7.6         7.2         7.6         7.2         7.6         7.2         7.6         7.2         7.6         7.7         7.6         7.7         7.6         7.7         7.6         7.7         7.6         7.7         7.6         7.7         7.6         7.7         7.6         7.7         7.6         7.7         7.7         7.6         7.7         7.6         7.2         7.7	
Linka Value         Loss         File         Linka         Vialia         Color         Linka         Linka <thlink< th="">         Linka         Linka</thlink<>	
Linka Gale         2017         30.7         17         20.7         43.0         12         10.70         -0.70         [1.50,0]         -0.70         [1.20,0]         -0.70         [1.20,0]	
Linko Gal, 2014         20.1         7.6         7.2         7.7         7.6         7.2         7.6         7.2         7.6         7.2         7.6         7.2         7.6         7.7         7.6         7.7         7.6         7.7         7.6         7.7         7.6         7.7         7.6         7.7         7.6         7.7         7.6         7.7         7.6         7.7         7.7         7.6         7.7         7.6         7.2         7.7	
Linko Gal, 2014         20.1         7.6         7.2         7.7         7.6         7.2         7.6         7.2         7.6         7.2         7.6         7.2         7.6         7.7         7.6         7.7         7.6         7.7         7.6         7.7         7.6         7.7         7.6         7.7         7.6         7.7         7.6         7.7         7.6         7.7         7.7         7.6         7.7         7.6         7.2         7.7	
Links Gale, 2014         39.5         17         11         25.7         47.8         12         1.0%         -0.70 [-1.59, 0.19]           Warlie & Oleg, 2014         39.5         17         11         52.5         18.6         10         1.0%         -0.70 [-1.59, 0.19]           Warlie & Oleg, 2014         39.5         17         11         52.5         18.6         10         1.0%         -0.70 [-1.59, 0.19]           Warlie & Oleg, 2014         48.3         20.1         12         64.2         24.6         12         1.0%         -0.68 [-1.51, 0.14]           Biglii, et al., 2016         14.27         10.1         15         23.27         15.8         15         1.1%         -0.66 [-1.52, 0.21]           Fujii-Abe et al., 2019         22.1         12.8         11         30.3         11.2         11         1.0%         -0.66 [-1.52, 0.21]           Shimoura, et al., 2019         5.1         8         25         11.4         10.9         25         1.2%         -0.65 [-1.22, -0.08]           Bjersa & Andersson, 2014         19.4         32.5         9         39.6         32         11         1.0%         -0.65 [-1.20, -0.08]           Stezen, et al., 2017         36.9         7.2 <t< td=""><td>  </td></t<>	
Linker Gari, 2007         20.7         7.0         7.1         2.5.7         7.0	
Linko Gal, 2014         20.1         7.6         7.2         7.7         7.6         7.2         7.6         7.2         7.6         7.2         7.6         7.2         7.6         7.7         7.6         7.7         7.6         7.7         7.6         7.7         7.6         7.7         7.6         7.7         7.6         7.7         7.6         7.7         7.6         7.7         7.7         7.6         7.7         7.6         7.2         7.7	
Links of al.         Dot         20.1         12         64.0         12         1.0%         -0.70         [-1.59, 0.19]           Warfield, et al., 1985         48.3         20.1         12         64.2         24.6         12         1.0%         -0.70         [-1.59, 0.19]           Warfield, et al., 1985         48.3         20.1         12         64.2         24.6         12         1.0%         -0.68         [-1.51, 0.14]           Bilgili, et al., 2016         14.27         10.1         15         23.27         15.8         15         1.1%         -0.66         [-1.40, 0.08]           Fujii-Abe et al., 2019         22.1         12.8         11         30.3         11.2         11         1.0%         -0.66         [-1.22, -0.08]           Shimoura, et al., 2019         5.1         8         25         11.4         10.9         25         1.2%         -0.66         [-1.22, -0.08]           Bjersa & Andersson, 2014         19.4         32.5         9         39.6         32         11         1.0%         -0.66         [-1.20, -0.08]           Sezen, et al., 2017         36.9         7.2         43         42         10.1         44         1.2%         -0.58         [-1.00, -	
Links Gale, 2014         39.5         17         11         25.7         47.8         12         1.0%         -0.70 [-1.59, 0.19]           Warlie & Oleg, 2014         39.5         17         11         52.5         18.6         10         1.0%         -0.70 [-1.59, 0.19]           Warlie & Oleg, 2014         39.5         17         11         52.5         18.6         10         1.0%         -0.70 [-1.59, 0.19]           Warlie & Oleg, 2014         48.3         20.1         12         64.2         24.6         12         1.0%         -0.68 [-1.51, 0.14]           Biglii, et al., 2016         14.27         10.1         15         23.27         15.8         15         1.1%         -0.66 [-1.52, 0.21]           Fujii-Abe et al., 2019         22.1         12.8         11         30.3         11.2         11         1.0%         -0.66 [-1.52, 0.21]           Shimoura, et al., 2019         5.1         8         25         11.4         10.9         25         1.2%         -0.65 [-1.22, -0.08]           Bjersa & Andersson, 2014         19.4         32.5         9         39.6         32         11         1.0%         -0.65 [-1.20, -0.08]           Stezen, et al., 2017         36.9         7.2 <t< td=""><td></td></t<>	
Linko Gal, 2014         20.1         7.6         7.2         7.7         7.6         7.2         7.6         7.2         7.6         7.2         7.6         7.2         7.6         7.7         7.6         7.7         7.6         7.7         7.6         7.7         7.6         7.7         7.6         7.7         7.6         7.7         7.6         7.7         7.6         7.7         7.7         7.6         7.7         7.6         7.2         7.7	
Linka Gale         2017         30.7         17         20.7         43.0         12         10.70         -0.70         [1.50,0]         -0.70         [1.20,0]         -0.70         [1.20,0]	
Link of all 2017         20.7         7.0         7.1         2.5.7         7.0	
Linka Gale         2017         30.7         17         20.7         43.0         12         10.70         -0.70         [1.50,0]         -0.70         [1.20,0]         -0.70         [1.20,0]	
Links Gale, 2014         39.5         17         11         25.7         47.8         12         1.0%         -0.70 [-1.59, 0.19]           Warlie & Oleg, 2014         39.5         17         11         52.5         18.6         10         1.0%         -0.70 [-1.59, 0.19]           Warlie & Oleg, 2014         39.5         17         11         52.5         18.6         10         1.0%         -0.70 [-1.59, 0.19]           Warlie & Oleg, 2014         48.3         20.1         12         64.2         24.6         12         1.0%         -0.68 [-1.51, 0.14]           Biglii, et al., 2016         14.27         10.1         15         23.27         15.8         15         1.1%         -0.66 [-1.52, 0.21]           Fujii-Abe et al., 2019         22.1         12.8         11         30.3         11.2         11         1.0%         -0.66 [-1.52, 0.21]           Shimoura, et al., 2019         5.1         8         25         11.4         10.9         25         1.2%         -0.65 [-1.22, -0.08]           Bjersa & Andersson, 2014         19.4         32.5         9         39.6         32         11         1.0%         -0.65 [-1.20, -0.08]           Stezen, et al., 2017         36.9         7.2 <t< td=""><td></td></t<>	
Link of all 2017         20.7         7.0         7.1         2.5.7         7.0	
Linko Gal, 2014         20.1         7.6         7.2         7.7         7.6         7.2         7.6         7.2         7.6         7.2         7.6         7.2         7.6         7.7         7.6         7.7         7.6         7.7         7.6         7.7         7.6         7.7         7.6         7.7         7.6         7.7         7.6         7.7         7.6         7.7         7.7         7.6         7.7         7.6         7.2         7.7	
Links of al.         Dot         20.1         12         64.0         12         1.0%         -0.70         [-1.59, 0.19]           Warfield, et al., 1985         48.3         20.1         12         64.2         24.6         12         1.0%         -0.70         [-1.59, 0.19]           Warfield, et al., 1985         48.3         20.1         12         64.2         24.6         12         1.0%         -0.68         [-1.51, 0.14]           Bilgili, et al., 2016         14.27         10.1         15         23.27         15.8         15         1.1%         -0.66         [-1.40, 0.08]           Fujii-Abe et al., 2019         22.1         12.8         11         30.3         11.2         11         1.0%         -0.66         [-1.22, -0.08]           Shimoura, et al., 2019         5.1         8         25         11.4         10.9         25         1.2%         -0.66         [-1.22, -0.08]           Bjersa & Andersson, 2014         19.4         32.5         9         39.6         32         11         1.0%         -0.66         [-1.20, -0.08]           Sezen, et al., 2017         36.9         7.2         43         42         10.1         44         1.2%         -0.58         [-1.00, -	
Links Gale, 2014         39.5         17         11         25.7         47.8         12         1.0%         -0.70 [-1.59, 0.19]           Warlie & Oleg, 2014         39.5         17         11         52.5         18.6         10         1.0%         -0.70 [-1.59, 0.19]           Warlie & Oleg, 2014         39.5         17         11         52.5         18.6         10         1.0%         -0.70 [-1.59, 0.19]           Warlie & Oleg, 2014         48.3         20.1         12         64.2         24.6         12         1.0%         -0.68 [-1.51, 0.14]           Biglii, et al., 2016         14.27         10.1         15         23.27         15.8         15         1.1%         -0.66 [-1.52, 0.21]           Fujii-Abe et al., 2019         22.1         12.8         11         30.3         11.2         11         1.0%         -0.66 [-1.52, 0.21]           Shimoura, et al., 2019         5.1         8         25         11.4         10.9         25         1.2%         -0.65 [-1.22, -0.08]           Bjersa & Andersson, 2014         19.4         32.5         9         39.6         32         11         1.0%         -0.65 [-1.20, -0.08]           Stezen, et al., 2017         36.9         7.2 <t< td=""><td></td></t<>	
Linker Gari, 2007         20.7         7.0         7.1         2.5.7         7.0	
Vitalii & Oleg, 2014         39.5         17         11         52.5         18.6         10         1.0%         -0.70 [-1.59, 0.19]           Warfield, et al., 1985         48.3         20.1         12         64.2         24.6         12         1.0%         -0.68 [-1.51, 0.14]           Bilgili, et al., 2016         14.27         10.1         15         23.27         15.8         15         1.1%         -0.66 [-1.52, 0.21]           Fujii-Abe et al., 2019         22.1         12.8         11         30.3         11.2         11         1.0%         -0.66 [-1.52, 0.21]           Shimoura, et al., 2019         5.1         8         25         11.4         10.9         25         1.2%         -0.66 [-1.52, 0.21]           Bjersa & Andersson, 2014         19.4         32.5         9         39.6         32         11         1.0%         -0.66 [-1.51, 0.30]           Sezen, et al., 2017         36.9         7.2         43         42         10.1         44         1.2%         -0.58 [-1.00, -0.15]	
Bilgili, et al., 2016         14.27         10.1         15         23.27         15.8         15         1.1%         -0.66         [-1.40, 0.08]           Fujil-Abe et al., 2019         22.1         12.8         11         30.3         11.2         11         1.0%         -0.66         [-1.40, 0.08]           Shimoura, et al., 2019         5.1         8         25         11.4         10.9         25         1.2%         -0.66         [-1.22, -0.08]           Bjersa & Andersson, 2014         19.4         32.5         9         32         11         1.0%         -0.60         [-5.10, 0.30]           Sezen, et al., 2017         36.9         7.2         43         42         10.1         44         1.2%         -0.58 [-1.00, -0.15]	
Fujii-Abe et al., 2019         22.1         12.8         11         30.3         11.2         11         1.0%         -0.66         [-1.52, 0.21]           Shimoura, et al., 2019         5.1         8         25         11.4         10.9         25         1.2%         -0.66         [-1.52, 0.21]           Bjersa & Andersson, 2014         19.4         32.5         9         39.6         32         11         1.0%         -0.66         [-1.52, 0.03]           Sezen, et al., 2017         36.9         7.2         43         42         10.1         44         1.2%         -0.58         [-1.00, -0.15]	
Shimoura, etal., 2019         5.1         8         25         11.4         10.9         25         1.2%         -0.665 [-1.22, -0.08]           Bjersa & Andersson, 2014         19.4         32.5         9         39.6         32         11         1.0%         -0.60 [-1.51, 0.30]           Sezen, etal., 2017         36.9         7.2         43         42         10.1         44         1.2%         -0.58 [-1.00, -0.15]	
Bjersa & Andersson, 2014         19.4         32.5         9         39.6         32         11         1.0%         -0.60 [-1.51, 0.30]           Sezen, et al., 2017         36.9         7.2         43         42         10.1         44         1.2%         -0.58 [-1.00, -0.15]	
Sezen, et al., 2017 36.9 7.2 43 42 10.1 44 1.2% -0.58 [-1.00, -0.15]	
	<u> </u>
Liu, et al., 2017 48.2 17.7 22 55.8 12.6 22 1.1% -0.49 [-1.09, 0.11]	
Grimmer, 1992 22 28 20 35 29 20 1.1% -0.45 [-1.09, 0.11]	+
Ferreira, et al., 2011 18 18 15 25 18 15 1.1% -0.38 [-1.10, 0.34]	-+
Rakel & Frantz, 2003 (3) 42 33.45 33 55 37.3 33 1.2% -0.36 [-0.85, 0.12]	+
Warke, et al., 2004 28.25 36.5 5 40.33 19.4 3 0.7% -0.33 [-1.78, 1.12]	
Hruby, et al., 2006 35 28.8 48 43.7 30.6 49 1.2% -0.29 [-0.69, 0.11]	
Robinson, et al., 2001 38.2 31.24 10 47.92 36.37 13 1.0% -0.27 [-1.10, 0.56]	
Hamza, et al., 1999 25 23 25 31 25 25 1.2% -0.25 [-0.80, 0.31] Machin, et al., 1988 13.47 13.72 15 16.29 13.65 15 1.1% -0.20 [-0.92, 0.52]	
Moore & Shurman, 1997 (4) 40.58 27.55 24 44.81 30.67 24 1.2% -0.14 [-0.71, 0.42]	-
Cuschieri, et al., 1985 25 21.8 53 28 21.8 53 1.2% -0.14 [-0.71, 0.42]	-+
Forster, et al., 1994 9.8 28.1 15 13.7 31.9 15 1.1% -0.13 [-0.84, 0.59]	-+-
Shimoji, et al., 2007 38 15 9 40 20 8 1.0% -0.11 [-1.06, 0.84]	-+-
Graff-Radford, et al., 1989 28.3 18.06 12 30.2 15.92 12 1.0% -0.11 [-0.91, 0.69]	-+-
Yilmazer, et al., 2012 54.6 32.1 33 57.5 30.5 32 1.2% -0.09 [-0.58, 0.40]	-
Sahin, et al., 2011 68.5 15.5 19 69.5 11.5 19 1.1% -0.07 [-0.71, 0.56]	
Thomas, et al., 1988 33 31.1 131 35 33.8 144 1.3% -0.06 [-0.30, 0.18]	1
Presser, et al., 2000 47 38.34 30 49 27.39 30 1.2% -0.06 [-0.57, 0.45] Ilhani, 2015 22.4 11.3 35 22.8 10.2 31 1.2% -0.04 [-0.52, 0.45]	<u>+</u>
Ilhani, 2015 22.4 11.3 35 22.8 10.2 31 1.2% -0.04 [-0.52, 0.45] Tucker, et al., 2015 56 56 35 57 57 35 1.2% -0.02 [-0.49, 0.45]	+
Tucker, et al., 2015 56 56 35 57 57 35 1.2% -0.02 [-0.49, 0.45] Bono, et al., 2015 80 20 54 80 20 54 1.2% 0.00 [-0.38, 0.38]	+
Lee, et al., 2015 55.6 9.2 18 54.4 12.9 18 1.1% 0.10 [-0.55, 0.76]	
Silva, et al., 2012 22.5 11.5 21 20 12.5 21 1.1% 0.20 [-0.40, 0.81]	
Siqueira et al., 2019 2.92 6.6 13 0.7 1.6 14 1.1% 0.46 [-0.31, 1.22]	
Kofotolis, et al., 2008 22 4 23 20 4 21 1.1% 0.49 [-0.11, 1.09]	
Kayman-Kose, et al., 2014 (5) 13.5 5.8 50 7.8 7 50 1.2% 0.88 [0.47, 1.29]	
Subtotal (95% CI) 1874 1863 82.7% -0.89 [-1.08, -0.70] Heterogeneity: Tau <sup>2</sup> = 0.57; Chi <sup>2</sup> = 529.24, df = 76 (P < 0.00001); l <sup>2</sup> = 86%	
Test for overall effect: $Z = 9.27$ ( $P < 0.00001$ )	+ + + + + + + + + + + + + + + + + + +
Total (95% Cl) 2426 2415 100.0% -0.96 [-1.14, -0.78] Heterogeneity: Tau <sup>2</sup> = 0.64; Chi <sup>2</sup> = 735.58, df = 91 (P < 0.00001); l <sup>2</sup> = 88%	+ + + + + + + + + + + + + + +
Test for every lefter $7 = 10.40 (P < 0.00001)$	+ + + + + + + + +
Test for subgroup differences: $Chi^2 = 1.91$ , df = 1 (P = 0.17), l <sup>2</sup> = 47.7%	+ + + + -2 -2 -2 -2 -2 -2 -2 -2 -2 -2 -2 -2 -2
Footnotes	

> (4) 'croshor peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml (5) Vaginal delivery sample



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#### BMJ Open Placebo Std. Mean Difference

Std. Mean Difference

TENS

	Mean		Total				Weight	IV, Random, 95% CI	IV, Random, 95% Cl
Cipriano, et al., 2014	10	5	20	80	30	18	0.9%	-3.27 [-4.28, -2.27]	
Mora, et al., 2006 Bertalanffy, et al., 2005	33.3 49	16 8	39 30	82.6 77	14.3 11	34 33	1.1% 1.1%	-3.20 [-3.91, -2.50] -2.85 [-3.57, -2.14]	<u> </u>
Tokuda, et al., 2014	5.9	6.5	16	23.8	5.9	16	0.9%	-2.81 [-3.82, -1.80]	
Shahoei, et al., 2017	49	25	30	97	5.9	30	1.1%	-2.61 [-3.31, -1.91]	
Ahmed, et al., 2010 Barker, et al., 2006	49.3 32.4	7 18	30 29	66.1 66.2	6.9 11.2	30 33	1.1% 1.1%	-2.39 [-3.06, -1.71] -2.26 [-2.91 -1.61]	
Barker, et al., 2006 Lang, et al., 2007	32.4 59	18 6	29 30	66.2 79	11.2	33	1.1% 1.1%	-2.26 [-2.91, -1.61] -2.20 [-2.83, -1.57]	
Desantana, et al., 2008	9	10.7	20	48	22.7	20	1.0%	-2.15 [-2.95, -1.36]	——
Kim, et al., 2012	19	12	50	48	15	50	1.2%	-2.12 [-2.61, -1.63]	<u> </u>
Baez-Suarez, et al., 2018 Desentana et al. 2009	62 43	14 15 3	21	83	12 14 7	21 21	1.1%	-1.58 [-2.28, -0.88] -1.54 [-2.22, -0.86]	
Desantana, et al., 2009 Jaafarpour, et al., 2008	43	15.3 5	23 54	66.5 12	14.7 4.2	21 54	1.1% 1.2%	-1.54 [-2.22, -0.86] -1.51 [-1.93, -1.08]	÷
Amer-Cuenca, et al., 2008	26.5	24.7	30	61.9	23.2	30	1.2%	-1.46 [-2.03, -0.88]	
Sadala, et al., 2018	29.3	19.5	28	56.8	17.7	27	1.1%	-1.45 [-2.05, -0.86]	
Park, et al., 2015	15	15	48	45	25	50	1.2%	-1.44 [-1.88, -0.99]	<u> </u>
Ordog, 1987 Luchesa, et al., 2009	30.4 5	2.8 6	25 15	54.8 21	25 15.4	25 15	1.1% 1.0%	-1.35 [-1.97, -0.73] -1.33 [-2.13, -0.53]	
Cipriano, et al., 2008	20	7.4	23	30	7.4	22	1.1%	-1.33 [-1.98, -0.68]	<u> </u>
Da Silva, et al., 2015	1	0.795	21	4	3.18	21	1.1%	-1.27 [-1.94, -0.60]	
Mahure, et al., 2017	36	21	15	58	12	15	1.0%	-1.25 [-2.04, -0.46]	<u> </u>
Kayman-Kose, et al., 2014 (1) Lison, et al., 2017	17.7 23.2	12.7 31.4	50 46	37.4 53.1	20.6 19.9	50 46	1.2% 1.2%	-1.14 [-1.57, -0.72] -1.13 [-1.57, -0.69]	<b></b>
Lison, et al., 1985	23.2 39.3	17.9	40	65.3	26.6	40	1.1%	-1.12 [-1.89, -0.34]	
Cuschieri, et al., 1987	30	11.25	10	49	20.25	10	1.0%	-1.11 [-2.07, -0.15]	
Emmiler, et al., 2008	24	11.8	20	39	14.8	20	1.1%	-1.10 [-1.77, -0.43]	
Abreu, et al., 2010 Chapdra, et al., 2010	68 7	23	10	88 14.7	10	10 30	1.0%	-1.08 [-2.03, -0.13]	
Chandra, et al., 2010 Pitangui, et al., 2014	ر 17.2	5.3 21.9	30 11	14.7 38.8	8.6 20.8	30 10	1.2% 1.0%	-1.06 [-1.61, -0.52] -0.97 [-1.89, -0.05]	
Yilmaz et al., 2019	7.3	9.8	26	20	15.7	26	1.2%	-0.96 [-1.53, -0.38]	
Aminisaman et al., 2020	26.6	5.4	30	31.2	4.8	30	1.2%	-0.89 [-1.42, -0.36]	
Oncel, et al., 2002	24	13	25	39	20	25	1.2%	-0.88 [-1.46, -0.29]	
Elboim et al., 2020 Zakariaee et al., 2019	41.7 31.8	19.2 20.4	23 40	61.2 47.5	25 16.5	18 40	1.1% 1.2%	-0.87 [-1.52, -0.22] -0.84 [-1.30, -0.38]	·
Domaille & Reeves, 1997	30.33	8.14	31	47.5	28.14	29	1.2%	-0.81 [-1.33, -0.28]	
Fiorelli, et al., 2012	39	8	23	45	7	23	1.1%	-0.78 [-1.39, -0.18]	
Likar et al. 2001	25.1	7.6	11	29.7	4.8	12	1.0%	-0.70 [-1.55, 0.14]	
Warfield, et al., 1985 Fujii-Abe et al., 2019	48.3 22.1	20.1 12.8	12 11	64.2 30.3	24.6 11.2	12 11	1.0% 1.0%	-0.68 [-1.51, 0.14] -0.66 [-1.52, 0.21]	<u> </u>
Bjersa, et al., 2015	13	12.0	15	30.3 26	24	13	1.1%	-0.63 [-1.39, 0.14]	
Bjersa & Andersson, 2014	19.4	32.5	9	39.6	32	11	1.0%	-0.60 [-1.51, 0.30]	+
Sezen, et al., 2017	36.9	7.2	43	42	10.1	44	1.2%	-0.58 [-1.00, -0.15]	<u> </u>
Galli, et al., 2015 Ferreira, et al., 2011	21 18	16 18	37 15	29 25	22 18	37 15	1.2% 1.1%	-0.41 [-0.87, 0.05] -0.38 [-1.10, 0.34]	
Rakel & Frantz, 2003 (2)	42	33.45	33	25 55	37.3	33	1.1%	-0.36 [-0.85, 0.12]	
Hruby, et al., 2006	35	28.8	48	43.7	30.6	49	1.2%	-0.29 [-0.69, 0.11]	-+
Robinson, et al., 2001	38.2	31.24	10	47.92		13	1.0%	-0.27 [-1.10, 0.56]	-+
Hamza, et al., 1999 Cuschieri, et al., 1985	25 25	23 21.8	25 53	31 28	25 21.8	25 53	1.2% 1.2%	-0.25 [-0.80, 0.31] -0.14 [-0.52, 0.24]	
Forster, et al., 1985	25 9.8	21.8	53 15	28 13.7	21.8 31.9	53 15	1.2%	-0.14 [-0.52, 0.24] -0.13 [-0.84, 0.59]	
Yilmazer, et al., 2012	54.6	32.1	33	57.5	30.5	32	1.2%	-0.09 [-0.58, 0.40]	-+-
Thomas, et al., 1988	33	31.1	131	35	33.8	144	1.3%	-0.06 [-0.30, 0.18]	+
Presser, et al., 2000	47	38.34	30	49	27.39	30			
							1.2%	-0.06 [-0.57, 0.45]	
Tucker, et al., 2015	56	56	35	57	57	35	1.2%	-0.02 [-0.49, 0.45]	÷
Tucker, et al., 2015 Lee, et al., 2015									
Tucker, et al., 2015 Lee, et al., 2015 Silva, et al., 2012 Beckwée, et al., 2018	56 55.6 22.5 39.2	56 9.2 11.5 25.1	35 18 21 25	57 54.4 20 30.6	57 12.9 12.5 23.2	35 18 21 28	1.2% 1.1% 1.1% 1.2%	-0.02 [-0.49, 0.45] 0.10 [-0.55, 0.76] 0.20 [-0.40, 0.81] 0.35 [-0.19, 0.90]	
Tucker, et al., 2015 Lee, et al., 2015 Silva, et al., 2012 Beckwée, et al., 2018 Kayman-Kose, et al., 2014 (3) Subtotal (95% CI)	56 55.6 22.5 39.2 13.5	56 9.2 11.5 25.1 5.8	35 18 21 25 50 <b>1667</b>	57 54.4 20 30.6 7.8	57 12.9 12.5 23.2 7	35 18 21 28 50 1681	1.2% 1.1% 1.1%	-0.02 [-0.49, 0.45] 0.10 [-0.55, 0.76] 0.20 [-0.40, 0.81]	+ + + + +
Tucker, et al., 2015 Lee, et al., 2015 Silva, et al., 2012 Beckwée, et al., 2018 Kayman-Kose, et al., 2014 (3) Subtotat (95% Cl) Heterogeneity: Tau <sup>2</sup> = 0.64; Cl Test for overall effect: Z = 9.03	56 55.6 22.5 39.2 13.5 hi <sup>2</sup> = 493.7	56 9.2 11.5 25.1 5.8 '8, df =	35 18 21 25 50 <b>1667</b>	57 54.4 20 30.6 7.8	57 12.9 12.5 23.2 7	35 18 21 28 50 1681	1.2% 1.1% 1.1% 1.2% 1.2%	-0.02 [-0.49, 0.45] 0.10 [-0.55, 0.76] 0.20 [-0.40, 0.81] 0.35 [-0.19, 0.90] 0.88 [0.47, 1.29]	• •
Tucker, et al., 2015 Lee, et al., 2015 Silva, et al., 2012 Beckwée, et al., 2014 Kayman-Kose, et al., 2014 (3) Subtotati (95% CI) Heterogeneity: Tau <sup>2</sup> = 0.64; CI Test for overall effect: Z = 9.02 <b>7.10.2 Chronic Pain</b>	56 55.6 22.5 39.2 13.5 hi <sup>2</sup> = 493.7 3 (P < 0.00	56 9.2 11.5 25.1 5.8 '8, df =	35 18 21 25 50 <b>1667</b> 57 (P <	57 54.4 20 30.6 7.8 0.0000	57 12.9 12.5 23.2 7 1); I <sup>2</sup> =	35 18 21 28 50 <b>1681</b> 88%	1.2% 1.1% 1.1% 1.2% 1.2% 65.0%	-0.02 [-0.49, 0.45] 0.10 [-0.55, 0.76] 0.20 [-0.40, 0.81] 0.35 [-0.19, 0.90] 0.88 [0.47, 1.29] -1.02 [-1.25, -0.80]	+ + + + +
Tucker, et al., 2015 Lee, et al., 2015 Silva, et al., 2012 Beckwée, et al., 2018 Kaymar-Kose, et al., 2014 (3) Subtotal (95% CI) Heterogeneity: Tau <sup>2</sup> = 0.64; CI Test for overall effect Z = 9.00 7.10.2 Chronic Pain Barbarisi, et al., 2010	56 55.6 22.5 39.2 13.5 hi <sup>2</sup> = 493.7 3 (P < 0.00 25.11	56 9.2 11.5 25.1 5.8 '8, df = 1001) 0.92	35 18 21 25 50 <b>1667</b> 57 (P < 9	57 54.4 20 30.6 7.8 0.0000	57 12.9 12.5 23.2 7 1); I <sup>2</sup> = -	35 18 21 28 50 1681 88%	1.2% 1.1% 1.2% 1.2% 65.0%	-0.02 [-0.49, 0.45] 0.10 [-0.55, 0.76] 0.20 [-0.40, 0.81] 0.35 [-0.19, 0.90] 0.88 [0.47, 1.29] -1.02 [-1.25, -0.80] -1.02 [-1.7.39, -7.61]	• •
Tucker, et al., 2015 Lee, et al., 2015 Silva, et al., 2012 Beckwée, et al., 2018 Kayman-Kose, et al., 2014 (3) Subtotai (95% Cl) Heterogeneity: Tau <sup>2</sup> = 0.64; Cl Test for overall effect: Z = 9.03 <b>7.10.2 Chronic Pain</b> Barbarisi, et al., 2010 Hokenek et al., 2019	56 55.6 22.5 39.2 13.5 hi <sup>2</sup> = 493.7 3 (P < 0.00 25.11 22	56 9.2 11.5 25.1 5.8 '8, df = 0001) 0.92 12.49	35 18 21 25 50 <b>1667</b> 57 (P < 9 39	57 54.4 20 30.6 7.8 0.0000 39 72	57 12.9 12.5 23.2 7 1); I <sup>2</sup> = - 1.19 18.7	35 18 21 28 50 <b>1681</b> 88% 8 839	1.2% 1.1% 1.2% 1.2% 65.0% 0.1% 1.1%	-0.02 [-0.49, 0.45] 0.10 [-0.55, 0.76] 0.20 [-0.40, 0.81] 0.35 [-0.19, 0.90] 0.88 [0.47, 1.29] -1.02 [-1.25, -0.80] -1.250 [-17.39, -7.61]	•
Tucker, et al., 2015 Lee, et al., 2015 Silva, et al., 2012 Beckwée, et al., 2018 Kayman-Kose, et al., 2014 (3) Subtotal (95% CI) Heterogeneity: Tau <sup>2</sup> = 0.64; CI Test for overall effect: Z = 9.05 <b>7.10.2</b> Chronic Pain Barbarisi, et al., 2010 Hokenek et al., 2019 Lauretti, et al., 2005 Ekim et al., 2008	56 55.6 22.5 39.2 13.5 hi <sup>2</sup> = 493.7 8 (P < 0.00 25.11 22 20 47.2	56 9.2 11.5 25.1 5.8 (8, df = 0001) 0.92 12.49 10 5.6	35 18 21 25 50 <b>1667</b> 57 (P < 9 39 20 10	57 54.4 20 30.6 7.8 0.00000 39 72 70 65.3	57 12.9 12.5 23.2 7 (1); I <sup>2</sup> = - 1.19 18.7 20 6.3	35 18 21 28 50 1681 88% 8 39 20 9	1.2% 1.1% 1.2% 1.2% 65.0% 0.1% 1.1% 1.0% 0.7%	-0.02 [-0.49, 0.45] 0.10 [-0.55, 0.76] 0.20 [-0.40, 0.81] 0.35 [-0.19, 0.90] 0.88 [0.47, 1.29] -1.02 [-1.25, -0.80] -1.02 [-1.25, -0.80] -1.02 [-1.25, -0.81] -1.01 [-1.25, -2.15] -2.91 [-4.29, -1.54]	•
Tucker, et al., 2015 Lee, et al., 2015 Silva, et al., 2012 Beckwiee, et al., 2014 (3) Subtotal (95% C1) Heterogeneity: Tau <sup>2</sup> = 0.64; C1 Test for overall effect: Z = 9.03 <b>7.10.2 Chronic Pain</b> Barbarisi, et al., 2010 Hokenek et al., 2010 Hokenek et al., 2015 Ekim et al., 2018 Ekim et al., 2008 Dailey, et al., 2018 (4)	56 55.6 22.5 39.2 13.5 hi <sup>2</sup> = 493.7 8 (P < 0.00 25.11 22 20 47.2 40	56 9.2 11.5 25.1 5.8 '8, df = 0001) 0.92 12.49 10 5.6 4	35 18 21 25 50 <b>1667</b> 57 (P < 9 39 20 10 41	57 54.4 20 30.6 7.8 0.00000 39 72 70 65.3 47	57 12.9 12.5 23.2 7 1); I <sup>2</sup> = - 1.19 18.7 20 6.3 4	35 18 21 28 50 1681 88% 8 39 20 9 41	1.2% 1.1% 1.2% 1.2% 65.0% 0.1% 1.1% 1.0% 0.7% 1.2%	-0.02 [-0.49, 0.45] 0.10 [-0.55, 0.76] 0.20 [-0.40, 0.81] 0.35 [-0.19, 0.90] 0.88 [0.47, 1.29] -1.02 [-1.25, -0.80] -1.250 [-17.39, -7.61] -3.11 [-3.78, -2.44] -3.10 [-4.05, -2.15] -2.91 [-4.29, -1.54] -1.73 [-2.24, -1.22]	• •
Tucker, et al., 2015 Lee, et al., 2015 Silva, et al., 2012 Beckwiee, et al., 2018 Kayman-Kose, et al., 2014 (3) Subtotal (95% Cl) Heterogeneily: Tau <sup>2</sup> = 0.64; Cl Test for overall effect: Z = 9.02 <b>7.10.2 Chronic Pain</b> Barbarisi, et al., 2010 Hokenek et al., 2010 Lauretti, et al., 2015 Ekim et al., 2008 Dailey, et al., 2020	56 55.6 22.5 39.2 13.5 hi <sup>2</sup> = 493.7 3 (P < 0.00 25.11 22 20 47.2 40 21.2	56 9.2 11.5 25.1 5.8 '8, df = 0001) 0.92 12.49 10 5.6 4 12.2	35 18 21 25 50 <b>1667</b> 57 (P < 9 39 20 10 41 31	57 54.4 20 30.6 7.8 0.00000 39 72 70 65.3 47 47.6	57 12.9 12.5 23.2 7 1); I <sup>2</sup> = - 1.19 18.7 20 6.3 4 19.6	35 18 21 28 50 1681 88% 8 39 20 9 41 30	1.2% 1.1% 1.2% 1.2% 65.0% 0.1% 1.1% 1.0% 0.7% 1.2%	-0.02 [-0.49, 0.45] 0.10 [-0.55, 0.76] 0.20 [-0.40, 0.81] 0.35 [-0.19, 0.90] 0.88 [0.47, 1.29] -1.02 [-1.25, -0.80] -1.02 [-1.25, -0.80] -1.12.50 [-17.39, -7.61] -3.10 [-4.05, -2.15] -2.91 [-4.29, -1.54] -1.73 [-2.24, -1.22] -1.60 [-2.18, -1.02]	• •
Tucker, et al., 2015 Lee, et al., 2015 Silva, et al., 2012 Beckwée, et al., 2018 Kayman-Kose, et al., 2014 (3) Subtotal (95% Cl) Heterogeneity: Tau <sup>2</sup> = 0.64; Cl Test for overall effect: Z = 9.03 <b>7.10.2 Chronic Pain</b> Barbarisi, et al., 2010 Hokenek et al., 2019 Lauretti, et al., 2019 Lauretti, et al., 2019 Dailey, et al., 2008 Dailey, et al., 2020 Zhang et al., 2020	56 55.6 22.5 39.2 13.5 hi <sup>2</sup> = 493.7 8 (P < 0.00 25.11 22 20 47.2 40	56 9.2 11.5 25.1 5.8 '8, df = 0001) 0.92 12.49 10 5.6 4	35 18 21 25 50 <b>1667</b> 57 (P < 9 39 20 10 41	57 54.4 20 30.6 7.8 0.00000 39 72 70 65.3 47	57 12.9 12.5 23.2 7 1); I <sup>2</sup> = - 1.19 18.7 20 6.3 4	35 18 21 28 50 1681 88% 8 39 20 9 41	1.2% 1.1% 1.2% 1.2% 65.0% 0.1% 1.1% 1.0% 0.7% 1.2%	-0.02 [-0.49, 0.45] 0.10 [-0.55, 0.76] 0.20 [-0.40, 0.81] 0.35 [-0.19, 0.90] 0.88 [0.47, 1.29] -1.02 [-1.25, -0.80] -1.02 [-1.25, -0.80] -1.02 [-1.25, -0.80] -1.03 [-1.25, -0.81] -3.11 [-3.78, -2.44] -3.10 [-4.05, -2.15] -2.91 [-4.29, -1.54] -1.73 [-2.24, -1.22] -1.60 [-2.18, -1.02] -1.46 [-2.48, -0.45]	• •
Tucker, et al., 2015 Lee, et al., 2015 Silva, et al., 2012 Beckwée, et al., 2018 Kayman-Kose, et al., 2014 (3) Subtotal (95% CI) Test for overall effect: Z = 9.05 <b>7.10.2 Chronic Pain</b> Barbarisi, et al., 2010 Hokenek et al., 2019 Lauretti, et al., 2019 Ekim et al., 2018 Ekim et al., 2018 Dailey, et al., 2013 Zhang et al., 2020 De Oliverira et al., 2012	$56 \\ 55.6 \\ 22.5 \\ 39.2 \\ 13.5 \\ hi^2 = 493.7 \\ 3 (P < 0.000 \\ 25.11 \\ 22 \\ 20 \\ 47.2 \\ 40 \\ 21.2 \\ 17 \\ 17 \\ 100 \\ 21.2 \\ 17 \\ 100 \\ 21.2 \\ 17 \\ 100 \\ 21.2 \\ 17 \\ 100 \\ 21.2 \\ 21.2 \\ 100 \\ 21.2$	56 9.2 11.5 25.1 5.8 (8, df = 0001) 0.92 12.49 10 5.6 4 12.2 3	35 18 21 25 50 <b>1667</b> 57 (P < 9 39 20 10 41 31 31	57 54.4 20 30.6 7.8 0.0000 39 72 70 65.3 47 47.6 31	57 12.9 12.5 23.2 7 11); I <sup>2</sup> = - 1.19 18.7 20 6.3 4 19.6 12.6	35 18 21 28 50 1681 88% 8 39 20 9 41 30 10	1.2% 1.1% 1.2% 1.2% 65.0% 0.1% 1.1% 1.0% 0.7% 1.2% 0.9%	-0.02 [-0.49, 0.45] 0.10 [-0.55, 0.76] 0.20 [-0.40, 0.81] 0.35 [-0.19, 0.90] 0.88 [0.47, 1.29] -1.02 [-1.25, -0.80] -1.02 [-1.25, -0.80] -1.12.50 [-17.39, -7.61] -3.10 [-4.05, -2.15] -2.91 [-4.29, -1.54] -1.73 [-2.24, -1.22] -1.60 [-2.18, -1.02]	+ + + 
Tucker, et al., 2015 Lee, et al., 2015 Silva, et al., 2012 Beckwiee, et al., 2014 Subtotal (95% CI) Heterogeneity: Tau <sup>2</sup> = 0.44; CI Test for overall effect: Z = 9.03 <b>7.10.2 Chronic Pain</b> Barbarist, et al., 2010 Hokenek et al., 2019 Lauretti, et al., 2019 Dailey, et al., 2013 Dailey, et al., 2013 Dailey, et al., 2020 De Oliverira et al., 2012 Bi, et al., 2020	56 55.6 22.5 39.2 13.5 hi <sup>2</sup> = 493.7 8 (P < 0.00 25.11 22 20 40 21.2 17 30 21.4 37.3	56 9.2 11.5 25.1 5.8 (8, df = 0001) 0.92 12.49 10 5.6 4 12.2 3 16.4 9.1 16.2	35 18 21 25 50 <b>1667</b> 57 (P < 9 39 20 10 41 31 10 5 26 15	57 54.4 20 30.6 7.8 0.00000 39 72 70 65.3 47 47.6 31 54 38.7 59.1	57 12.9 12.5 23.2 7 1); I <sup>2</sup> = 1.19 18.7 20 6.3 4 19.6 12.6 12.6 13.6 14.5 13.7	35 18 21 28 50 1681 88% 8 39 20 9 41 30 5 26 12	1.2% 1.1% 1.2% 1.2% 65.0% 0.1% 1.1% 1.0% 0.7% 1.2% 0.9% 0.9% 0.7% 1.2%	-0.02 [-0.49, 0.45] 0.10 [-0.55, 0.76] 0.20 [-0.40, 0.81] 0.35 [-0.19, 0.90] 0.88 [0.47, 1.29] -1.02 [-1.25, -0.80] -1.02 [-1.25, -0.80] -3.11 [-3.78, -2.44] -3.10 [-4.05, -2.15] -2.91 [-4.29, -1.54] -1.73 [-2.24, -1.22] -1.60 [-2.18, -1.02] -1.46 [-2.48, -0.45] -1.44 [-2.92, 0.04] -1.41 [-2.02, -0.80] -1.41 [-2.25, -0.54]	+ + + 
Tucker, et al., 2015 Lee, et al., 2015 Silva, et al., 2012 Beckwiee, et al., 2018 Kayman-Kose, et al., 2014 (3) Subtotal (95% CI) Heterogeneily: Tau <sup>2</sup> = 0.64; CI Test for overall effect: Z = 9.05 <b>7.10.2 Chronic Pain</b> Barbarisi, et al., 2010 Hokenek et al., 2010 Lauretti, et al., 2010 Lauretti, et al., 2015 Ekim et al., 2020 Dailey, et al., 2020 De Oliverira et al., 2012 Bi, et al., 2013	56 55.6 22.5 39.2 13.5 hi <sup>2</sup> = 493.7 8 (P < 0.00 47.2 20 47.2 20 47.2 20 47.2 17 30 21.2 17 30 21.4 37.3 38.8	56 9.2 11.5 25.1 5.8 (8, df = 0001) 0.92 12.49 10 5.6 4 12.2 3 16.4 9.1 16.2 25	35 18 21 25 57 (P < 9 39 20 10 41 31 10 526 15 17	57 54.4 20 30.6 7.8 0.00000 39 72 70 65.3 47 47.6 31 54 38.7 59.1 67.7	57 12.9 12.5 23.2 7 1); I <sup>2</sup> = 1.19 18.7 20 6.3 4 19.6 12.6 13.6 14.5 13.7 14.2	35 18 21 28 50 1681 88% 8 39 20 9 41 30 100 5 26 12 16	1.2% 1.1% 1.2% 65.0% 0.1% 1.2% 1.0% 0.7% 1.2% 1.2% 0.9% 0.7% 1.1%	-0.02 [-0.49, 0.45] 0.10 [-0.55, 0.76] 0.20 [-0.40, 0.81] 0.35 [-0.19, 0.90] 0.88 [0.47, 1.29] -1.02 [-1.25, -0.80] -1.02 [-1.25, -0.80] -1.02 [-1.25, -0.80] -1.03 [-2.44] -1.73 [-2.24, -1.22] -1.60 [-2.18, -1.02] -1.44 [-2.48, -0.45] -1.44 [-2.28, -0.45] -1.44 [-2.28, -0.45] -1.44 [-2.25, -0.54] -1.43 [-2.25, -0.54] -1.43 [-2.24, -0.61]	+ + + +
Tucker, et al., 2015 Lee, et al., 2015 Silva, et al., 2012 Beckwiee, et al., 2018 Kayman-Kose, et al., 2014 (3) Subtotal (95% CI) Heterogeneity: Tau <sup>2</sup> = 0.64; CI Test for overall effect: Z = 9.02 <b>7.10.2</b> Chronic Pain Barbarisi, et al., 2019 Hokenek, et al., 2019 Lauretti, et al., 2019 Lauretti, et al., 2019 Lauretti, et al., 2019 Dailey, et al., 2013 (Khaer et al., 2020) Zhang et al., 2012 Khaer et al., 2020 Colliser et al., 2012 Disput, et al., 2015 Topuz, et al., 2014 Celik, et al., 2013 Lauretti, et al., 2013	56 55.6 22.5 39.2 13.5 hi <sup>2</sup> = 493.7.3 8 (P < 0.00 25.11 22 20 47.2 40 21.2 17 30 21.4 37.3 38.8 60	56 9.2 11.5 25.1 5.8 (8, df = 1001) 10.92 12.49 10.001) 10.92 12.49 10.001) 10.92 12.49 10.001) 10.92 10.93 10.92 10.93 10.92 10.92 10.92 10.92 10.92 10.92 10.92 10.920	35 18 21 50 <b>1667</b> 57 (P < 9 39 20 10 41 31 10 5 26 15 17 13	57 54.4 20 30.6 7.8 0.00000 65.3 47 47.6 31 54 47.6 31 54 47.6 31 59.1 67.7 80	57 12.9 12.5 23.2 7 1); I <sup>2</sup> = - 1.19 18.7 20 6.3 4 19.6 12.6 13.6 14.5 13.7 14.2 20	35 18 21 28 5 6 1681 88% 8 8 39 20 9 41 30 10 5 26 12 12 12 16 10	1.2% 1.1% 1.2% 65.0% 0.1% 1.2% 0.7% 1.2% 0.7% 1.2% 0.9% 0.7% 1.1% 1.0%	-0.02 [-0.49, 0.45] 0.10 [-0.55, 0.76] 0.20 [-0.40, 0.81] 0.35 [-0.19, 0.90] 0.88 [0.47, 1.29] -1.02 [-1.25, -0.80] -1.02 [-1.25, -0.80] -1.02 [-1.25, -0.80] -1.01 [-4.29, -1.54] -3.10 [-4.05, -2.15] -2.91 [-4.29, -1.54] -1.60 [-2.18, -1.02] -1.60 [-2.18, -1.02] -1.60 [-2.18, -1.02] -1.60 [-2.18, -1.02] -1.60 [-2.18, -1.02] -1.60 [-2.18, -1.02] -1.60 [-2.28, -0.45] -1.44 [-2.92, 0.04] -1.44 [-2.22, 0.54] -1.38 [-2.14, -0.61] -1.38 [-2.14, -0.61] -1.38 [-2.19, 0.36]	+ + + +
Tucker, et al., 2015 Lucker, et al., 2017 Beckwie, et al., 2018 Beckwie, et al., 2018 Kayman-Kose, et al., 2014 (3) Subtotal (95% CI) Heterogeneity: Tau <sup>2</sup> = 0.64; CI Test for overall effect: Z = 9.03 <b>7.10.2 Chronic Pain</b> Barbarisi, et al., 2010 Hokenek et al., 2019 Lauretti, et al., 2019 Lauretti, et al., 2015 Ekim et al., 2018 Dolliey, et al., 2012 Zhang et al., 2012 De Oliverira et al., 2012 Bi, et al., 2015 Topuz, et al., 2015	56 55.6 22.5 39.2 13.5 hi <sup>2</sup> = 493.7 8 (P < 0.00 47.2 20 47.2 20 47.2 20 47.2 17 30 21.2 17 30 21.4 37.3 38.8	56 9.2 11.5 25.1 5.8 (8, df = 0001) 0.92 12.49 10 5.6 4 12.2 3 16.4 9.1 16.2 25	35 18 21 25 57 (P < 9 39 20 10 41 31 10 526 15 17	57 54.4 20 30.6 7.8 0.00000 39 72 70 65.3 47 47.6 31 54 38.7 59.1 67.7	57 12.9 12.5 23.2 7 1); I <sup>2</sup> = 1.19 18.7 20 6.3 4 19.6 12.6 13.6 14.5 13.7 14.2	35 18 21 28 50 1681 88% 8 39 20 9 41 30 100 5 26 12 16	1.2% 1.1% 1.2% 65.0% 0.1% 1.2% 1.0% 0.7% 1.2% 1.2% 0.9% 0.7% 1.1%	-0.02 [-0.49, 0.45] 0.10 [-0.55, 0.76] 0.20 [-0.40, 0.81] 0.35 [-0.19, 0.90] 0.88 [0.47, 1.29] -1.02 [-1.25, -0.80] -1.02 [-1.25, -0.80] -1.02 [-1.25, -0.80] -1.03 [-2.44] -1.73 [-2.24, -1.22] -1.60 [-2.18, -1.02] -1.44 [-2.48, -0.45] -1.44 [-2.28, -0.45] -1.44 [-2.28, -0.45] -1.44 [-2.25, -0.54] -1.43 [-2.25, -0.54] -1.43 [-2.24, -0.61]	
Tucker, et al., 2015 Lee, et al., 2015 Silva, et al., 2012 Beckwiee, et al., 2014 Beckwiee, et al., 2014 (3) Subtotal (95% CI) Heterogeneily: Tau <sup>2</sup> = 0.64; CI Test for overall effect: Z = 9.02 <b>7.10.2</b> Chronic Pain Barbarisi, et al., 2019 Hokenek, et al., 2019 Hokenek, et al., 2019 Lauretti, et al., 2019 Dailey, et al., 2013 Exim et al., 2020 Dailey, et al., 2020 Dailey, et al., 2020 De Oliverira et al., 2012 Be, et al., 2015 Topuz, et al., 2013 Lauretti, et al., 2013 Celik, et al., 2013 Suh, et al., 2013 Suh, et al., 2015 Neighbours, et al., 1987 Vialia & Oleg, 2014	56 55.6 22.5 5 39.2 13.5 hi <sup>2</sup> = 493.7 3 (P < 0.00 25.11 225.11 22 20 40 21.2 17 30 21.4 37.8 38.8 60 18.7 17.5 39.5	56 9.2 11.5 25.1 5.8 (8, df = 1001) 0.92 12.49 10 5.6 4 12.2 3 16.4 9.1 16.2 25 10 0.7.46 30.3 317	35 18 21 25 50 1667 57 (P < 9 9 39 20 10 41 31 10 5 26 5 17 13 24 10 21 5 17 13 24 10 11	57 54.4 200 7.8 0.0000 65.3 47 47.6 31 54 47.6 31 59.1 67.7 80 30.7 40.7 52.5	57 12.9 12.5 23.2 7 1); l <sup>2</sup> = 1.19 18.7 20 6.3 4 19.6 12.6 13.6 14.5 13.7 14.2 20 17.67 20.74 18.6	35 18 21 28 50 1681 88% 8 8 39 20 9 9 9 9 9 9 9 41 30 10 5 26 26 12 16 10 23 10 0 10 10 10 10 10 10 10 10 10 10 10 1	1.2% 1.1% 1.1% 1.2% 65.0% 0.1% 1.2% 0.7% 1.2% 0.7% 1.2% 0.7% 1.2% 0.7% 1.2% 0.7% 1.1% 1.0% 1.1%	-0.02 [-0.49, 0.45] 0.10 [-0.55, 0.76] 0.20 [-0.40, 0.81] 0.35 [-0.19, 0.90] 0.88 [0.47, 1.29] -1.02 [-1.25, -0.80] -1.02 [-1.25, -0.80] -1.15 [-1.54] -3.11 [-3.78, -2.44] -3.10 [-4.05, -2.15] -2.91 [-4.29, -1.54] -1.73 [-2.24, -1.22] -1.60 [-2.18, -1.02] -1.46 [-2.24, -0.42] -1.46 [-2.24, -0.42] -1.44 [-2.92, 0.04] -1.44 [-2.92, 0.04] -1.44 [-2.25, -0.64] -1.28 [-2.19, -0.61] -1.28 [-2.19, -0.36] -0.88 [-1.48, -0.28] -0.86 [-1.78, 0.07] -0.70 [-1.59, 0.19]	
Tucker, et al., 2015 Lee, et al., 2015 Silva, et al., 2012 Beckwie, et al., 2018 Kayman-Kose, et al., 2014 (3) Subtotal (95% CI) Heterogeneily: Tau <sup>2</sup> = 0.64; CI Test for overall effect: Z = 9.02 <b>7.10.2 Chronic Pain</b> Barbarisi, et al., 2010 Hokenek et al., 2010 Hokenek et al., 2019 Lauretti, et al., 2019 Lauretti, et al., 2016 Ekim et al., 2020 Doliveyri et al., 2020 Doliveyri et al., 2012 Bi, et al., 2015 Topuz, et al., 2013 Lauretti, et al., 2013 Sub, et al., 2015 Neighbours, et al., 1987 Vitali & Oleg, 2014 Bigli, et al., 2016	56 55.6 22.5 39.2 33.7 8 (P < 0.00 25.11 22 20 47.2 40 21.2 177 30 21.4 37.3 38.8 60 18.7 17.5 39.5 14.27	56 9.2 11.5 25.1 5.8 (8, df = 0001) 0.922 12.49 10 5.6 4 12.2 3 16.4 9.1 16.2 25 10 7.46 30.3 17 10.1	35 18 21 25 50 1667 57 (P < 9 9 39 20 10 41 31 10 5 266 15 17 13 24 10 113 24 10 15 57	57 54.4 20 30.6 7.8 0.0000 65.3 47 72 70 65.3 47 7 47.6 31 54 38.7 59.1 67.7 80 30.7 40.7 22.5 23.27	57 12.9 12.5 23.2 23.2 7 7 1); I <sup>2</sup> = - 1.19 18.7 20 6.3 4 9.6 13.6 13.6 13.6 13.6 13.6 13.7 14.2 20 17.67 20.74 4.8.6 15.8	35 18 21 28 50 1681 88% 8 8 8 9 20 9 9 20 9 9 41 30 10 5 266 12 12 16 10 23 10 10 15	1.2% 1.1% 1.2% 1.2% 65.0% 0.1% 1.2% 1.0% 0.7% 1.2% 1.2% 1.2% 1.1% 1.0% 1.1% 1.0%	-0.02 [-0.49, 0.45] 0.10 [-0.55, 0.76] 0.20 [-0.40, 0.81] 0.35 [-0.19, 0.90] 0.88 [0.47, 1.29] -1.02 [-1.25, -0.80] -1.02 [-1.25, -0.80] -1.03 [-1.73, -2.44] -3.10 [-4.05, -2.15] -2.91 [-4.29, -1.54] -1.73 [-2.24, -1.22] -1.60 [-2.18, -1.02] -1.44 [-2.24, -1.22] -1.44 [-2.24, -1.22] -1.44 [-2.24, -1.22] -1.44 [-2.25, -0.54] -1.38 [-2.14, -0.61] -1.28 [-2.19, -0.36] -0.88 [-1.78, 0.07] -0.70 [-1.59, 0.19] -0.66 [-1.40, 0.08]	
Tucker, et al., 2015 Lee, et al., 2015 Silva, et al., 2012 Beckwiee, et al., 2018 Kayman-Kose, et al., 2014 (3) Subtotal (95% Cl) Heterogeneity: Tau <sup>2</sup> = 0.64; Cl Test for overall effect: Z = 9.02 7.10.2 Chronic Pain Barbarisi, et al., 2019 Hokenek et al., 2019 Lauretti, et al., 2019 Lauretti, et al., 2015 Dailey, et al., 2015 De Oliverira et al., 2013 De Oliverira et al., 2013 Bi, et al., 2015 Topuz, et al., 2015 Topuz, et al., 2013 Lauretti, et al., 2013 Lauretti, et al., 2013 Suh, et al., 2015 Simioura, et al., 1987 Vitaili & Oleg, 2014 Bilgili, et al., 2019	56 55.6 22.5 3 39.2 13.5 hi <sup>2</sup> = 493.7 25.11 22 20 47.2 20 47.2 20 47.2 21.4 37.3 38.8 60 18.7 7 7.5 39.5 14.27 5.1	56 9.2 25.1 5.8 8, df = 12, 5.8 8, df = 12, 49 10 5.6 4 4 12, 2 3 16, 4 4 12, 2 5 10 7, 46 30, 3 17 10, 11 8	35 18 21 25 50 1667 57 (P < 9 9 39 20 10 10 31 10 5 5 17 7 13 31 10 5 26 15 17 7 13 24 10 115 15 25 25	57 54.4 20 30.6 7.8 0.0000 65.3 47 47.6 31 59.1 67.7 80 30.7 40.7 52.5 23.27 11.4	57 12.9 12.5 23.2 7 1); l <sup>2</sup> = 1.19 18.7 20 6.3 4 19.6 12.6 13.6 12.6 13.6 13.6 13.7 14.2 20 17.67 20.74 18.5 13.7 14.2 20 17.67 14.5 5 14.5 14.5 15.5 14.5 14.5 14.5 14	35 18 21 28 50 1681 88% 8 8 8 39 20 9 41 30 10 5 26 6 12 16 10 23 10 10 10 10 5 25 5	1.2% 1.1% 1.2% 1.2% 65.0% 0.1% 1.2% 0.7% 1.2% 0.7% 1.2% 1.2% 0.7% 1.2%	-0.02 [-0.49, 0.45] 0.10 [-0.55, 0.76] 0.20 [-0.40, 0.81] 0.35 [-0.19, 0.90] 0.88 [0.47, 1.29] -1.02 [-1.25, -0.80] -1.02 [-1.25, -0.80] -1.02 [-1.25, -0.80] -1.02 [-1.25, -0.80] -1.02 [-1.28, -1.02] -1.60 [-2.18, -1.02] -1.60 [-2.18, -1.02] -1.46 [-2.48, -0.45] -1.44 [-2.22, -0.45] -1.44 [-2.22, -0.84] -1.38 [-2.14, -0.61] -1.28 [-2.19, -0.36] -0.88 [-1.48, -0.28] -0.86 [-1.48, -0.08] -0.66 [-1.40, -0.08] -0.66 [-1.40, -0.08] -0.66 [-1.40, -0.08] -0.66 [-1.40, -0.08] -0.66 [-1.40, -0.08] -0.65 [-1.22, -0.08]	
Tucker, et al., 2015 Lee, et al., 2015 Silva, et al., 2012 Beckwie, et al., 2018 Kayman-Kose, et al., 2014 (3) Subtotal (95% CI) Heterogeneily: Tau <sup>2</sup> = 0.64; CI Test for overall effect: Z = 9.03 <b>7.10.2 Chronic Pain</b> Barbarisi, et al., 2010 Hokenek et al., 2010 Lauretti, et al., 2011 Ekim et al., 2015 Ekim et al., 2015 Daliey, et al., 2012 Daliey, et al., 2012 Daliey, et al., 2012 Bi, et al., 2015 Topuz, et al., 2015 Opuz, et al., 2015 Neighbours, et al., 1987 Vitali & Oleg. 2014 Bigili, et al., 2015 Shimoura, et al., 2019 Liu, et al., 2017	56 55.6 22.5 39.2 33.7 8 (P < 0.00 25.11 22 20 47.2 40 21.2 177 30 21.4 37.3 38.8 60 18.7 17.5 39.5 14.27	56 9.2 11.5 25.1 5.8 (8, df = 0001) 0.922 12.49 10 5.6 4 12.2 3 16.4 9.1 16.2 25 10 7.46 30.3 17 10.1	35 18 21 25 50 1667 57 (P < 9 9 39 20 10 41 31 10 5 266 15 17 13 24 10 113 24 10 15 57	57 54.4 20 30.6 7.8 0.0000 65.3 47 72 70 65.3 47 7 47.6 31 54 38.7 59.1 67.7 80 30.7 40.7 22.5 23.27	57 12.9 12.5 23.2 23.2 7 7 1); I <sup>2</sup> = - 1.19 18.7 20 6.3 4 9.6 13.6 13.6 13.6 13.6 13.6 13.7 14.2 20 17.67 20.74 4.8.6 15.8	35 18 21 28 50 1681 88% 8 8 8 9 20 9 9 20 9 9 41 30 10 5 266 12 12 16 10 23 10 10 15	1.2% 1.1% 1.2% 1.2% 65.0% 0.1% 1.2% 1.0% 0.7% 1.2% 1.2% 1.2% 1.1% 1.0% 1.1% 1.0%	-0.02 [-0.49, 0.45] 0.10 [-0.55, 0.76] 0.20 [-0.40, 0.81] 0.35 [-0.19, 0.90] 0.88 [0.47, 1.29] -1.02 [-1.25, -0.80] -1.02 [-1.25, -0.80] -1.02 [-1.25, -0.80] -1.03 [-2.24, -1.22] -1.60 [-2.18, -1.02] -1.60 [-2.18, -1.02] -1.60 [-2.18, -1.02] -1.46 [-2.48, -0.45] -1.44 [-2.92, -0.80] -1.44 [-2.92, -0.80] -1.44 [-2.92, -0.61] -1.38 [-2.14, -0.61] -1.38 [-2.14, -0.61] -1.38 [-2.14, -0.61] -0.86 [-1.78, 0.07] -0.70 [-1.59, 0.19] -0.66 [-1.40, 0.08] -0.65 [-1.22, -0.63] -0.68 [-1.20, -0.61]	
Tucker, et al., 2015 Lee, et al., 2017 Beckwee, et al., 2018 Beckwee, et al., 2018 Kayman-Kose, et al., 2014 (3) Subtotal (95% C1) Heterogeneity: Tau² = 0.64; Cl Test for overall effect: Z = 9.02 <b>7.10.2 Chronic Pain</b> Barbarisi, et al., 2019 Lauretti, et al., 2019 Lauretti, et al., 2019 Lauretti, et al., 2019 Lauretti, et al., 2019 Daliey, et al., 2010 Daliey, et al., 2020 De Oliverira et al., 2012 Bi, et al., 2020 De Oliverira et al., 2012 Bi, et al., 2013 Chauretti, et al., 2020 Zhang et al., 2020 De Oliverira et al., 2012 Bi, et al., 2013 Suh, et al., 2013 Suh, et al., 2015 Neighbours, et al., 1987 Vitalia & Oleg, 2014 Biloiji, et al., 2017 Grimmer, 1982 Daliey et al., 2020	566 55.6 c 22.5 5 39.2 2 13.5 13.5 22.5 11 22 25.11 22 25.11 22 25.11 22 24 40 21.2 17 7 7 30 0 21.2 17 17 33 8.8 60 18.7 7,75 5,11 48.2 22,2 5 46 24,21 5 46 24,55 5 24,555 24,5555 24,5555 24,5555 24,5555 24,5555 24,5555 24,5555 24,5555 24,5555 24,55555 24,55555 24,555555 24,5555555555	56 9.2 25.1 5.8 8, df = 0001) 0.92 12.49 10 5.6 4 12.2 3 3 16.4 9.1 16.2 25 13.4 9.1 16.2 25 10.7 46 30.3 317 10.1 8 30.7 10.1 5 10.5 10.	35 18 21 25 50 1067 57 (P < 9 9 39 20 10 41 31 10 5 266 15 17 13 225 225 225 222 222 220 103	57 54.4 20 30.6 7.8 0.00000 65.3 47 47.6 31 54 38.7 59.1 67.7 80 30.7 40.7 52.5 52.5 23.27 11.4 55.8 55	57 12.9 12.5 23.2 7 1); I <sup>2</sup> = 1.19 18.7 20 6.3 4 6 13.6 12.6 13.6 12.6 13.6 12.6 13.6 12.6 13.7 14.2 20 17.7 20.74 4 18.7 5 20.74 13.7 20.74 13.7 20.75 20.72 20.75 20.	35 18 21 28 50 1681 88% 8 8 8 39 20 9 9 20 9 9 20 9 9 41 30 10 10 5 26 12 16 12 16 10 23 10 10 5 25 22 22 20 99 9	1.2% 1.1% 1.1% 1.2% 65.0% 0.1% 1.2% 0.7% 0.9% 0.7% 0.9% 0.7% 1.2% 1.1% 1.0% 1.1% 1.1% 1.1% 1.1%	$\begin{array}{c} -0.02 \left[-0.49, 0.45\right] \\ 0.10 \left[-0.55, 0.76\right] \\ 0.20 \left[-0.40, 0.81\right] \\ 0.35 \left[-0.19, 0.90\right] \\ 0.38 \left[0.47, 1.29\right] \\ -1.02 \left[-1.25, -0.80\right] \\ \end{array}$	
Tucker, et al., 2015 Lee, et al., 2015 Silva, et al., 2012 Beckwie, et al., 2018 Kayman-Kose, et al., 2014 (3) Subtotal (95% CI) Heterogeneily: Tau <sup>2</sup> = 0.64; CI Test for overall effect. Z = 9.03 <b>7.10.2</b> Chronic Pain Barbarisi, et al., 2010 Hokenek et al., 2019 Lauretti, et al., 2019 Lauretti, et al., 2019 Lauretti, et al., 2016 Ekim et al., 2020 Doliveyria et al., 2012 Doliveyria et al., 2012 Bi, et al., 2015 Neighbours, et al., 2015 Shimoura, et al., 2016 Shimoura, et al., 2017 Grimmer, 1992 Dailey et al., 2020 Dailey et al., 2015	$ \begin{array}{c} 566\\ 522,5\\ 392,2\\ 392,21,5\\ 392,21,5\\ 392,21,5\\ 392,21,5\\ 392,21,5\\ 392,21,5\\ 392,21,22\\ 392,22\\ 392,$	56 9.2 11.5 25.1 5.8 (8, df = 10001) 0.92 12.49 10 0 5.6 4 12.29 3 16.4 9.1 16.2 25 10 7.46 3 17 7 10.1 1 8 20 3 6.5 3 3 17.5 5 8 5 6 10 5 5 10 5 10 5 10 5 10 5 10 5 10 5 10 5 10 5 10 10 5 10 10 5 10 10 10 10 10 10 10 10 10 10 10 10 10	35 18 21 25 57 57 (P < 9 9 39 20 0 10 41 31 13 11 15 26 5 17 13 24 40 111 15 5 222 20 103 5 5	57 54.4 20 30.6 7.8 0.00000 65.3 47 70 65.3 47.6 31 54 38.7 75.1 55.7 30.7 40.7 52.2 23.27 11.4 55.8 35 53 340.33	57 12.9 12.5 23.2 7 1); l <sup>2</sup> = 1.19 18.7 200 6.3 4 19.6 6.3 4 19.6 6.3 12.6 12.6 13.6 13.6 13.6 13.6 13.6 13.6 14.2 200 20.7 4 18.7 20.7 20.7 20.7 20.7 20.7 20.7 20.7 20	35 18 21 28 50 1681 88% 8 39 200 9 41 300 5 266 122 16 10 23 310 10 15 5 222 20 9 9 3	$\begin{array}{c} 1.2\% \\ 1.1\% \\ 1.1\% \\ 1.2\% \\ 65.0\% \\ \end{array}$	$\begin{array}{c} -0.02 \left[-0.49, 0.45\right] \\ 0.10 \left[-0.55, 0.76\right] \\ 0.20 \left[-0.40, 0.81\right] \\ 0.35 \left[-0.19, 0.90\right] \\ 0.88 \left[0.47, 1.29\right] \\ -1.02 \left[-1.25, -0.80\right] \\ \end{array}$	
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Tucker, et al., 2015 Lee, et al., 2015 Silva, et al., 2012 Beckwee, et al., 2014 Kayman-Kose, et al., 2014 (3) Subtotal (95% CI) Heterogeneily: Tau <sup>2</sup> = 0.64; CI Tast for overall effect. Z = 9.02 <b>7.10.2</b> Chronic Pain Barbarisi, et al., 2010 Hokenek et al., 2019 Lauretti, et al., 2019 Lauretti, et al., 2019 Lauretti, et al., 2016 Ekim et al., 2020 Dolieyr, et al., 2020 Dolieyr, et al., 2015 Bi, et al., 2015 Neighbours, et al., 2017 Shimoura, et al., 2019 Lauretti, et al., 2013 Shimoura, et al., 2017 Grimmer, 1992 Dailey et al., 2020 Warke, et al., 2020 Warke, et al., 2020 Warke, et al., 2015 Shimoi, et al., 2020 Warke, 20	$ \begin{array}{c} 566\\ 526\\ 526\\ 526\\ 527\\ 539\\ 225\\ 392\\ 135\\ 10\\ 225\\ 11\\ 22\\ 02\\ 02\\ 12\\ 12\\ 22\\ 02\\ 02\\ 12\\ 12\\ 22\\ 02\\ 10\\ 21\\ 22\\ 10\\ 12\\ 12\\ 22\\ 22\\ 22\\ 13\\ 14\\ 27\\ 15\\ 11\\ 27\\ 15\\ 11\\ 22\\ 22\\ 22\\ 22\\ 13\\ 14\\ 27\\ 13\\ 14\\ 27\\ 15\\ 11\\ 22\\ 22\\ 22\\ 22\\ 13\\ 14\\ 27\\ 15\\ 11\\ 27\\ 15\\ 11\\ 27\\ 10\\ 10\\ 10\\ 10\\ 10\\ 10\\ 10\\ 10\\ 10\\ 10$	566 9.2 11.5 25.1 5.8 8, df = 0001) 0.92 12.49 10 5.6 4 12.2 3 3 4 12.2 9 10 5.6 4 12.2 9 10 5.6 4 12.2 25 10 0 7.46 30.3 177 10.1 8 20 3.6 5.1 5.8 10.5 10.5 10.5 10.5 10.5 10.5 10.5 10.5	36 18 21 25 50 57 57 (P < 9 39 20 1667 57 (P < 9 39 20 41 31 10 55 26 26 20 115 15 17 7 12 22 20 0 105 15 57 57 57 57 57 57 57 57 57 57 57 57 57	57 54.4 20 30.6 7.8 7.8 7.8 7.0 65.3 47 47.6 38.7 59.1 54 43.8.7 59.1 54 40.3 30.7 40.7 52.57 23.27 11.4 55.8 55 30.7 40.7 52.57 23.27 11.4 55.8 55 30.7 40.30 53.57 40.30 53.57 40.30 53.57 40.30 53.57 40.30 53.57 54.57 55.57 53.57 54.57 54.57 55.57 54.57 55.57 54.57 54.57 55.57 55.57 54.57 555	57 12.9 12.5 23.2 7 1); l <sup>2</sup> = 1.19 18.7 200 6.3 4 19.6 6.3 4 19.6 6.3 4 19.6 6.3 4 19.6 13.6 13.6 14.5 13.7 14.2 20 7 20.74 18.6 14.5 13.7 20.7 20.7 20.7 20.7 20.7 20.7 20.7 20	35 18 21 28 20 1681 88% 88% 89 20 99 30 100 100 100 100 100 100 100 105 222 200 00 99 3 3 155 222 200 99 93 3 155 222 200 10 88 10 10 88 10 10 88 10 10 88 10 10 88 10 10 88 10 10 88 10 10 88 10 10 88 10 10 88 10 10 88 10 10 88 10 10 88 10 10 88 10 10 88 10 10 88 10 10 88 10 10 88 10 10 10 10 10 10 10 10 10 10 10 10 10	$\begin{array}{c} 1.2\%\\ 1.1\%\\ 1.1\%\\ 1.1\%\\ 1.2\%\\ 65.0\%\\ 0.1\%\\ 1.2\%\\ 65.0\%\\ 0.7\%\\ 1.2\%\\ 1.2\%\\ 1.2\%\\ 1.2\%\\ 1.0\%\\ 1.0\%\\ 1.0\%\\ 1.0\%\\ 1.0\%\\ 1.1\%\\ 1.0\%\\ 1.1\%\\ 1.1\%\\ 1.0\%\\ 1.1\%$	$\begin{array}{c} -0.02 \left[-0.49, 0.45\right] \\ 0.10 \left[-0.55, 0.76\right] \\ 0.20 \left[-0.40, 0.81\right] \\ 0.35 \left[-0.19, 0.90\right] \\ 0.38 \left[0.47, 1.29\right] \\ -1.02 \left[-1.25, -0.80\right] \\ \end{array}$	
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Tucker, et al., 2015 Lee, et al., 2015 Beckwee, et al., 2018 Kayman-Kose, et al., 2014 (3) Subtotal (95% C1) Heterogeneily: Tau <sup>2</sup> = 0.64; C1 Test for overall effect: Z = 9.02 <b>7.10.2 Chronic Pain</b> Barbarisi, et al., 2010 Hokenek et al., 2019 Lauretti, et al., 2019 Lauretti, et al., 2019 Lauretti, et al., 2015 Ekim et al., 2020 Zhang et al., 2020 Daliey, et al., 2020 Doliveyria et al., 2012 Bi, et al., 2013 Coluc, et al., 2013 Lauretti, et al., 2014 Celik, et al., 2015 Shimoura, et al., 2015 Shimoura, et al., 2016 Shimoura, et al., 2017 Grimmer, 1982 Daliey et al., 2020 Warke, et al., 2020 Warke, et al., 2020 Warke, et al., 2017 Grimmer, 1982 Daliey et al., 2020 Warke, et al., 2020	$ \begin{array}{c} 566\\ 525, 6\\ 526, 526, 5\\ 392, 2\\ 392, 2\\ 392, 3\\ 392, 5\\ 5\\ 392, 5\\ 5\\ 5\\ 5\\ 5\\ 5\\ 5\\ 5\\ 5\\ 5\\ 5\\ 5\\ 5\\ $	566 9.2 11.5 25.1 5.8 78, df = 0.92 12.49 100 5.6 4 4 2.2 5 5 10 7.46 30.3 17 10.1 8 7.75 13.72 27.55 13.72 27.55 13.72 27.55 15.3 20 20 20 13.72 27.55 11.55 20.55 11.55 20.55 11.55 20.55 11.55 20.55 11.55 20.55 11.55 20.55 11.55 20.55 20.55 11.55 12.55 11.55 12.55 11.55 12.55 11.55 12.55 11.55 12.55 11.55 12.55 11.55 12.55 11.55 12.55 11.55 12.55 11.55 12.55 11.55 12.55 11.55 12.55 11.55 12.55 11.55 12.55 11.55 12.55 11.55 12.55 11.55 12.55 11.55 12.55 11.5	35 18 21 25 50 57 77 9 9 39 20 0 10 41 31 10 5 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7	57 54.4 20 30.6 7.8 0.0000 39 72 70 65.3 47 7 47.6 31 54.3 347 759.1 52.5 23.27 40.7 52.5 53 30.7 7.11.4 55.8 53 30.7 11.4 55.3 40.3 30.7 21.2 52.5 53 40.3 30.6 7.8 80 30.7 70 70 70 70 70 70 70 70 70 70 70 70 70	57 12.9 12.5 23.2 7 1): I <sup>2</sup> = 1.19 18.7 200 6.3 4 6.3 4 6.3 4 6.3 13.6 13.6 13.6 13.6 13.6 13.6 13.6	35 188 21 28 50 1681 88% 88% 88% 88% 88% 9 20 9 9 20 9 9 20 9 9 20 9 9 20 9 9 20 10 10 10 5 26 6 12 20 20 9 9 30 10 5 26 26 20 20 9 9 30 10 5 26 5 26 5 20 20 9 9 20 9 9 20 0 10 10 10 10 10 10 10 10 10 10 10 10	$\begin{array}{c} 1.2\%\\ 1.1\%\\ 1.1\%\\ 1.1\%\\ 1.2\%\\ 65.0\%\\ 0.1\%\\ 1.2\%\\ 65.0\%\\ 1.1\%\\ 1.2\%\\ 1.2\%\\ 0.7\%\\ 1.2\%\\ 1.2\%\\ 1.2\%\\ 1.2\%\\ 1.1\%\\ 1.0\%\\ 1.1\%\\ 1.1\%\\ 1.1\%\\ 1.1\%\\ 1.1\%\\ 1.1\%\\ 1.1\%\\ 1.1\%\\ 1.1\%\\ 1.1\%\\ 1.1\%\\ 1.1\%\\ 1.1\%\\ 1.1\%\\ 1.2\%\\ 0.7\%\\ 1.1\%\\ 1.1\%\\ 1.2\%\\ 0.7\%\\ 1.1\%\\ 1.2\%\\ 1.1\%\\ 1.2\%\\ 1.1\%\\ 1.2\%\\ 1.1\%\\ 1.2\%\\ 1.1\%\\ 1.2\%\\ 1.1\%\\ 1.2\%\\ 1.1\%\\ 1.2\%$	$\begin{array}{c} -0.02 \left[-0.49, 0.45\right] \\ 0.10 \left[-0.55, 0.76\right] \\ 0.20 \left[-0.40, 0.81\right] \\ 0.35 \left[-0.19, 0.90\right] \\ 0.88 \left[0.47, 1.29\right] \\ -1.02 \left[-1.25, -0.80\right] \\ \end{array}$	
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Tucker, et al., 2015 Lee, et al., 2015 Silva, et al., 2012 Beckwiée, et al., 2018 Kayman-Kose, et al., 2014 (3) Subtotal (95% CI) Heterogeneity: Tau <sup>2</sup> = 0.64; CI Test for overall effect: Z = 9.05 7.10.2 Chronic Pain Barbarisi, et al., 2010 Hokenek et al., 2019 Lauretti, et al., 2010 Ekim et al., 2010 Zhang et al., 2010 Zhang et al., 2012 De Oliverine at al., 2012 Bi, et al., 2013 De Oliverine at al., 2012 Bi, et al., 2013 Celik, et al., 2013 Lauretti, et al., 2013 Lauretti, et al., 2013 Suh, et al., 2015 Neighbours, et al., 1987 Vitalii & Oleg, 2014 Biglil, et al., 2017 Grimmer, 1992 Dailey et al., 2017 Grimmer, 1992 Dailey et al., 2010 Shimoji, et al., 2004 Machin, et al., 1988 Moore & Shuman, 1997 (5) Shimoji, et al., 2011 Ilhani, 2015 Bono, et al., 2011 Kinaj, 2015 Bono, et al., 2011 Kinaj, 2015 Bono, et al., 2011 Kofotolis, et al., 2019 Atamaz, et al., 2018	$ \begin{split} & 566 \\ & 55.6 \\ & 52.5 \\ & 39.2 \\ & 22.5 \\ & 39.2 \\ & 39.2 \\ & 39.2 \\ & 20.2 \\$	566 9.2 11.5 25.1 5.8 8, df = 10001) 0.92 12.49 10 5.6 4 12.2 10 3 3 4 12.2 12.49 10 5.6 4 4 12.2 25 10 10 5.6 4 4 12.2 25 10 10 5.6 5.1 5.8 11.5 5.8 1001) 10 5.6 5.8 1001) 10 5.6 5.8 10 5.8 10 5.8 10 5.8 10 10 10 5.6 5.8 10 10 10 10 5.6 5.8 10 10 10 10 5.6 5.8 10 10 10 10 5.6 5.8 10 10 10 10 5.6 5.8 10 10 10 10 10 5.6 5.8 10 10 10 10 10 5.6 5.8 10 10 10 10 10 5.6 5.8 10 10 10 10 10 5.6 5.8 10 10 10 10 10 5.6 5.8 10 10 10 10 10 5.6 10 10 10 10 10 5.6 10 10 10 10 10 10 10 10 5.6 10 10 10 10 10 10 5.6 10 10 10 10 10 10 10 10 5.6 10 10 10 10 10 10 5.6 10 10 10 10 10 5.6 10 10 10 10 10 5.6 10 10 10 10 5.6 10 10 10 10 10 5.6 10 10 10 10 5.6 10 10 10 10 10 10 10 10 10 10 10 10 10	355 184 255 50 57 (P < 9 9 39 9 20 100 101 311 100 155 266 155 266 155 244 200 103 103 5 155 262 200 1133 252 200 115 252 200 105 116 7 115 255 200 100 100 100 100 100 100 100 100 100	57 54.4 20 30.6 7.8 0.0000 39 72 70 65.3 47 47.6 31 31 47.6 31 47.6 31 55.8 37 70 70 70 70 70 70 70 70 70 70 70 70 70	57 12.9 12.5 23.2 7 1.19 18.7 20 6.3 4 19.6 13.6 13.6 14.5 13.7 13.7 14.2 20 14.6 13.6 14.5 13.7 14.2 20 14.2 20 14.2 14.2 14.2 14.2 12.6 14.2 14.2 14.2 12.6 14.2 12.6 14.5 13.6 14.5 12.6 14.2 20 14.2 14.2 20 14.2 14.2 12.6 15.8 10.9 12.66 15.8 10.9 12.66 15.8 10.9 12.66 15.8 10.9 12.66 15.8 10.9 12.67 10.9 12.66 10.9 12.67 10.9 12.67 10.9 12.67 10.9 12.67 10.9 12.67 10.9 12.67 10.9 12.67 10.9 12.67 10.9 12.67 10.9 12.67 10.9 12.67 10.9 12.67 10.9 12.67 10.9 10.9 10.9 10.9 10.9 10.9 10.9 10.9 10.9 10.9 10.9 10.9 10.2 20	355 188 21 288% 88% 88% 88% 88% 89 200 9 9 41 300 55 262 20 200 10 10 23 31 525 222 200 99 3 3 155 24 8 8 12 4 8 8 12 12 12 8 8 8 9 10 10 8 11 8 8 8 9 10 10 8 10 10 8 8 8 9 10 10 8 10 10 10 8 10 10 10 8 10 10 10 10 10 10 10 10 10 10 10 10 10	$\begin{array}{c} 1.2\%\\ 1.1\%\\ 1.1\%\\ 1.1\%\\ 1.2\%\\ 65.0\%\\ 0.1\%\\ 1.2\%\\ 65.0\%\\ 0.7\%\\ 1.2\%\\ 1.2\%\\ 1.2\%\\ 1.2\%\\ 1.0\%\\ 1.0\%\\ 1.0\%\\ 1.0\%\\ 1.0\%\\ 1.1\%\\ 1.0\%\\ 1.1\%\\ 1.0\%\\ 1.1\%$	$\begin{array}{c} -0.02 \ [-0.49, 0.45] \\ 0.10 \ [-0.55, 0.76] \\ 0.20 \ [-0.40, 0.81] \\ 0.35 \ [-0.19, 0.90] \\ 0.38 \ [0.47, 1.29] \\ -1.02 \ [-1.25, -0.80] \\ \end{array}$	
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Tucker, et al., 2015 Lee, et al., 2015 Beckwee, et al., 2018 Beckwee, et al., 2018 Kayman-Kose, et al., 2014 (3) Subtotal (95% C1) Heterogeneily: Tau² = 0.64; C1 Test for overall effect: Z = 9.02 <b>7.10.2 Chronic Pain</b> Barbarisi, et al., 2010 Hokenek et al., 2011 Hokenek et al., 2012 Lauretti, et al., 2012 Daliey, et al., 2013 Lauretti, et al., 2012 Daliey, et al., 2020 Zhang et al., 2020 Doliverira et al., 2012 Bi, et al., 2013 Duity, et al., 2013 Duity, et al., 2013 Duity, et al., 2014 Celik, et al., 2015 Shimoura, et al., 1987 Vitali & Oleg. 2014 Bigili, et al., 2017 Grimmer, 1982 Daliey et al., 2020 Warke, et al., 2020 Warke, et al., 2019 Shimoura, et al., 1987 Vitali & Oleg. 2014 Bigili, et al., 2017 Grimmer, 1982 Daliey et al., 2020 Warke, et al., 2020 Warke, et al., 2019 Shimoi, et al., 2019 Shimoi, et al., 2019 Shimi, et al., 2015 Bono, et al., 2015 Machado et al., 2019 Akanaz, et al., 2019 Subtotal (95% C1) Heterogeneily: Tau² = 0.67; C1 Test for overall effect: Z = 5.28 <b>7.10.3 Not Reported</b> Cheing & Luk, 2005	$ \begin{array}{c} 566\\ 55.6\\ 55.6\\ 22.5\\ 39.2\\ 22.5\\ 39.2\\ 22.5\\ 39.2\\ 22.5\\ 20\\ 20\\ 21.2\\ 20\\ 20\\ 21.4\\ 20\\ 20\\ 21.4\\ 20\\ 20\\ 21.4\\ 20\\ 20\\ 21.4\\ 20\\ 20\\ 21.4\\ 40\\ 20\\ 21.4\\ 20\\ 21.2\\ 20\\ 20\\ 21.4\\ 40\\ 20\\ 20\\ 21.4\\ 40\\ 20\\ 20\\ 21.4\\ 40\\ 20\\ 20\\ 20\\ 20\\ 20\\ 20\\ 20\\ 20\\ 20\\ 2$	566 9.2 11.5 25.1 5.8 8, df = 10001) 10.92 12.49 10 5.6 4 12.2 3 16.4 4 12.2 25 11.4 9 11 16.2 25 17 10.1 8 20 7.46 30.3 17 7 28 5 15.7 18.06 13.72 27.55 18.06 15.5 13.72 24.1 14.00 10 10 10 10 10 10 10 10 10 10 10 10 1	365 18 29 10 1667 50 10 167 57 10 20 10 10 57 10 10 10 10 10 10 10 10 10 10	57 54.4 20 30.6 7.8 0.00000 39 72 70 65.3 47 47.6 38.7 59.1 67.7 59.1 67.7 59.1 67.7 59.1 67.7 59.1 67.7 59.1 67.7 59.1 67.7 59.1 67.8 30.7 79.2 50.8 30.0 0.0000 30.7 70.0 50.0 50.0 50.0 50.0 50.0 50.0 5	577 12.99 12.5 23.22 7 1.19 18.77 20 6.3 4 19.66 13.66 13.66 13.66 13.67 13.77 14.22 20.77 13.65 13.77 14.22 20.77 13.55 10.22 20.22 20.22 20.22 4 1); I <sup>2</sup> = =	35 18 21 28 50 1681 88% 8 39 20 9 9 4 30 100 5 5 266 216 100 105 5 266 216 100 105 5 266 216 209 9 9 3 3 15 22 200 9 9 3 3 15 22 6 0 0 9 9 3 3 15 20 0 0 9 9 9 15 5 0 0 0 0 9 9 9 15 5 0 0 0 0 9 9 9 15 5 0 0 0 0 9 9 9 15 5 0 0 0 0 9 9 9 16 8 8 8 8 8 8 8 8 8 9 9 9 9 10 10 10 10 10 10 10 10 10 10 10 10 10	$\begin{array}{c} 1.2\%\\ 1.1\%\\ 1.1\%\\ 1.1\%\\ 1.2\%\\ 65.0\%\\ 0.1\%\\ 1.2\%\\ 65.0\%\\ 1.1\%\\ 1.2\%\\ 1.2\%\\ 0.7\%\\ 1.2\%\\ 1.2\%\\ 1.2\%\\ 1.2\%\\ 1.2\%\\ 1.1\%\\ 1.0\%\\ 1.1\%\\ 1.1\%\\ 1.1\%\\ 1.1\%\\ 1.1\%\\ 1.1\%\\ 1.1\%\\ 1.1\%\\ 1.2\%\\ 1.1\%\\ 1.1\%\\ 1.1\%\\ 1.2\%\\ 1.1\%$	$\begin{array}{c} -0.02 \left[-0.49, 0.45\right] \\ 0.10 \left[-0.55, 0.76\right] \\ 0.20 \left[-0.40, 0.81\right] \\ 0.35 \left[-0.19, 0.90\right] \\ 0.38 \left[0.47, 1.29\right] \\ -1.02 \left[-1.25, -0.80\right] \\ \end{array}$	
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Tucker, et al., 2015 Lee, et al., 2015 Silva, et al., 2012 Beckwee, et al., 2014 Kayman-Kose, et al., 2014 (3) Subtotal (95% CI) Heterogeneily: Tau <sup>2</sup> = 0.64; CI Test for overall effect: Z = 9.02 <b>7.10.2</b> Chronic Pain Barbarisi, et al., 2010 Hokenek et al., 2010 Lauretti, et al., 2019 Lauretti, et al., 2019 Lauretti, et al., 2015 Ekim et al., 2020 Zhang et al., 2020 Doliver; at et al., 2012 Bi, et al., 2015 Neighbours, et al., 2013 Bi, et al., 2015 Neighbours, et al., 2017 Grimmar, 1982 Warke, et al., 2017 Grimmar, 1982 Warke, et al., 2017 Grimmar, 1982 Wacht, et al., 2018 Shimoura, et al., 1988 Moore & Shimman, 1997 (5) Shimoji, et al., 2017 Graff-Radford, et al., 2018 Shimo, et al., 2018 Shimo, et al., 2018 Shimo, et al., 2019 Atamaz, et al., 2019 Markind, 2015 Subtotal (95% CI) Heterogeneiky: Tau <sup>2</sup> = 0.67; CI Test for overall effect: Z = 5.28 <b>7.10.3 Not Reported</b> Cheing & Luk, 2005 Mansuri, et al., 2019 Siqueira et al., 2019 Sique	$ \begin{array}{c} 566\\ 55.6\\ 6\\ 55.6\\ 22.5\\ 39.2\\ 22.5\\ 39.2\\ 39.2\\ 13.5\\ 14.2\\ 22.5\\ 10.2\\ 10$	566 9.2 11.5 25.1 5.8 6.8 df = 10001) 10 5.6 4 12.49 10 5.6 4 12.2 12.49 10 10 5.6 4 12.2 12.49 10 10 5.6 4 12.2 2 5 10 10 10 5.6 4 12.2 2 5 10 10 10 5 6 4 12.2 2 5 10 10 10 10 5 6 6 10 2 5 10 10 10 10 5 6 6 10 10 10 10 10 5 6 6 10 10 10 10 10 5 6 6 10 10 10 10 10 10 5 6 6 10 10 10 10 10 10 5 6 6 10 10 10 10 10 10 5 10 10 10 10 10 5 10 10 10 10 10 10 5 10 10 10 10 10 10 10 10 5 10 10 10 10 10 10 5 10 10 10 10 10 10 10 10 10 10 10 10 10	355 18 25 50 50 1667 57 (P < 9 9 30 20 10 0 10 57 17 25 26 57 17 13 13 10 0 10 5 17 24 10 10 5 17 24 10 22 20 10 3 10 5 17 24 10 5 17 24 10 10 5 17 24 10 10 5 17 17 24 10 10 5 17 17 24 10 10 5 17 17 13 13 13 13 13 13 10 10 10 10 10 10 10 10 10 10	57 54.4 20 30.6 7.8 0.00000 39 72 70 65.3 47 47.6 33.7 47.6 33.7 47.7 59.1 59.1 67.7 80 30.7 40.7 52.5 23.27 70 0.30.7 40.7 52.5 23.27 40.30.7 16.29 44.81 40.30.2 26.95 52.28 800 46 50.4 200 46 50.4 200 46 50.4 200 46 50.4 200 40 40.0000 46 50.4 200 40 40.0000 46 50.0000 46 50.0000 40.00000 40.00000 40.00000 40.00000 40.00000 40.00000000	57 12.9 12.5 23.2 7 1.19 12.5 23.2 7 1.19 12.5 23.2 12.5 23.2 23.2 12.5 12.5 12.5 13.7 12.6 13.6 13.6 13.6 13.6 13.7 14.2 20 17.67 20.74 18.6 13.7 14.2 20 17.67 20.74 18.6 13.6 13.7 14.2 20 17.67 20.74 18.6 13.65 30.67 20.9 19.9 19.9 19.9 19.9 19.9 19.9 19.4 13.65 30.67 20 20 20.24 13.65 30.67 20.24 1.5 10.52 20.24 1.52 20.24 1.52 20.24 1.52 20.22	355 188 21 288 50 1681 88% 8 39 9 9 411 30 10 10 10 10 10 10 10 10 10 10 10 10 10	1.2% 1.1% 1.1% 1.2% 65.0% 0.1% 1.2% 65.0% 0.7% 1.2% 1.0% 1.2% 1.1% 1.0% 1.2% 1.1% 1.0% 1.1% 1.1% 1.1% 1.2% 1.1% 1.1% 1.2% 0.9% 1.1% 32.0%	-0.02 [-0.49, 0.45] 0.10 [-0.55, 0.76] 0.20 [-0.40, 0.81] 0.35 [-0.19, 0.90] 0.88 [0.47, 1.29] -1.02 [-1.25, -0.80] -1.02 [-1.25, -0.80] -1.02 [-1.25, -0.80] -1.03 [-2.24, -1.22] -1.04 [-2.24, -1.22] -1.04 [-2.24, -1.22] -1.04 [-2.24, -1.22] -1.04 [-2.25, -0.54] -1.34 [-2.24, -0.61] -1.34 [-2.25, -0.54] -1.38 [-2.14, -0.61] -1.38 [-2.14, -0.61] -0.86 [-1.78, 0.07] -0.70 [-1.59, 0.19] -0.66 [-1.40, 0.08] -0.45 [-1.09, 0.11] -0.45 [-1.09, 0.11] -0.45 [-1.09, 0.11] -0.33 [-1.78, 1.12] -0.20 [-0.92, 0.52] -0.14 [-0.71, 0.66] -0.07 [-0.71, 0.56] -0.04 [-0.55, 0.63] 0.04 [-0.55, 0.63] 0.04 [-0.55, 0.64] -0.76 [-1.19, -0.55] -1.50 [-2.55, -0.45] -0.74 [-1.49, 0.00] -0.86 [-1.40, 0.01] -0.76 [-1.39, 0.19] -0.77 [-1.9, -0.55]	
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Tucker, et al., 2015 Lee, et al., 2015 Silva, et al., 2012 Beckwie, et al., 2014 Beckwie, et al., 2014 Kayman-Kose, et al., 2014 (3) Subtotal (95% CI) Heterogeneily: Tau <sup>2</sup> = 0.64; CI Test for overall effect: Z = 9.02 <b>7.10.2</b> Chronic Pain Barbarisi, et al., 2010 Hokenek et al., 2010 Hokenek et al., 2010 Lauretti, et al., 2010 Dailey, et al., 2013 Lauretti, et al., 2015 Ekim et al., 2020 Do Cliverira et al., 2012 Bi, et al., 2013 Do Cliverira et al., 2012 Bi, et al., 2013 Collik, et al., 2013 Shimot et al., 2015 Neighbours, et al., 1987 Vitali & Oleg, 2014 Bijili, et al., 2015 Shimotra, et al., 2020 Dailey et al., 2020 Dailey et al., 2015 Shimotra, et al., 2019 Liu, et al., 2017 Grimmer, 1992 Dailey et al., 2020 Warke, et al., 2019 Shimoji. et al., 2019 Shimoji. et al., 2019 Shimot, et al., 2019 Shimot, et al., 2019 Haterogeneily: Tau <sup>2</sup> = 0.67; CI Test for overall effect: Z = 5.262 <b>7.10.3</b> Not Reported Cheing & Luk, 2005 Mansuri, et al., 2019	$ \begin{split} & 566 \\ & 55.6 \\ & 52.5 \\ & 39.2 \\ & 22.5 \\ & 39.2 \\ & 39.2 \\ & 39.2 \\ & 22.5 \\ & 11.5 \\ & 21.2 \\ & 20 \\ & 22.5 \\ & 11.2 \\ & 20 \\ & 21.2 \\ & 21.2 \\ &$	566 9.2 11.5 25.1 5.8 8, df = 8 10001) 0.92 12.49 10 5.6 4 12.2 10 10 5.6 4 12.2 12.49 10 10 5.6 4 12.2 12.49 10 10 5.6 4 12.2 12.49 10 10 5.6 4 12.2 25 15.1 10.2 10 27.55 15.1 13.72 27.55 10.1 14.4 15.2 15.1 15.1 15.1 15.1 15.1 15.1 15.1	355 18 21 255 50 1667 57 (P < 9 9 39 9 20 10 10 11 10 55 266 157 17 13 266 157 17 13 266 167 17 13 266 167 17 13 266 167 17 13 266 167 17 13 266 167 17 13 266 167 17 13 266 17 13 266 167 17 13 266 17 13 266 17 13 266 17 13 266 17 17 13 267 17 13 267 10 11 10 11 10 10 11 10 10 11 10 10	57 54.4 20 30.6 7.8 0.00000 39 72 70 70 65.3 47 47.6 31 59.1 59.1 59.1 59.1 59.1 59.1 59.1 59.	57 12.9 12.5 23.2 7 7 1.1); I <sup>2</sup> = 1.19 18.7 20 4 19.6 13.6 13.6 13.6 13.6 13.6 13.6 13.6 13	35 18 21 28 50 1681 88% 8 39 9 9 411 88% 8 30 9 9 411 30 10 5 266 10 21 26 1681 30 26 1681 30 10 5 26 26 10 30 10 5 26 26 20 9 9 41 10 30 10 5 26 26 20 9 9 41 10 10 5 26 20 9 9 30 10 10 5 26 20 9 9 30 10 10 5 26 20 9 9 30 10 10 5 26 20 9 9 3 10 10 15 22 20 9 9 3 15 24 4 8 8 8 20 20 9 9 3 15 24 8 8 8 9 9 9 411 10 15 25 22 20 9 9 3 15 24 8 8 8 9 9 9 3 15 24 8 8 8 9 9 9 9 3 15 24 8 8 8 9 9 9 9 3 15 24 8 8 8 9 9 9 9 3 15 24 8 8 8 9 9 9 9 9 9 3 15 24 4 8 8 8 9 9 9 3 15 24 8 8 8 8 8 8 8 8 8 8 8 8 8	1.2% 1.1% 1.1% 1.2% 65.0% 0.1% 1.2% 65.0% 0.7% 1.2% 1.0% 1.2% 1.1% 1.0% 1.2% 1.1% 1.0% 1.1% 1.1% 1.1% 1.2% 1.1% 1.1% 1.2% 0.9% 1.1% 32.0%	-0.02 [-0.49, 0.45] 0.10 [-0.55, 0.76] 0.20 [-0.40, 0.81] 0.35 [-0.19, 0.90] 0.88 [0.47, 1.29] -1.02 [-1.25, -0.80] -1.02 [-1.25, -0.80] -1.02 [-1.25, -0.80] -1.03 [-1.05, -2.15] -2.91 [-4.29, -1.54] -1.73 [-2.24, -1.22] -1.60 [-2.18, -1.02] -1.44 [-2.24, -1.22] -1.44 [-2.24, -1.22] -1.44 [-2.24, -1.22] -1.44 [-2.25, -0.54] -1.38 [-2.14, -0.61] -1.38 [-2.14, -0.61] -0.86 [-1.78, 0.07] -0.70 [-1.59, 0.19] -0.66 [-1.40, 0.08] -0.45 [-1.09, 0.11] -0.45 [-1.09, 0.11] -0.45 [-1.09, 0.11] -0.33 [-1.78, 1.12] -0.20 [-0.92, 0.52] -0.14 [-0.71, 0.66] -0.07 [-0.71, 0.56] -0.04 [-0.55, 0.63] 0.09 [-0.71, 0.56] -0.04 [-0.55, 0.64] 0.00 [-0.38, 0.38] 0.04 [-0.55, 0.64] 0.07 [-0.71, 0.56] -0.44 [-0.71, 0.56] -0.44 [-0.75, 0.65] 0.49 [-0.71, 0.56] -0.44 [-0.55, 0.63] 0.49 [-0.71, 0.56] -0.44 [-0.55, 0.64] 0.00 [-0.38, 0.38] 0.49 [-0.27, 0.65] -0.44 [-0.71, 0.56] -0.44 [-0.71, 0.56] -0.44 [-0.75, 0.64] 0.07 [-1.19, -0.55] -1.50 [-2.55, -0.45] -0.74 [-1.49, 0.00] 0.46 [-3.11, 1.22]	

(1) Cesarian delivery sample 

(2) \*Crossover

(a) volginal delivery sample (a) \*ch@&@peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml (5) \*Crossove

# ONLINE TABLE 4

# **Adverse Events**

Reference	Reference number	Extracted Text	AEs related to TENS	Statement	Extractable Data	Comment
(Abbasi et al., 2019)	1	No statements present	No information to extract	N	N	
(Abelson et al., 1983)	2	The only side effect was a slight skin irritation at the site of electrode placement in some of the patients in the transcutaneous electrical nerve stimulation treated group	Skin irritation due to electrodes	Y	N	No numerical data to extract
(Abreu et al., 2010)	3	No statements present	No information to extract	Ν	Ν	
(Acedo et al., 2015)	4	No statements present	No information to extract	Ν	Ν	
(Adedoyin et al., 2005)	5	No statements present	No information to extract	Ν	Ν	
(Ahmed, 2010)	6	Due to the absence of complications and adverse effects of TENS compared to conventional opioids and non-opioid analgesics, we suggest that TENS is a safe and reliable therapeutic procedure. – in Discussion	No information to extract	$\begin{array}{c} Y-0\\ tally \end{array}$	N – 0 tally	Unclear whether the statement on AEs was generic or in relation to the study findings
(Ahmed et al., 2020)	7	No statements present	No information to extract	Ν	Ν	
(Alcidi et al., 2007)	8	No statements present	No information to extract	Ν	Ν	
(Ali et al., 1981)	9	No statements present	No information to extract	Ν	Ν	
(Alizade and Ahmadizad, 2009)	10	No statements present	No information to extract	Ν	N	Only mentions potential irritation of skin in introductory section
(Allais et al., 2003)	11	No serious side effects occurred in any group during the study.	Reported no adverse events	Y - 0 tally	N-0 tally	
(Alm et al., 1979)	12	In our group of 75 patients we found no significant skin reactions	No information to extract	N	N	Only relates to skin reaction, not other AEs
(Al-Smadi et al., 2003)	13	No statements present	No information to extract	Ν	Ν	
(Altay et al., 2010)	14	No statements present	No information to extract	N	Ν	
(Alvarez-Arenal et al., 2002)	15	No statements present	No information to extract	Ν	Ν	
(Alves Silverio et al., 2015)	16	No statements present	No information to extract	N	N	
(Amer-Cuenca et al., 2011)	17	No subject reported adverse events such as skin allergy, pain or burning at the electrode site in either active TENS or placebo TENS groups.	Reported no adverse events	Y - 0 tally	N-0 tally	
(AminiSaman et al., 2020)	18	No statements present	No information to extract	N	N	
(Angulo and Colwell Jr, 1990)	19	No statement present	No information to extract	N	N	
(Ardic et al., 2002)	20	No statements present	No information to extract	Ν	Ν	
(Arvidsson and Eriksson, 1986)	21	No statements present	No information to extract	Ν	Ν	Conclusion states that TENS lacks side-effects.
(Asgari et al., 2018)	22	Student's t-test and chi-square were applied to compare baseline characteristics and side effects among groups.	No information to extract	Ν	Ν	No mention of adverse events in results or discussion despite

Reference	Reference number	Extracted Text	AEs related to TENS	Statement	Extractable Data	Comment
						the method describing how these would be analysed
(Atamaz et al., 2012)	23	No statements present	No information to extract	N	Ν	Flow chart in Fig 1 shows the 6 participants in TENS group dropped out because of worsening symptoms
(Aydin et al., 2005)	24	No complications occurred as a result of the treatments given.	Reported no adverse events	Y - 0 tally	N - 0 tally	
(Azatcam et al., 2017)	25	No statements present	No information to extract	N	N	
(Báez-Suárez et al., 2018)	26	No patients in any group reported adverse events such as skin allergy or burning at the electrode site.	Reported no adverse events on mothers or new-born	Y – 0 tally	N - 0 tally	
			babies	ully	cuity	
(Bai et al., 2017)	27	The results of the present study demonstrate that TENS can reduce the intensity of the pain associated with PD without any AEs.	Reported no adverse events	Y – 0 tally	N - 0 tally	
(Baki et al., 2015)	28	In our study, TENS has beneficial effects for pain relief after thoracotomy without any side effects;	Reported no adverse events	Y = 0 tally	N - 0 tally	
(Ballegaard et al., 1985)	29	No statements present	No information to extract	N	N	
(Barbarisi et al., 2010)	30	No statements present	No information to extract	N	N	In the final visit (visit IX), at the groups underwent a clinical-neurologic examination and routine blo tests to evaluate the possibili of side effects.
(Barker et al., 2006)	31	We can recommend this technique because of its simple use and the lack of side-effects in our study population.	Reported no adverse events	Y – 0 tally	N - 0 tally	
(Barker et al., 2008)	32	No statements present	No information to extract	N	N	Authors state that patients were asked to report adverse events but these were not recorded in results.
(Başkurt et al., 2006)	33	No statements present	No information to extract	N	Ν	
(Bayindir et al., 1991)	34	No statements present Low cost, lack of undesirable side effects, and ease of application can make TENS an acceptable method of reducing postoperative chest pain	No information to extract	Ν	N	No specific mention of monitoring adverse events i methods or results
(Beckwée et al., 2018)	35	No statements present TENS could be experienced as painful instead of pain relieving, and thus, TENS could have an adverse effect on pain in a subgroup of patients.	No information to extract	Ν	N	Authors comments refer to patients with central sensitisation
(Benedetti et al., 1997)	36	No statements present. We emphasize that the absence of complications and side effects of TENS compared with conventional opioid and nonopioid analgesics makes electrical stimulation a safe and reliable therapeutic procedure.	No information to extract	N	N	

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Reference	Reference number	Extracted Text	AEs related to TENS	Statement	Extractable Data	Comment
(Bennett et al., 2010)	37	Overall, 9 patients experienced adverse events and median number of adverse events per patient was 2 (range 1, 6). Distribution of adverse events was similar following active or placebo TENS applications (describe in Table 4 of their report)	One adverse event directly related to placebo TENS treatment. Two participants withdrew because of increasing pain.	Y	Y	Authors do not describe na of adverse events reported table 4. Data: TENS = 3 events Placebo = 2 events
(Bergeron-Vezina et al., 2018)	38	No harms or unintended effects were reported by the participants.	Reported no adverse events	Y - 0 tally	N - 0 tally	
(Bertalanffy et al., 2005)	39	No statements present Due to its simplicity and lack of side effects, this method should be considered in these patients.	No information to extract	N	N	
(Bi et al., 2015)	40	No statements present	No information to extract	Ν	Ν	
(Bilgili et al., 2016)	41	No statements present	No information to extract	Ν	Ν	
(Binder et al., 2011)	42	No statements present	No information to extract	Ν	Ν	
(Bjersa and Andersson, 2014)	43	No statements present	No information to extract	N	Ν	
(Bjersa et al., 2015)	44	No statements present	No information to extract	Ν	Ν	
(Bloodworth et al., 2004)	45	No statements present	No information to extract	Ν	Ν	
(Bolat et al., 2019)	46	" prevention of unpleasant feelings or complications. A reddish coloration and burning or itching at the electrode–skin junction can occur due to increased blood circulation. However, we observed none of these side effects in the present study".	Reported no adverse events	Y - 0 tally	N	
(Bono et al., 2015)	47	Neither adverse events nor side effects occurred in the real or sham group.	Reported no adverse events	Y - 0 tally	N - 0 tally	
(Borjesson et al., 1997)	48	No adverse effects were seen	Reported no adverse events	Y = 0 tally	N = 0 tally	
(Borjesson et al., 1998)	49	No statements present	No information to extract	N	N	
(Borup et al., 2009)	50	No signs of serious or prolonged side effects were found, neither by using acupuncture nor TENS.	84% of TENS group stated it had no side-effects.	Y = 0tally	N = 0 tally	No information included or any participants who did experience side-effects.
(Breit and Van der Wall, 2004)	51	No statements present	No information to extract	N	Ν	
(Buchmuller et al., 2012)	52	Twelve patients presented a serious adverse event during the study: five in the active TENS group and seven in the sham TENS group. None of these events was considered to be attributable to the treatment studied. Skin irritation was observed in 11 patients in the active TENS group (leading to study discontinuation in one patient) and in three patients in the sham TENS group.	No details about adverse events included in report (except for skin irritation)	Y	Y	Data: TENS = 11 events Placebo = 3 events
(Bulut et al., 2011)	53	When side effects were compared, there was no difference between the groups, except skin irritation only in one patient in Group A ( $p$ >0.05).	One patient with skin irritation.	Y	Ν	No numerical data – implie all groups were zero except

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Reference	Reference number	Extracted Text	AEs related to TENS	Statement	Extractable Data	Comment
						Group A but cannot be certain so not extracting
(Bundsen et al., 1982)	54	It can thus be concluded that no adverse effect of TNS is demonstrable by clinical, laboratory or neurological examination of the infants after pain relief by TNS	Reported no adverse events	Y = 0 tally	N = 0 TENS ONLY	
(Can et al., 2003)	55	No statements present	No information to extract	Ν	Ν	
(Casale et al., 2013)	56	No statements present	No information to extract	Ν	Ν	
(Çebi, 2019)	57	No statements present	No information to extract	Ν	Ν	
(Celik et al., 2013)	58	No side effects of low frequency TENS were seen	Reported no adverse events	Y	Y	No numerical data
(Cetin et al., 2008)	59	No statements present	No information to extract	Ν	Ν	
(Chandra et al., 2010)	60	The incidence of side effects was negligible in both the groups.	Reported no adverse events	Y = 0 tally	N = 0 tally	
(Cheing and Hui-Chan, 1999)	61	No statements present	No information to extract	N	N	
(Cheing and Luk, 2005)	62	No statements present	No information to extract	Ν	Ν	
(Cheing et al., 2002)	63	No statements present	No information to extract	Ν	Ν	
(Cheing et al., 2003)	64	No statements present	No information to extract	Ν	Ν	
(Chellappa and Thirupathy, 2020)	65	No statements present	No information to extract	N	N	
(Cherian et al., 2016a) – Primary Report Secondary Report (Cherian et al., 2016b)	66 _ Prim ary Repo rt Seco ndar y Repo rt 67	Patients were observed for adverse effects due to the TENS device throughout the study. Reports were rare but included local irritation at site of pad placement ( $n = 2$ ) and irritation due to improper brace fitting ( $n = 1$ ). All of these were minor and self-limited and did not prevent any patients from continuing a full course of TENS treatment (3 months). There were no serious adverse reactions reported. In addition, patients were evaluated for the need for surgery, either total knee arthroplasty or arthroscopy. From <sup>67</sup> secondary report: Adverse events seen during the trial included skin irritation, increased pain, and local skin breakdown.	Skin irritation – no further information	Y	N	No numerical data from the control group means cannot extract
(Chesterton et al., 2013)	68	No adverse reactions to treatment were recorded.	Reported no adverse events	Y = 0 tally	N = 0tally	
Secondary Report (Lewis et al., 2015)	Seco ndar y Repo rt 69			Ĵ		
(Chia et al., 1990)	70	No statements present	No information to extract	N	N	
(Chiou et al., 2019)	71	No statements present	No information to extract	N	N	

Reference	Reference number	Extracted	AEs related to TENS	Statement	Extractable Data	Comment
(Chitsaz et al., 2009)	72	TENS: Lost to follow-up (n=1) due to difficulties keeping appointments. Nortriptyline: Withdrawal (n=3) due to adverse effects. Nortriptyline was generally well tolerated and most of the adverse events reported were mild in severity. The most common side effects of nortriptyline were dry mouth (n=13), dizziness (n=6), constipation (n=5), urinary retention (n=5), nausea and headache (n=4). In 3 participants, this resulted in early discontinuation of nortriptyline and the dose of nortriptyline could not be increased per protocol due to these side effects. There were no statements about adverse events for TENS present.	Adverse events only in Nortriptyline group.	Y	Y	Data: Use dropout data resulting from AEs TENS = 0 Nortriptyline = 3
(Chiu et al., 2005)	73	No complications occurred because of any of the treatments given. The reasons for the withdrawals included insufficient time, dissatisfaction with treatment outcome and worsening of symptoms (Figure 2). 1 withdrawal from TENS group due to worsening of symptoms	Reported no adverse events	Y = 0 tally	N = 0 tally	
(Cipriano et al., 2008)	74	Electrical stimulation was well-tolerated by all patients and no relevant side effect was observed.	Reported no adverse events	Y = 0 tally	N = 0 TENS ONLY	
(Cipriano et al., 2014)	75	TENS was well tolerated by all patients with no reported side effects.	Reported no adverse events	Y = 0 tally	N = 0 TENS ONLY	
(Coelho de Amorim et al., 2014)	76	No statements present	No information to extract	Ν	Ν	
(Cooperman et al., 1977)	77	No statements present	No information to extract	Ν	Ν	
(Coyne et al., 1995)	78	No statements present	No information to extract	Ν	Ν	
(Crompton et al., 1992)	79	However, a substantial proportion of women who used the device found it frightening or unpleasant, which we consider unacceptable in the absence of an improvement in pain scores.	Participants found the TENS device 'frightening' and 'unpleasant'.	Y	N	No numerical data
(Cuschieri et al., 1985)	80	All patients tolerated the TES device well.	Reported no adverse events	Y = 0 tally	N = 0 TENS ONLY	
(Cuschieri et al., 1987)	81	No untoward side effects were noted.	Reported no adverse events	Y = 0 tally	N = 0 tally	
(da Silva et al., 2008)	82	No statements present	No information to extract	N	N	
(da Silva et al., 2015)	83	No adverse effects were observed in the TENS group, but 33.3 % of patients in the control group reported drowsiness and nausea.	Reported no adverse events in TENS group	Y	Y	The authors reported stated that 'adverse events for TE was an outcome and they presented this data as AEs attributable to the intervent per se. For this reason, we have extracted the data. Nevertheless, we are

Reference	Reference number	Extracted Text	AEs related to TENS	Statement	Extractable Data	Comment
		For Do				concerned that this data reflects efficacy of interventions to reduce AEs (drowsiness, nausea,) associated with drugs (morphine, Dipyrone) rather than TENS Data: TENS = 0 events / 21 Control = 7 events / 21 participants
(Dailey et al., 2013)	84	No statements present	No information to extract	N	N	
(Dailey et al., 2020)	85	There were 30 adverse events related to TENS intervention in 30 participants on visits 1, 2, or 3. The most common adverse events were pain with TENS (4.8% in the active TENS group, 4% in the placebo TENS group, and 1% in the no TENS group) and skin irritation with electrodes (4.8% in the active TENS group, 1% in the placebo TENS group, and 0% in	Y	Y	Y	TENS = 17/103 Placebo = 3/119 Taken from data in Supplementary Table 7, available on the Arthritis & Rheumatology web site at http://onlin elibrary.wiley.com/doi/10.100 2/art.41170/ abstract, shows rates of TENS-related Adverss events by visit. There were 4 serious adverse events, with none related to TENS use (Supplementary Results, http://onlin e library.wiley.com/doi/10.1002 art.41170/ abstract).

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Reference	Reference number	Extracted Text	AEs related to TENS	Statement	Extractable Data	Comment
		categorized by medication (opioid, n=1 and non-opioid, n=3) and location (TN, n=3 and IA, n=1).				
(Davies, 1982)	86	No statements present	No information to extract	Ν	Ν	
(Dawood and Ramos, 1990)	87	Four subjects noticed muscle vibrations, change in stimulation with movements, tightness, headaches after use, and a slight redness or a burning sensation with TENS treatment. No mention of AEs in the Ibuprofen group	Reported no adverse events	Y	N = 0 TENS ONLY	No numerical data for the comparison groups (plac- ibuprofen)
(De Angelis et al., 2003)	88	No differences in side effects were observed between TENS versus no TENS groups. the incidence of nausea was quite high in this patient sample as compared with other studies (group TENS, 8.5%; group No TENS, 11.3%) (11, 12), but this symptom was mentioned by the patient only when specifically elicited and it was probably the result of psychosomatic factors or emotional stress. However, shoulder pain was more frequent, albeit not significantly, in group TENS than in group Control (group A, 3%; group B, 0%). This is probably due to the fact that the examination lasted longer in group A than in group B (group A, 134.1 60 seconds; group B, 117 49 seconds; P .054) (using the same CO2 flow) and that the patients' acceptance of the procedure was higher with the use of the TENS device. It is completely safe, noninvasive, and free from any side effects as far as side effects are concerned, there were no statistically significant differences in favor of the TENS device	Coded as: Reported no adverse events Extract data AEs = Nausea and Shoulder pain but not attributed to pain	Y = 0 tally	N = 0 tally	No data extracted It is difficult to ascertain whether these symptoms AEs or due to treatment intervention of surgical procedure No data extracted
(De Giorgi et al., 2017)	89	No side effects were referred by the patients during the 10-week TENS treatment.	Reported no adverse events	Y = 0 tally	N = 0 TENS ONLY	
(de Oliveira, 2012)	90	No statements present	No information to extract	N	Ν	
(de Orange et al., 2003)	91	No statements present	No information to extract	N	Ν	
(de Sousa et al., 2014)	92	No statements present	No information to extract	N	Ν	
(DeSantana et al., 2008)	93	We reinforce that the absence of complications and adverse effects of TENS compared with conventional opioids and nonopioid analgesics makes TENS a safe and reliable therapeutic procedure.	Reported no adverse events	Y = 0 tally	N = 0 TENS ONLY	
(DeSantana et al., 2009)	94	We conclude that the absence of complications and adverse effects of TENS compared with conventional opioids and nonopioid analgesics makes TENS a safe and reliable therapeutic procedure.	Reported no adverse events	Y = 0 tally	N = 0 TENS ONLY	
(Dewan and Sharma, 2011)	95	No statements present	No information to extract	Ν	Ν	
Deyo et al. (1990)	Deyo , Wals h <sup>96</sup>	Approximately one-third of the subjects reported minor skin irritation at the sites of electrode placement, with equal proportions in the true-TENS and sham-TENS groups.	Skin irritation. One subject had to discontinue due to severe dermatitis.	Y	N	No numerical data
(Dibenedetto et al., 1993)	97	Both treatments were well-tolerated and no side-effects reported.	Reported no adverse events	Y = 0 tally	N = 0 tally	

Reference	Reference number	Extracted Text	AEs related to TENS	Statement	Extractable Data	Comment
(Dilekci et al., 2016)	98	No statements present	No information to extract	N		
(Dissanayaka et al., 2016)	99	No statements present	No information to extract	Ν	Ν	
(Dogu et al., 2008)	100	No statements present	No information to extract	Ν	Ν	
(Domaille and Reeves, 1997)	101	No statements present	No information to extract	Ν	Ν	
(Ebadi et al., 2018)	102	As for side effects, 8 patients in the Diadynamic group reported a burning sensation in the first 3-4 min of the treatment.	Reported no adverse events in TENS group.	Y	N	No numerical data for TENS
(Ekblom and Hansson, 1987)	103	No statements present	No information to extract	N	N	
(Ekim et al., 2008)	104	No statements present	No information to extract	Ν	Ν	
(Elboim-Gabyzon et al., 2019)	105	No statements present	No information to extract	N	Ν	
(Elserty et al., 2016)	106	No statements present	No information to extract	Ν	N	
(Emmiler et al., 2008)	107	Post-op complications (atelectesia) were tabulated but not stated whether these were attributed to the intervention TENS = 1/20(5%) Placebo = 1/20(5%) Control = 4/20 (20%)	Reported adverse events (complication) atelectesis	Y	Ν	No data extracted – unclear whether 'complications' attributable to the treatment
(Engen et al., 2016)	108	No statements present	No information to extract	Ν	Ν	
(Erden and Senol Celik, 2015)	109	No statements present	No information to extract	Ν	N	
(Erdogan et al., 2005)	110	We did not observe any side effects using TENS, although we did not use TENS in patients who had cardiac disease.	Reported no adverse events	Y = 0 tally	N = 0 TENS ONLY	
(Erkkola et al., 1980)	111	No statements present	No information to extract	Ν	Ν	
(Escortell-Mayor et al., 2011) Secondary Report (Escortell Mayor et al., 2008)	Seco ndar y Repo rt 113	It is remarkable, as it is described in a publication done by this group, that no important adverse effects were observed from either therapy - Reported no adverse events <sup>112</sup> p70 Translated from <sup>113</sup> p340 16.3% of treated patients with TENS (n = 7) and 6.4% of those treated with manual therapy (n = 3) reported adverse effects related to treatment. Three of them presented increased pain in the treated area and 1, general poor	Information to extract	Y	Y	Data extracted from seconda report <sup>113</sup> : TENS = 7 events Manual Therapy = 3 The statement on AEs in <sup>112</sup> p70 appears to contradict data presented in <sup>113</sup>
(Esteban Gonzalez et al., 2015)	114	physical condition in the group treated with TENS Of those who received therapy manual, 1 patient referred a clinical worsening the first days and the rest did not detail symptoms. There were no complications, intolerances or other problems that required the intervention with TENS to be suspended in any of the 50 patients.	Reported no adverse events	Y = 0 tally	N = 0 TENS	
(T. 1. 2000)	115	NT		N	ONLY	
(Eyigor et al., 2008)	115	No statements present	No information to extract	Ν	Ν	

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Reference	Reference number	Extracted Text	AEs related to TENS	Statement	Extractable Data	Comment
(Eyigor et al., 2010)	116	No significant adverse event was reported in either of the two groups (p>0.05).	Reported no adverse events	Y = 0 tally	N = 0 tally	
(Facci et al., 2011)	117	No statements present	No information to extract	Ν	Ν	
(Farahani et al., 2014)	118	No statements present	No information to extract	Ν	Ν	
(Farina et al., 2004)	119	No statements present	No information to extract	Ν	Ν	
(Fatima and Sarfraz, 2019)	120	No statements present	No information to extract	Ν	Ν	
(Ferraz and Moreira, 2009)	121	No statements present	No information to extract	Ν	Ν	
(Ferreira et al., 2011)	122	No statements present	No information to extract	Ν	Ν	
(Ferreira et al., 2017)	123	No statements present	No information to extract	N	Ν	Dropouts reported but reas not given
(Finsen et al., 1988)	124	No statements present	No information to extract	Ν	Ν	
(Fiorelli et al., 2012)	125	We did not observe any side effects; thus, TENS may be particularly useful	Reported no adverse events	$\mathbf{Y} = 0$	N = 0	
		for patients that have liver or kidney disease		tally	tally	
(Fodor-Sertl et al., 1990)	126	No statements present	No information to extract	Ν	Ν	
(Forogh et al., 2019)	127	No adverse events occurred and the rate of compliance to the exercise	Reported no adverse events	$\mathbf{Y} = 0$	N = 0	
		program was high in both groups		tally	tally	
(Forst et al., 2004)	128	No statements present	No information to extract	Ν	Ν	
(Forster et al., 1994)	129	No statements present	No information to extract	Ν	Ν	
(Fujii-Abe et al., 2019)	130	None of the study patients suffered any abnormal or harmful effects.	Reported no adverse events	Y = 0 tally	Ν	
(Galli et al., 2015)	131	No statements present	No information to extract	Ν	Ν	
(Galloway et al., 1984)	132	Only one of our patients demonstrated any adverse effects of the treatment in the form of an allergic rash with blistering which, in patter, was seen to correspond exactly with the areas of contact with the adhesive incorporated in the sterile wound electrodes.	Allergic skin irritation in one participant	Y	N	No numerical data
(Garcia-Perez et al., 2018)	133	No statements present	No information to extract	N	Ν	
(Gerson et al., 1977)	134	No statements present	No information to extract	N	Ν	
(Ghoname et al., 1999a)	135	No statements present	No information to extract	Ν	Ν	
(Ghoname et al., 1999b)	136	No statements present	No information to extract	Ν	Ν	
(Gilbert et al., 1986)	137	No statements present	No information to extract	N	Ν	
(Grabiańska et al., 2015)	138	No statements present	No information to extract	Ν	Ν	
(Graff-Radford et al., 1989)	139	No statements present	No information to extract	Ν	Ν	Patients were informed ab possible side-effects beforehand
(Grant et al., 1999)	140	three TENS patients developed skin reactions. Other than these, reported side effects were minimal: three acupuncture patients reported dizziness and three TENS patients developed skin reactions.	Skin reactions in 3 participants	Y	Y	Data extracted: TENS = 3 events Acupuncture = 3 events
(Gregorini et al., 2010)	141	No statements present	No information to extract	Ν	Ν	
(Grimmer, 1992)	142	No statements present	No information to extract	Ν	Ν	
(Gschiel et al., 2010)	143	Overall, there were no side effects.	Inferred no adverse events	Y	N = 0 tally	No numerical data

Reference	Reference number	Extracted Text	AEs related to TENS	Statement	Extractable Data	Comment
(Gunay Ucurum et al., 2018)	144	No statements present	No information to extract	N	N	
(Guo and Jia, 2005)	145	No statements present	No information to extract	Ν	Ν	
(Hamza et al., 1999)	146	16 -20% of the patients in each of the four groups complained that the TENS adversely influenced their quality of sleep because of the presence of the cutaneous electrodes and wires.	Sleep interference because of electrodes/wires.	Y	N	No numerical data for other groups
(Hanfy and El-Bigawy, 2004)	147	No statements present During the study TENS therapy was safe and allowed the patients to remain ambulatory.	No information to extract	N	N	No specific comments on adverse events included
(Hansson and Ekblom, 1983)	148	it should be noted that most patients found the muscle twitches produced by the low frequency TENS uncomfortable.	No information to extract	N	N	No specific comments on adverse events included
(Hansson et al., 1986)	149	No statements present	No information to extract	Ν	Ν	
(Hargreaves and Lander, 1989)	150	No statements present	No information to extract	N	N	Authors state that TENS is safe but no specific comment on side-effects in this study
(Harrison et al., 1986)	151	In the present study, like all others reported to-date, no side-effects were noted from the therapy.	Reported no adverse events	Y	N = 0 tally	No numerical data
(Hart et al., 2012)	152	No statements present	No information to extract	Ν	Ν	
(Hazneci et al., 2005)	153	No statements present	No information to extract	Ν	Ν	
(Herrera-Lasso et al., 1993)	154	No statements present	No information to extract	Ν	Ν	
(Hershman M, 1989)	155	No statements present	No information to extract	Ν	Ν	
(Hou et al., 2002)	156	No statements present	No information to extract	Ν	Ν	
(Hokenek et al., 2020)	157	No treatment-related skin reactions or unwanted effects were encountered during the trial. Of the verum group, 3 patients declined continuation of treatment due to intolerance to paresthesia, and 2 patients in the sham group declined to continue treatment due to intolerable pain. These patients opted to instead receive 0.75 mg/kg meperidine rescue therapy and were excluded from the trial.	Unclear whether these are adverse events or dislike of TENS sensation and worsening pain due to non response to sham	Y	N	
(Hruby et al., 2006)	158	No statements present	No information to extract	N	Ν	
(Hsieh et al., 1992)	159	No statements present One-shot TENS treatment may be recommended due to the rarity of side effects and its convenient application.	No information to extract	N	Ν	
(Hsueh et al., 1997)	160	No statements present	No information to extract	Ν	Ν	
(Hughes et al., 1988)	161	The use of TENS had no adverse effects upon the newborn	Reported no adverse events	Y	N = 0 TENS ONLY	No numerical data
(Husch et al., 2020)	162	No statements present	No information to extract	Ν	N	
(Ilhanli, 2015)	163	There were no adverse events due to treatment regimens.	Reported no adverse events	Y	N = 0	
(Inal et al., 2016)	164	No statements present	No information to extract	Ν	Ν	

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Reference	Reference number	Extracted Text	AEs related to TENS	Statement	Extractable Data	Comment
(Isik et al., 2017)	165	There were no serious side effects in both groups. In the TENS group no side effects were reported although 21 of the patients reported the treatment as boring due to the long hospital stay. In the leech therapy group, there was a mild local itching and skin redness in 31 patients (12 patients required topical antihistamine therapy) and severe local itching and reddening in 3 patients (requiring oral plus topical antihistamine therapy).	Reported no adverse events	Y	Y	TENS = 0 events / 53 participants Leech = 34 events / 52 participants
(Jaafarpour et al., 2008)	166	No statements present	No information to extract	Ν	Ν	
(Jamison et al., 2019)	167	None of the participants reported experiencing any long-term adverse effects from using the hfTENS.	Reported no adverse events	Y	N = 0 TENS ONLY	No numerical data
(Jarzem et al., 2005)	168	No statements present	No information to extract	Ν	Ν	
(Jensen et al., 1985)	169	No statements present	No information to extract	Ν	Ν	
(Jensen et al., 1991)	170	No statements present	No information to extract	Ν	Ν	
(Jones and Hutchinson, 1991)	171	Three patients complained of dizziness after Entonox inhalation. There were no other side-effects of any of the treatments. TENS produced no side-effects, is easier to handle and was subjectively preferred by the patients.	Reported no adverse events	Y	N = 0	No data extracted Multiple cross over study wi possibility of contamination between treatments
(Kara et al., 2011)	172	Furthermore, there were no adverse effects or negative results related to TENS application.	Reported no adverse events	Y	N = 0 TENS ONLY	No numerical data
(Kararmaz et al., 2004)	173	TENS is a non-invasive, safe, and simple treatment method, which does not have any systemic side effects. We did not observe any difficulties in the use of TENS. NOTE: Table 4 records side effects associated with ESWL procedure as an efficacy measure	Reported no adverse events	Y	N = 0 TENS ONLY	No numerical data associated with AEs due to treatment interventions under study The only side-effects reporte
(Kayman-Kose et al., 2014)	174	No adverse effects due to TENS occurred during the study period - for both Cesarean and vaginal delivery data	Reported no adverse events	Y	N = 0 TENS ONLY	were medication-induced No numerical data
(Keskin et al., 2012)	175	No adverse effect of TENS application on pregnant women was observed during the study.	Reported no adverse events	Y	Ν	No numerical data for comparison group
(Kibar et al., 2020)	176	No statements present	No information to extract	Ν	Ν	
(Kim et al., 2012)	177	There were no significant differences in the incidences of side effects such as erythema and itching between the groups ( $P > 0.05$ ). TENS Group 7/50 (14%) had erythema and 1/50 (2%) had itching. Table II of their report	Erythema and itching.	Y	Y	Data extracted: TENS = 8 events / 50 participants Placebo = 7 / 50 participants
(Kim et al., 2014)	178	No major adverse effects were reported by participants in any treatment group. One patient in the monotherapy group, one patient in the TENS+Np group, and one patient in the CAP+Np group experienced skin itching. One patient in the TENS+Np group and one patient in the HEAT+Np group	Itching and sleep disturbance	Y	Y	Data extracted (skin itching): TENS + NSAID patch = 1 event / 24 participants

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Reference	Reference number	Extracted Text	AEs related to TENS	Statement	Extractable Data	Comment
		reported sleep disturbance. Light somnolence was reported by one patient in the monotherapy group. However, all adverse effects had spontaneously resolved by the end of this study without any treatment. Participants' vital signs were in the normal				NSAID patch alone = 1 event 25 participants
(Kirupa et al., 2019)	179	No statements present	No information to extract	Ν	Ν	
(Knobel et al., 2005)	180	In this survey, more than 50% of women reported some discomfort in the use of electrodes type SSP and 25% in the use of electrodes plate type (Tab. 4). In the application of stimulation, no woman reported discomfort in none of the study groups. To assess the effectiveness of this care, therefore, research is needed to reveal the woman's opinion about the method	Discomfort during stimulation	Y	N	No data extracted Discomfort was an outcome measure – comparing two TENS electrodes. We did not consider discomfort as an adverse ever in this study
(Koca et al., 2014)	181	No serious complication was associated with the treatments in any group, and all patients generally tolerated the treatments well. Only two patients in the TENS group experienced mild tenderness at the application site.	Mild tenderness	Y	N	No numerical data
(Kofotolis et al., 2008)	182	No statements present	No information to extract		Ν	
(Koke et al., 2004)	183	During the first period, skin irritation occurred in 9.4% (17/180) of all patients, adherence problems of electrodes in 12.2% (22/180) and problems attaching electrodes in 2.2% (4/180). In four patients, the adverse effects resulted in withdrawal from the study (skin-irritation 2X, problems attaching electrodes 2 X). During the second period, skin irritation was reported by 5.8% (10/171), adherence problems of electrodes 4.7% (8/171), and problems attaching electrodes body 2.9% (5/171). No significant differences in adverse effects were found between groups. At 6 months follow-up, 6 patients (3 in HFT–COT group and 3 in HIT–COT group) reported skin irritation due to TENS, but still could use TENS regularly.	Skin irritation Problems attaching electrodes	Y	N	Could not extract data at 6 months follow-up (skin irritation) because could not ascertain the number of participants remaining in eac group High frequency TENS = 3 events High intensity = 3 Cross-over study whereby al participants received an activ TENS for all possible
(Korkmaz et al., 2010)	184	No serious side-effects or complications were observed in either of the two	Reported no adverse events	Y = 0	$\mathbf{N} = 0$	interventions No numerical data
(KOIKIIIaz et al., 2010)		groups (P>0.05).	Reported no adverse events	tally	tally	no numerical data
(Kumar and Raje, 2014)	185	No statements present	No information to extract	N	N	
(Labrecque et al., 1999)	186	No statements present	No information to extract	Ν	Ν	
(Laitinen and Nuutinen, 1991)	187	No statements present	No information to extract	Ν	N	
(Lang et al., 2007)	188	Because of its simple use and lack of side effects in our study population, we can recommend this technique for pain therapy.	Reported no adverse events	Y	N = 0 TENS ONLY	No numerical data

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Reference	Reference number	Extracted Text	AEs related to TENS	Statement	Extractable Data	Comment
(Langley et al., 1984)	189	No adverse side-effects were reported by patients receiving TNS or placebo.	Reported no adverse events	Y = 0 tally	N = 0 tally	
(Lauretti et al., 2013)	190	Concerning adverse effects, 2 patients from the STG got in sleep after the device application and complained of muscle sore due to more than 70-min active device application, which was subsequently improved by local hot application.	Muscle soreness in TENS group (2 patients)	Y	N	Note: the poor English in the quotation is how the text was written!
(Lauretti et al., 2015)	191	In conclusion, the portable TENS device demonstrated to be efficacious for pain relief and improvement of quality of life with no adverse effects for control of menstruation cramp pain.	Reported no adverse events	Y	N = 0 TENS ONLY	
(Law and Cheing, 2004)	192	No statements present	No information to extract	Ν	Ν	
(Law et al., 2004)	193	No statements present	No information to extract	Ν	Ν	
(Leandri et al., 1990)	194	No statements present	No information to extract	Ν	Ν	
(Lee et al., 1990)	195	No negative effects on the mothers and babies were reported.	Reported no adverse events	$\mathbf{Y} = 0$	N = 0	
				tally	tally	
(Lee et al., 2015)	196	Neither expected nor unexpected AEs occurred in the study and control	Reported no adverse events	$\mathbf{Y} = 0$	N = 0	
		groups.		tally	tally	
(Lee et al., 2019)	197	No statements present	No information to extract	Ν	Ν	
(Leo et al., 1986)	198	No statements present	No information to extract	Ν	Ν	
(Leonard et al., 2011)	199	No statements present	No information to extract	Ν	Ν	
(Lewers et al., 1989)	200	No statements present	No information to extract	Ν	Ν	
(Lewis et al., 1984)	201	No statements present	No information to extract	Ν	Ν	One patient dropped out because of worsening pain.
(Lewis et al., 1994)	202	No statements present	No information to extract	Ν	Ν	
(Likar et al., 2001)	203	The side effects 1 patient in the Verum group about vomiting, 5 patients in the placebo group suffered from nausea and vomiting that are considered easy and were classified as medium. TENS + analgesics = 1 event / 11 participants Placebo TENS + analgesics = 5 event / 12 participants	· 0/	Y	N	Data related to nausea and vomiting. Debatably this is related to AE associated with post op drugs rather than TENS. We decided not to extract th data because nausea and vomiting AE of drugs reflect efficacy of TENS rather than AE of TENS
(Lim et al., 1983)	204	No statements present	No information to extract	Ν	Ν	
(Lima et al., 2011)	205	No statements present	No information to extract	Ν	Ν	
(Limoges and Rickabaugh, 2004)	206	In addition, no adverse events secondary to TENS use or procedural complications occurred.	Reported no adverse events	Y	N = 0 TENS ONLY	No numerical data
(Lin et al., 2015)	207	No statements present	No information to extract	Ν	Ν	
(Lin et al., 2019)	208	First, there were no adverse events (such as discomfort, hematoma, injury, or hyperalgia) throughout this study.	Reported no adverse events	Y = 0 tally	N = 0 tally	

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Reference	Reference number	Extracted Text	AEs related to TENS	Statement	Extractable Data	Comment
(Linde et al., 1995)	209	The most common side effect during TENS treatment is some type of hypersensibility reaction of the skin. It was mostly seen in slightly underweight patients, in whom contact between skin and electrode was not at its maximum, especially in the area of the TMJ	Skin reaction (no other details)	Y	N	No numerical data
(Linn et al., 1999)	210	No statements present	No information to extract	Ν	Ν	
(Lison et al., 2017)	211	No patients in either the active or placebo TENS groups reported adverse events such as skin allergy, pain, or burning at the electrode site.	Reported no adverse events	Y = 0 tally	N = 0 tally	
(Liu et al., 1985)	212	No statements present	No information to extract		Ν	
(Liu et al., 2017)	213	During treatment, only 1 patient in the 2-Hz tONS group reported an adverse event. This was intolerance to a form of pinch pain induced by electrical stimulation. However, when the intensity of stimulation was reduced from 10 to 9 mA, the uncomfortable feeling subsided. In the TPM group, 9 of 22 patients experienced (mostly mild) paresthesia, especially of the hands and feet. No other adverse events were reported. tONS = transcutaneous occipital nerve stimulation	Pain at 10mA. Pain lessened when intensity reduced.	Y	Y	Data extracted TENS = 1 event / 22 - Pinch pain Topiramate = 9 / 22 - Mild paraesthesia of hands
(Lofgren and Norrbrink, 2009)	214	In this study few side-effects were reported. Three patients reported increased pain, 2 after TENS and one after warmth.	Increased pain in 2 patients	Y	Y	Data extracted (increased pair TENS = 2 events / 32 participants Warmth therapy = 1 event / 32 32 participants
(Luchesa et al., 2009)	215	No statements present	No information to extract	Ν	Ν	
(Lundeberg, 1984)	216	No statements present	No information to extract	Ν	Ν	
(Lundeberg et al., 1985)	217	No statements present	No information to extract	Ν	Ν	
(Machado et al., 2019)	218	No statements present	No information to extract	Ν	Ν	
(Machin et al., 1988)	219	No statements present	No information to extract	Ν	Ν	
(Mahure et al., 2017)	220	No TENS machine-related complication, such as localized pain or erythema at the electrode site, occurred in either group of patients.	Reported no adverse events	Y	N = 0 Tally	No numerical data despite clear statement of no events i both groups
(Manigandan et al., 2014)	221	No statements present	No information to extract	Ν	Ν	
(Mannheimer and Carlsson, 1979)	222	No side effects were observed.	Reported no adverse events	Y = 0 tally	N = 0 tally	
(Mannheimer and Whalen, 1985)	223	No statements present	No information to extract	N	N	
(Mannheimer et al., 1978)	224	No side effects of the treatment were observed. One patient reported that when the pain recurred it was more severe than before TNS, however.	Pain recurred more severe than before TNS	Y	Ν	
(Mannheimer et al., 1985)	225	One patient in the treatment group was excluded because of skin irritation from the electrodes	Skin irritation	Y	Ν	
(Mansourian et al., 2019)	226	No statements present	No information to extract	Ν	Ν	1
(Mansuri et al., 2019)	227	No statements present	No information to extract	N	N	1
(Mansuri et al., 2020)	228	No statements present	No information to extract	N	N	1
(Marchand et al., 1993)	229	No statements present	No information to extract	N	N	1

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Reference	Reference number	Extracted Text	AEs related to TENS	Statement	Extractable Data	Comment
(Mascarin et al., 2012)	230	No statements present	No information to extract	N	N	
(McCallum et al., 1988)	231	No statements present	No information to extract	Ν	Ν	
(Melzack et al., 1983)	232	No statements present	No information to extract	Ν	Ν	
(Merrill, 1989)	233	No statements present	No information to extract	Ν	Ν	
(Miller et al., 2007)	234	No statements present	No information to extract	Ν	Ν	
(Milsom et al., 1994)	235	Ten of the 12 women considered the high-intensity transcutaneous nerve stimulation to be painful. However, stimulation lasted only a few seconds, and all the women were prepared to accept again this short period of pain to obtain pain relief from dysmenorrhea.	Painful at high-intensity stimulation	Y	N	
(Moharic et al., 2009)	236	As already indicated in the Methods section, three patients in the pregabalin group experienced such severe somnolence and dizziness that they had to withdraw from the study. Complaints in the combined group beside somnolence and dizziness included peripheral oedema, weight gain, elevated blood glucose values and withdrawal headache, while one patient from the combined group withdrew from the study because of a traffic accident (tractor overturning) caused by somnolence induced (with all likelihood) by pregabalin. In the TENS group, none of the patients reported any local or systemic side effects, neither did they report any problems with continuous TENS application for three hours daily.	Reported no adverse events	Y	Y	Data extracted (severe somnolence and dizziness) TENS = 0 events / 46 participants Pregabalin alone = 3 events / 8 participants resulting in study withdrawal
(Mondal et al., 2019)	237	No statements present	No information to extract	Ν	Ν	
(Moore and Shurman, 1997)	238	No adverse treatment effects were reported and no subject reported the addition of any new pain medication, physical therapy, or other pain-related treatment during the course of their study participation.	Reported no adverse events	Y = 0 tally	N = 0 tally	
(Mora et al., 2006)	239	We can recommend this technique due to its simple use and the lack of side effects in our study population.	Reported no adverse events	Y = 0 tally	N = 0 TENS ONLY	
(Morgan et al., 1996)	240	No statements present	No information to extract	N	Ν	
(Møystad et al., 1990)	241	No statements present. TNS may have advantages as a non-invasive method with few side effects that is simple to administer for the patients themselves.	No information to extract	N	N	
(Murray et al., 2004)	242	No statements present	No information to extract	Ν	Ν	
(Mutlu et al., 2013)	243	No statements present	No information to extract	Ν	N	There were dropouts to follow- up but no explanation for these.
(Nabi et al., 2015)	244	The therapeutic methods studied here were well tolerated were not associated with any serious adverse effects. However, skin irritation was reported in a few TENS group subjects.	Skin irritation	Y	N	No numerical data
(Nash et al., 1990)	245	The only side effected noted in the series were occasional skin rashes due to allergy to the electrode jelly or fixing tape, and occasional patients had transient increase in pain which settled to previous levels with cessation of treatment.	Skin irritation Transient increase in pain	Y	N	No numerical data

Reference	Reference number	Extracted Text	AEs related to TENS	Statement	Extractable Data	Comment
(Navarathnam et al., 1984)	246	Some of the patients in both groups developed blisters around the electrode edges in the distribution of the adhesives. In addition, two patients developed small areas of pressure necrosis in the region of the lumbosacral electrodes which might be avoided by more attention to posture of the patients with these electrodes.	Skin irritation Lumbosacral pressure necrosis	Y	N	No numerical data
(Neary, 1981)	247	No cases of infection or skin reaction were observed. TENS did not mask the pain symptoms from complications.	Reported no adverse events	Y = 0 tally	N = 0 tally	
(Neighbours et al., 1987)	248	No statements present	No information to extract	N	N	
(Nesheim, 1981)	249	No statements present	No information to extract	Ν	Ν	
(Neumark et al., 1978)	250	No statements present	No information to extract	Ν	Ν	
(Ng et al., 2003)	251	No statements present	No information to extract	Ν	Ν	
(Nordemar and Thorner, 1981)	252	No statements present	No information to extract	Ν	Ν	
(Norrbrink, 2009)	253	Three patients experienced discomfort or increased pain during treatment, and one patient experienced local muscle spasms.	Increased pain during treatment Local muscle spasms	Y	N	No numerical data Unclear which group experienced side effects
(Olsén et al., 2007)	254	No adverse effects except for discomfort during stimulation were recorded. Discomfort from the stimulation itself was greater in the HI TENS group than in the LI TENS group (pB/0.01). In the HI TENS group, two women experienced severe discomfort, two women experienced moderate discomfort, five women experienced mild discomfort, and two women experienced no discomfort. Seven women in the LI TENS group experienced no discomfort and one woman experienced mild discomfort from the stimulation given. No adverse effects except for discomfort during stimulation were recorded.	Discomfort during stimulation	Y	N	No numerical data other that stimulation discomfort Decided not to extract this
(Fagevik Olsen et al., 2019)	255	No statements present	No information to extract	Ν	Ν	Dropouts recorded but reaso not given
(Oncel et al., 2002)	256	No complications due to TENS therapy or Naproxen sodium were seen during the study.	Reported no adverse events	Y = 0 tally	N = 0 tally	
(Oosterhof et al., 2006) Secondary reports (Oosterhof et al., 2008, Oosterhof et al., 2012a, Oosterhof et al., 2012b)	257 Seco ndar y repor ts 258-260	No statements present in <sup>257</sup> . No statements present in secondary report <sup>259</sup> Secondary report - <sup>260</sup> Skin irritation occurred at some time point in half of the patients but could easily be cured by changing the type of electrode, except for 4 patients who had to stop treatment. Because there was no difference between TENS and sham TENS, we assume there was no interaction of the electric current with electrode material, which has been suggested.	Skin irritation	Y	N	No numerical data
(Ordog, 1987)	261	No complications of treatment were found. No side effects were reported, except a mild tingling sensation at higher TENS-PAC® output levels.	Reported no adverse events Mild tingling sensation is part of the TENS treatment	Y = 0 tally	N = 0 TENS ONLY	

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Reference	Reference number	Extracted Text	AEs related to TENS	Statement	Extractable Data	Comment
		Overall, 20% of the patients reported this effect, but none had to discontinue usage of the TENS-PAC® because of it.				
(Ozkaraoglu et al., 2020)	262	No statements present	No information to extract	N	N	
(Ozkul et al., 2015)	263	No unwanted effects occurred during the application of both treatments.	Reported no adverse events	Y = 0 tally	N = 0 tally	
(Oztas and Iyigun, 2019)	264	No statements present	No information to extract	N	N	
(Ozturk et al., 2016)	265	No statements present	No information to extract	Ν	Ν	
(Padma et al., 2000)	266	In the present study, no side effects were noted, and the stimulation was acceptable to all the patients, but the willingness to accept TENS as a mode of relief was equivocal.	Reported no adverse events	Y = 0 tally	N = 0 TENS ONLY	
(Paker et al., 2006)	267	In the present study, no serious adverse effects were reported in the intra- articular hylan group or in the TENS group.	Reported no adverse events	Y	N = 0 Tally	One dropout due to worse pain – not attributable to treatment
(Palmer et al., 2014)	268	No statements present	No information to extract	Ν	Ν	
(Pan et al., 2003)	269	Five patients complained of soreness in the upper arm after ESWT, but this soreness had subsided before their next visit. One patient had cardiac palpitations during the first ESWT session as a result of anxiety but was calm after taking a break. Otherwise, no specific side effect (e.g., hematoma, paresthesia) occurred in either group.	No adverse events recorded in TENS group	Y	Y	Extractable data: (soreness TENS = 0 events /30 participants ESWT = 5 eve 33 participants
(Park et al., 2015)	270	No adverse reactions related to TENS were observed.	Reported no adverse events	Y	N = 0 TENS ONLY	No numerical data
(Patil and Aileni, 2017)	271	No statements present	No information to extract	Ν	Ν	
(Peacock et al., 2019)	272	and no adverse events were reported in relation to the administration of the Biomodulator, traditional Chinese acupuncture, or TENS device in the study.	Reported no adverse events	Y = 0 tally	N = 0 tally	No numerical data
(Pietrosimone et al., 2009)	273	No statements present	No information to extract	Ν	Ν	
(Pietrosimone et al., 2011) Secondary Report (Pietrosimone et al., 2010)	274 Seco ndar y Repo rt 275	No adverse events were reported to the study personnel regarding TENS or placebo usage.	Reported no adverse events	Y = 0 tally	N = 0 tally	
(Pietrosimone et al., 2020)	276	No statements present	No information to extract	Ν	Ν	
(Pike, 1978)	277	The duration of stimulation, whether intermittent or continuous, is unimportant since neither tachyphylaxis nor side-effects occurred.	Reported no adverse events	Y	N = 0 TENS ONLY	No numerical data
(Pitangui et al., 2012)	278	No reports of side effects or dissatisfaction were made, supporting the results of other studies.	Reported no adverse events	Y = 0 tally	N = 0 tally	

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Reference	Reference number	Extracted Text	AEs related to TENS	Statement	Extractable Data	Comment
(Pitangui et al., 2014)	279	HFT and LFT are safe and effective resources without side effects and presenting good acceptance	Reported no adverse events	Y = 0 tally	N = 0 tally	
(Platon et al., 2010)	280	The only reported side effect of TENS during the study was discomfort during 1 min of the initial stimulation, which was noticed in some patients.	Slight discomfort during stimulation	Y	N	No numerical data
(Platon et al., 2018)	281	Some patients reported an uncomfortable stimulation during the 1 min of the initial stimulation with TENS as a side effect.	Slight discomfort during stimulation	Y	N	No numerical data
(Prabhakar and Ramteke, 2011)	282	No statements present	No information to extract	N	N	
(Presser et al., 2000)	283	No statements present	No information to extract	Ν	Ν	
(Rainov et al., 1994)	284	No statements present	No information to extract	Ν	Ν	
(Rajfur et al., 2017)	285	No statements present	No information to extract	Ν	Ν	
(Rajpurohit et al., 2010)	286	No statements present	No information to extract	Ν	Ν	
(Rakel and Frantz, 2003)	287	No statements present	No information to extract	Ν	Ν	
(Rakel et al., 2014)	288	No statements present	No information to extract	Ν	Ν	
0	290	but numerical data not clear Of note, 11 patients (9.48%) reported popular rash and/or cutaneous blistering around the placement site of adhesive electrodes Two patients were withdrawn for persistent cutaneous blistering. Other reasons for withdrawal were and skin hypersensitivity to adhesive electrodes (n=3, 6.81%) Authors note that withdrawals due to 'device-related discomfort' were in the active group (n=3 6.81%).	electrode sites			clear numerical data betwee the different intervention groups
(Ramos et al., 2018)	290	No statements present	No information to extract	N	N	
(Rani et al., 2020)	291 292	No statements present	No information to extract	N	N	
(Ratajczak et al., 2011)	292 293	No statements present	No information to extract	N	N	
(Rawat et al., 1991) (Renovato França et al., 2019)	294	No statements present No adverse events were observed in this study.	No information to extract Reported no adverse events	N $Y = 0$ tally	N = 0tally	
(Reuss et al., 1988)	295	No statements present	No information to extract	N	Ν	
(Revadkar and Bhojwani, 2019)	296	No statements present	No information to extract	N	Ν	
(Ringel and Taubert, 1991)	297	No statements present	No information to extract	Ν	Ν	
(Robb et al., 2007)	298	No statements present	No information to extract	Ν	Ν	
(Robinson et al., 2001)	299	No statements present	No information to extract	Ν	Ν	
(Roche et al., 1985)	300	No statements present	No information to extract	Ν	Ν	
(Rooney et al., 1983)	301	No statements present. Authors state that TENS is 'safe' in the conclusion. No further info.	No information to extract	N	N	
(Rosenberg et al., 1978)	302	No complications were observed in this study from the use of TENS and the only morbidity reported has involved skin reactions at the electrode sites	Skin reaction at electrode sites	Y	N	No numerical data
(Rutgers et al., 1988)	303	No statements present	No information to extract	Ν	Ν	

Reference	Reference number	Extracted Text	AEs related to TENS	Statement	Extractable Data	Comment
(Sadala et al., 2018)	304	No statements present	No information to extract	N	N	
(Sahin et al., 2011)	305	No statements present	No information to extract	Ν	Ν	
(Samadzadeh et al., 2017)	306	No statements present	No information to extract	Ν	N	States in conclusion that TEN is safe but no info on adverse events in main text.
(Sangtong et al., 2019)	307	Table 3 shows adverse events, patient global assessment, and patient satisfaction after treatment. More subjects in the study group had increased knee swelling than subjects in the control group (four patients ( $6.3\%$ ) vs. two patients ( $2.9\%$ ), respectively), but no significant difference (P = $0.430$ ). Table 3 of their report	Joint swelling Rash	Y	Y	Data extracted (joint swelling and skin rash) TENS + US = 4 events / 64 participants US alone = 3 events / 68 participants
(Santamato et al., 2013)	308	None of the patients reported adverse effects during the study period.	Reported no adverse events	Y = 0 tally	N = 0tally	
(Santana et al., 2016)	309	No statements present	No information to extract	Ν	Ν	
(Saranya et al., 2019)	310	No statements present	No information to extract	Ν	Ν	
(Sayilir and Yildizgoren, 2017)	311	No statements present	No information to extract	Ν	Ν	
(Seo et al., 2013)	312	A total of 7 adverse events that required admission in 6 participants were reported during the study. The adverse events included a traffic accident, acute appendicitis, cellulitis, worsening of lower back pain, shoulder pain, uterine myoma, and spontaneous abortion. There was a possible relationship between the treatment and spontaneous abortion that occurred 21 days after BTX-A injection and electrical stimulation. She answered "no" to the question "Are you pregnant or do you have a plan for pregnancy?" before study enrolment. The other events were not related to the treatment in this study.	Spontaneous abortion possibly related to treatment. Other adverse events unrelated to treatment.	Y	N	Numerical data not necessar related to TENS/interventio
(Serry et al., 2016)	313	No statements present	No information to extract	Ν	Ν	
(Sezen et al., 2017)	314	We observed a small number of complications in the patients who were administered TENS in our study, but there was no statistically significant difference between the two groups. Table 4 of their report	Authors do not say whether complications were felt to be due to TENS	Y	N	Data related to post-operative complications. Debatably the is related to AE associated with op procedures rather the TENS. We decided not to extract the data because AE from operation reflects efficacy of TENS rather than AE of TE Not extracted data (complications) TENS (T) = 6 events / 43 Control placebo TENS = 10 events / 44

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Reference	Reference number	Extracted Text	AEs related to TENS	Statement	Extractable Data	Comment
						Not definitely attributed to the intervention
(Shahoei et al., 2017)	315	No statements present Since it has no negative consequences for mothers and their fetus, it is considered a safe pain relief method.	No information to extract	N	N	
(Shehab and Adham, 2000)	316	No statements present	No information to extract	Ν	Ν	
(Sherry et al., 2001)	317	No statements present	No information to extract	Ν	Ν	
(Shimoji et al., 2007)	318	There were three cases of skin flash at sites of electrode placement in subjects treated with TENS using CPWs, but these disappeared within a day without intervention. No such skin irritation occurred in subjects who received TENS using BMWs. No other complications were reported in both groups. There was also a sham TENS group but no mention of AEs/complications	'Skin flash' (3 cases) in CPW group	Y	Y	Data extracted (skin irritation TENS (CPWs) = 3 / 9 BMWs (bidirectional modulated sine waves) = 0 events / 11
(Shimoura et al., 2019)	319	No adverse effect was noted with the TENS or sham-TENS treatment.	Reported no adverse events	Y = 0 tally	N = 0 tally	
(Shoukry and Al-Ansary, 2019)	320	Adverse effect during or after the procedure was recorded and treated. Table 3 shows that adverse effects [were significantly less frequent among group-A [TENS + i.v. fentanyl] compared to group-B [i.v. fentanyl]. These statements relate to adverse effects associated with ESWT procedure rather than TENS	O2 desaturation Nausea and vomiting Dizziness	N		The data provides informati about effect of TENS on incidence of adverse events associated with ESWT procedure + fentanyl treatm
(Siemens et al., 2020)	321	Two patients experienced an uncomfortable feeling caused by the current, one after IMT and one after PBT One out of 20 (5%) patients perceived the electric current as uncomfortable after the IMT phase and 1/20 (5%) after the PBT phase. No other TENS-related adverse events were reported. Four patients (20%) generally criticized that cables were impractical and one (5%) patient felt disturbed by the electrodes. After testing both TENS modes, 7/20 (35%) patients requested a prescription for the TENS device in order to use TENS after discharge. A usability problem rather than a safety problem was the fact that the main reason for stopping the study after period 2 was the burden in using TENS (5/15, 33%), e.g., because of the disturbing cables of the device (see Online Resource 5 for further reasons).	1 On	Ν	N	Frequency data between placebo and TENS interventions not provided
(Sikiru et al., 2008)	322	The results demonstrated a significant decrease in the NIH-CPSI ( $P = 0.0002$ ) with no urethral, anal complaints or other side effects	Reported no adverse events	Y = 0 tally	N = 0 tally	
(Silva et al., 2012)	323	No statements present	No information to extract	N	N	
(Silva et al., 2014)	324	No statements present	No information to extract	Ν	Ν	
(Sim, 1991)	325	No statements present	No information to extract	Ν	Ν	
(Siqueira et al., 2019)	326	No statements present	No information to extract	Ν	Ν	
(Sloan et al., 1986)	327	No statements present	No information to extract	Ν	Ν	

Reference	Reference number	Extracted Text	AEs related to TENS	Statement	Extractable Data	Comment
(Smania et al., 2005)	328	No statements present	No information to extract	N	N	There was data missing from final analysis but no explanation given
(Smedley et al., 1988)	329	No statements present	No information to extract	Ν	Ν	
(Smith et al., 1983)	330	Only one patient noticed any adverse effects from the treatment, a mild skin reaction to the electrode jelly.	Skin irritation in 1 patient.	Y	N	No numerical data to extrac
(Smith et al., 1986)	331	No statements present	No information to extract	Ν	Ν	
(Sodipo et al., 1980)	332	No statements present	No information to extract	Ν	Ν	
(Solak et al., 2007)	333	No statements present	No information to extract	Ν	Ν	
(Solak et al., 2009)	334	No statements present	No information to extract	Ν	Ν	
(Sonde et al., 1998)	335	No statements present	No information to extract	Ν	Ν	
(Stepanovic et al., 2015)	336	Adverse effects were associated with a specific treatment of herpes zoster $(n = 5)$ and analgesics prescribed $(n = 20)$ . Most common complication was a bacterial superinfection, in either group there was no serious complication.	Reported no adverse events	Y	N = 0 TENS ONLY	
(Steptoe and Bo, 1984)	337	TENS is almost free from adverse events	No information to extract	Ν	Ν	
(Stratton and Smith, 1980)	338	No statements present	No information to extract	Ν	Ν	
(Stubbing and Jellicoe, 1988)	339	No statements present	No information to extract	Ν	Ν	
(Suh et al., 2015)	340	No statements present	No information to extract	Ν	Ν	
(Talbot et al., 2020)	341	No statements present	No information to extract	Ν	Ν	
(Tantawy et al., 2018)	342	No statements present	No information to extract	Ν	Ν	
(Taylor et al., 1981)	343	No statements present	No information to extract	Ν	Ν	
(Taylor et al., 1983)	344	No statements present	No information to extract	Ν	Ν	
(Thakur and Patidar, 2004)	345	Side effects were more in the tramadol group in the form of nausea 7%, vomiting 3%, drowsiness 2% and fetal distress 2%, what while in the control group only one percent had fetal distress. Intense group none had any side effects Data in Table 6	Reported no adverse events	Y	Y	Data extracted TENS = 0 events / 100 Control (no intervention) = event / 100 participants (Fe distress) Also: Tramadol = 14 / 100 participants (nausea, vomit drowsiness, fetal distress) – did not add to forest plo prevent double counting in
(Thomas et al., 1988)	346	No statements present	No information to extract	N	N	group analysis
(Thomas et al., 1995)	347	No statements present	No information to extract	N	Ν	
(Thorsteinsson et al., 1978)	348	No statements present	No information to extract	N	N	
(Tilak et al., 2016)	349	No statements present	No information to extract	N	N	

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Reference	Reference number	Extracted Text	AEs related to TENS	Statement	Extractable Data	Comment
(Tokuda et al., 2014)	350	We observed no side effects; thus, TENS may be particularly useful for patients who have liver or kidney disease considering that analgesics are excreted through the kidney.	Reported no adverse events	Y = 0 tally	N = 0 tally	
(Tonella et al., 2006)	351	No statements present	No information to extract		Ν	
(Topuz et al., 2004)	352	No statements present	No information to extract	Ν	Ν	
(Tosato et al., 2007)	353	No statements present	No information to extract	Ν	Ν	
(Treacy, 1999)	354	No statements present	No information to extract	Ν	Ν	
(Tsen et al., 2000)	355	Some have raised the concern that TENS could interfere with fetal heart rate tracings,1 1 however, this was not witnessed in our review of fetal tracings, nor did we observe any incidents of non-reassuring fetal tracings2 4 subsequent to the CSE placement in either group.	Reported no adverse events.	Y = 0 tally	N = 0 tally	
(Tsen et al., 2001)	356	No statements present	No information to extract	N	N	Authors stated they would record adverse events but no comments included in result or discussion.
(Tsukayama et al., 2002)	357	No adverse events were reported by the evaluator. The therapists reported some transient adverse events, for the EA group: transient aggravation of LBP (1 case), discomfort due to press tack needles (1 case), pain on needle insertion (1 case) and small subcutaneous bleeding (10mm in diameter, 1 case); in the TENS group: transient aggravation of back pain (1 case), transient fatigue (1 case), itching with electrode (1 case). Seven patients in each group did not experience any adverse events.	Increased back pain Transient fatigue Itching with electrode	Y	Y	Data extracted (symptom aggravation, skin reaction, fatigue) TENS = 3 events / 10 participants Electroacupuncture = 4 even / 9 participants
(Tucker et al., 2015)	358	There were no clinically significant adverse events related to TENS in either group. In table 2 of their report	Reported no adverse events	Y = 0 tally	N = 0 tally	
(Tugay et al., 2007)	359	No adverse effects were observed, supporting the findings of the related literature.	Reported no adverse events	Y = 0 tally	N = 0 TENS ONLY	
(Tulgar et al., 1991a)	360	No statements present	No information to extract	N	Ν	
(Tulgar et al., 1991b)	361	No statements present	No information to extract	N	Ν	
(Unterrainer et al., 2010)	362	In conclusion, the use of TENS before skin incision and postoperative is noninvasive, safe, simple, and free of systemic side effects in postoperative pain treatment after major spinal surgery.	Reported no adverse events	$\mathbf{Y} = 0$ tally	N = 0 TENS ONLY	
(Unterrainer et al., 2012)	363	No statements present	No information to extract	Ν	Ν	
(Upton et al., 2017)	364	No adverse effects reported during the study.	Reported no adverse events	Y = 0 tally	N = 0 tally	
(Vaidya, 2018)	365	However, no negative effects were found with the use of TENS in any stage of pregnancy which supports the finding of our study [9]. No negative effects were reported for any of the patients.	Reported no adverse events	Y = 0 tally	N = 0 tally	
(Vaillancourt et al., 2019)	366	No statements present	No information to extract	Ν	Ν	

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Reference	Reference number	Extracted Text	AEs related to TENS	Statement	Extractable Data	Comment
(Valenza et al., 2016)	367	No adverse effects were reported by any participant after any of the interventions.	Reported no adverse events	Y = 0 tally	N = 0 tally	
(van der Ploeg et al., 1996)	368	No adverse side-effects occurred.	Reported no adverse events	Y = 0 tally	N = 0 tally	
(van der Spank et al., 2000)	369	No statements present	No information to extract	Ν	N	
(Vance et al., 2012)	370	No statements present	No information to extract	Ν	Ν	
(Vitalii and Oleg, 2014)	371	No side effects of LF-TENS were seen. Mean gabapentin dose was 1036.36 mg in the study group and 1560 mg in the control group, thus the basic dose was increased by 136.36 mg of gabapentin in the study group and by 560 mg in the control group (P=0.004; Fig. 2). Three patients from the control group reported drowsiness and dizziness on the ninth day of treatment (doses of gabapentin increased to 2700, 2400 and 1800 mg) and one patient reported blurred vision (dose of gabapentin increased to 2700 mg). No side effects of gabapentin were reported in the study group.	Reported no adverse events	Y	N	No data extracted because AEs due to the higher doses of gabapentin in control group. Thus, data reflects TENS efficacy in reducing AEs associated with gabapentin TENS + gabapentin = 0 events Placebo TENS + gabapentin = 4 events (drowsiness + dizziness, blurred vision related to gabapentin)
(Vrouva et al., 2019)	372	No statements present	No information to extract	Ν	Ν	
(Walker et al., 1991)	373	No statements present	No information to extract	Ν	Ν	
(Wang et al., 2009)	374	No statements present	No information to extract	Ν	Ν	
(Warfield et al., 1985)	375	There were no complications in either group as a result of TENS. We conclude that TENS is a safe, effective adjunctive therapy for post thoracotomy pain.	Reported no adverse events	Y = 0 tally	N = 0 tally	
(Warke et al., 2004)	376	No statements present	No information to extract	N	Ν	
(Warke et al., 2006)	377	No statements present	No information to extract	N	Ν	
(Yameen et al., 2011)	378	No statements present	No information to extract	N		Transcutaneous electrical nerve stimulation is an effective, easy to use and with minimal side effects in patient suffering from trigeminal neuralgia not responding to conventional therapy.
(Yesil et al., 2018)	379	No adverse events due to electrotherapy such as irritation or burning of the skin were observed.	Reported no adverse events	Y = 0 tally	N = 0 TENS ONLY	
(Yilmaz et al., 2020)	380	We did not observe any side effects or intolerance associated with TENS in our patients. Also, TENS application did not cause any negative changes in vital signs. This result indicates that TENS is easily applied, and its efficacy and safety could help in pain relief for inguinal herniorrhaphy.	Reported no adverse events	Y = 0 tally	N = 0 TENS ONLY	

Reference	Reference number	Extracted Text	AEs related to TENS	Statement	Extractable Data	Comment
(Yilmazer et al., 2012)	381	No statements present	No information to extract	Ν	Ν	
(Yokoyama et al., 2004)	382	No statements present	No information to extract	Ν	Ν	
(Yoshimizu et al., 2012)	383	No adverse effects or carryover effect were detected.	Reported no adverse events	$\mathbf{Y} = 0$	N = 0	
			_	tally	tally	
(Yüksel et al., 2019)	384	No statements present	No information to extract	Ν	Ν	
(Yurtkuran and Kocagil, 1999)	385	No statements present	No information to extract	Ν	N	
(Zakariaee et al., 2019)	386	No statements present	No information to extract	N	N	Mentions that adverse events will be documented but then fails to provide data or clear statement in results nor discussion
(Zhang et al., 2020)	387	No statements present	No information to extract	Ν	Ν	
(Zhou et al., 2018)	388	No adverse events were observed in either of the groups during the 8-week	Reported no adverse	$\mathbf{Y} = 0$	N = 0	
		follow-up.	events.	tally	tally	

## Legend

 Information was identified by searching for text and/or numerical data that referred to adverse events. Information was 'cut and pasted' into this Table. Where available, data on the occurrence of adverse events in each intervention arm was tallied as events (irrespective of severity) per number participants exposed (i.e. number in intervention arm), pooled and meta-analysed. If trial reports included a statement that no adverse events were observed during the study this was identified as such in our table. 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), in line with advice from the Cochrane Collaboration. Y, yes; N, no; TENS, transcutaneous electrical nerve stimulation.

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\*Note: Reference numbering in this list relates only to studies cited in this table

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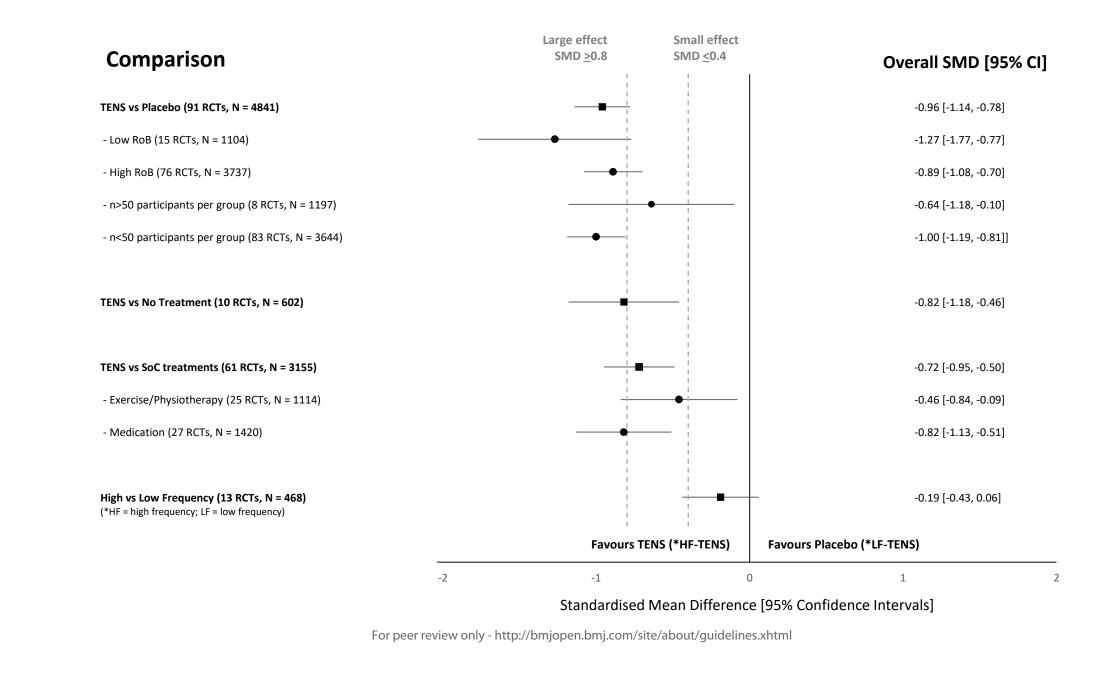
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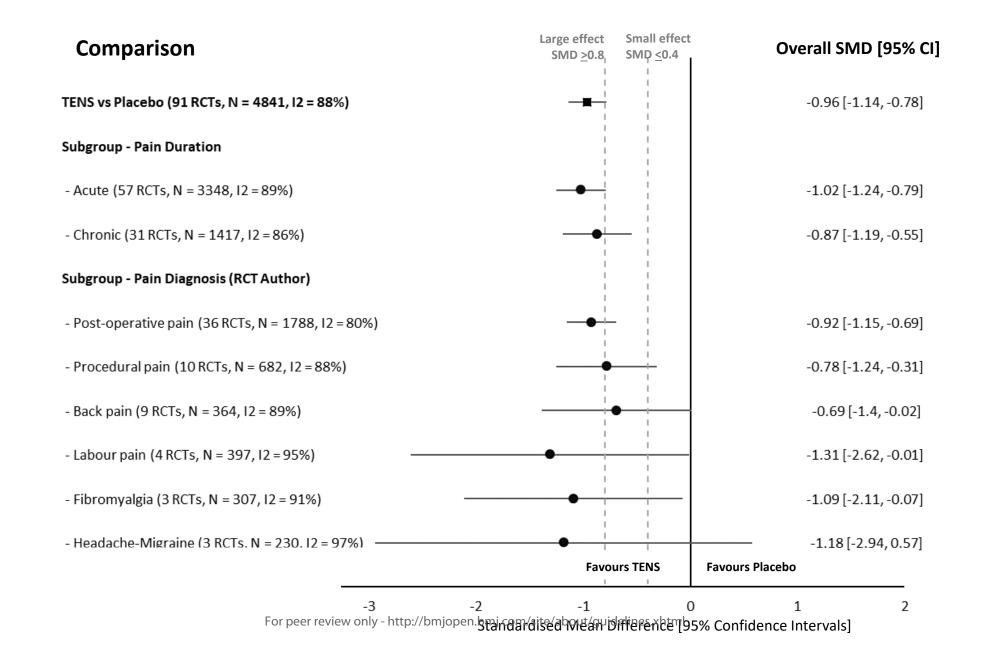
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# PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			1
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT	· · · ·		
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	3
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	3
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	3
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	3
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	3
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	3
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	3
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	4
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	4
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	4
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I <sup>2</sup> ) for each meta-analysis. For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml	4

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# **PRISMA 2009 Checklist**

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	4
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	4
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	5
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	5
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	5
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	5
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	6
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	6
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	6
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	6
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	6-7
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	7
FUNDING	<u> </u>	·	
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	3

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# **BMJ Open**

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

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Secondary Subject Heading:	Evidence based practice, Anaesthesia, Neurology, Nursing, Rehabilitation medicine
Keywords:	PAIN MANAGEMENT, REHABILITATION MEDICINE, COMPLEMENTARY MEDICINE, NEUROLOGY, Pain management < ANAESTHETICS





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

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# ABSTRACT

# Objective

To investigate the efficacy and safety of transcutaneous electrical nerve stimulation (TENS) for relief of pain.

# Design

Systematic review and meta-analysis.

#### Data Sources

Medline, Cochrane Central, Embase (and others) from inception to July 2019 and updated on 17 May 2020.

## Eligibility criteria for study selection

Randomised controlled trials (RCTs) comparing strong non-painful TENS at or close to the site of pain versus placebo or other treatments in adults with pain, irrespective of diagnosis.

## Data extraction and synthesis

Reviewers independently screened, extracted data, and assessed risk of bias (RoB, Cochrane tool), and certainty of evidence (GRADE). Mean pain intensity and proportions of participants achieving reductions of pain intensity ( $\geq$  30% or  $\geq$  50%) during or immediately after TENS. Random effects models were used to calculate standardised mean differences (SMD) and risk ratios (RR). Subgroup analyses were related to trial methodology and characteristics of pain.

#### Results

The review included 381 RCTs (24532 participants). Pain intensity was lower during or immediately after TENS compared with placebo (91 RCTs, 92 samples, n = 4841, SMD = -0.96 [95% CI, -1.14, -0.78]). Methodological (e.g., RoB, sample size) and pain characteristics (e.g., acute vs chronic, diagnosis) did not modify the effect. Pain intensity was lower during or immediately after TENS compared with pharmacological and non-pharmacological treatments used as part of standard of care (61 RCTs, 61 samples, n = 3155, SMD = -0.72 [95% CI, -0.95, -0.50]). Levels of evidence were downgraded because of small sized trials contributing to imprecision in magnitude estimates. Data was limited for other outcomes including adverse events which were poorly reported, generally mild, and not different to comparators.

# Conclusion

There was moderate-certainty evidence that pain intensity is lower during or immediately after TENS compared with placebo and without serious adverse events.

Systematic review registration PROSPERO - CRD42019125054

# Keywords

Transcutaneous electrical nerve stimulation (TENS), Pain management, Therapeutic neuromodulation, Meta-analysis

# Strengths and limitations of this study

- This meta-analysis is the first to pool data from pain irrespective of diagnosis, and meets 'rule of thumb' threshold standards for pooling pain data for meta-analysis (i.e., <a>500 participants per trial arm)</a>
  - Effect sizes were calculated during or immediately after strong non-painful TENS because this is ecologically valid, and overcomes problems of analysing data gathered from a wide variety of TENS regimens, such as PRN, where participants are using TENS intermittently
- There was a preponderance of small sample sized studies, so a judicious approach was taken in interpretation of findings
- Sub-group analyses were used to explore statistical heterogeneity and the effect of combining different types of pain; the trim and fill method was used to explore publication bias
- GRADE criteria were used to judge the impact of risk of bias, imprecision, inconsistency, indirectness, and publication bias on the certainty of effect size estimates

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#### BACKGROUND

Pain is a global health problem with negative consequences for patients, society, and health care systems [1,2]. Transcutaneous electrical nerve stimulation (TENS) is used throughout the world for symptomatic relief of pain, supported by physiological evidence that TENS inhibits the activity and excitability of central nociceptive transmission neurons, irrespective of diagnosis (for review see [3]). In most countries TENS equipment and accessories are available without prescription; running costs and follow-up clinical support for TENS is inexpensive. Treatment can be self-administered without fear of toxicity, potentially offering symptomatic relief of pain throughout the day.

Uncertainty about the clinical efficacy of TENS has fuelled a longstanding debate as to whether TENS should be offered to patients in public health systems (e.g., within the National Health Service in the U.K.), or covered by private healthcare insurance (e.g., by the Center for Medicare Services in the USA). Clinicians and policy makers are confused about the benefits and harm associated with TENS, and clinical practice guidelines are inconsistent. In 2021, the National Institute of Health and Care Excellence (NICE) released guidance for the management of chronic pain in over 16s that recommends not to offer TENS [4]. The NICE does not recommend TENS for intrapartum care [5] or non-specific chronic low back pain [6] but does recommend TENS as an adjunct for osteoarthritis [7] and rheumatoid arthritis [8]. These guidelines are organised according to a traditional-pathology based classification of pain. This restricts the quantity of RCTs included for evaluation, despite many of these conditions having commonalities in the way that pain presents. Moreover, there is strong evidence that TENS acts via non-specific therapeutic neuromodulation irrespective of pathology, and that the lived experience of pain and response to pain relieving interventions results from a complex interplay of biopsychosocial factors (for review see [3]).

The debate about the efficacy of TENS has been ongoing since the 1970s, despite the publication of more than 350 RCTs [9]. A comprehensive appraisal of literature identified 169 systematic reviews, including Cochrane reviews, and at least 49 meta-analyses of TENS for specific pain conditions [10]. Most reviews are inconclusive due to insufficient pooled data. A recent overview of eight Cochrane reviews on TENS for chronic pain analysed 51 RCTs (2895 participants) and was inconclusive, with reviewers reluctant to pool data for meta-analysis because of clinical heterogeneity [11]. There is an absence of convincing or consistent evidence that TENS outcome is related to pathology, pain characteristics, medical diagnoses, or clinical context [9,12].

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It seems logical to evaluate efficacy from a phenomenological perspective, i.e., by pooling pain intensity data irrespective of medical condition. This would increase the likelihood of exceeding thresholds for adequacy of pooled data. The intention of TENS is to provide symptomatic relief of pain and discomfort 'in-the-moment', so it would be ecologically valid to evaluate outcomes during or immediately after a single strong non-painful TENS treatment. Assessing TENS at a single time point would mitigate for heterogeneity associated with variable treatment schedules used in RCTs. Clinical heterogeneity associated with combining pain conditions arising from different pathologies and settings can be explored through subgroup analyses. Concerns about the impact of risk of bias, imprecision, inconsistency, indirectness, and publication bias can be assessed using GRADE criteria. To date, there has been no attempt to undertake a meta-analyse of this nature, possibly because of the enormity of the task.

The aim of our systematic review and meta-analysis was to evaluate the efficacy and safety of TENS for pain, irrespective of medical diagnoses in adults.

#### **METHODS**

This systematic review and meta-analysis were conducted and reported in accordance with guidelines from the Cochrane Collaboration of Systematic Reviews; Grading and Recommendations, Assessment, Development and Evaluation (GRADE) and the Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA). The study was registered on PROSPERO (CRD42019125054) and the protocol published (<u>https://bmjopen.bmj.com/content/9/10/e029999</u>)[13]. Ethical approval for the review was granted by Leeds Beckett University (Application Ref: 78097). See supplementary file 1 for full details of search strategy, eligibility screening, data extraction, and analysis.

#### Search strategy and selection criteria

One reviewer (PGW) searched electronic databases (Medline, Embase, Cochrane Central, CINAHL, PsycINFO, LILACS, PEDRO, Web of Science, AMED, SPORTDiscus) from inception to July 2019 and updated on 17 May 2020, for full text publications of randomised controlled trials (RCTs) and for systematic reviews that evaluated TENS for adults with clinical pain versus:

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

There were no language restrictions and articles were translated where possible.

# **Types of TENS interventions**

The TENS intervention was defined as pulsed electrical currents generated by a 'standard TENS device' administered across the intact surface of the skin using surface electrodes at the site of pain or over nerve bundles proximal (or near) to the site of pain, with the intention of stimulating peripheral nerves to alleviate pain [3]. We included any type of pulse pattern and excluded pulse frequencies >250 pulses per second (pps), pulse durations >500 microseconds ( $\mu$ s) and peak-to-peak amplitudes >60 milliamperes (mA).

We included TENS administered by a therapist and/or participant; as a sole treatment or in combination with other treatments, for any duration or regularity of treatment; as a single or multiple treatment intervention with or without follow-up. However, we only extracted data for the measurement timepoint during or immediately after a TENS treatment, as this is the most ecologically valid outcome (see Introduction). We considered participant-reported strong but comfortable TENS sensations as optimal and used this as our primary TENS comparison group. We excluded RCTs evaluating non-painful outcomes (e.g., bladder dysfunction, constipation, dementia), or administering TENS at acupuncture points (unless over nerve bundles at the site of pain), using probes or electrode arrays, or using TENS-like currents (e.g., interferential current, microcurrent).

Two review authors (PGW and MIJ) independently screened titles, abstracts, and full texts, and extracted trial characteristics and numerical data. Disagreements were resolved by consensus with a third review author as arbiter (CAP or GJ). Records were not anonymised before assessment. Reasons for exclusion were coded and tabulated. The characteristics of included trials were extracted and tabulated including design, sample population, TENS intervention, comparator(s), and outcome measures. Decisions, trial characteristics and codes for analyses were documented in Excel spreadsheets.

#### Types of outcome measures

Pain outcomes were mean (continuous data) patient-reported intensity of spontaneous or evoked pain (at rest or on movement) using standard subjective scales (e.g., numerical rating scale (NRS) or visual analogue scale (VAS)), and the proportion of participants reporting a reduction in pain intensity of  $\geq$  30% (moderate) or  $\geq$  50% (substantial) relative to baseline [14]. A between-group difference of  $\geq$ 10 mm on a 100 mm VAS was set as the threshold for clinical importance in-line with IMMPACT criteria [15].

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For standardised mean difference (SMD) we used 'Rules of thumb' based on Cohen's d [16,17] for interpreting effect sizes as follows:

<0.4 = small effect</li>

- 0.4<0.7 = moderate effect
- $\geq 0.7 = \text{large effect}$

We considered a SMD of 0.5 as a rule of thumb for an important difference [17]. We were mindful that interpretations of this nature can be problematic due a variety of factors including settings and context in which pain was evaluated.

We only extracted data at the last during TENS timepoint (i.e., whilst TENS was switched on) or the first timepoint immediately after TENS had been switched off. If TENS was administered as a course of treatments, we extracted data from the last treatment session.

We analysed the proportion of participants experiencing an adverse event, irrespective of severity. 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).

# **Evaluation of TENS Effects**

Full details of the process used to categorise comparators is provided in supplementary file 1

# TENS versus Placebo

We included any type of placebo TENS and conducted a subgroup analysis of the different types of approaches such as sham devices with no electrical current or pulses of current that fade to 0mA within one minute. We considered the use of a sham TENS device coupled with appropriate briefing information as an adequate method of blinding.

# TENS versus No treatment or waiting list control

We considered an intervention as 'no treatment' if we were confident that participants did not receive any other 'active' treatment. Comparators described as 'controls' were not included if patients were taking any type of active treatment, including *ad hoc* non-prescriptive medication or advise to undertake regular exercises. RCTs that compared TENS in combination with a

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pharmacological agent versus a control consisting of the pharmacological agent on its own were not included in this analysis.

#### TENS versus standard of care (SoC) comparators

We considered an intervention as 'standard of care' when trial authors described the intervention(s) to be fully or part of 'common', 'routine', or 'standard' practice and/or care. Thus, comparisons 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). If a study had more than one treatment comparator, we planned to select only one comparator for meta-analysis to avoid unit-of-analysis errors, although there were no instances of this.

#### TENS versus other treatment comparators

This analysis compared TENS with another treatment that had not been categorised as SoC. There was a variety of other treatment comparators and instances of studies with multiple treatment comparators. We produced a Forest plot for visual inspection but did not undertake a subgroup analysis because this would violate criteria for unit of analysis (i.e., double counting of primary TENS group data). None of these other treatment subgroups met our criteria for adequate sample size in treatment arms.

#### **Data analysis**

Meta-analyses were conducted using Review Manager 5.3 and Stata 16 software. We calculated standardised mean difference (SMD) for continuous data and risk ratio (RR) for dichotomous data. Pre-specified criteria were used to select the primary TENS comparison and we did not enter several interventions into the same meta-analysis to avoid 'double-counting' and unit-of-analysis errors. We used an intention-to-treat analysis and combined data from first and second periods in cross-over trials because there was sufficient washout between interventions to eliminate contamination. We produced Forest plots for visual inspection and calculated overall treatment effect sizes when there were at least 100 data points in both trial arms pooled from at least two RCTs. Data was considered imprecise if the TENS treatment arm was below 500 participants for pooled data or below 200 participants for a single RCT [18].

Two review authors (CAP and MIJ) independently assessed risk of bias (RoB) using the Cochrane tool. We examined heterogeneity using visual inspection of forest plots, the I<sup>2</sup> statistic, the Chi<sup>2</sup> test and the Cochrane Collaboration's rough guide to interpretation. Small study effects were analysed using

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Egger's regression test (p-value set at  $\leq 0.1$ ), and the Trim and Fill method was used to analyse potential publication bias.

Pre-specified subgroup analyses were related to

- trial methodology e.g., overall risk of bias, trial arm sample size, and access to other treatments
- characteristics of pain e.g., duration acute vs chronic, medical diagnosis pain conditions, mechanistic descriptors - nociceptive or neuropathic, and systems or organs involved – musculoskeletal, visceral, somatosensory; and
- characteristics of TENS and comparators e.g., high versus low frequency TENS, types of placebos, and types of SoC.

Eligibility criteria had optimised TENS technique by excluding RCTs that did not deliver TENS above sensory detection threshold or close to the site of pain, making subgroup analyses of optimal versus suboptimal intensity or site of stimulation impossible. There were insufficient data to undertake subgroup analyses of conventional versus acupuncture-like TENS.

We interpreted subgroup analyses by considering: a p-value of  $\leq 0.1$  to indicate a statistically significant subgroup effect (interaction); the direction of each subgroup effect (i.e. qualitative or quantitative); and the extent to which individual trials differed in treatment effects within each subgroup (i.e. heterogeneity), in-line with Richardson et al. [19]. We evaluated the certainty of evidence using the GRADE system (GRADEpro GDT 2015, https://gradepro.org/)[20].

Full details about the principles and operational procedures of subgroup analyses and GRADE assessments, including interpreting the findings, are provided in supplementary file 1.

Patient and public involvement There was no patient or public involvement in any aspect of this study or its write-up.

#### RESULTS

Our searches yielded 7679 records (Figure 1). After removal of duplicates, we screened 5747 records and reviewed 623 full text reports of which 381 RCTs were included (383 samples, 24532 participants, 334 parallel-group, see supplementary file 2 for characteristics of included studies) and 19 RCTs are awaiting classification (supplementary file 3 for studies awaiting classification).

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Violations of pre-specified criteria for TENS were the most common reasons for excluding studies (supplementary file 4 for reasons for excluding studies). See supplementary file 1 for full details of screening, extraction, main and subgroup analyses, and interpretation, including risk of bias and GRADE judgements.

Included trials consist of 176 samples with chronic pain (osteoarthritis = 32 samples), 162 samples with acute pain (post-operative pain = 95 samples), 10 samples mixed, and 35 samples unclear. There were 26 trials with overall low RoB (Figure 2 and supplementary file 1). Small sample size was an issue with 341 trials having fewer than 50 participants in the TENS group (mean  $\pm$  SD TENS group = 27.71  $\pm$  21.89 participants; 13 RCTs had  $\geq$ 100 participants in the TENS group). There were at least 216 TENS interventions where participants had access to other treatments, most commonly medication or exercise as part of ongoing SoC, as a combination treatment or as rescue analgesia. Often, monitoring and/or reporting of concurrent treatment(s) was deficient.

All studies met our pre-specified criteria for TENS, although unclear reporting hindered characterisation of specific aspects of TENS technique. We categorised 276 interventions as high frequency TENS (100Hz = 109 interventions) and 35 interventions as low frequency TENS. Participants in some RCTs were instructed to adjust the pulse frequency of TENS as needed. TENS interventions varied considerably; supervised (therapist) or unsupervised (self-administered); prescribed or pro re nata (prn); single or multiple treatments; short treatment duration <1 minute for procedural pain or up to 2 years 'as required' for chronic pain. Inconsistency in treatment duration was mitigated by assessing TENS during or immediately after TENS treatment.

There were 352 of 381 RCTs that gathered continuous data for pain intensity and 164 RCTs had extractable data for meta-analysis. Figure 3 summarises overall effect sizes for treatment comparisons with at least 100 pooled data points per arm and Figure 4 summarises subgroup analyses for types of pain. There was insufficient extractable data to conduct responder analyses of participants reporting a  $\geq$ 30% or  $\geq$ 50% pain reduction unless otherwise stated.

Supplementary file 1 provides details about analyses (i.e., main, subgroup and sensitivity), Forest and Funnel plots, and GRADE judgements with summary of findings tables.

#### **TENS versus Placebo**

We extracted mean (continuous) data from 91 of 202 RCTs comparing TENS with placebo. There was a significant overall effect in favour of TENS and substantial statistical heterogeneity (TENS = 2426 participants, placebo = 2415 participants, SMD = -0.96 [95% CI -1.14, -0.78], I<sup>2</sup> = 88%).

Subgroup analyses found that the effect of TENS was not modified by methodological variables including overall RoB (score  $\leq$ 6, supplementary file 5), sample size, or the type of placebo. Subgroup analyses found that the effect of TENS was not modified by any pain characteristic including the duration (acute versus chronic, (supplementary file 6), mechanistic descriptors, or physiological structure involved.

The test for subgroup differences for pain diagnoses was statistically significant (Chi<sup>2</sup> = 202.12, df = 23 (P < 0.001),  $I^2 = 88.6\%$ ) but there were more trials (and participants) contributing data from some pain conditions than others, and there was considerable unexplained heterogeneity between the trials within each of these subgroups. A sensitivity analysis following removal of subgroups with pooled sample sizes fewer than 100 participants in the TENS trial arm, rendered the test for subgroup differences for pain diagnoses not statistically significant (Figure 5). Therefore, we interpret these findings as pain diagnosis does not modify the effect of TENS in comparison to placebo.

We downgraded evidence by one level for the combined effects of unexplained heterogeneity and possible publication bias. Egger's regression test showed significant evidence of a small-study effect (p < 0.0001) and trim and fill analysis showed evidence of publication bias, indicating that eight trials might be missing to the right of the mean for an adjusted SMD of -0.78 (95% Cl -0.995 to -0.565). Trim and fill did not alter the SMD to any appreciable degree. Approximately 90% of studies had 'low' or 'unclear' overall risk of bias scores although sub-group and sensitivity analyses of RoB did not modify the effect of TENS. We did not judge there to be serious limitations for blinding of placebo because sham TENS devices have been shown to create uncertainty about whether a device is correctly functioning [21]; and there was less than 10% incidence of high RoB for random sequence generation and allocation concealment. Thus, it was not appropriate to downgrade further, and we judged there to be moderate-certainty evidence.

We extracted dichotomous data from nine RCTs and found a statistically significant difference in the proportion of participants reporting a reduction of pain intensity  $\geq$ 50% in favour of TENS (TENS = 106/241 responders, placebo 28/219 responders, RR = 2.89 [2.02, 4.13], p < 0.00001, l<sup>2</sup> = 0%). There

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 were too few RCTs and participants to be entirely certain of the validity of the treatment effect estimate so we downgraded by one level to low-certainty evidence.

#### **TENS versus No Treatment**

We extracted mean (continuous) data from 10 of 16 RCTs (602 participants) comparing TENS with a no treatment control. There was a statistically significant difference in favour of TENS and substantial statistical heterogeneity (TENS = 298 participants, no treatment = 304 participants, SMD = -0.82 [95% Cl -1.18, -0.46], l<sup>2</sup> = 76%) (Figure 4). There was insufficient data to undertake subgroup analyses to explore the effect of methodological nor clinical characteristics on outcome. 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. We downgraded one level to low-certainty evidence due to unexplained heterogeneity and small study effect.

#### TENS versus treatment(s) used as standard of care

We extracted mean (continuous) data from 61 of 127 RCTs (3155 participants) comparing TENS with treatment(s) used as standard of care. There was a statistically significant difference in favour of TENS and substantial statistical heterogeneity (TENS = 1594 participants, SoC = 1561 participants, SMD = -0.72 [95% CI -0.95 to -0.5],  $I^2 = 88\%$ ). (Figure 3). Subgroup analyses suggested that the type of SoC intervention (predominantly exercise/physiotherapy versus predominantly pharmacological) did not modify the effect of TENS. 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 [95% -1.31, -0.76]. We downgraded one level for imprecision (unexplained heterogeneity effect) and one level for publication bias, small study effect and a RoB associated with unblinded treatment, i.e., to low certainty evidence.

#### TENS versus other treatment(s)

We extracted mean (continuous) data from 67 of 118 RCTs that compared TENS with a treatment, not categorised by RCT authors as SoC (67 RCTs, 131 samples, 3327 participants). We chose not to report the meta-analysis due to the heterogeneous mix of comparators, the inclusion of duplicate data in the TENS arm, and sub-groups with too few comparisons. Therefore, we did not GRADE this evidence.

#### **High versus Low Frequency TENS**

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We extracted mean (continuous) data from 13 of 37 RCTs (468 participants) that compared high with low frequency TENS and found no statistically significant difference (High Frequency TENS = 235 participants, Low Frequency TENS = 233 participants, SMD = -0.19 [95% CI -0.43 to -0.06], I<sup>2</sup> = 39%). (Figure 3). 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. We downgraded by one level to moderate-certainty evidence of no difference because the pooled data sample size did not meet pre-specified threshold of at least 500 participants per trial arm.

#### Safety

There were 136 reports that included a statement about adverse events (59/136 = no adverse events in all intervention groups, 90/136 = no adverse events related to TENS, see supplementary file 7 for characteristics of adverse events). Often statements were unclear. Adverse events associated with TENS were mild in severity, infrequent in occurrence and included skin irritation, tenderness/soreness, and TENS discomfort. There were no reports of a serious adverse event directly attributable to TENS. We extracted dichotomous data from 18 RCTs (1587 participants) and found no statistically significant difference in the risk of an adverse event, irrespective of severity, between TENS and comparators (RR = 0.73 [95% Cl 0.36, 1.48], p = 0.38, l<sup>2</sup> = 66%). The type of comparator did not modify the effect. We downgraded by two levels for indirectness because of the use of spontaneous detection of adverse events based on ill-defined criteria, and two levels for RoB, and one level for imprecision and for publication bias, i.e., to very low certainty evidence.

#### DISCUSSION

#### Statement of principal findings

Our meta-analysis of 91 RCTs (4841 participants) found that pain intensity was lower during or immediately after strong non-painful TENS administered to painful body parts, when compared with placebo. Risk of bias or trials with fewer than 50 participants per arm did not modify the effect of TENS, allaying at least in part, concerns that small study size may undermine the veracity of our conclusion [22]. Pain characteristics and diagnosis did not modify the effect of TENS compared with placebo. Inconsistency in individual trial results generated uncertainty in the magnitude of effect estimates for different types of pain but this was quantitative in nature (i.e., in the same direction and always in favour of TENS). Thus, we are confident that pain intensity is lower during or immediately after TENS treatment when compared with placebo.

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We judged there to be moderate certainty evidence that the magnitude of the effect size estimate exceeds the threshold for clinical importance, i.e., surpassed our 0.5 'rules of thumb' for Cohen's d. The magnitude of the SMD suggests that mean pain score in the TENS groups was 0.96 standard deviations lower than placebo (95% CI, 1·14 lower to 0·78 lower). The lower boundary of the 95% CI exceeds our pre-specified threshold for a large and clinically meaningful difference using Cohen's interpretation of effect size. This can be re-expressed by back transforming the SMD to a familiar scale such as a 0 mm (no pain) to 100 mm (worst pain imaginable) visual analogue scale. To do this we selected a low RoB study that was representative of the population and intervention in the metaanalysis (i.e., by Atamaz et al. [23] - knee osteoarthritis) and multiplied the standard deviation of the control group (20.3) by the pooled SMD (-0.96) producing a mean difference (MD) of 19.49 mm in favour of TENS [17] (chapter 15.5.3.2). This exceeds our prespecified criterion for clinical importance in-line with IMMPACT criteria (i.e., set ≥10 mm on a 100 mm VAS) [15]. Likewise, we backtransformed the SMD of Dailey et al. [24] (fibromyalgia, high frequency TENS, low risk of bias, used a 0-10 numerical rating scale) and calculated mean difference to be 1.91 points. This also exceeded our criterion for clinical importance. We emphasise that effect sizes re-expressed in this way should be interpreted with extreme caution because they are based on the standard deviation of only one study.

There was low certainty evidence that more participants reported at least 50% reduction in pain during or immediately after TENS than placebo. There was low certainty evidence that pain intensity was lower during TENS compared with exercise/physiotherapy or analgesic medications when they were used wholly or as part of standard/routine care (61 RCTs, 3155 participants). Adverse events were minor with no serious adverse events reported in 381 RCTs, but there was very low certainty evidence of the estimation of risk ratio of an adverse event, irrespective of severity. Consequently, we could not judge the clinical meaningfulness of these outcomes.

#### Strengths of the study

Our systematic review of 381 RCTs (24532 participants) is the most comprehensive to date and is the first to undertake an 'all-encompassing' meta-analysis. Our analysis is logical, systematic, rigorous, and transparent, and we have been judicious when interpreting the analysis using the GRADE approach.

Our estimates of effect size during or immediately after a treatment of TENS at, or close to the site of pain, is ecologically valid because symptomatic relief of pain 'in-the-moment' is of primary

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importance. In practice, patients tailor treatment regimens to match the temporal characteristics of their pain at that moment in time. Our primary endpoint accounts for confounders associated with variability of TENS techniques and regimens, such as PRN, where participants may be using TENS intermittently. Credence is given to effect size estimates of long-term follow-up, but analysis of such outcomes is complex for TENS. Often trials reports are unclear whether data was collected within an ongoing course of treatment, or after a course of TENS treatment had finished (i.e., follow-up) and this would compromise simple pooling of long-term and/or follow-up data [10]. Our analysis of outcomes during or immediately after treatment also reduces the influence of participants who stop using TENS within a prolonged course of treatment. We noted a scarcity of data at six weeks, three months, six months, and 12 months after the end of a course of TENS treatment in studies included in our review. Thus, we suspect that effect sizes for long-term and/or follow-up outcomes will be less precise than those during or immediately after a TENS treatment.

#### Weaknesses of the study

An overview of Cochrane reviews on TENS for chronic pain did not pool data from small sized trials because of concern about imprecision [11,25]. We quantified small-study effect and publication bias, although the adjusted SMD using the trim and fill method did not alter the effect size estimate for TENS versus placebo. Our meta-analyses exposed high levels of unexplained statistical heterogeneity. Valentine et al. argues that a prospective or retrospective power analysis can be of value [26], although we preferred to make inferences based on pre-specified thresholds for pooling data suggested by Moore et al. [18](i.e. >500 participants per trial arm, and credence given to Individual trial arm sample sizes of  $\geq$ 200 participants). There were insufficient studies with extractable data of at least 100 participants in the TENS group to conduct a sensitivity analysis, although removing studies with fewer than 50 participants did not affect the effect size estimates of any of our primary comparisons. The largest TENS trial arm sample size was 144 participants [27]. There is potential to undertake further analyses in the future, such as examination of confidence interval width and retrospective power analysis based on a clinically important effect size rather than the observed effect size [26]. Meta-regression and network analyses could also explore the impact of inter-study heterogeneity and the relationships between different types of comparators on outcome.

The impact of unclear reporting contributed to a high frequency of unclear risk of bias judgements and impacted negatively on the ability to categorise types of pain, the nature of comparators and whether participants used additional treatments. Remarkably few reports followed standards for

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design and reporting of TENS trials [28]. In placebo comparisons, blinding of participants was achieved using a sham TENS device (commonly without current) and pre-study briefings to create uncertainty about which intervention was functioning properly. This has been shown to be a valid method of reducing performance bias, although few of the included studies measured blinding success [29]. Contamination of effect size estimates by concurrent treatment was also an issue [30]. We decided not to use generic inverse variance to correct for paired data associated with crossover trial data because of sufficient washout periods and an overwhelming number of parallel group data points.

Most investigators reported spontaneous detection of adverse events based on ill-defined criteria resulting in very low certainty for the precision of our estimate of risk ratio. Inadequate adverse event reporting remains a concern in RCTs of non-pharmacological interventions for pain [31].

Judgements of the impact of study limitations (risk of bias), imprecision, inconsistency, indirectness, and publication bias resulted in downgrading the certainty of all effect size estimates according to GRADE criteria (supplementary file 1). Decisions to downgrade rely on judgements of the authorship team. Our decision to downgrade TENS versus placebo by only one level may be challenged. We decided that high statistical heterogeneity and possible publication bias was not sufficient enough to downgrade by two levels of evidence. Trim and fill did not alter the SMD to any appreciable degree. We did not downgrade for study limitation because sub-group analyses did not modify the effect of TENS and sensitivity analyses did not affect the overall affect size estimate. We argued that there would be low risk of blinding using sham TENS devices because their use has been shown to create uncertainty about whether a device is correctly functioning [21].

#### Strengths and weaknesses in relation to other studies

The findings of our meta-analysis are consistent with clinical experience and physiological plausibility. Since its inception over 50 years ago, clinical experience and expert opinion has remained resolute that TENS provides immediate short-term relief of pain by therapeutic neuromodulation, in a manner akin to rubbing the skin (for review see [3]). Physiological evidence demonstrates that selective activation of low threshold somatosensory peripheral afferents by TENS reduces activity and excitability of sensitised and non-sensitised central nociceptive transmission cells; and this effect does not persist far beyond the duration of stimulation [32,33]. Different frequencies of pulsed current influence central neuropharmacological actions in animal studies [34], but clinical research has failed to find relationships between electrical characteristics, type of pain

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and clinically meaningful outcome [12]. Our finding that adverse events were minor and mostly erythema and itchiness at the site of electrodes is consistent with evaluations of safety by professional bodies [35].

Previous systematic reviews and meta-analyses, including Cochrane reviews are inconsistent and/or inconclusive (for review see [3]). The 2021 NICE guidelines for chronic pain did not recommend TENS for chronic primary pain based on analyses of two RCTs on fibromyalgia [4]. The NICE excluded RCTs that had been evaluated in previous NICE guidelines (e.g., non-specific low back pain [6]), reducing the quantity of extractable data for meta-analysis. We analysed data from 20 trials that we coded as chronic primary pain according to ICD-11 and found a statistically significant overall effect in favour of TENS compared with placebo (SMD = -0.66 [-1.20, -0.29], P < 0.0004, supplementary file 1). Moreover, our finding that pain characteristics and diagnosis did not moderate the effect of TENS is of critical importance. Thus, we hope that these findings will be considered by future guideline panels.

#### Meaning of the study

Our all-encompassing analysis of RCTs provides clinicians and policy makers with evidence that TENS is efficacious at reducing the intensity of pain 'in-the-moment'. Data was extracted and combined from a variety of settings (i.e., hospital, clinic, and home) and when TENS was administered on its own or in combination with other treatments. Scrutiny of data and sub-group analyses did not suggest that these factors influence outcome to an appreciable degree.

#### Implications for clinical practice

Pain mechanisms are complex often causing uncertainty in finite diagnoses. Contemporary pain science suggests that pain acts to protect the integrity of tissue rather than monitor the status of tissue damage, i.e., hurt does not always mean harm. Our findings suggest that TENS *may* be beneficial for pain irrespective of pain characteristics or medical diagnosis, supporting the view that TENS should primarily be indicated according to symptoms i.e., the presence of pain rather than medical diagnosis. We encourage guideline panels to consider this evidence when evaluating TENS in the future. Nevertheless, we do not claim that TENS is efficacious for *all* types of pain because there were (and will never be) sufficient RCTs to judge for every pain characteristic or diagnosis.

Optimal pain management strategies adopt a biopsychosocial approach and a self-management framework to aid recovery, including return to activities of daily living and improvements in quality

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of life. Core treatment involves physical activity and psychological interventions supported by pain education and lifestyle adjustments towards healthy living. Neuromodulation techniques such as TENS are used as adjuncts to core treatment, and used to alleviate sensations of pain, muscle tension and spasm, reducing the negative impact of an 'overprotective brain'. Patients report that TENS provides indirect benefits including enhanced function, improved psychological well-being, better sleep, and medication reduction; therefore, TENS is widely accepted by patients because it is in-expensive, can be self-administered, and has no toxicity [36,37]. In clinical practice, users are advised to personalise their treatment strategy, including the electrical characteristics of currents, according to their personal needs.

Recently, Johnson [9] argued that the long-standing search for optimal TENS parameters for specific pathology-based pain conditions has been futile, and that the quality of the TENS sensation rather than specific electrical characteristics of current is the critical factor for success. Our analysis suggested that the frequency of currents does not modify outcome when a strong non-painful TENS sensation is generated within or close to the site of pain, and we suspect this would also be the case for pulse duration (width) and pulse pattern if sufficient data became available. This supports best practice guidelines to advise patients to self-administer strong non-painful TENS within or close to the site of pain, and pattern to what is most comfortable. Patients are advised to administer TENS as often as is necessary, although there is evidence that physiological tolerance may develop [38]. This does not appear to have a significant impact in clinical practice when a variety of troubleshooting strategies are used, including the use of modulated currents to create a novel input to the nervous system [39].

In summary, TENS should be considered in a similar manner to rubbing, cooling, or warming the skin to provide symptomatic relief of pain via neuromodulation. One advantage of TENS is that users can adjust electrical characteristics to produce a wide variety of TENS sensations such as pulsate and paraesthesiae to combat the dynamic nature of pain. Consequently, patients need to learn how to use a systematic process of trial and error to select electrode positions and electrical characteristics to optimise benefits and minimize problems on a moment to moment basis [40].

#### Unanswered questions and future research

Our findings should discourage publication of small sized RCTs and new systematic reviews until larger RCTs become available. For decades, systematic reviewers have called for large multicentred RCTs to resolve the efficacy-impasse. This situation is unlikely to change in the foreseeable future,

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due in part to a lack of funding [9]. We recommend the delivery of an enriched enrolment randomised withdrawal design with trial arm sample sizes greater than 200 participants to overcome methodological issues [9,28]. We suspect that such a trial would produce an effect size estimate close to our analysis of TENS versus placebo.

Our findings justify the need for pragmatic ecologically valid studies gathering real-world data about how best to integrate TENS into practice. Recently, a 30-minute TENS treatment was shown to predict longer-term outcome in women with fibromyalgia [41]. Real world data can be used to develop educational packages to train and support patients to optimise TENS treatment within a self-care model of pain management [36,37]. We did not undertake a cost-benefit analysis, although previous analyses provide evidence that TENS equipment, running costs and follow-up clinical support is inexpensive and can reduce annual costs for chronic low back pain and knee osteoarthritis [42,43].

#### Conclusions

This systematic review resolves long-term uncertainty about the efficacy of TENS. The meta-analysis provides moderate-certainty evidence that strong non-painful TENS within or close to the site of pain, produces clinically important reductions in the intensity of pain during or immediately after treatment, with no reports of serious adverse events. Clinicians, policy makers and funders should consider TENS as an adjunct to core treatment for immediate-short-term relief of pain, irrespective of diagnosis. Patients should be advised to tailor TENS treatment according to their individual needs.

Author contributions

Based on CRediT (Contributor Roles Taxonomy) http://credit.niso.org/

- Conceptualization: MIJ
- Data curation: MIJ, PGW, CAP (GJ cross checking)
- Formal Analysis: MIJ, PGW, CAP, MRM, GJ
- Funding acquisition: MIJ
- Investigation: MIJ, PGW, CAP, MRM, GJ
  - Development and delivery of search strategy: PGW, MIJ
  - Screening for eligibility: PGW, MIJ (CAP and GJ as arbiters)
  - Data extraction: MIJ, PGW, (CAP, GJ cross checking)
  - Assessment of risk of bias: MIJ, CAP, (PGW as arbiter)
  - Assessment of adverse events: MIJ, CAP, PGW
  - Assessment of effects of interventions: MIJ, PGW, CAP (GJ and MRM arbiters)
  - Assessment of publication bias: MRM, PGW, MIJ
  - GRADE assessment against criteria: MIJ, CAP (PGW, GJ as arbiters)
  - Overall GRADE judgement: MIJ, CAP, PGW, MRM, GJ
  - o Interpreting the results: MIJ, PGW, CAP, MRM, GJ
- Methodology (Protocol development): MIJ, PGW, CAP, GJ
- Project administration: MIJ
- Resources: MIJ
- Software: MIJ, MRM
- Supervision: MIJ
- Validation: MIJ
- Visualization: MIJ
- Writing original draft: MIJ
- Writing review & editing: MIJ, PGW, CAP, GJ, MRM

All authors had access to the data and took responsibility for the integrity of the data and the accuracy of the data analysis. All authors approved the final version of the review.

Data sharing: Extracted data is available on request from Prof. Mark I. Johnson

Transparency declaration: I (Prof. Mark I. Johnson) affirm that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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Competing interests: All authors have completed the ICMJE uniform disclosure form and declare the following:

## Prof. Mark I. Johnson (taken from ICMJE form)

Dr. Johnson reports grants from GlaxoSmithKline, during the conduct of the study; other from GlaxoSmithKline, other from TENSCare, other from Actegy Ltd , personal fees from Oxford University Press, other from LifeCare Ltd, other from GlaxoSmithKline, other from Eurocept Pharmaceuticals,

outside the submitted work; and I was involved in conducting the following studies that were considered for inclusion in the work submitted for publication

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Drs Carole A. Paley, Gareth Jones, Mathew R. Mulvey and Priscilla G. Wittkopf declare no competing interests

Patient and public involvement: There was no patient or public involvement in any aspect of this study or its write-up.

Patient consent for publication: Not required.

Ethics Statement: Not applicable/No human participants included

Dissemination to participants and related patient and public communities: We plan to disseminate our findings to patient organisations and media outlets.

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# FIGURE LEGENDS

# Figure 1

PRISMA Flow Chart

# Figure 2

Methodological quality graph: review authors' judgments about each methodological quality item presented as percentages across all included studies.

# Figure 3

Summary of standardised mean difference (SMD) and 95% confidence intervals (95%CI) of pain intensity for intervention comparisons and main subgroup group analyses of risk of bias (RoB) and trial arm size.

## Figure 4

Summary of subgroup group analyses of type of pain for the standardised mean difference (SMD) and 95 % confidence intervals (95%CI) of pain intensity between TENS and placebo. RCTs; randomised controlled trials.

## Figure 5

Forest plot of subgroup group analyses of diagnoses for the standardised mean difference (SMD) and 95 % confidence intervals (95%CI) of pain intensity between TENS and placebo. RCTs; randomised controlled trials.

## SUPPLEMENTARY MATERIALS

# Supplementary file 1 (File: SF1\_MetaTENS\_SuppMaterial\_File1\_BMJO\_06-10-2021.docx)

Supplementary material providing details of all operational processes associated with our systematic review and meta-analysis including methods, data analyses and interpretation of findings.

## Supplementary file 2 (File: SF2\_TABLE\_SF2\_IncludedStudies.pdf)

Summary of the characteristics of the included randomised controlled trials

## Supplementary file 3 (File: SF3\_TABLE\_SF3\_AwaitingClassification.pdf)

Studies awaiting classification

# Supplementary file 4 (File: SF4\_TABLE\_SF4\_ExcludedStudies.pdf)

Summary of the reasons for excluding studies

## Supplementary file 5 (File: SF5\_Fig\_SF5\_SUBMIT.pdf)

Forest plot of standardised mean difference (SMD) and 95% confidence intervals (95%CI) of pain intensity rating between TENS and placebo with subgroup group analysis of risk of bias (RoB)

## Supplementary file 6 (File: SF6\_Fig\_SF6\_SUBMIT.pdf)

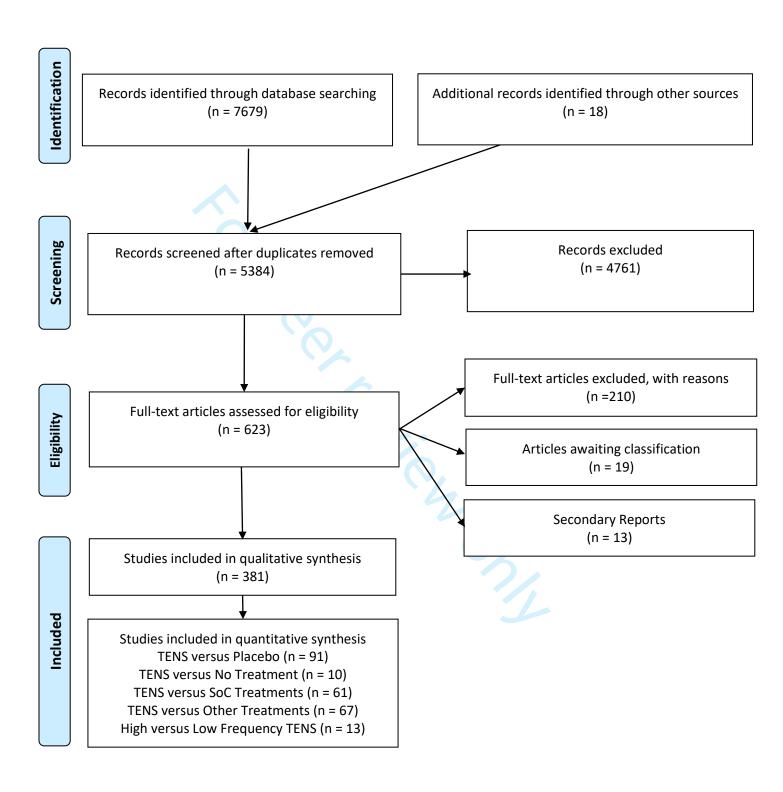
Forest plot of standardised mean difference (SMD) and 95% confidence intervals (95%CI) of pain intensity rating between TENS and placebo with subgroup group analysis of acute versus chronic pain

# Supplementary file 7 (File: SF7\_TABLE\_SF7\_AdverseEvents.pdf)

Summary of the characteristics of TENS-related adverse events

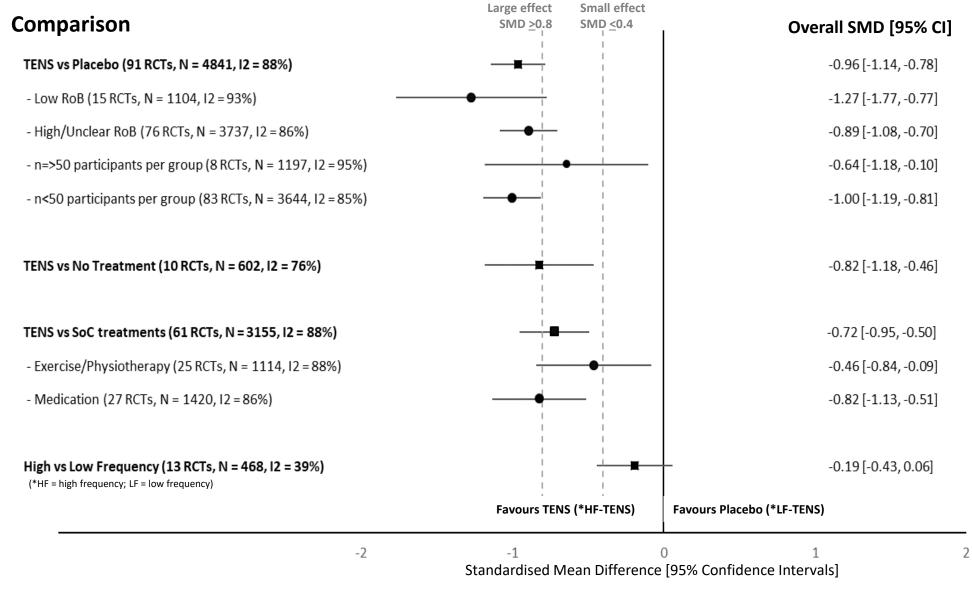
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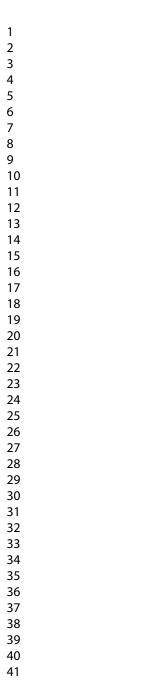
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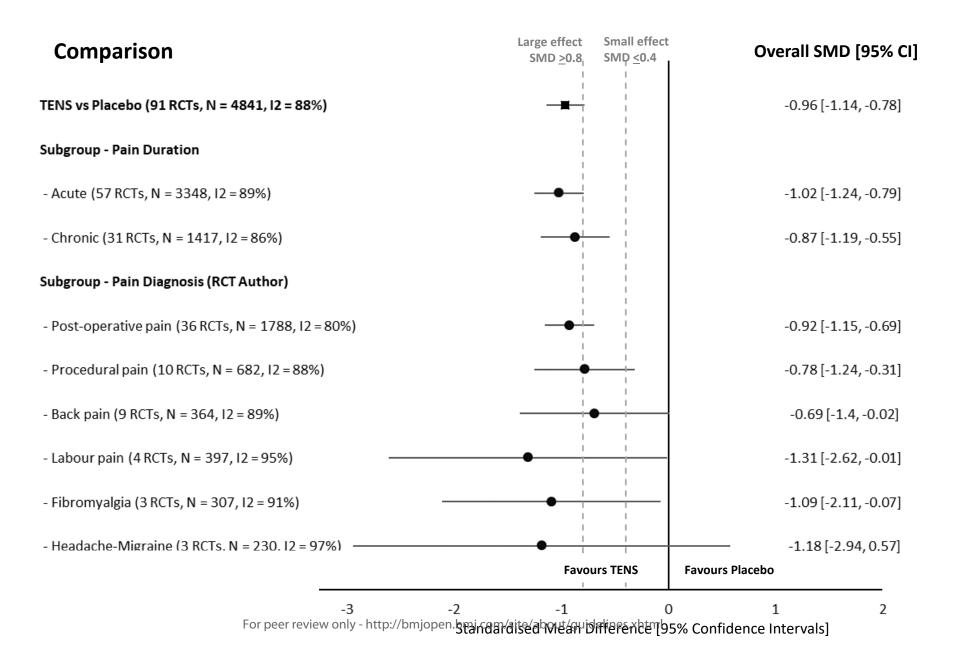
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#### **Supplementary Material**

# 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

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# SECTION 1 – SUPPLEMENTARY DETAILS OF METHODS

The protocol for this study has been published [1] and is available from <a href="https://bmjopen.bmj.com/content/9/10/e029999">https://bmjopen.bmj.com/content/9/10/e029999</a>. 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.

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- 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
- 58 59 60

## **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).

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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.

BMJ Open

## 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60

## 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

 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

**BMJ** Open

- 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
    - $\circ$  Age, gender
    - Pain diagnosis, duration of pain and symptoms
- Sample size
- Active and comparator groups
  - o 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
  - о Туре
  - $\circ$  Time points used, including follow-up
  - Withdrawals
  - Adverse and serious adverse effects
  - o Other
- Sponsorship, country of origin, conflict of interest statements.

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# 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 decisionmaking 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.

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## 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
  - $\circ$   $\;$  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)
  - o 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  $\ge 20\%$  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 prespecified 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  $\ge$  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

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# • 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

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### Cochrane RoB aide memoire annotated for our study on TENS

#### **RANDOM SEQUENCE GENERATION**

Selection bias (biased allocat sequence.	ion to interventions) due to inadequate generation of a randomised							
Criteria for a judgement of 'Low risk' of bias.	The investigators describe a random component in the sequence generation process such as:							
	<ul> <li>Referring to a random number table;</li> </ul>							
	<ul> <li>Using a computer random number generator;</li> </ul>							
	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:							
	<ul> <li>Sequence generated by odd or even date of birth;</li> </ul>							
	<ul> <li>Sequence generated by some rule based on date (or day) of admission;</li> </ul>							
	<ul> <li>Sequence generated by some rule based on hospital or clinic record number.</li> </ul>							
	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:							
	<ul> <li>Allocation by judgement of the clinician;</li> </ul>							
	<ul> <li>Allocation by preference of the participant;</li> </ul>							
	<ul> <li>Allocation based on the results of a laboratory test or a series of tests;</li> </ul>							
	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:

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	<ul> <li>Central allocation (including telephone, web-based and pharmacy-controlled randomization);</li> </ul>
	<ul> <li>Sequentially numbered drug containers of identical appearance;</li> </ul>
	• 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:
	<ul> <li>Using an open random allocation schedule (e.g., a list of random numbers);</li> </ul>
	<ul> <li>Assignment envelopes were used without appropriate safeguards (e.g., if envelopes were unsealed or nonopaqu or not sequentially numbered);</li> </ul>
	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.	<ul> <li>Any one of the following:</li> <li>No blinding or incomplete blinding, but the review authors judge that the outcome is not likely to be influenced by lack of blinding;</li> <li>Blinding of participants and key study personnel ensured, and unlikely that the blinding could have been broken.</li> <li>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.</li> </ul>
Criteria for the judgement of 'High risk' of bias.	<ul> <li>Any one of the following:</li> <li>No blinding or incomplete blinding, and the outcome is likely to be influenced by lack of blinding;</li> </ul>

Criteria for the judgement of 'Unclear risk' of bias.	<ul> <li>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.</li> <li><i>High = Statement that not blinded; or statements suggesting definitely not blinded</i></li> <li>Any one of the following:         <ul> <li>Insufficient information to permit judgement of 'Low risk' or</li> </ul> </li> </ul>
	<ul> <li>'High risk';</li> <li>The study did not address this outcome.</li> </ul> Unclear = No statement; or blinding inferred but not directly stated
	oncieur – No statement, or binning injerred bat not directly stated
	BLINDING OF PERSONNEL
Performance bias due to kno during the study.	wledge of the allocated interventions by participants and personnel
Criteria for a judgement of 'Low risk' of bias.	<ul> <li>Any one of the following:</li> <li>No blinding or incomplete blinding, but the review authors judge that the outcome is not likely to be influenced by lack of blinding;</li> <li>Blinding of participants and key study personnel ensured, and unlikely that the blinding could have been broken.</li> <li>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.</li> </ul>
Criteria for the judgement of 'High risk' of bias.	<ul> <li>Any one of the following:</li> <li>No blinding or incomplete blinding, and the outcome is likely to be influenced by lack of blinding;</li> <li>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.</li> <li>High = Statement that not blinded; or statements suggesting definitely not blinded</li> </ul>
Criteria for the judgement of 'Unclear risk' of bias.	<ul> <li>Any one of the following:</li> <li>Insufficient information to permit judgement of 'Low risk' o 'High risk';</li> <li>The study did not address this outcome.</li> </ul> Unclear = No statement; or blinding inferred but not directly stated

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

	to have a clinically relevant impact on the intervention effect estimate;
	<ul> <li>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;</li> </ul>
	<ul> <li>Missing data have been imputed using appropriate methods.</li> </ul>
Criteria for the judgement	Any one of the following:
of 'High risk' of bias.	<ul> <li>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;</li> </ul>
	<ul> <li>For dichotomous outcome data, the proportion of missing outcomes compared with observed event risk enough to induce clinically relevant bias in intervention effect estimate;</li> </ul>
	<ul> <li>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;</li> </ul>
	• 'As-treated' analysis done with substantial departure of the intervention received from that assigned at randomization;
	<ul> <li>Potentially inappropriate application of simple imputation.</li> </ul>
Criteria for the judgement	Any one of the following:
of 'Unclear risk' of bias.	<ul> <li>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);</li> </ul>
	• The study did not address this outcome.
	SELECTIVE REPORTING
Reporting bias due to selecti	ve outcome reporting.
Criteria for a judgement of	Any of the following:
'Low risk' of bias.	<ul> <li>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;</li> </ul>
	• 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	Any one of the following:
of 'High risk' of bias.	<ul> <li>Not all of the study's pre-specified primary outcomes have been reported;</li> </ul>
	-

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Criteria for the judgement of 'Unclear risk' of bias.	<ul> <li>One or more primary outcomes is reported using measurements, analysis methods or subsets of the data (e.g., subscales) that were not pre-specified;</li> <li>One or more reported primary outcomes were not prespecified (unless clear justification for their reporting is provided, such as an unexpected adverse effect);</li> <li>One or more outcomes of interest in the review are reported incompletely so that they cannot be entered in a meta-analysis;</li> <li>The study report fails to include results for a key outcome that would be expected to have been reported for such a study.</li> <li>Insufficient information to permit judgement of 'Low risk' or 'High risk'. It is likely that the majority of studies will fall into this category.</li> </ul>
	risk' as study protocol is not available, and/or suspected study's primary and secondary outcomes were not pre-specified and/or or or more outcomes of interest in the review are reported incompletely so that they cannot be entered in a meta-analysis
	incompletely so that they cannot be entered in a meta-analysis
	SAMPLE SIZE
Criteria for a judgement of 'Low risk' of bias.	
	SAMPLE SIZE         Sample size $\geq$ 200 participants in trial arm of the primary TENS
'Low risk' of bias. Criteria for the judgement	SAMPLE SIZE         Sample size ≥ 200 participants in trial arm of the primary TENS comparison         Sample size <50 participants in trial arm of the primary TENS
<ul><li>'Low risk' of bias.</li><li>Criteria for the judgement of 'High risk' of bias.</li><li>Criteria for the judgement</li></ul>	SAMPLE SIZE Sample size ≥ 200 participants in trial arm of the primary TENS comparison Sample size <50 participants in trial arm of the primary TENS comparison Sample size = 50-199 participants in trial arm of the primary TENS comparison
<ul><li>'Low risk' of bias.</li><li>Criteria for the judgement of 'High risk' of bias.</li><li>Criteria for the judgement</li></ul>	SAMPLE SIZE         Sample size ≥ 200 participants in trial arm of the primary TENS comparison         Sample size <50 participants in trial arm of the primary TENS comparison
<ul><li>'Low risk' of bias.</li><li>Criteria for the judgement of 'High risk' of bias.</li><li>Criteria for the judgement</li></ul>	SAMPLE SIZE Sample size ≥ 200 participants in trial arm of the primary TENS comparison Sample size <50 participants in trial arm of the primary TENS comparison Sample size = 50-199 participants in trial arm of the primary TENS comparison
'Low risk' of bias. Criteria for the judgement of 'High risk' of bias. Criteria for the judgement of 'Unclear risk' of bias. Criteria for a judgement of	SAMPLE SIZE         Sample size ≥ 200 participants in trial arm of the primary TENS comparison         Sample size <50 participants in trial arm of the primary TENS comparison
'Low risk' of bias. Criteria for the judgement of 'High risk' of bias. Criteria for the judgement of 'Unclear risk' of bias. Criteria for a judgement of	SAMPLE SIZE         Sample size ≥ 200 participants in trial arm of the primary TENS comparison         Sample size <50 participants in trial arm of the primary TENS comparison

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 carryo	ver 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.
igure A1 Risk of bias criteria.	
igure A1 Risk of bias criteria.	
igure A1 Risk of bias criteria.	
igure A1 Risk of bias criteria.	
igure A1 Risk of bias criteria.	
igure A1 Risk of bias criteria.	
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igure A1 Risk of bias criteria.	
igure A1 Risk of bias criteria.	
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igure A1 Risk of bias criteria.	
igure 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 <a>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  $\geq 10$  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  $\geq 50\%$  [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
- <u>></u>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 metaanalysis 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<sup>2</sup> statistic and the Chi<sup>2</sup> test [18]. We used the Cochrane Collaboration's rough guide to interpretation and graded heterogeneity as:

- Not important (I<sup>2</sup> = 0% to 40%)
- Moderate (I<sup>2</sup> = 30% to 60%)
- Substantial (I<sup>2</sup> = 50% to 90%)
- Considerable (I<sup>2</sup> = 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

- 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

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

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### **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 10/383 samples 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 postpartum 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 selfadministered 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 <u>m.johnson@leedsbeckett.ac.uk</u> on request.

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

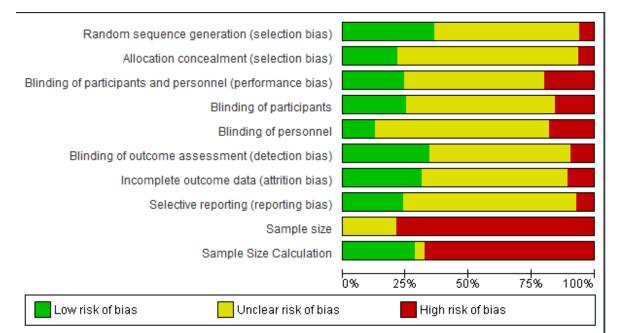


Figure A2 Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

### **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 ( $\geq$ 200 participants in the TENS arm). There were 13/381 RCTs that used  $\geq$ 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 + 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

#### BMJ Open

### MetaTENS\_Appendix\_BMJO\_05-10-2021 – Supplementary File 1

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Study or Subgroup	Mean	TENS SD	Total		lacebo SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI	Std. Mean Difference IV, Random, 95% Cl
2.2.1 Whole Data									
Barbarisi, et al., 2010	25.11	0.92	9	39	1.19	8	0.1%	-12.50 [-17.39, -7.61]	٩
Cipriano, et al., 2014 More, et al., 2006	10	5 16	20	80	30	18	0.9%	-3.27 [-4.28, -2.27]	
Mora, et al., 2006 Hokenek et al., 2019 (1)	33.3 22	16 12.49	39 39	82.6 72	14.3 18.7	34 39	1.1% 1.1%	-3.20 [-3.91, -2.50] -3.11 [-3.78, -2.44]	
Lauretti, et al., 2015	20	12.49	39 20	70	20	39 20	1.0%	-3.10 [-4.05, -2.15]	
Ekim et al., 2008 (2)	47.2	5.6	10	65.3	6.3	20	0.8%	-2.91 [-4.29, -1.54]	
Bertalanffy, et al., 2005	49	8	30	77	11	33	1.1%	-2.85 [-3.57, -2.14]	
Tokuda, et al., 2014 (3)	5.9	6.5	16	23.8	5.9	16	0.9%	-2.81 [-3.82, -1.80]	
Shahoei, et al., 2017 (4)	49	25	30	97	5.9	30	1.1%	-2.61 [-3.31, -1.91]	
Ahmed, et al., 2010 Review et al., 2009	49.3	7	30 29	66.1	6.9	30	1.1%	-2.39 [-3.06, -1.71]	
Barker, et al., 2006 Lang, et al., 2007	32.4 59	18 6	29	66.2 79	11.2 11	33 33	1.1% 1.1%	-2.26 [-2.91, -1.61] -2.20 [-2.83, -1.57]	
Desantana, et al., 2008 (5)	9	10.7	20	48	22.7	20	1.1%	-2.15 [-2.95, -1.36]	
Kim, et al., 2012 (6)	19	12	50	48	15	50	1.2%	-2.12 [-2.61, -1.63]	
Dailey, et al., 2013 (7)	40	4	41	47	4	41	1.2%	-1.73 [-2.24, -1.22]	
Kimbar et al., 2020 (8)	21.2	12.2	31	47.6	19.6	30	1.2%	-1.60 [-2.18, -1.02]	
Baez-Suarez, et al., 2018	62	14	21	83	12	21	1.1%	-1.58 [-2.28, -0.88]	
Desantana, et al., 2009 (9)	43	15.3	23	66.5	14.7	21	1.1%	-1.54 [-2.22, -0.86]	
Jaafarpour, et al., 2008 Cheing & Luk, 2005	5 17	5 17	54 10	12 46	4.2 20	54 9	1.2% 0.9%	-1.51 [-1.93, -1.08] -1.50 [-2.55, -0.45]	
Zhang et al., 2020a (10)	17	3	10	31	12.6	10	0.9%	-1.46 [-2.48, -0.45]	
Amer-Cuenca, et al., 2011	26.5	24.7	30	61.9	23.2	30	1.2%	-1.46 [-2.03, -0.88]	
Sadala, et al., 2018	29.3	19.5	28	56.8	17.7	27	1.2%	-1.45 [-2.05, -0.86]	
De Oliverira et al., 2012 (11)	30	16.4	5	54	13.6	5	0.7%	-1.44 [-2.92, 0.04]	
Park, et al., 2015 (12)	15	15	48	45	25	50	1.2%	-1.44 [-1.88, -0.99]	
Bi, et al., 2015 Topuz, et al., 2004	21.4	9.1	26	38.7	14.5	26	1.2%	-1.41 [-2.02, -0.80]	
Topuz, et al., 2004 Celik, et al., 2013	37.3 38.8	16.2 25	15 17	59.1 67.7	13.7 14.2	12 16	1.0% 1.1%	-1.40 [-2.25, -0.54] -1.38 [-2.14, -0.61]	
Ordog, 1987 (13)	30.4	2.8	25	54.8	25	25	1.1%	-1.35 [-1.97, -0.73]	
Luchesa, et al., 2009 (14)	5	2.0	15	21	15.4	15	1.1%	-1.33 [-2.13, -0.53]	
Cipriano, et al., 2008 (15)	20	7.4	23	30	7.4	22	1.1%	-1.33 [-1.98, -0.68]	——
Lauretti, et al., 2013 (16)	60	10	13	80	20	10	1.0%	-1.28 [-2.19, -0.36]	<u> </u>
Mahure, et al., 2017 (17)	36	21	15	58	12	15	1.1%	-1.25 [-2.04, -0.46]	—— I
Kayman-Kose, et al., 2014 (18)	17.7	12.7	50	37.4	20.6	50	1.2%	-1.14 [-1.57, -0.72]	
Lison, et al., 2017 (19) Liu, et al., 1985 (20)	23.2 39.3	31.4 17.9	46 15	53.1 65.3	19.9 26.6	46 15	1.2% 1.1%	-1.13 [-1.57, -0.69] -1 12 [-1 89 -0 34]	
Liu, et al., 1985 (20) Cuschieri, et al., 1987 (21)	39.3 30	17.9	10	65.3 49	20.0	10	1.1%	-1.12 [-1.89, -0.34] -1.11 [-2.07, -0.15]	
Emmiler, et al., 2008	24	11.8	20	39	14.8	20	1.1%	-1.10 [-1.77, -0.43]	<u> </u>
Abreu, et al., 2010 (22)	68	23	10	88	10	10	1.0%	-1.08 [-2.03, -0.13]	
Chandra, et al., 2010	7	5.3	30	14.7	8.6	30	1.2%	-1.06 [-1.61, -0.52]	
Pitangui, et al., 2014 (23)	17.2	21.9	11	38.8	20.8	10	1.0%	-0.97 [-1.89, -0.05]	
Yilmaz et al., 2019 (24)	7.3	9.8	26	20	15.7	26	1.2%	-0.96 [-1.53, -0.38]	
Aminisaman et al., 2020 Suh, et al., 2015	26.6 18.7	5.4 7.46	30 24	31.2 30.7	4.8 17.67	30 23	1.2% 1.2%	-0.89 [-1.42, -0.36] -0.88 [-1.48, -0.28]	
Oncel, et al., 2002 (25)	24	13	25	39	20	25	1.2%	-0.88 [-1.46, -0.29]	
Elboim et al., 2020 (26)	41.7	19.2	23	61.2	25	18	1.1%	-0.87 [-1.52, -0.22]	
Neighbours, et al., 1987 (27)	17.5	30.3	10	40.7	20.74	10	1.0%	-0.86 [-1.78, 0.07]	
Zakariaee et al., 2019 (28)	31.8	20.4	40	47.5	16.5	40	1.2%	-0.84 [-1.30, -0.38]	
Domaille & Reeves, 1997 (29)	30.33	8.14	31	47	28.14	29	1.2%	-0.81 [-1.33, -0.28]	
Fiorelli, et al., 2012 (30)	39	8	23	45	7	23	1.2%	-0.78 [-1.39, -0.18]	
Mansuri, et al., 2019 (31) Bjersa, et al., 2015 (32)	26.67 10	22.57 13	15 15	45.33 23	26.15 21	15 13	1.1% 1.1%	-0.74 [-1.49, 0.00] -0.74 [-1.51, 0.04]	
Likar et al. 2001 (33)	25.1	7.6	11	29.7	4.8	12	1.0%	-0.70 [-1.55, 0.14]	
Vitalii & Oleg, 2014	39.5	17	11	52.5	18.6	10	1.0%	-0.70 [-1.59, 0.19]	
Warfield, et al., 1985 (34)	48.3	20.1	12	64.2	24.6	12	1.0%	-0.68 [-1.51, 0.14]	
Bilgili, et al., 2016	14.27	10.1	15	23.27	15.8	15	1.1%	-0.66 [-1.40, 0.08]	
Fujii-Abe et al., 2019 (35)	22.1	12.8	11	30.3	11.2	11	1.0%	-0.66 [-1.52, 0.21]	
Shimoura, et al., 2019 (36)	5.1	8	25	11.4	10.9	25	1.2%	-0.65 [-1.22, -0.08]	
Bjersa & Andersson, 2014	19.4	32.5	9	39.6	32	11	1.0%	-0.60 [-1.51, 0.30]	
Sezen, et al., 2017 (37) Liu, et al., 2017 (38)	36.9 48.2	7.2 17.7	43 22	42 55.8	10.1 12.6	44 22	1.2% 1.2%	-0.58 [-1.00, -0.15] -0.49 [-1.09, 0.11]	
Grimmer, 1992 (39)	40.2	28	20	35	29	20	1.1%	-0.45 [-1.08, 0.18]	
Galli, et al., 2015	21	16	37	29	22	37	1.2%	-0.41 [-0.87, 0.05]	
Ferreira, et al., 2011 (40)	18	18	15	25	18	15	1.1%	-0.38 [-1.10, 0.34]	+
Rakel & Frantz, 2003 (41)	42	33.45	33	55	37.3	33	1.2%	-0.36 [-0.85, 0.12]	+
Dailey et al., 2020 (42)	46	20	103	53	19.9	99	1.3%	-0.35 [-0.63, -0.07]	
Warke, et al., 2004 (43)	28.25	36.5		40.33	19.4	3	0.7%	-0.33 [-1.78, 1.12]	
Hruby, et al., 2006 (44) Robinson, et al., 2001	35	28.8	48	43.7	30.6	49	1.2%	-0.29 [-0.69, 0.11]	
Robinson, et al., 2001 Hamza, et al., 1999 (45)	38.2	31.24 23	10 25	47.92 31	36.37 25	13 25	1.0% 1.2%	-0.27 [-1.10, 0.56] -0.25 [-0.80, 0.31]	
Hamza, et al., 1999 (45) Machin, et al., 1988	13.47	13.72		31 16.29	25 13.65	∠5 15	1.2%	-0.20 [-0.92, 0.52]	
Moore & Shurman, 1997 (46)	40.58	27.55	24	44.81	30.67	24	1.2%	-0.14 [-0.71, 0.42]	_ <del>_</del>
Cuschieri, et al., 1985 (47)	25	21.8	53	28	21.8	53	1.3%	-0.14 [-0.52, 0.24]	<del>_+</del>
Forster, et al., 1994 (48)	9.8	28.1	15	13.7	31.9	15	1.1%	-0.13 [-0.84, 0.59]	<u> </u>
Shimoji, et al., 2007 (49)	38	15	9	40	20	8	1.0%	-0.11 [-1.06, 0.84]	
Graff-Radford, et al., 1989 (50)		18.06	12	30.2		12	1.1%	-0.11 [-0.91, 0.69]	_ <del>_</del> _
Yilmazer, et al., 2012 (51)	54.6	32.1	33	57.5	30.5	32	1.2%	-0.09 [-0.58, 0.40]	-+
Sahin, et al., 2011 Thomas, et al., 1988 (52)	68.5	15.5	19	69.5 35	11.5	19	1.1%	-0.07 [-0.71, 0.56] -0.06 [-0.30, 0.18]	
Thomas, et al., 1988 (52) Presser, et al., 2000 (53)	33 47	31.1 38.34	131 30	35 49	33.8 27.39	144 30	1.3% 1.2%	-0.06 [-0.30, 0.18] -0.06 [-0.57, 0.45]	_ <u></u>
Presser, et al., 2000 (53) Ilhani, 2015 (54)	22.4	38.34 11.3	30	49 22.8	10.2	30	1.2%	-0.04 [-0.52, 0.45]	
Tucker, et al., 2015 (55)	56	56	35	57	57	35	1.2%	-0.02 [-0.49, 0.45]	<u> </u>
Bono, et al., 2015	80	20	54	80	20	54	1.3%	0.00 [-0.38, 0.38]	+
Da Silva, et al., 2015 (56)	1	0	21	4	0	21		Not estimable	
Machado et al., 2019 (57)	47	25	22	46	22	22	1.2%	0.04 [-0.55, 0.63]	_ <del></del>
Lee, et al., 2015	55.6	9.2	18	54.4	12.9	18	1.1%	0.10 [-0.55, 0.76]	- <del> </del>
Atamaz, et al., 2012 Silve, et al., 2012 (50)	54.7	24.1	37	50.4	20.3	37	1.2%	0.19 [-0.27, 0.65]	<u>+-</u>
Silva, et al., 2012 (58) Reclavée, et al., 2019	22.5	11.5 26.1	21	20	12.5	21	1.2%	0.20 [-0.40, 0.81]	
Beckwée, et al., 2018 Siqueira et al., 2019 (59)	39.2 2.92	25.1 6.6	25 13	30.6 0.7	23.2 1.6	28 14	1.2% 1.1%	0.35 [-0.19, 0.90] 0.46 [-0.31, 1.22]	
Kofotolis, et al., 2008	2.92	6.6	23	20	4	21	1.1%	0.49 [-0.31, 1.22]	<u> </u>
Kayman-Kose, et al., 2008	13.5	5.8	50	7.8	7	50	1.2%	0.88 [0.47, 1.29]	
Subtotal (95% CI)		0.0	2426				100.0%	-0.96 [-1.14, -0.78]	♦
Heterogeneity: Tau <sup>2</sup> = 0.64; Chi <sup>2</sup> = Test for overall effect: Z = 10.37 (P			(P < 0.	00001)	<b>2</b> = 88'				
	0.00					2445	100.0%	0.061444.030	
Total (DEV, Ch								-0.96 [-1.14, -0.78]	
Total (95% CI) Heterogeneity: Tau <sup>2</sup> = 0.64; Chi <sup>2</sup> =	733.33	df = 90	2426 (P ≤ 0	000045	2 = 000		100.070	-0.50 [-1.14, -0.10]	-4 -2 0 2

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.,  $\geq 6$  low RoB items out of a total of 9 items). The test for subgroup differences was not statistically significant (Chi<sup>2</sup> = 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

Ch. 1 C. 1		ENS	Tetal	Placeb		Maint -	Std. Mean Difference	Std. Mean Difference	
Study or Subgroup 2.3.1 Low RoB - 6 or more low R	Mean oB items	SD	Total	Mean S	) Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI	_
Mora, et al., 2006 Bertalanffy, et al., 2005	33.3 49	16 8	39 30	82.6 14. 77 1		1.1% 1.1%	-3.20 [-3.91, -2.50] -2.85 [-3.57, -2.14]		
land at al 2007	49	6	30	79 1	1 33 1 33	1.1%	-2.85 [-3.57, -2.14] -2.20 [-2.83, -1.57]		
Desantana, et al., 2008 (1) Dailey, et al., 2013 (2)	9	10.7	20	48 22.	7 20	1.1%	-2.15 (-2.95, -1.36)		
Dailey, et al., 2013 (2) Beez Russez, et al., 2010	40	.4	41	47	4 41	1.2%	-1.73 [-2.24, -1.22]		
Baez-Suarez, et al., 2018 Desantana, et al., 2009 (3)	62 43	14 15 3	21 23	83 1 66.5 14	2 21	1.1%	-1.58 [-2.28, -0.88] -1.54 [-2.22, -0.86]		
Desantana, et al., 2009 (3) Amer-Cuenca, et al., 2011	26.5	15.3 24.7	23 30	61.9 23.	2 30	1.2%	-1.54 [-2.22, -0.86] -1.46 [-2.03, -0.88]		
Park, et al., 2015 (4)	15 23.2	15 31.4	48 46	45 2	5 50 9 46	1.2%	-1.44 [-1.88, -0.99] -1.13 [-1.57, -0.69]		
Lison, et al., 2017 (5) Galli, et al., 2015	23.2	31.4	46	53.1 19. 29 2	9 40 2 37	1.2%	-0.41 [-0.87, 0.05]		
Dailey et al., 2020 (6)	46	20	103	53 19.	9 99	1.3%	+0.35 [+0.63, +0.07]		
Machado et al., 2019 (7) Atamaz, et al., 2012	47 54.7	25 24.1	22 37	46 2 50.4 20.	2 22 3 37	1.2% 1.2%	0.04 [-0.55, 0.63] 0.19 [-0.27, 0.65]		
Beckwée, et al., 2012	39.2	24.1	25	30.6 23.	2 28	1.2%	0.35 (-0.19, 0.90)		
Beckwée, et al., 2018 Subtotal (95% CI) Heterogeneity: Tau# = 0.89; Chi#:			552		552	1.2% 17.5%	0.35 [-0.19, 0.90] -1.27 [-1.77, -0.77]	◆	
Test for overall effect: Z = 4.97 (P	< 0.00001 < 0.00001	ar= 14 1)	(P < 0.)	00001), P= 1	3%				
2.3.2 High-Unclear 5 or more hig									
Barbarisi, et al., 2010 Cinriano, et al., 2014	25.11 10	0.92	9 20	39 1.1 80 3	98 118	0.1%	-12.50 [-17.39, -7.61] -3.27 [-4.28, -2.27]	' <u> </u>	
Cipriano, et al., 2014 Hokenek et al., 2019 (8)	22	12.49	39	72 18	7 39	1.1%	-3.11 [-3.78, -2.44]		
Lauretti, et al., 2015	20	10	20 10	70 2	0 20	1.0%	-3.10 F4.052.15	[	
Ekim et al., 2008 (9) Tokuda, et al., 2014 (10)	47.2 5.9	5.6 6.5	10 16	65.3 6. 23.8 5.	9 16	0.8% 0.9%	-2.91 [-4.29, -1.54] -2.81 [-3.82, -1.80]		
Shahoei, et al., 2017 (11)	49	25	30	97 5.	9 30	1.1%	-2.61 [-3.31, -1.91]		
Ahmed, et al., 2010	49.3	7	30	66.1 6.	9 30	1.1%	-2.61 [-3.31, -1.91] -2.39 [-3.06, -1.71] -2.26 [-2.91, -1.61]		
Barker, et al., 2006 Kim, et al., 2012 (12)	32.4 19	18 12	29 50	66.2 11. 48 1	2 33 5 50	1.1% 1.2%	-2.26 [-2.91, -1.61] -2.12 [-2.61, -1.63]	I	
Kimbar et al., 2020 (13)	21.2	12.2	31	47.6 19.	6 30	1.2%	-2.12 [-2.61, -1.63] -1.60 [-2.18, -1.02] -1.51 [-1.93, -1.08]		
Jaafarpour, et al., 2008 Chaing 8 July 2005	5 17	5	54	12 4.	2 54	1.2%	-1.51 [-1.93, -1.08]		
Cheing & Luk, 2005 Zhang et al., 2020a (14)	17	3	10 10	46 2 31 12	6 10	0.9%	-1.50 [-2.55, -0.45] -1.46 [-2.48, -0.45] -1.45 [-2.05, -0.86]		
Sadala, et al., 2018	29.3	19.5	28	56.8 17	7 27	1.2%	-1.45 [-2.05, -0.86]		
De Oliverira et al., 2012 (15) Bi. et al., 2015	30 21.4	16.4	5 26	54 13.	6 5	0.7%	-1.44 [-2.92, 0.04]		
Bi, et al., 2015 Topuz, et al., 2004	21.4 37.3	9.1 16.2	15	38.7 14. 59.1 13.	7 12	1.2% 1.0%	-1.44 [-2.92, 0.04] -1.41 [-2.02, -0.80] -1.40 [-2.25, -0.54]		
Celik, et al., 2013	38.8	25	17 25	67.7 14.	2 16	1.1%	-1.38 (-2.14, -0.61)	——	
Ordog, 1987 (16)	30.4	2.8	25	54.8 2	5 25	1.1%	-1.35 [-1.97, -0.73]		
Luchesa, et al., 2009 (17) Cipriano, et al., 2008 (18)	5 20	6 7.4	15 23	21 15. 30 7.	4 15	1.1% 1.1%	-1.33 [-2.13, -0.53]		
Lauretti, et al., 2013 (19) Mahure, et al., 2017 (20)	60	10	23 13	80 2	0 10	1.0%	-1.33 [-1.98, -0.68] -1.28 [-2.19, -0.36]		
Mahure, et al., 2017 (20)	36	21	15	58 1	2 15	1.1%	-1.25 [-2.04, -0.46]		
Kayman-Kose, et al., 2014 (21) Liu, et al., 1985 (22)	17.7 39.3	12.7 17.9	50 15	37.4 20.	6 50 6 15	1.2%	-1.14 [-1.57, -0.72] -1.12 [-1.89, -0.34]		
Cuschieri, et al., 1987 (23)	30	11.25	10	49 20.2	5 10	1.0%	-1.11 F-2.070.15		
Emmiler, et al., 2008	24	11.8	20 10	39 14.	B 20	1.1%	-1.10 [-1.77, -0.43] -1.08 [-2.03, -0.13]		
Abreu, et al., 2010 Chandra, et al., 2010	68 7	23 5.3	10 30	88 1 14.7 8	0 10 6 30	1.0%	-1.08 [-2.03, -0.13] -1.06 [-1.61, -0.52]		
Pitangui, et al., 2014 (24)	17.2	21.9	11 26	38.8 20.	5 30 8 10 7 26	1.0%	-0.97 [-1.89, -0.05] -0.96 [-1.53, -0.38]		
Yilmaz et al., 2019 (25)	7.3	9.8	26	20 15	7 26	1.2%	-0.96 [-1.53, -0.38]		
Aminisaman et al., 2020 Suh, et al., 2015	26.6 18.7	5.4 7.46	30	31.2 4. 30.7 17.6	8 30 7 33	1.2% 1.2%	-0.89 [-1.42, -0.36] -0.88 [-1.48, -0.28]		
Oncel. et al., 2002 (26)	24	13	24 25	39 2	0 25	1.2%	-0.88 (-1.46, -0.29)		
Elboim et al., 2020 (27)	41.7	19.2	23	61.2 2	5 18	1.1%	-0.87 [-1.52, -0.22]		
Neighbours, et al., 1987 (28) Zakariaee et al., 2019 (29)	17.5 31.8	30.3 20.4	10 40	40.7 20.7	4 10 5 40	1.0%	-0.86 [-1.78, 0.07] -0.84 [-1.30, -0.38]		
Domaille & Reeves, 1997 (30)	30.33	8.14	31	47 28.1	4 29	1.2%	-0.81 [-1.33, -0.28]		
Fiorelli, et al., 2012 (31) Mansuri, et al., 2019 (32)	39 26.67	8 22.57	23 15	45 45.33 26.1		1.2%	-0.78 [-1.39, -0.18] -0.74 [-1.49, 0.00]		
Biersa et al. 2015 (33)	26.67	13	15	45.33 26.1	1 13	1.1%	-0.74 [-1.49, 0.00] -0.74 [-1.51, 0.04]		
Likar et al. 2001 (34) Vitalii & Oleg, 2014	25.1	7.6	11	29.7 4.	B 12	1.0%	-0.70 [-1.55, 0.14]		
Vitalii & Oleg, 2014	39.5	17 20.1	11	52.5 18	6 10	1.0%	-0.70 [-1.59, 0.19]		
Warfield, et al., 1985 (35) Bilgili, et al., 2016	48.3 14.27	10.1	12 15	64.2 24 23.27 15	6 12 8 15	1.0%	-0.68 [-1.51, 0.14] -0.66 [-1.40, 0.08]		
Fujii-Abe et al., 2019 (36) Shimoura, et al., 2019 (37)	22.1	12.8	11	30.3 11.	2 11	1.0%	-0.66 [-1.52, 0.21]		
Shimoura, et al., 2019 (37) Rieres & Anderson, 2014	5.1 19.4	8 32.5	25 9	11.4 10.	9 25	1.2%	-0.65 [-1.22, -0.08]		
Bjersa & Andersson, 2014 Sezen, et al., 2017 (38)	19.4 36.9	32.5 7.2	43	39.6 3 42 10.	1 44	1.0%	-0.60 [-1.51, 0.30] -0.58 [-1.00, -0.15]		
Liu, et al., 2017 (39)	48.2	17.7	22	55.8 12	6 22	1.2%	-0.49 [-1.09, 0.11]	+	
Grimmer, 1992 (40) Ferreira, et al., 2011 (41)	22 18	28 18	20 15	36 2 25 1	9 20 8 15	1.1%	-0.45 [-1.08, 0.18] -0.38 [-1.10, 0.34]		
Rakel & Frantz, 2003 (42)	42	33.45	33	55 37.	3 33	1.2%	-0.361-0.85.0.121		
Warke, et al., 2004 (43)	28.25	36.5	5 48	40.33 19.	4 3	0.7%	-0.33 [-1.78, 1.12] -0.29 [-0.69, 0.11]		
Hruby, et al., 2006 (44) Robinson, et al., 2001	35 38.2	28.8 31.24	48 10	43.7 30. 47.92 36.3	6 49 7 13	1.2% 1.0%	-0.29 [-0.69, 0.11] -0.27 [-1.10, 0.56]		
Hobinson, et al., 2001 Hamza, et al., 1999 (45)	38.2	23	25	31 2	5 25	1.0%	-0.25 [-0.80, 0.31]		
Machin, et al., 1988	13.47	23 13.72		16.29 13.6	5 15	1.1%	-0.20 [-0.92, 0.52]	-+-	
Moore & Shurman, 1997 (46) Cupshipti et al. 1995 (47)	40.58	27.55	24	44.81 30.6 28 21	7 24	1.2% 1.3%	-0.14 [-0.71, 0.42]	±	
Cuschieri, et al., 1985 (47) Forster, et al., 1994 (48)	25 9.8	21.8 28.1	53 15	13.7 31.	8 53 9 15 0 8	1.1%	-0.14 [-0.52, 0.24] -0.13 [-0.84, 0.59]	_ <del>_</del>	
Shimoji, et al., 2007 (49)	38	15	9	40 2	0 8	1.0%	-0.11 [-1.06, 0.84]		
Graff-Radford, et al., 1989 (50) Yilmazer, et al., 2012 (51)	28.3 54.6	18.06 32.1	12 33	30.2 15.9 57.5 30.	2 12	1.1%	-0.11 [-0.91, 0.69] -0.09 [-0.58, 0.40]		
Sahin, et al., 2011	54.6 68.5	32.1 15.5	19	69.5 11	5 19	1.2%	-0.09 [-0.58, 0.40] -0.07 [-0.71, 0.56]	_ <b>_</b>	
Thomas, et al., 1988 (52) Presser, et al., 2000 (53)	33	31.1	131 30	35 33.	B 144	1.3%	-0.06 [-0.30, 0.18]	+	
Presser, et al., 2000 (53)	47	38.34	30	49 27.3	9 30	1.2%	-0.06 (-0.57, 0.45)	<u>_</u>	
llhani, 2015 (54) Tucker, et al., 2015 (55)	22.4 56	11.3 56	35 35	22.8 10. 57 5		1.2%	-0.04 [-0.52, 0.45] -0.02 [-0.49, 0.45]	<b>—</b>	
Da Silva, et al., 2015 (56)	1	0	21	4	0 21		Not estimable		
Bono, et al., 2015	80	20	54	80 2		1.3%	0.00 [-0.38, 0.38]	+	
Lee, et al., 2015 Silva. et al., 2012 (57)	55.6 22.5	9.2 11.5	18 21	54.4 12. 20 12.		1.1%	0.10 [-0.55, 0.76] 0.20 [-0.40, 0.81]	1	
Siqueira et al., 2019 (58)	2.92	6.6	13	0.7 1.	6 14	1.1%	0.46 [-0.31, 1.22]	+	
Kofotolis, et al., 2008	22	4	23 50	20	4 21	1.2%	0.49 [-0.11, 1.09]	+	
Kayman-Kose, et al., 2014 (59) Subtotal (95% CI)	13.5	5.8	1874		7 50 1863	1.2%	0.88 [0.47, 1.29] -0.89 [-1.08, -0.70]	•	
Heterogeneity: Tau <sup>2</sup> = 0.58; Chi <sup>2</sup> : Test for overall effect: Z = 9.13 (P	= 526.33, < 0.0000-	df = 75	(P < 0.	00001); P= 1	6%	021070	100 [- 100, -010]	•	
Test for overall effect: Z = 9.13 (P Total (95% CI)	~ 0.0000		2426			100.0%	-0.96 [-1.140.78]		
Heterogeneity: Tau# = 0.64; Chi#:	= 733.23,	df = 90		00001); F= (		100.0%	-0.50 [-1.14, -0.78]	-4 -2 0 2 4 Favours TENS Favours Placebo	-
Test for overall effect: Z = 10.37 (I									

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.,  $\geq 6$  low RoB items).

#### Sample size $n \ge 100$ 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 $n \ge 50$ participants in the primary TENS group

A subgroup analysis was conducted to explore the effect of studies including 50 participants or more es geta,
inte effect.
setween results fi
effect estimate for ea. in the primary TENS group. The test for subgroup differences was not statistically significant (Chi<sup>2</sup> = 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

td. Mean Difference

IV, Random, 95% Cl

#### MetaTENS\_Appendix\_BMJO\_05-10-2021 – Supplementary File 1

Image: Description of the second se	2								
$ \begin{array}{c c c c c c c c c c c c c c c c c c c $		Church and Cal			* • •				
$ \begin{array}{c c c c c c c c c c c c c c c c c c c $		2.10.1 TENS sample n=>50							
$ \begin{array}{c c c c c c c c c c c c c c c c c c c $		Jaafarpour, et al., 2008	5	5	54	12 4	4.2 54	1.2%	-1.51 [-1.93, -1.08]
$\begin{array}{c c c c c c c c c c c c c c c c c c c $		Kayman-Kose, et al., 2014 (3) Dailey et al., 2020 (4)	17.7 46	12.7 20	103	37.4 20 53 19	0.6 50 9.9 99	1.2% 1.3%	-1.14 [-1.57, -0.72] -0.35 [-0.63, -0.07]
8 bital part of the set of the s		Thomas, et al., 1988 (6)	33	31.1	131	35 33	3.8 144	1.3%	-0.06 [-0.30, 0.18]
8         Integrate Turber 201, Other 403, 201 and 9 and		Kayman-Kose, et al., 2014 (7)			50		7 50	1.2%	0.88 [0.47, 1.29]
9         2.0.9 THE Second Control           10         0         0.0.9 THE Second Control         0.0.9 THE Second Contro         0.0.9 THE Seco	8	Heterogeneity: Tau <sup>2</sup> = 0.63; Chi <sup>2</sup>	= 155.33	2, df= 8		00001); I² = 9		11.2.70	-0.04[-1.10,-0.10]
10         Compare at a 2014         10         0         20         0	9		,						
11       Herman, etc., 2001       21       26       91       72       91       10	10	Cipriano, et al., 2014	10	5	20	80	30 18	0.9%	-3.27 [-4.28, -2.27]
$ \begin{array}{c} 12 \\ 13 \\ 14 \\ 15 \\ 15 \\ 15 \\ 16 \\ 16 \\ 17 \\ 16 \\ 17 \\ 18 \\ 16 \\ 17 \\ 18 \\ 16 \\ 17 \\ 18 \\ 18 \\ 10 \\ 18 \\ 10 \\ 18 \\ 10 \\ 18 \\ 10 \\ 10$	11	Hokenek et al., 2019 (8)	22	12.49	39	72 18	8.7 39	1.1%	-3.11 [-3.78, -2.44]
13       mode, etc., 2010       64       7       13       mode, etc., 2010       14       234       64       15       15       234       16       16       234       16       16       234       16       16       234       16       15       234       15       15       15       15       16       15       16       15       16       16       17       16       17       16       17       16       17       16       17       16       17       16       17       17       16       17       16       17       17       17       18       16       17       17       18       16       17       18       16       17       18       16       17       18       17       18       18       16       18       16       18       16       18       16       18       16       18       16       18       16       18       1		Ekim et al., 2008 (9)	47.2	5.6	10	65.3 8	6.3 9	0.8%	-2.91 [-4.29, -1.54]
14       Lease, et al., 200       22       14       26       61       23       15       23       15       23       23       15       23       23       15       23       23       15       23       23       15       23       23       15       23       23       15       23       23       15       23       23       15       23       23       15       23       23       15       23       23       15       23       23       15       23       23       15       23       23       15       23       23       15       23       23       15       23       23       16       23       23       16       23       23       16       23       23       16       23       23       16       23       23       16       23       23       16       23       24       16       23       24       16       23       24 <th24< th="">       26       26       2</th24<>		Tokuda, et al., 2014 (10) Shahoei, et al., 2017 (11)	49	25	30	97 5	5.9 30	0.9% 1.1%	-2.81 [-3.82, -1.80] -2.61 [-3.31, -1.91]
15       Determine (H, 2001 (2)       21       22       24		Barker, et al., 2006	32.4	18	29	66.2 11	1.2 33	1.1%	-2.26 [-2.91, -1.61]
15       Determed et al. 2020 (16)       121       121       124       140       160       124       100       124 <t< th=""><th></th><th>Desantana, et al., 2008 (12)</th><th>9</th><th>10.7</th><th>20</th><th>48 22</th><th>2.7 20</th><th>1.1%</th><th>-2.15 [-2.95, -1.36]</th></t<>		Desantana, et al., 2008 (12)	9	10.7	20	48 22	2.7 20	1.1%	-2.15 [-2.95, -1.36]
17 $200000 + 0.00000 + 0.0000000000000000000$	15	Kimbar et al., 2020 (14)	21.2	12.2	31	47.6 19	9.6 30	1.2%	-1.60 [-2.18, -1.02]
$ \begin{array}{c c c c c c c c c c c c c c c c c c c $	16	Cheing & Luk, 2005	17	17	10	46	20 9	0.9%	-1.50 [-2.55, -0.45]
18         De Olivers at , 2012 (7)         21         14         5         6         17         7 <th7< th=""><th>17</th><th>Amer-Cuenca, et al., 2011</th><th>26.5</th><th>24.7</th><th>30</th><th>61.9 23</th><th>3.2 30</th><th>1.2%</th><th>-1.46 [-2.03, -0.88]</th></th7<>	17	Amer-Cuenca, et al., 2011	26.5	24.7	30	61.9 23	3.2 30	1.2%	-1.46 [-2.03, -0.88]
$ \begin{array}{c} 19 \\ 19 \\ 19 \\ 10 \\ 10 \\ 10 \\ 10 \\ 10 \\$	18	De Oliverira et al., 2012 (17)	30	16.4	5	54 13	3.6 5	0.7%	-1.44 [-2.92, 0.04]
$ \begin{array}{c} \begin{array}{c} \mbox{Comp} & \mb$	-	Topuz, et al., 2004	37.3	16.2	15	59.1 13	3.7 12	1.0%	-1.40 [-2.25, -0.54]
20Comment et al. 2007 (20)20742121133 (20)21Liken et al. 2007 (20)20311446311541151 (20)22Liken et al. 2007 (20)2011.25101010101011.2523Liken et al. 2007 (20)2011.251010101011.2510.4524Comment et al. 2007 (20)17.211.91020.251011.911.151020.251011.911.1524Primage et al. 2017 (20)17.213.91020.41017.913.91011.911.1510.4520.2511.2526Sun et al. 2018 (20)17.213.920.41017.913.921.41011.9-0.461(4.4.0.20)27Comment et al. 2018 (21)11.920.410.411.711.3-0.461(4.4.0.20)27Comment et al. 2018 (21)11.920.410.411.711.3-0.461(4.4.0.20)28Beress, et al. 2016 (21)11.920.410.111.9-0.461(4.3.0.20)29Warries A. 2017 (20)20.410.411.411.3-0.461(4.3.0.20)20Law et al. 2017 (21)21.511.411.411.3-0.461(4.3.0.20)20Law et al. 2017 (20)20.410.111.9-0.461(4.3.0.20)21Law et al. 2017 (20)21.412.211.9-0.46	-	Ordog, 1987 (18) Luchesa, et al., 2009 (19)	30.4 5	2.8 6	25 15	54.8 21 15	25 25 5.4 15	1.1% 1.1%	-1.35 [-1.97, -0.73] -1.33 [-2.13, -0.53]
$ \begin{array}{c} 22 \\ 23 \\ 24 \\ 24 \\ 25 \\ 25 \\ 26 \\ 26 \\ 26 \\ 26 \\ 26 \\ 27 \\ 27 \\ 27$	-	Cipriano, et al., 2008 (20) Lauretti, et al., 2013 (21)	60	10	13	80	20 10	1.0%	-1.33 [-1.98, -0.68] -1.28 [-2.19, -0.36]
22Outstein011.251042.2251010.5511.15/2.70.4323Adver, et al., 201067231088101010.5511.05/2.70.4324Winner, et al., 201267231088101010.5510.05/2.00.2524Winner, et al., 20121088101010.5510.05/2.00.2525Bit Adv. 201210841010.7510.05/2.00.2510.05/2.00.2526Bit Adv. 20121010.07/2.00.271010.07/2.00.2710.05/2.00.2510.07/2.00.2527Bit Adv. 201210.07/2.00.2017.1710.07/2.2710.07/2.00.2110.07/2.00.2128Bit Adv. 201210.07/2.00.2017.1710.07/2.2710.07/2.10.2110.07/2.10.2129Winkley Adv. 201210.07/2.00.2017.1710.2221.0110.07/2.10.2129Winkley Adv. 201210.07/2.00.2017.1710.2221.0110.07/2.10.2120Winkley Adv. 201210.07/2.0010.07/2.1110.07/2.10.2110.07/2.10.2120Winkley Adv. 201610.07/2.10.2110.07/2.1110.07/2.10.2110.07/2.10.2121Winkley Adv. 201610.07/2.1110.07/2.1110.07/2.1110.07/2.10.2123Bit Adv. 201610.07/2.1110.07/2.1110.07/2.1110.07/2.10.2124Bit Adv. 201610.17/2.00.2110.07/2.10.2110.07/2.10.2125Bit Adv. 2		Lison, et al., 2017 (23)	23.2	31.4	46	53.1 19	9.9 46	1.2%	-1.13 [-1.57, -0.69]
23Areas, etal., 20106623108610101081.		Cuschieri, et al., 1987 (25)	30	11.25	10	49 20.	25 10	1.0%	-1.11 [-2.07, -0.15]
24Planua, et al. 2014 (20)1722161882061054.36 (1.8.0.0)25Sin, et al. 2015Sin, et al. 20151077.462420117.572117.672117.672117.672117.672117.672117.672117.672117.672117.672117.672117.6717.671117.671117.671117.6717.6717.6717.6717.6717.6717.6717.6717.6717.6717.67	23	Abreu, et al., 2010		23		88	10 10	1.0% 1.2%	-1.08 [-2.03, -0.13] -1.06 [-1.61, -0.52]
25Sen, #12, 20151077.462430717.672212.86-0.481+460.2926Besterning, 200, 16971031314322413.76-0.481+460.2927Domaile & Resex, 1997 (20)31.3381.43422.1611.16-0.481+460.2928Berse, 41.2015 (20)31.3381.43422.1611.16-0.481+1300.2828Berse, 41.2015 (26)2111.31422.1611.16-0.471+1300.2829Viail 6 Aleg, 201410.1511.22.118.611.16-0.471+1300.2830Berse, 41.2015 (26)22.111.211.0011.01.0-0.471+1300.2831Berse, 41.2015 (26)22.112.811.0023.1211.16-0.461+150.00132Gerse, 10.2016 (26)22.112.811.0023.1211.16-0.461+150.00133Ferrein, 41.2016 (26)22.112.812.912.912.011.06-0.461+150.00134Berse & Andersson, 201412.912.912.912.911.06-0.461+150.00135Berse & Andersson, 201412.912.912.912.911.06-0.461+150.00136Berse & Andersson, 201412.912.912.912.912.960.41+160.01636Berse & Andersson, 201412.912.912.912.960.41+160.01637Gorde & Andersson, 201412.912.9 <t< th=""><th>24</th><th>Pitangui, et al., 2014 (26) Yilmaz et al., 2019 (27)</th><th>7.3</th><th>9.8</th><th>11 26</th><th>38.8 20 20 15</th><th>0.8 10 5.7 26</th><th>1.0% 1.2%</th><th>-0.96 [-1.53, -0.38]</th></t<>	24	Pitangui, et al., 2014 (26) Yilmaz et al., 2019 (27)	7.3	9.8	11 26	38.8 20 20 15	0.8 10 5.7 26	1.0% 1.2%	-0.96 [-1.53, -0.38]
26Element rat, 2020 (26)471922361225101118408 (17)40227Dormalia R Ances (197 (20)31304047511610131-008 (17)28Blocks (14)313031314141475116113-008 (17)29Water (14)2016 (20)2862271545332111118-074 (15)30France (14)2016 (20)21671112271643216116-074 (15)30Funda Cong216 (27)11227154531116-066 (15)-066 (15)31Blocks (14)216 (27)1281115232118-066 (15)-066 (15)-066 (15)31Blocks (14)216 (27)1281115232118-066 (15)-066 (15)-066 (15)32Glocks (14)216 (27)2220128128128128-066 (15) </th <th>25</th> <th>Suh, et al., 2015</th> <th>18.7</th> <th>7.46</th> <th>24</th> <th>30.7 17.</th> <th>67 23</th> <th>1.2%</th> <th>-0.88 [-1.48, -0.28]</th>	25	Suh, et al., 2015	18.7	7.46	24	30.7 17.	67 23	1.2%	-0.88 [-1.48, -0.28]
$\begin{array}{c ccccccccccccccccccccccccccccccccccc$		Elboim et al., 2020 (29)	41.7	19.2	23	61.2	25 18	1.1%	-0.87 [-1.52, -0.22]
28Musui, etal., 2019 (26)266 7 225 715 4 63 2 21 6111 11 11 11 11 11 11 11 11 11 11 11 11	-	Zakariaee et al., 2019 (31)	31.8	20.4	40	47.5 18	6.5 40	1.2%	-0.84 [-1.30, -0.38]
Like et al. 2010 (26) 29 Walk 6 Qui 2010 (27) 30 Walk 1 (2012) (27) 31 Walk 2 (2012) (27) 31 Walk 2 (2012) (27) 31 Walk 2 (2012) (27) 31 Walk 2 (2012) (27) 31 Walk 2 (2012) (27) 31 Walk 2 (2012) (27) 32 Walk 2 (2012) (27) 32 Walk 2 (2012) (27) 33 Walk 2 (2012) (27) 34 Walk 2 (2012) (27) 35 Walk 2 (2012) (27) 36 Walk 2 (2012) (27) 37 Walk 2 (2012) (27) 38 Walk 2 (2012) (27) 39 Walk 2 (2012) (27) 30 Walk 2 (2012) (27) 31 Walk 2 (2012) (27) 32 Walk 2 (2012) (27) 33 Walk 2 (2012) (27) 34 Walk 2 (2012) (27) 35 Walk 2 (2012) (27) 36 Walk 2 (2012) (27) 37 Walk 2 (2012) (27) 36 Walk 2 (2012) (27) 37 Walk 2 (2012) (27) 38 Walk 2 (2012) (27) 39 Walk 2 (2012) (27) 30 Walk 2 (2012) (27) 31 Walk 2 (2012) (27) 32 Walk 2 (2012) (27) 34 Walk 2 (2012) (27) 35 Walk 2 (2012) (27) 36 Walk 2 (2012) (27) 37 Walk 2 (2012) (27) 36 Walk 2 (2012) (27) 37 Walk 2 (2012) (27) 38 Walk 2 (2012) (27) 39 Walk 2 (2012) (27) 30 Walk 2 (2012) (27) 30 Walk 2 (2012) (27) 31 Walk 2 (2012) (27) 32 Walk 2 (27) 34 Walk 2 (2012) (27) 35 Walk 2 (2012) (27) 36 Walk 2 (2012) (27) 37 Walk 2 (2012) (27) 38 Walk 2 (2012) (27) 39 Walk 2 (2012) (27) 30 Walk 2 (2012) (27) 30 Walk 2 (2012) (27) 30 Walk 2 (2012) (27) 30 Walk 2 (2012) (27) 31 Walk 2 (2012) (27) 32 Walk 2 (2012) (27) 33 Walk 2 (2012) (27) 34 Walk 2 (2012) (27) 35 Walk 2 (2012) (27) 36 Walk 2 (2012) (27) 37 Walk 2 (2012) (27) 38 Walk 2 (2012) (27) 39 Walk 2 (2012) (27) 30 Walk 2 (2012) (27) 30 Walk 2 (2012) (27) 30 Walk 2 (2012) (27) 30 Walk 2 (2012) (27) 31 Walk 2 (2012) (27) 32 Walk 2 (2012) (27) 33 Walk 2 (2012) (27) 34 Walk 2 (2012) (27) 35 Walk 2 (2012) (27) 36 Walk 2 (2012) (27) 37 Walk 2 (2012) (27) 38 Walk 2 (2012) (27) 39 Walk 2 (2012) (27) 30 Walk 2 (2012) (27) 30 Walk 2 (2012) (27) 30 Walk 2 (2012) (27) 30 Walk 2 (2012) (27) 30 Walk 2 (2012) (27) 30 Walk 2 (2012) (27) 30 Walk 2 (2012) (27) 30 Walk 2 (2012) (27) 30 Walk 2 (2012) (27) 30 Walk 2 (2012) (27) 30 Walk 2 (2012) (27) 30 Walk 2 (2012) (27) 30		Mansuri, et al., 2019 (34)		22.57	15	45.33 26.	15 15	1.1%	-0.78 [+1.39, -0.18] -0.74 [-1.49, 0.00]
259Warfeld, etal., 1985 (37)46.32011264.224.61210.810.861+15, 0.1430Full-Aber at., 2018 (30)2211211130.311.31111.51.681+15, 0.1331Breas, etal., 2017 (40)30.9222222233320.1111.68-0.061+15, 0.23132Origina, etal., 2017 (40)30.9222222233320.1111.69-0.061+15, 0.23133Funda, etal., 2017 (40)1011.61152511.311.28-0.461+16, 0.01134Origina, etal., 2010 (40)12.2623232311.311.28-0.461+16, 0.01134Hobrison, etal., 2001 (40)12.262324.252312.88-0.461+10, 0.01135Macrin, etal., 2001 (40)12.2312.2613.1511.38-0.220+09, 0.1136Hobrison, etal., 2001 (40)23.2312.6612.1311.28-0.020+00, 0.1136Hobrison, etal., 2001 (40)23.2312.6612.1311.28-0.020+00, 0.1137Vimaze, etal., 2001 (50)23.12612.1411.58-0.020+00, 0.1138Horrizon, etal., 2016 (50)23.12612.1111.58-0.020+00, 0.0236Finone, etal., 2016 (50)23.12612.1111.58-0.020+00, 0.0237Vimaze, etal., 2016 (50)23.12612.1111.58-0.020+00, 0.0238Horrizon, e	-	Likar et al. 2001 (36)	25.1	7.6	11	29.7 4	4.8 12	1.0%	-0.70 [-1.55, 0.14]
30Full-Abe et al. (2019 (3)) Bitmours, et al. (2019 (3)) Bitmours, et al. (2019 (3))221 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1	29	Warfield, et al., 1985 (37)	48.3	20.1	12	64.2 24	4.6 12	1.0%	-0.68 [-1.51, 0.14]
31Bers & Andersson, 201419432.5939.6221110.9-0.00[15], 10.9, 05]32Orriner, 192 (12)1212221332131-0.06[15], 10.9, 05]33Derminer, 192 (12)12122213532131-0.06[15], 10.9, 05]34Derminer, 192 (12)121223353311.2%-0.06[66, 013]34Rave & Franz, 2003 (40)12143135573311.2%-0.06[66, 013]35Machae, et al., 2004 (40)28283134340.2%-0.35[178, 113]36Haraz, et al., 2004 (40)2832313111.2%-0.06[66, 013]36Machae, et al., 2004 (40)382311.4114360.2%36Machae, et al., 2004 (40)382311.4134360.2%36Machae, et al., 2004 (40)382311.3131.6111.86-0.0116.9637Machae, et al., 1984 (40)3821.1113.271512.2111.86-0.0116.9638Presser, et al., 2012 (25)6432.14304223.1111.86-0.016.9639Machae, et al., 2012 (26)6432.211312.8-0.016.950.6339Machae, et al., 2016 (56)5462211312.8-0.016.950.6340Machae, et al., 2016 (56) <td< th=""><th>30</th><th>Fujii-Abe et al., 2019 (38)</th><th>22.1</th><th>12.8</th><th>11</th><th>30.3 11</th><th>1.2 11</th><th>1.0%</th><th>-0.66 [-1.52, 0.21]</th></td<>	30	Fujii-Abe et al., 2019 (38)	22.1	12.8	11	30.3 11	1.2 11	1.0%	-0.66 [-1.52, 0.21]
32ommer: 1992 (42)222820352920111616100 (107, 008)33Rake & Franz, 2003 (44)181525181511.5	31	Bjersa & Andersson, 2014		7.2	9	39.6	32 11	1.0%	-0.60 [-1.51, 0.30]
33 $remains interaction (10)10101010101011$	32	Grimmer, 1992 (42)	22	28	20	35	29 20	1.1%	-0.45 [-1.08, 0.18]
34Wate, etal., 2004 (45)28.2536.5540.3310.430.7311.780.035 (178, 11.28)35Herms, etal., 200136.231.21047.926.371310.430.72 (11.10, 080, 011)36Herms, etal., 1989 (47)13.271511.2313.2512.80.22 (11.10, 080, 011)36Matchin, etal., 1989 (47)13.4713.271511.240.20 (10.02, 010, 011)37Matchin, etal., 1984 (47)38.11514.1731.91511.180.01 (10.81, 080, 081)37Vimmaer, etal., 2012 (42.)46.821.333.635.212.111.180.01 (10.81, 080, 081)38Presser, etal., 2012 (42.)46.822.313.622.212.111.80.01 (10.82, 048)38Presser, etal., 2015 (56)10.2140.2124.80.04 (10.52, 048)39Dasline, etal., 2015 (56)10.2140.2124.80.00 (10.52, 048)40Lee, etal., 2015 (56)10.2140.2124.80.00 (10.52, 048)40Lee, etal., 2016 (56)10.2140.2222.212.2%0.02 (10.52, 048)41Betwee, etal., 2016 (56)10.2140.2124.80.00 (10.52, 048)40Lee, etal., 2016 (56)22.511.521.2%0.04 (10.55, 088)41Betwee, etal., 2016 (56)22.61.30.71.6 </th <th></th> <th>Ferreira, et al., 2011 (43)</th> <th>18</th> <th>18</th> <th>15</th> <th>25</th> <th>18 15</th> <th>1.1%</th> <th>-0.38 [-1.10, 0.34]</th>		Ferreira, et al., 2011 (43)	18	18	15	25	18 15	1.1%	-0.38 [-1.10, 0.34]
3-4Reduction etal. 2013-23-21-21-21-21-235Marx, etal. 1999 (47)223221221-236More & Shumm, 197 (46)9.822111511.3-0.21 (10.0 kg)37More & Shumm, 197 (46)9.822111511.3-0.01 (10.7)38Forester, etal. 1990 (47)9.8151.91.9-0.01 (10.6)37More & Shumm, 197 (46)9.82211511.3-0.01 (10.6)38More & Shumm, 197 (46)9.82211511.3-0.01 (10.6)38Minest, etal. 2017 (56)5.69.520.510.111.4-0.01 (50.10)38Minest, etal. 2016 (56)5.65.65.75.72512.3-0.05 (10.7)39De Shue, etal. 2016 (56)10.214.021.3No.05 (10.5)-0.05 (10.6)40Markado etal. 2019 (57)4.72522.44.221.4No.05 (10.6)41De Shue, atl. 2016 (56)5.65.62.021.1No.05 (10.6)40Markado etal. 2019 (57)4.725.22.12.50.04 (10.5)41De Shue, atl. 2017 (56)1.02.22.12.50.10.041Shue, atl. 2017 (50)2.22.12.50.10.00.041Shue, atl. 2016 (50)2.22.61.90.71.6 <th></th> <th>Warke, et al., 2004 (45)</th> <th>28.25</th> <th>36.5</th> <th>5</th> <th>40.33 19</th> <th>9.4 3</th> <th>0.7%</th> <th>-0.33 [-1.78, 1.12]</th>		Warke, et al., 2004 (45)	28.25	36.5	5	40.33 19	9.4 3	0.7%	-0.33 [-1.78, 1.12]
36Moore & Shumma, 1997 (49)40.5827.552444.8130.672412.8-0.14 [-07, 10.84, 0.99]37Shuma, 194, 140, 1960 (50)381594020610.1410.06 (20, 0.05,		Hamza, et al., 1999 (47)	25	23	25	31	25 25	1.0% 1.2%	-0.25 [-0.80, 0.31]
36Shimoje et al. 2007 (20)391594020810.110.0111.100.0137Vintrazer, et al. 2012 (25)54.632.13357.530.5221211.%-0.010.0938Presser, et al. 2012 (25)54.632.13357.530.5221211.%-0.010.070.8139Bahn, et al. 2015 (50)4739.3304927.393012.%-0.060.057.04839Da Silve, et al. 2015 (50)5652216412.34-0.060.052.04840Mater, et al. 2016 (50)170216022112.%-0.060.0140Mater, et al. 2016 (50)5652216412.340.010.050.010.050.041Beckwee et al. 201656522112.%0.010.050.010.050.010.050.041Beckwee et al. 201656522112.%0.010.050.010.050.010.050.041Beckwee et al. 201650022.26.1130.716.814.110.050.010.050.042Votobia et al. 2012 (56)22.26.6130.716.111.1%0.045.010.050.041Beckwee et al. 2016 (56)22.26.6130.716.814.110.050.010.050.042State al. 2016 (56)22.2		Moore & Shurman, 1997 (48)	40.58	27.55	24	44.81 30.	67 24	1.2%	-0.14 [-0.71, 0.42]
37Yimmater, etal, 2012 (25)6463213367.530.52211.8-0.00 [0.57], 0.5838Presser, etal, 2010 (35)4738.34304927.393011.78-0.00 [0.57], 0.5839Da Silo, etal, 2015 (56)56565657575712.54-0.04 [0.52], 0.45400Basilo, etal, 2015 (56)10.22112.8-0.04 [0.52], 0.4540Basilo, etal, 2016 (56)5652225412.34-0.04 [0.52], 0.4540Basilo, etal, 2016 (56)22.511.52112.80.04 [0.52], 0.6541Beskee, etal, 2016 (56)22.511.52112.80.04 [0.52], 0.6541Beskee, etal, 2016 (56)22.511.52112.80.04 [0.52], 0.6541Beskee, etal, 2016 (56)22.511.52112.80.04 [0.52], 0.6541Beskee, etal, 2016 (56)22.511.52112.80.04 [0.52], 0.6541Beskee, etal, 2016 (56)22.521.622.812.80.04 [0.52], 0.6542Kotobis, etal, 2008 (22.64)22.50.621.70.020.05 [0.14], 0.6541Beskee, etal, 2016 (56)22.50.622.281.280.04 [0.50], 0.0641Beskee, etal, 2016 (56)22.50.05 [0.14], 0.68110.6611.1842Beskee, etal, 2016 (56)22.50.05 [0.14], 0.6110.6644Beske		Shimoji, et al., 2007 (50)	38	15	9	40	20 8	1.0%	-0.11 [-1.06, 0.84]
38Presser, etal, 200 (33)47 38.43049 27.9301.28-0.05 (0.57, 0.65, 0.65)39Unixer, etal, 2015 (56)565858575757571.28-0.04 (0.52, 0.45)40Lee, etal, 2015 (56)10.2740.21Notestmake-0.02 (0.48, 0.52, 0.45)40Lee, etal, 2015 (56)2.577.271.120.04 (0.55, 0.76)41Betwee, etal, 2016 (56)2.571.152.121.120.04 (0.55, 0.76)41Betwee, etal, 2016 (56)2.571.152.101.252.110.04 (0.55, 0.76)41Betwee, etal, 2016 (56)2.221.250.122.180.02 (0.46, 0.51, 0.50)42Kotobis, etal, 2016 (56)2.224.222.121.280.04 (0.55, 0.76)42Wotobis, etal, 2016 (56)2.224.222.141.280.46 (0.31, 1.29)42Statutati (95% (7)2.222.201.281.280.46 (0.31, 1.29)43Tester overall effect 2-10.25 (P - 0.00001)1.00-0.06 (-1.14, -0.78)44Hearcognomic Tar*-0.63 (Ch*=73.22 (dr= 0.07 (* 0.00001), P= 89%)-0.06 (-1.14, -0.78)45Tester overall effect 2-10.25 (P - 0.00001)1.280.06 (-1.14, -0.78)46Figure A5 Forest plot of comparison TEN47effect of studies including 50 participant4815050participants, P < 0.000001, P= 0.20, P= 0.20, P= 0.20, P= 0.20, P= 0.20, P= 0.20, P= 0.20, P= 0.20, P= 0.20, P= 0.20, P=	37	Yilmazer, et al., 2012 (52)	54.6	32.1	33	57.5 30	0.5 32	1.2%	-0.09 [-0.58, 0.40]
39Desking etal, 2015 (56)10214021Not estimation40Machado etal, 2019 (57)472248221212%0.416055, 0.8340Mamaz etal, 2019656.2186.412.91811.1%0.116055, 0.8341Mamaz etal, 201264724.1756422.371.2%0.146055, 0.8341Betwee etal, 201922.54724.122.80.2212.52112.2%0.246040, 0.8142Wave, etal, 20120.224.222.212.2%0.45101, 0.800.900.9042Wave, etal, 20120.224.222.212.2%0.45101, 0.800.9042Wave, etal, 20120.224.222.212.2%0.45101, 0.8042Wave, etal, 20160.224.2320.44.10.461031, 0.2742Wave, etal, 20160.224.2320.44.10.461031, 0.2743Testfor overall effect 2-10.25 (P < 0.0001)Testfor overall effect 2-10.25 (P < 0.00001)11.1%0.46111, 0.478144Heterogeneity: Tau* 0.451(P* 0.20001)Testfor overall effect 2-10.25 (P < 0.00001)12.2%0.44101, 0.2%45Testfor overall effect 2-10.25 (P* 0.00001)Testfor overall effect 2-10.25 (P* 0.00001)12.2%0.4410, 0.478144Heterogeneity: Tau* 0.451(P* 0.20001)Testfor overall effect 2-10.25 (P* 0.00001)12.2%0.4611, 1.4, 0.78145Tes	38	Ilhani, 2015 (54)							-0.06 [-0.57, 0.45]
40 $a_{000}^{10}$ $566$ $32$ $16$ <	39	Tucker, et al., 2015 (55) Da Silva, et al., 2015 (56)	1	56 0	21	4	0 21		-0.02 [-0.49, 0.45] Not estimable
41       Bitwe, et al., 2012 (69)       22 5       11.5       21       22 6       21       12.5       0.35 (10.9, 0.9)         42       Kotobis, et al., 2019 (69)       222       6.6       13       0.7       16       14       11.5       0.45 (10.9)       0.45		Lee, et al., 2015	55.6	9.2	18	54.4 12	2.9 18	1.1%	0.10 [-0.55, 0.76]
421212412 <th>-</th> <th>Silva, et al., 2012 (58)</th> <th>22.5</th> <th>11.5</th> <th>21</th> <th>20 12</th> <th>2.5 21</th> <th>1.2%</th> <th>0.20 [-0.40, 0.81]</th>	-	Silva, et al., 2012 (58)	22.5	11.5	21	20 12	2.5 21	1.2%	0.20 [-0.40, 0.81]
421811 Basis - 1.00 [-1.19, -0.81]431811 Basis - 1.00 [-1.19, -0.81]43Testor overall effect $2 = 10.3$ ( $P^{+} = 456.0$ off $81 (P^{+} = 0.0001)$ )442428 2415 100.0% -0.06 [-1.14, -0.78]44Testor overall effect $2 = 10.3$ ( $P^{+} = 0.0001$ )452428 2415 100.0% -0.06 [-1.14, -0.78]46Figure A5 Forest plot of comparison TEN47effect of studies including 50 participant482849Estimation of sample size50There was a statistically significant differ51both for RCTs that stated in the report tl52samples, 2847 participants, P < 0.00001,		Siqueira et al., 2019 (59)	2.92	6.6	13	0.7 1	1.6 14	1.1%	0.46 [-0.31, 1.22]
45242624150.06 [1.14, 0.78]44Heterogeneity: Tau" = 0.84, Chf = 73.23, off = 90 (P < 0.0001); P = 89%45Testfor velocity off et 0.021, P = 33.3%46Figure A5 Forest plot of comparison TEN47effect of studies including 50 participant484949Estimation of sample size50There was a statistically significant differ51both for RCTs that stated in the report th52samples, 2847 participants, P < 0.00001,53participants, P < 0.00001, I <sup>2</sup> = 79%). The54our pre-specified threshold of P < 0.1 (CL)56inclusion of a statement in the report th		Subtotal (95% CI) Heterogeneity: Tau <sup>#</sup> = 0.63; Chi <sup>#</sup>	= 545.60	), df = 81		1.00001); I²=	1811	88.8%	-1.00 [-1.19, -0.81]
44Heterogenetic Tart To GAL (The T 33.23 of the OF < 0.0000); JF = 89%	43		P < 0.00	001)	2426		2415	100.0%	0.96[1.14]0.79]
<ul> <li>45</li> <li>46</li> <li>47</li> <li>48</li> <li>49</li> <li>49</li> <li>49</li> <li>49</li> <li>40</li> <li>41 (P=0.22), P= 33.3%</li> <li>48</li> <li>49</li> <li>49</li> <li>41</li> <li>49</li> <li>41</li> <li>49</li> <li>41</li> <li>49</li> <li>41</li> <li>41</li> <li>41</li> <li>42</li> <li>43</li> <li>49</li> <li>49</li> <li>40</li> <li>41</li> <li>41</li> <li>41</li> <li>42</li> <li>43</li> <li>44</li> <li>49</li> <li>48</li> <li>49</li> <li>49</li> <li>40</li> <li>41</li> <li>41</li> <li>42</li> <li>43</li> <li>44</li> <li>49</li> <li>40</li> <li>41</li> <li>42</li> <li>43</li> <li>44</li> <li>44</li> <li>49</li> <li>40</li> <li>41</li> <li>41</li> <li>42</li> <li>43</li> <li>44</li> <li>44</li> <li>45</li> <li>45</li> <li>46</li> <li>46</li> <li>47</li> <li>48</li> <li>48</li> <li>49</li> <li>48</li> <li>49</li> <li>48</li> <li>49</li> <li>40</li> <li>40</li> <li>41</li> <li>41</li> <li>42</li> <li>43</li> <li>44</li> <li>44</li> <li>44</li> <li>45</li> <li>45</li> <li>46</li> <li>46</li> <li>47</li> <li>47</li> <li>47</li> <li>47</li> <li>48</li> <li>48</li> <li>49</li> <li>48</li> <li>49</li> <li>48</li> <li>49</li> <li>49</li> <li>49</li> <li>40</li> <li>41</li> <li>41</li> <li>42</li> <li>43</li> <li>44</li> <li>44</li> <li>44</li> <li>45</li> <li>44</li> <li>45</li> <li>45</li> <li>46</li> <li>47</li> <li>47</li> <li>48</li> <li>48</li> <li>49</li> <li>40</li> <li>41</li> <li>41</li> <li>42</li> <li>42</li> <li>43</li> <li>44</li> <li>44</li> <li>44</li> <li>44</li> <li>44</li> <li>44</li> <li>44</li> <li>44</li> <li>44</li> <li>45</li> <li>44</li> <li>45</li> <li>45</li> <li>46</li> <li>46</li> <li>47</li> <li>47</li></ul>	44	Heterogeneity: Tau# = 0.64; Chi#	= 733.23 P × 0.00	3, df = 90 001)		1.00001); I#=		100.0%	-0.30 [-1.14, -0.76]
47effect of studies including 50 participant4849Estimation of sample size50There was a statistically significant differ51both for RCTs that stated in the report th52samples, 2847 participants, P < 0.00001,53participants, P < 0.00001, I² = 79%). The54our pre-specified threshold of P < 0.1 (Cl56inclusion of a statement in the report th	45	Test for subgroup differences: C	hi≇= 1.5	0, df = 1					
47effect of studies including 50 participant4849Estimation of sample size50There was a statistically significant differ51both for RCTs that stated in the report th52samples, 2847 participants, P < 0.00001,53participants, P < 0.00001, I² = 79%). The55our pre-specified threshold of P < 0.1 (Cl56inclusion of a statement in the report th	46	Figure A5 Fo	res	st p	lot	t of c	com	par	ison TENS
<ul> <li>48</li> <li>49 Estimation of sample size</li> <li>50 There was a statistically significant difference</li> <li>51 both for RCTs that stated in the report the</li> <li>52 samples, 2847 participants, P &lt; 0.00001,</li> <li>53 participants, P &lt; 0.00001, I<sup>2</sup> = 79%). The</li> <li>55 our pre-specified threshold of P &lt; 0.1 (CC</li> <li>56 inclusion of a statement in the report the</li> </ul>		effect of stu	die	s ir	ncl	udin	g 5(	) Da	rticipants
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19         12           6         6           15         15           17.7         12.7           48         20           25         21.8           80         20           13.5         5.8           :155.32, df= 8           =0.02)           25.11         0.92           10         5           22         12.49           20         10           47.2         5.6           49         8	48 45 50 37.4 103 53 26 131 35 54 80 593 (P < 0.00001) 9 35 20 80 39 82.6 39 72	2 4.2 5 25 4 20.6 3 19.9 3 21.8 5 33.8 1 5 33.8 1 0 20 8 7 6 1,19 0 30	50 1.29 54 1.29 50 1.29 99 1.39 53 1.39 54 1.39 54 1.39 50 1.29 804 11.29 8 0.19	-1.51 (-1.93, -1.08) -1.44 (-1.88, -0.99) -1.14 (-1.57, -0.72) -0.35 (-0.63, -0.07) -0.14 (-0.52, 0.24) -0.06 (-0.30, 0.18) 0.00 (-0.38, 0.38) 0.88 (0.47, 1.29)	++++ + + + + + + + + + + + + + + + + +	- - - 				
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40 4	41 47	7 4		-1.73 [-2.24, -1.22]						
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43 15.3	23 66.5	5 14.7	21 1.19	-1.54 [-2.22, -0.86]						
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				-1.25 [-2.04, -0.46]						
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68 23 7 53	30 147	3 10 7 86								
17.2 21.9	11 38.8	3 20.8								
7.3 9.8										
		2 4.8 7 17.67								
24 13	25 39	9 20	25 1.29	-0.88 [-1.46, -0.29]						
41.7 19.2	23 61.2	2 25	18 1.19	-0.87 [-1.52, -0.22]						
31.8 20.4			40 1.09	-0.84 [-1.30, -0.38]						
30.33 8.14	31 47	7 28.14	29 1.29	-0.81 [-1.33, -0.28]						
	23 45									
10 13	15 23	3 21	13 1.19	-0.74 [-1.51, 0.04]		-				
25.1 7.6	11 29.7			-0.70 [-1.55, 0.14]		t				
	11 52.5	5 18.6 7 24.6	10 1.09	-0.68[-1.59, 0.19]		T				
14.27 10.1	15 23.27	7 15.8	15 1.19	-0.66 [-1.40, 0.08]		ł				
						t				
						L				
36.9 7.2	43 42	2 10.1	44 1.29	-0.58 [-1.00, -0.15]						
	22 55.8	3 12.6		-0.49 [-1.09, 0.11]		İ				
21 16	37 29	9 22	37 1.29	-0.41 [-0.87, 0.05]	-	ł				
18 18	15 25	5 18	15 1.19	-0.38 [-1.10, 0.34]		t				
	33 55					<u> </u>				
35 28.8	48 43.7	7 30.6	49 1.29	-0.29 [-0.69, 0.11]	-	ł				
38.2 31.24	10 47.92	2 36.37	13 1.09	-0.27 [-1.10, 0.56]		F				
25 23	25 31	i 25 9 13,65		-0.25 (-0.80, 0.31) -0.20 (-0.92 -0.52)	_	L-				
40.58 27.55	24 44.81	1 30.67	24 1.29	-0.14 [-0.71, 0.42]	-	+				
9.8 28.1					_	E_				
				-0.11 [-1.06, 0.84] -0.11 [-0.91 0.691	_	<u> </u>				
54.6 32.1	33 57.6	5 30.5	32 1.29	-0.09 [-0.58, 0.40]	-	+				
68.5 15.5	19 69.5	5 11.5	19 1.19	-0.07 [-0.71, 0.56]	_	E				
	3U 49 35 22 P			-0.06 (-0.57, 0.45) -0.04 (-0.52, 0.45)	_	1				
56 56	35 57	7 57	35 1.29	-0.02 [-0.49, 0.45]	_	+				
1 0	21 4	4 0		Not estimable		L				
47 25 55.6 9.2	22 46				_	_				
54.7 24.1	37 50.4	\$ 20.3	37 1.29	0.19 [-0.27, 0.65]	-	<u></u>				
22.5 11.5	21 20	0 12.5	21 1.29	0.20 [-0.40, 0.81]	-	E.				
39.2 25.1 2.92 6.6					-	<u> </u>				
22 4	23 20	3 4	21 1.29	0.49 [-0.11, 1.09]	. •	<b>├</b>				
= 545.60. df = 81			811 88.89	-1.00 [-1.19, -0.81]	•					
P < 0.00001)	,									
733 33 44- 04	2426		15 100.0%	-0.96 [-1.14, -0.78]	•					
P < 0.00001)					-4 -2 (	b 2	4			
ni² = 1.50, df = 1	$(P = 0.22), I^{a}$	= 33.3%			Favours TENS	i avours Placebi	,			
					C voresse	-ا م م م ام		hare		. +
rest p	ποτ ο	I COL	пра	ISON LEN	s versus	placeb	o with s	ubgroup	anaiysi	s to explore
										-
	9 9 10.7 40 4 4 21.2 12.2 52 14 4 44 15.3 17 15.3 17 15.3 17 15.3 17 15.3 17 15.3 17 15.3 17 15.3 17 15.3 17 15.3 17 15.2 17 15.3 16.2 17 40.1 17 15.2 17 40.1 17 15.2 17 40.1 17 25.2 17 40.1 17 25.2 17 40.1 17 25.2 17 40.1 17 25.2 17 40.2 17 5.3 18 2.2 17 5.5 17 5.5 19 5.5 19 5.5 19 5.5 19 5.5 19 5.5 19 5.5 10 5.5	$\begin{array}{c c c c c c c c c c c c c c c c c c c $	$\begin{array}{c c c c c c c c c c c c c c c c c c c $	9         10.7         20         48         22.7         20         14           40         4         44         44         44         12.2         20         14           21.2         12.2         31         47.6         19.6         30         1.22           21.2         21.4         43         15.7         21.665         1.47         21         11.4           43         15.7         21.665         1.47         21         11.4         11.57         21.65         1.03         12.2         30         1.69         30         22.8         30         1.64         5         64         1.38         20         1.7         1.28         30         1.64         5         64         1.38         30         1.64         5         64         1.38         30         1.64         1.18 <td><math display="block">\begin{array}{c c c c c c c c c c c c c c c c c c c </math></td> <td><math display="block">\begin{array}{c c c c c c c c c c c c c c c c c c c </math></td> <td>9 107 20 44 227 20 11% -215525-138 -122 -216 123 -122 -217 22 31 478 196 30 12% -1602218-102 -217 22 31 478 196 30 12% -1602218-102 -217 22 -218 197 23 -218 197 23 -218 197 23 -218 197 23 -218 197 23 -218 197 24 -228 197 2</td> <td><math display="block">\begin{array}{cccccccccccccccccccccccccccccccccccc</math></td> <td>38 15 9 40 20 8 10% -0.011[108,084] 548 321 33 575 305 32 12 11% -0.01608,044] 548 321 33 575 305 32 12% -0.01608,044] 548 3155 19 625 115 11% -0.01608,044] 549 321 33 575 305 32 12% -0.01608,044] 549 321 33 575 305 32 12% -0.01608,044] 549 321 39 40 625 115 11% -0.01608,044] 549 321 40 625 115 51 12% -0.016055,076] 558 92 18 544 129 18 11% -0.016055,076] 558 92 18 544 129 18 11% -0.016055,076] 558 92 18 544 129 18 11% -0.016055,076] 558 92 18 544 129 18 11% -0.016055,076] 558 92 18 544 129 18 11% -0.016055,076] 558 92 18 544 129 18 11% -0.016055,076] 558 92 18 544 129 18 11% -0.016055,076] 558 92 18 544 129 18 11% -0.016055,076] 558 92 18 544 129 18 11% -0.016055,076] 558 92 18 544 129 18 11% -0.016040,081] 222 66 13 07 18 14 11% -0.46040,11 122] 54650,01 = 61 (P + 0.00001), P =65% * 0.0001) 73232,01 = 0.027, P = 33.3% rest plot of comparison TENS versus placebo with subgroup</td> <td>38       15       9       40       20       8       -0.011 [-0.6], 0.84]         54.8       32.1       33       57.5       30.5       32       1.28       -0.011 [-0.6], 0.84]         54.8       32.1       33       57.5       30.5       32       1.28       -0.011 [-0.6], 0.84]         47       33.4       30       49       27.38       30       1.28       -0.016 [-0.57, 0.45]         47       33.4       30       49       27.39       30       1.28       -0.06 [-0.57, 0.45]         54       52.2       10.2       15.2       1.28       -0.06 [-0.57, 0.45]       -0.01 [-0.10, 0.64]         54       9.2       16       54       7.41       1.3       0.40 [-0.55, 0.76]       -0.01 [-0.25, 0.76]         55.8       9.2       16       54.1       1.29       10.19 [-0.27, 0.55]       -0.25 [-0.6]       -0.25 [-0.76]         22.5       11.5       21       20.2       1.2%       -0.02 [-0.50, 0.76]       -0.02 [-0.001]       -0.02 [-0.001]       -0.02 [-0.001]       -0.02 [-0.001]       -0.02 [-0.001]       -0.02 [-0.001]       -0.02 [-0.001]       -0.02 [-0.001]       -0.02 [-0.001]       -0.02 [-0.001]       -0.02 [-0.001]       -0.02 [-0.001]       -0.02 [-0</td>	$\begin{array}{c c c c c c c c c c c c c c c c c c c $	$\begin{array}{c c c c c c c c c c c c c c c c c c c $	9 107 20 44 227 20 11% -215525-138 -122 -216 123 -122 -217 22 31 478 196 30 12% -1602218-102 -217 22 31 478 196 30 12% -1602218-102 -217 22 -218 197 23 -218 197 23 -218 197 23 -218 197 23 -218 197 23 -218 197 24 -228 197 2	$\begin{array}{cccccccccccccccccccccccccccccccccccc$	38 15 9 40 20 8 10% -0.011[108,084] 548 321 33 575 305 32 12 11% -0.01608,044] 548 321 33 575 305 32 12% -0.01608,044] 548 3155 19 625 115 11% -0.01608,044] 549 321 33 575 305 32 12% -0.01608,044] 549 321 33 575 305 32 12% -0.01608,044] 549 321 39 40 625 115 11% -0.01608,044] 549 321 40 625 115 51 12% -0.016055,076] 558 92 18 544 129 18 11% -0.016055,076] 558 92 18 544 129 18 11% -0.016055,076] 558 92 18 544 129 18 11% -0.016055,076] 558 92 18 544 129 18 11% -0.016055,076] 558 92 18 544 129 18 11% -0.016055,076] 558 92 18 544 129 18 11% -0.016055,076] 558 92 18 544 129 18 11% -0.016055,076] 558 92 18 544 129 18 11% -0.016055,076] 558 92 18 544 129 18 11% -0.016055,076] 558 92 18 544 129 18 11% -0.016040,081] 222 66 13 07 18 14 11% -0.46040,11 122] 54650,01 = 61 (P + 0.00001), P =65% * 0.0001) 73232,01 = 0.027, P = 33.3% rest plot of comparison TENS versus placebo with subgroup	38       15       9       40       20       8       -0.011 [-0.6], 0.84]         54.8       32.1       33       57.5       30.5       32       1.28       -0.011 [-0.6], 0.84]         54.8       32.1       33       57.5       30.5       32       1.28       -0.011 [-0.6], 0.84]         47       33.4       30       49       27.38       30       1.28       -0.016 [-0.57, 0.45]         47       33.4       30       49       27.39       30       1.28       -0.06 [-0.57, 0.45]         54       52.2       10.2       15.2       1.28       -0.06 [-0.57, 0.45]       -0.01 [-0.10, 0.64]         54       9.2       16       54       7.41       1.3       0.40 [-0.55, 0.76]       -0.01 [-0.25, 0.76]         55.8       9.2       16       54.1       1.29       10.19 [-0.27, 0.55]       -0.25 [-0.6]       -0.25 [-0.76]         22.5       11.5       21       20.2       1.2%       -0.02 [-0.50, 0.76]       -0.02 [-0.001]       -0.02 [-0.001]       -0.02 [-0.001]       -0.02 [-0.001]       -0.02 [-0.001]       -0.02 [-0.001]       -0.02 [-0.001]       -0.02 [-0.001]       -0.02 [-0.001]       -0.02 [-0.001]       -0.02 [-0.001]       -0.02 [-0.001]       -0.02 [-0

#### mple size

tistically significant difference in participant-reported pain intensity in favour of TENS at stated in the report that they had undertaken a sample size calculation (49 articipants, P < 0.00001,  $I^2 = 91\%$ ) and for those that did not (44 samples, 1994) 0.00001, I<sup>2</sup> = 79%). The test for subgroup differences was statistically significant at d threshold of P < 0.1 (Chi<sup>2</sup> = 3.63, df = 1, P = 0.06, I<sup>2</sup> = 72.4%), suggesting that the atement 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.

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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<sup>2</sup> = 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<sup>2</sup> = 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  $(Chi^2 = 2.03, df = 4 (P = 0.73), I^2 = 0\%).$ 

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### 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<sup>2</sup> = 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<sup>2</sup> = 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

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2	
3	TENS Piacebo Stat. Mean Difference Stat. Mean Difference Stat. Mean Difference Stat. Mean SD Total Weight IV. Random, 59% CI
4	2.4.1 Acute Palan Cipriano, et al., 2014 10 5 20 80 30 18 0.9% -3.27 [4.28,-2.27] ————————————————————————————————————
5	Mora, et al., 2006 33.3 16 39 82.6 14.3 34 1.1% -3.20 (5.34), -2.50)
6	Shaheel et al. 2017 (2) 49 25 30 681 69 30 1.1% - 261 [33, 1.9]
	Banker, (al., 2006 32.4 18 29 662 11.2 33 1.1% - 226/2.81, 1.61]
7	Desandara, et al., 2006 (3) 9 10.7 20 48 22.7 20 1.1% -21.5[2.26,1.36]
8	Base2ourarez etal, 2016 62 14 21 63 12 21 1.1% - 1.58/2.28,-0.08/
9	Jaanfaroour, et al. 2008 6 5 54 12 42 54 12% -151 [193,-108]
10	Sadala, etal., 2019 29.3 19.5 28 568 17.7 27 12% -1.45;2.05,-0.861
	Cipriano, et al., 2009 (9) 20 7.4 23 30 7.4 22 1.1% 1.33 [1.98, 0.66]
11	Mahung etal. 2017 (10) 36 21 15 58 12 15 1.1% -1.25 2.04, 0.06]
12	Lison, etal, 2017 (12) 23.2 31.4 46 53.1 19.9 46 12% -113 (15.7, 0.06)
13	Cuschieri, et al., 1987 (14) 30 11.25 10 49 20.25 10 1.0% -1.11 [2.07, 0.15]
14	Abreu etal, 2010 68 23 10 88 10 10 10% - 108/203,013)
15	Aminisaran et al., 2020 26.6 5.4 30 31.2 4.8 30 1.2% -0.89 [1.42, -0.36]
	Oncelestal, 2002 (17) 24 13 25 39 20 25 12% -0.895 (146, 0.29) —— Elisionin etal, 2020 (16) 41.7 192 23 612 25 16 1.1 % -0.875 (152, 0.22) ——
16	Zakanase et al. 2019 (19) 318 204 40 475 165 40 12% -0.84 (1.30, -0.38)
17	Florelli, et al., 2012 (21) 39 8 23 45 7 23 1.2% -0.78 [F1.39, -0.18]
18	Wardeld, et al., 1985 (23)         48.3         201         12         6.4         12         10%         -0.66[+151, 0.14]           Fuji-Roe et al., 2019 (24)         22.1         12.8         11         0.36         -0.66[+152, 0.21]           Fuji-Roe et al., 2015         13         16         15         24.21         19.4
19	Bjersa & Andersson, 2014         13         16         15         26         24         13         11%         -0.63[-139, 01.4]           Bjersa & Andersson, 2014         194         32.5         9         39.6         32         11         1.0%         -0.60[-151, 0.30]           Beren, etal., 2017 Zd)         30.8         7.2         4.2         10.1         4.4         1.2%         -0.68[-100, 0.115]
20	Osili, et al. 2015 21 16 37 29 22 37 12% -041; 6087,009
	Rakel & Frantz 2003 (27) 42 33.45 33 55 37.3 33 12% -0.36 [-0.95 0.12]
21	Homoson, et al., 2001 362, 31, 24 10 47, 92 363, 71 31 10 % -0.27 [-1,10, 0.56] Harraz, et al., 1998 (20) 25 23 25 31 25 25 12% -0.25 [-0.80, 0.31] Cuschieri, et al., 1985 (30) 25 21.8 53 28 21.8 53 1.3% -0.14 [-0.52, 0.24]
22	Foreiner, et al., 1994 (37) 98 281 15 137 319 15 11% -0.131084 (359)
23	Thornas, et al., 1088 (33) 33 31 1 131 35 338 144 1.3% -0.06 (-0.30, 018) + (-1.26, 013, 014, 014, 014, 014, 014, 014, 014, 014
24	Tucker, el al., 2015 (35) 56 56 35 57 57 35 1.2% -0.02 (0.49, 0.45) Da Silva, et al., 2015 (36) 1 0 21 4 0 21 Not estimatole Lee, et al., 2015 55 9 2 13 644 12.9 18 1.1% 0.10 (0.55, 0.76)
25	Leee, et al., 2015 50.6 9.2 15 94 4 12.9 16 1.156 0.02 (0.00) Sha, et al., 2012 (37) 22.5 115 21 20 12.5 21 12.% 0.20 (0.40, 0.81) Beckwee, et al., 2010 39.2 251 25 30.6 23.2 28 12.% 0.35 (0.19, 9.90)
	Kayman-Kose, etal. (214 (38) 13.5 58 50 7.8 7 50 1.2% 0.88 [047, 139] Subtotal (95% CD) 1667 1681 64.6% .0.26 1.24.7.109] ◆
26	Heterogeneity, "Jau" = 0.64, "Chi" = 491, 98, di = 56 (P < 0.00001);  P = 89% Test for overall effect Z = 8.88 (P < 0.00001)
27	2.4.2 Chronic Pain Barbarisi,etal, 2010 25.11 0.92 9 39 1.19 8 0.1% -12.50[-17.39,-7.61] 4
28	Holsenek at al. 2019 (20) 22 12.49 39 72 137 39 1.1% -311 [376,2.44]
29	Ekim et al., 2008 (40) 47.2 5.6 10 85.3 6.3 9 0.8% -2.91 (-4.29, -1.54)
30	Kibar et al, 2020 (42) 21.2 12.2 31 47.6 19.6 30 12% -1.60 (2.18, -1.02)
31	De comentar at a 2012 (44) 50 164 55 54 155 5 078 - 1.44 222, 0.001
	Colik, #14, 2013 388 25 17 677 14.2 16 1.1% -139[2:14,0.06] Lawrell, #14, 2013 (45) 60 10 13 60 20 10 1.0% -139[2:14,0.06]
32	Subje dal, 2015 18.7 7.46 24 30.7 17.67 23 12.% -0.88[+1.48,-0.28]
33	Vtbill & Oleg. 2014         39.5         17         11         52.5         18.6         10         10%         -0.70[+159,0.16]           Bliglit, etal., 2016         14.27         10.1         15         23.27         15.8         15         1.1%         -0.66[+140,006]           Shimoura, etal., 2019 (47)         5.1         1         1.2%         -0.66[+1.42,0.006]
34	Shimowa, etal., 2019 (47)         5.1         8         25         11.4         10.9         25         12.%         0.65 (1 22, -0.06)           Liu, etal., 2017 (48)         48.2         17.7         22         65.8         12.6         22         1.2%         -0.49 (-1.09, 0.11)           Gimmer, 1982 (48)         22         28         0.3         5.2         0.45 (-1.09, 0.11)
35	Dailey, et al., 2013 (41)       40       4       41       47       4       41       24       -1.73 (224, -1.22)
36	Machin, elai, 1988 13.47 13.72 15 16.29 13.65 15 1.1% -0.20 [-0.92, 0.52]
37	Sahin, etal., 2011 665 155 19 605 115 19 11% -007+071,056) Ilmani, 2015 (55) 22.4 11.3 35 22.8 10.2 31 1.2% -0.04 {-0.52,0.45} Bono, etal., 2015 60 20 54 00 20 54 1.3% -0.004 {-0.52,0.45}
38	Markado et al., 2019 (56) 47 25 22 46 22 12 12% 0.04 (0.05,0.05) Atamaz, et al., 2012 54.7 24.1 37 50.4 20.3 37 1.2% 0.19 [-0.27,0.85]
39	Kottonis,et at., 2008 22 4 23 20 4 21 1.2% 0.48 (+0.11,08) Subtrata[9% C]) 721 656 32.3% 0.487 (-119,0.55] ◆
40	Helerogenely, Tau#= 0 67, Chi#=222.02, d#=30 (P < 0.00001); P = 86% Test for overall effect Z = 5.28 (P < 0.00001)
41	2.4.3 Not Reported Cheing & Luk, 2005 17 17 10 46 20 9 0.9% -1.50 [-2.55,-0.45]
42	Mansaur, et al. 2019 (57) 26.67 22.57 15 45.33 20.15 15 11.3% -0.724 [r.4.9,0.00]
	Stational (195% CI) 38 38 3.1% -0.55 [-1.63, 0.52]
43	Testfor overall effect Z = 1.01 (P = 0.31) Total (95% CD 2426 2415 100.0% -0.96 [-1.14], -0.77] ♦
44	Heisrogeneity Tau*a 64, Chill = 73.32, df = 0.0001), P = 88%
45	Testfor subgroup differences: ChP=1.12, df=2 (P=0.57), P=D% Parous i Ento Farous i Ento
46	Figure A6 Forest plot of comparison TENS versus placebo with subgroup analysis to explore the
47	effect of pain duration categorised as acute and chonic pain.
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<del>4</del> 0	

#### 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 postoperative pain (36 samples, 1788, P < 0.00001, I<sup>2</sup> = 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<sup>2</sup> = 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

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MetaTENS\_Appendix\_BMJO\_05-10-2021 – Supplementary File 1

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<sup>2</sup> = 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

tor peer review only

TENS Placebo Sid. Mean Difference Study or Subgroup Mean SD Total Mean SD Total Weight IV, Random, 95% Cl	Std. Mean Difference IV, Random, 95% Cl		
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2.5.24 Varients active humanite juines - spraines, facebarres, locarditions           2.5.24 Varients active humanite juines - spraines, facebarres, locarditions           Constructions           Constructions           Ministrations           Direct operations           Direct operations </td <td>•</td> <td></td> <td></td>	•		

**BMJ** Open

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<sup>2</sup> = 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<sup>2</sup> = 80%), acute procedural pain (10 RCTs, 682 participants, P = 0.001, I<sup>2</sup> = 88%), and labour pain (4 sample, 397 participants, P = 0.05, I<sup>2</sup> = 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<sup>2</sup> = 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<sup>2</sup> = 41.5, df = 10 (P < 0.00001), I<sup>2</sup> = 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<sup>2</sup> = 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.

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#### MetaTENS\_Appendix\_BMJO\_05-10-2021 – Supplementary File 1

Study or Subgroup 2.12.1 Chronic Primary Pain	TENS Mean SD Tota		otal Weight	td. Mean Difference IV, Random, 95% Cl	Std. Mean Difference IV, Random, 95% Cl	
Holemek et al., 2019 (1) bloemek et al., 2013 (2) (3) (3) (2) (2) (2) (3) (3) (3) (3) (3) (3) (4) (2) (3) (4) (3) (3) (3) (3) (3) (3) (3) (3) (3) (3	$\begin{array}{cccccccccccccccccccccccccccccccccccc$		$\begin{array}{cccccccccccccccccccccccccccccccccccc$	$\begin{array}{c} 3.113.78, -2.44\\ 1.73+2.24, -1.22\\ 1.00+2.18, -1.02\\ 1.73+2.24, -1.02\\ 1.46+2.48, -0.45\\ 1.46+2.25, -0.54\\ 1.48+2.25, -0.54\\ 1.48+2.25, -0.54\\ 1.48, -2.25, -0.54\\ 1.48, -2.25, -0.54\\ 0.08+1.08, -0.07\\ 0.05+1.08, -0.07\\ 0.05+1.08, -0.07\\ 0.05+0.03, -0.07\\ 0.05+0.03, -0.07\\ 0.05+0.03, -0.07\\ 0.05+0.03, -0.07\\ 0.05+0.03, -0.07\\ 0.05+0.03, -0.07\\ 0.05+0.03, -0.07\\ 0.04+0.03, -0.03\\ 0.04+0.02, -0.43\\ 0.04+0.03, -0.03\\ 0.04+0, -0.03, -0.03\\ 0.04+0.03, -0.03\\ 0$		
Test for overall effect $Z = 3.54$ (P) 2.122 Otronic Neuropathic Pain Barbarisi, et al., 2010 (21) Ekim et al., 2008 (22) Cheing a Luk, 2008 (23) Bi, et al., 2013 (25) Vialia (0.16), 2014 (26) Warke, et al., 2014 (26) Warke, et al., 2014 (26) Warke, et al., 2004 (27) Warke, et al., 2004 (27) Hebrogoneity, Tau <sup>+</sup> = 1.02, Ch <sup>-</sup> = Test for overall effect $Z = 3.86$ (27)	25.11 0.92 9 47.2 5.6 11 17 17 11 21.4 9.1 21 39.5 17 1 28.25 36.5 8 4 28.95, df = 6 (P < 0.0	9 39 1.19 0 65.3 6.3 0 46 20 6 38.7 14.5 7 67.7 14.2 1 52.5 18.6 5 40.33 19.4 8	8 0.1% 9 0.8% 9 0.9% 26 1.2% 16 1.1% 10 1.0% 3 0.7% 81 5.7%	-12.50 [-17.39, -7.61] 4 -2.31 [42.29, -1.54] -1.50 [-2.55, -0.45] -1.41 [-2.02, -0.80] -0.70 [-1.59, 0.19] -0.33 [-1.78, 1.12] -1.68 [-2.58, -0.78]		
2.12.3 Chronic Secondary Musci Shimoura, et al., 2019 (28) Grimmer, 1992 (29) Atamaz, et al., 2012 (30) Subtotal (95% CI) Heterogeneity: Tau <sup>2</sup> = 0.15; Chi <sup>2</sup> = Test for overall effect: Z = 1.00 (P:	5.1 8 2 22 28 20 54.7 24.1 3 5.78, df = 2 (P = 0.06	0 35 29 7 50.4 20.3 2	25 1.2% 20 1.1% 37 1.2% 82 3.5%	-0.65 [-1.22, -0.08] -0.45 [-1.08, 0.18] 0.19 [-0.27, 0.65] - <b>0.27 [-0.81, 0.26]</b>		
2.12.4 Chronic Secondary Visce Lauretti, et al., 2015 (31) De Oliverira et al., 2012 (32) Neighbours, et al., 1987 (33) Machado et al., 2019 (34) Subtotal (95% CI) Heterogeneity. Tau <sup>2</sup> = 2.00; Ch <sup>2</sup> = Test for overall effect Z = 1.74 (P:	20 10 21 30 16.4 1 17.5 30.3 11 47 25 2: 57 31.01, df= 3 (P < 0.0	5 54 13.6 0 40.7 20.74 2 46 22 7	20 1.0% 5 0.7% 10 1.0% 22 1.2% 57 3.8%	-3.10 [-4.05, -2.15] -1.44 [-2.92, 0.04] -0.86 [-1.78, 0.07] 0.04 [-0.55, 0.63] -1.31 [-2.79, 0.17]		
2.12.5 Chronic Cancer Related P Subtotal (95% CI) Heterogeneity: Not applicable Test for overall effect: Not applica	ain	0	0	Not estimable		
2.12.8 Acute Postsurgical Pain Ciprimo, et al., 2014 (35) Ciprimo, et al., 2014 (35) Diamate, et al., 2014 (35) Diamate, et al., 2016 (37) Desantan, et al., 2008 (38) Judifrour, et al., 2008 (39) Judifrour, et al., 2008 (30) Admino, et al., 2008 (30) Admino, et al., 2008 (30) Admino, et al., 2018 (40) Ciprimo, et al., 2019 (41) Diamate, et al., 2014 (40) Pinnau, et al., 2014 (40) Pinnau, et al., 2014 (40) Pinnau, et al., 2014 (40) Pinnau, et al., 2014 (40) Pinnau, et al., 2014 (40) Pinnau, et al., 2014 (40) Pinnau, et al., 2014 (40) Pinnau, et al., 2014 (40) Pinnau, et al., 2014 (40) Pinnau, et al., 2014 (40) Pinnau, et al., 2015 (55) Diseas, et al., 2015 (55) Diseas, et al., 2015 (56) Diseas, et al., 2017 (50) Sezon, et al., 2017 (50) Ciprime, et al., 2015 (50) Diseas, et al., 2017 (50) Diseas, et al., 2017 (50) Diseas, et al., 2017 (50) Diseas, et al., 2017 (50) Diseas, et al., 2012 (50)	$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	$\begin{array}{cccccccccccccccccccccccccccccccccccc$		$\begin{array}{c} -3.27 \ (\pm 4.26, -2.27) \\ -2.51 \ (\pm 32, -1.60) \\ -2.51 \ (\pm 32, -1.60) \\ -2.51 \ (\pm 32, -1.60) \\ -1.51 \ (\pm 2.22, -1.30) \\ -1.51 \ (\pm 1.22, -2.0.86) \\ -1.51 \ (\pm 1.23, -1.06) \\ -1.51 \ (\pm 1.23, -1.06) \\ -1.51 \ (\pm 1.33, -1.06) \\ -1.51 \ (\pm 1.34, -1.06) \\ -1.51 \ (\pm 1.34, -1.06) \\ -1.51 \ (\pm 1.34, -1.06) \\ -1.51 \ (\pm 1.34, -1.06) \\ -1.51 \ (\pm 1.34, -1.06) \\ -1.51 \ (\pm 1.34, -1.06) \\ -1.51 \ (\pm 1.34, -1.06) \\ -1.51 \ (\pm 1.34, -1.06) \\ -1.51 \ (\pm 1.34, -1.06) \\ -1.51 \ (\pm 1.34, -1.06) \\ -0.57 \ (\pm 1.34, -1.06) \\ -0.57 \ (\pm 1.34, -1.06) \\ -0.57 \ (\pm 1.34, -1.06) \\ -0.57 \ (\pm 1.34, -1.06) \\ -0.57 \ (\pm 1.34, -1.06) \\ -0.57 \ (\pm 1.34, -1.06) \\ -0.57 \ (\pm 1.34, -1.06) \\ -0.57 \ (\pm 1.34, -1.06) \\ -0.57 \ (\pm 1.34, -1.06) \\ -0.57 \ (\pm 1.54$		
Sadala, et al., 2018 (7.3) Lison, et al., 2017 (7.4) Aminisaman et al., 2020 (75) Hruby, et al., 2001 (76) Robinson, et al., 2001 (77) Vilmazer, et al., 2017 (78) Presser, et al., 2017 (78) Presser, et al., 2018 (80) Subtotal (95% C) Heterogeneity: Tau" = 0.49; Chi <sup>a</sup> = Test for overall effect: Z = 3.29 (P	23.2 31.4 44 26.6 5.4 31 35 28.8 44 38.2 31.24 11 54.6 32.1 31 47 38.34 31 56 56 33 344 73.72, df = 9 (P < 0.0	6 53.1 19.9 0 31.2 4.8 8 43.7 30.6 0 47.92 36.37 3 57.5 30.5 0 49 27.39 5 57 57 0 3	27 1.2% 46 1.2% 30 1.2% 49 1.2% 49 1.2% 31 1.0% 32 1.2% 30 1.2% 35 1.2% 342 11.9%	-1.45 [-2.05, -0.86] -1.13 [1.57, -0.69] -0.89 [-1.42, -0.36] -0.29 [-0.69, 0.11] -0.27 [-1.10, 0.56] -0.09 [-0.58, 0.40] -0.06 [-0.57, 0.45] -0.02 [-0.49, 0.45] -0.78 [-1.24, -0.31]		
2.12.8 Acute Labour Pain Shahoei, et al., 2017 Baez-Suarez, et al., 2018 Abreu, et al., 2010 Thomas, et al., 1988 Subtotal (95% Ct) Heterogeneity: Tau <sup>2</sup> = 1.65; Chi <sup>2</sup> = Test for overall effect. Z = 1.98 (P	49 25 3 62 14 2 68 23 11 33 31.1 13 58.56, df = 3 (P < 0.0 = 0.05)	1 83 12 0 88 10 1 35 33.8 2 2	30 1.1% 21 1.1% 10 1.0% 144 1.3% 205 4.5%	-2.61 [-3.31, -1.91] -1.58 [-2.28, -0.86] -1.08 [-2.03, -0.13] -0.06 [-0.30, 0.18] -1.31 [-2.62, -0.01]	 •	
2.12.9 Acute Visceral Pain Mora, et al., 2006 (81) Barker, et al., 2006 (82) Kayman-Kose, et al., 2014 (83) Subtotal (95% C1) Heterogeneity. Tau <sup>2</sup> = 5.45; Chi <sup>a</sup> = Test for overall effect: Z = 1.11 (P:	32.4 18 2 13.5 5.8 5 111 127.36, df = 2 (P < 0	07.87 8.	34 1.1% 33 1.1% 50 1.2% 117 3.5%	-3.20 [-3.91, -2.50] -2.26 [-2.91, -1.61] 0.88 [0.47, 1.29] - <b>1.52 [-4.18, 1.15]</b>		
2.12.10 Acute Traumatic Pain Lang, et al., 2007 (84) Ordog, 1987 (85) Oncel, et al., 2002 (86) Subtotal (95% CI) Heterogeneity, Tau <sup>a</sup> = 0.35; Chi <sup>a</sup> = Test for overall effect: Z = 3.79 (P	24 13 29 80 9.22, df = 2 (P = 0.01	5 54.8 25 5 39 20 0	33 1.1% 25 1.1% 25 1.2% 83 3.5%	-2.20 [-2.83, -1.57] -1.35 [-1.97, -0.73] -0.88 [-1.46, -0.29] -1.47 [-2.23, -0.71]	 	
2.12.11 Acute Vascular Pain Cuschien, et al., 1987 (87) Subtotal (95% CI) Heterogeneity. Not applicable Test for overall effect. Z = 2.28 (P- 2.12.12 Acute Musculoskeletal F Bertalanffy, et al., 2005 (88) Subtotal (95% CI) Heterogeneity. Not applicable		0	10 1.0% 10 1.0% 33 1.1% 33 1.1%	-1.11 [-2.07, -0.15] -1.11 [-2.07, -0.15] -2.85 [-3.57, -2.14] -2.85 [-3.57, -2.14]	-	
Heterogeneity: Not applicable Test for overall effect: Z = 7.84 (P	< 0.00001)	6 24	15 100.0%	-0.96 [-1.14, -0.78]	•	

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<sup>2</sup> = 88%) and for pain conditions categorised as predominantly neuropathic in origin (7 samples, 191 participants, P < 0.0001, I<sup>2</sup> = 80%). The test for subgroup differences was statistically significant at our pre-specified threshold of P < 0.1 (Chi<sup>2</sup> = 2.83, df = 1 (P = 0.09), I<sup>2</sup> = 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<sup>2</sup> = 92%), musculoskeletal (26 samples, 1237 participants, P < 0.00001, I<sup>2</sup> = 83%), visceral (44 samples, 2543 participants, P < 0.00001, I<sup>2</sup> = 89%) and neural (7 samples, 191 participants, P = 0.0001, I<sup>2</sup> = 80%) structures. There were no statistically significant differences in painful experiences with predominant involvement from bone (5 samples, 260 participants, P < 0.06, I<sup>2</sup> = 89%). The test for subgroup differences was not statistically significant (Chi<sup>2</sup> = 7.62, df = 4 (P = 0.11), I<sup>2</sup> = 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

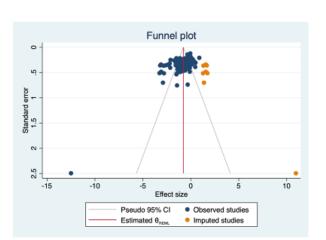


Figure A9 Funnel plot of TENS versus placebo comparison with trim and fill analysis. Actual results displayed in blue. Results corrected for the possibility of a publication bias displayed in orange.

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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  $\geq$ 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.

## 

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  $\geq$ 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<sup>2</sup> = 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.

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	TEN	s	Place	bo		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
Neighbours, et al., 1987 (1)	8	10	1	10	3.6%	8.00 [1.21, 52.69]	
Amer-Cuenca, et al., 2011 (2)	17	30	3	30	10.3%	5.67 [1.85, 17.34]	
Buchmuller, et al., 2012 (3)	26	104	7	104	20.6%	3.71 [1.69, 8.18]	│ <b>—</b> ●──
Hansson & Ekblom, 1983 (4)	7	22	2	20	6.1%	3.18 [0.75, 13.57]	+
Roche, et al., 1985 (5)	21	28	2	8	8.6%	3.00 [0.89, 10.15]	
Ekblom & Hansson, 1987 (6)	3	11	1	10	2.9%	2.73 [0.34, 22.16]	
Smith, et al., 1983 (7)	10	15	4	15	15.4%	2.50 [1.00, 6.23]	
Lewers, et al., 1989 (8)	8	10	4	11	18.2%	2.20 [0.95, 5.10]	
Langley, et al., 1984 (9)	6	11	4	11	14.2%	1.50 [0.58, 3.88]	
Total (95% CI)		241		219	100.0%	2.89 [2.02, 4.13]	•
Total events	106		28				
Heterogeneity: Tau <sup>2</sup> = 0.00; Chi	<sup>2</sup> = 5.66, d	lf = 8 (F	P = 0.69);	l <sup>2</sup> = 0%			
Test for overall effect: Z = 5.80 (	P < 0.000	01)					0.01 0.1 1 10 100 Favours Placebo Favours TENS

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<sup>2</sup> = 76%). There was insufficient data to undertake subgroup analyses to explore the effect of methodological nor clinical characteristics on outcome.

#### Forest plot

	TENS		No Trea	tmont Co				
Magn			No Treatment Control			2	Std. Mean Difference	Std. Mean Difference
Mean	an SD Total		Mean	SD	SD Total		IV, Random, 95% Cl	IV, Random, 95% Cl
40	16	20	70	16	21	8.8%	-1.84 [-2.58, -1.10]	_ <b></b>
13.6	15.3	20	41	21.8	20	9.1%	-1.43 [-2.13, -0.72]	_ <b>-</b>
29.3	19.5	28	56.3	18.4	28	10.1%	-1.40 [-1.99, -0.82]	
26.5	24.7	30	54.7	30.1	30	10.6%	-1.01 [-1.55, -0.47]	
45.1	13.5	15	56.7	11.7	15	8.6%	-0.89 [-1.65, -0.14]	_ <b></b>
37.1	20.6	71	50.7	20.3	71	12.4%	-0.66 [-1.00, -0.32]	
35.5	17.8	16	48.1	23.7	16	9.0%	-0.59 [-1.30, 0.12]	
11.65	16.71	10	20.96	18.44	12	7.8%	-0.51 [-1.36, 0.35]	
19	17	40	24	23	40	11.5%	-0.24 [-0.68, 0.20]	
35	28.8	48	34.4	30.5	51	11.9%	0.02 [-0.37, 0.41]	+
		298			304	100.0%	-0.82 [-1.18, -0.46]	•
= 37.38	. df = 9	(P < 0.0	001); l² =	76%				
		•						-4 -2 U 2 4 Favours TENS Favours No Treatment
=	13.6 29.3 26.5 45.1 37.1 35.5 11.65 19 35 37.38	13.6         15.3           29.3         19.5           26.5         24.7           45.1         13.5           37.1         20.6           35.5         17.8           11.65         16.71           19         17           35         28.8	13.6 15.3 20 29.3 19.5 28 26.5 24.7 30 45.1 13.5 15 37.1 20.6 71 55.5 17.8 16 11.65 16.71 10 19 17 40 35 28.8 48 <b>298</b> 37.38, df = 9 (P < 0.0	13.6 15.3 20 41 29.3 19.5 28 56.3 26.5 24.7 30 54.7 45.1 13.5 15 56.7 37.1 20.6 71 50.7 35.5 17.8 16 48.1 11.65 16.71 10 20.96 19 17 40 24 35 28.8 48 34.4 <b>298</b> 37.38, df= 9 (P < 0.0001); P=	$\begin{array}{cccccccccccccccccccccccccccccccccccc$	13.6     15.3     20     41     21.8     20       29.3     19.5     28     56.3     18.4     28       26.5     24.7     30     54.7     30.1     30       45.1     13.5     15     56.7     11.7     15       37.1     20.6     71     50.7     20.3     71       35.5     17.8     16     48.1     23.7     16       11.65     16.71     10     20.96     18.44     12       19     17     40     24     23     40       35     28.8     48     34.4     30.5     51 <b>298 304</b> 37.38, df = 9 (P < 0.0001); P = 76%	13.6       15.3       20       41       21.8       20       9.1%         29.3       19.5       28       56.3       18.4       28       10.1%         26.5       24.7       30       54.7       30.1       30       10.6%         45.1       13.5       15       56.7       11.7       15       8.6%         37.1       20.6       71       50.7       20.3       71       12.4%         35.5       17.8       16       48.1       23.7       16       9.0%         14.65       16.71       10       20.96       18.44       12       7.8%         19       17       40       24       23       40       11.5%         35       28.8       48       34.4       30.5       51       11.9% <b>298 304 100.0%</b> 37.38, df = 9 (P < 0.0001); P = 76%	13.6       15.3       20       41       21.8       20       9.1%       -1.43 [-2.13, -0.72]         29.3       19.5       28       56.3       18.4       28       10.1%       -1.40 [-1.99, -0.82]         26.5       24.7       30       54.7       30.1       30       10.6%       -1.01 [-1.55, -0.47]         45.1       13.5       15       56.7       11.7       15       8.6%       -0.89 [-1.65, -0.42]         37.1       20.6       71       50.7       20.3       71       12.4%       -0.66 [-1.00, -0.32]         35.5       17.8       16       48.1       23.7       16       9.0%       -0.59 [-1.30, 0.12]         11.65       16.71       10       20.96       18.44       12       7.8%       -0.51 [-1.36, 0.35]         19       17       40       24       23       40       11.5%       -0.24 [-0.68, 0.20]         35       28.8       48       34.4       30.5       51       11.9%       0.02 [-0.37, 0.41]         298       304       100.0%       -0.82 [-1.18, -0.46]         37.38, df = 9 (P < 0.0001); P = 76%

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.

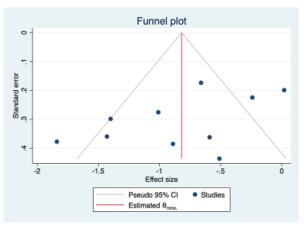


Figure A12 Funnel plot of TENS versus no treatment comparison.

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

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

for oper teries only

## 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<sup>2</sup> = 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

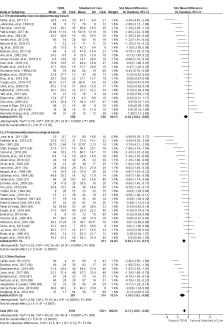


Figure A13 Forest plot of comparison TENS versus standard of care. Outcome: pain intensity - expressed as mean (continuous) data. Subgroup analysis comparing TENS either alone or when added to exercise/physiotherapy based interventions, pharmacologically based interventions, and SoC that was categorised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

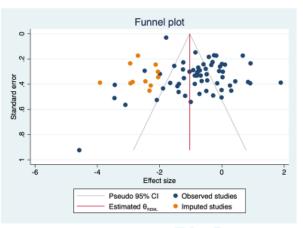


Figure A14 Funnel plot of TENS versus standard of care comparison with trim and fill analysis. Actual results displayed in blue. Results corrected for the possibility of a publication bias displayed in orange.

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]

## 

There were two RCTs with extractable data. It was not possible to conduct an analysis of the proportion of participant-reported pain relief of  $\geq$ 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  $\geq$ 30% reduction). Hence, it was not possible to conduct an analysis of the proportion of participant-reported pain relief of  $\geq$ 30% expressed as frequency (dichotomous) data because of insufficient data.

#### 

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  $\geq$ 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

**BMJ** Open

TENS         Other Treatment         St           Study or Subgroup         Mean         SD         Tetal         Mean         SD         Tetal         Weight           5.2.1 Interferential current therapy         Koia, 4(4), 2014 (1)         40         11.0         20         68.0         14.2         21         1.3%           Koiar et al, 2020 (2)         2.12         12.2         13         32         17.30         1.5%	Mass Difference Std. Mono Difference M. Randon, 95% G	
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	407         11         407         11         407         11         407         11         407         11         407	
$\label{eq:22} Promoved product of the state of the stat$	0.971102_013	
Hattery G100 (20)         456         11.6         16         6.8         0.3         14         12.6           Cells, et al., 1000 (20)         32         12         45         37.6         13.8         14         12.6         13.6         14         12.6         13.6         13.6         14.7         13.6         14.7         13.6         15.6         11.7         10         55.7         17.7         10         55.7         15.7         10.7	2185111-128 4012454.000 4012554.000 40125554.000 401255554.000 4012555555555555555555555555555555555555	
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	4. 23 1 1 60, 6 60 4. 31 9 1 60, 6 60 4. 31 9 1 60, 6 70 1. 47 1 9 12, 5 23 1. 47 1 9 12, 5 23 4. 37 12, 5 23 4. 37 12, 5 23 4. 37 12, 5 23 4. 37 12, 5 23 4. 37 12, 5 23 4. 37 12, 5 23 4. 37 12, 5 23 4. 37 12, 5 23 4. 37 12, 5 23 4. 37 12, 5 23 4. 37 12, 5 23 4. 37 12, 5 23 4. 37 12, 5 23 4. 37 12, 5 23 4. 37 12, 5 23 4. 37 12, 5 23 4. 37 12, 5 23 4. 37 12, 5 23 4. 37 12, 5 24 5. 37 12, 5 24	
\$2.25 Acquarks and InterfaceQuencture           \$2.25 Acquarks (E-Bipper, VG)         \$2.7 \$2.6 \$15 \$28.3 \$2.6 \$15 \$10%\$           \$0 chart, et al., 1997 (24)         \$2.7 \$2.1 \$27 \$42.9 \$34.6 \$20 \$15%\$           \$9.41, 2001 CD)         \$2.7 \$2.1 \$27 \$4.0 \$3 \$2.6 \$16 \$11%\$           \$9.41, 2001 CD)         \$2.1 \$16 \$32 \$2.1 \$6 \$15\$           \$9.41, 2001 CD)         \$2.1 \$16 \$32 \$2.1 \$6\$           \$9.41, 2001 CD)         \$2.1 \$16 \$2.2 \$2.0 \$2.1 \$21\$           \$9.41, 2001 CD)         \$2.0 \$1.0 \$15\$           \$9.41, 2001 CD)         \$2.0 \$1.0 \$2.0 \$1.0 \$1.0 \$1.0 \$1.0 \$1.0 \$1.0 \$1.0 \$1	-1.22[435,-200] -4.40[454,072] -4.40[44]12[460] -0.12[446,072] -4.40[448,049]	
Display         Display	-30(13)(-2-1)) 	
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	- 465 (1 A00) 0 20 (4 A0 A00) 0 20 (4 A0 A00) 0 20 (4 A1 A00) 0 40 (4 A53, 4 80)	
And etal.         214         112         24         28         168         25         148           Beyerd, H. 2, 000         124         112         24         28         158         25         148           Beyerd, H. 2, 000         58         124         24         28         21         158         158           Logen A. Normer, X002 (40)         68         224         24		
$\label{eq:2.2} \begin{array}{cccccc} 3.3 \ Product on which all on which a$		
Haterogranity: Tau <sup>2</sup> = 0.00; Ch <sup>2</sup> = 0.03; df = 1 (P = 0.86); P = 0% Test for overall effect: Z = 0.35 (P = 0.72) \$2,211 Low level laser therapy Ostanopiju et al., 2019 (56) 19.5 13.9 20 18.5 13.8 20 1.4%	-066(420.057) -0.106(420.057) -0.107(400.057) -0.107(400.057) -0.107(400.057) -0.107(4	
Cysalop, et al., 2013 (57)         68         10         10         44         14         10         1, 2%           Subsidia (90% CI)         30         20         30         30         20         20         30         21         45         30         21         45         30         21         45	0.45(46,0.10) 0.45(46,00)	
Statutat (95% C)         35         39         2,7%           Heregonistic Tura = 0.3%, Chir = 3.72, dF = 1,9 = 0.05%, F = 7.9%         Test for overall effect Z = 1.27.9° = 0.20%         Test for overall effect Z = 1.27.9° = 0.20%           S2,15 Plated radiative queriesy - transcritamenose (m, et al., 2015; 00%)         0.44         5.4         2.5         4.73         1.38         25         1.4%           Kolmmar, et al., 2010; 01%)         18         1.4         20         1.4%         5.4%         2.4%		
Statutati (9% C)         45         45         2.8%           Hextogramity: Tural = 0.02; Ch# = 119; df = 1 (P = 0.27; P = 16%         Test for overall effect; Z = 0.66 (P = 0.51)         S.2.14 Software Therapy           S.2.14 Software Therapy         Control = 0.5         S.2.14 Software Therapy         All (P = 0.27; P = 16%)         Software Therapy           S.2.14 Software Therapy         Control = 0.5         S.2.14 Software Therapy         Software Therapy         Software Therapy           Software Therapy         Software Therapy         Software Therapy         Software Therapy         Software Therapy           Software Therapy         Software Therapy         Software Therapy         Software Therapy         Software Therapy           Software Therapy         Software Therapy         Software Therapy         Software Therapy         Software Therapy           Software Therapy         Software Therapy         Software Therapy         Software Therapy         Software Therapy           Software Therapy         Software Therapy         Software Therapy         Software Therapy         Software Therapy           Software Therapy         Software Therapy         Software Therapy         Software Therapy         Software Therapy           Software Therapy         Software Therapy         Software Therapy         Software Therapy         Software Therapy     <		
Heterogenethy, Trait = 0.00; Ch = 0.04, df = 1 (P = 0.86); P = 0 %. Testfor overall effect Z = 0.90 (P = 0.37) S.25 (Stead III) Cobul, et al., 2014 (04) 491 12.4 24 49.1 12.1 24 14 %. Thick et al. 2016 (50) 24.6 156 13 208 152 12 13%.	100(497,167)	
Sakeisei (1955; C) 37 37 36 2.7% Heteogramity: Tard = 0.05; Chill = 0.22; cf = 1 (P = 0.84); Pr = 0.84; Test for owness effect 2 = 0.34 (P = 0.74) Sal 77 (Bp) Vallege Decktraic Al Carriert Radiary, et al. (2017) (66) 20 5 45 20 185 24 20 14% Heteogramity: Tardiary accords to 20 20 185 24 10 14% 20 14%	0.m (a.m, (a.m, 6.5) 0.54 (a.00, 1.10) 0.54 (a.00, 1.10)	
-Hentrogeneral, (70 applicable Filter forwards Hentro, 2 − 5 fil 0 = 0.00) 5.218 Hydrodinet app 0.58 Hydrogeneral, 2 − 000 (67) 34 22 5 65 15 5 0.0% Hentrogeneral, Not applicable 5 5 0.0% Hentrogeneral, Not applicable 5 5 0.0%	-1.54(3.05,-0.02) -1.54(3.05,-0.02)	
5.2.19 Intracutaneous starile water injections Lahrengun, et al. (1993 (初) 66 5 12 32 6 10 0.6% Satistatal (からい) 12 10 0.6% Heterogeneity: Not splicable Forsife normal factor 2 = 5.4.3 (* - 0.0001)	5.45 [2.63, 7.42]	
52.21 Lesch Thuragy         45         31         46         49         33         44         1.5%           Substatut (SVS: C)         46         44         1.5%         144         1.5%           Heitrogeneth: Not splicable         46         44         1.5%           Taxif to result affect 2 = 0.5 (9 = 0.5%)         5.22         14.5%           2.22 Heistrefendets-baharket af thera apy         2.5%         2.5%	-0.121 454, 0.231 -0.121 454, 0.231	
Testré pour direct, 2 + 6.0 % + 6.30 France, etc., 2 + 6.0 % + 6.30 France, etc., 2 + 6.0 % + 6.1 * 5.5 % + 6.4 % + 10.7 % + 5. * 5.5 % + 5.	0.197645.001	
Tredit-Querning, του αφορωσιαστ Treditor versali effect Z = 0.47 (P = 0.64) 5.2.24 rTMS Animad at al., 2020 50.7 7.3 15 49.2 9.1 15 1.3%, Secondard IOSC/ΓL 15 1.3%	0.191640,000 0.191640,000 0.191640,000	
Statistical (99): C1)         15         15         1,7%           Hardingsaming: Hot gap locable         Test for oreal effect; 2::0.48 (9::0.07)         24         8.9         16         19.4         6.8         16         1.3%           Statistical effect; 2::0.48 (9::0.07)         24         8.9         16         19.4         6.8         16         1.3%           Statistical effect; 2::0.18 (9::0.07)         24         8.9         16         19.4         6.8         16         1.3%           Mathematic effect; 2::0.18 (9::0.10)         16         16         1.5%         16.0         16         1.5%	0.57[4.54, 127] 0.57[4.54, 127]	
5.226 Splint Kong, ed. 2, 01 (72) 48 11.8 20 63.7 11.8 22 1.4% Substant (0%) C1 Material C2 2 1.4% Historgeneral: Not applicable For for events defect 2 = 300 0% = 0.0001)	-1.31(138,-0.63)	
52.22 TEAS and transido           52.23 TEAS and transidor           51.25 Alygon, 2019 (74)           21.9         12.2         16         13         16         1.2%           Satirotal Alygon, 2019 (74)         16         1.2%         16         1.3%           Heterogranity, Not applicable         16         1.3%         16         1.3%           Teafor overall effect 2 = 1.72 (9 = 0.01)         16         1.2%         1.2%         1.2%	-0.03 (134, 0.00) -0.03 (134, 0.00)	

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 metaanalysis 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

## 

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  $\geq$ 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.

Page **61** of **88** 

### 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

		<u> </u>							
	-	equency 1			quency			Std. Mean Difference	Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% Cl	IV, Random, 95% Cl
Desantana, et al., 2009 (1)	43	3.2	23	46.5	3.6	20	8.5%	-1.01 [-1.65, -0.37]	<b>_</b>
Fatima et al., 2019 (2)	25.6	9.2	25	36	13.8	25	9.5%	-0.87 [-1.46, -0.29]	_ <b>-</b>
Warke, et al., 2004 (3)	28.25	32.02	3	43.8	20.6	4	2.2%	-0.51 [-2.06, 1.04]	
Topuz, et al., 2004 (4)	37.3	16.2	15	42.6	20.5	15	7.4%	-0.28 [-1.00, 0.44]	
Pitangui, et al., 2014 (5)	17.2	21.9	11	22.5	16	12	6.1%	-0.27 [-1.09, 0.55]	
Graff-Radford, et al., 1989 (6)	28.3	18.06	12	33.7	29.02	12	6.4%	-0.22 [-1.02, 0.59]	+
Rajfur, et al., 2017 (7)	20.5	4.5	20	21.1	3.4	20	8.8%	-0.15 [-0.77, 0.47]	
Hamza, et al., 1999 (8)	25	23	25	28	19	25	9.9%	-0.14 [-0.70, 0.42]	
llhani, 2015 (9)	22.4	11.3	35	23.5	10.9	35	11.7%	-0.10 [-0.57, 0.37]	
De Oliverira et al., 2012	30	16.4	5	26	31.3	5	3.2%	0.14 [-1.10, 1.39]	
Sahin, et al., 2011 (10)	68.5	15.5	19	65.5	14.2	18	8.4%	0.20 [-0.45, 0.84]	<del></del>
Grimmer, 1992 (11)	22	28	20	15	18	20	8.8%	0.29 [-0.33, 0.91]	
Liu, et al., 2017 (12)	48.2	17.7	22	41.3	16.8	22	9.2%	0.39 [-0.20, 0.99]	+
Total (95% CI)			235			233	100.0%	-0.19 [-0.43, 0.06]	•
Heterogeneity: Tau <sup>2</sup> = 0.07; Chi	r = 19.69, i	df = 12 (P	= 0.07);1	<b>≈</b> = 39%					<u>    t       t        t        t        </u>
Test for overall effect: Z = 1.50 (	P = 0.13)								-4 -2 U 2 4 Favours High Frequency Favours Low Frequency
									ravours right requency ravours cow riequency

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.

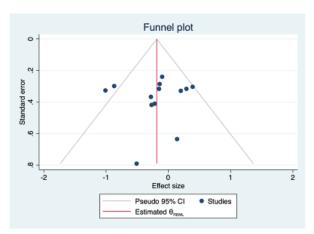


Figure A17 Funnel plot of high frequency versus low frequency TENS comparison.

## 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  $\geq$ 30% expressed as frequency (dichotomous) data because of insufficient data.

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  $\geq$ 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

	HF TE	NS	LF TE	NS		Risk Ratio	Risk Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	I M-H, Random, 95% Cl	
Nash, et al., 1990 (1)	12	50	19	50	38.5%	0.63 [0.34, 1.16]	i] — <b>=</b> +	
Hansson & Ekblom, 1983 (2)	7	22	9	20	23.3%	0.71 [0.32, 1.54]	.j — <b></b>	
Ekblom & Hansson, 1987 (3)	3	11	4	11	9.2%	0.75 [0.22, 2.60]	ı	
Langley, et al., 1984 (4)	6	11	7	11	28.9%	0.86 [0.43, 1.73]	ı] — <b>— —</b> —	
Nash, et al., 1990 (5)	13	50	11	50	0.0%	1.18 [0.59, 2.38]	]	
Total (95% CI)		94		92	100.0%	0.72 [0.49, 1.05]	1 🔶	
Total events	28		39					
Heterogeneity: Tau <sup>2</sup> = 0.00; Chi	<sup>2</sup> = 0.44, d	lf = 3 (F	<sup>o</sup> = 0.93);	$ ^{2} = 0\%$				00
Test for overall effect: Z = 1.71 (	P = 0.09)						Favours HF TENS Favours LF TENS	00

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<sup>2</sup> = 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

#### MetaTENS\_Appendix\_BMJO\_05-10-2021 – Supplementary File 1

Church and Carbon and	TENS		Comparison	•	104-1-1-4	Risk Ratio	Risk Ratio
Study or Subgroup	Events	lotal	Events	Total	weight	M-H, Random, 95% Cl	M-H, Random, 95% C
1.1.2 Placebo Control	_		_				
Da Silva, et al., 2015 (1)	0	21	7	21	3.9%	0.07 [0.00, 1.10]	
Thakur et al., 2004 (2)	0	100	1	100	3.3%	0.33 [0.01, 8.09]	
Kim, et al., 2012 (3)	8	50	7	50	8.4%	1.14 [0.45, 2.91]	
Bennett, et al., 2010 (4)	3	24	2	24	6.3%	1.50 [0.27, 8.19]	
Dailey et al., 2020 (5)	17	103	6	99	8.5%	2.72 [1.12, 6.62]	
Buchmuller, et al., 2012 (6)	11	117	3	119	7.5%	3.73 [1.07, 13.03]	
Subtotal (95% CI)		415		413	37.8%	1.45 [0.63, 3.32]	-
Total events	39		26				
Heterogeneity: Tau <sup>2</sup> = 0.47; Chi <sup>2</sup> =	: 9.78, df =	5 (P =	0.08); I² = 49%				
Test for overall effect: Z = 0.88 (P	= 0.38)						
1.1.3 Active Treatment							
lsik, et al., 2017 (7)	0	53	34	52	3.9%	0.01 [0.00, 0.23]	←
Moharic, et al., 2009 (8)	0	46	3	8	3.8%	0.03 [0.00, 0.49]	
Pan, et al., 2003 (9)	0	30	5	33	3.8%	0.10 [0.01, 1.73]	
Liu, et al., 2017 (10)	1	22	9	22	5.6%	0.11 [0.02, 0.80]	
Chitsaz, et al., 2009 (11)	0	29	3	30	3.7%	0.15 [0.01, 2.74]	
Tsukayama, et al., 2002 (12)	3	10	4	9	7.7%	0.68 [0.20, 2.23]	
Kim, et al., 2014 (13)	1	24	1	25	4.0%	1.04 [0.07, 15.73]	
Grant, et al., 1999 (14)	3	28	3	32	6.8%	1.14 [0.25, 5.21]	
Sangtong, et al., 2019 (15)	4	64	3	68	6.9%	1.42 [0.33, 6.08]	
Lofgren & Norrbrink, 2009 (16)	2	32	1	32	4.7%	2.00 [0.19, 20.97]	
Escortell-Mayor, et al., 2011 (17)	7	43	3	47	7.4%	2.55 [0.70, 9.24]	+
Shimoji, et al., 2007 (18)	3	9	0	11	3.8%	8.40 [0.49, 144.04]	
Subtotal (95% CI)		390		369	62.2%	0.51 [0.18, 1.39]	
Total events	24		69				
Heterogeneity: Tau <sup>2</sup> = 1.97; Chi <sup>2</sup> =	: 33.40, df:	= 11 (P	$= 0.0005$ ); $l^2 =$	67%			
Test for overall effect: Z = 1.32 (P							
Total (95% CI)		805		782	100.0%	0.73 [0.36, 1.48]	•
Total events	63		95				-
Heterogeneity: Tau <sup>2</sup> = 1.35; Chi <sup>2</sup> =	: 49.72. df:	= 17 (P	< 0.0001); <b> </b> <sup>2</sup> =	66%			L
Test for overall effect: Z = 0.87 (P							0.001 0.1 1 10 TENS Comparis

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: Tau<sup>2</sup> = 0.64; Chi<sup>2</sup> = 733.23, df = 90 (P < 0.00001); I<sup>2</sup> = 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: Tau<sup>2</sup> = 0.66; Chi<sup>2</sup> = 726.33, df = 88 (P < 0.00001); I<sup>2</sup> = 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 nonpharmacological 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 <u>https://gradepro.org/.</u>

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 <u>m.johnson@leedsbeckett.ac.uk</u>). 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 r	ates (%)		Anticipated effe		
Participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	(any) at last	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 <sup>b</sup>	not serious <sup>c</sup> not s	serious <sup>d</sup> none <sup>e</sup> $\bigoplus \bigoplus \bigoplus \bigcirc$ Moderate	2415	2426	-	-	SMD <b>0.96</b> <b>SD lower</b> (1.14 lower to 0.78 lower)
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Reduction of pain intensity of 50% or more

460 (9 RCTs)	not serious	not serious <sup>f</sup>	not serious <sup>c</sup>	serious	publication bias strongly suspected <sup>e</sup>	⊕⊕⊖⊖ Low <sup>e</sup>	28/219 (12.8%)	106/241 (44.0%)	<b>RR 2.89</b> (2.02 to 4.13)	128 per 1,000	<b>242 more</b> <b>per 1,000</b> (from 130 more to 400 more)
CI: confidence	interval.	RR: risk ratio; SM	ID: standardised	l mean differen	ce						

#### **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<sup>2</sup> >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 smallstudy 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<sup>2</sup> >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

		Cert	ainty asses	sment				Summary of findings					
							Study ev (%				ed absolute fects		
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 Inte	Pain Intensity Rating - last during or first post intervention												

602 (10 RCTs)	not seriousª	serious <sup>b</sup>	not serious <sup>c</sup>	serious <sup>d</sup>	none <sup>e</sup>	⊕⊕⊖⊖ Low	304	298	-	-	SMD <b>0.82 SD</b> lower (1.18 lower to 0.46 lower)
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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., 12 >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

		Cert	ainty asses	Summary of findings							
Participants (studies) Follow-up	Risk of bias		Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Study event rates (%)		Relative	Anticipated absolute effects	
		Inconsistency					With Standard of Care	With TENS	effect (95% CI)	Risk with Standard of Care	Risk difference with TENS
Pain Inte	nsity R	Rating									
3155 (61 RCTs)	not serious <sup>c</sup>	serious <sup>d</sup>	not seriousª	not serious <sup>e</sup>	publication bias strongly suspected <sup>b</sup>	⊕⊕⊖⊖ Low	1561	1594	-	-	SMD <b>0.72 SD</b> 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., 12 >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

		Cert	tainty asses	Summary of findings								
Participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Study event rates (%)			Anticipated absolute effects		
							With Low Frequency TENS	With High Frequency TENS	Relative effect (95% CI)	Risk with Low Frequency TENS	Risk difference with High Frequency TENS	
Pain Inte	Pain Intensity Rating											
468	not	not serious <sup>b</sup>	not serious <sup>c</sup>	serious <sup>d</sup>	none <sup>e</sup>	⊕⊕⊕⊖	233	235	-	-	SMD 0.19	

	not seriousª	not serious <sup>b</sup>	not serious <sup>c</sup>	serious <sup>d</sup>	none <sup>e</sup>	⊕⊕⊕⊖ Moderate	233	235	-	-	SMD <b>0.19</b> <b>lower</b> (0.43 lower to 0.06 higher)
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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 smallstudy 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				
Participants		l.	istency Indirectness Imprecision Publication			Overall	Study event rates (%)		Relative	Anticipated absolute effects		
(studies) Follow-up	Risk of bias	Inconsistency		bias	certainty of evidence	With Comparator	With TENS	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 <sup>a</sup>	not serious <sup>b</sup>	very serious <sup>c</sup>	serious <sup>d</sup>	publication bias strongly suspected <sup>e</sup>	⊕⊖⊖⊖ Very low <sup>d</sup>	95/782 (12.1%)	63/805 (7.8%)	<b>RR 0.73</b> (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., >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

**BMJ** Open

## 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

MetaTENS\_Appendix\_BMJO\_05-10-2021 – Supplementary File 1

- 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].

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#### 08\_OL-TABLE1\_IncludedStudies

## **ONLINE TABLE 1**

## Summary Characteristics of included RCTs

Reference	Design	Type	Condition	Sample size (women)	Primary TENS comparison	Comparison interventions	TENS regimen	<b>Primary</b> Outcome	Secondary Outcome
Abbasi et al., 2019 <sup>1</sup>	Р	Pr	Procedural - Throughout Pleurodesis	66 (NR)	TENS (HF) + Diclofenac = 33	Placebo TENS (0mA) + diclofenac = 33	Fixed 1 x 50 mins during procedure	Pain intensity (VAS)	Analgesic consumption Blood pressure, heart rate
Abelson et al., 1983 <sup>2</sup>	Р	Pr	Rheumatoid arthritis 🧹	32 (26W)	TENS (HF) = 13	Placebo TENS = 13 (0mA)	Fixed 1 x 15 mins / week x 3 weeks 3 sessions	Pain intensity (VAS) Resting pain Pain on movement (grip task)	Grip strength
Abreu et al., 2010 <sup>3</sup>	Р	Pr	Labour pain	20 (20W)	TENS (HF) = 10	Placebo TENS = 10 (mA barely perceptible)	PRN during labour - first stage	Pain intensity (VAS)	Time to analgesia Duration of analgesia
Acedo et al., 2015 <sup>4</sup>	Р	Pr	Neck pain - chronic non -specific	64 (64W)	TENS (LF, burst, - 100pps) = 32	IFT = 32	Fixed 30 mins / day on days 2, 3, 5 3 sessions	Pain intensity (VAS)	Muscle relaxation (EMG microV)
Adedoyin et al., 2005 <sup>5</sup>	Р	Pr	Osteoarthritis - knee	46 (28W)	TENS (HF) + Exercise = 15	IFT + Exercise = 16 Exercise alone (SoC, no TENS) = 15	Fixed 2 x 20min / week x 4 weeks 8 sessions	Pain intensity (NRS)	WOMAC
Ahmed, 2010 <sup>6</sup>	Р	Pr	Post-op – inguinal hernia repair	60 (0W)	TENS (HF) + paracetamol + diclofenac as needed = 30	Placebo TENS (0mA) + paracetamol + diclofenac as needed = 30	Fixed 2 x 30 mins / day x 5 days 10 sessions	Pain intensity (VAS)	Analgesic consumption Assessment of serum cortisol level
Ahmed et al., 2020 <sup>7</sup>	Р	Pr	Diabetic neuropathic pain	30 (19W)	TENS (LF, AL-TENS) + aerobic exercise = 15	Repetitive transcranial magnetic stimulation (rTMS) + aerobic exercise = 15	Fixed 1 x 20 mins / day x 5 days 10 sessions	Pain intensity (VAS)	Blood β-endorphin level
Alcidi et al., 2007 <sup>8</sup>	Р	Pr	Osteoarthritis - knee - acute	40 (35W)	TENS (HF) = 20	Electromagnetic radiation = 20	Fixed 1 x 20 mins /day x 5 days 5 sessions	Pain intensity (VAS)	Lequesne's index for knee OA
Ali et al., 1981 <sup>9</sup>	Р	Pr	Post-op – abdominal	40 (24W)	TENS (HF) + Demerol = 15	Placebo TENS (0mA) + Demerol = 10 Demerol + No TENS (SoC, no TENS) = 15	PRN 48h Post-operation	No primary outcome	Analgesic consumption Vc FRc arterial PO2
Alizade and Ahmadizad, 2009 <sup>10</sup>	Р	Pr	Back pain – low, chronic	24 (24W)	TENS (HF) + NSAIDs (ibuprofen and diclofenac) = 8	NSAIDs (ibuprofen and diclofenac) + exercise = 8 NSAIDs (ibuprofen and diclofenac, SoC, no TENS) = 8	Fixed 30 mins / day x 3 days / week x 5 weeks	No primary outcome	Modified Oswestry low back pain disability questionnaire

							15 sessions		
Allais et al., 2003 <sup>11</sup>	Р	Pr	Migraine - transformed	60 (60W)	TENS (HF, MF, LF) = 20	Infrared laser therapy = 20 Acupuncture = 20	Fixed 30 mins / day x 5 day / week x 2 weeks 10 sessions	No primary outcome	Number of days with headache per month
Alm et al., 1979 <sup>12</sup>	Р	Е	Post-op – podiatric surgery		TENS (HF) = 50	Placebo TENS (0mA) =25 Control Group (patient records) = 25	PRN Mean duration 20-40 mins / treatment repeated	Pain relief (4- point category scale)	Analgesic consumption
Al-Smadi et al., 2003 <sup>13</sup>	Р	Pr	Back pain – low, multiple sclerosis	15 (n/r)	TENS (HF) = 5 (110 Hz, 200 ms)	Placebo TENS = 5 (0mA) TENS (LF) = 5 (4Hz, 200 ms)	Fixed 1 x 45min / day x 3 days / week x 6 weeks 18 sessions	Pain intensity (VAS)	McGill Pain Questionnaire Roland Morris Disability Questionnaire Leeds MS Specific Quality of Life Questionnaire
Altay et al., 2010 <sup>14</sup>	Р	Pr	Osteoarthritis - knee	40 (30W)	TENS (HF) = 20	Placebo TENS = 20 (0mA)	Fixed 1 x 40 min / day x 3 weeks 21 sessions	Pain intensity (VAS)	WOMAC Beck Depression Inventory Short Form 36 10 steps stairs climbing up-dowr time 6-minute walk distance
Alvarez-Arenal et al., 2002 <sup>15</sup>	С	Ε	Temporomandibular disorder – bruxism	24 (9W)	TENS (LF) = 24	Splint = 24	Fixed 1 x 45-60 mins every 2 days 15 sessions	Pain intensity on palpation (4-point scale)	Tenderness on palpation (4-poin scale) Severity of TMD (pantographic reproducibility index -PRI) Joint noises associated with oral opening and closing (number of 'click' noises)
Alves Silverio et al., 2015 <sup>16</sup>	Р	Pr	Dysphonic – Muscle tension	20 (20W)	TENS $(LF) = 10$	Laryngeal manual therapy = 10	Fixed 2 x 20mins / week x 6 weeks 12 sessions	Pain intensity (VAS)	Nordic musculoskeletal sympton questionnaire Vocal quality - auditory perceptual analysis of voice.
Amer-Cuenca et al., 2011 <sup>17</sup>	Р	Pr	Procedural pain – colonoscopy	90 (50W)	TENS (RF) = 30	Placebo TENS = 30 (0mA) No treatment (unsedated) = 30	Fixed During procedure	Pain intensity (VAS and 5-point Likert scale)	Unusual or adverse events
AminiSaman et al., 2020 <sup>18</sup>	Р	Pr	Procedural pain - Needle insertion - Spinal anaesthesia	60 (25W)	TENS (HF) = 30	Placebo TENS (0mA) = 30	Fixed During needle insertion procedure	Pain intensity (VAS)	Number of attempts to insert needle Duration insertion time
Angulo and Colwell Jr, 1990 <sup>19</sup>	Р	Pr	Post-op – knee replacement	48 (28W)	TENS (sensory threshold) + continuous passive motion + opioids as needed (SoC, No TENS control) = 18	Placebo TENS (active <sdt) +<br="">continuous passive motion + opioids as needed = 18 No TENS + continuous passive motion + opioids as needed (SoC, no TENS) = 12</sdt)>	PRN 20 hours / day x 3 days	Pain intensity (VAS)	Analgesic consumption (Narcot Knee flexion range of motion
Ardic et al., 2002 <sup>20</sup>	Р	Pr	Myofascial pain	40 (36W)	TENS (HF) + Exercise = 15	Exercises (SoC, no TENS) = 10 Electrical muscle stimulation + Exercises = 15	Fixed 1 x 20mins / day x 2 weeks 14 sessions	Pain intensity (VAS)	Pain threshold on palpation Range of motion
Arvidsson and Eriksson, 1986 <sup>21</sup>	С	Е	Post-op –	15(3W)	TENS (HF) $= 15$	Placebo TENS = 15 (0mA)	Fixed 1 x 15-20 mins	Pain intensity (0- 20 Borg scale)	Quadriceps contraction ability (EMG)

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			knee ACL reconstruction			Epidural injection (lidocaine 2.5ug/ml) = 15	1 session	Resting pain Pain on movement (quadriceps contraction)	
Asgari et al., 2018 <sup>22</sup>	Р	Pr	Procedural pain – gynaecologic laparoscopy (shoulder pain)	80 (80W)	TENS (LF) = 40	Fentanyl (SoC, no TENS) = 40	Fixed 20 mins during procedure	Pain intensity (VAS)	Analgesic consumption
Atamaz et al., 2012 <sup>23</sup>	P	Pr	Osteoarthritis - knee	203 (167W)	TENS (HF) + Exercise + Education = 37	Placebo TENS + Exercise + Education = 37 (0mA) IFT + Exercise + Education = 31 Placebo IFT + Exercise + Education = 35 Shortwave diathermy + Exercise + Education = 31 Placebo shortwave diathermy + Exercise + Education = 32	Fixed 1 x 20 mins / day x 5 / week x 3 weeks 15 sessions	Pain intensity (VAS)	Analgesic consumption (Paracetamol) Pain free range of motion Patient's satisfaction with the treatment (VAS) WOMAC Nottingham Health Profile
Aydin et al., 2005 <sup>24</sup>	Р	Pr	Spasticity – SCI, lower limb pain	21 (15W)	TENS (HF) + exercise (range of motion, every morning) = 11	Baclofen + exercise (range of motion, every morning) (SoC) = 10	Fixed 1 x 15 min / day x 15 days 15 sessions	Painful spasm scale (3-point scale)	Clinical assessment of spasticit Self-reported and clinical examination Electrophysiologic Assessment Spasticity H-reflex
Azatcam et al., 2017 <sup>25</sup>	Р	Pr	Myofascial pain	69 (38W)	TENS (HF) + Exercise (Trapezius stretching) = 23	Exercise (Trapezius stretching)(SoC, no TENS) = 23 Kinesiology taping + Exercise (Trapezius stretching) = 23	Fixed 1 x 20 mins / day x 5 days / week x 2 weeks 10 sessions	Pain intensity (VAS)	Pain threshold (algometry) Neck Disability Index Cervical range of motion
Báez-Suárez et al., 2018 <sup>26</sup>	Р	Pr	Labour pain	63 (63W)	TENS (HF) = 21	Placebo TENS = 21 (0mA) TENS (MF) = 21	PRN >30 mins / treatment during labour	Pain intensity (VAS)	Care in Obstetrics Measure for Testing Satisfaction (COMFORTS) scale
Bai et al., 2017 <sup>27</sup>	Р	Pr	Dysmenorrhea	134 (134W)	TENS (AF) + Ibuprofen as needed = 67	Placebo TENS (0mA) + ibuprofen as needed) = 67 (0mA)	Fixed 1 x 30 mins / day x 3 days x 3 menstrual cycles 9 sessions	Pain intensity (NRS)	Analgesic consumption (Ibuprofen) Pain relief duration World Health Organization quality of life (WHOQOL)-BREF
Baki et al., 2015 <sup>28</sup>	Р	Pr	Post-op – thoracotomy	40 (15W)	TENS (HF) + tramadol PCA = 20	Paravertebral block+ tramadol PCA = 20	PRN 24 h post op	Pain intensity (VAS) • Resting pain • During cough	Analgesic consumption (Tramadol) Respiratory function FEV1, FEV1/FVC, mean arteri pressure, heart rate, saturation of oxygen
Ballegaard et al., 1985 <sup>29</sup>	C	E	Pancreatitis – chronic	16(NR)	TENS (HF, conventional followed by LF, acupuncture -like) + morphine on request = 11	Placebo TENS (NR) + morphine on request = 11	Fixed 1 x 30 mins / day x 1 week 7 sessions Repeated at each of 3 body sites	Pain intensity (VAS)	Analgesic consumption (Morphine) Treatment preference Daily assessment of well-being (VAS)

	4	L					21 sessions		
Barbarisi et al., 2010 <sup>30</sup>	Р	Pr	Post herpetic neuralgia	30 (15W)	TENS (HF) + Pregabalin = 16	Placebo TENS + Pregabalin (0mA) = 14	Fixed 1 x 30 mins / day x 9 visits (over 4 weeks) 9 sessions	Pain intensity (VAS)	SF-McGill Pain Questionnaire Sleep interference
Barker et al., 2006 <sup>31</sup>	Р	Pr	Pelvic pain – acute, during transport to hospital	62 (62W)	TENS (HF) = 29	Placebo TENS (0mA) = 33	PRN ~ 30 mins during transportation to hospital 1 session	Pain intensity (VAS)	Oscillometric blood pressure Heart rate Anxiety (VAS) Signs of sympathetic Activity (vasoconstriction/dilation of arms)
Barker et al., 2008 <sup>32</sup>	Р	Pr	Back pain – low, chronic	60 (30W)	TENS (HF) = 28	Sensory discrimination training using FairMed device = 32	PRN 2 x 30 min / day x 3 weeks 21 sessions	Pain intensity (VAS) • present pain • average pain over a week • worst pain over a week	Oswestry Disability Index Functional physical tests • 5-minute walking distance • 1-minute stair climb • 1 minute standing up and sitting down from a chair Health Anxiety and Depression Scale Tampa Scale Kinesiophobia Pain Coping Scale Pain Self Efficacy Questionnaire Patient Global Impression of Change scale
Başkurt et al., 2006 <sup>33</sup>	Р	Е	Shoulder impingement - stage I	92 (60W)	TENS (HF) = 30	Heat (39°, SoC no TENS) = 31 Heat + TENS = 31	Fixed 1 x 20 mins 1 session	Pain intensity (VAS)	Pressure algometry (pressure pair threshold)
Bayindir et al., 1991 <sup>34</sup>	Р	Е	Post-op – cardiac surgery	89 (29W)	TENS (LF, burst) = 59	Placebo TENS = 30 (0mA)	Fixed 1 x 180 mins	Pain intensity (VAS)	None
Beckwée et al., 2018 <sup>35</sup>	Р	Pr	Post-op – total knee arthroplasty	53 (34W)	TENS (LF, burst) + analgesics + physiotherapy (SoC) = 25	Placebo TENS + analgesics + physiotherapy (SoC) = 28 (0mA)	Fixed 1x 40 mins / day during passive mobilisation x 5 days 5 sessions	Pain intensity (VAS)	Analgesic consumption • Daily opioid analgesia • cumulative opioid analgesia • Non-opioid analgesia Range of motion - Knee flexion
Benedetti et al., 1997 <sup>36</sup>	Р	E	Post-op – thoracic	324 (NR)	TENS (HF) = 103	Placebo TENS (0mA) = 106 Conventional drugs (SoC, no TENS) = 115 (Control)	Fixed 2 x 60 mins in recovery room first 12 h only 2 sessions	Pain intensity (NRS)	Analgesic consumption Time to request further analgesia
Bennett et al., 2010 <sup>37</sup>	С	E	Cancer bone pain	24 (6W)	TENS (HF) =24	Placebo TENS = 24 (0mA)	Fixed 1 x 60 mins 1 session	Pain intensity (NRS and VRS 4 categories) • Resting pain • Pain on movement	SF-McGill Pain Questionnaire Satisfaction questionnaire
Bergeron-Vezina et al., 2018 <sup>38</sup>	С	Е	Back pain – chronic, low, non-specific	21 (11W)	TENS (HF) = 21 (maintaining pulse amplitude)	TENS (HF) = 21 (pulse amplitude fading)	Fixed 1 x 25 mins 1 session	Pain intensity (VAS)	Pain unpleasantness (VAS) Patient's Global Impression of Change scale

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Bertalanffy et al., 2005 <sup>39</sup>	Р	Pr	Back pain - acute, low, during emergency transport	74 (30W)	TENS (HF) = 35	Placebo TENS = 36 (0mA)	Fixed 1 x ~30 mins during transportation 1 session	Pain intensity (VAS)	Anxiety (VAS) Oscillometric blood pressure Heart rate
Bi et al., 2015 <sup>40</sup>	Р	Pr	Spinal cord injury	52 (16W)	TENS $(LF) = 26$	Placebo TENS = 26 (0mA)	Fixed 1 x 20mins/day x 3 / week x 12 weeks 36 sessions	Pain intensity (VAS)	McGill Pain Questionnaire
Bilgili et al., 2016 <sup>41</sup>	Р	Pr	Complex regional pain syndrome	30 (16W)	TENS (HF) + contrast bath + whirlpool bath + exercise = 15	Placebo TENS (0mA) + contrast bath + whirlpool bath + exercise = 15	Fixed 1 x 20 mins / day x 15 days 15 sessions	Pain intensity (VAS) at rest	LANSS Douleur Neuropathique en 4 Questions (DN-4) Volumetric oedema (mm) Hand mobility (distance betw the 2nd and 5th finger pulp and distal path line in cm) Range of motion - wrist Hand grip strength Duruöz Hand Index
Binder et al., 2011 <sup>42</sup>	Р	Pr	Post-op – caesarean	42 (42W)	TENS (HF) + morphine PCA = 22	Morphine PCA (SoC, no TENS) = 20	PRN Over 24 hours	Pain intensity (VAS)	Analgesic consumption (Morphine) - PCA Sedation perception (VAS)
Bjersa and Andersson, 2014 <sup>43</sup>	Р	E	Post-op – pancreatic surgery	20 (N/R)	TENS (HF) + SoC (medication) = 9	Placebo TENS = 11 (stimulation as low as possible) + SoC (medication)	PRN >30m/session	Pain intensity (VAS) • Resting (lying) • On movement (walking + deep breathing)	Analgesic consumption (Morphine) Quality of Recovery 40 (QoF EDA infusion rate (ml/h) Total time of TENS usage in minutes during the day of EL termination and the day after
Bjersa et al., 2015 <sup>44</sup>	Р	E	Post-op – colon surgery	30 (14W)	TENS (HF) + SoC (medication) = 24	Placebo TENS = 26 (stimulation as low as possible) + SoC (medication)	PRN >30m/session	Pain intensity (VAS) • Resting (lying) • On movement (walking + deep breathing)	Analgesic consumption (oxycodone) Time of TENS usage during 24 hours after EDA terminati Quality of Recovery 40 (QoR
Bloodworth et al., 2004 <sup>45</sup>	С	E	Radiculopathy – chronic	13 (7W)	TENS (HF, conventional TENS back) = 13	Placebo TENS ( $0mA$ , $back$ ) = 13 Placebo TENS ( $0mA$ , $leg$ ) = 13 TENS ( $HF$ , $leg$ ) = 13 TENS ( $RF$ , $back$ ) = 13 TENS ( $RF$ , $leg$ ) = 13	Fixed 1 x 10 mins 1 session	Pain intensity (VAS)	McGill Pain Questionnaire Walking speed (feet per seco
Bolat et al., 2019 <sup>46</sup>	Р	Pr	Procedural pain - transrectal prostatic biopsy	138 (0W)	TENS (HF) + antibiotic = 73	SoC - intrarectal administration of 60 mg lidocaine gel, an additional infiltration of 5 mL of prilocaine and bupivacaine mixture (5 mL of 2% prilocaine and 5 mL of 0.25% bupivacaine) = 65	Fixed During procedure	Pain intensity (NRS) • probe insertion • biopsy • post-biopsy	Biopsy times
Bono et al., 2015 <sup>47</sup>	Р	Pr	Migraine / tension-type headache - Chronic	160 (127W)	TENS (HF, occipital) + acute medications = 108	Placebo TENS + acute medications = 52 (0mA)	Fixed 3 x 30 mins / day x 14 days	Pain intensity (VAS)	Analgesic consumption Headache-free days per mon

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Borjesson et al., 1997 <sup>48</sup> Borjesson et al., 1998 <sup>49</sup>	P	E	Angina – unstable Procedural Pain - oesophageal	30 (11W) 18 (10W)	TENS (HF) + mediation (angina/analgesia) = 14 TENS (HF) = 18 (at pain - neck)	Placebo TENS (low level stimulation <10mA on hips) + mediation (angina/analgesia) = 16 Placebo TENS = 18 (active, >SDT, remote to pain -	14 sessions Fixed 4 x 30 mins / day plus PRN for attacks Fixed Before and during	Pain intensity (VAS) • Rest Pain intensity (11- point Borg scale)	Allodynia symptom check list (12-item) Migraine Disability Assessment Questionnaire Beck Depression Inventory-II Hamilton Anxiety Rating Scale Analgesic consumption Ischemic episodes, ECG and biochemical outcomes Treatment feasibility including <u>AEs</u> Hemodynamic BP, heart rate, ECG
			manometry pain	0	(at pam - neck)	(active, >SD1, remote to pain - hips)	procedure	<ul> <li>Oesophageal distension</li> </ul>	Manometric variables Oesophageal pH
Borup et al., 2009 <sup>50</sup>	Р	E	Labour pain	607 (607W)	TENS (HF) + analgesics as needed = 144	Traditional analgesics (Control) (SoC, no TENS) = 149 Acupuncture + analgesics as needed = 314	PRN 20-45 mins / sessions	Pain intensity (VAS)	Analgesic consumption Non-drug requirements Duration of labour Use of oxytocin Mode of deliver Postpartum Haemorrhage Apgar score Umbilical cord blood pH value
Breit and Van der Wall, 2004 <sup>51</sup>	Р	Е	Post-op - total knee arthroplasty	67 (37W)	TENS (NR) + morphine PCA = 25	Placebo TENS (0mA) + morphine PCA = 22 Morphine PCA (SoC, no TENS) = 22	PRN 1 x 24h post op	Pain intensity (VAS)	<ul><li>Analgesic consumption</li><li>Cumulative dose morphine by PCA</li></ul>
Buchmuller et al., 2012 <sup>52</sup>	Р	Pr	Back pain – chronic low non-specific with and without radicular pain	236 (148W)	TENS (HF+LF burst) + daily analgesic medication as required = 117	Placebo TENS (0mA) + daily analgesic medication as required = 119	Fixed 4 x 60 mins / day x 3 months ~?? sessions	Pain intensity (VAS) • Weekly	Analgesic consumption (anti-inflammatory) Roland Morris Disability Questionnaire Dallas questionnaire SF-36 Compliance with TENS treatmer Quality of life
Bulut et al., 2011 <sup>53</sup>	Р	Pr	Neuropathic pain – chronic peripheral	40 (23W)	TENS (HF) = 20	Placebo TENS = 20 (0mA)	Fixed 1 x 30 mins / day x 20 days 20 sessions	Pain intensity (VAS)	Pain grade (6 categories)
Bundsen et al., 1982 <sup>54</sup>	Р	Pr	Labour pain	24 (24W)	TENS (HF + LF burst) = 15	Conventional analgesia, control) (SoC, no TENS) = 9	PRN >1 x 15-30 mins During Labour	Pain intensity (5- point categorical scale) • low-back / abdominal pain	Pain experience questionnaire Uterine activity Foetal and neonatal condition
Can et al., 2003 <sup>55</sup>	Р	Е	Knee – chronic, patellofemoral pain	30 (22W)	TENS (HF) = $16 (23 \text{ knees})$	Diadynamic current = 14 (19 knees)	Fixed	Pain intensity (VAS)	Lysholm knee scoring scale and squat

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### 08\_OL-TABLE1\_IncludedStudies

							1 x 30 mins x 4 to 5 / week x 6 weeks <30 sessions		Number of squats performed in 30 seconds 4-level activity test
Casale et al., 2013 <sup>56</sup>	Р	Pr	Carpal tunnel syndrome	20 (10W)	TENS (HF) = 10	Low level laser therapy = 10	Fixed 1 x 30 mins / day x 3 weeks 15 sessions	Pain intensity (VAS)	Severity paraesthesia Median nerve distal motor latency and sensory nerve conduction velocity
Çebi, 2019 <sup>57</sup>	Р	Pr	Post op - pain after impacted third molar surgery	30 (15W)	TENS (HF) = ?15	Routine care (SoC, Pharmacological - Flurbiprofen 100 mg, amoxicillin, chlorhexidine gluconate) = ? 15	Fixed 1 x 15 mins / day x 5 days	Pain intensity (VAS)	None
Celik et al., 2013 <sup>58</sup>	Р	Pr	Spinal cord injury, neuropathic pain	33 (9W)	TENS (LF) = 17	Placebo TENS = 16 (0mA) = 16	Fixed 1x 30m /day x 10 days 10 sessions	Pain intensity (VAS)	None
Cetin et al., 2008 <sup>59</sup>	Р	Pr	Osteoarthritis - knee	100 (100W)	TENS (HF) + hot packs + isokinetic exercise = 20 (Group 2)	Hot packs + isokinetic exercise) (SoC, no TENS) = 20 Shortwave diathermy + hot packs + isokinetic exercise = 20 Ultrasound + hot packs + isokinetic exercise = 20 Isokinetic exercise = 20	Fixed 1 x 20 mins x 3 / week x 8 weeks 24 sessions	Pain intensity (VAS) • After walk	Ambulation Activity - time (secs) to walk 50 m Lequesne index Peak torque levels (N·m) knee flexion and extension
Chandra et al., 2010 <sup>60</sup>	Р	Е	Post-op – thoracotomy	60 (29W)	TENS (HF) + epidural 10 ml of 0.125% bupivacaine at 2- hourly = 30	Placebo TENS (0mA) + epidural 10 ml of 0.125% bupivacaine at 2- hourly = 30	Fixed 1 x 45 mins	Pain intensity (VAS)	Systolic blood pressure Side effects.
Cheing and Hui-Chan, 1999 <sup>61</sup>	Р	Е	Back pain - chronic low non-specific	30 (9W)	TENS (HF) = 15	Placebo TENS = 15 (0mA)	Fixed 1 x 60 mins	Pain intensity (VAS)	Pain intensity (VAS) to electrically-evoked pain
Cheing and Luk, 2005 <sup>62</sup>	Р	Е	Neuropathic pain	19 (3W)	TENS (HF) = 10	Placebo TENS = 9 (0mA)	Fixed 1x 20m/day x5 days x 2weeks 10 sessions	Pain intensity (VAS)	Downey Hand Centre Hand Sensitivity Test Flexion reflex
Cheing et al., 2002 <sup>63</sup>	Р	Е	Osteoarthritis - knee	62 (52W)	TENS (HF) = 16	Placebo TENS = 16 (0mA) Exercise (SoC, no TENS control) = 15 TENS + Exercise =15	Fixed 1 x 60 mins/day x 5 days / week x 4 weeks 20 sessions	Pain intensity (VAS)	None
Cheing et al., 2003 <sup>64</sup>	Р	E	Osteoarthritis - knee	38 (34W)	TENS (HF) = 10 (60 mins)	Placebo TENS = 8 (0mA) TENS = 10 (20 mins) TENS = 10 (40 mins)	Fixed 1 x 60 mins/day x 5 days / week x 2 weeks 10 sessions	Pain intensity (VAS) • On movement	Time of 'half-life' for analgesic effect
Chellappa and Thirupathy, 2020 <sup>65</sup>	Р	Pr	Temporomandibular joint disorder	60 (NR)	TENS (HF) = 30	LLLT = 30	Fixed 1 x 15 min/day x 2 / week x 3 weeks	Pain intensity (VAS, may be categorical scale)	Range of motion Palpation
Cherian et al., 2016 <sup>66</sup> – Primary Report	Р	Pr	Osteoarthritis - knee	70 (46)	TENS (AF) = 33	Standard of care = corticosteroid injections + exercises + pharmaceutical management) (SoC, no TENS) = 10	PRN mean = 27 hours / week x 3 months	Pain intensity (VAS)	Analgesic consumption Knee Society Scale (KSS) Lower extremity functional scale (LEFS)

Secondary Reports Cherian et al., 2015 <sup>67</sup> Cherian et al., 2016 <sup>68</sup>									SF-36 Timed up and-go (TUG) 5-repetition chair rise Timed stair climb test 6-inch step test 2-minute walk test Isokinetic strength Active and passive range of
Chesterton et al., 2013 <sup>69</sup> Secondary Report Lewis, et al., 2015 <sup>70</sup>	P	Pr	Tendinitis - Lateral epicondylitis - Tennis elbow	241 (109W)	TENS (HF) + Primary care management = 121	Primary care management (exercises + education) (SoC, no TENS) = 120	PRN > 1 x 45 mins / day whenever symptoms x 6 weeks	Pain intensity (NRS)	motion. Global change in elbow pain (5- point adjectival scale Pain and limitation in function (patient-rated tennis elbow evaluation) Number of days of sick leave du to tennis elbow EuroQoL EQ-5D (Quality of life SF-12 Changes in health beliefs and perceptions Adherence to treatment protocol
Chia et al., 1990 <sup>71</sup>	Р	Pr	Labour pain	Sample 1: 101 (101W) Sample 2: 20 (20W) -	Sample 1: TENS (AF) = 48 Sample 2: TENS (AF) = 10	Sample 1: Inhalation analgesia = 53 (ENTONOX) Sample 2: Inhalation analgesia = 10 (ENTONOX)	PRN During labour	Pain intensity (categorical scale) Pain relief (categorical scale)	Analgesic consumption • Request Treatment failure - request to change type of treatment Duration of use of treatment Cervical dilatation and number of contractions / 10 mins
Chiou et al., 2019 <sup>72</sup>	Р	Pr	Myofascial pain in neck and shoulder from spinal cord injury	64 (12W)	TENS (LF/HF, on trigger points) = 30	TENS (HF, on remote acupuncture Points) = 30	Fixed 1 x 20 mins / day x 7 days x 1 week	Pain intensity (VAS)	Short-form McGill Pain Questionnaire Hospital Anxiety and Depressio Scale Pittsburgh Sleep Quality Index
Chitsaz et al., 2009 <sup>73</sup>	Р	Pr	Spasticity – multiple sclerosis	59 (44W)	TENS (HF) = 29	Nortriptyline = 30	PRN >20-30 mins x 3/day x 8 weeks	Pain intensity (VAS) • Average	Intensity of sensory complaints (VAS)
Chiu et al., 2005 <sup>74</sup>	Р	Pr	Neck pain - chronic non -specific	218 (149W)	TENS (HF) + infrared radiation = 78	Exercise + Infrared radiation = 67 Infrared radiation alone (warmth) = 78	Fixed 1 x 30 mins / day x 2 / week x 6 weeks 12 sessions	Pain intensity (NRS, verbal)	Analgesic consumption Northwick Park Neck Pain questionnaire Percentage subjects on sick leav Peak isometric strength neck muscles.
Cipriano et al., 2008 <sup>75</sup>	Р	Pr	Post-op – cardiac surgery	45 (13W)	TENS (HF) = 23	Placebo TENS = 22 (active, >SDT-infrequent pulses)	Fixed 1 x 240mins (4h) on the third postoperative	Pain intensity (VAS) • Cough	Spirometry • vital capacity • tidal volume • respiratory rate Electrical muscle activity (EMC
Cipriano et al., 2014 <sup>76</sup>	Р	Е	Post-op cardiac surgery	38 (18W)	TENS (HF) + pethidine HCl, 20 mg = 20	Placebo TENS (active, >SDT- infrequent pulses) + pethidine HCl, 20 mg = 18 (active)	Fixed 4 x 30mins/day x 5 days 5 sessions	Pain intensity (VAS)	Analgesic consumption (Opioid) Physiological measurements Mean arterial pressure

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									Femoral blood flow Femoral vascular conductance Beta-Endorphin levels Sympathetic stimulation test 6-min walking test
Coelho de Amorim et al., 2014 <sup>77</sup>	Р	Pr	Osteoarthritis - knee	24 (20W)	TENS (HF) = 12	Manual therapy = 12	Fixed 1 x 20 mins / day x 3 / week x 4 weeks 12 sessions	Pain intensity (VAS)	WOMAC Stiffness Function
Cooperman et al., 1977 <sup>78</sup>	Р	Pr	Post-op – abdomen	50 (36W)	TENS (HF) + analgesics as rescue (diazepam, 10 mg i.m., meperidol, 75-100 mg i.m.) = 26	Placebo TENS = 24 (0mA)	PRN x 5 days	No primary outcomes	Analgesic consumption
Coyne et al., 1995 <sup>79</sup>	Р	Е	Procedural pain - intravenous needlesticks	61 (35W)	TENS (HF) = 19	Placebo TENS = 21 (not described)	Fixed 1 x 12-32 mins 1 session	Pain intensity (VAS)	Pain unpleasantness (VAS)
Crompton et al., 1992 <sup>80</sup>	Р	Pr	Procedural pain – cervical laser treatment	100 (100W)	TENS (HF) = 34	Local anaesthetic (SoC, no TENS) = 35 TENS + local anaesthetic (lignocaine) = 29	Fixed 1 x <20 mins (duration of procedure)	Pain intensity (VAS)	Satisfaction and utility of TEN
Cuschieri et al., 1985 <sup>81</sup>	Р	Pr	Post-op – abdomen	106 (62W)	TENS (HF) + morphine = 53	Placebo TENS + morphine = 53 (0mA)	PRN 72 hours	Pain intensity (VAS)	Analgesic consumption (Morphine) Arterial blood gas analysis Pulmonary complications
Cuschieri et al., 1987 <sup>82</sup>	Р	Pr	Ischaemic pain - critical leg at rest	20 (10W)	TENS (NR) + morphine = 10	Placebo TENS + morphine = 10 (0mA)	PRN 48 hours	Pain intensity (VAS)	Analgesic consumption (Morphine)
da Silva et al., 2008 <sup>83</sup>	Р	Pr	Fibromyalgia	10 (9W)	TENS (HF) = 5	Hydrotherapy = 5	Fixed 1 x 40 mins/day x3/week x 3 weeks 9 sessions	Pain intensity (VAS)	SF-36 Nottingham Health Profile Beck Depression Index Finger-to-floor test (flexibility test)
da Silva et al., 2015 <sup>84</sup>	Р	Pr	Post-op – liposuction	42 (42W)	TENS (HF) + analgesics (morphine + dipyrone) = 21	Placebo TENS + analgesics (morphine + dipyrone) = 21 (0mA)	Fixed 1 x 30 mins (2h after procedure 1 session)	Pain intensity (VAS)	Analgesic consumption Number and types of adverse effects McGill Pain Questionnaire Patient satisfaction
Dailey et al., 2013 <sup>85</sup>	С	E	Fibromyalgia	43 (40W)	TENS (HF) + other treatments (stable) = 43	Placebo TENS = 43 (fading) + other treatments (stable) No TENS + other treatments (stable) (SoC, no TENS) = 43	Fixed 1 x 60-75 mins 1 session	Pain intensity (VAS) • Resting pain • Pain on movement	Pressure pain threshold at tend points (algometry) Conditioned pain modulation Fatigue at rest and movement (VAS) 6 Minute Walk Test Range of Motion Sit to Stand Test Single Leg Stance
Dailey et al., 202086	Р	Pr	Fibromyalgia	301 (301W)	TENS (MF) + routine care (pharmacology) = $103$	Placebo TENS (F) = 99	PRN	Pain intensity (NRS)	Brief Pain Inventory

						No TENS (SoC, pharmacology) = 99	At home during activity > 1 x 2 hours / day x 4 weeks	Resting pain     Pain on     movement     (during 6min     walk test)	Fatigue to 6MWT (NRS) and Multidimensional Assessment of FatigueFunction - International Physical Activity Questionnaire (IPAQ) short form Disease impact Quality of life Global impression of change Fear of Movement Other psychological factors
Davies, 1982 <sup>87</sup>	Р	Pr	Post-op – caesarean	35 (35W)	TENS (HF) + analgesics (papaveretum i.m., paracetamol, Dextropropoxphene as required) = 21	Placebo TENS (0mA) + analgesics (papaveretum i.m., paracetamol, Dextropropoxphene as required) = 14	PRN 24 hours	Pain intensity (VAS)	Analgesic consumption (opioid)
Dawood and Ramos, 1990 <sup>88</sup>	С	Е	Dysmenorrhea - primary	32 (32W)	TENS (HF) + ibuprofen if needed = 32	Placebo TENS + ibuprofen if needed = 32 (0mA) Ibuprofen (SoC, no TENS) = 32	PRN continuously for first 8 hours then PRN	Pain intensity (5 item categorical scale)	Analgesic consumption (Ibuprofen) Pain relief (5 item category scale) Menstrual symptoms including pain intensity (5 categories)
De Angelis et al., 2003 <sup>89</sup>	Р	Pr	Procedural pain – hysterectomy	142 (142W)	TENS (HF) = 71	No treatment = 71	Fixed Duration of procedure	Pain intensity (VAS) during procedure	Pain relief Duration of hysteroscopy CO <sub>2</sub> flow Heart rate
De Giorgi et al., 2017 <sup>90</sup>	Р	Pr	Myalgia - Chronic facial (temporomandibular joint)	49 (49W)	TENS (HF) = 34	No treatment (waiting list control) = 15	Fixed 1 x 60 mins /day x 10 weeks 10 sessions	Pain intensity (VAS)	Pericranial Muscle Tenderness Score Cervical Muscle Tenderness Score
de Oliveira, 2012 <sup>91</sup>	Р	Е	Dysmenorrhea - primary	15 (15W)	TENS (HF) = 5	Placebo TENS = 5 (0mA) TENS (LF) = 5	Fixed 1 x 30 mins 1 session	Pain intensity (NRS)	Pain interference with daily activities (NRS)
de Orange et al., 2003 <sup>92</sup>	Р	Pr	Labour pain	22 (22W)	TENS (HF) + (Bupivacaine + Sufentanyl epidural) – 11	Analgesic - (Bupivacaine + Sufentanyl epidural (SoC, no TENS) = 11	PRN	Pain intensity (VAS)	Duration of labour Frequency of hypoxia Apgar score
de Sousa et al., 2014 <sup>93</sup>	Р	Е	Post-partum uterine contraction pain	32 (32W)	TENS (HF) = 16	No treatment = 16	Fixed 40 mins during breast feeding 1 session	Pain intensity (NRS)	Treatment satisfaction
DeSantana et al., 200894	Р	Pr	Post-op – inguinal herniorrhaphy	40 (0W)	TENS (HF) + Metamizole (Dipyrone) = 20	Placebo TENS (0mA) + Metamizole (Dipyrone) = 20	Fixed 12 x 30 mins at 2h then 4h Post-op	Pain intensity (NRS) • Resting pain	Analgesic consumption (Metamizole) Nausea medication consumption TENS-Related Questions
DeSantana et al., 2009 <sup>95</sup>	Р	E	Post-op – laparoscopic tubal ligation	64 (64W)	TENS (HF) + medication (Ketoprophen, Hioscin plus Dipyrone and Metochlopramide) = 23	Placebo TENS + medication (Ketoprophen, Hioscin plus Dipyrone and Metochlopramide) = 21 (0mA)	Fixed 1 x 20min 1 sessions	Pain intensity (NRS)	McGill Pain Questionnaire

						TENS (LF) + medication (Ketoprophen, Hioscin plus Dipyrone and Metochlopramide) = 20			
Dewan and Sharma, 2011 <sup>96</sup>	Р	Pr	Adhesive capsulitis	50 (NR)	TENS (HF) = 25	IFT= 25	Fixed 1 x 20 mins x 2 to 3 / week x 4 weeks 10 sessions	Pain intensity (VAS)	Range of motion Constant Murley Assessment (CMA) score
Deyo et al. (1990 <sup>97</sup>	Р	Pr	Back pain – chronic, low, non-specific	125 (73)	TENS (AF, HF, LF burst) = 31	Placebo TENS = 29 (0mA) Placebo TENS + exercises = 29 (0mA) TENS + exercises = 34	Fixed 1 x 45 min x 3/day 3 sessions	Pain intensity (VAS)	Pain improvement (6-point sca Pain improvement (VAS) Pain frequency (5-point scale) Sickness Impact profile Level of activity (self-assessed categories) Straight leg raising test Schober test Use of medical providers
Dibenedetto et al., 1993 <sup>98</sup>	Р	Pr	Fibromyalgia	30 (29W)	TENS (HF) = 15	S = Adenosyl–L methionine = 15	Fixed 1 x 20 mins / day at each of 4 MTPs 5 days / week x 6 weeks 30 sessions	Pain intensity (VAS)	Total tender point score • Number • Tenderness intensity (5-point scale) Pressure pain threshold (algometry) Hamilton Rating Scale for Depression Fatigue, sleep, and well-being (VAS) Laboratory tests (complete blo picture) Overall evaluation of efficacy
Dilekci et al., 2016 <sup>99</sup>	Р	Pr	Tendinitis - Lateral epicondylitis	65 (43W)	TENS (HF) + SoC including NSAIDs =30	Standard of care (SoC, no TENS) = 30	Fixed 1 x 30 mins / day 10 sessions	Pain intensity (VAS) • At rest • On movement	Patient-Rated Tennis Elbow Evaluation (PRTEE) questionnaire
Dissanayaka et al., 2016 <sup>100</sup>	Р	Pr	Myofascial pain – syndrome patients with up/ trapezius myofascial trigger point	105 (58W)	TENS (HF) + SoC = $35$	Standard care (SoC, no TENS) = 35 IFT+ standard care = 35	Fixed 1 x 20 mins x 2 / week x 4 weeks 8 sessions	Pain intensity (VAS)	Range of motion – cervical
Dogu et al., 2008 <sup>101</sup>	Р	Pr	Myofascial pain and temporomandibular disorders	30 (28W)	TENS (HF) + rescue analgesic (paracetamol) = 14	Occlusal splint (SoC) = 16	Fixed 1 x 30 mins / day x 5 days / week x 4 weeks 20 sessions.	No pain intensity	Pressure-pain threshold (algometry) during rest and functional activities Pain and range of motion Quality of life both general and specific to masticatory functions SF-36
Domaille and Reeves, 1997 <sup>102</sup>	Р	E	Post-op – coronary artery bypass	60 (0W)	TENS (HF) + 1 mg morphine PCA = 31	Placebo TENS+ 1 mg morphine PCA = 29 (0mA)	Fixed 1 x 3h	Pain intensity (VAS)	Analgesic consumption (Morphine) - PCA

Ebadi et al., 2018 <sup>103</sup>	Р	E	Back pain – chronic, low, non-specific	30 (15W)	TENS (HF) $= 15$	Diadynamic = 15	Fixed 1 x 15 mins	Pain intensity (VAS)	Pressure pain threshold (algometry) Depression Anxiety and Stress Scale (DASS)
Ekblom and Hansson, 1987 <sup>104</sup>	C	E	Oral – acute pain from teeth and/ or surrounding tissue	40 (17W)	TENS (HF) = 11	Placebo TENS = 5 (0mA) TENS (LF) = 11 Vibration = 8 Placebo vibration = 5	Fixed 1 x 30 mins 1 session	Pain intensity (VAS)	Thermal threshold (heat and cold
Ekim et al., 2008 <sup>105</sup>	Р	Pr	Hemiplegic Shoulder Pain	19 (8W)	TENS (HF) + Hemiplegia rehabilitation = 10	Placebo TENS (0mA) + Hemiplegia rehabilitation = 9	Fixed 1 x 20 minutes / day x 5 / week x 3 weeks 15 sessions	Pain Intensity (VAS)	Barthel Index Range of motion - upper limb
Elboim-Gabyzon et al., 2019 <sup>106</sup>	Р	Pr	Post op - following Gamma-nail surgical fixation of extracapsular hip fractures	41 (32W)	TENS (HF) + SoC – physiotherapy = 23	Placebo TENS (0mA) + SoC – physiotherapy = 18	Fixed 1 x 30 mins / day x 5 days 5 sessions	Pain Intensity (NRS) • rest • during night during ambulation	Functional Ambulation Classification instrument Time to complete five sit-to-stand tests Two-minute walk test
Elserty et al., 2016 <sup>107</sup>	Р	Pr	Back pain – chronic, low, non-specific	45 (31W)	TENS (HF) + exercise = 15 (pulse amplitude adjusted every 5 mins, Group B)	Exercises only (SoC, no TENS, Group C) = 15 TENS + exercise = 15 (Fixed pulse amplitude, Group A)	Fixed 1 x 40 mins x 3 / week x 4 weeks	Pain intensity (VAS)	Oswestry Disability Index (ODI) Lumbar range of motion (flexion and extension)
Emmiler et al., 2008 <sup>108</sup>	Р	Pr	Post-op – open cardiac operation	60 (18W)	TENS (HF) + analgesia (pethidine and metamizole) = 20	Placebo TENS + analgesia (pethidine and metamizole) = 20 (0mA) Analgesia (pethidine and metamizole (SoC, no TENS) = 20	Fixed 1 x 60 mins then 60 mins rest then 1 x 60 mins	Pain intensity (VAS)	Analgesic consumption
Engen et al., 2016 <sup>109</sup>	Р	Pr	Post-op – video assisted thoracoscopic surgery	40 (23W)	TENS (VF) + Opioids (morphine - oral) = 20	Opioids (morphine - oral) (SoC, no TENS) = 20	PRN for 48 hours after surgery	Pain intensity (VAS)	Analgesic consumption (opioids blocks) Rating of physical status TENS satisfaction and utility
Erden and Senol Celik, 2015 <sup>110</sup>	Р	Pr	Post-op -posterolateral thoracotomy	40 (10W)	TENS (HF) + analgesics (tramadol / tamoxicam) = 20	No TENS + analgesics (tramadol / tamoxicam) (SoC, no TENS) = 20	Fixed 3 x 30 mins / day x 2 days then 2 x 30 mins / day	Pain intensity (VAS) • Resting pain • During cough	Analgesic consumption (Opioid)
Erdogan et al., 2005 <sup>111</sup>	Р	Pr	Post-op thoracotomy pain	116 (46W)	TENS (HF) + standard medication as needed) = 60	Placebo TENS (0mA) + standard medication as needed = 56	PRN for 48 hours then 1 x 20 mins at 3-hour intervals for 2 days 5 days in total	Pain intensity (VAS) • Resting pain • During cough	Analgesic consumption Spirometric breath functions (FEV1 and FVC) Blood gases (PaO2 and PaCO2)
Erkkola et al., 1980 <sup>112</sup>	Р	Pr	Labour pain	200 (200W)	TENS (NR) + meperidine = 100	No TENS + meperidine (SoC, no TENS) = 100	PRN throughout delivery	Pain intensity (5- point categorical scale)	Pain questionnaire (no description) Desire for analgesics
Escortell-Mayor et al., 2011 <sup>113</sup> Secondary Report	Р	Е	Neck pain - chronic non -specific ('mechanical neck disorder')	90 (80W)	TENS (HF) + exercises and education = 43	Manual therapy + exercises and education (SoC, no TENS) = 47	Fixed 1 x 30 mins / day every 2 days total 10 sessions	Pain intensity (VAS)	Neck Disability Index SF-12 Physical Component Summary (PSC-12)

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Escortell Mayor 2008 <sup>114</sup>										Mental Component Summary (MCS-12) Duration of crisis (days) General Health Questionnaire-
Esteban Gonzal 2015 <sup>115</sup>	lez et al.,	Р	Pr	Post-op - thoracotomy (shoulder pain)	50 (10W)	TENS (HF) + analgesics (epidural - paracetamol and ibuprofen or metamizole) = 25	Placebo TENS = 25 (0mA) + analgesics (epidural - paracetamol and ibuprofen or metamizole)	Fixed 1 x 30 mins every 8 hours x 3 days	Pain intensity (VAS) • on movement	Range of motion
Eyigor et al., 20		Р	Pr	Osteoarthritis - Knee	45(34W)	TENS (HF) + superficial heat and exercise = 14	Control - superficial heat and exercise (SoC, no TENS) = 15 US + superficial heat and exercise = 15	Fixed 1 x 20 mins / day x 5 days / week x 3 weeks 15 sessions	Pain intensity (VAS)	20-meter walking test Lequesne index WOMAC Isokinetic muscle testing SF 36
Eyigor et al., 20	010 <sup>117</sup>	Р	Pr	Tendinitis – rotator cuff	40 (29W)	TENS (HF) + exercises (Codman) + Paracetamol = 20	Intra articular injection of corticosteroid (+ exercises (Codman) + Paracetamol) = 20	Fixed 5 x 30 mins / week for 3 weeks 15 sessions	Pain intensity (VAS) • Resting pain	Analgesic consumption (Paracetamol) Range of motion Shoulder disability questionna (SDQ) Beck depression inventory Doctors satisfaction
Facci et al., 201	1118	Р	Pr	Back pain – Chronic, low, non- specific	150 (109W)	TENS (HF) = 50	No treatment (waiting list) = 50 IFT= 50	Fixed 1 x 30 mins / day x 5 days x 2 weeks 10 sessions	Pain intensity (VAS)	McGill Pain Questionnaire Analgesic consumption Duration of pain relieve post intervention
Farahani et al.,	2014 <sup>119</sup>	Р	E	Headache – primary	45 (20W)	TENS (NR) = 15	No treatment = 15 Neurofeedback behavioural therapy = 15	Fixed 1 x 20 mins / day x 20 days 20 sessions	Pain intensity (? VAS – 100mm)	Frequency of pain Duration of headache Blanchard headache diary
Farina et al., 20	04 <sup>120</sup>	Р	Pr	Upper trapezius Myofascial pain syndrome	40 (30W)	TENS (HF) = 21	Frequency modulated neural stimulation = 19	Fixed 1 x 20 mins / day x 5 days / week x 2 weeks 10 sessions	No pain intensity	Disability (NPDVAS) Myofascial trigger point characteristics Pressure pain threshold (algometry). Range of motion
Fatima and Sart 2019 <sup>121</sup>	fraz,	Р	Pr	Post op - Caesarean	50 (50W)	TENS (HF) + exercises + analgesics as needed = 25	TENS (LF, 4Hz) + exercises + analgesics as needed = $25$	Fixed 2 x 20 mins / day x 3 days 6 sessions	Pain intensity (NRS)	Analgesic consumption
Ferraz and Mor 2009 <sup>122</sup>	eira,	Р	Е	Post-op - cardiac surgery	20 (6W)	TENS (HF) $= 10$	Placebo TENS = 10 (0mA)	Fixed 1 x 20 mins 1 session	Pain intensity (NRS)	Analgesic consumption
Ferreira et al., 2	2011 <sup>123</sup>	Р	E	Post-op - thoracotomy	30 (12W)	TENS (HF) + fentanyl / bupivacaine = 15	Placebo TENS (0mA) + fentanyl / bupivacaine = 15	Fixed 1 x 60 mins 1 h after epidural on second Post-op day 1 session	Pain intensity (VAS) • Resting pain • Changing decubitus • Pain on movement	None

								<ul> <li>During cough</li> </ul>	
Ferreira et al., 2017 <sup>124</sup>	Р	E	Temporomandibular disorder – chronic	40 (30W)	TENS (LF then HF) $= 20$	Placebo TENS = 20 (current fade away to 0mA after 40s)	Fixed 1 x 50 mins 1 session	Pain intensity (VAS)	Pressure pain threshold (algometry) EMG activity
Finsen et al., 1988 <sup>125</sup>	Р	Pr	Post op - major amputation	51 (24W)	TENS (LF) + analgesics (NR) = 17	Placebo TENS + analgesics (NR) = 19 (0mA) Chlorpromazine + placebo TENS (0mA) + analgesics (NR) = 15	Fixed 2 x 30 mins / day x 2 weeks 28 sessions	No primary outcome	Analgesic consumption Presence of phantom pain (tally yes or no answers)
Fiorelli et al., 2012 <sup>126</sup>	Р	Pr	Post-op - thoracotomy	50 (19W)	TENS (HF) + morphine PCA = 25	Placebo TENS + morphine PCA = 25 (0mA)	Fixed 1 x 30 mins at 4h intervals for first 48h then 2 x 30 mins / day from day 3-5 16 sessions	Pain intensity (VAS)	Analgesic consumption (morphine-PCA) Serum cytokines measurements Respiratory function (FVC, FE' 1)
Fodor-Sertl et al., 1990 <sup>127</sup>	Р	Pr	Post-op - thoracotomy	40 (7W)	TENS (HF, segmental) + medication = 16	Placebo TENS (non-segmental, placebo control) + analgesic medication = 18	Fixed 15-30 mins 6 post-operative days	No primary outcomes	Analgesic consumption
Forogh et al., 2019 <sup>128</sup>	Р	Pr	Rehabilitation – following ACL surgery	70 (0W)	TENS (HF) + exercise = 35	Exercise (SoC, no TENS) = 35	Fixed 1 x 35 mins / day x 5 days / week x 4 weeks 20 sessions	Pain intensity (VAS)	International knee documentatio committee (IKDC) questionnain Range of motion
Forst et al., 2004 <sup>129</sup>	P	Pr	Peripheral diabetic neuropathy	19 (9W)	TENS (LF) = 12	Placebo TENS = 7 (0mA)	PRN >30 mins / day /leg for 12 weeks	Pain intensity (VAS)	New total symptom score (NTS = 6) Sensory nerve threshold (temperature, vibration, pain) Neuropathy total symptom scor 6 (NTSS - 6) Intensity of dysaesthesia, hypaesthesia and muscle weakness (VAS) Peripheral nerve function – vibration perception and temperature thresholds Microvascular blood flow
Forster et al., 1994 <sup>130</sup>	Р	Pr	Post-op - coronary artery bypass graft surgery	45 (0W)	TENS (HF) + Analgesics (morphine/paracetamol) = 15	Placebo TENS Analgesics (morphine/paracetamol) = 15 (0mA) Control Analgesics (morphine/paracetamol), (SoC, no TENS) = 15 (no description)	PRN up to 72 hours post op	Pain intensity (NRS) • Resting pain • During cough	Analgesic consumption (Narcotic)
Fujii-Abe et al., 2019 <sup>131</sup>	Р	E	Post op – Wisdom tooth extraction	44 (23W)	HF TENS (non-noxious) = 11	Placebo TENS (0mA) = 11 TENS (noxious, conditioned pain modulation = 11 Combined TENS (non-noxious + noxious) = 11	Fixed 1 x 20 mins	Pain intensity (VAS)	None
Galli et al., 2015 <sup>132</sup>	Р	Е	Post-op - nephrectomy	74 (39W)	TENS (HF) + analgesics (unknown) = 37	Placebo TENS (fading) + analgesics (unknown) = 37	Fixed 1 x 60 mins	Pain intensity (NRS) • Resting pain	Respiratory muscle strength Pulmonary function Walk function

								<ul> <li>During cough</li> <li>During pulmonary testing</li> <li>During walking</li> </ul>	
Galloway et al., 1984 <sup>133</sup>	Р	Pr	Post-op - abdominal	40 (30W)	TENS (PRN) + analgesic (Cyclimorph) as required = 14	No treatment (SoC, no TENS) + analgesic (Cyclimorph) as required = 14 TENS + analgesic Ccyclimorph) as required = 12 (Remote - non = segmental)	PRN for 48 hours	Pain intensity (VAS, Likert scale)	Analgesic consumption Wound pain discomfort (VAS)
Garcia-Perez et al., 2018 <sup>134</sup>	Р	Pr	Pressure ulcers (injury)	17 (15W)	TENS (HF) + standard wound care = 9	Standard wound care (SoC, no TENS) = 8	Fixed 1 x 60 mins / day x 3 weeks total 20 sessions	No primary outcome	Pressure injury area Pressure injury healing rate Blood flow in affected lower lin Skin temp0erature Pain Assessment in Advanced Dementia Scale
Gerson et al., 1977 <sup>135</sup>	С	Е	Post herpetic neuralgia	29 (NR)	TENS (NR) = 13	Carbamazepine + Clomipramine = 16	Fixed 1 x 15 mins / week x 4 weeks then one x 15 mins put 2 weeks x 6 weeks ? x 8 weeks too	Pain intensity (VAS).	Analgesic consumption Plasma concentrations of drugs Physical activity and mental outlook (VAS)
Ghoname et al., 1999 <sup>136</sup>	С	E	Back pain - low	60 (31W)	TENS (LF) + analgesics (non-opioid) as required = 60	Placebo PENS (0mA) + analgesics as required = =64 PENS + analgesics as required = = 64 Exercise therapies + analgesics as required = (SoC, no TENS) = 64	Fixed 1 x 30 mins x 3 / week x 3 weeks 9 sessions	Pain intensity (VAS)	Analgesic consumption SF-36 Physical component summary Mental component summary Quality of sleep Well-being)
Ghoname et al., 1999 <sup>137</sup>	С	Е	Back pain - Sciatica	64 (34W)	TENS (LF) + analgesics (non-opioid) as required = 64	Placebo PENS + analgesics as required (0mA) = 64 PENS + analgesics as required = 64	Fixed 1 x 30 mins / day x 3 weeks 21 sessions	Pain intensity (VAS)	Analgesic consumption SF-36 Physical activity and quality of sleep during the 24 h interval prior to each treatment session (VAS)
Gilbert et al., 1986 <sup>138</sup>	Р	Pr	Post-op - inguinal herniorrhaphy	40 (0W)	TENS (HF) + Pethidine as required = $20$	Placebo TENS + Pethidine as required = 20 (0mA)	PRN	Pain intensity (VAS)	Analgesic consumption (Pethidine) Expiratory peak flow
Grabiańska et al., 2015 <sup>139</sup>	Р	Pr	Back pain low	60 (NR)	TENS (HF) $= 30$	IFT = 30	Fixed 10 x 20 mins / day	Pain intensity (VAS)	Laitinen Pain Questionnaire
Graff-Radford et al., 1989 <sup>140</sup>	Р	Е	Myofascial pain and trigger point sensitivity	60 (45W)	TENS (HF) =12	Sham Control (Staodynamics unit or Pain Suppressor unit. 0mA). =12 TENS (LF, 2hz, 250us, >MDT) = 12 TENS (HF, 50us, SBC) = 12 TENS (Pain Supressor, 4mA, 15Hz burst of 20Khz ,active <sdt) 12<="" =="" td=""><td>Fixed 1 x 30 mins 1 session</td><td>Pain intensity (VAS)</td><td>Pressure algometry</td></sdt)>	Fixed 1 x 30 mins 1 session	Pain intensity (VAS)	Pressure algometry
Grant et al., 1999 <sup>141</sup>	Р	Е	Back pain	60 (54W)	TENS (HF) = 28	Acupuncture = 32	PRN	Pain intensity (VAS)	Analgesic consumption Pain subscale of Nottingham Health Profile

							1 x <30 mins / session and < 6h / day for 4 weeks		Spinal flexion measured from C to S1
Gregorini et al., 2010 <sup>142</sup>	Р	E	Post-op - cardiac surgery	25 (7W)	TENS (HF) = 13	Placebo TENS (>SDT – infrequent pulses) = 12	Fixed 1 x 4 hours ?? on 3rd post-op day	Pain intensity (VAS)	Respiratory muscle strength Lung volumes and capacity
Grimmer, 1992 <sup>143</sup>	Р	E	Osteoarthritis - knee	60 (37W)	TENS (HF) = 20	Placebo TENS = 20 (0mA) TENS (LF, burst) = 20	Fixed 1 x 30 mins 1 session	Pain intensity (VAS)	Stiffness change (VAS) Pain relief time (in hours) Stiffness relied time (hours) Change on knee circumference Change in knee range of motion Physiological respiratory rate, heart rate and blood pressure
Gschiel et al., 2010 <sup>144</sup>	Р	Pr	Osteoarthritis – knee (gonarthrosis)	45 (32W)	TENS (AF) = 25	Placebo TENS (0mA) = 20	PRN >2 x 30 mins / day for 3-weeks	Pain intensity (VAS)	SF-36 WOMAC Lysholm score
Gunay Ucurum et al., 2018 <sup>145</sup>	Р	Pr	Shoulder impingement syndrome	79 (65W)	TENS (NR) + exercise = 20	Exercise (SoC, no TENS) = 19 IFT + Exercise = 20 US + Exercise = 20	Fixed 1 x ?? mins x 3 / week x 4 weeks 12 sessions	Pain intensity (VAS)	Short Form-36 (SF-36) Disabilities of the Arm, Shoulder and Hand questionnaire (DASH)
Guo and Jia, 2005 <sup>146</sup>	Р	Pr	Fibromyalgia	66 (45W)	TENS (HF) = 22	Routine medication (SoC, no TENS) = 22 EA = 22	Fixed 1 x 30 mins / day for 20 days [repeated for another 20 days] ?? 40 sessions	Pain intensity (VAS)	Analgesic consumption
Hamza et al., 1999 <sup>147</sup>	Р	Pr	Post-op - gynaecological	100 (100W)	TENS (HF) + morphine PCA = 25	Placebo TENS + morphine PCA = 25 (0mA) TENS (LF) + morphine PCA = 25 TENS (AF) + morphine PCA = 25	Fixed 1 x 30 mins at intervals of 2 h or longer while patient awake	Pain intensity (VAS)	Analgesic consumption (PCA morphine) levels of sedation, fatigue, discomfort and nausea
Hanfy and El-Bigawy, 2004 <sup>148</sup>	Р	Pr	Dysmenorrhea – primary	30 (30W)	TENS (HF) = 15	Acupressure = 15	Fixed 1 x 20 mins x 3 days x 3 menstrual cycles	Pain intensity (6- point scale)	Pain relief (5-point scale)
Hansson and Ekblom, 1983 <sup>149</sup>	С	Е	Orofacial pain – acute	62 (36W)	TENS (HF) = 22	Placebo TENS (0mA) = 20 TENS (LF, burst) = 20	Fixed 1 x 30 mins 1 session	Pain intensity (5- point verbal scale)	None
Hansson et al., 1986 <sup>150</sup>	Р	Е	Post-op - oral	28 (16W)	TENS (HF) + naloxone = $6$	TENS (LF, burst) + naloxone = 7 Vibration + Naloxone = 7 Naloxone = 8	Fixed 1 x 45 mins 1 session	Pain intensity (5- point verbal scale)	None
Hargreaves and Lander, 1989 <sup>151</sup>	Р	E	Post-op dressing changes following abdominal surgery	75 (34W)	TENS (HF) + meperidine and morphine = 25	Placebo TENS (0mA) + meperidine and morphine = 25 No treatment (+ meperidine and morphine, SoC, no TENS) = 25	Fixed 1 x 15 to 60 mins depending on duration of dressing change 1 session	Pain intensity (VAS) • During dressing change	Analgesic consumption (prescription and administration
Harrison et al., 1986 <sup>152</sup>	Р	Pr	Labour pain	150 (150W)	TENS (HF+LF burst) = 76	Placebo TENS = 73 (0mA)	PRN During labour	Pain intensity (5- point scale)	Analgesic consumption Hours pf labour Mode of delivery Pain relief reported by the midwife (5-point scale)

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Hart et al., 2012 <sup>153</sup>	Ρ	Pr	Rehabilitation - Anterior cruciate ligament	30 (10W)	TENS (HF) + exercise = 10	Exercise alone (SoC, no TENS) = 10 Cryotherapy + Exercise = 10	PRN Daily x 2 weeks and during in clinic exercise session	Pain intensity (VAS)	Various functional outcomes for knee Tegner activity rating International Knee Documentation Committee subjective knee evaluation form. Circumferential girth (measured at mid-patella) Range of motion Quadriceps central activation
Hazneci et al., 2005 <sup>154</sup>	Р	Pr	CRPS - reflex sympathetic dystrophy syndrome upper limb	30 (0W)	TENS (HF) +, contrast bathing and exercise programme = 16	Pulsed US on stellate ganglion + contrast bathing and exercise programme = 14	Fixed 1 x 20 mins / day for 3 weeks 21 sessions	<ul><li>Pain intensity (???)</li><li>spontaneous pain</li><li>provocative pain</li></ul>	Loss of mobility, muscle power Oedema
Herrera-Lasso et al., 1993 <sup>155</sup>	Р	Pr	Shoulder – painful syndrome	29 (23W)	TENS (HF) + Exercises + Heat (superficial) = 15	US + Exercises + Heat (superficial) = 14	Fixed 1 x 20 mins / day x 2-5 / week 13 sessions	Pain intensity (VAS)	Range of motion
Hershman, 1989 <sup>156</sup>	Р	Pr	Post op - colorectal or cholecystectomy	95 (47W)	TENS (HF) + omnopon (opiate) = 48	Placebo TENS + omnopon (opiate) (0mA) = 47	PRN 48h post-operative	No primary outcome	Analgesic consumption - Opiate Anti- emetic consumption Duration of hospital stay
Hokenek et al., 2020 <sup>157</sup>	Р	Pr	Migraine – presenting to emergency department	83 (NR)	TENS (HF) + rescue medication = 39	Placebo TENS (0mA) + rescue medication = 39	Fixed 1 x 20mins	Pain intensity (VAS)	Analgesic consumption
Hou et al., 2002 <sup>158</sup>	Ρ	Е	Cervical Myofascial Pain and Trigger Point Sensitivity	71 (59W)	TENS (HF) + hot pack active ROM + stretch with spray (B5) = 9	Hot pack + active ROM + stretch with spray (SoC, no TENS) (B4) = 10 Ischemic compression + TENS (HF) + hot pack + active range of motion + = 9 Hot pack + active range of motion + ischemic compression = 12 Hot pack + active range of motion = 21 IFT+ myofascial release + Hot pack + active range of motion (B6) = 9	Fixed 1 x 20 mins 1 session	Pain intensity (VAS)	Pressure pain threshold and tolerance (algometry) Range of motion
Hruby et al., 2006 <sup>159</sup>	Р	Pr	Procedure pain - Office-based flexible cystoscopy	148 (40W)	TENS (HF) = 48	Placebo TENS (0mA) = 49 No treatment (no analgesics) = 51	Fixed < 5min During procedure 1 session	Pain intensity (VAS)	International Prostate Symptom Score questionnaire Changes in vital signs and IPSS
Hsieh and Lee, 2002 <sup>160</sup>	Р	E	Back pain - chronic low non-specific	133 (89W)	TENS + Medication = 49	Medication - Diclofenac (NSAID), mephenoxalone (muscle relaxant) and antacid (SoC, no TENS) = 31 PENS + medication = 53	Fixed 1 x 15 mins 1 session	Pain intensity (VAS)	Pain drawing instrument Pressure pain threshold (algometry) Quebec Back Pain Disability sc
Hsueh et al., 1997 <sup>161</sup>	Р	Е	Myofascial trigger points	60 (35W)	TENS (HF) $= 20$	Placebo electrotherapy (0mA) = 18	Fixed 1 x 20 mins	Pain intensity (VAS)	Pressure algometry (pain threshold)

						Functional electrical muscle stimulation = 22	1 session		Range of motion
Hughes et al., 1988 <sup>162</sup>	Р	Pr	Labour pain	89 (89W)	TENS (NR) + opioids rescue = 29	Placebo TENS (0mA) + opioids rescue = 30 Conventional medication, opioids (SoC, no TENS) = 30	PRN 24h	Pain intensity (VAS)	Analgesic consumption Pain relief (5-point category rat scale) Infant condition Apgar
Husch et al., 2020 <sup>163</sup>	Р	Pr	Post op - thoracotomy	45 (25W)	TENS (HF) + physiotherapy + analgesics = 15	Placebo TENS (fading to 0mA) + physiotherapy + analgesics = 15 Control (SoC, physiotherapy) + analgesics = 15	Fixed 3 x 30 mins / day x 2 days 6 sessions	Pain intensity (VAS)	Analgesic consumption Pulmonary function, respirator muscle strength
Ilhanli, 2015 <sup>164</sup>	P	Pr	chronic low back pain with lumbar disc herniation	160 (108W)	Conventional TENS (HF) Hot pack, ultrasound and exercise	Group1= Group2= Acupuncture- like TENS, Group3= Brief-intense TENS, Group4= Sham TENS.	Fixed 5 days/week for 3 weeks	Pain intensity (VAS) Rest Movement	Ostwestry Low Back Pain Disability Questionnaire Short-Form 36 physical component Mental component Scores Modified Lumbar Schober test, Straight Leg Raising test and Femoral Stretching test
Inal et al., 2016 <sup>165</sup>	Р	Pr	Osteoarthritis - knee	90 (90W)	TENS (HF) + physiotherapy (hot pack, US, exercise) = 30	Placebo TENS (0mA) + physiotherapy (hot pack, US, exercise) = 30 TENS (LF) physiotherapy (hot pack, US, exercise) = 30	Fixed 1 x 20 mins / day x 5 weeks 35 sessions	Pain intensity (VAS) • Resting pain • Pain on movement	WOMAC Walking speed (50 metres) Climbing stairs speed (ten stairs
Isik et al., 2017 <sup>166</sup>	Р	Pr	Osteoarthritis - knee	105 (80W)	TENS (HF) = 53	Leech therapy = 52	Fixed 1 x 20min / day x 5 days / week x 3 weeks (in clinic) 15 sessions	Pain intensity (VAS)	WOMAC
Jaafarpour et al., 2008 <sup>167</sup>	Р	Pr	Post-op - caesarean	108 (108W)	TENS (MF) = 54	Placebo TENS (0mA) = 54	PRN 24h continuous	Pain intensity (VAS)	Analgesic consumption
Jamison et al., 2019 <sup>168</sup>	Р	Pr	Back pain - chronic low non-specific	68 (41W)	TENS (HF) = 35	Usual treatment (SoC, no TENS) = 33	PRN daily x 3 months	Pain intensity (NRS) • Current pain • Average pain	Pressure algometry (PPT) Quantitative sensory testing Anxiety, depression, and irritability (NRS) Brief Pain Inventory Pain Disability Inventory (PDI) Pain Catastrophizing Scale (PC Hospital Anxiety and Depression Scale (HADS).
Jarzem et al., 2005 <sup>169</sup>	С	E	Back pain - chronic low non-specific	50 (21W)	TENS (NR, conventional) = 25	Placebo TENS (0mA) = 25	Fixed 3 x 20 mins 3 sessions	Pain intensity (VAS)	Range of motion Straight leg raising Sit-ups and oblique sit-ups
Jensen et al., 1985 <sup>170</sup>	Р	Pr	Arthroscopic knee surgery	90 (18W)	TENS (HF) = 30	Placebo TENS (0mA) = 30 Analgesic (SoC, no TENS control) = 30	PRN < 7 days - discontinuation day measured	Pain intensity (6- point category scale)	Analgesic consumption Medicine rating Range of motion Isokinetic muscle examination Leg volume

Jensen et al., 1991 <sup>171</sup>	Р	Pr	Osteoarthritis - knee	20 (18W)	TENS (HF) = 10	TENS (LF) = 10	Fixed 1 x 30 mins / day x 5 days 5 sessions	Pain intensity (4- point Likert scale) • Resting pain • Pain on movement • Exercise induced	Analgesic consumption (NSAID)
Jones and Hutchinson, 1991 <sup>172</sup>	С	Е	Post-op pain – abdominal	31 (16W)	TENS (HF, Para incision) + physiotherapy = 31	Placebo TENS ('modified placebo' remote site, leg) + physiotherapy = 31 Entonox + physiotherapy = 31	Fixed 1 x 20 mins 1 session	Pain intensity (VAS)	Respiratory function Peak expiratory flow rate
Kara et al., 2011 <sup>173</sup>	Р	Pr	Post-op spinal surgery	54 (28W)	TENS (AF,) + Meperidine PCA = 25	Meperidine PCA (SoC, no TENS control) = 29	Fixed 2 x 30- 40 mins with a 3 to 4-hour rest interval	Pain intensity (VAS) • Resting pain • Pain on movement	Analgesic consumption Beck Depression Inventory Timed Up and Go (TUG) test
Kararmaz et al., 2004 <sup>174</sup>	Р	Pr	Procedural pain - during extracorporeal shock wave lithotripsy	66 (42W)	TENS (HF, conventional) = 22	Placebo TENS (active, <sdt) 22<br="" =="">TENS (LF, acupuncture-like) = 22</sdt)>	Fixed ~45-60mins throughout the procedure 1 session	Pain intensity (VAS)	Analgesic consumption (Alfentanil) Nausea and vomiting (tally of yes/no) Aldrete score Patients' satisfaction (4-point scale)
Kayman-Kose et al., 2014 <sup>175</sup>	Р	E	Post-partum pain following (a) Caesarean section – post operative pain + uterine contractions (b) Vaginal delivery – post trauma pain + uterine contractions	(a) = 50 (50W) (b) = 50 (50W)	(a) TENS (HF) = 50 (b) TENS (HF)= 50	(a) Placebo TENS (0mA) = 50 (b) Placebo TENS (0mA) = 50	Fixed 1 x 30min 1 session	Pain intensity (VAS and verbal rating scale)	Analgesic consumption
Keskin et al., 2012 <sup>176</sup>	Р	Pr	Back pain – low, pregnancy-related	79 (79W)	TENS (HF) = 20	Control group (no treatment control) = 21 Exercise (SoC) = 19 Acetaminophen = 19	2 x ? mins / week x 3 weeks	Pain intensity (VAS)	Roland Morris Disability Questionnaire
Kibar et al., 2020 <sup>177</sup>	Р	Pr	Back pain - chronic low non-specific	123 (87W)	TENS (HF) + hot pack + exercise + rescue paracetamol = 31	Placebo TENS (Sham TENS/IFT device, 0mA) + hot pack + exercise + rescue paracetamol = 30 IFT + hot pack + exercise + rescue paracetamol = 30 TENS + IFT + hot pack + exercise + rescue paracetamol = 32	1 x 30 mins / day x 5 / week x 3 weeks 15 sessions	Pain intensity (VAS) • During activity	Lumbar range of motion (ROM) via inclinometer and modified Schober test, patient and physician global assessments Rolland-Morris Disability Questionnaire
Kim et al., 2012 <sup>178</sup>	Р	Е	Pain during venous cannulation	100 (60W)	TENS (HF) = 50	Placebo TENS (0mA) = 50	Fixed 1 x 20 min before cannulation 1 session	Pain intensity (NRS)	Adverse effects
Kim et al., 2014 <sup>179</sup>	Р	Pr	Myofascial pain syndrome Mixed	99 (86W)	TENS (NR) + Ketoprofen (NSAID) patch = 24	Ketoprofen (NSAID) patch (SoC) = 25	Fixed 2 x 20 mins / day x 2 weeks	Pain intensity (NRS)	Active range of motion Pressure pain threshold (algometry)

						Heating pad + ketoprofen (NSAID) patch = 25 Topical capsaicin + ketoprofen (NSAID) patch = 25	28 sessions		Neck Disability Index (NDI) Safety
Kirupa et al., 2019 <sup>180</sup>	Р	Pr	Temporomandibular joint	30 (NR)	TENS (HF) = 15	Ultrasound = 15	Fixed 1 x 15 mins / day x unclear /week x 4 weeks ? 10 sessions	Pain intensity (VAS)	None
Knobel et al., 2005 <sup>181</sup>	Р	Pr	Labour pain	60 (60W)	TENS (HF, 'tablet electrode') = 20	Placebo TENS (0mA) = 20 TENS using silver spike point electrode = 20	PRN 1 x 120 mins	Pain intensity (VAS)	Analgesic consumption Epidural analgesia Pain relief (calculated from pai intensity (VAS) Discomfort (NR)
Koca et al., 2014 <sup>182</sup>	Р	Pr	Carpal tunnel syndrome	75 (43W)	TENS (HF) = 25	IFT= 25 Splint therapy = 25	Fixed 1 x 20 mins / day x 5 days / week x 3 weeks 15 sessions	Pain intensity (VAS)	Symptom severity scale BCTQ Neurophysiology (median moto nerve latency and sensory nerve conduction velocity)
Kofotolis et al., 2008 <sup>183</sup>	Р	Pr	Back pain - chronic low non-specific	92 (92W)	TENS (LF) = 23	Placebo TENS (0mA) = 23 Rhythmic stabilisation = 23 TENS (LF) + Rhythmic stabilisation = 23	Fixed 1 x 40-45 mins x 5 days/week x 4 weeks 20 sessions	Pain intensity (VAS/BORG)	Physical activity questionnaire Oswestry Low Back Pain Disability Questionnaire Range of motion Flexion and extension trunk endurance tests
Koke et al., 2004 <sup>184</sup>	C	Pr	Chronic pain	180 (116W)	TENS (HF, HI, >SDT) = 62	Control (HF, intensity of choice) = 60 TENS (HF, LI, SDT) = 58	PRN 30 mins (HI) or 60 mins (LI) 4 to 6 times / day x 2 weeks 56 sessions	Pain intensity (VAS)	Desire to continue (TENS continuation questionnaire)
Korkmaz et al., 2010 <sup>185</sup>	P	Pr	Shoulder pain	40 (28W)	TENS (HF) + exercise = 20	Pulsed radiofrequency + exercise = 20	Fixed 1 x 20 mins /day x 5 / week 20 sessions	<ul> <li>Pain intensity (VAS)</li> <li>Resting pain (maximum and mean)</li> <li>Pain on movement (maximum and mean)</li> <li>Pain at night (maximum and mean)</li> </ul>	Range of motion Shoulder Pain and Disability Index SF-36
Kumar and Raje, 2014 <sup>186</sup>	Р	Pr	Tension-type headache	36 (20W)	TENS (LF) = 17	Exercises - Progressive muscular relaxation (SoC) = 19	Fixed 1 x 15 mins / day x 7 days 7 sessions	Pain intensity (VAS)	Lakaev Academic Stress Response Scale
Labrecque et al., 1999 <sup>187</sup>	Р	E	Labour pain (Low back pain)	34 (34W)	TENS (HF) =12	Standard care (massage, whirlpool bath, mobilisation, SoC, no TENS) = 12	PRN During labour	Pain intensity (VAS)	Analgesic consumption (narcotics) Pain unpleasantness (VAS) Labour Agentry Scale (LAS)

### 08\_OL-TABLE1\_IncludedStudies

						Intracutaneous sterile water injections (as a treatment) = 11			Labour and Delivery Satisfac Index
Laitinen and Nuutinen, 1991 <sup>188</sup>	Р	Pr	Post-op cholecystectomy	60 (53W)	TENS (HF) + Indomethacin = 20	Control opioid analgesics (SoC, no TENS or Indomethacin) = 10 Indomethacin = 10 TENS (LF) + Indomethacin = 20	Unclear > 16 hours	Pain intensity (4 point categorical)	Analgesic consumption (Opic Blood pressure Heart rate Respiratory frequency Reported side effects
Lang et al., 2007 <sup>189</sup>	Р	Pr	Acute Posttraumatic hip pain during emergency transport	101 (58W)	TENS (HF) = 30	Placebo TENS (0mA) = 33	Fixed ~30 mins throughout transport to hospital	Pain intensity (VAS)	Anxiety (VAS) Morphometric characteristics
Langley et al., 1984 <sup>190</sup>	Р	E	Rheumatoid arthritis (hand) + chronic pain (hand)	33 (24W)	TENS (HF) =11	Placebo TENS (0mA) = 11 TENS (LF, acupuncture -like) = 11	Fixed 1 x 20 mins 1 session	Pain intensity (VAS) • Resting pain • Pain on movement (grip)	Pressure algometry (joint tenderness) Grip strength
Lauretti et al., 2013 <sup>191</sup>	Р	Pr	Fibromyalgia	39 (34W)	TENS (AF, single device) + placebo TENS device = 13	Placebo TENS (0mA, 2 devices) = 10 TENS (AF, two devices) = 13	Fixed 1 x 20min every 12 h x 7 days	Pain intensity (VAS)	Analgesic consumption Quality of sleep and fatigue
Lauretti et al., 2015 <sup>192</sup>	Р	Pr	Dysmenorrhea	40 (40W)	TENS (Alternating between HF continuous, LF burst) = 20	Placebo TENS (0mA) = 20	Fixed 1 x 30mins at 8 h interval x 7 days ~14 sessions	Pain intensity (VAS)	Analgesic consumption (Diclofenac) Quality of life questionnaire
Law and Cheing, 2004 <sup>193</sup>	Р	Pr	Osteoarthritis - knee	34 (unclear)	TENS (HF) = 12	Placebo TENS (0mA) = 10 TENS (LF) = 13 TENS (AF 2/100pps) = 13	Fixed 1 x 40 mins / day x 5 / week x 2 weeks 10 sessions	Pain intensity (VAS) • Pain on movement	Range of motion Time-up-and-Go
Law et al., 2004 <sup>194</sup>	Р	Pr	Osteoarthritis - knee	39 (37W)	TENS (HF) = 22	Placebo TENS (0mA) = 17	Fixed 1 x 40 mins / day x 5 days x 2 weeks 10 sessions	Pain intensity (VAS) • Pain on movement	Range of motion Timed-up-and-Go
Leandri et al., 1990 <sup>195</sup>	Р	Pr	Post stroke - Hemiplegic shoulder pain	60 (44W)	TENS (HF) = 20	Placebo TENS (0mA) = 20 TENS (HF, LI) = 20	Fixed 3 days week x 4 weeks 12 sessions	No primary outcome	Range of motion - pain free
Lee et al., 1990 <sup>196</sup>	Р	Pr	Labour pain	125 (125W)	TENS (HF continuous, LF burst) + analgesics on demand = 58	Placebo TENS (0mA) + analgesics on demand = 33 No treatment (pethidine injections and Entonox inhalation) (SoC, no TENS) = 34	PRN During labour	Pain intensity (NRS)	Analgesic consumption Pain interval TENS satisfaction questionne
Lee et al., 2015 <sup>197</sup>	Р	Pr	Post-op Colle's fracture	36 (NR)	TENS (HF) = 18	Placebo TENS (0mA) = 18	Fixed 1 x 15min / day x 5 days	Pain intensity (VAS)	Analgesic consumption (PCS morphine and Cataflan)
Lee et al., 2019 <sup>198</sup>	С	Е	Cancer pain - head and neck	41 (6W)	TENS (HF) = 40	Placebo TENS (fading) = 40 No treatment = 40	Fixed 1 x 30 mins x 1 / week 1 session	Pain intensity (VAS)	McGill Pain Questionnaire Perception of TENS effective (VAS) Oral function tasks Fatigue (VAS)
Leo et al., 1986 <sup>199</sup>	C	Е	Mixed pain	192 (NR)	TENS (HF, 60pps, 250us, tolerance) = 16	TENS (HF, 60pps, 50us, tolerance) = 16	Fixed 1 x 30 mins 1 session	Pain intensity (VAS)	None

Limoges and Rickabaugh, 2004 <sup>207</sup>	Р	Pr	Procedural pain - Screening flexible sigmoidoscopy	90 (39 W)	TENS (HF) $= 30$	Placebo TENS (0mA) = 30 Verbal encouragement (SoC, no TENS) = 30	Fixed	Pain intensity (NRS, categorical scale)	McGill Pain Questionnaire 12-item questionnaire (Bloating, nausea, electrode site burning or
Lima et al., 2011 <sup>206</sup>	P	Pr	Post-op - coronary artery bypass graft	20 (10W)	TENS (HF) + usual care (Physiotherapy and analgesics) = 10	Usual care (Physiotherapy and analgesics, SoC, no TENS) = 10	Fixed 1 x 30 mins x 3 / day	Pain intensity (VAS)	Analgesic consumption Muscle strength (MIP) and expiratory muscle strength (MEP) Functional residual capacity (FRC)
Lim et al., 1983 <sup>205</sup>	Р	Pr	Postop pain - abdominal	30 (17W)	TENS (NR) = 15	Placebo TENS (0mA) = 15	PRN	Pain intensity (VAS)	Analgesic consumption (morphine)
Likar et al., 2001 <sup>204</sup>	Р	Pr	Postop pain	30 (9W)	TENS (HF) + analgesics = 11	Placebo TENS (0mA) + analgesics = 12	PRN	Pain intensity (VAS) • At rest • On movement (abduction)	Analgesic consumption - time of taking the 1st analgesic Blood pressure, Heart rate, Respiratory rate, Side effects,
Lewis et al., 1994 <sup>203</sup>	С	Е	Osteoarthritis - knee	36 (21W)	TENS (HF) + placebo pills = 36	Placebo TENS (0mA) + placebo pills = 36 Placebo TENS (0mA) + Naproxen (SoC, sham TENS) = 36	PRN > 3 x 30-60 mins / day x 3 weeks	Pain intensity (VAS)	Pain relief (VAS) Pain Index for the Knee Patient Opinion of Treatment Efficacy Piper Pain Intensity Scale
Lewis et al., 1984 <sup>202</sup>	C	E	Osteoarthritis - knee	30 (22W)	TENS (HF) = 30	Placebo TENS (0mA) = 30	Fixed 3 x 30-60 mins / day x 3 weeks 21 sessions	Pain intensity (VAS)	Analgesic consumption Paracetamol intake Duration of pain relief Pain free range of motion Questionnaire of patients' opinio
Lewers et al., 1989 <sup>201</sup>	Р	Е	Dysmenorrhea - primary	21 (21W)	TENS (LF, acupuncture-like) =10	Placebo pill = 11	Fixed 1 x 30 mins 1 session	Pain intensity (VAS)	McGill Pain Questionnaire Pain rating index
Leonard et al., 2011 <sup>200</sup>	C	Е	Chronic pain - various	23 (15W)	TENS (HF, conventional) =	TENS (LF, acupuncture-like) = 23	Fixed 1 x 25 mins 1 session	Pain intensity (NRS)	Pain unpleasantness (NRS) The Patient Global Impression o Change (PGIC) scale
200				~		TENS (HF, 60pps, 250us, $<$ SDT) = 16 TENS (HF, 60pps, 50us, $<$ SDT) = 16 TENS (HF, 60pps, 250us, SDT) = 16 TENS (HF, 60pps, 50us, SDT) = 16 TENS (LF, 3pps, 250us, tolerance) = 16 TENS (LF, 3pps, 50us, tolerance) = 16 TENS (LF, 3pps, 50us, SDT) = 16 TENS (LF, 3pps, 250us, $<$ SDT) = 16 TENS (LF, 3pps, 250us, $<$ SDT) = 16 TENS (LF, 3pps, 50us, $<$ SDT) = 16 TENS (LF, 3pps, 50us, $<$ SDT) = 16 TENS (LF, 3pps, 50us, $<$ SDT) = 16			

							10-20 mins throughout procedure 1 session		tingling, present versus previous SFS pain comparison, and degree of procedural difficulty)
Lin et al., 2015 <sup>208</sup>	Р	Pr	Shoulder pain – chronic	33 (25W)	TENS (LF, 2Hz) = 17	Transcutaneous pulsed radiofrequency = 16	Fixed 1 x 15 mins x 3 / week x 1 week 3 sessions	Pain intensity (VAS)	Serum cortisol level
Lin et al., 2019 <sup>209</sup>	Р	Pr	Shoulder pain – chronic	50 (34W)	TENS (HF) $= 25$	Transcutaneous pulsed radiofrequency = 25	Fixed 1 x 15 mins every other day x 1 week 3 sessions	Pain intensity (VAS)	Treatment comfort level Constant–Murley shoulder (CM score PEG (pain, enjoyment of life, a general activity) score
Linde et al., 1995 <sup>210</sup>	Р	Pr	Temporomandibular joint disk displacement	31 (26W)	TENS (HF) = 16	Flat occlusal splint (SoC, no TENS) = 15	Fixed 3 x 30 mins / day x 6 weeks 66 sessions	Pain intensity (VAS)	Frequency and intensity of complaints (6-step verbal scale Pain-Track system (pain intens VAS, sleep or waking hours, mealtimes)
Linn et al., 1999 <sup>211</sup>	Р	Pr	Post-stroke – shoulder subluxation	40 (22W)	TENS (HF, AM) + standard care (conventional physiotherapy and occupational therapy) = 20	Standard care (conventional physiotherapy and occupational therapy, SoC, no TENS) = 20	Fixed 4 x 30-60 mins / day x 4 weeks 112 sessions	Pain intensity (5- point NRS)	Pain free range of motion Shoulder subluxation (radiological) Upper arm girth
Lison et al., 2017 <sup>212</sup>	Р	Pr	Procedural pain - office hysteroscopy	138 (138W)	TENS (RF) = 46	Placebo TENS (0mA) = 46 Standard care without analgesia (SoC, no TENS) = 46	Fixed 5-30 mins throughout procedure 1 session	Pain intensity (VAS and 5-point verbal scale)	Duration of the procedure Vital parameters Vasovagal symptoms Unusual or adverse TENS even Level of satisfaction with the procedure (NRS)
Liu et al., 1985 <sup>213</sup>	Р	Pr	Post-op - thoracotomy	30 (8W)	TENS (NR) = $15$	Placebo TENS (active, <sdt) 15<="" =="" td=""><td>Fixed 1 x 20min / day x 10days 10 sessions</td><td>Pain intensity (NRS)</td><td>Passive range of motion Functional activities score</td></sdt)>	Fixed 1 x 20min / day x 10days 10 sessions	Pain intensity (NRS)	Passive range of motion Functional activities score
Liu et al., 2017 <sup>214</sup>	Р	Pr	Migraine	110 (87W)	TENS (HF, TONS) = 22	Placebo TENS (0mA) = 22 Topiramate (SoC, no TENS) = 22 TENS (LF, TONS) = 22 TENS (AF, TONS) = 22	Fixed 1 x 30m/day x 4 weeks 28 sessions	Pain intensity (VAS)	Analgesic consumption Headache diary (frequency, headache intensity, duration) Self-rating depression scale (S Self-rating anxiety scale (SAS) Headache Impact Test Patient satisfaction with treatm
Lofgren and Norrbrink, 2009 <sup>215</sup>	C	Е	Fibromyalgia	32 (32W)	TENS (HF) = 16	Heat therapy (Superficial warmth) = 16	PRN 1 x >30 mins / session as needed x 3 weeks	Pain intensity (VAS, NRS)	Duration of analgesia Fibromyalgia impact questionnaire Treatment preference
Luchesa et al., 2009 <sup>216</sup>	Р	Pr	Post-op coronary artery bypass graft	30 (5W)	TENS (HF) = 15	Placebo TENS (0mA) = 15	PRN 2 x 50 min / day x 5 days	Pain intensity (NRS)	Expiratory flux peak Forced vital capacity Forced expiratory volume
Lundeberg, 1984 <sup>217</sup>	C	Pr	Myalgia - chronic	36 (20W)	TENS (HF) = 9	Placebo pill = 9 EA = 9 Vibration = 9	Fixed ~ 2 x 45 mins / week x 3 weeks 6 sessions	Pain intensity (VAS)	Duration of pain relief

Lundeberg et al., 1985 <sup>218</sup>	С	Е	Dysmenorrhea - primary	21 (21W)	TENS (HF) $= 21$	Placebo TENS =21 (0mA) TENS (LF, burst) = 21	Fixed 1 x 45 mins 1 session	Pain intensity (VAS)	Analgesic consumption McGill Pain Questionnaire Duration of pain relief
Machado et al., 2019 <sup>219</sup>	Р	E	Dysmenorrhea	88 (88W)	TENS (HF) + placebo thermotherapy = 22	Placebo TENS + placebo thermotherapy = 22 Thermotherapy (microwave diathermy) + placebo TENS = 22 TENS + Thermotherapy (microwave diathermy) = 22	Fixed 1 x 30 mins 1 session	Pain intensity (NRS)	McGill Pain Questionnaire Conditioned pain modulation tes
Machin et al., 1988 <sup>220</sup>	Р	Е	Back pain - chronic low non-specific	30 (?NR)	TENS (HF) = 15	Placebo TENS = 15 (0mA)	Fixed 1 x 20 mins/day, unclear x days/week x 3 weeks 15 sessions	Pain intensity (VAS and verbal descriptive scale)	Pain diary information
Mahure et al., 2017 <sup>221</sup>	Р	Pr	Post-op arthroscopic rotator cuff repair	37 (19W)	TENS (HF) = 21	Placebo TENS = 16 (0mA)	Fixed 4 x 45 min /day x 7 days 28 sessions	Pain intensity (VAS)	Analgesic consumption (Narcotic)
Manigandan et al., 2014 <sup>222</sup>	Р	Pr	Post stroke - subluxation	24 (7W)	TENS (HF, at supraspinatus, posterior deltoid + long head of biceps) + physiotherapy + occupational therapy = 12	TENS (HF, at supraspinatus and posterior deltoid) + physiotherapy + occupational therapy = 12	Fixed 1 x 30-60mins / day x 5 weeks 35 sessions	No primary outcome	Shoulder subluxation in mm (x- ray) Pain - free range of passive later rotation and active shoulder abduction range of motion
Mannheimer and Carlsson, 1979 <sup>223</sup>	С	Е	Rheumatoid arthritis	20 (13W)	TENS (HF) = 20	TENS (LF) = 20 TENS (LF, burst) = 20	Fixed 1 x 10 mins 1 session	Pain intensity (5- point scale)	Loading test (time patient could hold weight) Duration of analgesia
Mannheimer and Whalen, 1985 <sup>224</sup>	Р	Pr	Dysmenorrhea	27 (27W)	TENS (HF) $= 9$	Placebo TENS (0mA) = 9 TENS (LF, acupuncture-like) = 9	Fixed 1 x 30 mins 1 session	Pain intensity (VAS)	Total number of painful days Duration of pain relief
Mannheimer et al., 1978 <sup>225</sup>	С	Е	Rheumatoid arthritis	19 (17W)	TENS (HF, SBC at pain, Group 1) = 19	TENS (SDT at pain, group 2) = 19 TENS (HF, SDT at remote site, Group 3) = 19	Fixed 5 mins / day x 15 days 15 sessions	No primary outcome	Degree of pain relief Loading test (time patient could hold weight)
Mannheimer et al., 1985 <sup>226</sup>	Р	Pr	Severe angina pectoris	23 (4W)	TENS (HF) + antianginal medication as needed = 12	Antianginal medication (SoC, no TENS, 'no treatment' control) = 11	Fixed 3 x 60 mins / day x 10 weeks during anginal attacks 30 sessions	Pain intensity (5- point scale)	Recovery time (min) Frequency of anginal attacks Consumption nitroglycerin Work during exercise Pulse rate, blood pressure Dyspnoea (5-point scale) Electrocardiograms
Mansourian et al., 2019 <sup>227</sup>	Р	Pr	TMJ - Myofascial pain	108 (88W)	TENS (HF) + medication = NR (36)	Medication Control (SoC, no intervention) = NR (36) LLLT + medication = NR (36)	Fixed 1 x 10 mins / day x 3 / week x 3 weeks 10 sessions	Pain intensity (VAS) • at rest • on movement - variety of face and jaw movements	Mouth opening Lateral protrusive movements

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Mansuri et al., 2019 <sup>228</sup>	Р	E	Musculoskeletal pain - Muscle tension dysphonia	30 (20W)	TENS (HF) $= 15$	Placebo TENS (0mA) = 15	Fixed 1 x 20 mins 1 session	Pain intensity (VAS)	Vocal tract discomfort scale Extended Nordic musculoskeletal symptoms questionnaire Auditory-perceptual assessment
Mansuri et al., 2020 <sup>229</sup>	Р	Pr	Musculoskeletal pain - Muscle tension dysphonia	20 (20W)	TENS (LF) + vocal tract training = 10	Vocal tract training (SoC) = 10	Fixed 1 x 50 mins / day x 2 / week x 2 weeks 10 sessions	Pain intensity (VAS)	Extended Nordic Musculoskeleta Symptoms Questionnaire Vocal tract discomfort
Marchand et al., 1993 <sup>230</sup>	Р	Pr	Back pain - chronic low non-specific	42 (22W)	TENS (HF) $= 14$	Placebo TENS (0mA) = 12 No treatment = 16	Fixed 1 x 30 mins / day x 2 / week x 10 weeks 20 sessions	Pain intensity (VAS)	Pain unpleasantness (VAS)
Mascarin et al., 2012 <sup>231</sup>	Р	Pr	Osteoarthritis - knee	38 (38W)	TENS (MF) = $12$	Kinesiology taping = 16 Ultrasound = 10	Fixed 1 x 20 mins / day x 2 / week x 12 weeks 24 sessions	Pain intensity (VAS)	WOMAC Range of motion - knee flexion and extension Six-minute walking test (6-MWT
McCallum et al., 1988 <sup>232</sup>	Р	Pr	Post-op decompressive lumbar laminectomy	20 (13W)	TENS (HF) = 10	Placebo TENS (0mA) = 10	PRN (NR)	No primary outcome	Analgesic consumption Plasma morphine concentrations
Melzack et al., 1983 <sup>233</sup>	Р	Pr	Back pain – acute and chronic low non- specific	41 (22W)	TENS (LF) = 20	Gentle massage = 21	Fixed 2 x 30 mins / week x 5 weeks 10 sessions	Pain intensity (PPI)	McGill Pain Questionnaire Range of motion
Merrill, 1989 <sup>234</sup>	Р	Pr	Post-op urologic surgery	96 (0W)	TENS (NR) + analgesics as needed = 48	Analgesics (SoC, no TENS) = 48	PRN	No primary outcome	Analgesic consumption
Miller et al., 2007 <sup>235</sup>	С	Pr	Spasticity – multiple sclerosis	32 (17W)	TENS (HF, for 8 hrs) = 32	TENS (HF, for 60 mins) = 32	Fixed 1 x 8 hours or 60 mins / day x 2 weeks 14 sessions	Pain intensity (VAS)	Global Spasticity Scale (GSS) Penn Spasm Scale (PSS) TENS experience questionnaire
Milsom et al., 1994 <sup>236</sup>	С	E	Dysmenorrhea - primary	12 (12W)	TENS (HF, HI) = $12$	Naproxen (500 mg, SoC not TENS) = 12	Unclear 1 x 10 seconds repeated as necessary	Pain intensity (5- point scale)	Uterine contractility and intrauterine pressure
Moharic et al., 2009 <sup>237</sup>	Р	Pr	Peripheral diabetic neuropathy	65 (NR)	TENS (HF) = 46	Pregabalin = 5 TENS (HF) + Pregabalin = 14	Fixed 1 x 3h / day x 7 days / week 3 weeks 21 sessions	Pain intensity (VAS)	Pain unpleasantness (VAS Pain interference with daily activities and sleep (VAS) SF-36
Mondal et al., 2019 <sup>238</sup>	Р	Pr	Myofascial pain	109 (86W)	TENS (HF) + + SoC (exercises + heat + medication) = 34	Ultrasound therapy + SoC (exercises + heat + medication) = 36 Trigger point injection (steroid + local anaesthetic) + SoC (exercises + heat + medication) = 39	Fixed 1 x 20 mins per trigger point / day x 2 weeks 14 sessions	Pain intensity (VAS)	Index score of trigger point after palpation Neck disability Index
Moore and Shurman, 1997 <sup>239</sup>	С	E	Chronic back pain	24 (16W)	TENS (HF) = 24	Placebo TENS (0mA) = 24 NMES = 24 NMES + TENS = 24	Fixed 1 x 5 hours / day x 2 days 2 sessions	Pain intensity (VAS)	Pain relief (VAS)
Mora et al., 2006 <sup>240</sup>	Р	Pr	Renal colic in Emergency care	100 (29W)	TENS (HF) = 39	Placebo TENS (sham, 0mA) = 34	Fixed 1 x 30 mins 1 session	Pain intensity (VAS)	Anxiety (VAS) Morphometric characteristics

Morgan et al., 1996 <sup>241</sup>	Р	Pr	Procedural pain - Distention shoulder arthrography	60 (32W)	TENS (HF) + Lignocaine = 20	Placebo TENS (active, ≤SDT) + Lignocaine = 20 Lignocaine (SoC, no TENS, control) = 20	Fixed 1 x 20 mins before procedure then throughout procedure 1 session	Pain intensity (VAS)	None
Møystad et al., 1990 <sup>242</sup>	С	E	Rheumatic disease involving the temporomandibular joint.	19 (17W)	TENS (HF) = 19	Placebo TENS (0mA) = 19 TENS (LF) = 19	Fixed 1 x 30 mins 1 session	Pain intensity (VAS) • At rest • on movement	Muscle tenderness to palpation (3 point scale) Range of motion
Murray et al., 2004 <sup>243</sup>	C	E	Angina pectoris	10 (2W)	TENS (HF) = 10	Placebo pills = 10	Fixed 3 x 60 mins / day x 2 / week 10 sessions	No primary outcome	Treadmill exercise tests • exercise time • Time to maximum ST depression • Rate-pressure product at peak exercise • Time to onset of angina
Mutlu et al., 2013 <sup>244</sup>	Р	Pr	Fibromyalgia	66 (66W)	TENS + Exercise (supervised) = 33	Supervised exercise (SoC, no TENS) = 33	Fixed 1 x 30 mins / day x 5 days x 5 weeks 25 sessions	Pain intensity (VAS – within FIQ)	Fibromyalgia Impact Questionnaire (FIQ) Tender point count) Myalgic pain score SF-36
Nabi et al., 2015 <sup>245</sup>	Р	Pr	Peripheral diabetic neuropathy	65 (29W)	TENS (HF) = 30	Pulsed radiofrequency = 30	Fixed 1 x 20 mins every 2 days x 2 weeks 10 sessions	Pain intensity (NRS)	None
Nash et al., 1990 <sup>246</sup>	Р	E	Chronic pain	200 (126W)	TENS (HF, continuous, 100pps) = 50	TENS (HF, continuous, 10pps) = 50 TENS (LF, burst, 10pps) = 50 TENS (LF, burst 100pps) = 50	PRN < 2 years	Pain intensity (VAS)	Responders ( $\geq$ 50% reduction in pain) Time to $\geq$ 50% reduction in pain
Navarathnam et al., 1984 <sup>247</sup>	Р	Pr	Post-op cardiac surgery	31 (6W)	TENS (NR) + analgesics on demand = 14	Placebo TENS (0mA) + analgesics on demand = 17	PRN	Pain intensity (5- point scale)	Analgesic consumption Spirometry Experience of cardiac surgery (Questionnaire)
Neary, 1981 <sup>248</sup>	Р	Pr	Post incisional surgical pain	200 (NR)	TENS (HF) = 100	Morphine sulphate or Meperidine Hydrochloride (SoC, no TENS) = 100	PRN 1 x 30 mins or as needed	No primary outcome	Analgesic consumption
Neighbours et al., 1987 <sup>249</sup>	Р	Е	Dysmenorrhea	20 (20W)	TENS (LF, acupuncture-like) = 10	Placebo pill = 10	Fixed 1 x 30 mins 1 session	Pain intensity (VAS)	Analgesic consumption McGill Pain Questionnaire Pain rating index
Nesheim, 1981 <sup>250</sup>	Р	Pr	Labour pain	70 (70W)	TENS (LF, burst) = $35$	Placebo TENS (0mA) = 35	PRN during labour	No primary outcome	Pain relief (4-point category scale)
Neumark et al., 1978 <sup>251</sup>	Р	Pr	Labour pain	30 (30W)	TENS (NR) = 10	Pethidine (SoC, no TENS) = 5 Placebo TENS (0mA) = 5 Remote TENS (electrodes in wrong positions) = 5 No treatment = 5 (no analgesia	Fixed 70 mins 1 session	Pain intensity (6- point scale)	None
Ng et al., 2003 <sup>252</sup>	Р	Pr	Osteoarthritis - knee	24 (23W)	TENS (LF) + Education about knee care = 8	Education about knee care (SoC, no TENS) = 8 EA + Education about knee care = 8	Fixed 1 x 20 mins on alternative days x each session over 2 weeks	Pain intensity (NRS)	Range of motion Timed Up-and-Go test

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		ļ	<u> </u>				8 sessions		
Nordemar and Thorner, 1981 <sup>253</sup>	Р	Pr	Neck pain - acute cervical pain	30 (18W)	TENS (HF) + neck collar + analgesics = 10	Neck collar + analgesics (SoC, no TENS) = 10 Manual therapy + neck collar + analgesics = 10	Fixed 1 x 30 mins x 3 / week 3 session	Pain intensity (VAS) • at rest • on movement	Analgesic consumption Range of motion
Norrbrink, 2009 <sup>254</sup>	С	Pr	Spinal cord injury neuropathic pain	24 (4W)	TENS (HF) = 24	TENS (LF) = 24	Fixed 3 x 30 to 40 mins / day x 7 days x 2 weeks 42 sessions	Pain intensity (Borg CR-10)	Pain unpleasantness (BORG CR - 10) Global pain relief (5-point scale) Multidimensional Pain Inventory Hospital Anxiety and Depression Scale Nordic Basic Sleep Questionnaire Life Satisfaction Instrument-9 Ability to cope with pain (NRS)
Olsén et al., 2007 <sup>255</sup>	Р	Е	Postpartum uterine contractions	21 (21W)	TENS (HF, brief HI) = 12	TENS (HF, LI) = 8	Fixed 1 x 1 min repeated 2 times if necessary 1 session	Pain intensity (VAS)	Uterine contraction discomfort (5- point verbal scale) Discomfort from treatment (5- point verbal scale)
Olsen et al., 2019 <sup>256</sup>	С	Е	Dysmenorrhea - primary	16 (16W)	TENS (HF, brief HI) = 7 (7W)	Control (SoC, no TENS, 'delayed intervention) = 9 (9W)	PRN 1 x 60 seconds repeated as needed	Pain intensity (VAS)	Analgesic consumption Limitation in physical function (VAS) Discomfort from the treatment
Oncel et al., 2002 <sup>257</sup>	Р	Pr	Minor rib fracture	100 (41W)	TENS (HF) = 25	Placebo TENS (0mA) + Naproxen NSAID = 25 Naproxen NSAID (SoC, no TENS) = 25 Placebo pills = 25	Fixed 2 x 30 mins / day x 3 days 6 sessions	Pain intensity (VAS)	None
Dosterhof et al., $2006^{258}$ Secondary reports Dosterhof et al., $2008^{259}$ , Dosterhof et al., $2012^{260}$ , Dosterhof et al., $2012^{261}$	Р	Pr	Chronic pain, various types	163 (97W)	TENS (HF) = 81	Placebo TENS = 82 (0mA)	PRN x 10 days	Pain intensity (VAS)	TENS satisfaction
Ordog, 1987 <sup>262</sup>	Р	Pr	Acute traumatic pain	100 (NR)	TENS (NR) = 25	Placebo TENS (0mA) = 25 TENS (NR) + acetaminophen with codeine = 25 Placebo TENS (0mA) + acetaminophen with codeine = 25	PRN	Pain intensity (VAS)	TENS satisfaction Side effects
Ozkaraoglu et al., 2020 <sup>263</sup>	Р	Pr	Back pain - low non- specific	40 (19W)	TENS (HF) + ultrasound, hot pack and exercise = 20	High Intensity Laser Therapy (HILT) + ultrasound, hot pack and exercise = 20	Fixed 1 x 20 mins / day x 5 days a week for a total of 20 sessions.	Pain intensity (VAS)	Range of motion Oswestry Disability Questionnaire Beck Depression Inventory
Ozkul et al., 2015 <sup>264</sup>	С	Pr	Neuropathic pain in patients with spinal cord injury	24 (6W)	TENS (HF) = 12	Visual illusion = 12	Fixed 1 x 30 mins / day x 5 days x 2 weeks 10 sessions	Pain intensity (VAS)	Neuropathic sign and symptoms (DNa) McGill pain questionnaire Neuropathic Pain Scale (NPS) Brief Pain Inventory

Oztas and Iyigun, 2019 <sup>265</sup>	Р	Pr	Post-op abdominal surgery	48 (10W)	TENS (LF-HF) + Tramadol PCA + rescue Pethidine = 16	Analgesic Medication (tramadol PCA + rescue pethidine (SoC, no TENS) = 16 TAES + tramadol PCA + rescue pethidine = 16	Fixed 1 x 30 mins at 2h, 18h, 22h, 42, 46h post-op 5 sessions	Pain intensity (VAS)	Analgesic consumption (Tramadol - PCA) Nausea severity (VAS) Vomiting (frequency) Antiemetic consumption Pulmonary function tests
Ozturk et al., 2016 <sup>266</sup>	Р	Pr	Post-op cardiac surgery	120 (39W)	TENS (HF) + morphine (PCA) = 40	Placebo TENS + placebo parasternal block (saline) + morphine (PCA) (Control) = 37 Placebo TENS + Parasternal block = 38	PRN 60 mins treatments with 60 mins rest as needed	Pain intensity (VAS)	Analgesic consumption (morphine - PCA) Mean arterial pressure, heart rate, and arterial blood gas analysis Duration of extubating, ICU and hospital stay Opioid-related side effects
Padma et al., 2000 <sup>267</sup>	Р	Pr	Labour pain	70 (70W)	TENS (HF) = 50	Placebo TENS (0mA) = 20	PRN	No primary outcome	<ul> <li>Pain relief (4 categories)</li> <li>Subjective assessment (by the patient)</li> <li>Observer Assessment</li> <li>Monitoring mother and foetus</li> <li>Duration of labour APGAR score</li> </ul>
Paker et al., 2006 <sup>268</sup>	Р	Pr	Knee AO	60 (NR)	TENS (HF) = NR	Intra-articular hyaluronic acid injection = NR	Fixed 1 x 20 mins / day x 5 / week x 3 weeks 15 sessions	Pain intensity (5- point scale) from WOMAC	WOMAC Lequesne Index SF-36
Palmer et al., 2014 <sup>269</sup>	Р	Pr	Osteoarthritis - knee	224 (141W)	TENS (HF) + Exercise + education = 73	Placebo TENS (0mA) + Exercise + education = 74 Exercise + education + exercise (SoC, no TENS control) = 77	PRN x 6 weeks	Pain intensity (5- point scale) from WOMAC	WOMAC Maximum knee extensor torque Patient global assessment of change scale Self-efficacy for exercise
Pan et al., 2003 <sup>270</sup>	Р	Е	Tendinitis - Chronic calcific of the Shoulders	60 (39W)	TENS (HF) + hydrocollator pack = 28 (30 shoulders)	Extracorporeal shock wave = 32 (33 shoulders)	Fixed 1 x 20 mins / day x 3 / week x 4 weeks 12 sessions	Pain intensity (VAS)	Constant score Manual muscle test (MMT)
Park et al., 2015 <sup>271</sup>	Р	Pr	Post op thyroidectomy - neck pain	100 (NR)	TENS (HF) = 50	Placebo TENS = 50 (0mA)	Fixed throughout surgery 1 session	Pain intensity (NRS) • Anterior wound pain	Analgesic consumption post- operative
Patil and Aileni, 2017 <sup>272</sup>	Р	Pr	Temporomandibular disorder	36 (23W)	TENS (HF) = 18	Exercise home programme = 18	Fixed 1 x 30 mins / day x once / week x 4 weeks 1 session	Pain intensity (VAS)	Pain free range of motion masticatory muscle tenderness (VAS)
Peacock et al., 2019 <sup>273</sup>	Р	Pr	Chronic pain - Various	100 (22W)	TENS (LF, AL-TENS) + SoC =30	Tennant Biomodulator + SoC = 34 Acupuncture + SoC = 36	PRN 2 x 20min / day x 6 weeks 12 sessions	Pain intensity (VAS, as pain log)	Million visual analogue scale PTSD checklist – military Center for Epidemiological Studies - depression scale
Pietrosimone et al., 2009 <sup>274</sup>	Р	Е	Tibiofemoral OA	33 (16W)	TENS (HF) = 10	No treatment (control) = 12 Focal joint knee cooling = 11	Fixed 1 x 45 mins 1 session	Pain intensity (VAS)	WOMAC Quadriceps CAR

### 08\_OL-TABLE1\_IncludedStudies

									Peak knee extension torque maximal voluntary isometr contractions (MVIC)
Pietrosimone et al., 2011 <sup>275</sup> Secondary report Pietrosimone et al., 2010 <sup>276</sup>	Р	Pr	Tibiofemoral OA	36 (21W)	TENS (HF) + Exercises (strengthening) = 12	Placebo TENS (Fading) = 12 Exercise (strengthening, SoC, no TENS control) = 12	PRN >8 hours / day x 4 weeks 21 sessions	No primary outcome	WOMAC Quadriceps strength Peak knee extension torque maximal voluntary isometr contractions
Pietrosimone et al., 2020 <sup>277</sup>	Р	Pr	OA, knee [during therapeutic exercise]	90 (39W)	TENS (HF) + Exercises (strengthening) = 30	Placebo TENS (0mA) + Exercises Exercises = 30	PRN during all exercise sessions and during activities of daily living for 4 weeks	No primary outcomes	WOMAC Quadriceps Strength and Voluntary activation Peak knee extension torque maximal voluntary isometr contractions
Pike, 1978 <sup>278</sup>	Р	Pr	Post-op hip replacement	40 (19W)	TENS (HF) + medication (pethidine) = 20	Medication (pethidine, SoC, no TENS control) = 20	PRN > 8 hours / day	No primary outcome	Analgesic consumption (Pethidine) Pain relief (4 categories) Nausea and vomiting (frequ
Pitangui et al., 2012 <sup>279</sup>	Р	Pr	Post episiotomy pain	40 (40W)	TENS (HF) = 20	No treatment = 20	Fixed 1 x 60 mins 1 session	Pain intensity (NRS) • rest • standing • walking	McGill Pain Questionnaire TENS-related questions Functional limitations
Pitangui et al., 2014 <sup>280</sup>	Р	E	Post episiotomy pain	33 (40W)	TENS (HF) = 11	Placebo TENS (0mA) = 10 TENS (LF) = 13	Fixed 1 x 30 mins pre- injection 1 session	Pain intensity (NRS) • Resting pain • Pain on movement	Treatment satisfaction TENS–related questions
Platon et al., 2010 <sup>281</sup>	Р	Pr	Post-op surgical abortion	200 (200W)	TENS (HF, HI) = 100	Fentanyl i.v. (SoC, no TENS control) = 100	Fixed 1 x 1 min (repeated if necessary)	Pain intensity (VAS)	Analgesic consumption Nausea (VAS) Time in recovery ward Ramsay sedation score
Platon et al., 2018 <sup>282</sup>	C	Е	Post-op gynaecologic laparoscopic surgery	93 (93W)	TENS (HF, HI) = 47	Morphine i.v. (SoC, no TENS control) = 46	Fixed 1 x 1 min (repeated if necessary)	Pain intensity (VAS)	Analgesic consumption (Opioids) Nausea (VAS) Time in recovery ward Ramsay sedation score
Prabhakar and Ramteke, 2011 <sup>283</sup>	Р	E	Radiculopathy - cervical	75 (39W)	TENS (HF) + Hot fomentation + Exercises, Isometric neck (Group B) = 25	Hot fomentation + Exercises, Isometric neck (SoC, no TENS control, Group C) = $25$ Cervical contralateral lateral flexion mobilization + Hot fomentation + Exercises, Isometric neck (Group A) = $25$	Fixed 1 x 30 mins 1 session	Pain intensity (VAS)	Northwick Park neck pain questionnain Neuropathic pain scale, SF-McGill Pain Questionna
Presser et al., 2000 <sup>284</sup>	Р	Е	Procedural pain - Injection of epidural steroids	90 (30W)	TENS (HF) = 30	Placebo TENS (active, <sdt) +<br="">Local anaesthetic = 30 Local anaesthetic (SoC, no TENS control) = 30</sdt)>	Fixed Throughout procedure	Pain intensity (VAS)	None

Rainov et al., 1994 <sup>285</sup>	Р	Pr	Post-op spinal surgery	234 (121W)	TENS (Alternating F) + analgesic medication = 126	Analgesic medication (SoC, no TENS control) = 108	Fixed 1 x 60 mins every 2 hours ? how many days?	Pain intensity (VAS)	Analgesic consumption Pain unpleasantness (VAS)
Rajfur et al., 2017 <sup>286</sup>	P	Pr	Back pain - chronic low non-specific	127 (73W)	TENS (HF) + exercise = 20	Exercise (SoC, no TENS control) = 21 TENS (LF, acupuncture = like) + exercise = 20 High-voltage electrical stimulation) + exercise = 22 IFT) + exercise = 22 Diadynamic current) + exercise = 22	Fixed I x 60 mins / day x 5 / week x 3 weeks 15 sessions	Pain intensity (VAS)	Modified Laitinen pain scale The Oswestry questionnaire Roland-Morris Disability Questionnaire Lasègue test Schober test Postural stability
Rajpurohit et al., 2010 <sup>287</sup>	Р	Pr	Masticatory muscle	60 (24W)	TENS (HF) = 30	Microcurrent electrical nerve stimulation (= 30	Fixed 1 x 20 mins / day x 7 days 7 sessions	Pain intensity (VAS)	Muscle tenderness (algometry)
Rakel and Frantz, 2003 <sup>288</sup>	С	Е	Post-op abdominal surgery	33 (17W)	TENS (MF) + analgesics = 33	Placebo TENS (0mA) + analgesics = 33 Analgesics (SoC, no TENS control) = 33	Fixed 1 x 15 mins for duration of measurements	Pain intensity (NRS)	Iowa Gait Test Pulmonary status
Rakel et al., 2014 <sup>289</sup>	Р	Pr	Post-op knee arthroplasty (control of pain during exercises)	317 (173W)	TENS (HF) + analgesics = 122	Placebo TENS (Fading) + analgesics = 123 Analgesics (SoC, no TENS control) = 72	Fixed 1 x 20 mins before exercise, then during exercise x 1 to 2 / day x 6 weeks	Pain intensity (NRS) • At rest • On movement	Pain catastrophizing State and trait anxiety" Geriatric depression scale Knee injury and osteoarthritis outcome score Quantitative sensory testing Range of motion Gait speed test
Ramanathan et al., 2017 <sup>290</sup>	Р	Pr	Pot op knee arthroplasty	116 (30W)	TENS (NR) + opioid analgesics + femoral nerve block = 58	Placebo TENS (Fading to 0mA) + opioid analgesics + femoral nerve block = 58	PRN 1 x 2 hours followed by 30 mins rest as needed for 6 weeks	Pain intensity (VAS)	Analgesic consumption Time up and go test Range of motion Knee injury and osteoarthritis outcome score SF-12
Ramos et al., 2018 <sup>291</sup>	Р	Pr	Back pain - low, lumbar disc herniation	29 (14W)	TENS (HF) = 14	Exercises (segmental stabilisation, SoC) = 15	Fixed 1 x 60 mins / day x 2 / week x 8 weeks 18 sessions	Pain intensity (VAS)	LM Muscular Fatigue Fatigue Test Transversus abdominis activatic capacity Oswestry Disability Index
Rani et al., 2020 <sup>292</sup>	Р	Pr	Rotator cuff	76 (34W) 70 (32W) analysed	TENS (HF) + SoC + rescue meds = 35	Exercises (SoC, no TENS control) + rescue meds = 35	Fixed 1 x 20mins /day x 5 days	Pain intensity (NRS, pain item from Shoulder Pain and Disability Index)	Shoulder Pain and Disability Index
Ratajczak et al., 2011 <sup>293</sup>	Р	Pr	Back pain – low, desmopathy	80 (57W)	TENS = 40	Diadynamic currents = 40 Healthy participants groups (no TENS) = 40	Fixed 1 x 30 mins / day x 5 days / week x 2 weeks 10 sessions	Pain intensity (VAS)	Functional pain index by Lequesne Range of motion

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Rawat et al., 1991 <sup>294</sup>	Р	Pr	Procedural pain - during biliary extracorporeal shockwave lithotripsy	100	TENS (MF, on back) = 25	Placebo TENS (0mA, on back) = 25 TENS (MF, back and acupoints on leg) = 25 Placebo TENS (0mA, on back and acupoints on leg) = 25	PRN throughout procedure	Pain intensity (5- point scale)	Analgesic consumption
Renovato França et al., 2019 <sup>295</sup>	Р	Pr	Radiculopathy – lumbar disc herniation	40 (25W)	TENS = 20	Exercises (Motor control training, SoC) = 20	Fixed 2 x 60 mins / week x 8 weeks 16 session	Pain intensity (VAS)	McGill Pain Questionnaire Oswestry Disability Index Transversus Abdominis Activation Capacity
Reuss et al., 1988 <sup>296</sup>	Р	Pr	Post-op cholecystectomy	64 (50W)	TENS (HF) = 30	No treatment (+ meperidine on demand) = 34	PRN	No primary outcomes	Analgesic consumption Complications
Revadkar and Bhojwani, 2019 <sup>297</sup>	Р	Pr	Dysmenorrhea	30 (30W)	TENS (HF) + rescue medication = 15	IFT + rescue medication= 15	Fixed 1 x 20mins 1 session	Pain intensity (NRS)	None
Ringel and Taubert, 1991 <sup>298</sup>	Р	Pr	Migraine	57 (48W)	TENS (NR) = 31	Ergocomb (prophylactic buccal tablets for migraine) (SoC, no TENS) = 26	PRN >1 x 30 mins / day as needed for 3 months	Pain intensity (4- point scale)	Number of headache days
Robb et al., 2007 <sup>299</sup>	С	Е	Chronic pain associated with breast cancer treatment	41 (411W)	TENS (HF) = 41	Placebo TENS (0mA) = 41 Transcutaneous spinal electroanalgesia = 41	PRN >10-30 mins / day x 3 weeks	Pain intensity (NRS) – from BPI	Analgesic consumption BPI Hospital Anxiety and Depressic (HAD) Scale Range of motion Patient satisfaction questionnain
Robinson et al., 2001 <sup>300</sup>	Р	E	Procedural pain – colonoscopy	33 (NR)	TENS (various F) + standard medication = 10	Placebo TENS (0mA) + standard medication = 13 Standard medication (SoC, no TENS control) = 10	Fixed 1 x 5mins pre- procedure, 1x 5 mins during procedure, 1 x 5 mins post procedure 1 session	Pain intensity (NRS)	Post-procedure evaluation questionnaire
Roche et al., 1985 <sup>301</sup>	Р	Pr	Haemophilia	36 (NR)	TENS (HF) = 28	Placebo TENS (0mA) = 8	PRN 1 x 25 mins continuous from recovery room for 5 days as needed	Pain intensity (NRS)	McGill Pain Questionnaire
Rooney et al., 1983 <sup>302</sup>	Р	Е	Post-op – thoracotomy	44 (17W)	TENS (HF) $= 22$	Placebo TENS (0mA) = 22	Fixed 1 x 25 mins 1 session	No primary outcome	Analgesic consumption – (Narcotic)
Rosenberg et al., 1978 <sup>303</sup>	Р	Pr	Post-op cholecystectomy	12 (NR)	TENS (HF) + analgesics = $6$	Analgesics (SoC, no TENS control) = 6	PRN 3 days as needed	No primary outcome	Analgesic consumption Pulmonary function
Rutgers et al., 1988 <sup>304</sup>	Р	Pr	Postherpetic neuralgia	23 (13W)	TENS (HF) = 13	Acupuncture = 10	PRN 3 x 30 mins / week x 1 week then as needed for 6 weeks	Pain intensity (NRS)	None
Sadala et al., 2018 <sup>305</sup>	Р	E	Procedural pain - during carboxytherapy	84 (84W)	TENS (HF) $= 28$	Placebo TENS (Fading) - 28 No treatment (Control) = 28	Fixed 1 min / puncture 1 session	Pain intensity (VAS)	None
Sahin et al., 2011 <sup>306</sup>	Р	Е	Cervical myofascial pain syndrome	80 (40W)	TENS (HF, conventional) = 20	Placebo TENS (Fading) = 20 TENS (LF, acupuncture = like) = 20	Fixed 1 x 30min/day x 3 / week	Pain intensity (VAS)	SF-36 Bodily pain subscale

						TENS (LF, burst) = $20$	?? no. weeks? 1 session		
Samadzadeh et al., 2017 <sup>307</sup>	Р	Pr	Labour pain	120 (120W)	TENS (HF, continuous, LF, burst) + meperidine as rescue analgesia = 40	Entonox + meperidine as rescue analgesia = 40 TENS + Entonox + meperidine as rescue analgesia = 40	PRN During labour	Pain intensity (VAS)	Analgesic consumption
Sangtong et al., 2019 <sup>308</sup>	Р	Pr	Osteoarthritis - knee	148 (135W)	TENS (HF) + US = $64$	US = 68	Fixed 1 x 10 mins / day x 5 days x 2 weeks 10 session	Pain intensity (NRS) • At rest • On movement (walking, climbing stairs)	6-min walk test Patient global assessment Adverse events
Santamato et al., 2013 <sup>309</sup>	Р	Pr	Botulinum toxin type A injection for post - stroke spasticity	32 (18W)	TENS (LF) = 16	Shock wave therapy = 16	Fixed 1 x 30 mins / day x 2 / day x 5 days 10 sessions	Pain intensity (VAS)	Spasticity scale Spasm scale
Santana et al., 2016 <sup>310</sup>	Р	Pr	Labour pain	46 (46W)	TENS (HF) + routine obstetric care = 23	Routine obstetric care (SoC, no TENS control) = 23	Fixed 1 x 30 mins / day x 5 days x 2 weeks 10 sessions	Pain intensity (VAS)	Time to analgesic requirement Pain location
Saranya et al., 2019 <sup>311</sup>	Р	Pr	Muscle pain – Temporomandibular Masticatory Muscle Pain	60 (42W)	TENS (HF) + jaw exercises + hot fomentation = 30	Microcurrent electrical stimulation + jaw exercises + hot fomentation = 30	Fixed 1 x 20min / day x 5 days 5 sessions	Pain intensity (VAS)	Mouth opening and functional assessment
Sayilir and Yildizgoren, 2017 <sup>312</sup>	Р	Pr	Back pain - chronic low non-specific	55 (32W)	TENS (HF) = 26	Diadynamic currents = 29	Fixed 1 x 30 mins / day x 5 days/week x 2 weeks 10 sessions	Pain intensity (VAS) • Rest • On movement	Roland Morris Disability Questionnaire Oswestry Disability Index (ODI) Hand finger floor distance (HFFD)
Seo et al., 2013 <sup>313</sup>	Р	Pr	Chronic myofascial pain syndrome	76 (64W)	TENS (LF, burst) + Botulinum toxin A = 38	Botulinum toxin A + electrical stimulation with muscle contraction = 38	Fixed 1 x 30 mins / day x 3 days 3 sessions	Pain intensity (VAS)	Neck Pain and Disability Scal (NPAD) Global Assessment of Improvement Scale (GAS) Pressure algometry (pain threshold)
Serry et al., 2016 <sup>314</sup>	Р	Pr	Peripheral diabetic neuropathy	60 (32W)	TENS (HF) + pharmacological therapy = 20	Pharmacological therapy (SoC, no TENS control) = 20 Exercise (aerobic) + pharmacological therapy =20	Fixed 1 x 30 mins / day x 3 / week x 8 weeks 24 sessions	Pain intensity (VAS)	Nerve conduction studies
Sezen et al., 2017 <sup>315</sup>	Р	Pr	Post-op thoracotomy	87 (25W)	TENS (HF) + Analgesics (diclofenac i.m., tramadol i.v. + paracetamol i.v.) = 43	Placebo TENS + Analgesics (diclofenac i.m., tramadol i.v. + paracetamol i.v.)= 44 (0mA)	PRN During labour at 8 h intervals	Pain intensity (VAS)	Analgesic consumption Pulse rate Blood pressure Saturation Complication
Shahoei et al., 2017 <sup>316</sup>	Р	Pr	Labour pain	90 (90W)	TENS (PRN) = 30	Placebo TENS = 30 (0mA) Routine care (SoC, no TENS control) = 30	PRN During labour	Pain intensity (VAS)	

Shehab and Adham, 2000 <sup>317</sup>	Р	Pr	Shoulder pain	50 (50W)	TENS (HF) + cold pack + stretching exercises = 26	Ultrasound therapy + cold pack + stretching exercises = 24	Fixed 1 x 30 mins / day x 3 to 5 / week x 3 to 5 weeks 13 sessions	Pain intensity (VAS)	Range of motion
Sherry et al., 2001 <sup>318</sup>	Р	Pr	Back pain - chronic low non-specific	44 (21W)	TENS (NR) + analgesics if needed = 22	Vertebral axial decompression = 22	Fixed 1 x 10 mins / day x 20 days then 1 x 10 mins / week x 4 weeks 24 sessions	Pain intensity (VAS)	Disability (4-point scale)
Shimoji et al., 2007 <sup>319</sup>	Р	Е	Back pain - chronic low non-specific	28 (24W)	TENS (HF) $= 9$	Placebo TENS (0mA) = 8 TENS (Bidirectional modulated sine waves) = 11	Fixed 1 x 15 mins 1 session	Pain intensity NRS	None
Shimoura et al., 2019 <sup>320</sup>	Р	E	Osteoarthritis - knee	50 (35W)	TENS (MF) = 25	Placebo TENS = 25 (0mA)	Fixed Details NR 1 session	Pain intensity (VAS) • on movement	Climb test Timed Up and Go (TUG) 6-minute walk test (6MWT) Knee extensor strengths 2-step test Stand-up test in the locomotive syndrome risk test.
Shoukry and Al-Ansary, 2019 <sup>321</sup>	Р	Pr	Procedural pain - during Extracorporeal Shock-Wave Lithotripsy (ESWL)	60 (26W)	TENS (HF) + IV fentanyl = 30	IV fentanyl = 30	Fixed 1 treatment Duration not reported but less than 40 mins	Pain intensity (VAS)	Analgesic consumption Modified Post- Anaesthetic Discharge Scoring System adverse effect during or after the procedure Discharge time
Siemens et al., 2020 <sup>322</sup>	С	Pr	Cancer pain - advanced cancer, inpatients	25 (12W)	TENS (HF) + medication = 20	Placebo TENS (0mA) + medication = 20	PRN For 1 day Mean $\pm$ SD = 9.1+7.5h for TENS and 7 $\pm$ 5.6 for placebo 24 h washout	Pain intensity (NRS)	Analgesic consumption Brief Pain Inventory (BPI) Edmonton Classification System for Cancer Pain Douleur Neuropathique en 4 Questions 7-point verbal pain rating scale EORTC QLQC30
Sikiru et al., 2008 <sup>323</sup>	Р	Pr	Pelvic pain, prostatitis - chronic	24 (24M)	TENS (HF) + antibiotics = 8	Placebo pill + antibiotics = 8 Analgesics (Ibuprofen 400mg) + antibiotics (SoC, no TENS control) = 8	Fixed 1 x 20 mins / day x 5 / week x 4 weeks 20 sessions	Pain intensity (NRS)	NIH chronic prostatitis sympton index questionnaire (pain domai
Silva et al., 2012 <sup>324</sup>	Р	Pr	Post-op cholecystectomy	42 (39W)	TENS (HF) + analgesics (Tramadol + Dipyrone) = 21	Placebo TENS (0mA) + analgesics (Tramadol + Dipyrone) = 21	PRN 1 x 30 mins / session as needed	Pain intensity (VAS, verbal NRS)	Occurrence of nausea and emesi
Silva et al., 2014 <sup>325</sup>	Р	Е	Post-mastectomy pain syndrome – chronic, intercostobrachial	18 (18W)	TENS (LF, burst) = 9	TENS (MF, acupuncture-like,) = 9	Fixed 1 x 10-15 mins 1 session	Pain intensity (VAS)	Electroencephalography (EEG) measures
Sim, 1991 <sup>326</sup>	Р	Pr	Post-op cholecystectomy	30 (27W)	TENS (HF) + analgesics (Papaveretum) = 15	Papaveretum, i.m. on demand (SoC, no TENS control) = 15	PRN 1 x 60 mins / day? x 5 days 5 sessions	Pain intensity (VAS) • Resting pain • Coughing • Deep breathing.	Analgesic consumption Spirometer function

Siqueira et al., 2019 <sup>327</sup>	Р	Pr	Musculoskeletal pain – behavioural dysphonia	27 (27W)	TENS (LF) + vocal training	Placebo TENS (0mA) + vocal therapy	Fixed 1 x 20mins / day 12 sessions	Pain intensity (VAS)	Self-perception of musculoskeletal pain frequency (4-point Likert scale) and intensity Pressure algometry - Pain Threshold
Sloan et al., 1986 <sup>328</sup>	Р	Pr	Rib fracture	24 (NR)	TENS (HF) + paracetamol + dihydrocodeine as required = 12	Naproxen + paracetamol + dihydrocodeine as required (SoC, no TENS control) = 12	PRN 2 post op days	Pain intensity (VAS)	Pain relief (VAS) Arterial blood assays Peak expiratory flow rate Treatment effectiveness (VAS)
Smania et al., 2005 <sup>329</sup>	Р	Pr	Myofascial pain syndrome	53 (36W)	TENS (HF) = 18	Placebo (ultrasound turned off) = 18 Repetitive magnetic stimulation = 17	Fixed 1 x 20 mins / day x 5 days / week x 2 weeks 10 sessions	Pain intensity (Pain and disability VAS)	Pressure pain threshold (algometry) Range of motion
Smedley et al., 1988 <sup>330</sup>	Р	Pr	Post-op inguinal herniorrhaphy	62 (62W)	TENS (HF) + Omnopon = 34	Placebo TENS (0mA) + Omnopon = 28	PRN 2 days continuously post op Unclear	Pain intensity (VAS)	Analgesic consumption Expiratory flow
Smith et al., 1983 <sup>331</sup>	Р	Pr	Osteoarthritis - knee	30 (20W)	TENS (HF) = 15	Placebo TENS (0mA) = 15	Fixed 1 x 20 mins / day x 8 occasions over 4 weeks 8 sessions	Pain intensity (VAS)	Analgesic consumption Pain chart Sleep disturbance (VAS)
Smith et al., 1986 <sup>332</sup>	Р	Pr	Post-caesarean pain	18 (18W)	TENS (HF) + analgesics = 9	Placebo TENS (0mA) + analgesics = 9	PRN Continuous with 15 mins rest for 3 days post up	Pain intensity (5- point scale)	Analgesic consumption McGill Pain Questionnaire
Sodipo et al., 1980 <sup>333</sup>	Р	Pr	Post-op	30 (NR)	TENS (NR) + analgesics = 15	Narcotic medication (SoC, no TENS control) = 15	PRN 2 days post op	No primary outcome	Analgesic consumption Pulmonary function
Solak et al., 2007 <sup>334</sup>	Р	Pr	Post-op thoracotomy	40 (8W)	TENS (LF) + (no morphine PCA) = 20	Morphine (PCA) (SoC, no TENS control) = 20	Fixed 1 x 30 mins / day ? x 10 days 10 sessions	Pain intensity (VAS)	Analgesic consumption (Morphine - PCA) Prince Henry pain scale Pulmonary function
Solak et al., 2009 <sup>335</sup>	Р	Pr	Post-op coronary bypass grafting	100 (13W)	TENS (HF, continuously) + morphine (PCA) = 25	Placebo TENS + morphine (PCA) = 25 Morphine (PCA)(SoC, no TENS control) = 25 TENS (HF, intermittently) + morphine (PCA) = 25	PRN continuously one day Continuously = on for 24h without break Intermittently = 1h on 1 hr off	Pain intensity (VAS)	Analgesic consumption Duration operation, extubation, hospital stay Oximetry Respiratory function
Sonde et al., 1998 <sup>336</sup>	Р	Pr	Post stroke – shoulder pain	44 (17W)	TENS (LF) + Physiotherapy (usual care) = 26	Physiotherapy (SoC, no TENS control) = 18	Fixed 1 x 60 mins / day x 5 days / week x 12 weeks 60 sessions	Pain intensity (VAS)	Fugl-Meyer Ashworth scale Autonomy in activities of daily living
Stepanovic et al., 2015 <sup>337</sup>	Р	Pr	Post-herpetic neuralgia	222 (133W)	TENS (HF) = 36	Analgesics (SoC, no TENS control) = 38 Antiviral agents = 71 TENS + antiviral agents = 77	Fixed 1 x 30 mins / day 10 to 15 sessions	Pain intensity (VAS)	Analgesic consumption Allodynia, hyperalgesia or paraesthesia
Steptoe and Bo, 1984338	Р	Pr	Labour pain	25 (25W)	TENS $(HF + LF) = 12$	Placebo TENS $(0mA) = 13$	PRN	Pain intensity	Analgesic consumption

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							1 x 30 mins?		
Stratton and Smith, 1980 <sup>339</sup>	Р	Pr	Plantar fasciitis	26 (NR)	TENS (HF) + exercise (stretching) + orthoses = 13	Exercise (stretching) + orthoses (SoC, no TENS control) = 13	Fixed 1 x 20 mins / day x 7 days x 4 weeks 28 sessions	Pain intensity (VAS)	Activities of daily living subs of Foot and Ankle Ability Measure
Stubbing and Jellicoe, 1988 <sup>340</sup>	Р	Pr	Post-op thoracotomy	40 (12W)	TENS (HF) + opioids (Papaveretum, i.v.) = 20	Papaveretum (i.v.) (SoC, no TENS control) = 20	PRN for 48 hours	Pain intensity (5- categories)	Analgesic consumption Time to transfer to oral analge Peak expiratory flow rate
Suh et al., 2015 <sup>341</sup>	Р	Pr	Musculoskeletal pain - (various types, work- related)	47 (36W)	TENS (HF) = 24	Placebo TENS = 23 (0mA)	Fixed 1 x 60 mins 1 session	Pain intensity (VAS) • resting • on movement	Pressure pain threshold (algometry) Range of motion Fatigue (VAS) • Resting pain • Pain on movement
Talbot et al., 2020 <sup>342</sup>	Р	Pr	Knee pain, Patellofemoral pain syndrome	130 (29W)	TENS (HF) + exercise (home programme) = 33	Exercise (home programme) alone (SoC) = 34 Neuromuscular electrical stimulation + exercise (home programme) = 33 Alternating Neuromuscular electrical stimulation and TENS + exercise (home programme) = 30	Fixed 1x 20 mins / day 1 x every 2 days X 9 weeks	Pain intensity (VAS)	Lower Extremity Isometric Strength 30-Second Chair Stand Test ( SCST) Timed Stair Climb Test (SCT Forward Step-Down Test Six-Minute Timed Walk Test MWT)
Tantawy et al., 2018 <sup>343</sup>	Р	Pr	Chronic orchialgia	71 (0W)	TENS (HF) + analgesic medication = 36	Analgesic medication (SoC, no TENS control) = 35	Fixed 1 x 30 mins / day x 5 / week x 4 weeks 20 sessions	Pain intensity (VAS)	Pin prick Quality of life
Taylor et al., 1981 <sup>344</sup>	С	E	Osteoarthritis - knee	10 (9W)	TENS (Freq. PRN) = 10	Placebo TENS (0mA) = 10	PRN 1 x 30 to 60 mins or continuously / day 2 weeks at home	Pain intensity (5- point category scale)	Analgesic consumption (5 categories) Ambulation (5 categories)
Taylor et al., 1983 <sup>345</sup>	Р	Pr	Post op abdominal surgery	77 (45W)	TENS (HF) + analgesics = 30	Placebo TENS (0mA) + analgesics = 22 Analgesic medication (SoC, no TENS control) = 25	Fixed 1 x 60 mins x 4 / day (q4h) x 3 post days 12 sessions	Pain intensity (NRS)	Analgesic consumption (Morphine) Physiological depression Patient ambulation Fluid intake
Thakur and Patidar, 2004 <sup>346</sup>	Р	Pr	Labour pain	300 (300W)	TENS (HF) = 100	No treatment = 100 Tramadol (100mg) = 100	PRN	No primary outcome	Pain relief (5 categories) Time taken for onset of analg action Duration of analgesia
Thomas et al., 1988 <sup>347</sup>	Р	Pr	Labour pain	280 (280W)	TENS (NR) = 132	Placebo TENS (0mA) = 148	PRN	Pain intensity (VAS)	Analgesic consumption Labour questionnaire
Thomas et al., 1995 <sup>348</sup>	С	E	Dysmenorrhea - primary	29 (29W)	TENS (HF) = 12	Placebo TENS (0mA) = 12 TENS (LF) = 12	Fixed 1 x 20 mins / day x 2 days 2 sessions	Pain intensity (VAS)	Analgesic consumption Patients perception of improvement (3 category scale) Blood loss (3 category scale) Nausea and vomiting (4 categor scale) Hours of work lost (3 categor scale)

Thorsteinsson et al., 1978 <sup>349</sup>	С	Е	Chronic pain	93 (53W)	TENS (NR) = 93	Placebo TENS = 93 (0mA)	Fixed 1 x treatment at each of the following (i) at painful site (ii) over main nerve bundle (iii) at remote site 3 sessions	No primary outcomes	Pain relief (4-categories) • Minnesota • Multiphasic • Personality Inventory • Duration of pain relief
Tilak et al., 2016 <sup>350</sup>	Р	Pr	Phantom limb pain	26 (3W)	TENS (LF, burst) = 13	MVF = 13	Fixed 1 x 20 mins x 4 days 4 sessions	Pain intensity (VAS)	Universal pain score
Tokuda et al., 2014 <sup>351</sup>	Р	Pr	Post-op abdominal	48 (19W)	TENS (HF) + Fentanyl (PCA) + No TENS (Control) = 16	Placebo TENS (fading) + Fentanyl (PCA) = 16 Fentanyl (PCA) (SoC, no TENS control) = 16	PRN 1 x 60 min/day x 3 days	Pain intensity (VAS) • Resting pain • Coughing • Seating	Pulmonary Functions
Tonella et al., 2006 <sup>352</sup>	Р	E	Post-op abdominal	48 (20W)	TENS (HF) + usual care (analgesics and physiotherapy) = NR	Placebo TENS (0mA) + usual care (analgesics and physiotherapy)) = NR Usual care ((analgesics and physiotherapy) SoC, no TENS control) = NR	Fixed 1 x 30 mins for one day? 1 session	Pain intensity (VAS)	Analgesic consumption
Topuz et al., 2004 <sup>353</sup>	Р	Pr	Back pain - chronic low non-specific	60 (41W)	TENS (HF, conventional) = 15	Placebo TENS (0mA) = 12 TENS (LF) =15 Percutaneous neuromodulation therapy = 13	Fixed 1 x 20 min/day x 5 days x 2 weeks 10 sessions	Pain intensity (VAS) • Resting • On movement	Low back pain outcome scale Oswestry disability index Beck Depression Inventory
Tosato et al., 2007 <sup>354</sup>	Р	Е	Temporomandibular disorders	20 (20W)	TENS (NR) = 10	Massage therapy = 10	Fixed 1 x 30 mins 1 session	Pain intensity (VAS)	Electromyography (EMG) measures
Treacy, 1999 <sup>355</sup>	Ρ	Pr	Bruxism	23 (10W)	TENS (LF) = 8	Placebo TENS (0mA) = 8 Relaxation (muscular awareness training) = 8	Fixed 20 to 30 mins / day x 2 / week x 4 months 20 sessions	No primary outcome	Muscle pain from physical examination Degree of discomfort (7-point scale) EMG Cognitive-Somatic Anxiety Questionnaire Beck Depression Inventory Multidimensional health locus control scales
Tsen et al., 2000 <sup>356</sup>	Р	Pr	Labour pain	40 (40W)	TENS (MF) = NR	Placebo TENS (0mA) = NR	PRN During labour 1 session	Pain intensity (VAS)	Duration of analgesia Pin Prick
Tsen et al., 2001 <sup>357</sup>	Р	Pr	Labour pain	40 (40W)	TENS (MF) = NR	Placebo TENS (0mA) = NR	PRN During labour 1 session	Pain intensity (VAS)	Duration of analgesia Pin Prick
Tsukayama et al., 2002 <sup>358</sup>	Р	Pr	Back pain - chronic low non-specific	20 (16W)	TENS (LF) = 10	Electroacupuncture = 9	Fixed 1 x 15 mins / day x 2 / week x 2 weeks 4 sessions	Pain intensity (VAS)	Back pain profile Adverse events
Tucker et al., 2015 <sup>359</sup>	Р	Pr	Procedural pain - bone marrow sampling	70 (32W)	TENS (HF) $= 35$	Placebo TENS (sub threshold) = $35$	Fixed	Pain intensity (NRS)	Treatment perception questionnaire

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							throughout procedure 1 session		
Tugay et al., 2007 <sup>360</sup>	Р	Е	Dysmenorrhea - primary	32 (32W)	TENS (HF) = 17	IFT = 15	Fixed 1 x 20 mins 1 session	Pain intensity (VAS) • Menstrual pan • Referred lower limbs pain • Low back pain	None
Tulgar et al., 1991 <sup>361</sup>	C	E	Several painful conditions	27 (11W)	TENS (HF, conventional) = 27	TENS (LF, burst = 27 TENS (modulated frequency) = 27	Fixed 1 x 30 mins / day switch next day 3 days	Pain intensity (VAS)	None
Tulgar et al., 1991 <sup>362</sup>	С	Е	Several painful conditions	14 (7W)	TENS (HF, conventional) = 14	TENS (LF, burst) = 27 TENS (high rate frequency modulation) = 27 TENS (low rate frequency modulation) = 27	Fixed 1 x 20 mins / day switch each day 4 days equals 4 tests 1 session	Pain intensity (VAS)	Duration of pain relief
Unterrainer et al., 2010 <sup>363</sup>	Р	Pr	Post-op lumbar	38 (19W)	TENS + PCA = 13	Placebo TENS + PCA (control) = 11 Placebo TENS + PCA (Pre) + TENS + PCA (post) = 14	Fixed 1 x 30 mins pre-op + 1 x 8 hours post-op + 1 x 30 mins post- op day 1 2 sessions	Pain intensity (VAS)	Analgesic consumption Mini Mental State Examination The Short Cognitive Performan Test
Unterrainer et al., 2012 <sup>364</sup>	Р	Pr	Post-op lumbar interbody fusion	35 (17W)	TENS (HF) + placebo PCA = 17	PCA (piritramide) + Placebo TENS (0mA) (SoC, sham TENS control) = 18	Fixed 1 x 30 mins pre-op 1 x 24 hours post up 1 session	Pain intensity (VAS)	Analgesic consumption (PCA - rescue meds)
Upton et al., 2017 <sup>365</sup>	C	E	Peripheral diabetic neuropathy	5	TENS (HF, conventional) = 5	TENS (LF, acupuncture-like) = 5	Fixed 1 x 30 mins / day x 10 days 10 sessions	Pain intensity (NRS)	McGill Pain Questionnaire Mechanical detection threshold Patient's Global Impression of Change
Vaidya, 2018 <sup>366</sup>	Р	Pr	Pregnancy induced posterior pelvic pain	30 (30W)	TENS (HF) = 15	Mobilisation of sacroiliac Joint = 15	Fixed 1 x 30 mins / day x 3 / week 5 sessions	Pain intensity (VAS)	Roland Morris disability Questionnaire
Vaillancourt et al., 2019 <sup>367</sup>	Р	Pr	Chronic pain - Various	18 (18W)	TENS (HF) + exercise = 7	Placebo TENS (0mA) + exercise = 8	Fixed 2 x 45mins / session x 2 / week x 4 weeks, 8 sessions	Pain intensity (NRS)	Short-Form McGill Pain Questionnaire Brief Pain Inventory Beck Depression Inventory
Valenza et al., 2016 <sup>368</sup>	Р	Е	Knee pain - anterior	84 (52W)	TENS = 28	No treatment = 28 Stretching = 28	Fixed 1 x 20 mins 1 session	No primary outcome	Analgesic consumption Roland Morris disability score Pressure algometry
van der Ploeg et al., 1996 <sup>369</sup>	Р	Pr	Labour pain	94 (94W)	TENS (HF, continuous + LF, burst) + analgesics (pethidine/promethazine PCA) = 46	Placebo TENS (NR) + analgesics (pethidine/promethazine, PCA) = 48	PRN	Pain intensity (VAS)	Duration of stages of labour Mode of delivery, Foetal status Apgar scores

#### 08\_OL-TABLE1\_IncludedStudies

van der Spank et al., 2000 <sup>370</sup>	Р	E	Labour pain	59 (94W)	TENS (HF, continuous, burst) + Epidural (drug NR) = 24	Epidural (drug NR) (SoC, no TENS control) = 35	PRN	Pain intensity (VAS)	Analgesic consumption TENS satisfaction questionnaire
Vance et al., 2012 <sup>371</sup>	P	E	Osteoarthritis - knee	75 (46W)	TENS (HF) = 25	Placebo TENS (Fading) = 25 TENS (LF) = 25	Fixed 1 x 40 to 50 mins 1 session	Pain intensity (VAS) • Rest • On movement (Timed-up-and- go) • Heat evoked - temporal summation	Quantitative sensory testing Pressure algometry, Cutaneous mechanical pain threshold, pressure pain threshold (PPT), heat pain threshold, heat temporal summation] Timed up and go
Vitalii and Oleg, 2014 <sup>372</sup>	Р	Pr	Neuropathic pain associated with spinal cord injury	21 (2W)	TENS (LF) + gabapentin = 11	Placebo TENS (no current stimulation) + gabapentin = 10	Fixed 1 x 30 mins / day x 10 days 10 sessions	Pain intensity (VAS)	Analgesic consumption
Vrouva et al., 2019 <sup>373</sup>	Р	Pr	Rotator cuff	42 (20W)	TENS (HF) + kinesiotherapy	microcurrent electrical nerve stimulation + kinesiotherapy	Fixed 1 x 20 mins / day x 5 / week x 3 weeks 15 sessions	Pain intensity (NRS)	Shoulder pain and disability index (SPADI) EuroQoL-5 (Quality of life)
Walker et al., 1991 <sup>374</sup>	Р	Pr	Post-op (rehabilitation - total knee arthroplasty	48 (NR)	TENS (HF) + continuous passive motion + analgesic (various opioids) = 18	TENS (subthreshold) + continuous passive motion + analgesics (various opioids) = 18 Continuous passive motion + analgesics (various opioids) (SoC, no TENS control) = 12	PRN continuously 3 days post op	No primary outcome	Analgesic consumption
Wang et al., 2009 <sup>375</sup>	C	E	Dysmenorrhea - primary	21 (21W)	TENS (HF) = 21	Placebo TENS (0mA) = 21	Fixed 1 to 2 x 30 mins / day x 2 days	Pain intensity (NRS, 11-point scale)	Pain location Autonomic and related symptoms questionnaire SF-36
Warfield et al., 1985 <sup>376</sup>	Р	Pr	Post-op thoracotomy	24 (NR)	TENS (NR) + opioids = 12	Placebo TENS (0mA) + opioids = 12	PRN Continuous stimulation x ? days	Pain intensity (NRS)	Analgesic consumption Ability to tolerate chest physical therapy (3 categories) Recovery room stay
Warke et al., 2004 <sup>377</sup>	Р	Pr	Back pain – low, multiple sclerosis	15 (NR)	TENS (HF) = 5	Placebo TENS (0mA) = 5 TENS (LF) = 5	Fixed 1 x > 45 mins/day x 6 weeks >42 sessions	Pain intensity (VAS)	Roland Morris Disability Questionnaire Barthel Activities of Daily Living Rivermead Mobility Index McGill Pain Questionnaire Leeds Multiple Sclerosis Quality of Life Questionnaire SF-36
Warke et al., 2006 <sup>378</sup>	Р	Pr	Back pain – low, multiple sclerosis	90 (69W)	TENS (HF) = 30	Placebo TENS (0mA) = 30 TENS (LF) = 30	PRN >2 x 45 mins / day x 6 weeks >42 sessions	Pain intensity (VAS)	Analgesic consumption McGill Pain Questionnaire Roland Morris Disability Questionnaire Barthel Index Rivermead Mobility Index Multiple Sclerosis Quality of Life-54 Instrument

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Yameen et al., 2011 <sup>379</sup>	Р	Pr	Neuralgia - trigeminal	31 (20W)	TENS (HF, continuous pattern) = 16	TENS (LF, Burst) = 15	PRN x 3 weeks	Pain intensity (VAS)	None
Yesil et al., 2018 <sup>380</sup>	Р	Pr	Neck pain - chronic non -specific	81 (56W)	TENS (HF) + Exercise (neck stabilisation) = 27	Exercise (neck stabilisation) (SoC, no TENS control) = 26 IFT + Exercise (neck stabilisation) = 27	Fixed 1 x 25 mins / day x 5 / week x 3 weeks 15 sessions	Pain intensity (VAS)	Range of motion Neck Disability index SF-36 Beck Depression Inventory
Yilmaz et al., 2020 <sup>381</sup>	Р	Pr	Post op - inguinal herniorrhaphy	52 (3W)	TENS (HF) + intramuscular NSAID = 26	Placebo TENS (0mA) + intramuscular NSAID = 26	Fixed 5 x 30 mins / day x 1 day 5 sessions	Pain intensity (VAS)	Analgesic consumption, Newcastle Satisfaction with Nursing Care Scale Vital signs
Yilmazer et al., 2012 <sup>382</sup>	Р	Pr	Procedural pain - office endometrial biopsy	65 (65W)	TENS (NR) + Oral naproxen = 33	Placebo TENS + oral naproxen (0mA) = 32	Fixed 10 mins pre and during procedure 1 session	Pain intensity (VAS)	Blood pressure and pulse Vasovagal symptoms questionnaire
Yokoyama et al., 2004 <sup>383</sup>	Р	Pr	Back pain - chronic low non-specific	53 (30W)	TENS (HF) + analgesics = 18	Percutaneous electrical nerve stimulation + analgesics = 18 PENS + TENS + analgesics = 17	Fixed 1 x 20 mins / day x 2 / week x 8 weeks 16 sessions	Pain intensity (VAS)	Analgesic consumption Degree of impairment (5 categories)
Yoshimizu et al., 2012 <sup>384</sup>	С	E	Neck pain - chronic non -specific ('Shoulder and neck pain')	90 (52W)	TENS (LF) = 90	Electroacupuncture = 90	Fixed 1 x 15 mins 1 session	Pain intensity (VAS)	SF-36
Yüksel et al., 2019 <sup>385</sup>	Р	E	Fibromyalgia	42 (NR)	TENS (HF) = 21	Acupuncture = 21	Fixed 1 x 20 mins 1 session	Pain intensity (VAS)	Pressure algometry pain threshold Beck Depression Inventory Fibromyalgia Impact Questionnaire
Yurtkuran and Kocagil, 1999 <sup>386</sup>	Р	Pr	Osteoarthritis - knee	100 (91W)	TENS (LF) = 25	Electroacupuncture = 25 Ice massage = 25 Placebo TENS (no current) = 25	Fixed 1 x 20 mins / day x 5 / week x 2 weeks 10 sessions	Pain intensity (5 categories) • Present pain • Overall pain	50-foot walking time Quadriceps muscle strength Range of motion
Zakariaee et al., 2019 <sup>387</sup>	Р	Pr	Post op - episiotomy	120 (120W)	TENS (HF) + routine care = 40	Placebo TENS (0mA) + routine care = 40 Routine care = 40	Fixed 1 x 60 mins 1 session	Pain intensity (NRS)	TENS' complications satisfaction rate
Zhang et al., 2020 <sup>388</sup>	Р	Е	Chronic TMJ pain (TMJ disc displacement without reduction)	20 (10W)	TENS (LF, AL-TENS) = 10	Placebo TENS (0mA) = 10	Fixed 1 x 45 mins 1 session	Pain intensity (NRS) • Movement – jaw opening and closing	Mandibular motor function using Cranio-Mandibular Evaluation System
Zhou et al., 2018 <sup>389</sup>	Р	Pr	Hemiplegic shoulder pain	90 (19W)	TENS (HF) + rehab programme = 32	NMES + rehabilitation programme = 31 Conventional rehab programme (SoC, no TENS control) = 18	Fixed 1 x 60 mins / day x 5 days x 4 weeks 20 sessions	Pain intensity (NRS)	Fugl-Meyer Modified Ashworth scale Barthel Index Stroke specific quality of life scale

• Design: P = Parallel group; C = Crossover.

• Type: E = Predominantly Explanatory; Pr = Predominantly Pragmatic (mixed).

• Sample: W = women

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44 45 46 • Primary TENS intervention group as selected by reviewers: Size of sample arm '=' on enrolment; HF = high frequency >10 pps); LF = low frequency < 10 pps or LF burst pattern. AF = alternating frequency, MF = modulated frequency; VF = various frequencies; burst = burst pattern of pulse delivery; HI = High Intensity TENS

• Comparison Intervention(s). Listed in reviewers' order of priority; number in trial arm '='; Placebo TENS (0mA - sham device or dead batteries); Fading = TENS current administered briefly and then turned off e.g. applied for 30 seconds and then drifted off to 0mA over a 15 second time frame; Active = Placebo TENS used currents above 0mA, >SDT- infrequent pulses = current above sensory detection threshold and time between pulses modified so that they were delivered very infrequently (e.g. inter-pulse interval adjusted from 330 ms to 33 s to avoid any analgesic effect), >SDT- TENS remote = current above sensory detection threshold and delivered at a site considered to be completely unrelated to the site of the pain; categorised as considered as standard of care (SoC)

• TENS regimen: Fixed = regimen either delivered as such or advice given to patient on regimen to use themselves; PRN = 'pro re nata', when necessary; Extracted elements of regimen as min. each session / no. sessions / day / session days / week / weeks / course of treatment (no. of TENS sessions));

- Primary outcome measures in relation to this review: Pain intensity as dichotomous or continuous data
- Secondary outcomes: Analgesic consumption general term to encompass any time of measurement associated with analgesic medication
- Other Abbreviations: IFT=Interferential current therapy; NSAID = Non-Steroidal Anti-Inflammatory Drugs; PENS = Percutaneous electrical nerve stimulation, TONS = transcutaneous occipital nerve stimulation EA = electroacupuncture; VAS = visual analogue scale; NRS = Numerical rating scale; PCA = Patient controlled analgesia; BPI = Brief Pain Inventory LANSS = Leeds Assessment of Neuropathic Symptoms and Signs; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index; NR = Not reported

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## **Records Awaiting Classification**

Reference	Language	Reason
Aiyejusunle et al. 2007 <sup>1</sup>	Not reported	Need to obtain PDF
Chen et al. 2007 <sup>2</sup>	Chinese	Needs translation
Houshyar et al. 2015 <sup>3</sup>	Persian	Needs translation
Kim et al. 2020 <sup>4</sup>	Not reported	Need to obtain PDF
Kumar and Rahim 2019 <sup>5</sup>	Not reported	Need to obtain PDF
Mehlhorn et al. 2005 <sup>6</sup>	German	Needs translation
Pourmomeny et al. 2009 <sup>7</sup>	Persian	Needs translation
Renklitepe et al. 1995 <sup>8</sup>	Not reported	Need to obtain PDF
Sakai et al. 2001 <sup>9</sup>	Japanese	Needs translation
Tokuda et al. 2013 <sup>10</sup>	Japanese	Needs translation
Tunc et al. 2002 <sup>11</sup>	Not reported	Need to obtain PDF
van der Pierjil et al. 1998 <sup>12</sup>	Not reported	Needs translation
Wang et al. 2005 <sup>13</sup>	Not reported	Need to obtain PDF
Xiao et al. 2002 <sup>14</sup>	Not reported	Need to obtain PDF
Zati et al. 2004 <sup>15</sup>	Italian	Needs translation
Zheng et al., 2011 <sup>16</sup>	Chinese	Needs translation
Zhang et al. 2014 <sup>17</sup>	Chinese	Needs translation
Zhong and Zhang 2017 <sup>18</sup>	Not reported	Need to obtain PDF
Zhou et al. 2009 <sup>19</sup>	Not reported	Need to obtain PDF

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### **ONLINE TABLE 3**

### Excluded studies, with reasons, based on screening full text records

Reference	Reason for exclusion	Description of study
Aguilar Ferrandiz et al., 2016 <sup>1</sup>	Not standard TENS - auto-targeted neurostimulation	Evaluated Nervomatrix Soleve® auto-targeted neurostimulation device providing TENS-stimulation and mechanical pressure for chronic low back pain. Technical specifications differ from a standard TENS device
Albayrak, 2017 <sup>2</sup>	Not an RCT	Evaluated TENS on persistent post-surgical pain after total knee arthroplasty. Retrospective study of prospectively collected data
Alhusaini et al., 2019 <sup>3</sup>	No pain outcomes – Primary outcomes grip strength and function; secondary outcome manual ability	Evaluated TENS combined with therapeutic exercises for hand function by reducing spasticity in children with hemiplegic cerebral palsy
Altas et al., 2019 <sup>4</sup>	Not possible to isolate TENS	Evaluated the effect of physical therapy modalities on pain, sleep, mental status, and quality of life of patients with osteoarthritis.
Al Zamil et al., 2019 <sup>5</sup>	Not full report - Abstract of conference presentation	Evaluated TENS of median nerves and acupuncture in the treatment of carpal tunnel syndrome
Askin et al., 2014 <sup>6</sup>	Not possible to isolate effect of TENS	Evaluated ultrasound therapy for stellate ganglion blockade in complex regional pain syndrome type I. TENS delivered in combination with drug medication, contrast bath and exercise to all groups.
Atalay et al., 2009	No pain outcomes	Evaluated TENS for viability of skin flaps created during mastectomy in breast cancer patients. No pain outcomes
Augustinsson et al., 1977 <sup>8</sup>	Not an RCT	Evaluated TENS for pain during delivery labour pain). Open label pre-post study single group study without comparison intervention(s)
Avramidis et al., 2003 <sup>9</sup>	Not standard TENS – neuromuscular electrical stimulation	Evaluated electric muscle stimulation during rehabilitation after total knee arthroplasty - MicroStim 2-channel (MS-2) neuromuscular stimulator
Aydın et al., 2015	TENS administered internally - intravaginal	Evaluated vaginal electrical stimulation for sexual function using the insertion of a vaginal probe inserted delivering medium- frequency (50 Hz) alternating current (duty cycle 5 seconds on followed by 5 seconds off) generated by a MyoBravo electro stimulation instrument (MTR+ Vertiebs GmbH, Berlin)
Aydogan et al., 2014 11	Not standard TENS - Frequency Rhythmic Electrical Modulation System	Evaluated pre-emptive frequency rhythmic electrical modulation using a Phyback device (PBK2C) in patients undergoing lumbar stabilization
Ayyildiz et al. 2004 <sup>12</sup>	Not an RCT	Evaluated TENS for pain associated with extracorporeal short-wave lithotripsy. Open label pre-post study single group study without comparison intervention(s).
Bai et al., 2018 <sup>13</sup>	Not standard TENS - transcutaneous electric acupoint stimulation	Evaluated transcutaneous electric acupoint stimulation (TEAS) on stress response during extubation after general anaesthesia in patients undergoing elective supratentorial craniotomy. Primary purpose of TEAS was not to treat pain. TEAS was administered using a Hwato electronic acupuncture treatment instrument (model no.: SDZ-II) delivering an alternate dense- disperse frequency of 2/10 Hz (2 Hz for 10 s and 10 Hz) to various acupuncture points
Behm et al., 2019	Not pain outcomes - Fatigue rather than pain	Evaluated if TENS-induced pain suppression would augment force output during a fatiguing protocol in the treated and contralateral muscles.
Belmonte et al., 2012 <sup>15</sup>	Not standard TENS - microcurrent electrical stimulation and bioresonance device	Evaluated low-frequency low-intensity electrotherapy in the treatment of chronic upper limb breast cancer-related lymphoedema. Used a Flowave2Home device delivering microcurrents via a wave of carrier frequency ranging from 0.31 to 6.16 Hz and a modulation between 400 and 2120 Hz; the low offset voltage is always between +12 and -12 V.
Bouafif and Ellouze, 2019 <sup>16</sup>	Not an RCT	Evaluated modulated PWM-TENS for non-cancer pain. PWM-TENS used sinusoidal waves sinusoidal carrier whose frequency varies according to the mode of stimulation. There was a comparison with 'classical TENS' but this was not a RCT.
Bundsen et al., 1981 <sup>17</sup>	Not an RCT	Evaluated TENS for labour pain. Retrospective (stated as prospective in title) open label questionnaire with each patient matched with a control without randomisation.
Burch et al., 2008	Not standard TENS - low-current TENS (0.5mA used as control	Evaluated combination of interferential and patterned muscle stimulation for osteoarthritis of knee. Control group received low- current TENS biphasic square wave with a 0.2 Hz frequency and a fixed amplitude of 60 mA, with pulse width adjusted to provide a net output of 73 nC and delivered across 300 microseconds equivalent to a peak output of 0.5 mA. This did not meet ou criteria for standard TENS
Burssens et al., 2003 <sup>19</sup>	No pain outcomes	Evaluated burst TENS on the healing of Achilles tendon suture
Carbonario et al., 2013 <sup>20</sup>	Not an RCT	Evaluated TENS for tender points in fibromyalgia. Patients were allocated 'sequentially' and there was no mention of randomisation within the report (quasi-RCT). This was included in the Cochrane review on Fibromyalgia.

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Reference	Reason for exclusion	Description of study
Chao et al., 2007 <sup>21</sup>	TENS delivered to acupuncture points distant to pain	Evaluated TENS on acupuncture points for pain during the first stage of labour using two pairs of electrodes placed at bilateral L 4 (Hegu) points (midpoint between first and second carpal bones, first web space dorsal side) and Sp6 (Sanyinjiao) points (5 cm above medial malleolus in lower leg)
Chee and Walton 1986 22	Not standard TENS - microcurrent electrical stimulation	Evaluated treatment of trigger points with micro amperage TENS using an Electro-acuscope 80 stimulator
Cheing and Hui- Chan, 2004 23	No pain outcomes	Evaluated addition of TENS to exercise training for knee osteoarthritis but measured functional outcomes only. There were no pain outcomes in report
Chen et al., 2013 <sup>24</sup>	Not standard TENS electrodes	Evaluated TENS for knee osteoarthritis using silver spike point electrodes, similar to IFT suction cups, rather than self-adhering carbon-rubber TENS electrodes
Chen et al. 2013 25	TENS on acupuncture points using TEAS	Evaluated electroacupuncture, TENS and acupoint massage on periarthritis of shoulder.
Chen et al., 2015 <sup>26</sup>	Not standard TENS - transcutaneous electric acupoint stimulation	Evaluated transcutaneous electric acupoint stimulation on post-procedural abdominal pain after colonoscopy at Jiaji (EX-B2) points were located on both sides of the spinous column using a Han's Acupoint Nerve Stimulator (HANS-200A, Nanjing Jisher Medical Technology Co., Ltd., Nanjing, China), delivering a dense-and-disperse frequency at 2/100 Hz for 30 min prior to induction.
Chen et al., 2015 <sup>27</sup>	Not standard TENS - transcutaneous electric acupoint stimulation	Evaluated transcutaneous electric acupoint stimulation for remifentanil-induced hyperalgesia in patients undergoing thyroidectomy and delivered as 30 min of stimulation (6-9 mA, 2/10 Hz) on the Hegu (LI4) and Neiguan (PC6) before anaesthes (pre-emptive) and terminated before the end of surgery. Stimulation was not at site of pain or over nerve bundles.
Chen et al., 2015 <sup>28</sup>	Not standard TENS - transcutaneous electric acupoint stimulation	Evaluated transcutaneous electric acupoint stimulation on postoperative quality of recovery after thyroidectomy with general anaesthesia administered at bilateral Hegu (LI4) and Neiguan (PC6) before induction of anaesthesia (pre-emptive). TEAS was delivered at a disperse-dense frequency of 2/10 Hz and an intensity of 6-9 mA for 30 min using the Hans electronic acupuncture apparatus (HANS-100A)
Chen et al., 2020 29	Not Standard TENS -TEAS	Evaluated efficacy of TEAS for sedation and postoperative analgesia in lung cancer patients undergoing thoracoscopic pulmonar resection.
Cheng and Pomeranz, 1986 <sup>30</sup>	Not standard TENS - Codetron	Evaluated 'acupuncture-like stimulation' using a Codetron device for chronic musculoskeletal pain and delivering currents randomly to acupuncture points at different locations on the body via seven electrodes.
Chiu et al., 1999 <sup>31</sup>	TENS delivered to acupuncture points distant to pain	Evaluated TENS for pain during hemorrhoidectomy. Electrodes were positioned on acupuncture points distant to the painful area (i.e. dorsal web between the first and the second metacarpal bones (Hegu, Large Intestine meridian, 4th ampoint, negative electrode) and on radial side 3 cm proximal to the wrist crease (Lieque, Lung meridian, 7th ampoint, positive electrode) using a Han Acutens, WQ1002F device
Coletta et al., 1988	Unable to isolate TENS effects	Evaluated TENS vs. TENS + ointment containing Etofenamate. Not possible to isolate effects of TENS
Conn et al., 1986 33	Some participants not adults	Evaluated TENS for pain following appendicectomy. Included children (minimum age = 13 years (TENS), 15 (sham) and 13 (control))
Cornell et al., 1984 34	Not an RCT	Evaluated TENS for pain following foot surgery. Data gathered prospectively during TENS was compared with retrospective da of patients that did not receive TENS harvested from medical records
Demidas et al., 2019 <sup>35</sup>	Healthy humans	Evaluated touch and pain sensations and the correlation between them in diadynamic current and TEN.S
Duzyj et al., 2020 Not full report – Abstract of conference poster presentation <sup>36</sup>		Evaluated effect of TENS therapy in the pain management of women after caesarean delivery.
Dodick et al., 2015	Not standard TENS - invasive technique	Evaluated peripheral nerve stimulation (PNS) of the occipital nerves for managing chronic migraine using implanted with a neurostimulation system Not TENS
Eidy et al., 2016 <sup>38</sup>	TENS given pre-emptive to general anaesthesia / surgery - pain measured after surgery with no TENS post op	Evaluated effects of preoperative TENS on post inguinal hernia repair pain
Ertzgaard et al., 2018 39	Not standard TENS electrodes	Evaluation of TENS for spasticity using an AT Mollii® electrotherapy system consisting of a two-piece garment equipped with electrodes and a control unit.
Fagade and Obilade, 2003 40	No pain outcomes	Evaluated TENS on post-IMF trismus and pain in Nigerian Patients. No pain outcomes

Reference	Reason for exclusion	Description of study
Fargas-Babjak et al., 1989 <sup>41</sup>	Not standard TENS – Codetron	Evaluated 'acupuncture-like stimulation' for osteoarthritis of the hip or knee using a Codetron device
Fargas-Babjak et al., 1992 <sup>42</sup>	Not standard TENS – Codetron	Evaluated 'acupuncture-like stimulation' for chronic pain syndrome or osteoarthritis using a Codetron device
Fary et al., 2011 <sup>43</sup>	Not standard TENS - subsensory pulsed electrical stimulation	Evaluated pulsed electrical stimulation for osteoarthritis of the knee using a commercially available TENS stimulator (Metron Digi-10s) that was modified by a biomedical engineer to deliver pulsed, asymmetrically biphasic, exponentially decreasing waveform currents with a frequency of 100 Hz and pulse width of 4 msec. Author's state " <i>Participants attached the device and turned the intensity up until they could feel pins and needles or a prickling sensation under one or both electrodes. After achieve sensory output, participants were instructed to turn the intensity down until they could no longer feel any electrical stimulation. this stage, a built-in locking mechanism was engaged that prevented subsequent adjustment of intensity without restarting the device." Thus, subsensory stimulation.</i>
Fletcher-Smith et al., 2019 <sup>44</sup>	Not standard TENS - Neuromuscular Electrical Stimulation " current intensity was increased to produce an alternating contraction of the flexors and extensors using a flex-hold-extend-hold pattern, ensuring that a pure movement was produced with no/minimal ulnar or radial deviation."	Evaluated feasibility of initiating electrical stimulation treatment of wrist extensors and flexors in patients early after stroke to prevent muscle contractures and pain.
Gadsby et al., 1997 45	TENS delivered to acupuncture points distant to pain	Evaluated acupuncture-like TENS within palliative care delivered to acupuncture points PC6 (Neiguan) and LI4 (Hegu) of the dominant hand
Gao et al., 2017 46	Not standard TENS - transcutaneous electric acupoint stimulation	Evaluated transcutaneous electric acupoint stimulation for procedural pain during and post thyroidectomy administered at PC6 (Neiguan) and LI4 (Hegu) and distant from the painful site. Full article in Chinese.
Garaud et al., 2018 47	Cannot isolate effects of TENS	Evaluated efficacy of TENS in the treatment LBP when associated to a therapeutic education program (TEP).
Garland et al., 2007 <sup>48</sup>	Not standard TENS - highly optimized, capacitively coupled, pulsed electrical stimulator	Evaluated highly optimized, capacitively coupled, pulsed electrical stimulator for osteoarthritis of the knee using a knee garmer with flexible, embedded electrodes and a small battery-operated generator that produced a 100-Hz, negative pulsed signal (BioniCare Medical Technologies, Inc., Sparks, Maryland.). Authors state - "They then turned on the device, increased the sign amplitude to between 0 and 12 V by rotating a dial until a tingling sensation was felt over the knee or thigh, and then reducing amplitude until this sensation disappeared. Thus, active treatment remained imperceptible and indistinguishable from placebo." P631 and "In fact, TENS and PES differ in many ways." P635
Gaul et al., 2016 49	Not standard TENS - invasive vagus nerve stimulation	Evaluated non-invasive vagus nerve stimulation for prevention and acute treatment of chronic cluster headache using " a low voltage electrical signal (5-kHz sine wave series that occurred for 1 ms and repeated every 40 ms (25Hz))." p 535
Geirsson et al., 1993 <sup>50</sup>	Not standard TENS - posterior tibial nerve stimulation	Evaluated TENS of the tibial nerve in patients with interstitial cystitis using electrodes positioned over the tibial nerve on the fo Thus, TENS delivered distant to symptoms. Posterior tibial nerve stimulation is a neuromodulation technique to treat overactive bladder and associated symptoms. TENS is administered over tibial nerve distant from sensations associated with urinary urgen
Ghoname et al., 1999c <sup>51</sup>	Not standard TENS - percutaneous electrical nerve stimulation	Evaluated the effect of stimulus frequency on response to percutaneous electrical nerve stimulation in patients with chronic low back pain delivered via ten, 32-gauge (0.2 mm) stainless steel acupuncture-like needle probes placed into soft tissue and/or mus in the low back region to a depth of 2–4 cm.
Gokce et al., 2020	Not RCT	Evaluated bilateral transcutaneous tibial nerve stimulation on constipation severity in geriatric patients with refractory chronic constipation.
Gottfried et al., 2019 <sup>53</sup>	Not focussed on pain - Not TENS - abstract	Evaluated transcutaneous vagal nerve stimulation improves symptoms, pain, and gastric emptying in patients with idiopathic gastroparesis.
Govil et al., 2020 <sup>54</sup>	Not RCT	Evaluated extent to which genetic variability modifies Transcutaneous Electrical Nerve Stimulation (TENS) effectiveness in osteoarthritic knee pain
Gu et al., 2019 55	Not standard TENS - TEAS	Evaluated effects of TEAS on gastrointestinal function recovery after laparoscopic radical gastrectomy
Gorodetskyi et al., 2007 <sup>56</sup>	Not standard TENS - non-invasive interactive neurostimulation (InterX)	Evaluated non-invasive interactive neurostimulation in the post-operative recovery of patients with a trochanteric fracture of the femur. Currents delivered using a handheld, non-invasive, interactive neurostimulation device (InterX 5000; Neuro Resource Group, Plano, Texas) device that " generates a high peak amplitude averaging 17 volts on the skin with a low current of about 6 mA, and damped biphasic electrical impulses which are delivered to the tissue through a pair of concentric electrodes placed direct contact with the target area. The device is able to adjust its strength and damping of the biphasic stimulus changes in accordance with the impedance of the underlying tissue (Fig. 1), resulting in a highly sensitive and variable voltage in order to maintain constant peak current."

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Reference	Reason for exclusion	Description of study
Harrison et al., 1987 <sup>57</sup>	Not an RCT – May also be using part of sample in Harrison 1986	Evaluated TENS for labour pain. Patient self-selected treatment – not random allocation/RCT "All patients were informed about the methods of analgesia available, including TENS. They were asked if they had decided upon a specific form of analgesia and what it was. Information regarding the trial and its aims was then given to all potential participants and those giving informed consent were enrolled in their specific group of choice."
Hedner et al., 1996	Not an RCT – narrative review	This is a narrative overview that describes the RCT by Milson et al., 1994 - included
Herman et al., 1994 <sup>59</sup>	Not standard TENS - Codetron	Evaluated 'acupuncture-like stimulation' using a Codetron device for acute occupational low back pain. Codetron is a neuromodulation technique described as the delivery of acupuncture-like stimulation to six locations on the body in a random order.
Hettrick et al., 2004 <sup>60</sup>	No pain outcome – measured itch	Evaluated the role of TENS for the management of burn-related pruritus
Hsieh et al., 1992	Not an RCT – analysis of scales used in an RCT by <sup>62</sup> which was excluded	Evaluated reliability of instruments used in a RCT of transcutaneous muscle stimulation on chronic low back pain. This publication pre-empted publication of RCT by Pope et al., 1994
Huang et al., 2017	Not standard TENS - transcutaneous electric acupoint stimulation	Evaluated transcutaneous electrical acupoint stimulation at different frequencies on perioperative anaesthetic dosage, recovery, complications, and prognosis in video-assisted thoracic surgical lobectomy delivered to acupoints Neiguan (PC6), Hegu (LI4), Lieque (LU7), and Quchi (LI11) distant from pain and using a HANS-200A Acupoint Stimulator and frequency set as 2/100, 2, o 100 Hz in the dense-and-disperse mode before, during and post-surgery
Huang et al., 2018	Not standard TENS - transcutaneous electric acupoint stimulation	Evaluated transcutaneous electrical acupoint stimulation for recovery after laparoscopic colorectal cancer resection delivered to ST36 (leg) distant to pain before and during surgery
Huang et al., 2019	Not standard TENS - transcutaneous electrical acupoint stimulation	Evaluated transcutaneous electrical acupoint stimulation for pain in patients "in expansion process of skin soft tissue dilator on forehead by water injection applied to acupuncture points at the wrist (PC6), forehead (shangxing) and diwei points. Article in Chinese
Ing et al., 2015 66	Not standard TENS - microampere rather than milliampere	Evaluated TENS for chronic postherpetic neuralgia using electronic neuroadaptive regulation (SCENAR) delivered using a Tennant Biomodulator (TBM) device. The authors state " <i>The major difference between SCENAR and TBM devices and the traditional TENS units is that the former devices utilize microamps, not the milliamps utilized by the TENS units.</i> " P477
Issenman et al., 1985 <sup>67</sup>	Not an RCT	Evaluated TENS for pain control after spinal fusion with Harrington rods and assessed 'hospital charts' of patients who used TENS with sex and age matched controls. It was described as an evaluation of the effectiveness of their postoperative pain management programme with no statement that this was a prospective study with randomisation
Itoh et al., 2008 68	Not standard TENS – electrical characteristics are interferential therapy	Evaluated TENS for osteoarthritis of the knee versus acupuncture or acupuncture combined with TENS or topical poultice. The authors describe this as TENS but inspection of the reported electric characteristics suggest this is IFT "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)."
Itoh et al., 2009 69	Not standard TENS – electrical characteristics are interferential therapy	Evaluated TENS for chronic low back pain versus acupuncture or acupuncture combined with TENS or topical poultice. The authors describe this as TENS but inspection of the reported electric characteristics suggest this is IFT "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)."
Jarden et al., 1999 <sup>70</sup>	Conference abstract - ? reporting RCT by Jarzem et al., 2005 (included	Evaluated conventional transcutaneous electrical nerve stimulation [TENS] with sham therapy using a randomized double-blind crossover design. Transcutaneous electrical nerve stimulation for non-acute low back pain: a randomized double-blind study of conventional, nu-waveform, acupuncture-type and sham therapies.
Jeans et al., 1979 71	Not an RCT	Evaluated the effect of brief, intense transcutaneous electrical stimulation on chronic pain
Jiang et al., 2019 72	Not standard TENS - Cefaly	Evaluated efficacy and safety of combination therapy of flunarizine plus transcutaneous supraorbital neurostimulation (tSNS) compared with either flunarizine or tSNS alone for migraine prophylaxis
Juarez-Albuixech et al., 2019 <sup>73</sup>	Not RCT	Evaluated efficacy of Volta Therapy and transcutaneous electrical nerve stimulation (TENS) in the treatment of lumbosciatica

Reference	Reason for exclusion	Description of study
Junger et al., 2008	Not standard TENS - microcurrent electrical stimulation	Evaluated Local therapy and treatment costs of chronic, venous leg ulcers treated with electrical stimulation using a Dermapulse device (Gerromed, Hamburg, Germany) delivering currents with varying polarity at a pulse frequency of 128 Hz and an average current strength of 300 microamperes (initially 300 mA, if pain or paraesthesia was noted, it was reduced)
Kaplan et al., 1994	Not an RCT	Evaluated TENS for dysmenorrhea. Open label single group without a comparison group
Katz and Melzack 1991 <sup>76</sup>	TENS delivered to acupuncture points distant to pain	Evaluated low frequency high intensity auricular TENS for phantom limb pain.
Kempf et al., 2018	Not standard TENS – H wave	Evaluated short-term application of High-Tone Electrical Muscle Stimulation (HTEMS) compared to Transcutaneous Electrical Nerve Stimulation (TENS) with chronic sciatica.
Kho et al., 1991 78	Unable to isolate TENS effects	Evaluated transcutaneous stimulation combined with acupuncture for surgery for retroperitoneal lymph node dissection major surgery. Not possible to isolate the effects of TENS from those of acupuncture
Kocyigit et al., 2012 <sup>79</sup>	Not an RCT – experimental study	Evaluated effects of Low-frequency Transcutaneous Electrical Nerve Stimulation on Central Pain Modulation in patients with subacromial impingement syndrome of the shoulder. The experimental paradigm was to evaluate pain-induced activation in the brain during low-frequency TENS application in response to experimentally induced painful stimuli although the nature of the stimuli unclear " <i>The involved arm of the patient was grasped by the researcher</i> "
Kolen et al., 2012	Not standard TENS device or electrodes	Evaluated different ways of delivering TENS for osteoarthritis of the knee. Used a prototype TENS device with a matrix electron array.
Kolu et al., 2018 81	Unable to isolate TENS effects	Evaluated transcutaneous nerve stimulation combined with high-intensity laser therapy and ultrasound treatment in patients with chronic lumbar radiculopathy. Not possible to isolate TENS
Koo et al., 2015 <sup>82</sup>	Unable to isolate TENS effects	Evaluated Noxipoint Therapy to conventional physiotherapy that consisted of TENS, exercise, and manual and heat therapies fo the treatment of chronic neck and shoulder. Noxipoint Therapy is a modified technique to deliver TENS over tender muscle poin to produce a sore pain and does not meet our criteria for standard TENS and the comparator group included TENS combined wi other treatments
Kumar et al., 1997 83	Not standard TENS – H-wave therapy	Evaluated transcutaneous electrostimulation for chronic painful peripheral neuropathy. The authors state "Electrotherapy was given by a portable, rechargeable unit, the H-Wave machine (Electronic Waveform Lab, Huntington Beach, CA), which has output parameters that are distinct from the other available transcutaneous electrical nerve stimulation (TENS) modalities." P 17 Current is biphasic, exponentially decaying waveform with pulse widths of 4 ms and $\leq$ 35 V The electric current strength varies with voltage setup to a maximum of 35 mA, and the pulse frequency is user adjustable (2-70 Hz).
Kumar et al., 1998	Not standard TENS - H-wave therapy	Evaluated transcutaneous electrostimulation for chronic painful peripheral neuropathy using H-Wave device with parameters distinct from standard TENS.
Labrunee et al., 2015 85	No pain outcomes	Evaluated randomized placebo control study to determine whether applying TENS before exercise in PAD patients could delay onset of pain and lead to longer walking distances
Lan et al., 2012 <sup>86</sup>	TENS delivered to acupuncture points distant to pain	Evaluated TENS on six acupuncture points for pain after total hip arthroplasty for elderly patients. Acupuncture points were generally distant to the site of pain (bilateral P6 on anterior surface of the forearm; L14 on dorsum of hand; ipsilateral to the surgery ST36 anterior crest of the tibia; GB31 between greater trochanter of femur and hiatus of sacrum).
Lanham et al., 1984 <sup>87</sup>	Not an RCT	Evaluated TENS combined with hypothermia in podiatric surgery by describing a series of 69 patients that received treatment. There was no comparison group
Lee et al., 1997 <sup>88</sup>	Not standard TENS - medium frequency AC plus galvanic	Evaluated electrical stimulation for pain associated with myofascial trigger points. The type of current was a combination of medium-frequency AC current and Galvanic current at a frequency of 50-100Hz Not standard TENS - combination of medium frequency AC plus galvanic
Lee et al., 2015 89	Unable to isolate TENS effects	Evaluated effect of a device combining high-frequency transcutaneous electrical nerve stimulation and thermotherapy (I-Rune I- 200L, Midirune Co.) for primary dysmenorrhea. Not possible to isolate TENS because TENS and thermal therapies combined
Lehmann et al., 1983 <sup>90</sup>	Not standard TENS characteristics – delivered below sensory detection threshold (subthreshold TENS – reporting data from same sample as Lehmann et al., 1986	Evaluated subtreshold TENS versus placebo TENS and electroacupuncture for chronic low back pain. Analysis of nonorganic findings.
Lehmann et al., 1986 <sup>91</sup>	Not standard TENS characteristics – delivered below sensory detection threshold (subthreshold TENS – probably reporting same data as Lehmann et al., 1983	Evaluated subthreshold TENS versus placebo TENS and electroacupuncture for chronic low back pain. Analysis of efficacy.

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Reference	Reason for exclusion	Description of study
Lerma et al., 2020	Not full report – Abstract of conference poster	Evaluated TENS for pain control during first-trimester abortion.
Li et al., 2019 93	Not standard TENS - TEAS	Explored effect and mechanisms of TEA on postoperative recovery after caesarean section
Lin et al., 2017 94	Not standard TENS – TEAS delivered to acupuncture points	Evaluated regulatory effects of acupoint electric stimulation on the analgesic substances and the relevant indices of nerve- immunity-endocrine system in the patients undergoing general anaesthesia anorectal operation
Liu et al., 2015 <sup>95</sup>	Not standard TENS - transcutaneous electric acupoint stimulation	Evaluated transcutaneous electrical acupuncture stimulation combined with sufentanil anaesthesia for intraoperative and postoperative supratentorial craniotomy. Electrodes applied at five pairs of acupuncture points: Hegu (LI4) and Waiguan (TE5). Jinmen (BL63) and Taichong (LR3), Zusanli (ST36) and Qiuxu (GB 40), and Fengchi (GB20) with Tianzhu (BL10) and Cuanz (BL2) with Yuyao (EX-HN4) on the craniotomy side and currents delivered using a Han's acupoint nerve stimulator (LH202H, Beijing Huawei Co, Ltd, Beijing, China) with a dense-disperse frequency of 2/100 Hz (alternated once every 3 s; 0.6 ms at 2 Hz and 0.2 ms at 100 Hz).
Loeser et al., 1975	Not an RCT	Evaluated TENS for various chronic pains. No comparison groups
Lone et al., 2003 97	Not an RCT	Evaluated TENS for osteoarthritis of the knee. Authors state "The results of this non-randomised controlled single-blind continuous trial" p481
Lorenzana et al., 1999 <sup>98</sup>	TENS on remote acupuncture points	Evaluated the efficacy of transcutaneous electrical nerve stimulation (TENS) versus lidocaine in the relief of episiotomy pain
Lv et al., 2018 99	Not standard TENS - transcutaneous electric acupoint stimulation	Evaluated transcutaneous acupoint electrical stimulation combined with sufentanil pre-treatment on incidence and severity of etomidate-induced myoclonus delivered bilaterally, at hegu and waiguan acupoints (on arm) using to 2/100Hz "dilatational waves". Acupoint not covering painful site
Macdonald and Coates, 1995 <sup>100</sup>	Not standard TENS - transcutaneous spinal electroanalgesia and TENS control group not applied at site of pain	Evaluated Transcutaneous Spinal Electroanalgesia for Chronic Pain. Used TENS as a control for comparison but stated "Norma one would not apply TENS to these locations" p656
Malmir et al., 2017	Not clinical pain - sample of pain-free participants	Evaluated TENS on experimentally induced delayed onset muscle soreness in Amateur Athletes
Maria Fernandez- Seguin et al., 2019	Not TENS	Evaluated radiological changes after combining static stretching and transcutaneous electrical stimulation of the plantar fascia in adults with idiopathic cavus foot
Matsuse et al., 2020 <sup>103</sup>	No pain outcomes - Not treating pain	Evaluated effectiveness of a hybrid training system with walking that simultaneously applies electrical stimulation to the knee extensors/flexors during walking in obese women with knee pain
McGough et al., 2019 <sup>104</sup>	No pain outcomes - Not pain	Evaluated efficacy and safety of TNS for Attention-Deficit/Hyperactivity Disorder and potential changes in brain spectral powe using resting state quantitative electroencephalography
Meade et al., 2010	Not standard TENS - transcutaneous electric acupoint stimulation	Evaluated transcutaneous electric acupoint stimulation as adjunctive treatment for opioid detoxification using a Han's Acupoint Nerve Stimulator to deliver currents to "hegu" and "neiguan" acupoints on dorsal and palmar surface of one hand, and dorsal an ventral surface of the other forearm. Frequency of stimulation alternated between 2 and 100 Hz at 3-second intervals. Primary outcome was opioid consumption although physical pain in past 24 hours assessed using the Brief Pain Inventory was a second outcome.
Meechan et al., 1998 <sup>106</sup>	TENS administered internally – intra-oral	Evaluated transcutaneous electronic nerve stimulation for discomfort associated with regional anaesthesia in dentistry using an injection-assist TENS machine (3M, St Paul, Minnesota, USA) with electrodes positioned in the mouth either side of the needle puncture point.
Melzack et al., 1975 <sup>107</sup>	Not standard TENS device and electrodes	Evaluated TENS for various chronic pains using a Grass model S8 stimulator and EEG disc electrode to deliver currents
Melzack et al., 1980 <sup>108</sup>	Not an RCT - "Patients were assigned alternately, as they arrived at the clinic, to each order of treatment."	Evaluated TENS versus ice massage in patients with chronic low back pain
Mi et al., 2018 <sup>109</sup>	Not standard TENS - transcutaneous electric acupoint stimulation	Evaluated the effect of transcutaneous electrical acupoint stimulation (TEAS) on the quality of recovery during the early period after laparoscopic cholecystectomy and the dosage of anaesthetic and analgesic
Miller Jones et al., 1980 <sup>110</sup>	Not an RCT	Evaluated TENS for labour Pain. Not prospective randomisation -patients were given TENS and followed. Then retrospectively they were compared with a sample taken from patients who had not received TENS - EXCLUDE AS NOT RADMOSIED
Monaco et al., 2013 111	No pain outcomes	Evaluated effect of TENS on electromyographic and kinesiographic activity in patients with temporomandibular disorder. No patients outcomes

Reference	Reason for exclusion	Description of study
Mucuk and Baser, 2014 <sup>112</sup>	Not standard TENS - TENS-acupuncture pen	Evaluated non-invasive electroacupuncture on labour pain using a TENS-acupuncture pen with a maximum output of 0.6mA administered to acupuncture points LI4 (hand)SP6 (leg/foot)
Mummolo et al., 2019 <sup>113</sup>	Not RCT – retrospective evaluation	Evaluated effects of ultra-low-frequency transcutaneous electrical nerve stimulation (ULF-TENS) on pain and electromyographic values in subjects affected by temporomandibular disorder
Murina et al., 2008	TENS administered internally - intravaginal	Evaluated TENS to treat vestibulodynia using a dual channel portable TENS unit (YSY-EST device) and a commercially availabl plastic vaginal probe with two gold metallic transversal rings as electrodes (Periprobe VAG2ST Beac, Pavia, Italy) inserted 20 mm into the vagina
Murina et al., 2018	TENS administered internally - intravaginal	Evaluated TENS plus diazepam to treat vestibulodynia using a dual channel portable TENS unit (NeuroTrac Continence; VerityMedical, London, UK) and a commercially available plastic vaginal probe with two gold metallic transversal rings (Periprobe VAG2ST Beac, Pavia, Italy) inserted 20 mm into the vagina
Mysliwiec et al., 2011 <sup>116</sup>	No pain outcomes	Evaluated effect of cervical traction and TENS on strength of painless grip
Naeser et al., 2002	Not standard TENS – microcurrent electrical stimulation	Evaluated carpal tunnel syndrome pain treated with low-level laser and microamperes transcutaneous electric nerve stimulation
Nakano et al., 2019	Not RCT	Evaluated effects of TENS on pain and other physical symptoms in 20 in-patients with advanced cancer receiving palliative care
Ngai et al., 2010 119	Not clinical pain	Evaluated Acu-TENS on functional capacity and beta-endorphin level in subjects with chronic obstructive pulmonary disease
Noehren et al., 2015 <sup>120</sup>	Protocol – ongoing study	Protocol of an RCT to evaluate TENS for fibromyalgia: a double-blind randomized clinical trial. Full RCT published <b>after our search</b> Dailey et al., 2019 Arthritis Rheumatol. 2019 Nov 18. doi: 10.1002/art.41170.
Nourbakhsh and Fearon, 2008 <sup>121</sup>	Not standard TENS device or electrodes	Evaluation of noxious level electrical stimulation on chronic lateral epicondylitis administered using a MRL Neuroprobe System V (CR Kesner Company, Geneva, IL, USA) as painful stimulation of trigger points for 30s using 4Hz interupted DC current and probe electrode
Okonkwo et al., 2018 <sup>122</sup>	Not an RCT	Evaluation of TENS for post-injection sciatic pain in a non-randomized controlled clinical trial.
Oyibo et al., 2004	Not standard TENS - microcurrent electrical stimulation	Evaluated electrical stimulation therapy through silver-plated nylon-Dacron <sup>™</sup> stocking electrodes (Micro-Z, Prizm Medical, Duluth, GA, USA) for painful diabetic neuropathy. Pulsed electric current were delivered a subsensory dose approximately 50 micro amps at 80 pulses per second for the first 10 min, then 8 pulses per second for the next 10 min each hour over an 8-h period
Ozen et al., 2019	Cannot isolate TENS - hotpack, transcutaneous electrical nerve stimulation (TENS, and ultrasound	Evaluated effects of physiotherapy modalities with those of acupuncture on pain, daily function, and quality of life in FMS patients.
Park et al., 2014 125	No pain outcomes	Evaluated TENS with exercise on spasticity, balance, and gait in patients with chronic stroke. No pain outcomes.
Patel et al., 2016	Unable to isolate TENS effects	Evaluated TENS with McKenzie method for lumbar radiculopathy. Not possible to isolate the effects of TENS from McKenzie
Peng et al., 2010	Not an RCT	Evaluated TENS on Acupoints for labour pain. Stated a Non-randomized Controlled Study
Polat et al., 2017	Not an RCT	Evaluated TENS combined with hot pack and home exercise program for osteoarthritis of the knee with and without neuropathic pain. There was no comparison intervention
Pope et al., 1994	Not standard TENS - neuromuscular electrical stimulation	Evaluated transcutaneous muscle stimulation for sub-acute low back pain using a Myocare PLUS device which is considered to be a neuromuscular stimulator and thus excluded. Note: Currents produced physiological stimulation that could be considered within the scope of 'standard TENS' Biphasic pulses 37pps pulse duration 225 us with pulse amplitude modulated (ramped up in 2 s held for 6s then ramped off in 2s then a pause before cycle repeated. 4 electrodes placed on back around pain and current delivered to maintain sensation as high as possible – no mention of muscle twitching
Pour et al., 2012 <sup>130</sup>	TENS applied to acupuncture points away from painful area [TENS applied to acupuncture points on foot and SP6 for labour pain]	Evaluated effect of two methods of compressive medicine and electrical stimulation of the skin on the severity of labour pains in the first pregnant women.
Quinton et al., 1987 <sup>131</sup>	Some participants not adults	Evaluated TENS in acute hand infections. Sample included at least one child under 16years of age (age range from 15 to 66 years).
Radhakrishna et al., 2020 <sup>132</sup>	TENS applied pre-emptive before general surgery and pain measured post operatively without TENS	Evaluated the effect of immediate preoperative TENS on intraoperative anaesthetic drug consumption in patients undergoing lumbar discectomy under general anaesthesia

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Reference	Reason for exclusion	Description of study
Rapoport et al., 2019 <sup>133</sup>	Not TENS - secondary report of Yartisky	Performed a post-hoc analysis on a subgroup of participants with migraine from a randomized, double-blind, parallel-group, sham-controlled, multicentre study
Razavi and Jansen, 2004 134	Not standard TENS - placebo TENS only	Evaluated acupuncture and placebo TENS in addition to exercise in treatment of rotator cuff tendinitis. No active TENS intervention.
Reich et al., 1989	Unable to isolate TENS effects	Evaluated various non-invasive treatments for vascular and muscle contraction headache including an 'Electrical Group' that received either traditional TENS or electrical neurotransmitter modulation, either singly or in combination. Data was analysed at group rather than modality level.
Reichstein et al., 2005 136	Not standard TENS – H wave characteristics delivered using a CEFAR Dumo TENS device	Evaluated effects of high-frequency external muscle stimulation HF) with those of TENS in patients with diabetic distal symmetrical sensory polyneuropathy.
Rodriguez- Fernandez et al., 2011 <sup>137</sup>	Not clinical pain - sample of pain-free participants	Evaluated burst-type TENS on cervical range of motion and latent myofascial trigger point sensitivity in a sample of individuals recruited from a pain-free population with at least 1 latent myofascial trigger point in their upper trapezius. Sample not recruited from clinical pain population.
Rooney et al., 1986	No pain outcomes	Evaluated cryoanalgesia and TENS on pulmonary function tests post thoracotomy. No pain outcome
Roth and Thrash, 1986 <sup>139</sup>	Not standard TENS - microampere currents, and not standard electrodes and invasive technique	Evaluated TENS for pain associated with orthodontic tooth movement. In one group TENS was applied externally over zygomatic arches using sponge pad electrodes – not standard TENS electrodes (0.5 Hz with an intensity of 500 mA). In one group TENS was applied internally (intraoral) directly to teeth using one probe electrode on the crown of each tooth and the other electrode on the palatal mucosa adjacent to the tooth (0.5 Hz, intensity of 50 mA) – Internal Currents were delivered using Alpha-Stim model 2000 which produces a biphasic waveform with varying pulse widths in the millisecond range and intensities in the microampere range (i.e. microcurrent). It is probable that 500mA and 50mA were typographical errors that should read 500 microampere and 50 microamperes. "Both groups were told that the intensity of the current was so small that the most they would feel was a very slight tingling, if anything at all." p133
Santiesteban et al., 1985 140	TENS delivered to acupuncture points distant to pain	Evaluated TENS on acupuncture points for primary spasmodic dysmenorrhea using a MRL pain control system (5Hz, 250us, intensity to patient tolerance). Acupuncture points were not covering painful site (GB34, Sp6, (leg).
Sari et al., 2019 <sup>141</sup>	Unable to isolate TENS	Evaluated intermittent pneumatic compression along with conventional treatment with cold pack treatment along with conventional treatment on clinical outcomes in patients with knee osteoarthritis
Schuster et al., 1980 142	Not an RCT - 26 control patients were selected at random. Records were matched as closely as possible	Evaluated use of TENS and narcotic analgesics in relieving post-operative pain.
Schoenen et al., 2013 <sup>143</sup>	Not standard TENS - supraorbital transcutaneous stimulator	Evaluated trigeminal neurostimulation with a supraorbital transcutaneous stimulator (Cefaly, STX-Med., Herstal, Belgium) for migraine prevention. Neurostimulation delivered with one 30 mm 3x94 mm self-adhesive electrode on forehead and delivery of biphasic rectangular pulsed currents (250 µs, 60 Hz, 16 mA).
Schomburg and Carter-Baker, 1983	Not an RCT	Evaluated TENS for post laparotomy pain compared with chart review to 75 patients who had undergone similar surgical procedures performed by the same surgeon before TENS postoperative pain management had been instituted.
Selfe et al., 2008	Not standard TENS - noninvasive interactive neurostimulation (InterX5000 device	Evaluated Noninvasive Interactive Neurostimulation on Symptoms of Osteoarthritis of the Knee using an InterX5000 device (Neuro Resource Group, Plano, TX)
Shirazi et al., 2014	Not an RCT	Evaluated TENS on joint position sense in patients with knee joint osteoarthritis. Pre-post study without a comparison group.
Silberstein et al., 2016 <sup>147</sup>	Not standard TENS - 5KHz sine wave	Evaluated non-invasive vagus nerve stimulation for chronic migraine headache prevention using low voltage 5KHz sine wave lasting 1 millisecond with such bursts repeated every 40 milliseconds (Electrocore Ltd)
Silberstein et al., 2016 <sup>148</sup>	Not standard TENS - 5KHz sine wave	Evaluated non-invasive vagus nerve stimulation for the acute cluster headache using low voltage 5KHz sine wave lasting 1 millisecond with such bursts repeated every 40 milliseconds (Electrocore Ltd)
Simon et al., 2015	Not an RCT	Evaluated TENS for chronic axial low back pain on a single cohort stratified for age. Dose-response study with no other intervention comparison groups.
Simpson and Ward, 2004 <sup>150</sup>	Not standard TENS - transcutaneous spinal electroanalgesia	Evaluated transcutaneous spinal electroanalgesia for pain from chronic critical limb ischemia. Transcutaneous spinal electroanalgesia uses two electrodes placed over dorsal spine and delivers currents that do not cause action potentials in peripheral nerves and no sensation of paraesthesia (4 us, 1800–2500 Hz, 100–300 V, Advanced Pain Management)

Reference	Reason for exclusion	Description of study
Solomon and Guglielmo, 1985	Not standard TENS - microcurrent electrical stimulation	Evaluated TENS for headache using a device that " differs from most other TENS equipment by its low amperage (maximum 4 milliamperes), high frequency (12,000 to 20,000 Hz rectified to monophasic wave form) and short pulse width (approximately 30 microsec)" p 12
Solomon et al., 1989 <sup>152</sup>	Not standard TENS - microcurrent electrical stimulation	Evaluated Cranial Electrotherapy in the Treatment of Tension Headache using " extremely low level, high frequency current applied transcranially" – microcurrent p 445
Sonde et al., 2000	No pain outcomes	Evaluated TENS for post-stroke paretic arm on functional outcomes including spasticity and activities of daily function but not pain
Stralka et al., 1998	Not standard TENS - high voltage pulsed direct current	Evaluated high voltage pulsed direct current built into a wrist splint for hand and wrist pain
Stratton and Smith, 1980 <sup>155</sup>	No pain outcomes	Evaluated TENS for postoperative thoracotomy on ventilatory function including forced vital capacity but not pain
Strayhorn et al., 1983 156	Not an RCT	Evaluated TENS on use of narcotic analgesics and occurrence of postoperative complications following gastric bypass surgery for control of obesity from chart review
Sun et al., 2017 <sup>157</sup>	Not standard TENS - transcutaneous electric acupoint stimulation	Evaluated Perioperative Transcutaneous Electrical Acupoint Stimulation for Postoperative Pain Relief Following Laparoscopic Surgery using a HANS Acupoint Nerve Stimulator (HANS-200A, Nanjing Jisheng Medical Technology Company, Nanjing, China) delivering an alternating dense and disperse stimulation (2Hz (0.6 ms pulse width) alternated with 100 Hz stimulation (0. ms pulse width) every 3 seconds to maximum current tolerated but subnoxious) to Hegu (LI4) and Neiguan (P6) distant from pair
Sunshine et al., 1996 <sup>158</sup>	Not standard TENS – microcurrent electrical stimulation	Evaluated microcurrent TENS and massage for fibromyalgia (Electroacuscope device)
Takla and Rezk- Allah, 2018 <sup>159</sup>	Not standard TENS - combination therapy, unable to isolate effect of TENS	Evaluated simultaneous application of TENS and ultrasound phonophoresis on active myofascial trigger points as a combined therapy using an Intelect Advanced Combo therapy system (2752CC; Chattanooga DJO France SAS Industries; Mexico) device. Using an ultrasound treatment head as an electrode and not possible to isolate TENS - Combined therapy
Takla et al., 2018	Not standard TENS - combination therapy, unable to isolate effect of TENS	Evaluated low-frequency high-intensity versus medium-frequency low-intensity TENS delivered as combined therapy with ultrasound phonophoresis for management of active myofascial trigger points using an Intelect Advanced Combo therapy system (2752CC; Chattanooga DJO France SAS Industries; Mexico) device. Using an ultrasound treatment head as an electrode and not possible to isolate TENS - Combined therapy
Thiese et al., 2013	Not an RCT	Evaluated electrical stimulation for chronic non-specific low back pain in a working-age population – Report of a Protocol
Thompson et al., $2008^{162}$	Not standard TENS - transcutaneous spinal electroanalgesia	Evaluated transcutaneous spinal electroanalgesia (TSE) on low back pain. "TSE bears a superficial resemblance to transcutaneous electrical nerve stimulation (TENS) but differs in that it is applied to the skin overlying the vertebral spine and uses stimulation frequencies far higher ( $2500 + H_2$ ) than those used for TENS (circa $1-150 H_2$ ) The pulse widths used for the two systems are also substantially different (4 ls for TSE compared with 50–200 ls for TENS)."
Tok et al., 2011 <sup>163</sup>	Unable to isolate TENS effects	Evaluated electrical stimulation combined with continuous passive motion on symptoms, functional capacity, quality of life and balance in knee osteoarthritis. Combination therapy not possible to isolate contribution of TENS.
Tousignant- Laflamme et al., 2017 <sup>164</sup>	Not an RCT - only one intervention	Evaluated acupuncture-like TENS for chronic low back pain. Design was a randomized, crossover study to determine the duration of analgesia following 15- and 30-minute treatment. No comparison intervention group.
Tu et al., 2019 <sup>165</sup>	TENS delivered to acupuncture points distant to pain	Evaluated transcutaneous electrical acupoint stimulation on postoperative analgesia after ureteroscopic lithotripsy delivered to bilateral Shenyu (BL23) outside spinous process of L2 and SP9 between posterior tibia border and gastrocnemius muscle using a HANS LH-202 electrical stimulator.
Vance et al., 2018	Not an RCT	Development of a method to maximize intensity of TENS used for fibromyalgia by analysing baseline data from an ongoing clinical RCT investigating the effects of TENS in women with fibromyalgia – the Fibromyalgia Activity Study with TENS (FAST; NCT01888640).
VanderArk and McGrath, 1975 <sup>167</sup>	Some participants not adults	Evaluated TENS for post-operative pain. Some participants were not adults (13 years to 87 years).
Vincenti et al., 1982 <sup>168</sup>	Not an RCT	Evaluated TENS for labour pain.
Vinterberg et al. 1978 <sup>169</sup>	Not an RCT	Evaluated TENS for rheumatoid arthritis.

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Reference	Reason for exclusion	Description of study
Wang et al., 1988	Some participants not adults	Evaluated TENS for sickle cell pain crises. Some participants were not adults (12years to 27 years)
Wang, 1997 171	Not standard TENS - transcutaneous electric acupoint stimulation	Evaluated transcutaneous electrical acupoint stimulation on analgesic consumption post operation lower abdomen surgery at acupuncture points (Hegu (LI14) and either side of the incision site) using dense-disperse current.
Wang et al., 2007	Not standard TENS - acupuncture acupoint stimulator	Evaluated TENS applied to acupoints for labour pain using an acupuncture acupoint stimulator (G-6502-2A). Acupuncture points LI4 PC6 SP6 LR3 not at site of pain.
Wang et al., 2007	TENS delivered to acupuncture points distant to pain	Evaluated abdominal acupuncture TENS on leg shoulder loin and neck pain using acupuncture points that are distant from pain LI4 PC6 SP6 LR3 – in Chinese Excluded based on abstract.
Wang et al., 2007	Not standard TENS - 'pen shaped' electrodes	Evaluated acupuncture-like electrical stimulation on chronic tension-type headache using a 'pen shaped' electrode with a tip diameter of 1mm delivering dense-and-disperse currents (TAO, MibiTech ApS, Helsingør, Denmark) to six acupoints distant to the pain, bilateral EX-HN5, GB 20, LI 4
Wang et al., 2008	Not standard TENS - transcutaneous electric acupoint stimulation	Evaluated pre and during surgery TEAS on blood bioactive compounds involving cerebral injury during craniotomy at LI4, LI11 ST36 SP6 distant to pain not at site of pain. No pain measure in Chinese Excluded based on abstract.
Wang et al., 2009	Not standard TENS - transcutaneous electric acupoint stimulation	Wang, Z. X. (2009) Clinical observation on electroacupuncture at acupoints for treatment of senile radical sciatica. [Chinese]. Zhongguo zhen jiu = Chinese acupuncture & moxibustion 29 (2), 126-128.
Wang et al., 2014	Not standard TENS - transcutaneous electric acupoint stimulation	Evaluated transcutaneous electric acupoint stimulation on intra-operative remifentanil consumption and postoperative side-effect in patients undergoing sinusotomy delivered to Hegu (LI4), Neiguan (PC6), and Zusanli (ST36) a 6–9mA,2/10 Hz before anaesthesia.
Ward et al., 2009	Not clinical pain - sample of pain-free participants	Evaluated A efficacy of medium frequency alternating current and TENS on healthy participants.
Wattrisse et al., 1993 179	Not standard TENS - Limoges currents	Evaluated effect of transcutaneous cranial electrical stimulation with Limoges currents - French. Excluded based on abstract.
Weng et al., 2005	Not standard TENS - 5KHz currents modulated at lower frequencies	Evaluated modulated-frequency mode of AL-TENS on tennis elbow pain. " treated with either 5 KHz modulated by 2 Hz frequency mode (LF group), 5 KHz modulated by 100 Hz frequency mode of TENS (HF group) on acupuncture points (L110 and L111)". Output characteristics seems to be a carrier wave of 5KHz modulated at 2Hz or 100Hz.
Whitehair et al., 2019 181	Not TENS	Evaluated acute effects of TENS, transcutaneous neuromuscular electrical stimulation and no stimulation on pain-free passive range of motion of the shoulder in subjects with hemiplegic shoulder pain
Wieselmann- Penkner et al., 2001 <sup>182</sup>	No pain outcomes	Evaluated TENS and EMG-biofeedback on muscular relaxation in bruxism.
Williams et al., 2019 <sup>183</sup>	Not TENS Not RCT - healthy humans	Evaluated conditioned pain modulation efficiency in persons with and without migraine headaches
Williams 2019 <sup>184</sup>	Not RCT - Abstract	Evaluated feasibility of TENS as adjunctive treatment for post-operative orthopaedic pain.
Wilson and Stanczak, 2020 <sup>185</sup>	Not an RCT - Review	Round-up of the current body of evidence of using TENS for pain control in patients with advanced cancer and palliative pain.
Wong et al., 2003	Not standard TENS - Codetron	Evaluated acupuncture-like TENS for radiation-induced xerostomia associated with radical radiotherapy using Codetron device that delivers electrical currents randomly between 6 electrodes. Report of phase 1 of the RCT trial. Not an RCT
Wong et al., 2012	Not standard TENS - Codetron	Evaluated acupuncture-like TENS for radiation-induced xerostomia associated with radical radiotherapy using Codetron device. " This particular TENS devicediffers from conventional TENS units, because it embeds a random circuit that enables rando switching among 6 electrodes to prevent brain habituation to continuous stimulation" page 4245. Report of phase 2 of the RCT
Wu et al., 2012 <sup>188</sup>	Not standard TENS - middle frequency electrical stimulation	Evaluation of middle frequency electrical stimulation for dysmenorrhea. Currents delivered at frequency of 1000 -10,0000 Hz to acupuncture points not covering pain site (LI4 SP6) using a GM390TE, GEMORE device
Xu et al., 2014 <sup>189</sup>	Cannot isolate TENS because all groups received identical TENS as combined therapy	Evaluated TENS in combination with cobalamin injection for postherpetic neuralgia.
Xie et al., 2017 <sup>190</sup>	Not standard TENS - transcutaneous electric acupoint stimulation	Evaluated transcutaneous electrical acupoint stimulation combined with palonosetron on chemotherapy-induced nausea and vomiting. No pain outcomes.
Yang et al., 2017	Not an RCT	Evaluated acupuncture like TENS on knee osteoarthritis (KOA) with low pain. Single intervention group divided according to lo and high pai.n

Reference	Reason for exclusion	Description of study
Yang et al., 2017	Not clinical pain - slow-transit constipation	Evaluated transcutaneous electrical stimulation in women with slow-transit constipation. Primary purpose of study was to evalua slow-transit constipation and associated symptoms of constipation, including abdominal pain as a secondary outcome. Target sample was women with slow-transit constipation rather than patients with clinical pain.
Yao et al., 2015 <sup>193</sup>	Not standard TENS - transcutaneous electric acupoint stimulation	Evaluated transcutaneous electric acupoint stimulation on quality of recovery and postoperative analgesia after gynaecological laparoscopic surgery to Hegu (LI4), Neiguan (PC6), Zusanli (ST36), and Sanyinjiao (SP6) acupoints distant from pain using a Hans electronic acupuncture apparatus (dense-disperse frequency (2/10 Hz), 6–9mA, HANS-100B, Nanjing Jisheng Medical Technology Company, Nanjing, China).
Yarnitsky et al., 2017) <sup>194</sup>	Not standard TENS - Remote Electrical Neuromodulation	Evaluated remote nonpainful electrical upper arm skin stimulation for reducing migraine attack pain. Remote Electrical Neuromodulation uses the principles of conditioned pain modulation applying high intensity TENS to the arm for migraine. Authors argue that REN on arm has neural relationship to migraine pain - we exclude because authors do not call this technique TENS, location of electrodes are remote, and currents delivered using parameters to simulate elicit conditioned pa modulation systems.
Yarnitsky et al., 2019) <sup>195</sup>	Not standard TENS and not at site of pain much debate in team on this though	Evaluated efficacy and safety of a remote electrical neuromodulation (REN) device for the acute treatment of migraine.
Yeh et al., 2010 196	Not standard TENS - transcutaneous electric acupoint stimulation	Evaluated transcutaneous acupoint electrical stimulation for postoperative pain in patients with patient-controlled analgesia. TE delivered at acupoints distant from pain, BL40, GB34, HT7, P6
Yeh et al., 2018 <sup>197</sup>	Not standard TENS - transcutaneous electric acupoint stimulation	Evaluated transcutaneous acupoint electrical stimulation on post-hemorrhoidectomy-associated pain, anxiety, and heartrate variability at acupoints distant from pain, <i>chengshan</i> (BL57) and <i>erbai</i> (EX-UE2) and a stimulator (D0205KL, Ching-Ming Co. Taiwan) delivering dense disperse currents
Yilmaz et al., 2020	Not possible to isolate the effects of TENS - "a combination of US, TENS"	Evaluated high-intensity laser therapy (HILT) and a combination of transcutaneous nerve stimulation (TENS) and ultrasound (t treatment on pain, range of motion (ROM) and functional activity on cervical pain associated with cervical disc herniation (CD)
Yip et al., 2007 199	Unable to isolate TENS effects	Evaluated combined transcutaneous acupoint electrical stimulation and electromagnetic millimetre waves for spinal pain. Not possible to isolate TENS
Yousesef et al., 2015 <sup>200</sup>	Not standard TENS - posterior tibial nerve stimulation	Evaluated transcutaneous electrical posterior tibial nerve stimulation versus lateral internal sphincterotomy for treatment of chronic anal fissure. Transcutaneous electrical nerve stimulation of posterior tibial nerve is used for faecal and urinary incontinence and was applied using an Endomed 182 device (Enraf Nonius, Holland) with the negative contact electrode on the ankle skin behind the medial malleolus, and the positive electrode, 10 cm above the negative electrode.
Yu et al., 2019 201	Not standard TENS - TEAS	Evaluated TEAS on early recovery in patients undergoing gynaecological laparoscopic surgery.
Zeb et al., 2019 202	Not RCT	Evaluated effectiveness TENS in management of neuropathic pain in post-traumatic incomplete spinal cord injury patients.
Zhan and Tian 2019 <sup>203</sup>	Not standard TENS - TEAS	Evaluated effect and adverse effects of transverse abdominis plane block and TEAS on postoperative outcomes.
Zhang et al., 2014 204	Not standard TENS - transcutaneous electric acupoint stimulation	Evaluated pre-treatment with transcutaneous electrical acupoint stimulation on the quality of recovery after ambulatory breast surgery. Transcutaneous electrical acupoint stimulation was delivered at acupoints distant from pain LI4, PC4, ST36 (hand and arm) using a TEAS - SDZ-V dense and disperse device.
Zhang et al., 2016	Not standard TENS - transcutaneous electric acupoint stimulation	Evaluated TEAS before the anaesthesia induction on opioids consumption in patients undergoing off-pump coronary artery byp grafting at distal-proximal acupoints combination (LI4 and CV17) and regional acupoints combination (CV17 and CV14) using <i>Hwato</i> electronic acupuncture treatment instrument (model No. SDZ-V, Suzhou Medical Appliances Co., Ltd, Suzhou, China). InJClinExpMed 9(12)
Zhang et al., 2017 206	TENS delivered to body sites distant to pain	Evaluated TENS of foot for postoperative bladder spasms and pain. Stimulation not on pain site
Zhang et al., 2020	E - Not pain	Evaluated effect of transcutaneous electrical stimulation treatment in combination with intraoperative nerve staining on sexual function after radical surgery.
Zhao et al., 2015 208	Not standard TENS - transcutaneous electric acupoint stimulation	Evaluated transcutaneous electrical acupoint stimulation for spasticity following Brain Injury using an acupoint nerve electrical stimulator (HANS-100A, Nanjing Gensun medical technology company, Nanjing, China) at Hegu (LI4)–Yuji (LU10) and Zusa (ST36)–Chengshan (BL57). Pain on Disability Assessment Scale was a secondary outcome.
Zhou et al., 2018 209	Not standard TENS - transcutaneous electric acupoint stimulation	Evaluated Transcutaneous Electrical Acupoint Stimulation for gastrointestinal dysfunction after caesarean section SP6 and ST3 acupoints using a Hwato electric acupuncture treatment instrument (model No. SDZV; Suzhou Medical Appliances Co. Ltd, Suzhou, China) with a dilatational wave of 2/10 Hz (2-second cycle) for 30 min. TEAS delivered at acupoints distant from pain

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Reference	Reason for exclusion	Description of study
Zizic et al., 1995	Not standard TENS – microcurrent electrical stimulation	Evaluated pulsed electrical stimulation for osteoarthritis of the knee using low voltage (mean = $6.2V$ peak volts). Characteristics like those of microcurrent electrical stimulation although no overt statement to this effect in the report.
*Note: Reference 1. Aguilar I Pain physician 20	016; <b>19</b> (5): E707-19.	ulation Is Not Superior to Placebo in Chronic Low Back Pain: A Fourfold Blind Randomized Clinical Trial.
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4. Altas EU		modalities on sleep quality in patients with primary knee osteoarthritis: A single-blind, prospective, $tion 2020$ : <b>66</b> (1): 73-83
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	ish]. <i>Turk Uroloji Dergisi</i> 2004; <b>30</b> (4): 446-50. , Yang YC, Teng XF, Wan YX, Wei W, Zhu JC. Effects of Tran	scutaneous Electrical Acupoint Stimulation on the Stress Response During Extubation After General
		Prospective Randomized Controlled Trial. <i>Journal of neurosurgical anesthesiology</i> 2018; <b>30</b> (4): 337-46. ve stimulation improves fatigue performance of the treated and contralateral knee extensors. <i>European</i>
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	ation 2012; <b>26</b> (7): 607-18.	ntensity electrotherapy in the treatment of breast cancer-related lymphoedema: a cross-over randomized trial.
	P, Peterson L, Selstam U. Pain relief in labor by transcutaneous	alation in medical pain therapy. <i>Current Signal Transduction Therapy</i> 2019; <b>14</b> (1): 75-83. e electrical nerve stimulation. A prospective matched study. <i>Acta obstetricia et gynecologica Scandinavica</i>

10\_OL-TABLE3\_ExcludedStudies

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10 OL-TABLE3 ExcludedStudies

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$     \begin{array}{c}         1 \\         1 \\         1 \\         $		Study or Subgroup					Std. Mean Difference	
$     \begin{array}{c}         1 \\             2 \\            $		7.3.1 Low RoB - 6 or more low	/ RoB items					
$ \begin{array}{c} \begin{array}{c} \begin{array}{c} \begin{array}{c} \begin{array}{c} \begin{array}{c} \begin{array}{c} \begin{array}{c}$	1	Bertalanffy, et al., 2005	49 8	30 77	11	33 1.	1% -2.85 [-3.57, -2.14]	
$ \begin{array}{c} \begin{array}{c} \begin{array}{c} \begin{array}{c} \begin{array}{c} \begin{array}{c} \begin{array}{c} \begin{array}{c}$	2	Desantana, et al., 2008	9 10.7	20 48	22.7	20 1.	0% -2.15 [-2.95, -1.36]	<u> </u>
$ \begin{array}{c} \begin{array}{c} \begin{array}{c} \begin{array}{c} \begin{array}{c} \begin{array}{c} \begin{array}{c} \begin{array}{c}$	3	Baez-Suarez, et al., 2018	62 14	21 83	12	21 1.	1% -1.58 [-2.28, -0.88]	<u> </u>
$ \begin{array}{c} \begin{array}{c} \begin{array}{c} \begin{array}{c} \begin{array}{c} \begin{array}{c} \begin{array}{c} \begin{array}{c}$	4							
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$     \begin{array}{c}         8 \\             9 \\            $	7	Machado et al., 2019	47 25	22 46	22	22 1.	1% 0.04 [-0.55, 0.63]	
$ \begin{array}{c} 9 \\ 10 \\ 11 \\ 11 \\ 12 \\ 12 \\ 13 \\ 14 \\ 14 \\ 14 \\ 15 \\ 16 \\ 16 \\ 16 \\ 16 \\ 16 \\ 16 \\ 16$	8	Beckwée, et al., 2018		25 30.6		28 1.	2% 0.35 [-0.19, 0.90]	▲ <del>  -</del>
$     \begin{array}{c}         13 \\         12 \\         12 \\         12 \\         12 \\         13 \\         14 \\         15 \\         14 \\         15 \\       $	9	Heterogeneity: Tau <sup>2</sup> = 0.89; Chi			1);  ² = !		5% -1.27 [-1.77, -0.77]	<b>→</b>
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$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	11		-		1.19	8 0.	1% -12.50 [-17.39, -7.61]	•
13      Lumer det, 203      Low rest, 203	12			20 80			9% -3.27 [-4.28, -2.27]	
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34       Markuri, et al., 2019       26.67       22.57       15       45.3       20.15       15       17.8       0.74       14.48       0000         35       Liker et al., 2015       23.1       7.6       11       22.7       15       43.3       20.7       15.5       0.41         36       Liker et al., 2010       23.1       7.6       11       22.7       15       65       10       0.05       0.71       15.5       0.41         36       Walk & Org. 2014       23.1       7.6       11       22.7       15.8       15       10.1       0.75       0.14       0.75       0.14       0.75       0.14       0.75       0.14       0.75       0.14       0.75       0.14       0.75       0.14       0.75       0.14       0.75       0.14       0.75       0.14       0.75       0.14       0.75       0.26       0.21       0.75       0.26       0.21       0.75       0.26       0.21       0.75       0.26       0.21       0.26       0.22       0.21       0.25       0.22       0.21       0.25       0.22       0.21       0.25       0.22       0.21       0.25       0.22       0.25       0.22       0.25       0.22 <th>14</th> <th>Tokuda, et al., 2014</th> <th>5.9 6.5</th> <th>16 23.8</th> <th>5.9</th> <th>16 0.</th> <th>9% -2.81 [-3.82, -1.80]</th> <th><u> </u></th>	14	Tokuda, et al., 2014	5.9 6.5	16 23.8	5.9	16 0.	9% -2.81 [-3.82, -1.80]	<u> </u>
34       Markuri, et al., 2019       26.67       22.57       15       45.3       20.15       15       17.8       0.74       14.48       0000         35       Liker et al., 2015       23.1       7.6       11       22.7       15       43.3       20.7       15.5       0.41         36       Liker et al., 2010       23.1       7.6       11       22.7       15       65       10       0.05       0.71       15.5       0.41         36       Walk & Org. 2014       23.1       7.6       11       22.7       15.8       15       10.1       0.75       0.14       0.75       0.14       0.75       0.14       0.75       0.14       0.75       0.14       0.75       0.14       0.75       0.14       0.75       0.14       0.75       0.14       0.75       0.14       0.75       0.14       0.75       0.26       0.21       0.75       0.26       0.21       0.75       0.26       0.21       0.75       0.26       0.21       0.26       0.22       0.21       0.25       0.22       0.21       0.25       0.22       0.21       0.25       0.22       0.21       0.25       0.22       0.25       0.22       0.25       0.22 <th>15</th> <th>Ahmed, et al., 2010</th> <th>49.3 7</th> <th>30 66.1</th> <th>6.9</th> <th>30 1.</th> <th>1% -2.39 [-3.06, -1.71]</th> <th></th>	15	Ahmed, et al., 2010	49.3 7	30 66.1	6.9	30 1.	1% -2.39 [-3.06, -1.71]	
34       Marxin, et al., 2019       26.67       22.57       15       45.3       20.15       15       17.% $-0.74[-1.49, 0.00]$ 35       Likar et al., 2015       23.1       17.% $-0.74[-1.49, 0.00]$ $-0.74[-1.49, 0.00]$ 36       Likar et al., 2011       23.5       17.%       17.% $-0.74[-1.49, 0.00]$ $-0.74[-1.49, 0.00]$ 37       Figubace       13.57	16							 
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34       Marxin, et al., 2019       26.67       22.57       15       45.3       20.15       15       17.% $-0.74[-1.49, 0.00]$ 35       Likar et al., 2015       23.1       17.% $-0.74[-1.49, 0.00]$ $-0.74[-1.49, 0.00]$ 36       Likar et al., 2011       23.5       17.%       17.% $-0.74[-1.49, 0.00]$ $-0.74[-1.49, 0.00]$ 37       Figubace       13.57	25	Kayman-Kose, et al., 2014 (2)	17.7 12.7	50 37.4	20.6	50 1.	2% -1.14 [-1.57, -0.72]	
34       Marxin, et al., 2019       26.67       22.57       15       45.3       20.15       15       17.% $-0.74[-1.49, 0.00]$ 35       Likar et al., 2015       23.1       17.% $-0.74[-1.49, 0.00]$ $-0.74[-1.49, 0.00]$ 36       Likar et al., 2011       23.5       17.%       17.% $-0.74[-1.49, 0.00]$ $-0.74[-1.49, 0.00]$ 37       Figubace       13.57	26	Cuschieri, et al., 1987	30 11.25	10 49	20.25	10 1.	0% -1.11 [-2.07, -0.15]	
34       Marxin, et al., 2019       26.67       22.57       15       45.3       20.15       15       17.% $-0.74[-1.49, 0.00]$ 35       Likar et al., 2015       23.1       17.% $-0.74[-1.49, 0.00]$ $-0.74[-1.49, 0.00]$ 36       Likar et al., 2011       23.5       17.%       17.% $-0.74[-1.49, 0.00]$ $-0.74[-1.49, 0.00]$ 37       Figubace       13.57	27		68 23	10 88		10 1.	0% -1.08 [-2.03, -0.13]	
34       Marxin, et al., 2019       26.67       22.57       15       45.3       20.15       15       17.% $-0.74[-1.49, 0.00]$ 35       Likar et al., 2015       23.1       17.% $-0.74[-1.49, 0.00]$ $-0.74[-1.49, 0.00]$ 36       Likar et al., 2011       23.5       17.%       17.% $-0.74[-1.49, 0.00]$ $-0.74[-1.49, 0.00]$ 37       Figubace       13.57       13.57       13.57       0.71[-1.50, 0.11] $-0.65[-1.22, 0.21]$ 38       Bieras & Anciesson, 2017       36.9       36.9       36.6       32.1       10.57       -0.065[-1.22, 0.21]         39       Lik, et al., 2017       36.9       36.6       32.2       11.57       -0.065[-1.22, 0.01]       -0.015[-1.22, 0.08]         40       Furtishos       13.43       15       25.5       13.03       13.27       -0.056[-1.02, 0.15]       -0.015[-1.22, 0.08]         41       Warke, et al., 2017       36.9       36.5       35.3       12.37       12.37       13.17       -0.056[-1.22, 0.015]       -0.015[-1.01]         42       Human, et al., 2017       36.9       36.5       35.37       12.37       -0.056[-1.02, 0.015]       -0.016[-0.05, 0.01]       -0.016[-0.016]       -0.016[-0.016]	28							
34       Marxin, et al., 2019       26.67       22.57       15       45.3       20.15       15       17.% $-0.74[-1.49, 0.00]$ 35       Likar et al., 2015       23.1       17.% $-0.74[-1.49, 0.00]$ $-0.74[-1.49, 0.00]$ 36       Likar et al., 2011       23.5       17.%       17.% $-0.74[-1.49, 0.00]$ $-0.74[-1.49, 0.00]$ 37       Figubace       13.57       13.57       13.57       0.71[-1.50, 0.11] $-0.65[-1.22, 0.21]$ 38       Bieras & Anciesson, 2017       36.9       36.9       36.6       32.1       10.57       -0.065[-1.22, 0.21]         39       Lik, et al., 2017       36.9       36.6       32.2       11.57       -0.065[-1.22, 0.01]       -0.015[-1.22, 0.08]         40       Furtishos       13.43       15       25.5       13.03       13.27       -0.056[-1.02, 0.15]       -0.015[-1.22, 0.08]         41       Warke, et al., 2017       36.9       36.5       35.3       12.37       12.37       13.17       -0.056[-1.22, 0.015]       -0.015[-1.01]         42       Human, et al., 2017       36.9       36.5       35.37       12.37       -0.056[-1.02, 0.015]       -0.016[-0.05, 0.01]       -0.016[-0.016]       -0.016[-0.016]	29	Yilmaz et al., 2019					2% -0.96 [-1.53, -0.38]	
34       Marxin, et al., 2019       26.67       22.57       15       45.3       20.15       15       17.% $-0.74[-1.49, 0.00]$ 35       Likar et al., 2015       23.1       17.% $-0.74[-1.49, 0.00]$ $-0.74[-1.49, 0.00]$ 36       Likar et al., 2011       23.5       17.%       17.% $-0.74[-1.49, 0.00]$ $-0.74[-1.49, 0.00]$ 37       Figubace       13.57       13.57       13.57       0.71[-1.50, 0.11] $-0.65[-1.22, 0.21]$ 38       Bieras & Anciesson, 2017       36.9       36.9       36.6       32.1       10.57       -0.065[-1.22, 0.21]         39       Lik, et al., 2017       36.9       36.6       32.2       11.57       -0.065[-1.22, 0.01]       -0.015[-1.22, 0.08]         40       Furtishos       13.43       15       25.5       13.03       13.27       -0.056[-1.02, 0.15]       -0.015[-1.22, 0.08]         41       Warke, et al., 2017       36.9       36.5       35.3       12.37       12.37       13.17       -0.056[-1.22, 0.015]       -0.015[-1.01]         42       Human, et al., 2017       36.9       36.5       35.37       12.37       -0.056[-1.02, 0.015]       -0.016[-0.05, 0.01]       -0.016[-0.016]       -0.016[-0.016]	30	Suh, et al., 2015	18.7 7.46	24 30.7	17.67	23 1.	1% -0.88 [-1.48, -0.28]	<u> </u>
34       Marxin, et al., 2019       26.67       22.57       15       45.3       20.15       15       17.% $-0.74[-1.49, 0.00]$ 35       Likar et al., 2015       23.1       17.% $-0.74[-1.49, 0.00]$ $-0.74[-1.49, 0.00]$ 36       Likar et al., 2011       23.5       17.%       17.% $-0.74[-1.49, 0.00]$ $-0.74[-1.49, 0.00]$ 37       Figubace       13.57       13.57       13.57       0.71[-1.50, 0.11] $-0.65[-1.22, 0.21]$ 38       Bieras & Anciesson, 2017       36.9       36.9       36.6       32.1       10.57       -0.065[-1.22, 0.21]         39       Lik, et al., 2017       36.9       36.6       32.2       11.57       -0.065[-1.22, 0.01]       -0.015[-1.22, 0.08]         40       Furtishos       13.43       15       25.5       13.03       13.27       -0.056[-1.02, 0.15]       -0.015[-1.22, 0.08]         41       Warke, et al., 2017       36.9       36.5       35.3       12.37       12.37       13.17       -0.056[-1.22, 0.015]       -0.015[-1.01]         42       Human, et al., 2017       36.9       36.5       35.37       12.37       -0.056[-1.02, 0.015]       -0.016[-0.05, 0.01]       -0.016[-0.016]       -0.016[-0.016]	31	Elboim et al., 2020	41.7 19.2	23 61.2	25	18 1.	1% -0.87 [-1.52, -0.22]	
34       Markuri, et al., 2019       26.67       22.57       15       45.3       20.15       15       17.8       0.74       14.48       0000         35       Liker et al., 2015       23.1       7.6       11       22.7       15       43.3       20.7       15.5       0.41         36       Liker et al., 2010       23.1       7.6       11       22.7       15       65       10       0.05       0.71       15.5       0.41         36       Walk & Org. 2014       23.1       7.6       11       22.7       15.8       15       10.1       0.75       0.14       0.75       0.14       0.75       0.14       0.75       0.14       0.75       0.14       0.75       0.14       0.75       0.14       0.75       0.14       0.75       0.14       0.75       0.14       0.75       0.14       0.75       0.26       0.21       0.75       0.26       0.21       0.75       0.26       0.21       0.75       0.26       0.21       0.26       0.22       0.21       0.25       0.22       0.21       0.25       0.22       0.21       0.25       0.22       0.21       0.25       0.22       0.25       0.22       0.25       0.22 <th>32</th> <th>Zakariaee et al., 2019</th> <th>31.8 20.4</th> <th>40 47.5</th> <th>16.5</th> <th>40 1.</th> <th>2% -0.84 [-1.30, -0.38]</th> <th></th>	32	Zakariaee et al., 2019	31.8 20.4	40 47.5	16.5	40 1.	2% -0.84 [-1.30, -0.38]	
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	33		39 8	23 45				
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	34							
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	35							
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	36	Warfield, et al., 1985	48.3 20.1	12 64.2	24.6	12 1.	0% -0.68 [-1.51, 0.14]	
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	37	Fujii-Abe et al., 2019	22.1 12.8	11 30.3	11.2	11 1.	0% -0.66 [-1.52, 0.21]	
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	38	Bjersa & Andersson, 2014	19.4 32.5	9 39.6	32	11 1.	0% -0.60 [-1.51, 0.30]	<u> </u>
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	39	Liu, et al., 2017	48.2 17.7	22 55.8	12.6	22 1.	1% -0.49 [-1.09, 0.11]	
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	40							
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	41							
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	42							
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	43	Hamza, et al., 1999	25 23	25 31	25	25 1.	-0.25 [-0.80, 0.31]	
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	44	Moore & Shurman, 1997 (4)	40.58 27.55	24 44.81	30.67	24 1.	2% -0.14 [-0.71, 0.42]	
$\begin{array}{cccccccccccccccccccccccccccccccccccc$	45	Forster, et al., 1994	9.8 28.1	15 13.7	31.9	15 1.	1% -0.13 [-0.84, 0.59]	
	46		28.3 18.06	12 30.2	15.92	12 1.	0% -0.11 [-0.91, 0.69]	
460       Presser, et al., 2000       47       83.34       30       49       27.39       30       1.2%       -0.06 [-0.57, 0.45]         49       Illhani, 2015       22.4       11.3       35       22.8       10.2       31       1.2%       -0.04 [-0.52, 0.45]         50       Bono, et al., 2015       56       56       35       57       35       1.2%       -0.00 [-0.48, 0.45]         51       Silva, et al., 2015       56.6       9.2       54       81.29       18       1.1%       0.01 [-0.55, 0.76]         51       Silva, et al., 2012       2.2.5       11.5       21       20       12.5       21       1.1%       0.01 [-0.55, 0.76]         52       Kofotolis, et al., 2018       2.92       4.2       1.1%       0.46 [-0.31, 1.22]       0.21 [-0.40, 0.81]         53       Subtral (95% Cl)       2.2.2       4.2       2.0       4.2.7%       0.08 [0.47, 1.29]         54       Test for overall effect: Z = 0.49 (P < 0.00001); P = 88%	47							
$\begin{array}{cccccccccccccccccccccccccccccccccccc$	48							+
$\begin{array}{cccccccccccccccccccccccccccccccccccc$	49	Ilhani, 2015	22.4 11.3	35 22.8	10.2	31 1.	2% -0.04 [-0.52, 0.45]	±
$\begin{array}{cccccccccccccccccccccccccccccccccccc$	50	Bono, et al., 2015	80 20	54 80	20	54 1.	2% 0.00 [-0.38, 0.38]	<u>+</u>
52       Kofotolis, et al., 2008       22       4       23       20       4       21       1,1%       0.49 [-0.11, 1.09]         53       Subtocal (95% Cl)       13.5       5.8       50       7.8       7       50       1.2%       0.88 [0.47, 1.29]         54       Heterogeneity: Tau <sup>2</sup> = 0.57; Ch <sup>2</sup> = 529.24, df = 76 (P < 0.00001); I <sup>2</sup> = 86%       52.7%       -0.89 [-1.14, -0.78]       -0.96 [-1.14, -0.78]         56       Total (95% Cl)       2426       2415       100.0%       -0.96 [-1.14, -0.78]       -4       -2       0       2       4         56       Total (95% Cl)       2426       2415       100.0%       -0.96 [-1.14, -0.78]       -4       -2       0       2       4         57       Test for overall effect: Z = 1.04, (P < 0.00001)       IP = 88%       -4       -2       0       2       4         57       Test for overall effect: Z = 1.04, 0 (P < 0.00001)       Favours TENS       </th> <th>Silva, et al., 2012</th> <th>22.5 11.5</th> <th>21 20</th> <th>12.5</th> <th>21 1.</th> <th>1% 0.20 [-0.40, 0.81]</th> <th>-<del>-</del></th>	51	Silva, et al., 2012	22.5 11.5	21 20	12.5	21 1.	1% 0.20 [-0.40, 0.81]	- <del>-</del>
Subtotal (95% Cl)       13.5       5.8       50       7.8       7       50       1.2%       0.88 [0.47, 1.29]         54       Heterogeneily: Tau <sup>2</sup> = 0.57; Ch <sup>2</sup> = 529.24, df = 76 (P < 0.00001); P = 86%		Kofotolis, et al., 2008	22 4	23 20	4	21 1.	1% 0.49 [-0.11, 1.09]	
54Test for overall effect: $Z = 9.27 (P < 0.00001)$ 55Total (95% Cl)24262415100.0%-0.96 [-1.14, -0.78]56Heterogeneity: Tau <sup>2</sup> = 0.64; Ch <sup>12</sup> = 735.58, df = 91 (P < 0.00001); l <sup>2</sup> = 88%-4-20257Test for subgroup differences: Ch <sup>12</sup> = 1.91, df = 1 (P = 0.17), l <sup>2</sup> = 47.7%Favours TENSFavours Placebo58(1) "Crossover(2) Cesarian delivery sample(3) "Crossover(2) Cesarian delivery sample59(2) Cesarian delivery sample(3) "Crossover"(4) "Crossover"(4) "Crossover"	53		13.5 5.8		7			♦   —
55 Total (95% Cl) 2426 2415 100.0% -0.96 [-1.14, -0.78] 56 Heterogeneity: Tau <sup>2</sup> = 0.64; Ch <sup>2</sup> = 735.58, df = 91 (P < 0.00001); I <sup>2</sup> = 88% Test for overall effect: Z = 10.49 (P < 0.00001) 57 Fost for subgroup differences: Ch <sup>2</sup> = 1.91, df = 1 (P = 0.17), I <sup>2</sup> = 47.7% 58 (1) "Crossover 59 (2) Cesarian delivery sample (3) "Crossover 60 (4) "Crossover				76 (P < 0.0000	1);  2 = 3	86%		
56 Heterogeneity: Tau <sup>2</sup> = 0.64; Ch <sup>2</sup> = 735.58, df = 91 (P < 0.0001); I <sup>2</sup> = 88% Test for overall effect: Z = 10.49 (P < 0.00001) 57 Test for subgroup differences: Ch <sup>2</sup> = 1.91, df = 1 (P = 0.17), I <sup>2</sup> = 47.7% 58 (1) *Crossover 59 (2) Cesarian delivery sample (3) *Crossover 60 (4) *Crossover 60 (4) *Crossover	55			2426		2415 100	0% -0.96 [-1.140.78]	•
57       Test for subgroup differences: Chi <sup>2</sup> = 1.91, df = 1 (P = 0.17), l <sup>2</sup> = 47.7%         58       Footnoles (1) *Crossover         59       (2) Cesarian delivery sample (3) *Crossover         60       (4) *Crossover	56	Heterogeneity: Tau <sup>2</sup> = 0.64; Chi			1);  2 = 4			
58       Footnotes.         59       (1) *Crossover         60       (2) Cesarian delivery sample         (3) *Crossover       (3) *Crossover         60       (4) *Crossover	57	Test for subgroup differences: C		1 (P = 0.17), I <sup>2</sup>	= 47.7%	6		Favours TENS Favours Placebo
60 (3) *Crossover (4) *Cross <b>60</b> (4) *Cross <b>60</b> (5) *Cross <b>60</b> (4) *Cross <b>60</b> (5) *Cross <b>60</b> (5) *Cross <b>60</b> (5) *Cross <b>60</b> (5) *Cross <b>60</b> (5) *Cross <b>60</b> (5) *Cross <b>60</b> (5) *Cross <b>60</b> (5) *Cross <b>60</b> (5) *Cross <b>60</b> (5) *Cross <b>60</b> (5) *Cross <b>60</b> (5) *Cross <b>60</b> (5) *Cross <b>60</b> (5) *Cross <b>60</b> (5) *Cross <b>60</b> (5) *Cross <b>60</b> (5) *Cross <b>60</b> (5) *Cross <b>60</b> (5) *Cross <b>60</b> (5) *Cross <b>60</b> (5) *Cross <b>60</b> (5) *Cross <b>60</b> (5) *Cross <b>60</b> (5) *Cross <b>60</b> (5) *Cross <b>60</b> (5) *Cross <b>60</b> (5) *Cross <b>60</b> (5) *Cross <b>60</b> (5) *Cross <b>60</b> (5) *Cross <b>60</b> (5) *Cross <b>60</b> (5) *Cross <b>60</b> (5) *Cross <b>60</b> (5) *Cross <b>60</b> (5) *Cross <b>60</b> (5) *Cross <b>60</b> (5) *Cross <b>60</b> (5) *Cross <b>60</b> (5) *Cross <b>60</b> (5) *Cross <b>60</b> (5) *Cross <b>60</b> (5) *Cross <b>60</b> (5) *Cross <b>60</b> (5) *Cross <b>60</b> (5) *Cross <b>60</b> (5) *Cross <b>60</b> (5) *Cross <b>60</b> (5) *Cross <b>60</b> (5) *Cross <b>60</b> (5) *Cross <b>60</b> (5) *Cross <b>60</b> (5) *Cross <b>60</b> (5) *Cross <b>60</b> (5) *Cross <b>60</b> (5) *Cross <b>60</b> (5) *Cross <b>60</b> (5) *Cross <b>60</b> (5) *Cross <b>60</b> (5) *Cross <b>60</b> (5) *Cross <b>60</b> (5) *Cross <b>60</b> (5) *Cross <b>60</b> (5) *Cross <b>60</b> (5) *Cross <b>60</b> (5) *Cross <b>60</b> (5) *Cross <b>60</b> (5) *Cross <b>60</b> (5) *Cross <b>60</b> (5) *Cross <b>60</b> (5) *Cross <b>60</b> (5) *Cross <b>60</b> (5) *Cross <b>60</b> (5) *Cross <b>60</b> (5) *Cross <b>60</b> (5) *Cross <b>60</b> (5) *Cross <b>60</b> (5) *Cross <b>60</b> (5) *Cross <b>60</b> (5) *Cross <b>60</b> (5) *Cross <b>60</b> (5) *Cross <b>60</b> (5) *Cross <b>60</b> (5) *Cross <b>60</b> (5) *Cross <b>60</b> (5) *Cross <b>60</b> (5) *Cross <b>60</b> (5) *Cross <b>60</b> (5) *Cross <b>60</b> (5) *Cross <b>60</b> (5) *Cross <b>60</b> (5) *Cross <b>60</b> (5) *Cross <b>60</b> (5) *Cross <b>60</b> (5) *Cross <b>60</b> (5) *Cross <b>60</b> (5) *Cross <b>60</b> (5) *Cross <b>60</b> (5) *Cross <b>60</b> (5) *Cross <b>60</b> (5) *Cross <b>60</b> (5) *Cross <b>60</b> (5) *Cross <b>60</b> (5) *Cross <b>60</b> (5) *Cross <b>60</b> (5) *Cross <b>60</b> (5) *Cross <b>60</b> (5) *Cross <b>60</b> (5) *Cross <b>60</b> (5) *Cross <b>60</b> (5) *Cross <b>60</b> (5) *Cross <b>60</b> (5) *Cross <b>60</b> (5) *Cross <b>60</b> (5) *Cross <b>60</b> (5) *Cross <b>60</b> (5) *Cross <b>60</b> (5) *Cross <b>60</b> (5) *Cross <b>60</b> (5) *Cross <b>60</b> (5) *Cross <b>60</b> (5) *Cross <b>60</b> (5) *Cross <b>60</b> (5) *Cross <b>60</b> (5) *Cross <b>60</b> (5) *Cross <b>60</b> (5) *Cross <b>60</b> (5) *Cross <b>60</b> (5) *Cross <b>60</b> (5) *Cross <b>60</b> (5) *Cross <b>60</b> (5) *Cross <b>60</b> (5)		(1) *Crossover						
60 (4) *Crostpoor peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml (5) Vaginal delivery sample		(3) *Crossover			4			
	60	(4) *Crostro@r peer rev (5) Vaginal delivery sample	iew only	- nttp:/	/bm	jopen.	pmj.com/site/a	about/guidelines.xhtml

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7.10.1 Acute Pain	Mean	SD	ıotal	Mean	SD	ıotal	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Cipriano, et al., 2014	10	5	20	80	30	18	0.9%	-3.27 [-4.28, -2.27]	
Mora, et al., 2006	33.3	16	39	82.6	14.3	34	1.1%	-3.20 [-3.91, -2.50]	
Bertalanffy, et al., 2005 Tokuda, et al., 2014	49 5.9	8 6.5	30 16	77 23.8	11 5.9	33 16	1.1% 0.9%	-2.85 [-3.57, -2.14] -2.81 [-3.82, -1.80]	
Shahoei, et al., 2014	5.9 49	25	30	23.0 97	5.9 5.9	30	1.1%	-2.61 [-3.31, -1.91]	<u> </u>
Ahmed, et al., 2010	49.3	7	30	66.1	6.9	30	1.1%	-2.39 [-3.06, -1.71]	
Barker, et al., 2006	32.4 59	18 6	29 30	66.2 79	11.2 11	33 33	1.1% 1.1%	-2.26 [-2.91, -1.61]	
Lang, et al., 2007 Desantana, et al., 2008	59 9	6 10.7	30 20	79 48	11 22.7	33 20	1.1% 1.0%	-2.20 [-2.83, -1.57] -2.15 [-2.95, -1.36]	
Kim, et al., 2012	19	12	50	48	15	50	1.2%	-2.12 [-2.61, -1.63]	
Baez-Suarez, et al., 2018	62	14	21	83	12	21	1.1%	-1.58 [-2.28, -0.88]	
Desantana, et al., 2009 Jaafarpour, et al., 2008	43 5	15.3 5	23 54	66.5 12	14.7 4.2	21 54	1.1% 1.2%	-1.54 [-2.22, -0.86] -1.51 [-1.93, -1.08]	
Amer-Cuenca, et al., 2008	26.5	5 24.7	54 30	61.9	4.2 23.2	54 30	1.2%	-1.46 [-2.03, -0.88]	<u> </u>
Sadala, et al., 2018	29.3	19.5	28	56.8	17.7	27	1.1%	-1.45 [-2.05, -0.86]	
Park, et al., 2015 Ordea, 1987	15	15	48	45	25	50 25	1.2%	-1.44 [-1.88, -0.99]	<u> </u>
Ordog, 1987 Luchesa, et al., 2009	30.4 5	2.8 6	25 15	54.8 21	25 15.4	25 15	1.1% 1.0%	-1.35 [-1.97, -0.73] -1.33 [-2.13, -0.53]	
Cipriano, et al., 2009	20	7.4	23	30	15.4 7.4	22	1.1%	-1.33 [-2.13, -0.53] -1.33 [-1.98, -0.68]	<u> </u>
Da Silva, et al., 2015	1	0.795	21	4	3.18	21	1.1%	-1.27 [-1.94, -0.60]	
Mahure, et al., 2017 Kayman Kasa, et al. 2014 (1)	36	21	15	58	12	15	1.0%	-1.25 [-2.04, -0.46]	- <u>-</u>
Kayman-Kose, et al., 2014 (1) Lison, et al., 2017	17.7 23.2	12.7 31.4	50 46	37.4 53.1	20.6 19.9	50 46	1.2% 1.2%	-1.14 [-1.57, -0.72] -1.13 [-1.57, -0.69]	
Lison, et al., 2017 Liu, et al., 1985	23.2 39.3	17.9	46	65.3	26.6	46	1.1%	-1.12 [-1.89, -0.34]	<u> </u>
Cuschieri, et al., 1987	30	11.25	10	49	20.25	10	1.0%	-1.11 [-2.07, -0.15]	<u> </u>
Emmiler, et al., 2008	24	11.8	20	39	14.8	20	1.1%	-1.10 [-1.77, -0.43]	
Abreu, et al., 2010 Chandra, et al., 2010	68 7	23 5.3	10 30	88 14.7	10 8.6	10 30	1.0% 1.2%	-1.08 [-2.03, -0.13] -1.06 [-1.61, -0.52]	
Pitangui, et al., 2010	/ 17.2	5.3 21.9	30	14.7 38.8	20.8	30 10	1.2%	-0.97 [-1.89, -0.05]	
Yilmaz et al., 2019	7.3	9.8	26	20	15.7	26	1.2%	-0.96 [-1.53, -0.38]	
Aminisaman et al., 2020	26.6	5.4	30	31.2	4.8	30	1.2%	-0.89 [-1.42, -0.36]	
Oncel, et al., 2002 Elboim et al., 2020	24 41.7	13 19.2	25 23	39 61.2	20 25	25 18	1.2% 1.1%	-0.88 [-1.46, -0.29] -0.87 [-1.52, -0.22]	
Zakariaee et al., 2019	31.8	20.4	40	47.5	16.5	40	1.1%	-0.84 [-1.30, -0.38]	
Domaille & Reeves, 1997	30.33	8.14	31	47	28.14	29	1.2%	-0.81 [-1.33, -0.28]	
Fiorelli, et al., 2012	39 25.1	8	23	45	7	23	1.1%	-0.78 [-1.39, -0.18]	
Likar et al. 2001 Warfield, et al., 1985	25.1 48.3	7.6 20.1	11 12	29.7 64.2	4.8 24.6	12 12	1.0% 1.0%	-0.70 [-1.55, 0.14] -0.68 [-1.51, 0.14]	
Fujii-Abe et al., 2019	22.1	12.8	11	30.3	11.2	11	1.0%	-0.66 [-1.52, 0.21]	+
Bjersa, et al., 2015	13	16	15	26	24	13	1.1%	-0.63 [-1.39, 0.14]	
Bjersa & Andersson, 2014	19.4	32.5	9	39.6	32	11	1.0%	-0.60 [-1.51, 0.30]	
Sezen, et al., 2017 Galli, et al., 2015	36.9 21	7.2 16	43 37	42 29	10.1 22	44 37	1.2% 1.2%	-0.58 [-1.00, -0.15] -0.41 [-0.87, 0.05]	
Ferreira, et al., 2015	18	18	15	29 25	18	15	1.1%	-0.38 [-1.10, 0.34]	<del></del> +
Rakel & Frantz, 2003 (2)	42	33.45	33	55	37.3	33	1.2%	-0.36 [-0.85, 0.12]	+
Hruby, et al., 2006 Rebinson et al., 2001	35	28.8	48	43.7	30.6	49 12	1.2%	-0.29 [-0.69, 0.11]	
Robinson, et al., 2001 Hamza, et al., 1999	38.2 25	31.24 23	10 25	47.92 31	36.37 25	13 25	1.0% 1.2%	-0.27 [-1.10, 0.56] -0.25 [-0.80, 0.31]	
Cuschieri, et al., 1999	25	23	53	28	21.8	53	1.2%	-0.14 [-0.52, 0.24]	+
Forster, et al., 1994	9.8	28.1	15	13.7	31.9	15	1.1%	-0.13 [-0.84, 0.59]	-+-
Yilmazer, et al., 2012 Thomas, et al., 1988	54.6	32.1	33	57.5	30.5	32 144	1.2%	-0.09 [-0.58, 0.40]	1
Thomas, et al., 1988 Presser, et al., 2000	33 47	31.1 38.34	131 30	35 49	33.8 27.39	144 30	1.3% 1.2%	-0.06 [-0.30, 0.18] -0.06 [-0.57, 0.45]	+
Tucker, et al., 2015	56	56	35	49 57	57	35	1.2%	-0.02 [-0.49, 0.45]	+
Lee, et al., 2015	55.6	9.2	18	54.4	12.9	18	1.1%	0.10 [-0.55, 0.76]	+
Silva, et al., 2012 Reclamón et al., 2018	22.5	11.5	21	20	12.5	21	1.1%	0.20 [-0.40, 0.81]	±
Beckwée, et al., 2018 Kayman-Kose, et al., 2014 (3)	39.2 13.5	25.1 5.8	25 50	30.6 7.8	23.2 7	28 50	1.2% 1.2%	0.35 [-0.19, 0.90] 0.88 [0.47, 1.29]	
Heterogeneity: Tau <sup>2</sup> = 0.64; Ch			1667 57 (P <	0.0000	01); I² =	1681 38%	65.0%	-1.02 [-1.25, -0.80]	•
Subtotal (95% CI) Heterogeneity: Tau <sup>2</sup> = 0.64; Ch Test for overall effect: Z = 9.03 7.10.2 Chronic Pain Ratharia et al. 2010	(P < 0.00	001)	57 (P <		,-	88%			•
Heterogeneity: Tau <sup>2</sup> = 0.64; Ch Test for overall effect: Z = 9.03				0.0000 39 72	11); I <sup>2</sup> = - 1.19 18.7		0.1% 1.1%	-1.02 [-1.25, -0.80] -12.50 [-17.39, -7.61] <b>4</b> -3.11 [-3.78, -2.44]	• 
Heterogeneity: Tau <sup>2</sup> = 0.64; Ch Test for overall effect: Z = 9.03 7.10.2 Chronic Pain Barbarisi, et al., 2010	(P < 0.00 25.11	0001)	57 (P < 9	39	1.19	88%	0.1%	-12.50 [-17.39, -7.61]	
Heterogeneity: Tau <sup>2</sup> = 0.64; Ch Test for overall effect: Z = 9.03 7.10.2 Chronic Pain Barbarisi, et al., 2010 Hokenek et al., 2019 Lauretti, et al., 2015 Ekim et al., 2008	(P < 0.00 25.11 22 20 47.2	0.92 12.49	9 9 39 20 10	39 72 70 65.3	1.19 18.7 20 6.3	88% 8 39 20 9	0.1% 1.1% 1.0% 0.7%	-12.50 [-17.39, -7.61] 4 -3.11 [-3.78, -2.44] -3.10 [-4.05, -2.15] -2.91 [-4.29, -1.54]	
Heterogeneity: Tau <sup>2</sup> = 0.64; Ch Test for overall effect: Z = 9.03 <b>7.10.2 Chronic Pain</b> Barbarisi, et al., 2010 Hokenek et al., 2010 Lauretti, et al., 2015 Ekim et al., 2008 Dailey, et al., 2013 (4)	(P < 0.00 25.11 22 20 47.2 40	0.92 12.49 10 5.6 4	9 9 39 20 10 41	39 72 70 65.3 47	1.19 18.7 20 6.3 4	88% 8 39 20 9 41	0.1% 1.1% 1.0% 0.7% 1.2%	-12.50 [-17.39, -7.61] -3.11 [-3.78, -2.44] -3.10 [-4.05, -2.15] -2.91 [-4.29, -1.54] -1.73 [-2.24, -1.22]	
Heterogeneity: Tau <sup>2</sup> = 0.64; Ch Test for overall effect: Z = 9.03 <b>7.10.2 Chronic Pain</b> Barbarisi, et al., 2010 Hokenek et al., 2019 Lauretti, et al., 2015 Ekim et al., 2008 Dailey, et al., 2013 (4) Kibar et al., 2020	(P < 0.00 25.11 22 20 47.2	0.92 12.49 10	9 9 39 20 10	39 72 70 65.3	1.19 18.7 20 6.3	88% 8 39 20 9	0.1% 1.1% 1.0% 0.7%	-12.50 [-17.39, -7.61] 4 -3.11 [-3.78, -2.44] -3.10 [-4.05, -2.15] -2.91 [-4.29, -1.54]	
Heterogeneity: Tau <sup>2</sup> = 0.64; Ch Test for overall effect: Z = 9.03 7.10.2 Chronic Pain Barbarisi, et al., 2010 Hokenek et al., 2010 Lauretti, et al., 2019 Ekim et al., 2008 Dailey, et al., 2013 (4) Kibar et al., 2020 Zhang et al., 2020 De Oliverira et al., 2012	(P < 0.00 25.11 22 20 47.2 40 21.2 17 30	0.92 12.49 10 5.6 4 12.2 3 16.4	9 39 20 10 41 31 10 5	39 72 70 65.3 47 47.6 31 54	1.19 18.7 20 6.3 4 19.6 12.6 13.6	88% 8 39 20 9 41 30 10 5	0.1% 1.1% 1.0% 0.7% 1.2% 1.2% 0.9% 0.7%	-12.50 [-17.39, -7.61] 4 -3.11 [-3.78, -2.44] -3.10 [-4.05, -2.15] -2.91 [-4.29, -1.54] -1.73 [-2.24, -1.22] -1.60 [-2.18, -1.02] -1.46 [-2.48, -0.45] -1.44 [-2.92, 0.04]	
Heterogeneity: Tau <sup>2</sup> = 0.64; Ch Test for overall effect: Z = 9.03 7.10.2 Chronic Pain Barbarisi, et al., 2010 Hokenek et al., 2019 Lauretti, et al., 2019 Lauretti, et al., 2019 Dailey, et al., 2018 Dailey, et al., 2020 Zhang et al., 2020 De Oliverira et al., 2012 Bi, et al., 2015	(P < 0.00 25.11 22 20 47.2 40 21.2 17 30 21.4	0.92 12.49 10 5.6 4 12.2 3 16.4 9.1	57 (P < 9 39 20 10 41 31 10 5 26	39 72 70 65.3 47 47.6 31 54 38.7	1.19 18.7 20 6.3 4 19.6 12.6 13.6 14.5	88% 8 39 20 9 41 30 10 5 26	0.1% 1.1% 1.0% 0.7% 1.2% 0.9% 0.7% 1.1%	-12.50 [-17.39, -7.61] 4 -3.11 [-3.78, -2.44] -3.10 [-4.05, -2.15] -2.91 [-4.29, -1.54] -1.73 [-2.24, -1.22] -1.60 [-2.48, -1.02] -1.46 [-2.48, -1.04] -1.44 [-2.02, -0.80]	
Heterogeneity: Tau <sup>2</sup> = 0.64; Ch Test for overall effect: Z = 9.03 7.10.2 Chronic Pain Barbarisi, et al., 2010 Hokenek et al., 2010 Hokenek et al., 2010 Hokenek, et al., 2010 Dailey, et al., 2013 (4) Kibar et al., 2020 De Oliverira et al., 2012 Bi, et al., 2015 Topuz, et al., 2004	(P < 0.00 25.11 22 20 47.2 40 21.2 17 30 21.4 37.3	0.92 12.49 10 5.6 4 12.2 3 16.4 9.1 16.2	57 (P < 9 39 20 10 41 31 10 5 26 15	39 72 70 65.3 47 47.6 31 54 38.7 59.1	1.19 18.7 20 6.3 4 19.6 12.6 13.6 13.6 14.5 13.7	88% 8 39 20 9 41 30 10 5 26 12	0.1% 1.1% 1.0% 1.2% 1.2% 0.9% 0.7% 1.1% 1.0%	-12.50 [-17.39, -7.61] 4 -3.11 [-3.78, -2.44] -3.10 [-4.05, -2.15] -2.91 [-4.29, -1.54] -1.73 [-2.24, -1.22] -1.60 [-2.18, -1.02] -1.46 [-2.48, -0.45] -1.44 [-2.92, 0.04] -1.41 [-2.02, -0.80] -1.40 [-2.25, -0.54]	
Heterogeneity: Tau <sup>2</sup> = 0.64; Ch Test for overall effect: Z = 9.03 7.10.2 Chronic Pain Barbarisi, et al., 2010 Hokenek et al., 2010 Lauretti, et al., 2015 Ekim et al., 2015 Dailey, et al., 2013 (4) Kibar et al., 2020 De Oliverira et al., 2012 Bi, et al., 2015 Topuz, et al., 2004 Celik, et al., 2013	(P < 0.00 25.11 22 20 47.2 40 21.2 17 30 21.4 37.3 38.8	0.92 12.49 10 5.6 4 12.2 3 16.4 9.1 16.2 25	57 (P < 9 39 20 10 41 31 10 5 26 15 17	39 72 70 65.3 47 47.6 31 54 38.7 59.1 67.7	1.19 18.7 20 6.3 4 19.6 12.6 13.6 14.5 13.7 14.2	88% 8 39 20 9 41 30 10 5 26 12 16	0.1% 1.1% 1.0% 0.7% 1.2% 0.9% 0.7% 1.1% 1.0%	-12.50 [-17.39, -7.61] 4 -3.11 [-3.78, -2.44] -3.10 [-4.05, -2.15] -2.91 [-4.29, -1.54] -1.73 [-2.24, -1.22] -1.60 [-2.18, -1.02] -1.46 [-2.48, -0.45] -1.44 [-2.92, 0.04] -1.41 [-2.02, -0.80] -1.40 [-2.25, -0.54] -1.38 [-2.14, -0.61]	
Heterogeneity: Tau <sup>2</sup> = 0.64; Ch Test for overall effect: Z = 9.03 <b>7.10.2 Chronic Pain</b> Barbarisi, et al., 2010 Hokenek et al., 2010 Hokenek et al., 2019 Lauretti, et al., 2015 Ekim et al., 2008 Dailey, et al., 2020 Dailey, et al., 2020 De Oilverira et al., 2012 Bi, et al., 2015 Topuz, et al., 2013 Lauretti, et al., 2013	(P < 0.00 25.11 22 20 47.2 40 21.2 17 30 21.4 37.3	0.92 12.49 10 5.6 4 12.2 3 16.4 9.1 16.2	57 (P < 9 39 20 10 41 31 10 5 26 15	39 72 70 65.3 47 47.6 31 54 38.7 59.1	1.19 18.7 20 6.3 4 19.6 12.6 13.6 14.5 13.7 14.2 20	88% 8 39 20 9 41 30 10 5 26 12	0.1% 1.1% 1.0% 1.2% 1.2% 0.9% 0.7% 1.1% 1.0%	-12.50 [-17.39, -7.61] 4 -3.11 [-3.78, -2.44] -3.10 [-4.05, -2.15] -2.91 [-4.29, -1.54] -1.73 [-2.24, -1.22] -1.60 [-2.18, -1.02] -1.46 [-2.48, -0.45] -1.44 [-2.92, 0.04] -1.41 [-2.02, -0.80] -1.40 [-2.25, -0.54]	
Heterogeneity: Tau <sup>2</sup> = 0.64; Ch Test for overall effect: Z = 9.03 <b>7.10.2 Chronic Pain</b> Barbarisi, et al., 2010 Hokenek et al., 2019 Lauretti, et al., 2019 Lauretti, et al., 2019 Dailey, et al., 2013 Dailey, et al., 2013 Dailey, et al., 2020 Zhang et al., 2020 De Oliverira et al., 2012 Bi, et al., 2015 Topuz, et al., 2013 Lauretti, et al., 2013 Suh, et al., 2015 Neighbours, et al., 1987	(P < 0.00 25.11 22 20 47.2 17 30 21.4 37.3 38.8 60 18.7 17.5	0.92 12.49 10 5.6 4 12.2 3 16.4 9.1 16.2 25 10 7.46 30.3	57 (P < 9 39 20 10 41 31 5 26 15 15 17 13 24 10	39 72 70 65.3 47 47.6 31 54 38.7 59.1 67.7 80 30.7 40.7	1.19 18.7 20 6.3 4 19.6 12.6 13.6 13.5 13.7 14.2 20 17.67 20.74	88% 8 39 20 9 41 30 10 5 26 12 12 16 10 23 10	0.1% 1.0% 0.7% 1.2% 1.2% 0.9% 0.7% 1.1% 1.0% 1.1% 1.0%	-12.50 [-17.39, -7.61] 4 -3.10 [-4.05, -2.15] -2.91 [-4.29, -1.54] -1.73 [-2.24, -1.22] -1.60 [-2.18, -1.02] -1.46 [-2.48, -0.45] -1.44 [-2.02, -0.80] -1.41 [-2.02, -0.80] -1.40 [-2.25, -0.54] -1.38 [-2.14, -0.61] -1.28 [-2.19, -0.36] -0.88 [-1.48, -0.28] -0.88 [-1.78, 0.07]	
Heterogeneity: Tau <sup>2</sup> = 0.64; Ch Test for overall effect: Z = 9.03 <b>7.10.2 Chronic Pain</b> Barbarisi, et al., 2010 Hokenek et al., 2019 Lauretti, et al., 2019 Dailey, et al., 2015 Ekim et al., 2008 Dailey, et al., 2020 De Oliverira et al., 2012 Bi, et al., 2015 Topuz, et al., 2014 Celik, et al., 2015 Suh, et al., 2015 Suh, et al., 2015 Suh, et al., 2015 Neighbours, et al., 1987 Vitalii & Oleg, 2014	(P < 0.00 25.11 22 20 47.2 40 21.2 17 30 21.4 37.3 38.8 60 18.7 717.5 39.5	0.92 12.49 10 5.6 4 12.2 3 16.4 9.1 16.2 25 10 7.46 30.3 17	57 (P < 9 39 20 10 41 31 5 26 15 15 15 17 13 24 10 11	39 72 70 65.3 47 47.6 31 54 38.7 59.1 67.7 80 30.7 40.7 52.5	1.19 18.7 20 6.3 4 19.6 12.6 13.6 14.5 13.7 14.2 20 17.67 20.74 18.6	88% 8 39 20 9 41 30 10 5 26 12 16 12 16 23 10 23	0.1% 1.1% 1.0% 0.7% 1.2% 0.9% 0.7% 1.1% 1.0% 1.1% 1.0% 1.1% 1.0%	-12.50 [-17.39, -7.61] 4 -3.11 [-3.78, -2.44] -3.10 [-4.05, -2.15] -2.91 [-4.29, -1.54] -1.73 [-2.24, -1.22] -1.60 [-2.18, -1.02] -1.44 [-2.92, 0.04] -1.41 [-2.02, 0.80] -1.40 [-2.25, -0.54] -1.38 [-2.14, -0.61] -1.28 [-2.19, -0.36] -0.86 [-1.78, 0.07] -0.70 [-1.59, 0.19]	
Heterogeneity: Tau <sup>2</sup> = 0.64; Ch Test for overall effect: Z = 9.03 <b>7.10.2 Chronic Pain</b> Barbarisi, et al., 2010 Hokenek et al., 2010 Hokenek et al., 2019 Lauretti, et al., 2015 Ekim et al., 2008 Dailey, et al., 2000 De Oliverira et al., 2020 De Oliverira et al., 2020 De Oliverira et al., 2020 De Oliverira et al., 2012 Bi, et al., 2015 Topuz, et al., 2015 Copuz, et al., 2015 Neighbours, et al., 1987 Vitalii & Oleg, 2014 Biglii, et al., 2016	(P < 0.00 25.11 22 20 47.2 40 21.2 17 30 21.4 37.3 38.8 60 18.7 17.5 39.5 14.27	0.92 12.49 10 5.6 4 12.2 3 16.4 9.1 16.2 25 10 7.46 30.3 17 10.1	57 (P < 9 39 20 10 41 31 5 26 15 15 15 17 13 24 10 11	39 72 70 65.3 47 47.6 31 54 38.7 59.1 67.7 80 30.7 40.7 52.5 23.27	1.19 18.7 20 6.3 4 19.6 12.6 13.6 14.5 13.7 14.2 20 17.67 20.74 18.6 15.8	88% 8 39 20 9 41 30 10 5 26 12 16 10 23 10 10 10 15	0.1% 1.1% 1.0% 0.7% 1.2% 0.9% 0.7% 1.1% 1.0% 1.1% 1.0% 1.1% 1.0%	-12.50 [-17.39, -7.61] 4 -3.11 [-3.78, -2.44] -3.10 [-4.05, -2.15] -2.91 [-4.29, -1.54] -1.73 [-2.24, -1.22] -1.60 [-2.18, -1.02] -1.46 [-2.48, -0.45] -1.44 [-2.92, 0.04] -1.41 [-2.25, -0.54] -1.38 [-2.14, -0.61] -1.28 [-2.19, -0.36] -0.88 [-1.48, -0.28] -0.86 [-1.48, -0.07] -0.70 [-1.59, 0.19] -0.66 [-1.40, 0.08]	
Heterogeneity: Tau <sup>2</sup> = 0.64; Ch Test for overall effect: Z = 9.03 <b>7.10.2 Chronic Pain</b> Barbarisi, et al., 2010 Hokenek et al., 2010 Lauretti, et al., 2015 Ekim et al., 2008 Dailey, et al., 2008 Dailey, et al., 2013 (4) Kibar et al., 2020 De Oliverira et al., 2012 Bi, et al., 2020 De Oliverira et al., 2012 Bi, et al., 2014 Celik, et al., 2014 Celik, et al., 2013 Suh, et al., 2015 Neighbours, et al., 1987 Vitali & Oleg, 2014 Biglii, et al., 2016 Shimoura, et al., 2019 Liu, et al., 2017	(P < 0.00 25.11 22 20 47.2 40 21.2 17 30 21.4 37.3 38.8 60 18.7 717.5 39.5	0.92 12.49 10.5.6 4 12.2 3 16.4 9.1 16.2 25 10 7.46 30.3 17 10.1 8 17.7	9 9 39 20 10 41 31 31 31 31 5 26 5 15 17 13 24 10 11 5 25 22 22	39 72 700 65.3 47 47.6 31 54 38.7 59.1 67.7 80 30.7 40.7 52.5 23.27 11.4 55.8	1.19 18.7 20 6.3 4 19.6 12.6 13.6 13.6 13.7 14.2 20 17.67 20.74 18.6 15.8 10.9 12.6	888% 8 399 200 9 9 41 300 100 5 266 12 12 12 16 10 23 100 105 25 222	0.1% 1.0% 0.7% 1.2% 1.2% 0.9% 0.7% 1.1% 1.0% 1.1% 1.0% 1.0% 1.0% 1.0% 1.2% 1.1%	-12.50 [-17.39, -7.61] 4 -3.11 [-3.78, -2.44] -3.10 [-4.05, -2.15] -2.91 [-4.29, -1.54] -1.73 [-2.24, -1.22] -1.60 [-2.18, -1.02] -1.46 [-2.48, -0.45] -1.44 [-2.92, 0.04] -1.41 [-2.02, -0.80] -1.40 [-2.25, -0.54] -1.38 [-2.14, -0.61] -1.28 [-2.14, -0.61] -1.28 [-2.14, -0.61] -0.86 [-1.78, 0.07] -0.70 [-1.59, 0.19] -0.66 [-1.40, 0.08] -0.65 [-1.22, -0.08] -0.65 [-1.22, -0.08]	
Heterogeneity: Tau <sup>2</sup> = 0.64; Ch Test for overall effect: Z = 9.03 <b>7.10.2 Chronic Pain</b> Barbarisi, et al., 2010 Hokenek et al., 2019 Lauretti, et al., 2015 Ekim et al., 2008 Dailey, et al., 2015 Kibar et al., 2020 Zhang et al., 2020 Zhang et al., 2020 Zhang et al., 2020 Celik, et al., 2015 Topuz, et al., 2015 Goltz, et al., 2013 Suh, et al., 2015 Sub, et al., 2015 Sub, et al., 2015 Sub, et al., 2015 Shimoura, et al., 2019 Shimoura, et al., 2019 Liu, et al., 2019 Liu, et al., 2017	(P < 0.00 25.11 22 20 40 21.2 17 30 21.4 37.3 38.8 60 18.7 17.5 39.5 14.27 5.1 48.2 22	0001) 12.49 10 5.6 4 12.2 3 16.4 9.1 16.2 25 10 7.46 30.3 17 10.1 8 17.7 28	57 (P < 9 39 20 10 41 31 10 5 26 15 17 13 32 4 4 10 11 11 5 25 22 22 20	39 72 70 65.3 47 47.6 31 54 38.7 59.1 67.7 80 30.7 40.7 52.5 23.27 11.4 55.8 35	1.19 18.7 20 6.3 4 19.6 12.6 13.6 14.5 13.7 14.2 20 17.67 20.74 18.6 15.8 10.9 12.6 29	88% 8 8 39 20 9 41 30 100 5 26 12 16 10 5 23 10 10 10 15 5 22 22 20	0.1% 1.1% 1.0% 0.7% 1.2% 1.2% 1.2% 1.1% 1.0% 1.1% 1.0% 1.1% 1.0% 1.1% 1.2%	-12.50 [-17.39, -7.61] 4 -3.10 [-4.05, -2.15] -2.91 [-4.29, -1.54] -1.73 [-2.24, -1.22] -1.60 [-2.18, -1.02] -1.46 [-2.48, -0.45] -1.44 [-2.02, -0.80] -1.41 [-2.02, -0.80] -1.48 [-2.14, -0.61] -1.28 [-2.14, -0.61] -1.28 [-2.14, -0.61] -0.86 [-1.78, -0.07] -0.70 [-1.59, -0.19] -0.66 [-1.40, -0.08] -0.45 [-1.09, -0.11] -0.45 [-1.08, 0.11]	
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Heterogeneity: Tau <sup>2</sup> = 0.64; Ch Test for overall effect: Z = 9.03 <b>7.10.2 Chronic Pain</b> Barbaris, iet al., 2010 Hokenek et al., 2010 Hokenek et al., 2019 Lauretti, et al., 2019 Lauretti, et al., 2018 Ekim et al., 2008 Dailey, et al., 2018 Dailey, et al., 2020 De Oliverira et al., 2012 Bi, et al., 2015 Topuz, et al., 2013 Duretti, et al., 2013 Suh, et al., 2015 Neighbours, et al., 2013 Suh, et al., 2015 Nitalii & Oleg, 2014 Biglil, et al., 2018 Shimoura, et al., 2019 Liu, et al., 2019 Dialey et al., 2020	(P < 0.00 25.11 22 20 40 21.2 17 30 21.4 37.3 38.8 60 18.7 17.5 39.5 14.27 5.1 48.2 22	0001) 12.49 10 5.6 4 12.2 3 16.4 9.1 16.2 25 10 7.46 30.3 17 10.1 8 17.7 28	57 (P < 9 39 20 10 41 31 10 5 5 26 15 15 17 13 34 40 11 15 25 22 20 20 103	39 72 70 65.3 47.6 31 54 38.7 59.1 67.7 80 30.7 40.7 52.5 23.27 11.4 55.8 53 40.33	1.19 18.7 20 6.3 4 19.6 12.6 13.6 14.5 13.7 14.2 20 17.67 20.74 18.6 15.8 10.9 12.6 29	88% 8 8 39 20 9 41 30 100 5 26 12 16 10 5 23 10 10 10 15 5 22 22 20	0.1% 1.1% 1.0% 0.7% 1.2% 1.2% 1.2% 1.1% 1.0% 1.1% 1.0% 1.1% 1.0% 1.1% 1.2%	-12.50 [-17.39, -7.61] 4 -3.10 [-4.05, -2.15] -2.91 [-4.29, -1.54] -1.73 [-2.24, -1.22] -1.60 [-2.18, -1.02] -1.46 [-2.48, -0.45] -1.44 [-2.02, -0.80] -1.41 [-2.02, -0.80] -1.48 [-2.14, -0.61] -1.28 [-2.14, -0.61] -1.28 [-2.14, -0.61] -0.86 [-1.78, -0.07] -0.70 [-1.59, -0.19] -0.66 [-1.40, -0.08] -0.45 [-1.09, -0.11] -0.45 [-1.08, 0.11]	• ++++++++++++++++++++++++++++++++++++
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Heterogeneity: Tau <sup>2</sup> = 0.64; Ch Test for overall effect: Z = 9.03 <b>7.10.2 Chronic Pain</b> Barbaris, iet al., 2010 Hokenek et al., 2011 Lauretti, et al., 2019 Lauretti, et al., 2019 Lauretti, et al., 2019 Dailey, et al., 2015 Kibar et al., 2020 De Oliverira et al., 2012 Bi, et al., 2020 De Oliverira et al., 2012 Bi, et al., 2015 Colik, et al., 2013 Suh, et al., 2013 Suh, et al., 2013 Neighbours, et al., 1987 Vitali & Oleg, 2014 Biglii, et al., 2016 Shimoura, et al., 2019 Liu, et al., 2016 Shimoura, et al., 2019 Dailey et al., 2020 Warke, et al., 2014 Machin, et al., 2020 Warke, et al., 2007 Graff-Radford, et al., 1989 Sahin, et al., 2011 Ilhani, 2015 Bono, et al., 2011 Bono, et al., 2011 Kofotolis, et al., 2019 Atamaz, et al., 2018	(P < 0.00 25.11 22.12 20 20 47.2 20 40 47.2 40 47.2 40 47.2 30 38.8 80 60 61.87 71.55 33.88 80 60 61.87 71.55 34.22 46.42 40.58 82.33 88.5 40.58 82.43 80.33 88.5 82.44 40.58 82.33 86.5 40.58 82.45 82.25 82.45 8	0001) 0.922 12.49 10 5.6 4 12.2 3 16.4 9.1 16.2 25 10 7.46 30.3 17 10.1 8 17 7.46 30.3 17 10.1 8 10 27.55 13.72 27.55 18.06 15.5 11.3 20 25 24.11 4 20 25 24.19 27.55 13.72 27.55 24.11 20 27.55 24.11 20 27.55 24.11 20 27.55 24.11 20 27.55 24.11 20 27.55 24.11 20 27.55 24.11 20 27.55 24.11 20 20 27.55 24.11 20 20 20 20 20 20 20 20 20 20	57 (P < 9 9 9 20 10 41 11 10 5 26 15 7 13 24 4 10 11 15 22 20 10 13 14 15 26 15 7 13 24 10 11 15 26 20 10 10 10 10 10 10 10 10 10 1	399 72 70 65.3 47.6 31 54 80 30.7 52.5 23.27 11.4 55.8 35 53 31.6 29.2 40.33 16.29 44.81 40 30.2 22.8 80 0 30.5 22.8 80 0 30.2 28 46 50.4 20 50.4 20 50.4 20 50.4 51.5 51.5 51.5 51.5 51.5 51.5 51.5 51	1.19 18.7 20 6.3 4 19.6 13.6 13.6 13.6 13.6 13.6 13.6 13.6 14.2 20 17.67 20.74 18.6 15.8 29 19.9 19.9 19.9 19.9 19.9 19.9 19.9 1	88% 8 8 8 9 9 41 10 10 12 26 12 12 10 10 12 26 12 12 10 10 15 22 20 9 3 15 22 20 9 3 15 22 20 9 9 30 10 10 10 15 26 20 12 12 12 12 10 10 15 26 12 12 12 10 10 10 15 26 20 12 12 10 10 10 15 26 20 10 10 10 15 26 20 10 10 10 10 10 10 10 10 10 1	0.1% 1.1% 1.2% 0.7% 1.2% 0.9% 1.0% 1.0% 1.1% 1.0% 1.1% 1.2% 1.1% 1.2% 1.1% 1.2% 1.1% 1.2% 1.2	$\begin{array}{c} -12.50 \left[ -17.39, -7.61 \right] & 4\\ -3.11 \left[ -3.78, -2.44 \right] \\ -3.10 \left[ -4.05, -2.15 \right] \\ -2.91 \left[ -4.29, -1.54 \right] \\ -1.73 \left[ -2.24, -1.22 \right] \\ -1.60 \left[ -2.18, -1.02 \right] \\ -1.46 \left[ -2.48, -0.45 \right] \\ -1.44 \left[ -2.92, -0.04 \right] \\ -1.44 \left[ -2.92, -0.04 \right] \\ -1.41 \left[ -2.25, -0.54 \right] \\ -1.38 \left[ -2.14, -0.61 \right] \\ -1.28 \left[ -2.14, -0.61 \right] \\ -1.28 \left[ -2.14, -0.61 \right] \\ -0.88 \left[ -1.48, -0.28 \right] \\ -0.88 \left[ -1.78, 0.07 \right] \\ -0.70 \left[ -1.59, 0.19 \right] \\ -0.66 \left[ -1.29, -0.08 \right] \\ -0.66 \left[ -1.40, 0.08 \right] \\ -0.65 \left[ -1.22, -0.08 \right] \\ -0.45 \left[ -1.08, 0.11 \right] \\ -0.45 \left[ -1.08, 0.11 \right] \\ -0.45 \left[ -1.08, 0.12 \right] \\ -0.33 \left[ -0.63, -0.07 \right] \\ -0.33 \left[ -1.78, 1.12 \right] \\ -0.20 \left[ -0.92, -0.52 \right] \\ -0.14 \left[ -0.71, 0.42 \right] \\ -0.11 \left[ -0.71, 0.65 \right] \\ -0.04 \left[ -0.52, 0.45 \right] \\ -0.04 \left[ -0.52, 0.45 \right] \\ -0.04 \left[ -0.55, 0.63 \right] \\ -0.45 \left[ -0.27, 0.65 \right] \\ -0.44 \left[ -0.27, 0.65 \right] \\ -0.44 \left[ -0.27, 0.65 \right] \\ -0.44 \left[ -0.27, 0.65 \right] \\ -0.44 \left[ -0.27, 0.65 \right] \\ -0.44 \left[ -0.27, 0.65 \right] \\ -0.44 \left[ -0.27, 0.65 \right] \\ -0.44 \left[ -0.27, 0.65 \right] \\ -0.44 \left[ -0.27, 0.65 \right] \\ -0.44 \left[ -0.11, 1.09 \right] \\ -0.45 \left[ -0.27, 0.65 \right] \\ -0.44 \left[ -0.27, 0.65 \right] \\ -0.44 \left[ -0.11, 1.09 \right] \\ -0.45 \left[ -0.11$	
Heterogeneity: Tau <sup>2</sup> = 0.64; Ch Test for overall effect: Z = 9.03 <b>7.10.2 Chronic Pain</b> Barbarisi, et al., 2010 Hokenek et al., 2010 Hokenek et al., 2019 Lauretti, et al., 2015 Ekim et al., 2008 Dailey, et al., 2020 De Oliverira et al., 2012 Bi, et al., 2020 De Oliverira et al., 2013 Celik, et al., 2013 Suh, et al., 2015 Topuz, et al., 2014 Celik, et al., 2013 Suh, et al., 2015 Neighbours, et al., 2013 Suh, et al., 2015 Neighbours, et al., 2018 Dimours, et al., 2019 Liu, et al., 2019 Diu, et al., 2020 Warke, et al., 2020 Warke, et al., 2020 Warke, et al., 2020 Warke, et al., 2020 Warke, et al., 2020 Warke, et al., 2020 Warke, et al., 2020 Warke, et al., 2020 Warke, et al., 2015 Shimoji, et al., 2015 Machado et al., 2019 Atamaz, et al., 2015 Machado et al., 2019 Katamaz, et al., 2018 Subtotal (95% CI)	$\begin{array}{c} (P < 0.000\\ 25.11\\ 12\\ 20\\ 0\\ 21.2\\ 40\\ 21.2\\ 40\\ 21.2\\ 40\\ 21.2\\ 40\\ 21.4\\ 80\\ 21.4\\ 80\\ 21.4\\ 80\\ 80\\ 38\\ 80\\ 80\\ 80\\ 80\\ 80\\ 80\\ 80\\ 80\\ 80\\ 8$	0001) 0.922 12.49 10 5.6 4 12.2 3 16.4 9.1 16.2 25 5 10.7 4 30.3 17.7 28.2 27.55 13.72 27.55 15.6 10.5 10.7 27.55 15.6 10.5 20.7 10.7 27.55 10.5 10.7 20.7 10.7 27.55 10.7 20.7 10.7 27.55 10.7 20.7 27.55 10.7 20.7 27.55 10.7 20.7	57 (P < 9 9 309 200 411 311 311 311 5 266 155 177 15 222 200 103 103 5 5 155 225 220 103 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5	399 72 70 65.3 47 47.6 31 54 38.7 52 3.27 11.4 55.8 35 53 53 53 53 40.33 16.29 40.33 16.29 44.81 40 30.2 22.8 80 46 55,22 22.8 80 46 50.4 42 20 20 20 20 20 20 20 20 20 20 20 20 20	1.19 18.7 20 6.3 4 19.6 12.6 13.6 14.5 20 17.67 20.74 13.6 15.9 10.9 12.6 299 19.4 13.65 10.9 12.6 10.9 19.9 19.4 13.6 15.9 12.6 10.9 10.9 12.6 10.9 10.9 12.6 10.9 1	88% 8 8 39 20 9 41 30 15 266 12 16 10 10 15 22 20 9 3 15 5 26 4 8 11 10 15 22 20 9 3 15 5 26 8 8 12 16 16 12 16 16 12 16 16 12 16 16 12 23 10 10 15 26 20 12 16 16 12 20 10 12 16 16 10 10 10 10 10 10 10 10 10 10	0.1% 1.1% 1.0% 1.2% 0.7% 1.2% 0.7% 1.1% 1.0% 1.1% 1.0% 1.1% 1.2% 1.1% 1.2% 1.1% 1.2% 1.2% 1.1% 1.2%	-12.50 [-17.39, -7.61] -3.11 [-3.78, -2.44] -3.10 [-4.05, -2.15] -2.91 [-4.29, -1.54] -1.73 [-2.24, -1.22] -1.60 [-2.18, -1.02] -1.46 [-2.48, -0.45] -1.44 [-2.92, 0.04] -1.41 [-2.02, -0.80] -1.40 [-2.25, -0.54] -1.38 [-2.14, -0.61] -1.28 [-2.19, -0.36] -0.86 [-1.78, 0.07] -0.70 [-1.59, 0.19] -0.66 [-1.22, -0.08] -0.86 [-1.78, 0.07] -0.70 [-1.59, 0.19] -0.66 [-1.22, -0.08] -0.49 [-1.09, 0.11] -0.45 [-1.08, 0.18] -0.35 [-0.63, -0.07] -0.33 [-1.78, 1.12] -0.20 [-0.92, 0.52] -0.14 [-0.71, 0.42] -0.11 [-1.06, 0.84] -0.11 [-0.91, 0.68] -0.07 [-0.71, 0.56] -0.04 [-0.52, 0.45] -0.04 [-0.52, 0.63] 0.04 [-0.52, 0.63] 0.04 [-0.52, 0.63] 0.04 [-0.52, 0.63] -0.49 [-0.27, 0.65] -0.49 [-0.27, 0.65] -0.49 [-0.27, 0.65] -0.49 [-0.27, 0.65] -0.49 [-0.27, 0.65] -0.49 [-0.27, 0.65] -0.49 [-0.11, 1.09] -0.87 [-1.19, -0.55]	
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(1) Cesarian delivery sample (2) \*Crossover 

> (a) value delivery sample (a) \*ch@wpeer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml (5) \*Crossove

# **ONLINE TABLE 4**

# **Adverse Events**

Reference	Reference number	Extracted Text	AEs related to TENS	Statement	Extractable Data	Comment
(Abbasi et al., 2019)	1	No statements present	No information to extract	N	N	
(Abelson et al., 1983)	2	The only side effect was a slight skin irritation at the site of electrode placement in some of the patients in the transcutaneous electrical nerve stimulation treated group	Skin irritation due to electrodes	Y	N	No numerical data to extract
(Abreu et al., 2010)	3	No statements present	No information to extract	Ν	Ν	
(Acedo et al., 2015)	4	No statements present	No information to extract	Ν	Ν	
(Adedoyin et al., 2005)	5	No statements present	No information to extract	Ν	Ν	
(Ahmed, 2010)	6	Due to the absence of complications and adverse effects of TENS compared to conventional opioids and non-opioid analgesics, we suggest that TENS is a safe and reliable therapeutic procedure. – in Discussion	No information to extract	$\begin{array}{c} Y-0\\ tally \end{array}$	N – 0 tally	Unclear whether the statement on AEs was generic or in relation to the study findings
(Ahmed et al., 2020)	7	No statements present	No information to extract	Ν	Ν	
(Alcidi et al., 2007)	8	No statements present	No information to extract	Ν	Ν	
(Ali et al., 1981)	9	No statements present	No information to extract	Ν	Ν	
(Alizade and Ahmadizad, 2009)	10	No statements present	No information to extract	Ν	N	Only mentions potential irritation of skin in introductory section
(Allais et al., 2003)	11	No serious side effects occurred in any group during the study.	Reported no adverse events	Y – 0 tally	N-0 tally	
(Alm et al., 1979)	12	In our group of 75 patients we found no significant skin reactions	No information to extract	Ν	Ν	Only relates to skin reaction, not other AEs
(Al-Smadi et al., 2003)	13	No statements present	No information to extract	Ν	Ν	
(Altay et al., 2010)	14	No statements present	No information to extract	N	Ν	
(Alvarez-Arenal et al., 2002)	15	No statements present	No information to extract	Ν	Ν	
(Alves Silverio et al., 2015)	16	No statements present	No information to extract	N	N	
(Amer-Cuenca et al., 2011)	17	No subject reported adverse events such as skin allergy, pain or burning at the electrode site in either active TENS or placebo TENS groups.	Reported no adverse events	Y - 0 tally	N - 0 tally	
(AminiSaman et al., 2020)	18	No statements present	No information to extract	N	N	
(Angulo and Colwell Jr, 1990)	19	No statement present	No information to extract	Ν	N	
(Ardic et al., 2002)	20	No statements present	No information to extract	Ν	Ν	
(Arvidsson and Eriksson, 1986)	21	No statements present	No information to extract	Ν	N	Conclusion states that TENS lacks side-effects.
(Asgari et al., 2018)	22	Student's <i>t</i> -test and chi-square were applied to compare baseline characteristics and side effects among groups.	No information to extract	Ν	Ν	No mention of adverse events in results or discussion despite

Reference	Reference number	Extracted Text	AEs related to TENS	Statement	Extractable Data	Comment
						the method describing how these would be analysed
(Atamaz et al., 2012)	23	No statements present	No information to extract	N	N	Flow chart in Fig 1 shows tha 6 participants in TENS group dropped out because of worsening symptoms
(Aydin et al., 2005)	24	No complications occurred as a result of the treatments given.	Reported no adverse events	Y - 0 tally	N - 0 tally	
(Azatcam et al., 2017)	25	No statements present	No information to extract	N	N	
(Báez-Suárez et al., 2018)	26	No patients in any group reported adverse events such as skin allergy or burning at the electrode site.	Reported no adverse events on mothers or new-born babies	Y – 0 tally	N – 0 tally	
(Bai et al., 2017)	27	The results of the present study demonstrate that TENS can reduce the intensity of the pain associated with PD without any AEs.	Reported no adverse events	Y - 0 tally	N - 0 tally	
(Baki et al., 2015)	28	In our study, TENS has beneficial effects for pain relief after thoracotomy without any side effects;	Reported no adverse events	Y - 0 tally	N - 0 tally	
(Ballegaard et al., 1985)	29	No statements present	No information to extract	N	N	
(Barbarisi et al., 2010)	30	No statements present	No information to extract	Ν	N	In the final visit (visit IX), al the groups underwent a clinical-neurologic examination and routine bloo tests to evaluate the possibili of side effects.
(Barker et al., 2006)	31	We can recommend this technique because of its simple use and the lack of side-effects in our study population.	Reported no adverse events	Y - 0 tally	N - 0 tally	
(Barker et al., 2008)	32	No statements present	No information to extract	N	N	Authors state that patients were asked to report adverse events but these were not recorded in results.
(Başkurt et al., 2006)	33	No statements present	No information to extract	N	Ν	
(Bayindir et al., 1991)	34	No statements present Low cost, lack of undesirable side effects, and ease of application can make TENS an acceptable method of reducing postoperative chest pain	No information to extract	N	N	No specific mention of monitoring adverse events ir methods or results
(Beckwée et al., 2018)	35	No statements present TENS could be experienced as painful instead of pain relieving, and thus, TENS could have an adverse effect on pain in a subgroup of patients.	No information to extract	N	N	Authors comments refer to patients with central sensitisation
(Benedetti et al., 1997)	36	No statements present. We emphasize that the absence of complications and side effects of TENS compared with conventional opioid and nonopioid analgesics makes electrical stimulation a safe and reliable therapeutic procedure.	No information to extract	N	N	

Reference	Reference number	Extracted Text	AES related to TENS	Statement	Extractable Data	Comment
(Bennett et al., 2010)	37	Overall, 9 patients experienced adverse events and median number of adverse events per patient was 2 (range 1, 6). Distribution of adverse events was similar following active or placebo TENS applications (describe in Table 4 of their report)	One adverse event directly related to placebo TENS treatment. Two participants withdrew because of increasing pain.	Y	Y	Authors do not describe n of adverse events reported table 4. Data: TENS = 3 events Placebo = 2 events
(Bergeron-Vezina et al., 2018)	38	No harms or unintended effects were reported by the participants.	Reported no adverse events	Y - 0 tally	N - 0 tally	
(Bertalanffy et al., 2005)	39	No statements present Due to its simplicity and lack of side effects, this method should be considered in these patients.	No information to extract	N	N	
(Bi et al., 2015)	40	No statements present	No information to extract	Ν	Ν	
(Bilgili et al., 2016)	41	No statements present	No information to extract	Ν	Ν	
(Binder et al., 2011)	42	No statements present	No information to extract	Ν	Ν	
(Bjersa and Andersson, 2014)	43	No statements present	No information to extract	N	N	
(Bjersa et al., 2015)	44	No statements present	No information to extract	Ν	Ν	
(Bloodworth et al., 2004)	45	No statements present	No information to extract	Ν	Ν	
(Bolat et al., 2019)	46	" prevention of unpleasant feelings or complications. A reddish coloration and burning or itching at the electrode–skin junction can occur due to increased blood circulation. However, we observed none of these side effects in the present study".	Reported no adverse events	Y - 0 tally	N	
(Bono et al., 2015)	47	Neither adverse events nor side effects occurred in the real or sham group.	Reported no adverse events	Y - 0 tally	N-0 tally	
(Borjesson et al., 1997)	48	No adverse effects were seen	Reported no adverse events	Y = 0 tally	N = 0 tally	
(Borjesson et al., 1998)	49	No statements present	No information to extract	N	Ν	
(Borup et al., 2009)	50	No signs of serious or prolonged side effects were found, neither by using acupuncture nor TENS.	84% of TENS group stated it had no side-effects.	Y = 0tally	N = 0 tally	No information included of any participants who did experience side-effects.
(Breit and Van der Wall, 2004)	51	No statements present	No information to extract	N	Ν	
(Buchmuller et al., 2012)	52	Twelve patients presented a serious adverse event during the study: five in the active TENS group and seven in the sham TENS group. None of these events was considered to be attributable to the treatment studied. Skin irritation was observed in 11 patients in the active TENS group (leading to study discontinuation in one patient) and in three patients in the sham TENS group.	No details about adverse events included in report (except for skin irritation)	Y	Y	Data: TENS = 11 events Placebo = 3 events
(Bulut et al., 2011)	53	When side effects were compared, there was no difference between the groups, except skin irritation only in one patient in Group A ( $p$ > 0.05).	One patient with skin irritation.	Y	N	No numerical data – impli all groups were zero excep

Reference	Reference number	Extracted Text	AEs related to TENS	Statement	Extractable Data	Comment
						Group A but cannot be certa so not extracting
(Bundsen et al., 1982)	54	It can thus be concluded that no adverse effect of TNS is demonstrable by clinical, laboratory or neurological examination of the infants after pain relief by TNS	Reported no adverse events	Y = 0 tally	N = 0 TENS ONLY	
(Can et al., 2003)	55	No statements present	No information to extract	Ν	Ν	
(Casale et al., 2013)	56	No statements present	No information to extract	Ν	Ν	
(Çebi, 2019)	57	No statements present	No information to extract	Ν	Ν	
(Celik et al., 2013)	58	No side effects of low frequency TENS were seen	Reported no adverse events	Y	Y	No numerical data
(Cetin et al., 2008)	59	No statements present	No information to extract	N	N	
(Chandra et al., 2010)	60	The incidence of side effects was negligible in both the groups.	Reported no adverse events	Y = 0	N = 0	
(Chandra et al., 2010)		The incidence of side cricets was negligible in boar the groups.	Reported no adverse events	tally	tally	
(Cheing and Hui-Chan, 1999)	61	No statements present	No information to extract	N	N	
(Cheing and Luk, 2005)	62	No statements present	No information to extract	Ν	Ν	
(Cheing et al., 2002)	63	No statements present	No information to extract	Ν	Ν	
(Cheing et al., 2003)	64	No statements present	No information to extract	N	N	
(Chellappa and Thirupathy, 2020)	65	No statements present	No information to extract	N	N	
(Cherian et al., 2016a) – Primary Report Secondary Report (Cherian et al., 2016b)	66 _ Prim ary Repo rt Seco ndar y Repo rt 67	Patients were observed for adverse effects due to the TENS device throughout the study. Reports were rare but included local irritation at site of pad placement (n = 2) and irritation due to improper brace fitting (n = 1). All of these were minor and self-limited and did not prevent any patients from continuing a full course of TENS treatment (3 months). There were no serious adverse reactions reported. In addition, patients were evaluated for the need for surgery, either total knee arthroplasty or arthroscopy. From <sup>67</sup> secondary report: Adverse events seen during the trial included skin irritation, increased pain, and local skin breakdown.	Skin irritation – no further information	Y	N	No numerical data from the control group means canno extract
(Chesterton et al., 2013)	68	No adverse reactions to treatment were recorded.	Reported no adverse events	Y = 0 tally	N = 0 tally	
Secondary Report (Lewis et al., 2015)	Seco ndar y Repo rt 69					
(Chia et al., 1990)	70	No statements present	No information to extract	N	N	
(Chiou et al., 2019)	71	No statements present	No information to extract	N	N	

Reference	Reference number	Extracted	AEs related to TENS	Statement	Extractable Data	Comment
(Chitsaz et al., 2009)	72	TENS: Lost to follow-up (n=1) due to difficulties keeping appointments. Nortriptyline: Withdrawal (n=3) due to adverse effects. Nortriptyline was generally well tolerated and most of the adverse events reported were mild in severity. The most common side effects of nortriptyline were dry mouth (n=13), dizziness (n=6), constipation (n=5), urinary retention (n=5), nausea and headache (n=4). In 3 participants, this resulted in early discontinuation of nortriptyline and the dose of nortriptyline could not be increased per protocol due to these side effects. There were no statements about adverse events for TENS present.	Adverse events only in Nortriptyline group.	Y	Y	Data: Use dropout data resulting from AEs TENS = 0 Nortriptyline = 3
(Chiu et al., 2005)	73	No complications occurred because of any of the treatments given. The reasons for the withdrawals included insufficient time, dissatisfaction with treatment outcome and worsening of symptoms (Figure 2). 1 withdrawal from TENS group due to worsening of symptoms	Reported no adverse events	Y = 0 tally	N = 0 tally	
(Cipriano et al., 2008)	74	Electrical stimulation was well-tolerated by all patients and no relevant side effect was observed.	Reported no adverse events	Y = 0 tally	N = 0 TENS ONLY	
(Cipriano et al., 2014)	75	TENS was well tolerated by all patients with no reported side effects.	Reported no adverse events	Y = 0 tally	N = 0 TENS ONLY	
(Coelho de Amorim et al., 2014)	76	No statements present	No information to extract	Ν	Ν	
(Cooperman et al., 1977)	77	No statements present	No information to extract	Ν	Ν	
(Coyne et al., 1995)	78	No statements present	No information to extract	Ν	Ν	
(Crompton et al., 1992)	79	However, a substantial proportion of women who used the device found it frightening or unpleasant, which we consider unacceptable in the absence of an improvement in pain scores.	Participants found the TENS device 'frightening' and 'unpleasant'.	Y	N	No numerical data
(Cuschieri et al., 1985)	80	All patients tolerated the TES device well.	Reported no adverse events	Y = 0 tally	N = 0 TENS ONLY	
(Cuschieri et al., 1987)	81	No untoward side effects were noted.	Reported no adverse events	Y = 0 tally	N = 0 tally	
(da Silva et al., 2008)	82	No statements present	No information to extract	N	N	
(da Silva et al., 2015)	83	No adverse effects were observed in the TENS group, but 33.3 % of patients in the control group reported drowsiness and nausea.	Reported no adverse events in TENS group	Y	Y	The authors reported stated that 'adverse events for TE was an outcome and they presented this data as AEs attributable to the intervent per se. For this reason, we have extracted the data. Nevertheless, we are

Reference	Reference number	Extracted Text	AEs related to TENS	Statement	Extractable Data	Comment
						concerned that this data reflects efficacy of interventions to reduce AEs (drowsiness, nausea,) associated with drugs (morphine, Dipyrone) rather than TENS Data: TENS = 0 events / 21 Control = 7 events / 21 participants
(Dailey et al., 2013)	84	No statements present	No information to extract	N	N	
(Dailey et al., 2020)	85	There were 30 adverse events related to TENS intervention in 30 participants on visits 1, 2, or 3. The most common adverse events were pain with TENS (4.8% in the active TENS group) and skin irritation with electrodes (4.8% in the active TENS group) and skin irritation with electrodes (4.8% in the active TENS group, 1% in the placebo TENS group, and 0% in the no TENS group). Adverse events reported on visit 2 occurred during the first treatment at that visit, and adverse events reported on visit 3 were during treatment at that visit and during the 4-week period of home use. Serious Adverse Events. In the course of the trial, four serious adverse events (study related, n=1 and non-study related, n=3) were reported between April 2014 and April 2016 and all were categorized as hospitalization. For the study related event, the participant complained of chest pain during the 6MWT, was admitted to ER, hospitalized with changes for thyroid medication and recovered with treatment (2) report of GI symptoms, admitted to hospital for dehydration and recovered with treatment (2) report of GI symptoms, admitted to hospital for dehydration and recovered with treatment and condition was still present and being treated at the end of her participant in the study. As a group, for these four participants, the average age was 49.75 years, ranging from 40 to 59 years. With respect to treatment group, one event occurred prior to reatment groups (placebo-TENS), n=1 and no-TENS, n=2). The participants were further	Y	Y	Y	TENS = 17/103 Placebo = 3/119 Taken from data in Supplementary Table 7, available on the Arthritis & Rheumatology web site at http://onlin elibrary.wiley.com/doi/10.100 2/art.41170/ abstract, shows rates of TENS-related Adverss events by visit. There were 4 serious adverse events, with none related to TENS use (Supplementary Results, http://onlin e library.wiley.com/doi/10.1002 art.41170/ abstract).

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Reference	Reference number	Extracted Text	AEs related to TENS	Statement	Extractable Data	Comment
		categorized by medication (opioid, n=1 and non-opioid, n=3) and location (TN, n=3 and IA, n=1).				
(Davies, 1982)	86	No statements present	No information to extract	Ν	Ν	
(Dawood and Ramos, 1990)	87	Four subjects noticed muscle vibrations, change in stimulation with movements, tightness, headaches after use, and a slight redness or a burning sensation with TENS treatment. No mention of AEs in the Ibuprofen group	Reported no adverse events	Y	N = 0 TENS ONLY	No numerical data for th comparison groups (plac ibuprofen)
(De Angelis et al., 2003)	88	No differences in side effects were observed between TENS versus no TENS groups. the incidence of nausea was quite high in this patient sample as compared with other studies (group TENS, 8.5%; group No TENS, 11.3%) (11, 12), but this symptom was mentioned by the patient only when specifically elicited and it was probably the result of psychosomatic factors or emotional stress. However, shoulder pain was more frequent, albeit not significantly, in group TENS than in group Control (group A, 3%; group B, 0%). This is probably due to the fact that the examination lasted longer in group A than in group B (group A, 134.1 60 seconds; group B, 117 49 seconds; P .054) (using the same CO2 flow) and that the patients' acceptance of the procedure was higher with the use of the TENS device. It is completely safe, noninvasive, and free from any side effects as far as side effects are concerned, there were no statistically significant differences in favor of the TENS device	Coded as: Reported no adverse events Extract data AEs = Nausea and Shoulder pain but not attributed to pain	Y = 0 tally	N = 0 tally	No data extracted It is difficult to ascertain whether these symptoms AEs or due to treatment intervention of surgical procedure No data extracted
(De Giorgi et al., 2017)	89	No side effects were referred by the patients during the 10-week TENS treatment.	Reported no adverse events	Y = 0 tally	N = 0 TENS ONLY	
(de Oliveira, 2012)	90	No statements present	No information to extract	N	N	
(de Orange et al., 2003)	91	No statements present	No information to extract	Ν	Ν	
(de Sousa et al., 2014)	92	No statements present	No information to extract	N	Ν	
(DeSantana et al., 2008)	93	We reinforce that the absence of complications and adverse effects of TENS compared with conventional opioids and nonopioid analgesics makes TENS a safe and reliable therapeutic procedure.	Reported no adverse events	Y = 0 tally	N = 0 TENS ONLY	
(DeSantana et al., 2009)	94	We conclude that the absence of complications and adverse effects of TENS compared with conventional opioids and nonopioid analgesics makes TENS a safe and reliable therapeutic procedure.	Reported no adverse events	Y = 0 tally	N = 0 TENS ONLY	
(Dewan and Sharma, 2011)	95	No statements present	No information to extract	Ν	Ν	
Deyo et al. (1990)	Deyo , Wals h <sup>96</sup>	Approximately one-third of the subjects reported minor skin irritation at the sites of electrode placement, with equal proportions in the true-TENS and sham-TENS groups.	Skin irritation. One subject had to discontinue due to severe dermatitis.	Y	N	No numerical data
(Dibenedetto et al., 1993)	97	Both treatments were well-tolerated and no side-effects reported.	Reported no adverse events	Y = 0 tally	N = 0 tally	

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Reference	Reference number	Extracted Text	AEs related to TENS	Statement	Extractable Data	Comment
(Dilekci et al., 2016)	98	No statements present	No information to extract	N		
(Dissanayaka et al., 2016)	99	No statements present	No information to extract	Ν	Ν	
(Dogu et al., 2008)	100	No statements present	No information to extract	Ν	Ν	
(Domaille and Reeves, 1997)	101	No statements present	No information to extract	N	Ν	
(Ebadi et al., 2018)	102	As for side effects, 8 patients in the Diadynamic group reported a burning sensation in the first 3-4 min of the treatment.	Reported no adverse events in TENS group.	Y	Ν	No numerical data for TENS
(Ekblom and Hansson, 1987)	103	No statements present	No information to extract	Ν	Ν	
(Ekim et al., 2008)	104	No statements present	No information to extract	Ν	Ν	
(Elboim-Gabyzon et al., 2019)	105	No statements present	No information to extract	N	Ν	
(Elserty et al., 2016)	106	No statements present	No information to extract	Ν	Ν	
(Emmiler et al., 2008)	107	Post-op complications (atelectesia) were tabulated but not stated whether these were attributed to the intervention TENS = 1/20(5%) Placebo = 1/20(5%) Control = 4/20 (20%)	Reported adverse events (complication) atelectesis	Y	Ν	No data extracted – unclear whether 'complications' attributable to the treatment
(Engen et al., 2016)	108	No statements present	No information to extract	Ν	Ν	
(Erden and Senol Celik, 2015)	109	No statements present	No information to extract	N	Ν	
(Erdogan et al., 2005)	110	We did not observe any side effects using TENS, although we did not use TENS in patients who had cardiac disease.	Reported no adverse events	Y = 0 tally	N = 0 TENS ONLY	
(Erkkola et al., 1980)	111	No statements present	No information to extract	Ν	Ν	
(Escortell-Mayor et al., 2011) Secondary Report (Escortell Mayor et al.,	Seco ndar y	It is remarkable, as it is described in a publication done by this group, that no important adverse effects were observed from either therapy - Reported no adverse events <sup>112</sup> p70 Translated from <sup>113</sup> p340	Information to extract	Y	Y	Data extracted from seconda report <sup>113</sup> : TENS = 7 events Manual Therapy = 3
2008)	Repo rt 113	16.3% of treated patients with TENS ( $n = 7$ ) and 6.4% of those treated with manual therapy ( $n = 3$ ) reported adverse effects related to treatment. Three of them presented increased pain in the treated area and 1, general poor physical condition in the group treated with TENS Of those who received therapy manual, 1 patient referred a clinical worsening the first days and the rest did not detail symptoms.				The statement on AEs in <sup>112</sup> p70 appears to contradict data presented in <sup>113</sup>
(Esteban Gonzalez et al., 2015)	114	There were no complications, intolerances or other problems that required the intervention with TENS to be suspended in any of the 50 patients.	Reported no adverse events	Y = 0 tally	N = 0 TENS ONLY	
(Eyigor et al., 2008)	115	No statements present	No information to extract	Ν	N	

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Reference	Reference number	Extracted Text	AEs related to TENS	Statement	Extractable Data	Comment
(Eyigor et al., 2010)	116	No significant adverse event was reported in either of the two groups (p>0.05).	Reported no adverse events	Y = 0 tally	N = 0 tally	
(Facci et al., 2011)	117	No statements present	No information to extract	Ν	Ν	
(Farahani et al., 2014)	118	No statements present	No information to extract	Ν	Ν	
(Farina et al., 2004)	119	No statements present	No information to extract	Ν	Ν	
(Fatima and Sarfraz, 2019)	120	No statements present	No information to extract	Ν	Ν	
(Ferraz and Moreira, 2009)	121	No statements present	No information to extract	Ν	Ν	
(Ferreira et al., 2011)	122	No statements present	No information to extract	Ν	Ν	
(Ferreira et al., 2017)	123	No statements present	No information to extract	Ν	Ν	Dropouts reported but reasons not given
(Finsen et al., 1988)	124	No statements present	No information to extract	Ν	Ν	
(Fiorelli et al., 2012)	125	We did not observe any side effects; thus, TENS may be particularly useful	Reported no adverse events	$\mathbf{Y} = 0$	N = 0	
		for patients that have liver or kidney disease		tally	tally	
(Fodor-Sertl et al., 1990)	126	No statements present	No information to extract	Ν	Ν	
(Forogh et al., 2019)	127	No adverse events occurred and the rate of compliance to the exercise program was high in both groups	Reported no adverse events	Y = 0 tally	N = 0 tally	
(Forst et al., 2004)	128	No statements present	No information to extract	Ν	Ν	
(Forster et al., 1994)	129	No statements present	No information to extract	Ν	Ν	
(Fujii-Abe et al., 2019)	130	None of the study patients suffered any abnormal or harmful effects.	Reported no adverse events	Y = 0 tally	Ν	
(Galli et al., 2015)	131	No statements present	No information to extract	Ν	Ν	
(Galloway et al., 1984)	132	Only one of our patients demonstrated any adverse effects of the treatment in the form of an allergic rash with blistering which, in patter, was seen to correspond exactly with the areas of contact with the adhesive incorporated in the sterile wound electrodes.	Allergic skin irritation in one participant	Y	N	No numerical data
(Garcia-Perez et al., 2018)	133	No statements present	No information to extract	N	Ν	
(Gerson et al., 1977)	134	No statements present	No information to extract	N	Ν	
(Ghoname et al., 1999a)	135	No statements present	No information to extract	N	Ν	
(Ghoname et al., 1999b)	136	No statements present	No information to extract	N	Ν	
(Gilbert et al., 1986)	137	No statements present	No information to extract	N	Ν	
(Grabiańska et al., 2015)	138	No statements present	No information to extract	Ν	Ν	
(Graff-Radford et al., 1989)	139	No statements present	No information to extract	N	N	Patients were informed about possible side-effects beforehand
(Grant et al., 1999)	140	three TENS patients developed skin reactions. Other than these, reported side effects were minimal: three acupuncture patients reported dizziness and three TENS patients developed skin reactions.	Skin reactions in 3 participants	Y	Y	Data extracted: TENS = 3 events Acupuncture = 3 events
(Gregorini et al., 2010)	141	No statements present	No information to extract	Ν	Ν	
(Grimmer, 1992)	142	No statements present	No information to extract	Ν	Ν	
(Gschiel et al., 2010)	143	Overall, there were no side effects.	Inferred no adverse events	Y	N = 0 tally	No numerical data

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Reference	Reference number	Extracted Text	AEs related to TENS	Statement	Extractable Data	Comment
(Gunay Ucurum et al., 2018)	144	No statements present	No information to extract	N	N	
(Guo and Jia, 2005)	145	No statements present	No information to extract	Ν	Ν	
(Hamza et al., 1999)	146	16 -20% of the patients in each of the four groups complained that the TENS adversely influenced their quality of sleep because of the presence of the cutaneous electrodes and wires.	Sleep interference because of electrodes/wires.	Y	N	No numerical data for other groups
(Hanfy and El-Bigawy, 2004)	147	No statements present During the study TENS therapy was safe and allowed the patients to remain ambulatory.	No information to extract	N	N	No specific comments on adverse events included
(Hansson and Ekblom, 1983)	148	it should be noted that most patients found the muscle twitches produced by the low frequency TENS uncomfortable.	No information to extract	N	Ν	No specific comments on adverse events included
(Hansson et al., 1986)	149	No statements present	No information to extract	Ν	Ν	
(Hargreaves and Lander, 1989)	150	No statements present	No information to extract	N	N	Authors state that TENS is safe but no specific commen on side-effects in this study
(Harrison et al., 1986)	151	In the present study, like all others reported to-date, no side-effects were noted from the therapy.	Reported no adverse events	Y	N = 0 tally	No numerical data
(Hart et al., 2012)	152	No statements present	No information to extract	Ν	Ν	
(Hazneci et al., 2005)	153	No statements present	No information to extract	Ν	Ν	
(Herrera-Lasso et al., 1993)	154	No statements present	No information to extract	Ν	Ν	
(Hershman M, 1989)	155	No statements present	No information to extract	Ν	Ν	
(Hou et al., 2002)	156	No statements present	No information to extract	Ν	Ν	
(Hokenek et al., 2020)	157	No treatment-related skin reactions or unwanted effects were encountered during the trial. Of the verum group, 3 patients declined continuation of treatment due to intolerance to paresthesia, and 2 patients in the sham group declined to continue treatment due to intolerable pain. These patients opted to instead receive 0.75 mg/kg meperidine rescue therapy and were excluded from the trial.	Unclear whether these are adverse events or dislike of TENS sensation and worsening pain due to non response to sham	Y	N	
(Hruby et al., 2006)	158	No statements present	No information to extract	N	Ν	
(Hsieh et al., 1992)	159	No statements present One-shot TENS treatment may be recommended due to the rarity of side effects and its convenient application.	No information to extract	N	N	
(Hsueh et al., 1997)	160	No statements present	No information to extract	Ν	Ν	
(Hughes et al., 1988)	161	The use of TENS had no adverse effects upon the newborn	Reported no adverse events	Y	N = 0 TENS ONLY	No numerical data
(Husch et al., 2020)	162	No statements present	No information to extract	Ν	Ν	
(Ilhanli, 2015)	163	There were no adverse events due to treatment regimens.	Reported no adverse events	Y	N = 0	
(Inal et al., 2016)	164	No statements present	No information to extract	Ν	Ν	

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Reference	Reference number	Extracted Text	AEs related to TENS	Statement	Extractable Data	Comment
(Isik et al., 2017)	165	There were no serious side effects in both groups. In the TENS group no side effects were reported although 21 of the patients reported the treatment as boring due to the long hospital stay. In the leech therapy group, there was a mild local itching and skin redness in 31 patients (12 patients required topical antihistamine therapy) and severe local itching and reddening in 3 patients (requiring oral plus topical antihistamine therapy).	Reported no adverse events	Y	Y	TENS = 0 events / 53 participants Leech = 34 events / 52 participants
(Jaafarpour et al., 2008)	166	No statements present	No information to extract	Ν	Ν	
(Jamison et al., 2019)	167	None of the participants reported experiencing any long-term adverse effects from using the hfTENS.	Reported no adverse events	Y	N = 0 TENS ONLY	No numerical data
(Jarzem et al., 2005)	168	No statements present	No information to extract	Ν	Ν	
(Jensen et al., 1985)	169	No statements present	No information to extract	Ν	Ν	
(Jensen et al., 1991)	170	No statements present	No information to extract	Ν	Ν	
(Jones and Hutchinson, 1991)	171	Three patients complained of dizziness after Entonox inhalation. There were no other side-effects of any of the treatments. TENS produced no side-effects, is easier to handle and was subjectively preferred by the patients.	Reported no adverse events	Y	N = 0	No data extracted Multiple cross over study wi possibility of contamination between treatments
(Kara et al., 2011)	172	Furthermore, there were no adverse effects or negative results related to TENS application.	Reported no adverse events	Y	N = 0 TENS ONLY	No numerical data
(Kararmaz et al., 2004)	173	TENS is a non-invasive, safe, and simple treatment method, which does not have any systemic side effects. We did not observe any difficulties in the use of TENS. NOTE: Table 4 records side effects associated with ESWL procedure as an efficacy measure	Reported no adverse events	Y	N = 0 TENS ONLY	No numerical data associated with AEs due to treatment interventions under study The only side-effects reporte
(Kayman-Kose et al., 2014)	174	No adverse effects due to TENS occurred during the study period - for both Cesarean and vaginal delivery data	Reported no adverse events	Y	N = 0 TENS ONLY	were medication-induced No numerical data
(Keskin et al., 2012)	175	No adverse effect of TENS application on pregnant women was observed during the study.	Reported no adverse events	Y	Ν	No numerical data for comparison group
(Kibar et al., 2020)	176	No statements present	No information to extract	Ν	Ν	
(Kim et al., 2012)	177	There were no significant differences in the incidences of side effects such as erythema and itching between the groups ( $P > 0.05$ ). TENS Group 7/50 (14%) had erythema and 1/50 (2%) had itching. Table II of their report	Erythema and itching.	Y	Y	Data extracted: TENS = 8 events / 50 participants Placebo = 7 / 50 participants
(Kim et al., 2014)	178	No major adverse effects were reported by participants in any treatment group. One patient in the monotherapy group, one patient in the TENS+Np group, and one patient in the CAP+Np group experienced skin itching. One patient in the TENS+Np group and one patient in the HEAT+Np group	Itching and sleep disturbance	Y	Y	Data extracted (skin itching): TENS + NSAID patch = 1 event / 24 participants

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Reference	Reference number	Extracted Text	AEs related to TENS	Statement	Extractable Data	Comment
		reported sleep disturbance. Light somnolence was reported by one patient in the monotherapy group. However, all adverse effects had spontaneously resolved by the end of this study without any treatment. Participants' vital signs were in the normal				NSAID patch alone = 1 event 25 participants
(Kirupa et al., 2019)	179	No statements present	No information to extract	Ν	Ν	
(Knobel et al., 2005)	180	In this survey, more than 50% of women reported some discomfort in the use of electrodes type SSP and 25% in the use of electrodes plate type (Tab. 4). In the application of stimulation, no woman reported discomfort in none of the study groups. To assess the effectiveness of this care, therefore, research is needed to reveal the woman's opinion about the method	Discomfort during stimulation	Y	Ν	No data extracted Discomfort was an outcome measure – comparing two TENS electrodes. We did not consider discomfort as an adverse even in this study
(Koca et al., 2014)	181	No serious complication was associated with the treatments in any group, and all patients generally tolerated the treatments well. Only two patients in the TENS group experienced mild tenderness at the application site.	Mild tenderness	Y	N	No numerical data
(Kofotolis et al., 2008)	182	No statements present	No information to extract		Ν	
(Koke et al., 2004)	183	During the first period, skin irritation occurred in 9.4% (17/180) of all patients, adherence problems of electrodes in 12.2% (22/180) and problems attaching electrodes in 2.2% (4/180). In four patients, the adverse effects resulted in withdrawal from the study (skin-irritation 2X, problems attaching electrodes 2 X). During the second period, skin irritation was reported by 5.8% (10/171), adherence problems of electrodes 4.7% (8/171), and problems attaching electrodes body 2.9% (5/171). No significant differences in adverse effects were found between groups. At 6 months follow-up, 6 patients (3 in HFT–COT group and 3 in HIT–COT group) reported skin irritation due to TENS, but still could use TENS regularly.	Skin irritation Problems attaching electrodes	Y	N	Could not extract data at 6 months follow-up (skin irritation) because could not ascertain the number of participants remaining in each group High frequency TENS = 3 events High intensity = 3 Cross-over study whereby all participants received an activ TENS for all possible interventions
(Korkmaz et al., 2010)	184	No serious side-effects or complications were observed in either of the two groups (P>0.05).	Reported no adverse events	Y = 0 tally	N = 0 tally	No numerical data
(Kumar and Raje, 2014)	185	No statements present	No information to extract	Ν	Ν	
(Labrecque et al., 1999)	186	No statements present	No information to extract	Ν	Ν	
(Laitinen and Nuutinen, 1991)	187	No statements present	No information to extract	Ν	Ν	
(Lang et al., 2007)	188	Because of its simple use and lack of side effects in our study population, we can recommend this technique for pain therapy.	Reported no adverse events	Y	N = 0 TENS ONLY	No numerical data

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Reference	Reference number	Extracted Text	AEs related to TENS	Statement	Extractable Data	Comment
(Langley et al., 1984)	189	No adverse side-effects were reported by patients receiving TNS or placebo.	Reported no adverse events	Y = 0 tally	N = 0 tally	
(Lauretti et al., 2013)	190	Concerning adverse effects, 2 patients from the STG got in sleep after the device application and complained of muscle sore due to more than 70-min active device application, which was subsequently improved by local hot application.	Muscle soreness in TENS group (2 patients)	Y	N	Note: the poor English in the quotation is how the text was written!
(Lauretti et al., 2015)	191	In conclusion, the portable TENS device demonstrated to be efficacious for pain relief and improvement of quality of life with no adverse effects for control of menstruation cramp pain.	Reported no adverse events	Y	N = 0 TENS ONLY	
(Law and Cheing, 2004)	192	No statements present	No information to extract	Ν	Ν	
(Law et al., 2004)	193	No statements present	No information to extract	Ν	Ν	
(Leandri et al., 1990)	194	No statements present	No information to extract	Ν	Ν	
(Lee et al., 1990)	195	No negative effects on the mothers and babies were reported.	Reported no adverse events	$\mathbf{Y} = 0$	N = 0	
			±	tally	tally	
(Lee et al., 2015)	196	Neither expected nor unexpected AEs occurred in the study and control	Reported no adverse events	$\mathbf{Y} = 0$	N = 0	
		groups.	1	tally	tally	
(Lee et al., 2019)	197	No statements present	No information to extract	N	N	
(Leo et al., 1986)	198	No statements present	No information to extract	Ν	Ν	
(Leonard et al., 2011)	199	No statements present	No information to extract	Ν	Ν	
(Lewers et al., 1989)	200	No statements present	No information to extract	N	N	
(Lewis et al., 1984)	201	No statements present	No information to extract	N	N	One patient dropped out because of worsening pain.
(Lewis et al., 1994)	202	No statements present	No information to extract	Ν	Ν	C1
(Likar et al., 2001)	203	The side effects 1 patient in the Verum group about vomiting, 5 patients in the placebo group suffered from nausea and vomiting that are considered easy and were classified as medium. TENS + analgesics = 1 event / 11 participants Placebo TENS + analgesics = 5 event / 12 participants	"On	Y	N	Data related to nausea and vomiting. Debatably this is related to AE associated with post op drugs rather than TENS. We decided not to extract thi data because nausea and vomiting AE of drugs reflect efficacy of TENS rather than AE of TENS
(Lim et al., 1983)	204	No statements present	No information to extract	Ν	Ν	
(Lima et al., 2011)	205	No statements present	No information to extract	Ν	Ν	
(Limoges and Rickabaugh, 2004)	206	In addition, no adverse events secondary to TENS use or procedural complications occurred.	Reported no adverse events	Y	N = 0 TENS ONLY	No numerical data
(Lin et al., 2015)	207	No statements present	No information to extract	Ν	N	
(Lin et al., 2019)	208	First, there were no adverse events (such as discomfort, hematoma, injury, or hyperalgia) throughout this study.	Reported no adverse events	Y = 0 tally	N = 0 tally	

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Reference	Reference number	Extracted Text	AEs related to TENS	Statement	Extractable Data	Comment
(Linde et al., 1995)	209	The most common side effect during TENS treatment is some type of hypersensibility reaction of the skin. It was mostly seen in slightly underweight patients, in whom contact between skin and electrode was not at its maximum, especially in the area of the TMJ	Skin reaction (no other details)	Y	N	No numerical data
(Linn et al., 1999)	210	No statements present	No information to extract	Ν	Ν	
(Lison et al., 2017)	211	No patients in either the active or placebo TENS groups reported adverse events such as skin allergy, pain, or burning at the electrode site.	Reported no adverse events	Y = 0 tally	N = 0 tally	
(Liu et al., 1985)	212	No statements present	No information to extract		Ν	
(Liu et al., 2017)	213	During treatment, only 1 patient in the 2-Hz tONS group reported an adverse event. This was intolerance to a form of pinch pain induced by electrical stimulation. However, when the intensity of stimulation was reduced from 10 to 9 mA, the uncomfortable feeling subsided. In the TPM group, 9 of 22 patients experienced (mostly mild) paresthesia, especially of the hands and feet. No other adverse events were reported. tONS = transcutaneous occipital nerve stimulation	Pain at 10mA. Pain lessened when intensity reduced.	Y	Y	Data extracted TENS = 1 event / 22 - Pinch pain Topiramate = 9 / 22 - Mild paraesthesia of hands
(Lofgren and Norrbrink, 2009)	214	In this study few side-effects were reported. Three patients reported increased pain, 2 after TENS and one after warmth.	Increased pain in 2 patients	Y	Y	Data extracted (increased pair TENS = 2 events / 32 participants Warmth therapy = 1 event / 3 32 participants
(Luchesa et al., 2009)	215	No statements present	No information to extract	Ν	Ν	
(Lundeberg, 1984)	216	No statements present	No information to extract	Ν	Ν	
(Lundeberg et al., 1985)	217	No statements present	No information to extract	Ν	Ν	
(Machado et al., 2019)	218	No statements present	No information to extract	Ν	Ν	
(Machin et al., 1988)	219	No statements present	No information to extract	Ν	Ν	
(Mahure et al., 2017)	220	No TENS machine-related complication, such as localized pain or erythema at the electrode site, occurred in either group of patients.	Reported no adverse events	Y	N = 0 Tally	No numerical data despite clear statement of no events i both groups
(Manigandan et al., 2014)	221	No statements present	No information to extract	Ν	Ν	
(Mannheimer and Carlsson, 1979)	222	No side effects were observed.	Reported no adverse events	Y = 0 tally	N = 0 tally	
(Mannheimer and Whalen, 1985)	223	No statements present	No information to extract	N	N	
(Mannheimer et al., 1978)	224	No side effects of the treatment were observed. One patient reported that when the pain recurred it was more severe than before TNS, however.	Pain recurred more severe than before TNS	Y	Ν	
(Mannheimer et al., 1985)	225	One patient in the treatment group was excluded because of skin irritation from the electrodes	Skin irritation	Y	Ν	
(Mansourian et al., 2019)	226	No statements present	No information to extract	Ν	Ν	1
(Mansuri et al., 2019)	227	No statements present	No information to extract	N	N	1
(Mansuri et al., 2020)	228	No statements present	No information to extract	N	Ν	
(Marchand et al., 1993)	229	No statements present	No information to extract	Ν	Ν	

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Reference	Reference number	Extracted Text	AEs related to TENS	Statement	Extractable Data	Comment
(Mascarin et al., 2012)	230	No statements present	No information to extract	N	N	
(McCallum et al., 1988)	231	No statements present	No information to extract	Ν	Ν	
(Melzack et al., 1983)	232	No statements present	No information to extract	Ν	Ν	
(Merrill, 1989)	233	No statements present	No information to extract	Ν	Ν	
(Miller et al., 2007)	234	No statements present	No information to extract	Ν	Ν	
(Milsom et al., 1994)	235	Ten of the 12 women considered the high-intensity transcutaneous nerve stimulation to be painful. However, stimulation lasted only a few seconds, and all the women were prepared to accept again this short period of pain to obtain pain relief from dysmenorrhea.	Painful at high-intensity stimulation	Y	N	
(Moharic et al., 2009)	236	As already indicated in the Methods section, three patients in the pregabalin group experienced such severe somnolence and dizziness that they had to withdraw from the study. Complaints in the combined group beside somnolence and dizziness included peripheral oedema, weight gain, elevated blood glucose values and withdrawal headache, while one patient from the combined group withdrew from the study because of a traffic accident (tractor overturning) caused by somnolence induced (with all likelihood) by pregabalin. In the TENS group, none of the patients reported any local or systemic side effects, neither did they report any problems with continuous TENS application for three hours daily.	Reported no adverse events	Y	Y	Data extracted (severe somnolence and dizziness) TENS = 0 events / 46 participants Pregabalin alone = 3 events / 8 participants resulting in study withdrawal
(Mondal et al., 2019)	237	No statements present	No information to extract	Ν	Ν	
(Moore and Shurman, 1997)	238	No adverse treatment effects were reported and no subject reported the addition of any new pain medication, physical therapy, or other pain-related treatment during the course of their study participation.	Reported no adverse events	Y = 0 tally	N = 0 tally	
(Mora et al., 2006)	239	We can recommend this technique due to its simple use and the lack of side effects in our study population.	Reported no adverse events	Y = 0 tally	N = 0 TENS ONLY	
(Morgan et al., 1996)	240	No statements present	No information to extract	N	Ν	
(Møystad et al., 1990)	241	No statements present. TNS may have advantages as a non-invasive method with few side effects that is simple to administer for the patients themselves.	No information to extract	N	N	
(Murray et al., 2004)	242	No statements present	No information to extract	Ν	Ν	
(Mutlu et al., 2013)	243	No statements present	No information to extract	Ν	N	There were dropouts to follow up but no explanation for these.
(Nabi et al., 2015)	244	The therapeutic methods studied here were well tolerated were not associated with any serious adverse effects. However, skin irritation was reported in a few TENS group subjects.	Skin irritation	Y	N	No numerical data
(Nash et al., 1990)	245	The only side effected noted in the series were occasional skin rashes due to allergy to the electrode jelly or fixing tape, and occasional patients had transient increase in pain which settled to previous levels with cessation of treatment.	Skin irritation Transient increase in pain	Y	N	No numerical data

Reference	Reference number	Extracted Text	AEs related to TENS	Statement	Extractable Data	Comment
(Navarathnam et al., 1984)	246	Some of the patients in both groups developed blisters around the electrode edges in the distribution of the adhesives. In addition, two patients developed small areas of pressure necrosis in the region of the lumbosacral electrodes which might be avoided by more attention to posture of the patients with these electrodes.	Skin irritation Lumbosacral pressure necrosis	Y	N	No numerical data
(Neary, 1981)	247	No cases of infection or skin reaction were observed. TENS did not mask the pain symptoms from complications.	Reported no adverse events	Y = 0 tally	N = 0 tally	
(Neighbours et al., 1987)	248	No statements present	No information to extract	Ν	N	
(Nesheim, 1981)	249	No statements present	No information to extract	Ν	Ν	
(Neumark et al., 1978)	250	No statements present	No information to extract	Ν	Ν	
(Ng et al., 2003)	251	No statements present	No information to extract	Ν	Ν	
(Nordemar and Thorner, 1981)	252	No statements present	No information to extract	N	N	
(Norrbrink, 2009)	253	Three patients experienced discomfort or increased pain during treatment, and one patient experienced local muscle spasms.	Increased pain during treatment Local muscle spasms	Y	N	No numerical data Unclear which group experienced side effects
(Olsén et al., 2007)	254	No adverse effects except for discomfort during stimulation were recorded. Discomfort from the stimulation itself was greater in the HI TENS group than in the LI TENS group (pB/0.01). In the HI TENS group, two women experienced severe discomfort, two women experienced moderate discomfort, five women experienced mild discomfort, and two women experienced no discomfort. Seven women in the LI TENS group experienced no discomfort and one woman experienced mild discomfort from the stimulation given. No adverse effects except for discomfort during stimulation were recorded.	Discomfort during stimulation	Y	N	No numerical data other that stimulation discomfort Decided not to extract this
(Fagevik Olsen et al., 2019)	255	No statements present	No information to extract	N	Ν	Dropouts recorded but reaso not given
(Oncel et al., 2002)	256	No complications due to TENS therapy or Naproxen sodium were seen during the study.	Reported no adverse events	Y = 0 tally	N = 0 tally	
(Oosterhof et al., 2006) Secondary reports (Oosterhof et al., 2008, Oosterhof et al., 2012a, Oosterhof et al., 2012b)	257 Seco ndar y repor ts 258-260	No statements present in <sup>257</sup> . No statements present in secondary report <sup>259</sup> Secondary report - <sup>260</sup> Skin irritation occurred at some time point in half of the patients but could easily be cured by changing the type of electrode, except for 4 patients who had to stop treatment. Because there was no difference between TENS and sham TENS, we assume there was no interaction of the electric current with electrode material, which has been suggested.	Skin irritation	Y	N	No numerical data
(Ordog, 1987)	261	No complications of treatment were found. No side effects were reported, except a mild tingling sensation at higher TENS-PAC® output levels.	Reported no adverse events Mild tingling sensation is part of the TENS treatment	Y = 0 tally	N = 0 TENS ONLY	

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Reference	Reference number	Extracted Text	AEs related to TENS	Statement	Extractable Data	Comment
		Overall, 20% of the patients reported this effect, but none had to discontinue usage of the TENS-PAC® because of it.				
(Ozkaraoglu et al., 2020)	262	No statements present	No information to extract	N	Ν	
(Ozkul et al., 2015)	263	No unwanted effects occurred during the application of both treatments.	Reported no adverse events	Y = 0 tally	N = 0 tally	
(Oztas and Iyigun, 2019)	264	No statements present	No information to extract	N	N	
(Ozturk et al., 2016)	265	No statements present	No information to extract	Ν	Ν	
(Padma et al., 2000)	266	In the present study, no side effects were noted, and the stimulation was acceptable to all the patients, but the willingness to accept TENS as a mode of relief was equivocal.	Reported no adverse events	Y = 0 tally	N = 0 TENS ONLY	
(Paker et al., 2006)	267	In the present study, no serious adverse effects were reported in the intra- articular hylan group or in the TENS group.	Reported no adverse events	Y	N = 0 Tally	One dropout due to worse pain – not attributable to treatment
(Palmer et al., 2014)	268	No statements present	No information to extract	Ν	Ν	
(Pan et al., 2003)	269	Five patients complained of soreness in the upper arm after ESWT, but this soreness had subsided before their next visit. One patient had cardiac palpitations during the first ESWT session as a result of anxiety but was calm after taking a break. Otherwise, no specific side effect (e.g., hematoma, paresthesia) occurred in either group.	No adverse events recorded in TENS group	Y	Y	Extractable data: (soreness TENS = 0 events /30 participants ESWT = 5 ev 33 participants
(Park et al., 2015)	270	No adverse reactions related to TENS were observed.	Reported no adverse events	Y	N = 0 TENS ONLY	No numerical data
(Patil and Aileni, 2017)	271	No statements present	No information to extract	Ν	Ν	
(Peacock et al., 2019)	272	and no adverse events were reported in relation to the administration of the Biomodulator, traditional Chinese acupuncture, or TENS device in the study.	Reported no adverse events	Y = 0 tally	N = 0 tally	No numerical data
(Pietrosimone et al., 2009)	273	No statements present	No information to extract	N	Ν	
(Pietrosimone et al., 2011) Secondary Report (Pietrosimone et al., 2010)	274 Seco ndar y Repo rt 275	No adverse events were reported to the study personnel regarding TENS or placebo usage.	Reported no adverse events	Y = 0 tally	N = 0 tally	
(Pietrosimone et al., 2020)	276	No statements present	No information to extract	Ν	Ν	
(Pike, 1978)	277	The duration of stimulation, whether intermittent or continuous, is unimportant since neither tachyphylaxis nor side-effects occurred.	Reported no adverse events	Y	N = 0 TENS ONLY	No numerical data
(Pitangui et al., 2012)	278	No reports of side effects or dissatisfaction were made, supporting the results of other studies.	Reported no adverse events	Y = 0 tally	N = 0 tally	

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Reference	Reference number	Extracted Text	AEs related to TENS	Statement	Extractable Data	Comment
(Pitangui et al., 2014)	279	HFT and LFT are safe and effective resources without side effects and presenting good acceptance	Reported no adverse events	Y = 0 tally	N = 0 tally	
(Platon et al., 2010)	280	The only reported side effect of TENS during the study was discomfort during 1 min of the initial stimulation, which was noticed in some patients.	Slight discomfort during stimulation	Y	N	No numerical data
(Platon et al., 2018)	281	Some patients reported an uncomfortable stimulation during the 1 min of the initial stimulation with TENS as a side effect.	Slight discomfort during stimulation	Y	N	No numerical data
(Prabhakar and Ramteke, 2011)	282	No statements present	No information to extract	N	N	
(Presser et al., 2000)	283	No statements present	No information to extract	Ν	Ν	
(Rainov et al., 1994)	284	No statements present	No information to extract	Ν	N	
(Rajfur et al., 2017)	285	No statements present	No information to extract	Ν	N	
(Rajpurohit et al., 2010)	286	No statements present	No information to extract	Ν	N	
(Rakel and Frantz, 2003)	287	No statements present	No information to extract	Ν	Ν	
(Rakel et al., 2014)	288	No statements present	No information to extract	Ν	Ν	
(Ramanathan et al., 2017)	290	Consort identifies lost to follow due to AE in TENS and placebo group – but numerical data not clear Of note, 11 patients (9.48%) reported popular rash and/or cutaneous blistering around the placement site of adhesive electrodes Two patients were withdrawn for persistent cutaneous blistering. Other reasons for withdrawal were and skin hypersensitivity to adhesive electrodes (n=3, 6.81%) Authors note that withdrawals due to 'device-related discomfort' were in the active group (n=3 6.81%).	Skin irritation/blistering at electrode sites	N	N	clear numerical data betwee the different intervention groups
(Ramos et al., 2018)	290	No statements present	No information to extract	N	N	
(Rani et al., 2020)	291 292	No statements present	No information to extract	N	N	
(Ratajczak et al., 2011)	292 293	No statements present	No information to extract	N	N	
(Rawat et al., 1991) (Renovato França et al., 2019)	294	No statements present No adverse events were observed in this study.	No information to extract Reported no adverse events	N $Y = 0$ tally	N = 0tally	
(Reuss et al., 1988)	295	No statements present	No information to extract	Ν	Ν	
(Revadkar and Bhojwani, 2019)	296	No statements present	No information to extract	Ν	Ν	
(Ringel and Taubert, 1991)	297	No statements present	No information to extract	Ν	Ν	
(Robb et al., 2007)	298	No statements present	No information to extract	Ν	Ν	
(Robinson et al., 2001)	299	No statements present	No information to extract	Ν	Ν	
(Roche et al., 1985)	300	No statements present	No information to extract	Ν	Ν	
(Rooney et al., 1983)	301	No statements present. Authors state that TENS is 'safe' in the conclusion. No further info.	No information to extract	N	N	
(Rosenberg et al., 1978)	302	No complications were observed in this study from the use of TENS and the only morbidity reported has involved skin reactions at the electrode sites	Skin reaction at electrode sites	Y	N	No numerical data
(Rutgers et al., 1988)	303	No statements present	No information to extract	Ν	Ν	1

Reference	Reference number	Extracted Text	AEs related to TENS	Statement	Extractable Data	Comment
(Sadala et al., 2018)	304	No statements present	No information to extract	N	N	
(Sahin et al., 2011)	305	No statements present	No information to extract	Ν	Ν	
(Samadzadeh et al., 2017)	306	No statements present	No information to extract	Ν	N	States in conclusion that TEN is safe but no info on adverse events in main text.
(Sangtong et al., 2019)	307	Table 3 shows adverse events, patient global assessment, and patient satisfaction after treatment. More subjects in the study group had increased knee swelling than subjects in the control group (four patients ( $6.3\%$ ) vs. two patients ( $2.9\%$ ), respectively), but no significant difference (P = $0.430$ ). Table 3 of their report	Joint swelling Rash	Y	Y	Data extracted (joint swelling and skin rash) TENS + US = 4 events / 64 participants US alone = 3 events / 68 participants
(Santamato et al., 2013)	308	None of the patients reported adverse effects during the study period.	Reported no adverse events	Y = 0 tally	N = 0 tally	
(Santana et al., 2016)	309	No statements present	No information to extract	Ν	Ν	
(Saranya et al., 2019)	310	No statements present	No information to extract	Ν	Ν	
(Sayilir and Yildizgoren, 2017)	311	No statements present	No information to extract	Ν	Ν	
(Seo et al., 2013)	312	A total of 7 adverse events that required admission in 6 participants were reported during the study. The adverse events included a traffic accident, acute appendicitis, cellulitis, worsening of lower back pain, shoulder pain, uterine myoma, and spontaneous abortion. There was a possible relationship between the treatment and spontaneous abortion that occurred 21 days after BTX-A injection and electrical stimulation. She answered "no" to the question "Are you pregnant or do you have a plan for pregnancy?" before study enrolment. The other events were not related to the treatment in this study.	Spontaneous abortion possibly related to treatment. Other adverse events unrelated to treatment.	Y	N	Numerical data not necessar related to TENS/intervention
(Serry et al., 2016)	313	No statements present	No information to extract	N	Ν	
(Sezen et al., 2017)	314	We observed a small number of complications in the patients who were administered TENS in our study, but there was no statistically significant difference between the two groups. Table 4 of their report	Authors do not say whether complications were felt to be due to TENS	Y	N	Data related to post-operativ complications. Debatably thi is related to AE associated with op procedures rather the TENS. We decided not to extract the data because AE from operation reflects efficacy of TENS rather than AE of TEI Not extracted data (complications) TENS (T) = 6 events / 43 Control placebo TENS = 10 events / 44

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Reference	Reference number	Extracted Text	AEs related to TENS	Statement	Extractable Data	Comment
						Not definitely attributed to the intervention
(Shahoei et al., 2017)	315	No statements present Since it has no negative consequences for mothers and their fetus, it is considered a safe pain relief method.	No information to extract	N	N	
(Shehab and Adham, 2000)	316	No statements present	No information to extract	Ν	Ν	
(Sherry et al., 2001)	317	No statements present	No information to extract	Ν	Ν	
(Shimoji et al., 2007)	318	There were three cases of skin flash at sites of electrode placement in subjects treated with TENS using CPWs, but these disappeared within a day without intervention. No such skin irritation occurred in subjects who received TENS using BMWs. No other complications were reported in both groups. There was also a sham TENS group but no mention of AEs/complications	'Skin flash' (3 cases) in CPW group	Y	Y	Data extracted (skin irritatio TENS (CPWs) = 3 / 9 BMWs (bidirectional modulated sine waves) = 0 events / 11
(Shimoura et al., 2019)	319	No adverse effect was noted with the TENS or sham-TENS treatment.	Reported no adverse events	Y = 0 tally	N = 0 tally	
(Shoukry and Al-Ansary, 2019)	320	Adverse effect during or after the procedure was recorded and treated. Table 3 shows that adverse effects [were significantly less frequent among group-A [TENS + i.v. fentanyl] compared to group-B [i.v. fentanyl]. These statements relate to adverse effects associated with ESWT procedure rather than TENS	O2 desaturation Nausea and vomiting Dizziness	N		The data provides informati about effect of TENS on incidence of adverse events associated with ESWT procedure + fentanyl treatm
(Siemens et al., 2020)	321	Two patients experienced an uncomfortable feeling caused by the current, one after IMT and one after PBT One out of 20 (5%) patients perceived the electric current as uncomfortable after the IMT phase and 1/20 (5%) after the PBT phase. No other TENS-related adverse events were reported. Four patients (20%) generally criticized that cables were impractical and one (5%) patient felt disturbed by the electrodes. After testing both TENS modes, 7/20 (35%) patients requested a prescription for the TENS device in order to use TENS after discharge. A usability problem rather than a safety problem was the fact that the main reason for stopping the study after period 2 was the burden in using TENS (5/15, 33%), e.g., because of the disturbing cables of the device (see Online Resource 5 for further reasons).	12 On	Ν	N	Frequency data between placebo and TENS interventions not provided
(Sikiru et al., 2008)	322	The results demonstrated a significant decrease in the NIH-CPSI ( $P = 0.0002$ ) with no urethral, anal complaints or other side effects	Reported no adverse events	Y = 0 tally	N = 0 tally	
(Silva et al., 2012)	323	No statements present	No information to extract	N	N	
(Silva et al., 2014)	324	No statements present	No information to extract	Ν	Ν	
(Sim, 1991)	325	No statements present	No information to extract	Ν	Ν	
(Siqueira et al., 2019)	326	No statements present	No information to extract	Ν	Ν	
(Sloan et al., 1986)	327	No statements present	No information to extract	Ν	Ν	

Reference	Reference number	Extracted Text	AEs related to TENS	Statement	Extractable Data	Comment
(Smania et al., 2005)	328	No statements present	No information to extract	N	N	There was data missing fro final analysis but no explanation given
(Smedley et al., 1988)	329	No statements present	No information to extract	Ν	Ν	
(Smith et al., 1983)	330	Only one patient noticed any adverse effects from the treatment, a mild skin reaction to the electrode jelly.	Skin irritation in 1 patient.	Y	N	No numerical data to extra
(Smith et al., 1986)	331	No statements present	No information to extract	Ν	Ν	
(Sodipo et al., 1980)	332	No statements present	No information to extract	Ν	Ν	
(Solak et al., 2007)	333	No statements present	No information to extract	Ν	Ν	
(Solak et al., 2009)	334	No statements present	No information to extract	Ν	Ν	
(Sonde et al., 1998)	335	No statements present	No information to extract	Ν	Ν	
(Stepanovic et al., 2015)	336	Adverse effects were associated with a specific treatment of herpes zoster $(n = 5)$ and analgesics prescribed $(n = 20)$ . Most common complication was a bacterial superinfection, in either group there was no serious complication.	Reported no adverse events	Y	N = 0 TENS ONLY	
(Steptoe and Bo, 1984)	337	TENS is almost free from adverse events	No information to extract	Ν	Ν	
(Stratton and Smith, 1980)	338	No statements present	No information to extract	Ν	Ν	
(Stubbing and Jellicoe, 1988)	339	No statements present	No information to extract	N	N	
(Suh et al., 2015)	340	No statements present	No information to extract	Ν	Ν	
(Talbot et al., 2020)	341	No statements present	No information to extract	Ν	Ν	
(Tantawy et al., 2018)	342	No statements present	No information to extract	Ν	Ν	
(Taylor et al., 1981)	343	No statements present	No information to extract	Ν	Ν	
(Taylor et al., 1983)	344	No statements present	No information to extract	Ν	Ν	
(Thakur and Patidar, 2004)	345	Side effects were more in the tramadol group in the form of nausea 7%, vomiting 3%, drowsiness 2% and fetal distress 2%, what while in the control group only one percent had fetal distress. Intense group none had any side effects Data in Table 6	Reported no adverse events	Y	Y	Data extracted TENS = 0 events / 100 Control (no intervention) = event / 100 participants (F distress) Also: Tramadol = 14 / 100 participants (nausea, vomi drowsiness, fetal distress) – did not add to forest plo
(Thomas et al., 1988) (Thomas et al., 1995) (Thoratainesson et al. 1978)	346 347 348	No statements present No statements present	No information to extract No information to extract	N N	N N	prevent double counting in group analysis
(Thorsteinsson et al., 1978)	349	No statements present	No information to extract	N	N	
(Tilak et al., 2016)	549	No statements present	No information to extract	Ν	Ν	

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Reference	Reference number	Extracted Text	AEs related to TENS	Statement	Extractable Data	Comment
(Tokuda et al., 2014)	350	We observed no side effects; thus, TENS may be particularly useful for patients who have liver or kidney disease considering that analgesics are excreted through the kidney.	Reported no adverse events	Y = 0 tally	N = 0 tally	
(Tonella et al., 2006)	351	No statements present	No information to extract		Ν	
(Topuz et al., 2004)	352	No statements present	No information to extract	Ν	Ν	
(Tosato et al., 2007)	353	No statements present	No information to extract	Ν	Ν	
(Treacy, 1999)	354	No statements present	No information to extract	Ν	Ν	
(Tsen et al., 2000)	355	Some have raised the concern that TENS could interfere with fetal heart rate tracings,1 1 however, this was not witnessed in our review of fetal tracings, nor did we observe any incidents of non-reassuring fetal tracings2 4 subsequent to the CSE placement in either group.	Reported no adverse events.	Y = 0 tally	N = 0 tally	
(Tsen et al., 2001)	356	No statements present	No information to extract	N	N	Authors stated they would record adverse events but no comments included in result or discussion.
(Tsukayama et al., 2002)	357	No adverse events were reported by the evaluator. The therapists reported some transient adverse events, for the EA group: transient aggravation of LBP (1 case), discomfort due to press tack needles (1 case), pain on needle insertion (1 case) and small subcutaneous bleeding (10mm in diameter, 1 case); in the TENS group: transient aggravation of back pain (1 case), transient fatigue (1 case), itching with electrode (1 case). Seven patients in each group did not experience any adverse events.	Increased back pain Transient fatigue Itching with electrode	Y	Y	Data extracted (symptom aggravation, skin reaction, fatigue) TENS = 3 events / 10 participants Electroacupuncture = 4 even / 9 participants
(Tucker et al., 2015)	358	There were no clinically significant adverse events related to TENS in either group. In table 2 of their report	Reported no adverse events	Y = 0 tally	N = 0 tally	
(Tugay et al., 2007)	359	No adverse effects were observed, supporting the findings of the related literature.	Reported no adverse events	Y = 0 tally	N = 0 TENS ONLY	
(Tulgar et al., 1991a)	360	No statements present	No information to extract	N	Ν	
(Tulgar et al., 1991b)	361	No statements present	No information to extract	N	Ν	
(Unterrainer et al., 2010)	362	In conclusion, the use of TENS before skin incision and postoperative is noninvasive, safe, simple, and free of systemic side effects in postoperative pain treatment after major spinal surgery.	Reported no adverse events	$\mathbf{Y} = 0$ tally	N = 0 TENS ONLY	
(Unterrainer et al., 2012)	363	No statements present	No information to extract	Ν	Ν	
(Upton et al., 2017)	364	No adverse effects reported during the study.	Reported no adverse events	Y = 0 tally	N = 0 tally	
(Vaidya, 2018)	365	However, no negative effects were found with the use of TENS in any stage of pregnancy which supports the finding of our study [9]. No negative effects were reported for any of the patients.	Reported no adverse events	Y = 0 tally	N = 0 tally	
(Vaillancourt et al., 2019)	366	No statements present	No information to extract	Ν	Ν	

Reference	Reference number	Extracted Text	AEs related to TENS	Statement	Extractable Data	Comment
(Valenza et al., 2016)	367	No adverse effects were reported by any participant after any of the interventions.	Reported no adverse events	Y = 0 tally	N = 0 tally	
(van der Ploeg et al., 1996)	368	No adverse side-effects occurred.	Reported no adverse events	Y = 0 tally	N = 0 tally	
(van der Spank et al., 2000)	369	No statements present	No information to extract	Ν	N	
(Vance et al., 2012)	370	No statements present	No information to extract	Ν	Ν	
(Vitalii and Oleg, 2014)	371	No side effects of LF-TENS were seen. Mean gabapentin dose was 1036.36 mg in the study group and 1560 mg in the control group, thus the basic dose was increased by 136.36 mg of gabapentin in the study group and by 560 mg in the control group (P=0.004; Fig. 2). Three patients from the control group reported drowsiness and dizziness on the ninth day of treatment (doses of gabapentin increased to 2700, 2400 and 1800 mg) and one patient reported blurred vision (dose of gabapentin increased to 2700 mg). No side effects of gabapentin were reported in the study group.	Reported no adverse events	Y	N	No data extracted because AEs due to the higher doses of gabapentin in control group. Thus, data reflects TENS efficacy in reducing AEs associated with gabapentin TENS + gabapentin = 0 events Placebo TENS + gabapentin = 4 events (drowsiness + dizziness, blurred vision related to gabapentin)
(Vrouva et al., 2019)	372	No statements present	No information to extract	Ν	Ν	
(Walker et al., 1991)	373	No statements present	No information to extract	Ν	Ν	
(Wang et al., 2009)	374	No statements present	No information to extract	Ν	Ν	
(Warfield et al., 1985)	375	There were no complications in either group as a result of TENS. We conclude that TENS is a safe, effective adjunctive therapy for post thoracotomy pain.	Reported no adverse events	Y = 0 tally	N = 0 tally	
(Warke et al., 2004)	376	No statements present	No information to extract	Ν	Ν	
(Warke et al., 2006)	377	No statements present	No information to extract	Ν	Ν	
(Yameen et al., 2011)	378	No statements present	No information to extract	N		Transcutaneous electrical nerve stimulation is an effective, easy to use and with minimal side effects in patient suffering from trigeminal neuralgia not responding to conventional therapy.
(Yesil et al., 2018)	379	No adverse events due to electrotherapy such as irritation or burning of the skin were observed.	Reported no adverse events	Y = 0 tally	N = 0 TENS ONLY	
(Yilmaz et al., 2020)	380	We did not observe any side effects or intolerance associated with TENS in our patients. Also, TENS application did not cause any negative changes in vital signs. This result indicates that TENS is easily applied, and its efficacy and safety could help in pain relief for inguinal herniorrhaphy.	Reported no adverse events	Y = 0 tally	N = 0 TENS ONLY	

Reference	Reference number	Extracted Text	AEs related to TENS	Statement	Extractable Data	Comment
(Yilmazer et al., 2012)	381	No statements present	No information to extract	Ν	Ν	
(Yokoyama et al., 2004)	382	No statements present	No information to extract	Ν	Ν	
(Yoshimizu et al., 2012)	383	No adverse effects or carryover effect were detected.	Reported no adverse events	$\mathbf{Y} = 0$	N = 0	
				tally	tally	
(Yüksel et al., 2019)	384	No statements present	No information to extract	Ν	Ν	
(Yurtkuran and Kocagil, 1999)	385	No statements present	No information to extract	Ν	N	
(Zakariaee et al., 2019)	386	No statements present	No information to extract	N	N	Mentions that adverse events will be documented but then fails to provide data or clear statement in results nor discussion
(Zhang et al., 2020)	387	No statements present	No information to extract	Ν	Ν	
(Zhou et al., 2018)	388	No adverse events were observed in either of the groups during the 8-week	Reported no adverse	$\mathbf{Y} = 0$	N = 0	
		follow-up.	events.	tally	tally	

#### Legend

 Information was identified by searching for text and/or numerical data that referred to adverse events. Information was 'cut and pasted' into this Table. Where available, data on the occurrence of adverse events in each intervention arm was tallied as events (irrespective of severity) per number participants exposed (i.e. number in intervention arm), pooled and meta-analysed. If trial reports included a statement that no adverse events were observed during the study this was identified as such in our table. 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), in line with advice from the Cochrane Collaboration. Y, yes; N, no; TENS, transcutaneous electrical nerve stimulation.

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# PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE	•	·	
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT		·	
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4-5
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4-5
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	5
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	5
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	5-7
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	5-7
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	8-9
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	8-9
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	6-7
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I <sup>2</sup> ) for each meta-analysis. For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml	8-9

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## **PRISMA 2009 Checklist**

Section/topic	#	Checklist item	
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	8-9
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	8-9
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	9-10
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	9-10
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	9-10
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	10-13
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	10-13
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	9-10
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	10-13
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	13-15
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	15-16
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	17-19
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	20-21

41 From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. 42 doi:10.1371/journal.pmed1000097

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