PEER REVIEW HISTORY

This paper was submitted to a another journal from RAPM but declined for publication following peer review. The authors addressed the reviewers' comments and submitted the revised paper to BMJ Open. The paper was subsequently accepted for publication at BMJ Open.

(This paper received three reviews from its previous journal and three reviewers agreed to published their review.)

ARTICLE DETAILS

TITLE (PROVISIONAL)	Efficacy and Safety of Transcutaneous Electrical Nerve Stimulation (TENS) for Acute and Chronic Pain: A systematic review and meta-analysis (The Meta-TENS study)
AUTHORS	Johnson, Mark; Paley, C; Jones, Gareth; Mulvey, Matthew; Wittkopf, Priscilla

VERSION 1 – REVIEW

REVIEWER	Potru, Sudheer

GENERAL COMMENTS	Other than minor grammatical notes, this study appears to be well-done. I applaud the authors on such a tremendous undertaking in analyzing these numerous underpowered studies in a logical, systematic, and rigorous fashion. Some further statistical analysis regarding use of the TENS for acute versus chronic pain (in lieu of reviewing for all types of pain) would also be interesting, although I would anticipate similar results in either scenario.

REVIEWER	Youngren, Kimberly

GENERAL COMMENTS	Thank you performing this comprehensive systematic review and meta-analysis on the safety and efficacy of TENS for acute and chronic pain. Authors could consider additional discussion as to what makes this article important in terms of improving patient care and expand upon how this Meta-analysis may help to drive policy change to make this a covered therapy for patients, perhaps increasing it's availability/use in underserved populations Other minor suggestions: Page 7 Line 14 and 28: May consider removing this sentence on line 28 as it is essentially a duplicate of sentence in prior paragraph. Reference numbers in several instances do not correlate with the reference number in studies included, appearing to be off by one in many cases. For Example:

	Page 50 Line 38Sadala mislabeled article #305(as opposed to #304 in article listing) Page 52 Santong mislabeled article #308 (as opposed to #307 in article listing)

REVIEWER	Davis, Matthew

GENERAL COMMENTS	Thank you for giving me the opportunity to review the manuscript titled “Efficacy and Safety of Transcutaneous Electrical Nerve Stimulation (TENS) for Acute and Chronic Pain: A systematic review and meta-analysis (Meta-TENS study).” This is large systematic review and meta-analysis of TENS for acute and chronic pain that included review of nearly 400 RCTs. Outcomes included difference in pain (TENS versus comparison) and data on adverse events were collected. This is one of the largest and most comprehensive reviews I have seen. Data extraction and summarization of the results appear rigorous: data were abstracted by two separate reviewers, risk of bias was ascertained, and estimates pooled using random effects models (that is justified given the heterogeneity of the studies pooled). It’s nice as well to have tables with the exact language for adverse events reported, studies that required translation, excluded studies (including the reason for exclusion), etc. The appendices to this article are massive (and I assume there is not size restrictions for online content). • In several places the authors report a review that was later updated. Why the need to state two separate time periods? Wouldn’t it be more straightforward to say that the literature covered was simply up to May 2020? • I don’t particularly find the introduction to be very motivational to the analyses. In fact, the authors report this review has already been done many times before. Then what specifically is the uncertainty or way in which the current study makes a contribution beyond the previous systematic reviews of TENS. Is the scope or the fact it’s more up to date? The case for why this review is important should be more clearly made. • In my opinion the Methods could benefit from better organization. Consider separate subheadings to describe the operational definitions of the interventions and outcomes. • More attention could be given to the description regarding the timing of the outcomes. With so many studies it’s likely that the pain assessments varied – there is some mention of this in the methods. Would it be at all relevant to examine short- versus long-term endpoints? • Given the high level of heterogeneity I have some concern regarding the appropriateness of pooling the various estimates for chronic pain. • Figures 3 and 4 would benefit from including heterogeneity I2. • Minor, but some of the subheadings in the discussion could be removed.

VERSION 1 – AUTHOR RESPONSE

Reviewer 1 Comments to Author:
Other than minor grammatical notes, this study appears to be well-done. I applaud the authors on such a tremendous undertaking in analyzing these numerous underpowered studies in a logical, systematic, and rigorous fashion.

Some further statistical analysis regarding use of the TENS for acute versus chronic pain (in lieu of reviewing for all types of pain) would also be interesting, although I would anticipate similar results in either scenario.

OUR RESPONSE:
We conducted various subgroup analyses for pain characteristics, including acute vs. chronic, and pain diagnoses. We present specific details of the findings and exploration of the impact of RoB, heterogeneity etc. in the Supplementary Appendices (p44 of supplementary appendix onwards). We included a summary of these findings as figures in the main text (Figure 4).
We also conducted a variety of additional subgroup analyses for other pain characteristics including Broad ICD-11 categories, pain of predominantly nociceptive or neuropathic origin, and main physiological structure associated with pain. We decided not to include these in the Supplementary Appendix because the analyses did not reveal new knowledge and we to restrict the size of our already 'massive' supplementary appendix. We can include these analyses in the Supplementary Appendix if required. We have added a sentence to the manuscript to reflect this.

Reviewer 2 Comments to Author:
Thank you performing this comprehensive systematic review and meta-analysis on the safety and efficacy of TENS for acute and chronic pain. Authors could consider additional discussion as to what makes this article important in terms of improving patient care and expand upon how this Meta-analysis may help to drive policy change to make this a covered therapy for patients, perhaps increasing it's availability/use in underserved populations

OUR RESPONSE:
We have elaborated on this in the section Meaning of the Study. We have also referred to a recent comprehensive review by one of our authors (Johnson[1]) raising issues related to the acceptance or otherwise of the findings of our meta-analysis

Other minor suggestions: Page 7 Line 14 and 28: May consider removing this sentence on line 28 as it is essentially a duplicate of sentence in prior paragraph.

OUR RESPONSE:
Amended

Reference numbers in several instances do not correlate with the reference number in studies included, appearing to be off by one in many cases.
For Example: Page 50 Line 38Sadala mislabeled article #305(as opposed to #304 in article listing)
Page 52 Santong mislabeled article #308 (as opposed to #307 in article listing)

OUR RESPONSE:
We have amended these errors

Reviewer 3 Comments to Author:
This is large systematic review and meta-analysis of TENS for acute and chronic pain that included review of nearly 400 RCTs. Outcomes included difference in pain (TENS versus comparison) and

data on adverse events were collected. This is one of the largest and most comprehensive reviews I have seen. Data extraction and summarization of the results appear rigorous: data were abstracted by two separate reviewers, risk of bias was ascertained, and estimates pooled using random effects models (that is justified given the heterogeneity of the studies pooled). It's nice as well to have tables with the exact language for adverse events reported, studies that required translation, excluded studies (including the reason for exclusion), etc. The appendices to this article are massive (and I assume there is not size restrictions for online content).
In several places the authors report a review that was later updated. Why the need to state two separate time periods? Wouldn't it be more straightforward to say that the literature covered was simply up to May 2020?

OUR RESPONSE:
It is traditional to state the date of the original and subsequent updated search strategy in the text narrative of systematic reviews and we therefore have made no changes to the text. We have amended in the PRISMA flow chart to represent the search findings as one entity.

I don't particularly find the introduction to be very motivational to the analyses. In fact, the authors report this review has already been done many times before. Then what specifically is the uncertainty or way in which the current study makes a contribution beyond the previous systematic reviews of TENS. Is the scope or the fact it's more up to date? The case for why this review is important should be more clearly made.

OUR RESPONSE:
We have re-written parts of the Introduction to strengthen the rationale and justification for undertaking an all-encompassing meta-analysis and to argue the case for focussing this report on the analysis of pain intensity during or immediately after TENS treatment.

In my opinion the Methods could benefit from better organization. Consider separate subheadings to describe the operational definitions of the interventions and outcomes.

OUR RESPONSE:
We have added subsection headers.

More attention could be given to the description regarding the timing of the outcomes. With so many studies it's likely that the pain assessments varied – there is some mention of this in the methods. Would it be at all relevant to examine short- versus long-term endpoints?

OUR RESPONSE:
We argue that evaluating TENS on the intensity of pain in the moment is of primary concern and we have standardised the timing of outcomes by extracting data during or immediately after TENS, as described in our methods. This is of utmost importance to clinicians and patients because it helps to inform advice about treatment schedules and regimens for individual need. We have amended the Introduction to strengthen the justification of choice of this timepoint and discuss why this is more important and a more robust measure than long-term follow-up endpoints.
We recognise that credence is given to long-term follow-up outcome for intervention reviews. Analysing long-term outcome for TENS is far more complex than first appears, with a variety of confounders affecting outcome. Simplistic analyses can be, and have been, misleading. A robust analysis of long-term outcome is something that we intend to do in the future. We do not include an analysis of long-term outcomes in this report because it would (i) add considerable delay to publication of findings of immediate/short-term effects, (ii) reduce communication of detail about the analysis of immediate/short-term due to word count constraints, and (iii) deflect attention from the critical outcome (TENS effects on pain in the moment) which enables the design of appropriate TENS

treatment schedules. We predict that analysis of long-term effects will provide only very low certainty evidence. We have amended the Discussion (Strengths of the study and Meaning of the Study) to reflect the points identified above. We also direct the reader to our recent comprehensive review that discusses these issues in depth[1]. We do hope that this meets with your approval.

Given the high level of heterogeneity I have some concern regarding the appropriateness of pooling the various estimates for chronic pain.

OUR RESPONSE:
We agree and are explicit about the level of statistical heterogeneity throughout. Our exploration of statistical heterogeneity is provided in the Supplementary Appendix and we refer to the salient points of this in the text. We pooled chronic pain data in a variety of ways and failed to find any differences between sub-group estimates. We believe that concerns about the impact of heterogeneity on the appropriateness of pooling would be greater if we had observed differences and were making subsequent inferences. We argue that our findings that pain condition did not moderate effect size is physiologically and clinically plausible. Finally, concern about statistical heterogeneity was reflected in GRADE judgements.

Figures 3 and 4 would benefit from including heterogeneity I2.

OUR RESPONSE:
We have added the I^2 to the figures.

Minor, but some of the subheadings in the discussion could be removed.

OUR RESPONSE:
We are following recommendations of BMJ on structuring Discussion sections. However, we are prepared to modify at the request of the Editor

VERSION 2 – REVIEW

REVIEWER	Barlas, Panos Metro North Hospital and Health Service, Jamieson Trauma Institute
REVIEW RETURNED	17-May-2021

GENERAL COMMENTS	thank you for giving me the opportunity to review this manuscript. It is comprehensive and detailed in its approach to evaluate the usefulness of TENS in the treatment of pain, irrespective of its aetiology or chronicity. It takes into account the overall clinical impression of TENS upon patients with such conditions and it is a refreshing approach. My main comment rests mainly on the application of TENS: whilst the review covers the clinical efficacy of TENS, it does not offer much in relation to guidance to the clinician who wishes to apply TENS. There is a passing mention of duration, repetition and parameters of frequency and intensity but an actual discussion of these issues of dose in detail is lacking. As is the potential for current protocols of TENS application to cause tolerance (as highlighted in this paper: https://pubmed.ncbi.nlm.nih.gov/21144659/) It may be not the focus of the review, however if there is a meaningful contribution to be made in the use of TENS clinically,

	these issues should be at least identified and their importance strongly accented if the practice and future evaluation of TENS clinically is to move forward. I strongly encourage the authors to address these issues in the final version of this, otherwise notable and significant, manuscript.

REVIEWER	Comachio, Josielli The University of Sydney Faculty of Medicine and Health
REVIEW RETURNED	19-May-2021

GENERAL COMMENTS	Dear authors, Thank you for the opportunity to review this impressive manuscript. I have listed few comments below. 1. It is not clear how the authors will categorize the various types of clinical pain and many of them include combinations of the approaches the authors list on page 3 (e.g., standard of care, placebo, other treatment,), some a priori description of how you categorized therapies that contain multiple components would be important to do. 2. Pg 3 line 54. The authors described the TENS intervention and pulse frequencies. Can you explain and add references for that frequency and pulse chosen? 3. There is no attention to process variables, e.g., such as number of sessions attended, adherence with combinations of therapy which can impact treatment outcomes. 4. What criteria the investigators employ around whether sufficient number of studies are available for a given outcome to conduct a meta-analysis for that outcome? 5. Pg 8, Line 40: Your statement that you included '… acute or chronic pain of any origin' is misleading, in my view, because you later define the set of pain (pg. '… any comparison interventions' implies you will include all interventions. Please clarify?

REVIEWER	Woubishet Woldeamanuel, Yohannes Stanford University School of Medicine, Neurology and Neurological Sciences
REVIEW RETURNED	30-Aug-2021

GENERAL COMMENTS	- Given the significant inter-study heterogeneity, more sensitivity analysis needs to be included (e.g. degree of robustness to leave-one-out meta-analysis, temporal trend meta-analysis, meta-regression). In addition, Galbraith plot needs to be included to examine small-study effect/bias and heterogeneity. Authors speculated on small-study bias, hence this needs to be quantified or estimated. Especially in a subjective behavior such as pain intensity. - Stratified sub-group meta-analysis is needed to examine confounding from placebo vs other care controls. - There were extremely high levels of heterogeneity in many of the forest plots rendering the meta-analysis non-combinable. One reason could be that no a priori estimation of sample size and participant size per study was done. Particularly so when employing random effects weighted analysis. This needs to be stated/discussed. Please read the following references. - Jackson D, Turner R. Power analysis for random-effects meta-analysis. Res Syn Meth. 2017;8:290–302. https://doi.org/10.1002/jrsm.1240 - Valentine, J. C., Pigott, T. D. & Rothstein, H. R. (2010). How many studies do you need? A primer on statistical power for meta-

	analysis. Journal of Educational and Behavioral Statistics, 35(2), 215-247.\n– Chapters 4 -6 in Pigott, T. D. (2012). Advances in meta-analysis. New York, NY: Springer

REVIEWER	Denison, Eva Marie-Louise FHI, Health sevices
REVIEW RETURNED	30-Aug-2021

GENERAL COMMENTS	The systematic review process follows the PRISMA guideline and is very well documented in the manuscript and supplementary material. The meta-analysis procedures are well described and all forset plots are available in the supplementary material. The subgroup analyses were undertaken to explore heterogeneity, and unexplained heterogeneity was accounted for in the GRADE assessments. I have some concerns regarding some of the GRADE assessments, though. GRADE assessment TENS versus placebo, no treatment, standard of care. Study limitations: A summary of the Risk of Bias assessment shows that 75-80% of the information comes from studies with unclear or high risk of bias for randomization sequence and allocation concealment. As shown in the GRADE handbook, Table 5.6 there is an option not to downgrade for study limitations, but because sequence generation and allocation concealment are critical for conclusions about effect, I encourage the authors to justify their judgment in more detail. GRADE assessment TENS versus placebo, pain intensity The authors have upgraded for large effect under Publication bias. Upgrading is however associated with observational studies, and only RCTs were included in this reveiw. The GRADE handbook states that “Although it is theoretically possible to rate up results from randomized control trials, we have yet to find a compelling example of such an instance.” Please give a reference to support your judgment or consider revising, adjusting overall certainty of evidence to low. GRADE assessment TENS versus no treatment Confidence is downgraded one step for Inconsistency, Imprecision and Publication bias – wouldn’t that end up with very low overall certainty of evidence?

VERSION 2 – AUTHOR RESPONSE

Dear Sir/Madam

We submit a revised manuscript of our meta-analysis (clean and marked up), supplemental material, and a response to each of the reviewers’ comments. We have carefully considered all of the reviewers’ comments and are in general agreement with all of the points that have been raised. We have responded to each of their points and identified where in our manuscript amendments have been made in a marked up copy. Please be aware that the clean version of our manuscript has some additional minor proof edits. We have also supplied a marked up version of Supplemental File 1 which identifies the main amendments made to our supplementary appendix. We would also like to

draw the Editors' attention to the context section provided in our Response to Reviewers. Our review and meta-analysis are on the large side and seek Editorial advice about how best to present some of the material if it is accepted for publication.

We thank you for your careful consideration of our research.

VERSION 3 – REVIEW

REVIEWER	Woubishet Woldeamanuel, Yohannes Stanford University School of Medicine, Neurology and Neurological Sciences
REVIEW RETURNED	21-Oct-2021

GENERAL COMMENTS	All comments are addressed satisfactorily.

REVIEWER	Denison, Eva Marie-Louise FHI, Health sevices
REVIEW RETURNED	27-Oct-2021

GENERAL COMMENTS	Thank you for your careful responses to my concerns about the application of GRADE. There is always judgment involved in GRADE assessments, and I think you have justified your choices in a good way. The most important issue, incorrectly upgrading of RCTs has been corrected.